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Abstracts from the 19th International Symposium on Pediatric Neuro-Oncology (ISPNO 2020)

December 13 – 16, 2020
Karuizawa, Japan

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Abstracts

ABSTRACTS CATEGORY CODES

ATRT – ATYPICAL TERATOID/RHABDOID TUMORS

COVD - COVID-19 AND PEDIATRIC NEURO-ONCOLOGY

DIPG - DIFFUSE MIDLINE GLIOMA/DIPG

DDEL - DRUG DELIVERY/PHARMACOKINETICS

EPCT - EARLY PHASE CLINICAL TRIALS

EPEN - EPENDYMOMA

EPID - EPIDEMIOLOGY

ETMR - ETMR AND OTHER EMBRYONAL TUMORS

GCT - GERM CELL TUMORS

HGG - HIGH GRADE GLIOMA

IMG - IMAGING

IMMU – IMMUNOTHERAPY

LINC - PEDIATRIC NEURO-ONCOLOGY IN ASIA AND OTHER LOW/MIDDLE INCOME COUNTRIES

LGG - LOW GRADE GLIOMA

MBCL - MEDULLOBLASTOMA (CLINICAL)

MBRS - MEDULLOBLASTOMA (RESEARCH)

MODL - PRECLINICAL MODELS/EXPERIMENTAL THERAPY/ DRUG DISCOVERY

NFB - NEUROFIBROMATOSIS AND OTHER PREDISPOSITION SYNDROMES

NURS – NURSING/PATIENT CARE

OTHR - OTHERS (NOT FITTING ANY OTHER CATEGORY)

PATH - PATHOLOGY/CLASSIFICATION

QOL - NEUROPSYCHOLOGY/QUALITY OF LIFE

RARE - CRANIOPHARYNGIOMA AND RARE TUMORS

RONC - RADIATION ONCOLOGY

SURG - NEUROSURGERY

SWK - SOCIAL WORK/PATIENT SUPPORT/PALLIATIVE CARE

TBIO - TUMOR BIOLOGY (NOT FITTING A SPECIFIC DISEASE CATEGORY)

THER - VIRAL/GENE THERAPY AND OTHER NOVEL THERAPIES

ATYPICAL TERATOID/RHABDOID TUMORS (ATRT)

ATRT-01. UPREGULATION OF PROTEIN SYNTHESIS AND PROTEASOME DEGRADATION CONFERS SENSITIVITY TO PROTEASOME INHIBITOR BORTEZOMIB IN MYC-ATYPICAL TERATOID/RHABDOID TUMORS

Minh-Huy Tran[1,2], Kuo-Sheng Wu[3], Che-Chang Chang[4], and Tai-Tong Wong[5,6]; [1]International Master/Ph.D. Program in Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, [2]Department of Neurosurgery, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam, [3]Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, [4]The Ph,D, Program for Translational Medicine, Taipei Medical University, Taipei, Taiwan, [5]Department of Neurosurgery, Taipei Medical University Hospital, Taipei Medical University, Taipei, Taiwan, [6]Pediatric Brain Tumor Program, Taipei Cancer Center, Taipei Medical University, Taipei, Taiwan

BACKGROUND: Atypical teratoid rhabdoid tumors (ATRTs) are among the most malignant brain tumors in early childhood and remain incurable. Myc-ATRT is driven by the *Myc* oncogene, which directly controls the intracellular protein synthesis rate. Proteasome inhibitor bortezomib (BTZ) was approved by the Food and Drug Administration as a primary treatment for multiple myeloma. This study aimed to determine whether the upregulation of protein synthesis and proteasome degradation in Myc-ATRTs increases tumor cell sensitivity to BTZ. METHODS: We performed differential gene expression and gene set enrichment analysis on matched primary and recurrent patient-derived xenograft (PDX) samples from an infant with ATRT. The expressions of proteasome-encoding genes were compared among this paired model as well as between the 24 human ATRT samples and normal brain tissues. The antitumor effect of BTZ was evaluated in three human Myc-ATRT cell lines (PDX-derived tumor cell line Re1-P6, BT-12, and CHLA-266) and in the orthotopic xenograft models of Re1-P6 cell. RESULTS: Concomitant upregulation of the Myc pathway, protein synthesis, and proteasome degradation were identified in recurrent ATRTs. In ATRTs, the proteasome-encoding genes were highly expressed compared with in normal brain tissues, correlated with the malignancy of tumor cells, and were essential for tumor cell survival. BTZ inhibited proliferation and induced apoptosis through the accumulation of p53 in *in vitro* drug tests. Furthermore, BTZ inhibited tumor growth and prolonged survival in Myc-ATRT orthotopic xenograft mice. CONCLUSIONS: Our findings suggest that BTZ may be a promising targeted therapy for Myc-ATRTs.

ATRT-02. MEK/ERK SIGNALLING DEPENDENCY IN ATYPICAL TERATOID RHABDOID TUMOURS

Hui (Claire) Shi[1,2], Dhanya Sooraj[2], Claire Sun[2], Paul Daniel[2], Gabrielle Bradshaw[2], Jason Cain[2,1], and Ron Firestein[2,1]; [1]Monash University, Melbourne, Victoria, Australia, [2]Hudson Institute of Medical Research, Melbourne, Victoria, Australia

Atypical teratoid rhabdoid tumours (ATRTs) are high-grade malignant paediatric brain tumours with a less than one-year survival rate after diagnosis. Current treatment for ATRT, which includes high-intensive radiotherapy and chemotherapy, results in long-term side effects on ATRT patients. Hence, there is an urgent need to discover targeted therapies that could be used to treat patients with ATRT. As part of the Hudson Monash Paediatric Precision Medicine Program, we have collected 23 ATRT cell lines which we used to performed high-throughput small molecule and genetic (CRISPR) screening to identify new therapies and therapeutic targets. In parallel, we characterised the ATRT cell lines based on transcriptomic (RNA-seq) and epigenetic (methylation) signatures. An integrative multi-omic approach was then used to uncover discrete vulnerabilities in specific subsets of ATRT patients. Strikingly, these include a number of druggable dependencies, such as MEK, CDK, HDAC, and Topoisomerase, that offer a promise of rapid clinical translation. In our study, we focus on MEK dependency in a subtype of ATRT lines to further define the underlying mechanisms and biomarkers. While future studies validating the MEK/ERK signalling dependency in a wider cohort of patient models and in *in vivo* models are required, these data provide a framework for applying an integrative multi-omic approach in paediatric cancer precision medicine.

ATRT-03. IDENTIFICATION OF MICRORNA-BASED PROGNOSTIC BIOMARKERS AND CANDIDATE THERAPEUTIC AGENTS FOR ATYPICAL TERATOID/RHABDOID TUMOR

Yang Zhang, and Jianguo Xu; Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, Sichuan, China

BACKGROUND: MicroRNA (miRNA) has been found to be involved in development of many malignant pediatric brain tumors, including atypical teratoid/rhabdoid tumor (AT/RT) that is highly aggressive and carries a dismal prognosis. The current study investigated the potential value of miRNAs and pivotal genes associated with AT/RT using bioinformatics analysis, aiming to identify new prognostic biomarkers and candidate drugs for AT/RT patients. METHODS: Differentially expressed miRNAs (DEMs) and genes (DEGs) between AT/RT and normal control samples were obtained from GEO database. The target genes of DEMs were predicted via TargetScanHuman7.2 and miRDB, and then intersected with DEGs. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analyses of overlapping genes were conducted, followed by construction of protein-protein interaction network. Hub genes were determined by Cytoscape

software, and their prognostic values were evaluated using Kaplan-Meier analysis. Connectivity Map database was used to identify latent therapeutic agents. RESULTS: A total of 11 DEMs (hsa-miR-1224-5p, hsa-miR-128-3p, hsa-miR-17-5p, hsa-miR-18b-5p, hsa-miR-29c-5p, hsa-miR-329-3p, hsa-miR-379-5p, hsa-miR-433-3p, hsa-miR-488-5p, hsa-miR-656-3p and hsa-miR-885-5p) were screened. By intersecting 3275 predicted target genes and 925 DEGs, we finally identified 226 overlapping genes that were enriched in pathways in cancer and MAPK signaling pathway. Four hub genes (GRIA2, NRXN1, SLC6A1 and SYT1) were significantly associated with the overall survival of AT/RT patients. Candidate drugs included histone deacetylase inhibitor (givinostat), DNA synthesis inhibitor (floxuridine), cyclin-dependent kinase inhibitor (purvalanol) and janus kinase inhibitor (lestaurtinib). CONCLUSION: In summary, this study systematically analyzed AT/RT-related miRNAs and pivotal genes to provide novel prognostic biomarkers and potential therapeutic agents.

ATRT-04. INHERITED RHABDOID PREDISPOSITION SYNDROME: A CASE OF CHOROID PLEXUS CARCINOMA AND ATYPICAL TERATOID RHABDOID TUMOR IN SIBLINGS

Alexis Judd, Erin Wright, and Sarah Rush; Akron Children's Hospital, Akron, OH, USA

Choroid plexus carcinoma (CPC) and Atypical teratoid/rhabdoid tumor (ATRT) are aggressive, malignant brain cancers most commonly arising in children less than 3 years of age. These tumors often have genetic alterations in the tumor suppressor gene SMARCB1/INI1. Rhabdoid predisposition syndrome (RTPS) categorizes patients with germline mutations in SMARCB1 or SMARCA4, leading to a markedly increased risk of developing rhabdoid tumors. Both CPC and ATRT have been demonstrated in patients with these rhabdoid predisposition syndromes. In general, these tumors tend to have a poor prognosis. However, with the presence of a SMARCB1 mutation they may have improved overall survival. We present two interesting cases of siblings with maternally inherited SMARCB1 mutations: one a 21-month-old male who presented with an ATRT and another a 10 month old female who presented with a CPC. The ATRT was treated as per the Children's Oncology Group study ACNS0333 with high dose chemotherapy and stem cell rescue as well as cranial radiation. The CPC was treated as per CPT-SIOP 2009 with etoposide, cyclophosphamide and vincristine. Unlike other patients with these aggressive tumors, both of these patients are alive without evidence of disease recurrence 8 and 7 years post therapy, respectively. Additional genomic testing on both tumors is currently pending in order to potentially identify other mutations that may impact survival. These cases further illustrate the similar profile of two very different tumors with improved overall survival that may be secondary to mutations in SMARCB1 in RTPS.

ATRT-05. RESULTS OF MULTICENTER TRIAL CONCERNING THE TREATMENT OF CHILDREN WITH ATYPICAL TERATOID/ RHABDOID TUMORS (ATRT) OF THE CENTRAL NERVOUS SYSTEM

Olga Zheludkova[1], Lyudmila Olkhova[2], Yuri Kushel'[3], Armen Melikyan[3], Marina Ryzhova[3], Alexey Kislyakov[4], Evgeniy Shultz[3], Irina Borodina[5], Svetlana Gorbatykh[4], Vladimir Popov[6], Marina Mushinskaya[7], Olga Polushkina[1], Eugenia Inyushkina[8], Natalya Yudina[9], Lyudmila Privalova[10], Lyudmila Minkina[11], Artem Zaichikov[12], Eugenia Matsekha[13], Ivan Fisyun[14], Daniil Sakun[15], Nadezhda Dunaeva[16], Vladislav Mitrofanov[17], Sergey Kovalenko[18], Ekaterina Grishina[19], Eduard Chulkov[20], Nadezhda Pishchaeva[21], Asmik Gevorkyan[22], Evgeniy Nechesnyuk[5], Elena Slobina[23], Natalya Popova[24], Dmitriy Pogorelov[25], Alexander Matitsyn[26], Alexander Shapochnik[27], Valentina Timofeeva[28], Andrey Korchunov[29], and Nikolay Vorobiev[30]; [1]St.Luka`s Clinical Research Center for Children, Moscow, Russian Federation, [2]Russian Children's Clinical Hospital, Moscow, Russian Federation, [3]Federal State Autonomous Institution "N. N. Burdenko National Medical Research Center of Neurosurgery" of the Ministry of Health of the Russian Federation, Moscow, Russian Federation, [4]Morozov Children's Clinical Hospital, Moscow, Russian Federation, [5]Dmitry Rogachev National Medical Research Center Of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation, [6]Moscow Regional Research Clinical Institute named after M. F. Vladimirsky, Moscow, Russian Federation, [7]Perm Regional Hospital, Perm, Russian Federation, [8]Moscow Regional Oncology Center, Moscow, Russian Federation, [9]Voronezh Regional Clinical Hospital, Voronezh, Russian Federation, [10]Nizhny Novgorod Regional Clinical Hospital, Nizhny Novgorod, Russian Federation, [11]Regional Clinical Hospital, Vladivostok, Russian Federation, [12]Center for Pediatric Oncology and Hematology, Ekaterinburg, Russian Federation, [13]Regional Clinical Hospital, Chita, Russian Federation, [14]Regional Clinical Hospital, Orel, Russian Federation, [15]Regional Clinical Hospital, Simferopol, Russian Federation, [16]Regional Clinical Hospital, Vologda, Russian Federation, [17]Regional Clinical Hospital, Arkhangelsk, Russian Federation, [18]Regional Clinical Hospital, Chelyabinsk, Russian Federation, [19]Center for Pediatric Oncology and Hematology, Kazan, Russian Federation, [20]Regional Clinical Hospital, Krasnodar, Russian Federation, [21]Regional Clinical Hospital, Nizhnevartovsk, Russian Federation, [22]Research Institute of Pediatric Oncology, Hematology and transplantation, R, M, Gorbacheva, Saint Petersburg, Russian Federation, [23]Russian Scientific Center Of Radiology, Moscow, Russian Federation, [24]Regional Clinical Hospital, Volgograd, Russian Federation, [25]Regional Clinical Hospital, Lipetsk, Russian Federation, [26]Regional Clinical Hospital, Tambov, Russian Federation, [27]Regional Clinical Hospital, Orenburg, Russian Federation, [28]Regional Clinical Hospital, Ulyanovsk, Russian Federation, [29]Heidelberg University Hospital, Heidelberg, Germany, [30]Medical Institute named after Sergei Berezin, Saint Petersburg, Russian Federation

We analyzed 105 patients under 18 years. The median age was 21 months. There were 54 boys and 51 girls. The supratentorial tumors were in 53 patients, infratentorial in 48, and in spinal cord in 4. 60 had stage M0,29-M+and 16-Mx. All the patients got surgical treatment:total tumor removal in 34,subtotal in 37,partial in 30,and biopsy in 4;75 patients got chemoradiotherapy to ATRT-2006;6-CWS;13-EU-RHAB;5-HIT-SKK;individual schemes in 6. RESULTS: 47 are alive,1 was LFU, and 57 died. PFS was 32%±0.05; the five-year OS 40%±0.05. The median survival-30 months, the median progression-free survival-12 months, and the median of follow-up-23 months. PFS was significantly better in patients more than 12 months compared to patients younger than 12 months:40 and 12%;p=0.00161.After total resection PFS was higher compared to subtotal resection, partial resection, and tumor biopsy:48,38,0,and 0%(p=0.025). After chemoradiotherapy, PFS was higher compared to patients without radiotherapy: 49and 0%(p=0.0000000).PFS for stage M0 was higher compared to stage M+and stage Mx:41,15,and 27%,respectively(p=0.00032). PFS was better for the tumors in the spinal cord and infratentorial location compared to the supratentorial location:67,37,and 25%(p=0.0876). The survival rate was higher among the patients who got treatment according to the ATRT-2006 protocol compared to EU-RHAB, individual regimens, CWS, and HIT-SKK:39,19,17,17,and 0% respectively;p=0.00159. The survival was higher among the patients who got intraventricular/ intrathecal Methotrexate,Cytarabine, Prednisolone than among the patients who got only Methotrexate or none at all:40,0,and 5%, respectively; p=0.00015. CONCLUSIONS: Survival was significantly better in patients more than 12month, without metastases, with total removal tumor, chemotherapy by ATRT-2006 protocol with i/t, i/v Methotrexate/ Cytarabine/Prednisolone.

ATRT-06. SMARCB1 LOSS DRIVEN NON-CANONICAL PRC1 ACTIVITY REGULATES DIFFERENTIATION IN ATYPICAL TERATOID RHABDOID TUMORS (ATRT)

Irina Alimova[1,2], Etienne Danis[1], Marla Weetall[3], Angela M Pierce[1,2], Dong Wang[1], Natalie Serkova[4], Ilango Balakrishnan[1], Krishna Madhavan[1,2], Bridget Sanford[1], Cole Michel[5], Nicholas K Foreman[6,2], John Baird[3], Sujatha Venkataraman[1,2], and Rajeev Vibhakar[4,2]; [1]Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [2]Morgan Adams Foundation Pediatric Brain Tumor Research Program, Children's Hospital, Aurora, CO, USA, [3]PTC Therapeutics, INC, South Plainfield, NJ, USA, [4]Department of Radiology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [5]Department of Pharmaceutical Sciences Skaggs School of Pharmacy, University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [6]Department of Pediatrics, Department of Neurosurgery University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Loss of SMARCB1 is the hallmark genetic event that characterizes ATRT. SMARCB1 is a member of the SWI/SNF chromatin remodeling complex that is responsible for determining cellular pluripotency and lineage commitment. To identify co-operating epigenetic factors, we performed an unbiased shRNA screen targeting 408 epigenetic/chromatin molecules in patient-derived ATRT cell lines and identified BMI1, a component of the Polycomb Repressive Complex 1 (PRC1), as essential for ATRT cell viability. Genetic and Chemical inhibition of BMI1 inhibited clonogenic potential and induced apoptosis *in vitro*. *In vivo* PTC 596 significantly decreased growth of intracranial orthotopic ATRT tumors as evaluated by T2 MRI imaging and significantly prolonged survival compared to control animals. Using RNA-seq and ChIP-Seq our studies show that BMI1 co-operates with SMARCB1 loss to suppress transcription of pro-differentiation pathways and promote self-renewal of tumor stem cells. We then used a doxycycline-inducible SMARCB1 expression system and performed Immunoprecipitation for BMI1, followed by and mass spectrometry analysis. In SMARCB1 deficient cells BMI1 forms a partial PRC1 complex devoid of DNA binding components. Re-expression of SMARCB1 activates two PRC1 chromatin localizing components CBX4 and CBX8. CBX4 is implicated DNA damage response, tumor angiogenesis and self-renewal. CBX8 activates lineage-specific genes during differentiation of ESC. Our data suggest that SMARCB1 deletion results in reprograming of BMI1 chromatin occupancy away from lineage

specification by altering the components of the PRC1 complex. These studies identify the mechanistic basis of BMI1 co-operation with SMARCB1 loss in ATRT and establish BMI1 inhibition as a novel therapeutic approach in ATRT.

ATRT-07. HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR AN ADULT PRESENTATION OF THE ATYPICAL TERATOID-RHABDOID TUMOR (ATRT)

Maciej Mrugala[1], Aditya Raghunathan[2], and Jose Leis[1]; [1]Mayo Clinic, Phoenix, AZ, USA, [2]Mayo Clinic, Rochester, MN, USA

BACKGROUND: ATRT is a rare primary CNS tumor occurring predominantly in children with the peak age of onset at less than 3 years old. Adult presentations are exceedingly rare, associated with poor prognosis and no standard therapies exist. METHODS: Case presentation. RESULTS: 61 y old woman presented with headaches, sinus pressure, and cognitive decline. She was found to have a pineal tumor causing obstructive hydrocephalus. The patient underwent gross total resection of the tumor with pathology reported as ATRT. Her CNS staging, including CSF, was negative. She subsequently received radiotherapy to the resection bed. There was no consensus on what should be the next step in her therapy given lack of data in adults. Ultimately, we adopted a pediatric regimen and treated the patient with a combination of high-dose chemotherapy with cisplatin, cyclophosphamide, and vincristine followed by autologous stem cell transplantation (ASCT). This regimen called for up to 4 cycles of chemotherapy with ASCT and we had collected enough cells to complete 3 cycles. The patient completed 2 cycles of therapy with moderate toxicity. Her CNS imaging remained stable with no evidence of recurrence 14-months from the original diagnosis. CONCLUSIONS: ATRT continues to be an exceedingly rare diagnosis in adults. No standard therapies exist and treatment decisions are challenging given lack of data and lack of prospective clinical trials. Pediatric regimens can frequently be adopted for adults although high-dose chemotherapy with ASCT can be challenging. Our case exemplifies the feasibility of treating ATRT in an adult in the most aggressive fashion.

ATRT-08. A PHASE II STUDY OF CONTINUOUS LOW DOSE PANOBINOSTAT IN PAEDIATRIC PATIENTS WITH MALIGNANT RHABDOID TUMORS/ATYPICAL TERATOID RHABDOID TUMORS

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BACKGROUND: Panobinostat treatment has been shown to terminally differentiate malignant rhabdoid tumor (MRT)/atypical teratoid rhabdoid tumors (ATRT) in pre-clinical models. This is an open label, phase II study of panobinostat in patients with newly diagnosed or relapsed MRT/ATRT. AIMS: To assess the anti-tumor activity of low dose, continuous panobinostat, its associated toxicities, the biological activity of low dose panobinostat by measuring histone acetylation status in peripheral mononuclear cells (PMNC), and markers of differentiation in fresh tumor tissue specimens. METHODS: Following cycles of induction and consolidation chemotherapy and/or radiation treatment, patients were enrolled and commenced on panobinostat as a continuous daily oral dose starting at 10mg/m^2 following a three-week wash out period between therapies. Real-time acetylation status, measuring acetylated H4 on PMNC, was performed to determine the pharmacodynamics of panobinostat. Patients were monitored for drug toxicities with the possibility of dose reductions in decrements of 2mg/m^2. RESULTS: Six patients with newly diagnosed ATRT/MRT and one patient with relapsed MRT have been enrolled to date. The average age at enrollment was 2.5 years. Currently, six patients (85.7%) remain on study with a mean treatment duration of 170 days (range 44–327 days). One patient was removed from study at day 44 due to disease progression. The main dose-limiting toxicity observed to date has been myelosuppression. Panobinostat, at a dose of 10mg/m^2, caused significant acetylation of H4 in PMNC. CONCLUSIONS: Treatment with panobinostat appears to be well tolerated in infants with MRT/ATRT, with successful real-time pharmacodynamic assessment of H4 acetylation.

ATRT-09. IDENTIFICATION OF HUB GENES IN ATYPICAL TERATOID/RHABDOID TUMORS BY MULTIPLE-MICROARRAY ANALYSIS

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BACKGROUND: Atypical teratoid/rhabdoid tumors (ATRT) are rare, highly malignant neoplasms arising in infants and young children. However, the biological basis of ATRTs remains poorly understood. In the present study, we employed integrated bioinformatics to investigate the hub genes and potential molecular mechanism in ATRT. METHODS: Three microarray datasets, GSE35943, GSE6635 and GSE86574, were downloaded from Gene Expression Omnibus (GEO) which contained a total of 79 samples including 32 normal brain tissue samples and 47 ATRT samples. The RobustRankAggreg method was employed to integrate the results of these gene expression datasets to obtain differentially expressed genes (DEGs). The GO function and KEGG pathway enrichment analysis were conducted at the Enrichr database. The hub genes were screened according to the degree using Cytoscape software. Finally, transcription factor (TF) of hub genes were obtained by the NetworkAnalyst algorithm. RESULTS: A total of 297 DEGs, consisting of 94 downregulated DEGs and 103 upregulated DEGs were identified. Functional enrichment analysis revealed that these genes were associated with cell cycle, p53 signaling pathway and DNA replication. Protein-protein interaction (PPI) network analysis revealed that CDK1, CCNA2, BUB1B, CDC20, KIF11, KIF20A, KIF2C, NCAPG, NDC80, NUSAP1, PBK, RRM2, TPX2, TOP2A and TTK were hub genes and these genes could be regulated by MYC, SOX2 and KDM5B according to the results of TF analysis. CONCLUSIONS: Our study will improve the understanding of the molecular mechanisms and provide novel therapeutic targets for ATRT.

ATRT-10. ATYPICAL TERATOID/RHABDOID TUMOR OF THE PINEAL REGION IN A PEDIATRIC PATIENT

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BACKGROUND: Atypical teratoid/rhabdoid tumor (ATRT) is a malignant neoplasm of the central nervous system and corresponds to 1.5% of all intracranial tumors. Mainly affects children under three years of age and shows aggressive behavior (most pediatric patients succumb to their disease within a year after the initial diagnosis, despite the treatment performed). Its place of occurrence in children is preferably in the posterior fossa, and it is rare to appear in other regions. There are only seven patients with ATRT reported on literature; all of them are adults. We present the case of a pediatric patient with a tumor in the pineal region diagnosed as ATRT. CASE REPORT: Three-year-old female patient admitted with occipital headache, vomiting, and seizure. Magnetic resonance imaging (MRI) showed obstructive hydrocephalus secondary to a solid-cystic lesion located at the pineal region that was 3.0 x 3.0 x 3.5 cm in size. Spine MRI did not reveal leptomeningeal spreading. We performed an occipital transtentorial approach to achieve the best safe resection possible, and a ventriculoperitoneal shunt. Histological examination revealed ATRT. The patient received adjuvant treatment with radiotherapy and chemotherapy according to the "Head Start" protocol. One year after the surgery, MRI did not identify any remaining lesion. CONCLUSION: ATRT is an aggressive and rare neoplasm whose clinical picture depends on the location of the tumor; however, it must be considered in the differential diagnosis of tumors of the pineal region in the pediatric population.

ATRT-11. PREVALENCE OF GERMLINE VARIANTS IN SMARCB1 INCLUDING SOMATIC MOSAICISM IN AT/RT AND OTHER RHABDOID TUMORS

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BACKGROUND: Genetic hallmark of atypical teratoid/rhabdoid tumor (AT/RT) is loss-of-function variants or deletions in *SMARCB1* gene on 22q11.2 chromosome, which is common to extracranial malignant rhabdoid tumors (MRT). Previous studies demonstrated that approximately one-thirds of AT/RT and extracranial MRT patients harbored germline *SMARCB1* variants as the rhabdoid tumor predisposing syndrome. We studied herein intensive analysis of the *SMARCB1* gene in AT/RT and extracranial MRT patients focusing on prevalence of germline genetic variants. PROCEDURE: In total, 16 patients were included. Both tumor-derived DNA and germline DNA were obtained from all patients. First, screening for *SMARCB1* alterations in the tumor specimens was done by direct sequencing, ddPCR and SNP array analysis. Then, analysis of germline DNA samples focusing on the genomic abnormalities detected in the paired tumors in each case was performed. RESULTS: In eight of 16 cases (50%), genomic alterations observed in the tumor-derived DNA were also detected in the germline DNA. It is worth noting that three patients had germline mosaicism. Two of three patients had mosaic deletion, including *SMARCB1* region, and the average copy number of the deleted region in the *SMARCB1* gene in the germline was 1.60 and 1.76. For another patient, the fraction of *SMARCB1* variants in normal cells was as low as 1.7%. CONCLUSIONS: Approximately half the MRT cases in this study had *SMARCB1* germline alterations. Considering the presence of low-frequency mosaicisms which conventional methods might overlook, inherited germline variants in predisposition genes are more important than previously assumed for the pathogenesis of pediatric cancers.

ATRT-13. DIFFERENT CELLS OF ORIGIN PAVE THE WAY FOR MOLECULAR HETEROGENEITY IN RHABDOID TUMORS

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Rhabdoid tumors (RT) are rare but highly aggressive pediatric neoplasms. These tumors carry homozygous loss-of-function alterations of *SMARCB1* in almost all cases with an otherwise low mutational load. RT arise at different intracranial (ATRT) as well as extracranial (MRT) anatomical sites. Three main molecular subgroups (ATRT-SHH, ATRT-TYR, ATRT-MYC) have been characterized for ATRT which are epigenetically and clinically diverse, while MRT show remarkable similarities with ATRT-MYC distinct from ATRT-SHH and ATRT-TYR. Even though there are hypotheses about various cells of origin among RT subgroups, precursor cells of RT have not yet been identified. Previous studies on the temporal control of *SMARCB1* knockout in genetically engineered mouse models have unveiled a tight vulnerable time frame during embryogenesis with regard to the susceptibility of precursor cells to result in RT. In this study, we employed single-cell RNA sequencing to describe the intra- and intertumoral heterogeneity of murine ATRT-SHH and -MYC as well as extracranial MYC tumor cells. We defined subgroup-specific tumor markers for all RT classes but also observed a notable overlap of gene expression patterns in all MYC subgroups. By comparing these single-cell transcriptomes with available single-cell maps of early embryogenesis, we gained first insights into the cellular origin of RT. Finally, unsupervised clustering of published human RT methylation data and healthy control tissues confirmed the existence of different cells of origin for intracranial SHH tumors and MYC tumors independent of their anatomical localizations.

ATRT-14. MACROPHAGE-TUMOR CELL INTERACTION PROMOTES ATRT PROGRESSION AND CHEMORESISTANCE

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Atypical teratoid/rhabdoid tumors (ATRT) are pediatric brain neoplasms that are known for their heterogeneity concerning pathophysiology and outcome. The three genetically rather uniform but epigenetically distinct molecular subgroups of ATRT alone do not sufficiently explain the clinical heterogeneity. Therefore, we examined the tumor microenvironment (TME) in the context of tumor diversity. By using multiplex-immunofluorescent staining and single-cell RNA sequencing (scRNA-seq) we unveiled the pan-macrophage marker CD68 as a subgroup-independent negative prognostic marker for survival of ATRT patients. ScRNA-seq analysis of murine ATRT-SHH, ATRT-MYC and extracranial RT (eRT) provide a delineation of the TME, which is predominantly infiltrated by myeloid cells: more specifically a microglia-enriched niche in ATRT-SHH and a bone marrow-derived macrophage infiltration in ATRT-MYC and eRT. Exploring the cell-cell communication of tumor cells with tumor-associated immune cells, we found that Cd68+ tumor-associated macrophages (TAMs) are central to intercellular communication with tumor cells. Moreover, we uncovered distinct tumor phenotypes in murine ATRT-MYC that share genetic traits with TAMs. These intermediary cells considerably increase the intratumoral heterogeneity of ATRT-MYC tumors. *In vitro* co-culture experiments recapitulated the capability of ATRT-MYC cells to interchange cell material with macrophages extensively, in contrast to ATRT-SHH cells. We found that microglia are less involved in the exchange of information with ATRT cells and that direct contact is a prerequisite for incorporation. A relapse xenograft model implied that intermediary cells are involved in the acquisition of chemotherapy resistance. We show evidence that TAM-tumor cell interaction is one mechanism of chemotherapy resistance and relapse in ATRT.

ATRT-15. LY6D – A CANDIDATE FOR NANOPARTICLE-BASED TARGETED THERAPIES OF ATRT

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Atypical Teratoid Rhabdoid Tumors (ATRT) are aggressive brain malignancies of the infant. Despite intensive multimodal therapy, the overall prognosis remains poor, making investigations on targeted therapies crucial. Arsenic trioxide (ATO) is known to inhibit cell growth of ATRT *in vitro* and *in vivo* but its efficacy in solid tumors is limited by its adverse effects. We aimed to characterize whether a nanoparticle-based drug delivery could overcome these limitations. Therefore metal-organic frameworks containing ATO (MOF-ATO) were constructed. To improve drug specificity further, we searched for unique proteins on the surface of ATRT, in order to create antibody-drug-conjugates out of MOF-ATO and an ATRT-specific ligand. ATRT are marked by a biallelic loss of *SMARCB1*, which results in an activation of the repressive histone methyltransferase EZH2. After chemical inhibition of EZH2 with GSK126, a mass spectrometric based screening for differentially expressed surface proteins was performed. Treatment with ATO, as well as MOF-ATO and GSK126 each reduces the cell viability of ATRT cell lines. It results in a cell cycle arrest and an induction in apoptosis, being analysed *via* MTT test and flow cytometry. GSK126 treatment causes a significant upregulation of several cell surface proteins, upon them the Lymphocyte antigen 6 family member D (LY6D). Being rarely expressed on other human cells, this protein is an interesting candidate. An antibody-drug-conjugate consisting of MOF-ATO and LY6D-ligands could be a promising approach for future targeted therapies of ATRT.

ATRT-16. MODELLING ATRT THROUGH SWI/SNF COMPLEX DEFICIENCY IN GENETICALLY-ENGINEERED MOUSE MODELS

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Atypical Teratoid/Rhabdoid Tumours (ATRT) are highly malignant neoplasms arising primarily in the CNS of children. They are defined by loss of function mutations in *smarcb1*, a gene serving a vital role in neurogenesis and differentiation. In order to recapitulate ATRT in the mouse, we used a Cre-Lox recombination system to conditionally knockout *smarcb1* in specific cell compartments. Loss of *smarcb1* in BLBP-expressing cells of the developing brain led to severe neurologic defects. Mice exhibited seizures, ataxia, and median 12-day survival. Histological analysis revealed severe thinning of the cerebral cortex and cerebellum. Temporally-targeted *smarcb1* loss in BLBP/Nestin-expressing embryonic compartments did not result in tumour formation. Similarly, BLBP-expressing, *smarcb1*-deficient neural stem/progenitor cells (NSC/NPCs) were isolated and allografted but did not form tumours. These cells demonstrated decreased proliferation, higher apoptosis, and upregulation of p53, CDKN1A, and CDKN2A. In contrast, ubiquitous *smarcb1* loss at the earlier embryonic day 6.5 produced widespread tumorigenicity in the forebrain, hindbrain, skullbase, and spine; each with unique phenotypes, survival, and morphology. We employed a clinically-relevant Nanostring gene-panel screen to stratify tumours into genetically distinct subgroups. Our findings indicate that *smarcb1* plays an important role in CNS development. Loss of *smarcb1* in NSC/NPCs is lethal, and its developmental context influences cell fate. Targeted *smarcb1* loss likely plays a tumorigenic role at an earlier developmental stage than previously determined, in a diverse array of primitive stem cells. These data support the generation of a murine ATRT model capable of producing distinct tumour entities that recapitulate the human disease.

ATRT-17. TARGETING GLUTAMINE METABOLISM LOWERS METHYLATION POTENCIALS IN AT/RT AND SYNERGIZE WITH TAZEMETOSTAT

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Atypical teratoid/rhabdoid tumors (AT/RT) have a single recurring genetic mutation in *SMARCB1*. This deletion leads to an abnormal SWI/SNF chromatin remodeling complex and the constitutive activation of *EZH2*. S-adenosyl-L-methionine (SAM) donates a methyl group to EZH2 which then methylates DNA and histones leading to the abnormal gene expression responsible for AT/RT's aggressive phenotype. We have previously shown that glutamine metabolic inhibition with 6-diazo-5-oxo-L-norleucine (DON) confers a survival advantage in AT/RT. In this study, we identified with ultra-high performance liquid chromatography mass spectrometry that DON treatment lowered the methylation potential in AT/RT (Decreased SAM:SAH ratio, t-test in 5 AT/RT human-derived cell models comparing DON treatment to DMSO control, $p<0.05$). AT/RT cell lines grown in glutamine deplete media compared to normal growth conditions also had a reduced methylation potential (decreased SAM:SAH, t-test, $p<0.05$). DON treatment over 5 days decreased histone methylation (as determined by western blot for H3K27me3). Tazemetostat is a small molecule inhibitor that blocks the SAM methyl donor site on EZH2. We find that DON combines synergistically with Tazemetostat to slow AT/RT cell growth (MTS assay, $p<0.01$ t-test; MUSE viability assay, $p<0.01$ ANOVA) and enhances cytotoxicity (MUSE Annexin-V, $p<0.01$ by ANOVA). Synergies were especially pronounced at low concentrations of Tazemetostat which is significant given that Tazemetostat's efficacy in AT/RT has been limited by poor CNS penetration. These studies identify a novel treatment strategy that has potential to improve survival in AT/RT.

ATRT-18. SHH-SUBTYPE ATYPICAL TERATOID/RHABDOID TUMORS ARE SELECTIVELY SENSITIVE TO GEMCITABINE TREATMENT

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Atypical Teratoid Rhabdoid Tumors (ATRT) are highly malignant embryonal tumors of the central nervous system with a dismal prognosis. ATRT can be divided into three molecular subgroups of which the Sonic Hedgehog (SHH) subgroup is most prevalent. In this study, we developed and validated a novel patient-derived ATRT model, which we used along a panel of other primary ATRT models for large scale drug discovery assays. We found that ATRTs are selectively sensitive to the nucleoside analogue gemcitabine, with SHH-subtype ATRTs being the most sensitive subgroup. Gene expression profiles and protein analysis indicated that gemcitabine treatment causes degradation of Sirtuin 1 (SIRT1), which causes ATRT specific cell-death through NF-kB and p53 activation. Furthermore, we found that this gemcitabine induced loss of SIRT1 results in a nucleus-to-cytoplasm shift of the SHH signaling activator Gli, explaining the additional gemcitabine sensitivity in SHH-subtype ATRT. Treatment of SHH-subgroup ATRT xenograft-bearing mice resulted in a >40% increase in median survival ($p<0.01$, log-rank test) and long-term survivors in two independent models. To prepare translation of our findings to the clinic, we investigated potential gemcitabine induced resistance mechanisms by conducting kinome-wide CRISPR/Cas9 knockout screens in primary ATRT cells. Through these experiments we found that low-dose gemcitabine treatment combined with inhibition of protein kinase C zeta (PKCζ) prevents regrowth of resistant ATRT subclones. Together, these findings show that ATRT are highly sensitive to gemcitabine treatment; and as such we suggest that gemcitabine may be rapidly incorporated into future treatment regimens for SHH-ATRT.

ATRT-19. EPIGENETIC REPROGRAMMING LEADS TO INNATE IMMUNE PATHWAY ACTIVATION IN AT/RT

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BACKGROUND: Atypical teratoid/rhabdoid tumors (AT/RT) are highly aggressive brain tumors affecting early childhood and are characterized by bi-allelic inactivation of the *SMARCB1* gene. Though patients benefit from multimodal therapy, there is no improvement in overall survival necessitating exploration of alternative approaches including innate-based immune therapy and epigenetic therapy, which have shown promise in treating adult brain tumors and other cancers. Though reconstitution of SMARCB1 in *SMARCB1*-deficient cells leads to activation of interferon-stimulated genes, the role of innate immune signaling has not been investigated in AT/RTs. METHODS: Our data from a panel of AT/RT cell lines indicates loss of expression of key innate signaling components, like RIG-I, MDA-5, cGAS and STING that are required for sensing extracellular dsRNA and dsDNA. These cell lines also do not respond to dsDNA-based or dsRNA-based innate agonists. However, co-treatment of the BT-16 cell line with two epigenetic drugs, panobinostat and 5-azacytidine leads to re-expression of STING and RIG-I. Panobinostat/5-azacytidine co-treatment followed by either genomic DNA (dsDNA agonist) or poly(I:C) (dsRNA agonist) treatment results in induction of innate responses, measured by STAT1 phosphorylation and production of ISG-15 and IFIT-1. CONCLUSION: Our data suggests that AT/RT cell lines are unresponsive to innate agonists possibly due to the loss of expression of key innate immune components. However, these pathways can be reactivated by epigenetic drugs and further potentiated by dsDNA/dsRNA-based innate agonists. Combined epigenetic reprogramming and innate pathway stimulation may serve as a potential therapy option for treating AT/RT.

ATRT-20. CDK7 INHIBITION IN AT/RT

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Atypical teratoid/rhabdoid tumors (AT/RT) are characterized by loss-of-function mutations in the SMARCB1 component (and less commonly SMARCA4) of the SWI/SNF chromatin-remodeling complex. AT/RT demonstrate an overall silent genomic landscape with epigenetic dysregulation of the genome. CDK7 is a key transcriptional regulator that preferentially phosphorylates the Ser5 and Ser7 positions on RNA Polymerase C terminal domain and is involved early in transcription. In tumor cells, CDK7 is enriched at super enhancers which preferentially regulate genes involved in cell transformation, and expressed at significantly higher levels in transformed tissues than the surrounding normal brain. Our preliminary data shows that CDK7 is expressed in a number of AT/RT tumor cell lines and patient-derived tumor cultures, and that loss of CDK7 function though exposure to the novel CDK7 inhibitor THZ2 results in lack of proliferation at lower doses, and caspase-mediated apoptosis at higher concentrations. shRNA-based inhibition confirms that this effect is due specifically to loss of CDK7. RNA sequencing of cells treated with lower doses of THZ2 show significant alterations in transcript expression consistent with altered balance between antagonistic SWI/SNF and PRC2 chromatin-modeling complex activities, as

well as alterations in DNA damage response pathways, cell cycle checkpoints, miRNA transcription, and numerous proliferative factors. THZ2 penetrates the blood brain barrier (BBB), is well tolerated, and results in prolonged survival in murine xenograft models of AT/RT. CDK7 inhibition also synergizes with a number of currently-approved oncology drugs, as well as with ionizing radiation, in order to inhibit AT/RT growth and viability.

ATRT-21. RHABDOID PREDISPOSITION SYNDROME: REPORT OF MOLECULAR PROFILES AND TREATMENT APPROACH IN THREE CHILDREN WITH SYNCHRONOUS ATYPICAL TERATOID/ RHABDOID TUMOR AND MALIGNANT RHABDOID TUMOR

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BACKGROUND: Rhabdoid predisposition syndrome is characterized by germline alterations in *SMARCB1* or *SMARCA4*, leading to synchronous or metachronous central nervous system (CNS) and extra-CNS rhabdoid tumors. Rare survivors have been reported to date. METHODS: We describe the molecular profiling and treatment regimen of three patients with synchronous atypical teratoid/rhabdoid tumor (ATRT) and malignant rhabdoid tumor of the kidney (MRT-K). All patients underwent radical nephrectomy of the kidney, and gross total resection of the primary CNS tumor was achieved for two patients. An intensive chemotherapy regimen was administered; an induction phase based on the modified Third Intergroup Rhabdomyosarcoma Study (IRS-III) for ATRT followed by a consolidation phase with three cycles of high-dose chemotherapy and autologous hematopoietic progenitor cell rescue, without irradiation. All three patients were enrolled on an institutional comprehensive genomic profiling protocol. RESULTS: A germline focal 22q deletion, including *SMARCB1,* was detected in two patients, while the third patient had a maternally-inherited heterozygous frameshift variant in *SMARCB1*. Somatic loss of heterozygosity of 22q was identified in all patients, resulting in biallelic inactivation of *SMARCB1*. Divergent tumor subgroups were described using DNA methylation. The three MRT-K samples were classified as MYC subtype. One ATRT was classified as SHH while the other as TYR. One patient is currently three years off-therapy without evidence of disease, while the other two patients have completed the consolidation phase without recurrent disease. CONCLUSION: Molecular profiling of CNS and extra-CNS rhabdoid tumors revealed different epigenetic subgroups. An intensive multimodal therapeutic approach without irradiation may achieve prolonged survival.

ATRT-22. HIGH-THROUGHPUT DRUG SCREENING OF FDA-APPROVED CANCER DRUGS REVEALS POTENTIAL THERAPEUTIC APPROACHES FOR ATYPICAL TERATOID RHABDOID TUMOUR

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Atypical teratoid/rhabdoid tumors (ATRT), are the most common brain tumor in children under the age of 1 year with an overall survival of ~17%. Like extracranial rhabdoid tumors, ATRT is exclusively characterized by bi-allelic loss of *SMARCB1*, a critical subunit of the SWI/SNF chromatin remodeling complex, implicating epigenetic deregulation in the pathogenesis of disease. We have previously shown the ability of the histone deacetylase inhibitor, panobinostat, to mimic SMARCB1-mediated SWI/SNF functions in extracranial rhabdoid tumors to inhibit tumor growth by driving multi-lineage differentiation *in vitro* and *in vivo*. Whether this also applies to ATRT is unknown. Using a panel of human-derived ATRT cell lines, representing defined molecular subgroups, we have shown that prolonged treatment with panobinostat at nanomolar concentrations results in markedly reduced clonogenicity, and increased senescence, preceded by increased H3K27 acetylation, decreased H3K27 trimethylation and EZH2 expression. To determine potentially synergistic therapies, we performed high-throughput drug screening of 622 compounds already in advanced clinical trials or FDA-approved for other indications, across our panel of ATRT models and identified 30 common compounds, which decrease cell viability by >50%, with no effect on neural stem cell controls and 12 compounds which demonstrated subgroup specificity, highlighting the necessity to consider therapies in the molecular context. In addition to HDACi, consistent with our panobinostat in vitro findings, inhibitors of CDK, survivin and PI3K were the top hits. *In vitro* and *in vivo* validation of these compounds alone, and in combination with panobinostat is ongoing.

ATRT-23. THE DUAL MTORC1/2 INHIBITOR SAPANISERTIB DISRUPTS THE NRF2-MEDIATED STRESS RESPONSE AND COMBINES SYNERGISTICALLY WITH THE BH3 MIMETIC OBATOCLAX TO EXTEND AT/RT SURVIVAL

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Atypical teratoid/rhabdoid tumors are aggressive infantile tumors highly resistant to intensive therapies. We aim to identify and target critical factors driving this therapy resistance to improve AT/RT survival. Analysis of publically available RNASeq on 32 AT/RT identified elevated expression of NRF2 (median expression 40.78, normal brain 18.81). NRF2 is a master regulator of cell's stress response whose expression is correlated with therapy resistance and poor survival. NRF2 activation is sensitive to mTOR activity and is a biomarker predicting response to the dual mTORC1/2 inhibitor, Sapanisertib (TAK228, INK128). We performed RNASeq on 4 human-derived AT/RT cell models after Sapanisertib treatment. Pathway analysis reveals disruption of the NRF2-mediated stress response (-log p value 0.39, Z-score 1.0). As a result, Sapanisertib decreases ROS scavengers like glutathione (Metabolite analysis UHPLC-MS, *t*-test $p<0.05$) and induces a pro-death phenotype (decreased MCL-1 expression, western blot; gene-expression analysis, RNASeq). The brain-penetrant BH3 mimetic Obatoclax increases ROS generation and induces apoptosis (MUSE oxidative stress and ANNEXIN V assays, *t*-test $p<0.05$). These complementary mechanisms of action synergize to induce high rates of cell death (MUSE ANNEXIN V assay, ANOVA $p<0.05$, C-PARP western blot, Compusyn Synergy analysis CI<1.0) and slow cell growth (MUSE Cell viability, ANOVA $p<0.05$). Once-weekly treatments of Sapanisertib combined with Obatoclax in orthotopic mouse models of AT/RT are well tolerated, slow tumor growth (bioluminescence imaging) and significantly extend median survival from 35 to 55 days (Log-rank $p<0.05$). These findings support a new clinical trial aimed at improving AT/RT survival.

ATRT-24. CELL SURFACE PROTEOME ANALYSIS OF ATRT IDENTIFIES TARGETS FOR IMMUNOTHERAPY

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Atypical teratoid rhabdoid tumor (ATRT) is a rare and fast-growing childhood tumor of the brain and spinal cord. While the recent advances in DNA and RNA sequencing have given deep insights into the biology of cancer, about 90% of ATRTs harbor a single deletion which leads to uncontrolled tumor growth. The lack of targetable genetic abnormalities in ATRT makes it a tough target for therapy and hence radical new approaches are required to develop a treatment. In many cases, the gene expression profile alone DOES NOT represent the presence of the gene product on the surface and cannot detect post-translational modifications such as the addition of sugars which are essential for the interaction of surface proteins with the tumor microenvironment. The ability to escape from surveillance by the immune system is regarded as one of the essential hallmarks of cancer cells. Here we carried out a comprehensive unbiased large-scale surface receptor profiling using high throughput multicolor flow cytometry on surgically resected ATRT patient samples, primary ATRT cell lines, and patient-derived xenograft models. By multiplexing primary samples with antibodies for CD31, CD45, CD11b, CCR2, Cx3cr1, and CD4, and CD8 we eliminated endothelial and immune cells from analysis while also identifying immune populations within the tumor. We identified increased surface expression of CD44, CD146, CD59, CD151, and CD276. These were validated in our screening of primary tumor samples. A combination of CAR-T cell and function-blocking monoclonal antibody approaches have been tested to verify the proof of principle of this approach.

ATRT-25. INTEGRATED QUANTITATIVE SWATH-MS PROTEOMICS ANALYSIS OF ATRTS UNCOVERS NEW THERAPEUTIC OPPORTUNITIES

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The consequences of *SMARCB1* loss in Atypical Teratoid Rhabdoid Tumors (ATRTs) have been extensively characterized at the epigenetic/transcriptomic level. In this study we detail the functional effect of *SMARCB1* mutation on the MRT proteome, its relationship with RNA deregulation or lack thereof. We performed unlabeled discovery proteomics using MS-SWATH on MRT cells in which SMARCB1 was forcibly re-expressed (5 cell lines, +/-SMARCB1); analyzing changes in protein abundance within 3 fractions (total, membrane, nuclear). We generated a custom spectral library, covering >8,000 proteins, for analysis of the ATRT proteome using a pH fractionated pool of each cellular subfraction. This SMARCB1-dependent ATRT spectral library constitutes a powerful tool for profiling proteins of potentially therapeutic relevance in both model systems and primary ATRT samples. We show that whilst gene expression and protein abundance are significantly related there are many instances whereby expression changes do not reliably predict protein abundances. Several hundred proteins show significantly increased abundance ($p<0.01$) with no concomitant change by RNA-seq. *SMARCB1* mutation is able to invoke critical changes in post-transcriptional/translational regulation as well as sub-cellular localization. By integration with whole-genome CRISPR/cas9 screening we describe functionally essential SMARCB1 dependent pathway/membrane biomarkers, evident at the protein but not the RNA level. We describe several which are druggable and suggest certain therapeutic modalities e.g. specific combinations of RTKs, RNA-binding proteins/splicing factors (SpliceosomeA, U4:U5:U6 tri-snRNP complexes). Our analysis links, for the first time in ATRT, genome-wide transcriptomic and proteome aberrations and reveals broad mechanisms underlying the effect of *SMARCB1* mutation.

ATRT-26. META-ANALYSIS OF TREATMENT MODALITIES IN METASTATIC ATYPICAL TERATOID/RHABDOID TUMORS IN CHILDREN

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BACKGROUND: Metastatic atypical teratoid/rhabdoid tumors (AT/RT) are aggressive central nervous system tumors that present during infancy and are associated with dismal outcomes. Patients receive multimodal treatment including surgical resection, systemic chemotherapy and one or more of intrathecal chemotherapy (IT), marrow-ablative chemotherapy with autologous hematopoietic cell rescue (AuHCR) and radiation therapy (XRT). While data regarding treatment modalities for AT/RT patients exist, no comprehensive data have been published regarding the metastatic patient population. METHODS: We performed a meta-analysis of 1,578 articles published through September 2018, including 44 studies with a total of 123 subjects. Additionally, seven patients were incorporated through chart review of patients treated at Nationwide Children's Hospital. RESULTS: Analysis of 130 patients revealed a 3-year overall survival (OS) of 25%. Age at diagnosis had a significant impact on survival ($p=0.0355$); 3-year OS for infants < 18 months was 21%; 18–36 months was 26%; and > 36 months was 36%. Location of the primary tumor, metastatic stage and extent of surgical resection did not have significant impact on OS. On univariate analysis, XRT ($p<0.0001$), IT ($p=0.01$) and AuHCR ($p<0.0001$) were found to significantly improve survival. The most substantial effect was noted in patients who received AuHCR (3-year OS of 60% *versus* 9% in those who did not). On multivariable analysis XRT ($p=0.0006$), IT ($p=0.0124$) and AuHCR ($p<0.0001$) were independently associated with reduced risk of death.

ATRT-27. COST-EFFECTIVE ASSAYS TO SUBGROUP ATRT IN THE DAILY ROUTINE

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Three atypical teratoid rhabdoid tumors (ATRT) molecular subgroups with different bio-clinical characteristics have been reported (TYR, SHH and MYC). Molecular subgrouping relies on either methylation profiling (reference methods), or expression profiling. However, the cost-effectiveness of such pangenomic screening is questionable. This work aims to study the reliability of alternative techniques for subgroup classification in the daily routine. Illumina EPIC-arrays were performed on 46 samples. Among those cases, expression profiling were analysed by RNAseq (n=30). We designed a 26-gene panel to assess expression profiling using the Nanostring technology; this was applied to 35 tumors. Immunohistochemistry (IHC) was used for 20 samples; it relied on the expression of MITF, TYR, OTX2 and MYC. We first assessed the concordance between DNA methylation and RNAseq based profilings; then, between RNAseq and Nanostring and, finally, between methylation profiling and Nanostring or IHC, the two rapidest and cheapest tools. The concordance between the two expression-based profiling was 19/21. EPIC-arrays and RNAseq or Nanostring were concordant in 26/30 and 30/35 samples, respectively. The concordance was perfect for methylation-defined MYC subtype. Finally, 17/20 tumor samples were classified in the same subgroup by EPIC-arrays and IHC; the 3/20 misclassified tumors were SHH by methylation but consistently MYC by IHC, Nanostring and RNAseq. There was 90–100% of concordance for TYR subgroup (all techniques). We have designed a gene panel-based expression signature that shows promising concordance with RNAseq and methylation profiling. Nanostring assay and IHC well predict ATRT subgroup classification for MYC and TYR subclass, but less so for methylation-defined SHH ones.

ATRT-28. SINGLE NUCLEI SEQUENCING REVEALS THE DIFFERENT PHENOTYPIC COMPOSITION OF THE ATRT SUBGROUPS

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Atypical teratoid/rhabdoid tumors (ATRT) represents a genomically homogeneous disease characterized by loss of SMARCB1 protein in the vast majority of cases. In recent years, it has become clear that these tumors display a high degree of intertumoral heterogeneity with three molecularly distinct subgroups. However, the degree of intratumoral heterogeneity and the information on cellular subpopulations currently remains largely an unchartered territory. To explore the transcriptomic composition of ATRTs, we performed single nuclei RNA sequencing for 16 ATRTs representing all three molecular subgroups (5 ATRT-TYR, 7 ATRT-SHH, 4 ATRT-MYC). By performing tSNE cluster analyses of all the single cell data (~50.000 cells have been sequenced), we were able to gain unprecedented insights into the phenotypic composition of ATRTs and unravelled substantial differences between the three subgroups. Integrating transcriptomic information from non-neoplastic brain cells and the data derived from single nuclei sequencing, we found an OPC like gene signature in ATRT-SHH. In contrast, ATRT-TYR subpopulations overexpressed more markers of neuronal stem cells suggesting a larger fraction of undifferentiated cells in this subgroup. We also identified a subpopulation of cells with a clear overexpression of cell cycle associated genes (CDK4, CDKN3), predominantly present in ATRT-MYC samples, a finding which may harbour important consequences for a targeted therapy with e.g. CDK inhibitors. In summary, our analyses reveal different cellular compartments in ATRT and provide important insights into the cellular differentiation of the three ATRT-subgroups. Further analyses to achieve a specific mapping of ATRT to its physiological cell of origin are currently being pursued.

ATRT-30. RETROSPECTIVE ANALYSIS OF CHILDREN WITH ATYPICAL TERATOID RHABDOID TUMOR TREATED ACCORDING TO ACNS0333

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Atypical teratoid rhabdoid tumor (ATRT) is a central nervous system tumor with poor outcome. ACNS0333, a Children's Oncology Group phase 3 trial, enrolled 65 evaluable patients who received two cycles of induction chemotherapy, three cycles of consolidative high-dose chemotherapy (HDCT), and focal radiation therapy (RT) pre- or post-consolidation. Craniospinal irradiation (CSI) was left to clinician discretion. We retrospectively analyzed medical records of 27 children treated at our institutions according to ACNS0333. Median age at diagnosis was 14 months (range 4–165); 13 (48%) were male. M-stage was M0, M2, and M3 for 18 (66%), 5 (19%), and 4 (15%), respectively. Tumor location was supratentorial (n=14, 52%), infratentorial (n=12, 44%), or both (n=1, 4%). Complete resection was achieved for 17 (63%). All but one completed induction. Of 13 (51%)

with residual disease at diagnosis, 5 (36%) and 7 (50%), respectively, exhibited complete and partial response to induction. Three patients progressed on therapy, and six progressed after completion of therapy at a median of 9.7 months. In all, 18 patients completed RT (16 focal/4 CSI and 6 pre-/12 post-consolidation). Three died of therapy-related toxicity (two in primary therapy and one in relapse therapy), and 8 died of disease. Sixteen patients (59%) are alive at a median follow up of 53 months (range 9–114). Of 17 with germline testing, eight (47%) had rhabdoid predisposition syndrome of whom three are alive. At the time of presentation, data for approximately 50 patients is expected, and we will compare outcomes to soon-to-be published data from ACNS0333.

ATRT-31. SUCCESSFUL MULTIMODALITY MANAGEMENT OF ATRT OF THE LOWER DORSAL SPINE WITH SPINAL DROP METASTASIS

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A 6 year old boy presented with low backache for the last 5 months. MRI of the spine showed a 1.5x1.5x4.7cm intradural mass extending from D10-D12, causing compression of the conus medullaris. With a preoperative diagnosis of intradural ependymoma, a gross total resection (GTR) of tumour was performed. Post-operative histopathology showed a markedly cellular, malignant tumour with frequent mitotic figures. Cells were round to polygonal with vesicular nuclei, prominent nucleoli and were immunopositive for CK,EMA,p53 and immunonegative for MIC2,desmin,SMA,GFAP,INI-1(MIB1 labeling index-35–40%). The overall impression was spinal atypical teratoid rhabdoid tumour(ATRT). Post-operative neuraxis MRI revealed post-operative changes(D10-D12) with a 9 mm enhancing lesion at L5-S1 junction suggesting drop metastasis. There was no brain lesion. CSF cytology did not show any malignant cell. The metastatic work-up was normal. He was started on chemotherapy with ICE regimen (Ifosfamide-2g/m^2IVD1–D3,Carboplatin-500mg/m^2IVD3,Etoposide-100mg/m^2IVD1–D3q3weeks). Subsequently he received craniospinal irradiation (CSI)-36Gray/20fractions/4weeks→ focal boost to primary tumour bed and spinal drop metastasis-14.4Gray/8fractions/1.5 weeks. Thereafter he received 3 more cycles of ICE regimen. End-of-treatment MRI spine showed post-op changes(D10-D12) and 38.9%reduction of the L5-S1 lesion suggesting partial response. Six monthly spinal MRI showed serial reduction of the metastatic lesion leading to complete response (CR) 1 year after completion of treatment. On last follow-up (30 months from initial diagnosis), he was neurologically intact and in CR. Multimodality management comprising GTR,CSI followed by focal boost and multiagent chemotherapy(ICE) can lead to successful outcome in patients with this rare and aggressive spinal tumour.

ATRT-32. GENOME-WIDE CRISPR AND SMALL-MOLECULE SCREENS UNCOVER TARGETABLE DEPENDENCIES IN AT/RTS

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Brain tumors are the leading cause of cancer-related deaths in children and adolescents. Embryonal brain tumors are a group of high-grade neoplasms which primarily affect young patients, and atypical teratoid rhabdoid tumors (AT/RTs) are the second most common type of tumor within this group. In spite of intensive research efforts and the knowledge of molecular mechanisms driving subgroup-specific heterogeneity within ATRTs, survival estimates stay relatively low as compared to other tumor entities with a median survival of around 17 months. More efficacious and durable therapies are urgently needed to improve the situation of patients. We here used a combination of genome-wide CRISPR dependency screens and small-molecule drug assays to identify genetic vulnerabilities and novel therapeutic targets for this tumor entity. Here, we successfully generated a chemical library that shows preferential activity in AT/RT cell lines, thereby validating our CRISPR approach to identify tumor-specific vulnerabilities. Of note, none of the identified dependencies seemed to be subgroup-specific, suggesting that targets identified here can be used as pan-AT/RT therapeutic avenues. Among others, these include inhibition of EGF signaling and CDK4/6. Our data provide a comprehensive map of dependencies for AT/RTs which will serve as a starting point in the development of targeted therapies for this tumor entity.

ATRT-33. ENABLING RAPID CLASSIFICATION OF ATRT WITH NANOSTRING NCOUNTER PLATFORM

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In recent years, using gene expression and methylation array platform, multiple research groups have reported the presence of at least three major Atypical Teratoid Rhabdoid Tumor (ATRT) subtypes that exhibit distinct epigenetic, transcriptomic and clinical features. Yet, utilizing ATRT subtypes in a clinical setting remains challenging due to a lack of suitable biological markers, limited sample quantities and relatively high cost of current assays. To address this gap between research and clinical practice, we have designed an assay that utilizes a custom 35 signature genes panel for the NanoString nCounter System and have created a flexible machine learning classifier package for ATRT tumour subtyping. We have analyzed 71 ATRT primary tumours with matching gene expression data using the 35 genes panel. 60% of the data was used for models training (10 repeats of 10-fold cross validation with subgroup balanced sample splitting) resulting in overall 94.6% training accuracy. The remaining 40% of the samples were used for model validation and the assay was able to achieve 92–100% accuracy with no subgroup bias. To demonstrate the flexibility of the workflow, we have tested it against other transcriptome-based methods such as gene expression array and RNASeq. We have also demonstrated its use in samples that were not classifiable by methylation-based method. We are presenting here a rapid and accurate ATRT subtyping assay for clinical usage that is compatible with archived ATRT tissues.

COVID-19 AND PEDIATRIC NEURO-ONCOLOGY

COVD-01. VINBLASTINE MONOTHERAPY INDUCTION FOR LOCALISED CNS GERMINOMA DURING THE COVID-19 PANDEMIC

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INTRODUCTION: Patients with localised CNS-germinoma have excellent survival. More recently, intensive inpatient chemotherapy (carboPEI=carboplatin/etoposide/ifosfamide in Europe) has been effectively employed to reduce radiotherapy fields and/or dose. Current research priorities focus on reducing treatment burden and long-term sequelae. Of note, outpatient-based single-agent carboplatin chemotherapy is associated with excellent outcomes in metastatic testicular seminoma (an identical pathology) [Alifrangis,*EJC*,2020]. Recently, successful vinblastine monotherapy was reported in localised CNS-germinoma [Murray,*Neurooncol-Adv*,2020]. METHODS: Due to the COVID-19 pandemic, adapted UK guidelines for germ-cell-tumour management were distributed, including potential non-standard treatment options that would reduce hospital visits/admissions. A 30-year-old patient presented with a 32mmx30mmx35mm diameter solid+multi-cystic localised pineal CNS lesion, consistent radiologically with a germ-cell-tumour with prominent teratoma component. Investigation revealed negative AFP/HCG markers and biopsy-proven pure germinoma. After appropriate consent, the patient commenced 12-week induction with weekly vinblastine monotherapy (low-grade-glioma dosing [Lassaletta,*JCO*,2016]), with wk6&12 MRI re-assessment prior to definitive radiotherapy. RESULTS: Vinblastine was well-tolerated. After initial 4mg/m2 test-dosing (wk1), standard 6mg/m2 was delivered for wk2, but resulted in asymptomatic neutropenia (nadir 0.3x10^9/l) and missed dosing at wk3. Subsequent doses were 4mg/m2, with no further neutropenia. As expected, MRI showed moderate 40% tumour volume reduction by wk12. Surgical resection of the residual presumed teratoma component was undertaken prior to radiotherapy. CONCLUSION: Patients with CNS-germinoma have excellent outcomes and reduction of treatment-effects remains a priority. The exquisite chemosensitivity of germinoma, excellent results from monotherapy for metastatic testicular disease, and early promise of vinblastine monotherapy lend itself to further exploration for CNS-germinoma.

COVD-02. COVID-19 AND CHILDHOOD CANCER CARE - THEMATIC ANALYSIS OF PUBLISHED SCIENTIFIC AND CLINICAL LITERATURE

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INTRODUCTION: The SARS-CoV-2 pandemic has affected modern medicine and healthcare provision profoundly. National and regional ex-

periences with COVID-19 have been hugely variable across the globe, reflecting ethnic, governmental, cultural, economic and healthcare differences. This thematic analysis was performed to identify scientific and clinical literature relating to the impact of COVID-19 on children with cancer and treatment. METHODS: The NHS Evidence portal was used to conduct a healthcare database advanced literature search. Duplicates were removed. Remaining results were screened using clear inclusion and exclusion criteria. RESULTS: 172 results were identified and data extracted. Literature was identified from all 5 continents, with lower and middle income countries well represented. Key themes identified included: 1: Impact on patients already diagnosed, including decreased treatment regimens, impact on outpatient clinics, COVID susceptibility and travel restrictions; 2: Delays in presentation and diagnosis, and national screening programs; 3: The impact of COVID on healthcare professionals; 4: Impact on current and future research; 5: Consequence of global economic crisis on childhood cancer care; 6: Impact on long-term survivorship, late effects and surveillance monitoring. CONCLUSION: COVID-19 has had a profound effect on health care, and the literature reflects the extent to which communities involved in childhood cancer care have worked together to minimise the impact. It is inevitable that there have been consequences of the pandemic on the treatment of existing patients, and the diagnosis of new ones, but evidence suggest these effects in the short term are minimal. The greatest concerns are for immediate and short-term research conduct.

COVD-03. IMPACT OF COVID-19 ON THERAPY PROVISION FOR CHILDREN WITH CNS TUMOURS

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INTRODUCTION: The COVID-19 pandemic has led to widespread change in the delivery of rehabilitation. The Teenage Cancer Trust reported that 69% of young people with cancer saw their physiotherapist less than usual during the pandemic raising concerns about physiotherapy input. METHODS: Retrospective analysis of all children's therapy input managed under the Neuro Oncology Rehabilitation Team (NORT) between 1st April and 30th July 2020. Descriptive analysis of change to physiotherapy provision during this time period by Tertiary and local community services. RESULTS: 49 children were managed under the NORT Therapy Team during this timeframe. 9 children were newly diagnosed with CNS tumours. There was no impact on inpatient therapy provision, 3 had delayed local therapy provision on discharge requiring increased virtual input by the Tertiary centre. 40 children were outpatients managed under the NORT therapy team. 16 children were also receiving regular local physiotherapy input prior to the COVID-19 pandemic. 13 of these children subsequently had their local physiotherapy input suspended during this time period, 8 children were offered virtual input as an alternative by the Tertiary centre, 2 children received increased face to face appointments at the Tertiary centre. 14 of the 24 children managed solely under the Tertiary NORT Therapy Team changed to virtual therapy reviews. DISCUSSION: There is a clear change in therapy provision as a result of the COVID-19 pandemic. Future research should consider the effectiveness of neurorehabilitation conducted virtually and the impact on physical function of reduced local therapy provision in children with CNS tumours.

COVD-04. CHARACTERISTICS OF SARS-COV-2 IN 64 CHILDREN WITH CNS TUMORS: A REPORT FROM THE SIOP/ST. JUDE CHILDREN'S RESEARCH HOSPITAL (SJCRH) GLOBAL COVID-19 CHILDHOOD CANCER REGISTRY

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BACKGROUND: The GCCCR is a collaboration between SIOP and SJCRH to describe the natural history of SARS-CoV-2 in children with cancer across the world. METHODS: The GCCCR is a deidentified registry of patients <19 years of age with cancer or recipients of a hematopoietic stem cell transplant and laboratory-confirmed SARS-CoV-2 infection. Demographic data, cancer diagnosis, cancer-directed therapy, and clinical characteristics of SARS-CoV-2 infection were collected. Outcomes were collected at 30-days and 60-days post infection. RESULTS: As of August 10th 2020, the GCCCR included 730 cases from 35 countries, including 64 children with CNS tumors (8.8%) from 17 countries. The most frequent diagnoses were embryonal tumors (31.2%) and low-grade glioma (17.2%). Thirty-nine (60.9%) children were asymptomatic from infection, while 19 (29.7%) patients required hospital admission and 2 (6.3%) transferred to the intensive care unit. There was a significant association between infection severity and ANC <500 (p=0.04). At the time of infection, 44 (68.8%) patients were undergoing cancer-directed therapy. Thirty-two cases have follow-up data. No modification in cancer-directed therapy occurred in 11 (34.4%) patients, while chemotherapy was modified in 6 (18.8%), radiotherapy delayed in 2 (6.3%), and surgery postponed in 1 (3.1%). No patients died from SARS-CoV-2 infection, although 2 died from non-COVID-19 related causes. CONCLUSION: The frequency and severity of COVID infection among children with CNS tumors appears to be proportionally lower compared to other children with cancer. Although this is the largest cohort of patients reported to date, additional insight is needed, including the effects of treatment modifications on outcomes.

DRUG DELIVERY/PHARMACOKINETICS

DDEL-01. ENHANCING DRUG DELIVERY WITH MRGFUS FOR DIFFUSE INTRINSIC PONTINE GLIOMA MODEL

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Diffuse intrinsic pontine glioma (DIPG) is a surgically unresectable and devasting tumor in children. To date, there have been no effective chemotherapeutics despite a myriad of clinical trials. The intact blood-brain barrier (BBB) in part is responsible for the limited clinical response to chemotherapy. MRI guided focused ultrasound (MRgFUS) is a promising non-invasive tissue ablative method for CNS tumors. Moreover, MRgFUS allows for the temporary disruption of BBB. Our first objective was to determine the feasibility and safety of temporary BBB disruption within the brainstem using MRgFUS following intravenous (IV) administration of microbubbles in vivo. Our second objective was to select effective chemotherapeutics against DIPG cell lines, and to examine their therapeutic effects with MRgFUS in a mouse model of DIPG which exhibits an intact BBB. The non-invasive opening of the BBB was determined in the brainstem of normal rodents using physiological monitoring and histological analysis. Doxorubicin was selected from a drug screen consisting of conventional chemotherapeutics using SU-DIPG4 and SU-DIPG17 cell lines. We established SU-DIPG17 xenografts which demonstrated diffusely infiltrative tumor growth similar to human DIPG. By LC-MS/MS analysis, MRgFUS led to a 4-fold increase in doxorubicin concentrations within the brainstem tumors following IV administration when compared to IV administration alone, We demonstrated feasibility and safety of MRgFUS in the rodent brainstem and have shown that MRgFUS increases doxorubicin uptake in the brainstem of a rodent model of DIPG. These preclinical data will be helpful in designing clinical trials of BBB disruption using MRgFUS for DIPG in children.

DDEL-02. DECREASED TOXICITY OF CONVENTIONAL DOSE CHEMOTHERAPY UTILIZING BODY WEIGHT INSTEAD OF BODY SURFACE AREA FOR DOSING IN YOUNG CHILDREN <6 YEARS OLD ENROLLED ON THE "HEAD START" 4 CLINICAL TRIAL

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Metabolism of drugs in infants and young children is significantly different from older individuals due to differences in distribution, protein-binding capacity, hepatic metabolism and renal excretion. To be consistent with Children's Oncology Group (COG) guidelines, body surface area (BSA) was used to dose chemotherapeutics in children >3 years old enrolled on "Head Start" 4 clinical trial (HS 4). Four of 30 patients enrolled on HS 4 developed sinusoidal obstruction syndrome (SOS) while receiving induction chemotherapy with cisplatin, etoposide, vincristine, cyclophosphamide and high-dose methotrexate using BSA for dosing (mg/m^2). Patients #1 and #2 were both 2-years old at diagnosis, received and tolerated the first two cycles with mg/kg dosing uneventfully, then turned 3-years old and received cycle #3 with mg/m^2 dosing as per protocol guidelines, and developed SOS. Patient #3 was 3-years old at diagnosis, received induction chemotherapy with mg/m2 dosing, and developed SOS during the very first cycle. Patient #4

was 4-years old at diagnosis and received all 3 induction cycles with mg/m2 dosing, developed serious nephrotoxicity during cycle #1 followed by SOS during cycle #3. The HS 4 trial was amended and reopened after external, independent Data Safety Monitoring Board review to dose all chemotherapy drugs in children <6 years old with mg/kg dosing instead of BSA. None of 75 patients enrolled since the amendment developed SOS during induction. These data suggest using caution while dosing young children <6 years of age with intensive induction chemotherapy by BSA.

DDEL-03. LONG-TERM INTRAVENTRICULAR THERAPY ALTERNATING ETOPOSIDE AND LIPOSOMAL CYTARABINE: EXPERIENCE IN 75 CHILDREN AND ADOLESCENTS WITH MALIGNANT BRAIN TUMORS

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BACKGROUND: Malignant brain tumors of childhood carry a high risk for leptomeningeal dissemination and tumor cells floating in the CSF are often not amenable to systemic and/or antiangiogenic chemotherapy. We report on our experience with an intraventricular therapy consisting of alternating cycles of liposomal cytarabine and etoposide. PATIENTS AND METHODS: Between 2004 and 2017, 75 patients aged 0.6 to 22 years (median 11) with various malignant brain tumors received intraventricular etoposide 0.25mg (<1year) - 0.5mg on five consecutive days alternating with liposomal cytarabine at a dose of 25mg (<3 years) - 50mg via an Ommaya reservoir. RESULTS: 5533 doses of etoposide (5–277/patient, median 141) corresponding to 1–56 five-day-cycles/patient alternating with 534 doses of liposomal cytarabine (1–21/patient, median 11) were administered. Treatment was given over a period of 1 – 146 months (median 73.5). Toxicities did occur but were infrequent and mostly mild. Since all patients received some sort of concurrent anti-cancer therapy, the efficacy of intrathecal therapy cannot be assessed independently. However, 29/75 patients are still alive, and none of the patients had tumor cells in the CSF at their last evaluation. CONCLUSION: In conclusion, alternating intraventricular liposomal cytarabine and etoposide produced responses and proved to be an important adjunct for patients receiving drugs with a low penetrance into the CSF. Since production of liposomal cytarabine was discontinued in 2017 it remains to be determined whether substitution of the slow release formulation by aqueous cytarabine on days 1, 4, 8, and 11 may produce similar results.

DDEL-04. ENGINEERED NANOCARRIERS TO ENHANCE DRUG DELIVERY ACROSS THE BLOOD-BRAIN BARRIER

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Pediatric central nervous system tumors are the leading cause of cancer death in children. Promising therapeutics have been identified, but the ability to deliver an effective concentration to the tumor without causing excessive systemic toxicity remains a challenge. To address this, we leveraged a tunable nanocarrier platform to design a brain-penetrant nanocarrier with preferential uptake into tumor cells over healthy brain cells. First, we used the layer-by-layer technique to iteratively coat liposomes with nanometers-thick layers of oppositely charged polyelectrolytes. To investigate the influence of surface chemistry on cellular trafficking, a panel of layered liposomes was tested for interactions with cancer cell lines, identifying poly-L-aspartic acid and hyaluronic acid as the highest-performing formulations across brain tumor lines. To facilitate nanocarrier transit across the blood-brain barrier (BBB), we developed a click chemistry platform to functionalize the nanocarrier with BBB shuttle ligands. To investigate trafficking *in vitro*, we utilized a microfluidic brain microvascular model comprising endothelial cells, astrocytes, pericytes, and glioma cells that self-assemble into a perfusable vascular network. We found that nanocarrier size influenced vascular transport, and the addition of BBB shuttle ligands improved transport in the presence of a glioma spheroid. To investigate *in vivo* nanocarrier trafficking, we performed intravital imaging through a cranial window in anesthetized mice. After intravenous administration, nanocarrier transit across intact brain capillaries was visualized using two photon microscopy, and vessel permeability was quantified over time. Ongoing studies in mice bearing patient-derived xenograft medulloblastoma and glioma tumors are being conducted to further characterize trafficking across tumor-associated vasculature.

DDEL-05. BLOOD-BRAIN BARRIER DISRUPTION AND ENHANCED RADIOSENSITIZERS EXTRAVASATION UPON FOCUSED ULTRASOUND FOR TREATMENT OF DIFFUSE INTRINSIC PONTINE GLIOMA

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Poor prognosis of diffuse midline glioma, including diffuse intrinsic pontine glioma (DIPG), reflects the low efficacy of current treatment strategies, mainly due to (1) a largely intact blood-brain barrier (BBB) and (2) the proficiency of tumour tissues to upregulate multiple DNA repair genes, resulting into radio-resistance. *In vitro* studies showed therapeutic benefit by combining radiotherapy and radiosensitizers, while pre-clinical and clinical studies evidenced safe and transient opening of the BBB using microbubble mediated focused ultrasound (FUS). Previously, we demonstrated the enhanced extravasation of olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor in the mouse pons. Local drug delivery was applied using an in-house built X-ray image-guided FUS system with a 1 MHz mono-element transducer delivering a tone-burst pulse with a mechanical index of 0.4. Tissue/blood drug concentrations were analysed by LC-MS/MS, 30 minutes after intraperitoneal injection of 10 mg/kg olaparib. The FUS system allowed for precise treatment of the pons, proven by local extravasation of Evans Blue-conjugated albumin. A significant 5.1 fold median increase was observed in absolute concentrations in the pons after FUS intervention compared to the control and a 4.9 fold increase of the median tissue-blood ratio ($*p<0.05$). No significant differences were detected in brain regions outside the ultrasound focus and other organs, confirming the local intervention. With this, the 299 nM equivalent olaparib concentration found in the pons will facilitate PARP inhibition in future murine patient-derived xenograft tumour models, thus leading to a greater therapeutic effect when in combination with radiotherapy treatment of DIPG.

DDEL-06. DRUG INTERACTION BETWEEN EVEROLIMUS AND CANNABIDIOL IN PEDIATRIC PATIENTS WITH SUBEPENDYMAL GIANT CELL ASTROCYTOMAS: A SINGLE INSTITUTION EXPERIENCE

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Tuberous sclerosis complex (TSC) is an autosomal recessive genetic disorder associated with clinical manifestations including subependymal giant cell astrocytomas (SEGA) and seizures. The combination of everolimus and Epidiolex, a purified form of cannabidiol, has become an increasingly common treatment regimen in this population. Everolimus is primarily metabolized via CYP3A4, which may be inhibited by cannabidiol. We seek to describe our institution's experience with this drug interaction. METHODS: Investigators conducted a retrospective review of neuro-oncology patients with TSC and SEGA who were treated concurrently with everolimus and cannabidiol. Data collected included demographics, body surface area, everolimus dose, everolimus troughs, date of cannabidiol initiation, documented symptoms, liver and renal function tests, and reason for discontinuing therapy. RESULTS: Three patients (ages 11–17 years) met inclusion criteria. All patients were stable on everolimus doses ranging from 6.5 to 9.5 mg/m^2/day and achieving trough goals of 5–10 ng/mL. Two to four weeks after initiating cannabidiol, everolimus trough concentrations rose 200–860% above goal. One patient reported new-onset involuntary movements, but no other toxicities were noted. Cannabidiol was discontinued in all cases due to caregiver concerns regarding drug interactions. All patients were able to achieve goal trough concentrations on previously stable doses of everolimus after discontinuing cannabidiol. CONCLUSIONS: Cannabidiol appears to modulate everolimus metabolism leading to significantly elevated serum concentrations. Additional research is required to determine the need for empiric dose adjustments upon cannabidiol initiation. Patient counseling, frequent trough monitoring, and surveillance for adverse effects are crucial for optimizing outcomes in patients prescribed this regimen.

DDEL-07. A PHASE I STUDY EXAMINING THE FEASIBILITY OF INTERMITTENT CONVECTION-ENHANCED DELIVERY (CED) OF MTX110 FOR THE TREATMENT OF CHILDREN WITH NEWLY DIAGNOSED DIFFUSE MIDLINE GLIOMAS

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Convection-enhanced delivery (CED, the infusion of drugs under controlled pressure to the brain parenchyma via targeted micro-catheters, allows accurate anatomical targeting and delivery of higher (therapeutic) drug concentrations through clinically relevant volumes of brain tissue or tumor. Histone deacetylase inhibitors have been found *in vitro* to be the most active agents against Diffuse Midline Gliomas (DMGs) Using a novel device (implantable subcutaneous pump connected with catheter directly implanted into the pons/thalamus) we are performing a Phase I safety study of repeated infusions of MTX110 (MTX110, Midatech) in a dose escalation manner. Eligible patients include 3–18 years of age with newly diagnosed DMGs following radiation therapy without evidence of hemorrhage or cysts with intact organ function. Patients undergo a tumor biopsy and a single catheter (Spetzler lumbar shunt catheter, Integra, Plainsboro, NJ) is placed stereotactically into the geometric center of the tumor. A second catheter is inserted subcutaneously with the distal tubing connected to the infusion pump, (SynchroMed II (Medtronic)), also inserted subcutaneously. The infusion pump is prefilled with MTX110 and administered using wireless N'Vison Clinical programmer into two 24-hour infusions, consisting of 20 hours of drug infusions at 0.2mL/hr. The pulse is completed 7 days later. This is a dose escalation study with the infusate consisting of gadolinium and MTX110 (30, 60, or 90 microM). The study describing the first use in children of this device for direct-to-tumor drug delivery is open to recruitment (January 2020) and the preliminary data will be available for presentation by June 2020.

DDEL-08. CONVECTION-ENHANCED DELIVERY OF NIMUSTINE HYDROCHLORIDE (ACNU) AGAINST PEDIATRIC DIFFUSE INTRINSIC PONTINE GLIOMAS

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Diffuse intrinsic pontine gliomas (DIPGs) are amongst the most challenging tumors to treat. Surgery is not an option, the effects of radiation therapy are temporary, and no chemotherapeutic agent has demonstrated significant efficacy. Intracerebral infusion technique of convection-enhanced delivery (CED) for patients with brain tumors could offer a novel approach for effective chemotherapy. We have been working to develop an effective chemotherapy using nimustine hydrochloride (ACNU) with this drug delivery method. After several studies targeting supratentorial recurrent malignant gliomas and recurrent gliomas affecting brainstem, we conducted phase 1 study to evaluate the safety of combination of convection-enhanced delivery of nimustine hydrochloride and systemic temozolomide against recurrent gliomas affecting brainstem. In this study, we demonstrated the safety and feasibility of CED of ACNU as well as real time monitoring of drug distribution by mixing ACNU with contrast agent; Gd-DOTA. We also defined the maximum tolerable concentration in this study and proceeded to phase 2 trial against recurrent gliomas affecting brain stem. However, these trials revealed the difficulty of treating pediatric DIPG at the time of recurrence. Therefore, we decided to treat pediatric DIPG cases at their initial diagnosis in the subsequent study. Aiming at obtaining Shonin approval both for intraparenchymal infusion catheter and drug to infuse into brain parenchyma, we are now conducting Phase II physician-led trial against initially diagnosed pediatric DIPG cases.

DDEL-09. HIGH DOSE MTX110 (SOLUBLE PANOBINOSTAT) SAFELY ADMINISTERED INTO THE FOURTH VENTRICLE IN A NON-HUMAN PRIMATE MODEL

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OBJECTIVE: This study tested the safety and pharmacokinetics of short-term and long-term administration of MTX110 (soluble panobinostat; Midatech Pharma, UK) into the fourth ventricle of non-human primates. METHODS: Four rhesus macaque monkeys underwent posterior fossa craniectomy and catheter insertion into the fourth ventricle. In Group I (n=2), catheters were externalized and lumbar drain catheters were placed simultaneously to assess cerebrospinal fluid (CSF) distribution after short-term infusions. MTX110 (0.5 ml of 300 μM panobinostat solution) was infused into the fourth ventricle daily for five consecutive days. Serial CSF and serum panobinostat levels were measured. In Group II (n=2), fourth ventricle catheters were connected to a subcutaneously-placed port for subsequent long-term infusions. Four cycles of MTX110, each consisting of 5 daily infusions (0.5 ml of 300 μM panobinostat solution), were administered over 8 weeks. Animals underwent detailed neurological evaluations, MRI scans, and post-mortem histological analysis. RESULTS: Neurological assessments, MRI, and histology confirmed catheter placement and an absence of neurotoxicity. Panobinostat was undetectable in serum collected two and four hours after infusions in all samples in both groups. In Group I, mean peak panobinostat level in fourth ventricle CSF (6242 ng/ml) was significantly higher than in lumbar CSF (9 ng/ml; $p < 0.0001$). In Group II, mean peak CSF panobinostat level (11,042 ng/ml) was significantly higher than mean trough CSF level (33 ng/ml; $p<0.0001$). CONCLUSION: MTX110 can be safely delivered via 4th ventricle at supra-therapeutic doses. These results provide data for a pilot clinical trial in patients with recurrent medulloblastoma.

DDEL-10. A NANOPARTICLE PLATFORM FOR INTRATHECAL DELIVERY OF THE HISTONE DEACETYLASE INHIBITOR (HDACI) PANOBINOSTAT IN METASTATIC OR RECURRENT MEDULLOBLASTOMA

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INTRODUCTION: Panobinostat is a histone deacetylase inhibitor (HDACi) that is a clinical candidate for treatment of pediatric medulloblastoma and diffuse intrinsic pontine glioma. Panobinostat is poorly water-soluble and experiences a number of barriers to effective delivery. Here, we developed a novel drug delivery system consisting of β-cyclodextrin-poly(β-amino ester). These cyclodextrin-networks (CDNs) self-assemble into nanoparticles encapsulating a high quantity of HDACi for slow release. We sought to test the hypothesis that panobinostat-loaded CDNs would demonstrate a differentiated pharmacokinetic profile compared to free panobinostat in mice after direct administration to cerebrospinal fluid. METHODS: CDNs were synthesized via Michael addition and engineered to encapsulate a library of HDACi drugs. Nanoparticles were characterized for size, surface charge, loading, controlled release, and stability. CDNs or fluorescent surrogate nanoparticles were administered to the cisterna magna of mice. Tissues were collected for LC-MS/MS (pharmacokinetics [PK]: 1, 4, 8, 24, and 48 hrs) or microscopy (localization: 2, 6, 24, and 48 hrs, 1 and 3 wks). RESULTS: Intravital and confocal microscopy demonstrate that nanoparticles distribute rapidly in subarachnoid space and can localize with metastases, persisting for > 3 weeks. Nanoparticle panobinostat is released over weeks and is better tolerated than free drug. CDN-panobinostat delivery tended to be higher in the cerebellum and lower in the spinal cord at both early and late time points compared to freely administered drug. CONCLUSIONS: We present a nanoparticle platform for HDACi delivery with a differentiated PK profile in the CSF compared to free drug. Additional PK and therapeutic studies are ongoing.

DDEL-11. CONVECTION-ENHANCED DELIVERY OF EZH2 INHIBITOR FOR THE TREATMENT OF DIFFUSE INTRINSIC PONTINE GLIOMA

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BACKGROUND: Diffuse intrinsic pontine glioma (DIPG) is a fatal childhood brain tumor and the majority of patients die within 2 years after initial diagnosis. Factors that contribute to the dismal prognosis of these patients include the infiltrative nature and anatomic location in an eloquent area of the brain, which precludes total surgical resection, and the presence of the blood-brain barrier (BBB), which reduces the distribution of systemically administered agents. Convection-enhanced delivery (CED) is a direct infusion technique to deliver therapeutic agents into a target site in the brain and able to deliver a high concentration drug to the infusion site without systemic toxicities. OBJECTIVE: This study aims to assess the efficacy of enhancer of zeste homolog-2 (EZH2) inhibitor by CED against human DIPG xenograft models. METHODS: The concentration of EZH2 inhibitor (EPZ-6438) in the brainstem tumor was evaluated by liquid chromatography–mass spectrometry (LC/MS). We treated mice bearing human DIPG xenografts with EPZ-6438 using systemic (intraperitoneal) or CED administration. Intracranial tumor growth was monitored by bioluminescence image and the therapeutic response was evaluated by animal survival. RESULTS: LC/MS analysis showed that the concentration of EPZ-6438 in the brainstem tumor was 3.74% of serum concentration after systemic administration. CED of EPZ-6438 suppressed tumor growth and significantly extended animal survival when compared to systemic administration of EPZ-6438 (P=0.0475). CONCLUSION: Our results indicate that CED of an EZH2 in-

hibitor is a promising strategy to bypass the BBB and to increase the efficacy of an EZH2 inhibitor for the treatment of DIPG.

DDEL-12. NANOPARTICLE DELIVERY OF DOXORUBICIN FOR THE TREATMENT OF DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

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DIPGs are the most aggressive pediatric brain tumors. Currently, the only treatment is irradiation but due to its palliative nature patients die within 12 months. Effective delivery of chemotherapy across the blood-brain barrier (BBB) has been a key challenge for the eradication of this disease. We have developed a novel gold nanoparticle functionalised with human serum albumin (Au-NP, 98.8 ±19 nm) for the delivery of doxorubicin. In this study, we evaluated the cytotoxic efficacy of doxorubicin delivered through gold nanoparticles (Au-NP-Dox). We found that DIPG neurospheres were equally sensitive to doxorubicin and Au-NP-Dox (at equimolar concentration) by alamar blue assay. Colony formation assays demonstrated a significantly more potent effect of Au-NP-Dox compared to doxorubicin alone, while the Au-NP had no effect. Furthermore, western blot analysis indicated increased apoptotic markers cleaved Parp, caspase 3/7 and phosphorylated H2AX in Au-NP-Dox treated DIPG neurospheres. Live cell content and confocal imaging demonstrated significantly higher uptake of Au-NP-Dox compared to doxorubicin alone. Treatment of a DIPG orthotopic mouse model with Au-NP-Dox showed no signs of toxicity with stable weights being maintained during treatment. However, in contrast to the above *in vitro* findings the *in vivo* study showed no anti-tumor effect possibly due to poor penetration of Au-NP-Dox into the brain. We are currently evaluating whether efficacy can be improved using measures to open the BBB transiently. This study highlights the need for rigorous *in vivo* testing of new treatment strategies before clinical translation to reduce the risk of administration of ineffective treatments.

DDEL-13. FOCUSED ULTRASOUND MEDIATED BLOOD BRAIN BARRIER DISRUPTION IN A MURINE MODEL OF PONTINE GLIOMA: A SAFETY AND FEASIBILITY STUDY

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BACKGROUND: Drug delivery remains a major obstacle in DIPG, as the blood brain barrier (BBB) limits the penetration of systemic therapies to the brainstem. Focused ultrasound (FUS) is an exciting new technology that, when combined with microbubbles, can open the BBB permitting the entry of drugs across the cerebrovasculature. Given that the utility of FUS in brainstem tumors remains unknown, the purpose of our study was to determine the safety and feasibility of this technique in a murine pontine glioma model. METHODS: A syngeneic orthotopic model was established by stereotactic injection of PDGF-B^{+}PTEN$^{-/-}$p53$^{-/-}$ murine glioma cells (10,000/1ul) into the pons of B6 albino mice. A single-element, spherical-segment FUS transducer (center frequency=1.5MHz) driven by a function generator through a power amplifier (acoustic pressure=0.7MPa) was used with concurrent intravenous microbubble injection (FUS+MB) to sonicate the tumor on post-injection day 14. BBB opening was confirmed with gadolinium-enhanced MRI and Evans blue. Kondziela inverted screen (KIS) testing was completed to measure motor function. Mice were either immediately sacrificed for histopathological assessment or serially monitored for survival. RESULTS: In mice treated with FUS (n=11), there was no measured deficit in KIS testing. Additionally, the degree of intra-tumoral hemorrhage and inflammation on H&E in control (n=5) and treated mice (n=5) was similar. Lastly, there was no difference in survival between the groups (control, n=6, median=26 days; FUS, n=6, median=25 days, p>0.05). CONCLUSION: FUS+MB is a safe and feasible technique to open the BBB in a preclinical pontine glioma model.

DDEL-14. SAFETY OF INTERVENTRICULAR METHOTREXATE ADMINISTRATION FOLLOWING RADIATION IN PEDIATRIC PATIENTS WITH MALIGNANT BRAIN TUMORS

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BACKGROUND: Methotrexate has been used for intrathecal administration in leukemia as well as embryonal CNS tumors in children. Concerns about neurologic side effects including leukoencephalopathy, demyelination, and seizures have limited the use of methotrexate following exposure to focal radiation. OBJECTIVE: To evaluate and determine safety of Intraventricular administration of Methotrexate in pediatric patients with recurrent malignant brain tumors along with systemic Topotecan and Cyclophosphamide after exposure to prior radiation therapy. DESIGN/METHOD: Patients with recurrent cerebellar embryonal tumors after standard treatment that included radiation were enrolled on this IRB approved phase 2 study. An Ommaya reservoir was inserted in the lateral ventricle and used to administer 4 daily doses of methotrexate (2 mg/dose) along with (Topotecan [0.75mg/m2/day] and Cyclophosphamide [250 mg/m2/day]). A neurological evaluation was performed at baseline and daily during the intraventricular administration of the Methotrexate, this evaluation was repeated prior to each subsequent cycle and at completion of the protocol. RESULTS: Three patients (age range 3–20) received 2–3 cycles of intra-Ommaya Methotrexate and Topotecan/Cyclophosphamide. No MRI demyelination or white matter changes were seen after completion of the intraventricular Methotrexate therapy. None of the patients enrolled on this trial had adverse effects related to the therapy regimen received. Clinical neurological status was unchanged during the entire course of the treatment and upon completion of the scheduled therapy. CONCLUSION: Intraventricular administration of daily low dose Methotrexate is well tolerated in children with recurrent embryonal CNS tumors who had prior exposure to radiation.

DDEL-15. NANOTHERAPEUTIC TARGETING OF TUMOR ENDOTHELIUM FOR ENHANCING DRUG DELIVERY PAST THE BLOOD-BRAIN BARRIER

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OBJECTIVE: The Sonic Hedgehog (SHH) medulloblastoma subgroup accounts for ~25% of all cases and has an intermediate prognosis. Current therapies result in devastating morbidities including intellectual disability and secondary malignancies. Although molecularly targeted agents against the SHH pathway have demonstrated efficacy, on-target bone toxicities suggest new therapeutic approaches are needed. METHODS: We investigated the SHH pathway inhibitor, vismodegib, packaged in a fucoidan-based nanoparticle (Fi-Vis) that targets P-selectin expressed on endothelial cells and induced by low-dose ionizing radiation (XRT) in a time- and dose-dependent manner. This P-selectin targeting nanoparticle shows selectivity toward tumor and not normal brain vasculature in a GEM SHH medulloblastoma model as assessed by *ex vivo* infrared imaging and molecular studies. RESULTS: Quantitative RT-PCR analysis of SHH medulloblastoma following single dose XRT and Fi-Vis treatment (10mg/kg) showed synergistic reduction of Gli1 expression (>90% target inhibition). We demonstrate that low-dose XRT (0.25Gy) can induce P-selectin expression specifically on medulloblastoma tumor endothelium and synergize with low-dose Fi-Vis (10mg/kg) to significantly enhance mouse survival ($p<0.01$) compared to radiation or Fi-Vis alone. Assessment of bone toxicity using micro-CT and histological analysis following Fi-Vis administration in postnatal (P10) mice shows no bone toxicity when compared to free vismodegib. Finally, *in vitro* studies using bEnd.3 brain endothelial cells and *in vivo* studies using *Cav1* knockout mice suggest a caveolin-1 mediated transcytosis mechanism for nanoparticle entry across the blood-brain barrier. CONCLUSIONS: These data suggest applicability of combined XRT and tumor vasculature-targeted nanotherapeutic dose de-escalation strategies for SHH medulloblastoma with implications for other pediatric brain tumors.

DDEL-16. UNDERSTANDING OPTIMAL CONVECTION-ENHANCED DELIVERY PHYSICO-CHEMICAL INFUSION PARAMETERS: THE ROLE OF BBB EFFLUX PUMPS IN DRUG DISTRIBUTION AND CLEARANCE

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BACKGROUND: Diffuse midline gliomas harboring the H3K27M mutation are aggressive and universally fatal brain tumors that primarily occur in children. The blood-brain barrier (BBB) prevents many drugs from reaching

the tumor at cytotoxic concentrations and efflux pumps found on the epithelial cells of the BBB rapidly pump drugs out of the brain. Convection enhanced delivery (CED) is a drug delivery technique that bypasses the BBB by directly injecting the drug into the tumor site under a pressure gradient. Further clinical implementation of CED requires understanding drug distribution, as optimal drug physico-chemical properties have never been evaluated. METHODS: Sprague Dawley rats underwent a single injection of drug by CED to the brainstem with and without an efflux pump inhibitor. Animals were euthanized at 0, 2, 4, 8, 12 and 24 hours. Their brain drug concentration/distribution was analyzed by MALDI-MSI and plasma drug concentration was measured by LC-MS/MS. RESULTS: Drug distribution and brainstem concentration were increased following BBB efflux pump inhibition compared to no pump inhibition controls. Additionally, efflux pump inhibition resulted in slower drug clearance for those drugs that are known pump substrates. CONCLUSIONS: BBB efflux pump inhibition resulted in a larger volume of distribution, increased drug concentration and slower drug clearance following CED to the brainstem of known efflux substrates.

DDEL-17. TRIPLE INTRAVENTRICULAR CHEMOTHERAPY FOR TREATMENT OF RELAPSED CHOROID PLEXUS CARCINOMA

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Limited evidence for the optimal management of relapsed choroid plexus carcinoma (CPC) exists, with a few case reports involving surgery, radiotherapy and intravenous chemotherapy. However, the safety and tolerability of intraventricular chemotherapy in this setting has not been widely studied. We describe a case where triple intraventricular chemotherapy was administered to a child with relapsed metastatic CPC. A 7-year-old male with a history of CPC presented with relapsed metastatic disease. At initial diagnosis at 4 years of age, treatment involved gross total resection of an intraventricular mass in the left temporal region followed by chemotherapy and autologous stem cell transplantation (SCT) according to HEADSTART II-D. One year after SCT, craniospinal radiation was delivered following radiological relapse, achieving a partial response. Given previous treatment-limiting myelosuppression, intraventricular chemotherapy via Ommaya® reservoir with thiotepa 5mg, etoposide 0.5mg and topotecan 0.4mg twice a week (non-weight-based dosing) was commenced taking into consideration pharmaceutical formulation aspects for optimal intraventricular drug delivery. After six cycles of intraventricular chemotherapy, palliative radiotherapy was administered due to radiological progression. Following completion, weekly triple intraventricular chemotherapy continued for 9 months. The patient remained out of hospital with the main side effects being fatigue and occasional nausea amenable to ondansetron. This case study demonstrates the safety and tolerability of a triple intraventricular chemotherapy regimen used to delay disease progression and prolong quality of life in a child with relapsed CPC in the palliative setting. This could provide an alternative treatment regimen for patients with relapsed disease.

DIFFUSE MIDLINE GLIOMA/DIPG

DIPG-01. REIRRADIATION PRACTICES FOR DIFFUSE INTRINSIC PONTINE GLIOMA

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INTRODUCTION: Diffuse intrinsic pontine gliomas (DIPG) are a leading cause of brain tumor deaths in children. Current standard of care includes focal radiation therapy (RT). Despite clinical improvement in the majority of patients, the effect is temporary and median survival is less than one year. The use of reirradiation and possible benefit has been reported in progressive DIPG, yet standardized approaches are lacking. We conducted an internet-based survey to assess physicians' practices in pediatric DIPG. METHODS: A 14-question REDCap survey regarding re-irradiation practices was emailed to 396 physicians identified through an International Pediatric Neuro-Oncology and Radiation-Oncology database. RESULTS: Response rate was 35% overall (radiation-oncologists, 28%; pediatric oncologists, 57%). Two participants were excluded (did not treat DIPG). Participants included radiation-oncologists (62%), pediatric oncologists (7%), and pediatric neuro-oncologists (29%). Most physicians (62%) treated 1–5 DIPG patients per year, with 10% treating >10/ year. Reirradiation was considered a treatment option in 88%. Progressive disease or worsening clinical status were the most common reasons to consider reirradiation. The majority (84%) considered reirradiation a minimum of 6 months following initial RT. Doses varied, with median total dose 24Gy (range 12–60); 2Gy/fraction (range 1–9). Concurrent use of systemic agents with reirradiation was considered in 46%, mainly with targeted agents (37%), biologics (34%), or immunotherapy (25%). One-time reirradiation was the most common practice (71%). Interestingly, 9% of respondents would not consider reirradiation. CONCLUSION: Although, the vast majority of physicians agree with re-irradiation as a treatment option for DIPG the total doses varied, and further clinical trials are needed.

DIPG-02. USEFULNESS OF BEVACIZUMAB IN MAINTAINING QUALITY OF LIFE AT THE TIME OF DIFFUSE INTRINSIC PONTINE GLIOMA RELAPSE

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INTRODUCTION: Even in the age of molecular diagnosis, diffuse intrinsic pontine glioma (DIPG) is still a dismal disease. The usefulness of bevacizumab for DIPG relapse is reported. SUBJECTS AND METHODS: The treatment and outcomes of 10 patients with DIPG who were treated at our institute since 2001 were retrospectively reviewed. All patients were diagnosed with DIPG by MRI imaging and underwent radiation therapy first. Three cases did not receive chemotherapy at the time of relapse (Untreated Group). In 7 cases, chemotherapy was performed at the time of relapse with ACNU/vincristine or interferon beta (Other Treatment Group), and 2 cases with bevacizumab (Bv Group). The change in the Karnofsky Performance Status Scale (KPS) from the time of relapse was compared. RESULTS: The average overall survival (OS) for all 10 cases was 10.0 months. No prolongation of OS by bevacizumab was observed. However, it was only in the Bv Group that the KPS increased from the time of relapse. Comparison of the KPS at the time of relapse and the KPS after 4 months showed that the Bv Group remained unchanged or increased, while the Untreated Group and the Other Treatment Group decreased. In the Other Treatment Group, hospitalization was required for treatment, and side effects of bone marrow suppression were observed. However, in the Bv Group, outpatient treatment was possible, there were no side effects, and all could be observed at home. CONCLUSION: From the above results, bevacizumab appears useful for palliative treatment for maintaining quality of life after DIPG relapse.

DIPG-03. THERAPEUTIC TARGETING OF TRANSCRIPTIONAL ELONGATION IN DIFFUSE INTRINSIC PONTINE GLIOMA

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Diffuse intrinsic pontine glioma (DIPG) is highly aggressive brain stem tumor and needed to develop novel therapeutic agents for the treatment. The super elongation complex (SEC) is essential for transcription elongation through release of RNA polymerase II (Pol II). We found that AFF4, a scaffold protein of the SEC, is required for the growth of H3K27M-mutant DIPG cells. In addition, the small molecule SEC inhibitor, KL-1, increased promoter-proximal pausing of Pol II, and reduced transcription elongation, resulting in down-regulate cell cycle, transcription and DNA repair genes. KL-1 treatment decreased cell growth and increased apoptosis in H3K27M-mutant DIPG cells, and prolonged animal survival in our human H3K27M-mutant DIPG xenograft model. Our results demonstrate that the SEC disruption by KL-1 is a novel therapeutic strategy for H3K27M-mutant DIPG.

DIPG-04. THERAPEUTIC STRATEGY FOR DIFFUSE MIDLINE GLIOMAS. A SINGLE CENTER EXPERIENCE

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INTRODUCTION: Diffuse midline gliomas have unfavorable prognoses due to the difficulty of surgery and chemo-radiation resistances. The purpose of this study is to overview our surgical experiences and prognoses of this challenging neoplasm. MATERIALS AND METHODS: Five patients of diffuse midline gliomas who were treated between 2016 and 2019 were enrolled. Tumor locations, surgical procedures, molecular diagnoses, and prognoses were retrospectively reviewed. RESULTS: There were 3 male and 2 female patients, and the median age was 15 years ranged from 7 to 21 years. Tumors were located at the basal ganglia in 1 patient, thalamus in 1, brain stem in 2, and cervical spine in 1. Mutations of *H3 K27M* genes were detected in 4 surgically treated patients, except for 1 patient, who were radiologically diagnosed as diffuse intrinsic pontine glioma (DIPG). Focal irradiation of ranged 35 to 54Gy were administered in all cases along with temozolomide in 2 cases and bevacizumab in 2 cases. The median survival time was 13 months ranged from 4 to 18 months. DISCUSSION: Supratentorial tumors were maximumly resected, whereas just biopsies were performed in cases of exophytic brain stem and spinal tumors. Diagnosis of DIPG was made without using surgical specimens. Therapeutic strategies should be discussed with a concern to the patients' qualities of life for this tumor entity with dismal prognosis.

DIPG-05. HISTONE H3.3 K27M IMPAIRS SER31 PHOSPHORYLATION, RESULTING IN CHROMOSOMAL INSTABILITY, LOSS OF CELL CYCLE CHECKPOINT CONTROL, AND TUMOR FORMATION

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Diffuse midline gliomas with the H3.3 K27M mutation are lethal brain tumors in children. H3 K27M causes global loss of Lys27 triple methylation (Lys27me3), inducing epigenetic reprograming. Here we show that H3.3 K27M also causes decreased H3.3 Ser31 phosphorylation on mitotic chromosomes. We show that H3.3 K27M DIPG cells have reduced pericentromeric phospho-Ser31 and increased rates of chromosome missegregation compared to normal, diploid human cells. CRISPR-editing K27M to M27K restored phospho-Ser31 to WT levels and dramatically decreased the rate of chromosome missegregation. We confirm that Chk1 is the H3.3 Ser31 kinase: K27M mutant H3.3 protein exhibits ~60% reduced Chk1 phosphorylation of Ser31 in vitro. Chk1 knockdown completely abolishes phospho-Ser31 in cells and these have increased rates of chromosome missegregation. In normal, diploid cells, expression of K27M or an S31A non-phosphorylatable mutant increased chromosome missegregation; this is suppressed by expressing a phosphomimetic double mutant (K27M/S31E) that restores phospho-Ser31. WT cells arrest following chromosome missegregation. However, cells expressing H3.3 K27M or S31A fail to arrest - despite having WT p53. Finally, we expressed H3F3AS31A and PDGFb in an RCAS/TVA mouse model of DIPG and ~80% developed diffuse high-grade brain tumors and show significantly decreased survival. Our results suggest that loss of phospho-Ser31 alone is oncogenic because H3.3 S31A-expressing cells are WT for K27me3. Our results demonstrate that H3.3 K27M inhibits Ser31 phosphorylation both in vitro and in vivo, leading to both chromosome missegregation and loss of subsequent G1 arrest – thus creating diffuse midline gliomas with both dynamic, complex karyotypes and epigenetic reprogramming.

DIPG-07. HIGH THROUGHPUT DRUG SCREENING IDENTIFIES POTENTIAL NEW THERAPIES FOR DIFFUSE INTRINSIC PONTINE GLIOMAS (DIPGS)

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DIPGs are the most devastating of all brain tumors. There are no effective treatments, hence almost all children will die of their tumor within 12 months. There is an urgent need for novel effective therapies for this aggressive tumor. We performed a high-throughput drug screen with over 3,500 biologically active, clinically approved compounds against a panel of neurosphere-forming DIPG cells. We identified 7 compounds- auranofin, fenretinide, ivermectin, lanatoside, parthenolide, SAHA and mefloquine- that were confirmed to have potent anti-tumor activity against a panel of DIPG-neurospheres, with minimal effect on normal cells. Using cytotoxicity and clonogenic assays, we found that these drugs were able to inhibit DIPG-neurosphere proliferation and colony formation *in-vitro*. To determine whether the *in-vitro* efficacy could be replicated *in-vivo*, we tested the activity of each of these compounds in an orthotopic DIPG model. Of the agents tested, fenretinide and SAHA were the most active anti-tumor agents, significantly enhancing the survival of tumor bearing animals. Mechanistic studies showed fenretinide enhancing apoptotic cell death of DIPG cells via inhibition of PDGFRa transcription and downregulation of the PI3K/AKT/MTOR pathway. We therefore examined the therapeutic efficacy of fenretinide using a second orthotopic model with PDGFRa amplification. We used two different Fenretinide formulations (LYM-X-Sorb and NanoMicelle) which were found to enhance survival. Fenretinide is clinically available with safety data in children. Validation of the activity of Fenretinide in PDGFRa-amplified or overexpressed DIPGs will lead to the development of a clinical trial, allowing the advancement of fenretinide as potentially the first active therapy for DIPG.

DIPG-08. ELECTRONIC SEQUENCING PROVIDES OPTIMIZED QUANTIFICATION OF SERIAL, MULTI-GENE MOLECULAR RESPONSE IN THE CSF OF CHILDREN WITH HIGH-GRADE GLIOMA

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BACKGROUND: For pediatric high-grade glioma (pHGG), non-invasive methods for diagnosis and surveillance are needed. Tumors release DNA (tDNA) into cerebrospinal fluid (CSF), allowing for detection of tumor-associated mutations by CSF sampling. We hypothesized that direct, electronic analysis of tDNA with a novel, hand-held platform (Oxford Nanopore MinION) could quantify patient-specific CSF tDNA variant allele fraction (VAF) with improved speed and limit of detection compared to established methods. METHODS: We integrated required multi-timepoint (0, 2, and 6 months) correlate lumbar punctures (LP) in two ongoing pHGG clinical trials. Using Nanopore technology, we performed amplicon-based PCR on CSF tDNA for recurrent mutations from patient samples (n=19) and normal controls. VAF were determined via MinKNOW, Guppy, MiniMap2, and Integrated Genome Browser. RESULTS: Nanopore CSF tDNA demonstrated improved sensitivity (91%) when compare to NGS sequencing (50%). Nanopore analysis of serially diluted CSF sample demonstrated significantly lower limit of detection (attomolar) than typical NGS sample requirement (nanomolar). H3K27M mutation was reliably detected with 1,000x depth sequencing, which was achieved in less than 15 minutes of sequencing after amplification. Multiplexed Nanopore analysis of *H3F3A* and *HIST1H3B* was employed when H3 status was unknown. Serial CSF tDNA analysis confirmed multi-gene (*H3F3A* K27M, *PIK3CA*, and *TP53*) molecular remission in a 17-year-old with thalamic diffuse midline glioma that correlated with sustained clinical response to ONC201 (14 months and ongoing). CONCLUSIONS: Use of a hand-held, electronic DNA analysis platform allows quantification of multi-gene molecular response with improved speed and limit of detection in the CSF of children with high-grade glioma.

DIPG-10. OPTIMAL HDAC INHIBITION IN DIFFUSE INTRINSIC PONTINE GLIOMA

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As the majority of diffuse intrinsic pontine glioma (DIPG) have H3K27M mutations, epigenetic-targeting agents have been studied, though evaluations have been limited by their model systems, untranslatable drug concentrations, and/or evasive mechanisms of action. To develop a more translational model, we used biopsy samples from newly diagnosed DIPG patients to create treatment-naïve *in vitro* and *in vivo* models (molecular aberrations in parentheses), including PBT-09FH (*H3FA3*, *PI3KCA*), PBT-22FH (*H3F3A*,

TP53), PBT-24FH (*PMS2*), and PBT-27FH (*HIST1H3B, TP53, NTRK2*). Models demonstrated radiation-resistance similar to the patient from whom the culture was generated, supporting the models' relevance (e.g. cell viability after 8 Gy was 36%, 81%, 71%, and 61% in PBT-09FH, -22FH, -24FH, and -27FH, respectively, compared to 7% in the medulloblastoma model MED-411FH). We evaluated cell viability and apoptosis following treatment with a panel of HDAC inhibitors, identifying the low nanomolar IC_{50} of quisinostat (~50 nM) and romidepsin (~5 nM). While RNA expression changes induced by 100 nM panobinostat and quisinostat included shared overexpression of the top 20/25 genes (e.g. *FSTL5*, *ITIH5*) and shared downregulation of the top 22/25 (e.g. *GPR37L1*, *HEPACAM*), only 9/25 were downregulated by panobinostat, quisinostat, and romidepsin (e.g. *C21orf62, IFIT2*), identifying these as potential vulnerabilities or biomarkers of lethal HDAC inhibition. Mass-spectrometry (LC-MS) demonstrated panobinostat as the greatest acetylator of cortactin, potentially related to thrombocytopenia. While PBT-09 flank models demonstrated quisinostat's on-target acetylation and efficacy, orthotopic xenograft models did not, supporting our model's intact blood-brain barrier and emphasizing the need for CNS penetrant versions of potentially efficacious agents.

DIPG-11. A PHASE I DOSE ESCALATION STUDY OF BXQ-350 IN CHILDREN AND YOUNG ADULTS WITH RELAPSED SOLID TUMORS

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BXQ-350 is a novel agent composed of the multifunctional, lysosomal activator protein Saposin C (SapC) and dioleoyl- phosphatidylserine (DOPS). BXQ-350 demonstrated antitumor effects *in vitro and in vivo*. Many tumors, including diffuse intrinsic pontine glioma (DIPG), and cells of tumor vasculature have aberrantly-exposed PS-rich domains on the cell surface. BXQ-350 is an anti-tumor agent in development from Bexion Pharmaceuticals, Inc. that selectively targets tumor cell PS, particularly those translocated to the outer leaflet of the plasma membrane in tumor cells. BXQ-350 activates and participates in various cellular processes, including apoptosis and necrosis, and may also exhibit novel mechanisms leading to cell death that require further investigation. An adult Phase I trial with BXQ-350 completed enrollment in 2019 having dosed 86 recurrent solid tumor patients, including glioblastoma, with only one serious infusion-related reaction. The highest planned dose of 2.4 mg/kg was achieved and seven patients remain on study with multiple cases demonstrating an objective response. A Phase I pediatric dose escalation trial in recurrent solid tumors, including central nervous system (CNS) tumors, also completed enrollment in 2019. The highest planned dose of 3.2 mg/kg was achieved and there have been no BXQ-350 related serious adverse events. Eight patients (7 CNS and 1 non-CNS) completed at least one cycle with one DIPG patient completing cycle five. A pediatric Phase I trial in newly diagnosed DIPG and diffuse midline glioma (DMG) is planned for 2nd quarter 2020.

DIPG-12. TARGETING EPIGENETIC MODIFIERS TO INDUCE IMMUNE SIGNALING IN DIPG

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DIPG is a universally fatal pediatric brainstem tumor with no effective therapy. Recent work has shown that over 80% of DIPG cases harbor the H3K27M mutation leading to global loss of the repressive H3K27 trimethylation mark, global DNA hypomethylation, and a distinct gene expression signature. We sought to exploit epigenetic vulnerabilities in DIPG through the use of DNA methyltransferase inhibitors and histone deacetylase (HDAC) inhibitors. We find that treatment with low-dose 5-aza-2'-deoxycytidine (decitabine), alone and in combination with HDAC inhibitors, elicits profound genome-wide demethylation in DIPG patient-derived neurosphere cell lines, impairs proliferation, and induces apoptosis. We show that this treatment induces immune activation, with induction of type I interferon signaling, increased expression of major histocompatibility complexes, and expression of tumor antigens. These results suggest that the immunogenicity of DIPG may be modulated by epigenetic therapies, suggesting the possibility of novel combination approaches to immunotherapy of DIPG in the future.

DIPG-13. TARGETING HYPOXIA AND MITOCHONDRIA WITH REPURPOSED METABOLIC DRUGS AS AN APPROACH TO RADIOSENSITIZATION FOR DIFFUSE INTRINSIC PONTINE GLIOMAS (DIPG)

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DIPG is the leading cause of brain tumor-related death in children. Currently, radiation is the only treatment that offers transient benefit. Compared to normal brain tissue, DIPGs are hypoperfused with tumors being exposed to hypoxia, a potent barrier to effective radiotherapy. Biguanides are hypoglycemic agents that can reduce the oxygen consumption rate (OCR) in mitochondria, thereby reducing hypoxia. Our previous study has shown that metformin significantly improves the radiosensitivity of DIPG and extends survival in a patient-derived xenograft (PDX) model. In the present study, phenformin, a second biguanide derivative, demonstrated even greater anti-DIPG activity and radiosensitising effect *in vitro*. As a single agent, phenformin dose-dependently inhibited OCR and increased extracellular acidification rate (ECAR). Low-dose phenformin reduced mitoATP/glycoATP ratio, whereas high doses significantly suppressed net ATP production. To attenuate the phenformin-induced ECAR, phenformin was combined with dichloroacetate (DCA), a clinically relevant pyruvate dehydrogenase kinase inhibitor that can suppress the elevated glycolytic rate of cancers. This combination significantly blocked the phenformin-induced ECAR and killed DIPG cells synergistically by inducing apoptosis, DNA damage and metabolic catastrophe. Moreover, protein expression of HIF-1α and c-Myc, two master regulators that collaboratively enhance the metabolic capacity of tumor cells through increased glycolysis thereby contributing to radioresistance, were also suppressed by phenformin-DCA treatment *in vitro*. This combination therapy upregulated genes inhibiting cell proliferation while downregulating genes for DNA repair. The triple combination of phenformin, DCA and irradiation demonstrated the most potent efficacy *in vitro* and is currently being tested in our PDX cohort *in vivo*.

DIPG-14. TARGETING POLO-LIKE KINASE 1 IN COMBINATION WITH KEY ONCOGENIC DRIVERS IN DIPG: FROM SINGLE AGENT TO COMBINATION STRATEGIES

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Diffuse Intrinsic Pontine Glioma (DIPG) are devastating paediatric brainstem tumours. Loss of function mutations in DIPG decrease genetic stability and impair DNA damage response pathways promoting tumourigenesis. Polo-like Kinase 1 (PLK1) is a pivotal controller of cell growth, regulating key intermediaries of DNA replication, homologous repair, the cell cycle and cell division. We have found DIPG cultures consistently overexpress PLK1 with inhibition resulting in decreased tumour cell growth, heightened cell cycle arrest and apoptosis. Single agent treatment using PLK1 inhibitors unprecedentedly doubled the median survival of animals harbouring DIPG tumours. Through gene expression analysis, we've showed PLK1 inhibition affected multiple pathways which control the cell cycle, cell death regulation, microtubule organization and regulation of cell migration. We found these pathways of differentially expressed genes were significantly enriched for known targets of both E2F1 and E2F4. Analysis of gene expression and proteomic studies also revealed PLK1 inhibition decreased the activation and expression of key tumour promoting mediators within multiple phases of the cell cycle, decreased expression of tumour promoters including MYC and the PI3K/mTOR pathway and reactivated tumour suppressors p53 and PTEN. Assessing these changes in the treated transcriptome and proteome, we aim to develop multiple potentially translatable combination treatment strategies for DIPG. We have performed mechanistic studies and identified synergism with PLK1 inhibitors and the epigenetic regulator panobinostat, bet/bromodomain inhibitor JQ1, dual PI3K/mTOR inhibitor bimiralisib and PI3K inhibitor BKM120. Finally, we found PLK1 inhibitors act as potent radiosensitizers, enhancing the therapeutic effects of radiotherapy *in vitro* and *in vivo*.

DIPG-15. POLYAMINE PATHWAY INHIBITION IS A POTENT NOVEL THERAPEUTIC STRATEGY AGAINST DIFFUSE INTRINSIC PONTINE GLIOMA

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DIPG is an aggressive paediatric brainstem tumour, with a median survival of less than 1 year. Polyamines are intracellular polycations that control important aspects of cell growth and are often upregulated in cancer. Difluoromethylornithine (DFMO) is an FDA-approved inhibitor of the enzyme ornithine decarboxylase (ODC1) which is a key driver of polyamine synthesis. We investigated the efficacy of polyamine pathway inhibitors as a therapeutic strategy against DIPG. We found high expression levels of synthetic enzymes in the polyamine pathway in primary patient samples and cultures. Using cytotoxicity and clonogenic assays, we found that DFMO inhibited the proliferation of DIPG neurospheres. However, DIPG cells compensated for DFMO inhibition by increasing expression of the polyamine transporter SLC3A2. Gene expression analysis showed that the polyamine transporter, SLC3A2, was significantly overexpressed in DIPG compared with all other high-risk childhood cancers. Addition of polyamine transporter inhibitor AMXT 1501 to DFMO led to synergistic inhibition of DIPG proliferation. Consistent with the *in vitro* results, the combination treatment significantly prolonged the survival of mice bearing 3 different DIPG orthografts with 2/3 of the animals surviving up to 160 days. Addition of irradiation further improved the survival of mice treated with DFMO and AMXT 1501. Our results suggest that DIPG tumours are exquisitely sensitive to polyamine inhibitors and that dual blockade of polyamine synthesis and transport is a promising novel therapeutic strategy. AMXT 1501 is currently in clinical development for adult cancers (NCT03536728). A clinical trial for DIPG patients is planned through the CONNECT consortium.

DIPG-16. COMBINATION OF ARGININE DEPLETION AND POLYAMINE INHIBITION AS AN ANTICANCER STRATEGY FOR DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

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DIPG is an aggressive pediatric brainstem tumor, with a median survival below 12 months. Tumor cells are dependent upon arginine, a semi-essential amino acid, metabolised by arginase enzymes into ornithine, a pivotal precursor to the polyamine pathway. Polyamines, frequently upregulated in cancer, are intracellular polycations controlling key biological processes – the inhibition of which we have previously shown to be highly efficacious in preclinical DIPG models. Pegylated arginase (BCT-100) has recently been shown to significantly delay tumor development, prolonging survival of neuroblastoma-prone *Th-MYCN* mice. This study investigated the effects of arginine depletion therapy as a single agent and in combination with polyamine pathway inhibitors in DIPG. We found that ARG2, the gene encoding for arginase II, is expressed significantly more highly in DIPG tumors compared to normal brain. Arginine depletion via BCT-100 reduced DIPG cell proliferation and colony formation in patient-derived cell lines. Using orthotopic patient-derived xenograft models of DIPG, we found that frequent dosing of BCT-100 (4x/week) significantly delayed tumor development and increased the survival of the mice ($p<0.0001$). DFMO is an FDA-approved inhibitor of the enzyme ornithine decarboxylase, a key driver of polyamine synthesis. The combination of BCT-100 with DFMO led to significant enhancement in DIPG survival ($p<0.005$ compared to single agent treatments). Triple combination therapy with addition of the polyamine transport inhibitor AMXT-1501 led to a potent and profound improvement in survival. These data show that arginine depletion therapy using BCT-100 combined with dual polyamine inhibitory agents represents a potentially exciting new approach for the treatment of DIPG.

DIPG-17. BIOPSY-PROVEN DIFFUSE MIDLINE GLIOMA IN ADOLESCENTS AND YOUNG ADULTS

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INTRODUCTION: Diffuse midline glioma (DMG) mostly affects young children. The newly-introduced disease entity DMG, H3K27M-mutant uniformly portends poor prognosis, and therefore that in the pons is usually treated based upon radiological diagnosis without histological confirmation. DMG is rarer in adolescents and young adults (AYA), and remains poorly characterized. In this study, we sought to investigate the clinical, pathological, and molecular profiles of DMG in AYA generation. METHODS: Patients of age between 16 and 39 undergoing biopsy at the University of Tokyo Hospital between 2003 and 2019 were included in the study. Clinical data and images were retrospectively reviewed. Genetic analyses were performed in cases with abundant tissues. RESULTS: Ten patients included 8 brainstem and 2 thalamic DMG. The median age was 25 years (range, 19–38). Pathological diagnosis was DMG, H3K27M-mutant in 3 patients, glioblastoma, IDH-mutant in 1, anaplastic astrocytoma, IDH-wildtype in 4, diffuse astrocytoma, IDH-mutant in 1, and diffuse astrocytoma, IDH-wildtype in 1. Genetic analyses detected *H3F3A*-K27M mutation in 2, *HIST1H3B*-K27M mutation in 1, *IDH1*-R132H mutation in 1, and *IDH1*-R132S mutation in 1. With a median follow-up of 23 months (range, 2–61), only 3 patients died 29–61 months after diagnosis, and the remaining 7 patients survived for 2–59 months. Neither *IDH1* mutation nor H3K27M mutation was associated with survival in this series. CONCLUSION: Survival of AYA patients with DMG was seemingly variable with some long survivors. H3K27M mutation was present in a subset of patients. A further study is warranted to correlate molecular profile with clinical pictures including patient survival.

DIPG-18. IDENTIFICATION OF TARGETABLE PATHWAY DEPENDENCIES IN DIFFUSE INTRINSIC PONTINE GLIOMA

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Diffuse Intrinsic Pontine Glioma (DIPG) is a highly aggressive paediatric brainstem tumour with a dismal prognosis. Recurrent heterozygous mutations (p.K27M) in Histone H3 variant genes have been identified in the majority of DIPG cases. While the exact mechanism of H3K27M's function is poorly understood, evidence suggests a role for epigenetic dysregulation in disease pathogenesis. This study aims to use functional genomics to identify novel therapeutic dependencies in H3K27M DIPG. DIPG drug sensitivity screening was carried out in twelve established and validated patient derived cell lines (10 H3.3K27M and 2 Wt) using an FDA approved drug library containing 1480 compounds. Highly prevalent targets identified from this screen include HDAC, microtubule, proteasome and CDK inhibitors. Additionally, a custom pooled CRISPR knockout library of druggable targets (300 genes, 1200 guide RNAs) was used to identify key DIPG cell survival pathways. To date five DIPG cell lines (1 Wt; 1 H3.1; 3 H3.3) have undergone screening. Knockdown of known DIPG driver genes (*TP53; PDGFRA*; *PIK3CA* and *PIK3CR1*) resulted in reduced cell viability, consistent with their proposed function and validating knockout screen utility. Preliminary data demonstrates Wt and H3K27M DIPGs cluster independently based on genes required for survival, suggesting differing tumorigenesis mechanisms and the potential for therapeutically targeting genotype specific pathways. Correlation of parallel drug screen and RNA-seq data will potentially reveal H3-dependent pathways for therapeutic exploitation. Collectively, we show a functional genomics approach is able to identify genotype-specific pathway dependencies in DIPG, paving the way for molecularly informed personalized therapies for patients.

DIPG-19. TARGETING ATM MUTATION IN METASTATIC DIFFUSE MIDLINE GLIOMA – A CASE OF SUSTAINED RESPONSE USING PARP INHIBITOR

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Diffuse midline glioma (DMG) with H3.3K27M mutation is associated with an extremely poor prognosis, with a median survival of 10 to 12 months. Radiation remains the standard of care however there is no established curative therapy available. We describe a patient diagnosed with a diffuse intrinsic pontine glioma at 5 years of age by clinical and radiological criteria. He was treated with focal radiation 59Gy which resulted in reduction in size of the tumour, and partial improvement of T2 changes on MRI. At 18 months post diagnosis, the patient developed metastatic recurrence at the anterior fornix. This was biopsied and histopathology demonstrated a high grade glioma. Next generation sequencing revealed a H3F3A K27M mutation, and an ATM R3008H mutation. He received whole ventricular radiation 36Gy and boost to the lesion to 45Gy, followed by Olaparib 135mg/m2/day twice daily. He remains in radiological remission 20 months post metastatic relapse and has no organ toxicity to Olaparib. CONCLUSION: H3.3K27M and ATM co-segregating muta-

tions are described in DMG. This is the first case report of targeting ATM mutation with a PARP inhibitor which resulted in prolonged remission of metastatic DMG. Olaparib was well tolerated.

DIPG-20. DETERMINATION AND MANAGEMENT OF HYDROCEPHALUS IN PATIENTS WITH DIPG, AN INSTITUTIONAL EXPERIENCE

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BACKGROUND: The is no consensus in best practices for the management of hydrocephalus in patients with Diffuse Intrinsic Pontine Glioma (DIPG). To date, the impact on survival of hydrocephalus and Cerebro-Spinal Fluid (CSF) diversion in this population remains to be elucidated. Herein, we describe our institutional experience. METHODS: Patients with a clinical and radiological diagnosis of DIPG were identified at the Hospital for Sick Children between 2000–2019. Images at diagnosis and at disease progression were assessed for hydrocephalus using the frontal-occipital ratio (FOR) method. Proportional hazard analyses were used to identify factors correlated with survival. RESULTS: Eighty-nine consecutive patients diagnosed with DIPGs were treated at our institution. At diagnosis, 29% (n=26) of patients presented with hydrocephalus, seven patients underwent CSF diversion. Out of the remaining nineteen patients, n=6 had stable or improved hydrocephalus in follow-up scans, n=6 had persistent hydro and n=2 required CSF diversion at the time of disease progression. Seven did not undergo a follow-up scan. Out of sixty-five patients with imaging at the time of progression, fifty-five percent of patients (n=36) presented with hydrocephalus and ten of them required CSF diversion. On univariate analysis, the presence of hydrocephalus or CSF diversion at diagnosis and/or did not correlate with a survival advantage. CONCLUSIONS: CSF diversion for the management of hydrocephalus in patients with DIPG does not impact survival and in some cases resolves spontaneously after the initiation of radiotherapy and steroids. This observation needs to be validated in a prospective cohort.

DIPG-21. INDUCTION OF MITOTIC ABNORMALITIES AND BMI-1 MODULATION TO TREAT DIFFUSE INTRINSIC PONTINE GLIOMA

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Diffuse intrinsic pontine glioma (DIPG) is a poor-prognosis pediatric brain tumor with a median survival of less than one year. No effective therapy is currently available, and no therapeutic advances have been made in several decades. BMI-1 is a member of the multimeric protein complex Polycomb repressor complex 1 (PRC1). It has been implicated in self-renewal of normal and cancer cells, and in DNA damage signaling. We have previously identified BMI-1 as a potential therapeutic target in DIPG and have shown that BMI-1 is highly expressed in DIPG tumors regardless of histone 3 subtype. In the present study, we show that the modulation of BMI-1 leads to DNA damage, M phase cell cycle arrest, chromosome abnormalities and cell death. Furthermore, modulation of BMI-1 sensitizes DIPG patient-derived stem-like cells to ionizing radiation (IR). Treatment of DIPG stem-like cells with PTC596, a BMI-1 modulator, and IR, impairs the kinetics of DNA damage response (DDR). Both DDR foci formation and resolution were delayed, resulting in further reduction in cell viability compared with either treatment alone. *In vivo*, treatment of mice bearing DIPG xenografts with PTC596 leads to decreased tumor volume and growth kinetics, increased in-tumor apoptosis and sustained animal survival benefit. Gene expression analysis indicates that *BMI-1* expression correlates positively with DIPG stemness and BMI-1 signature. Together our findings indicate that BMI-1 modulation is associated with mitotic abnormalities, impaired DDR and cell death, supporting the combination of BMI-1 modulation and radiation as a promising novel therapy to treat children with DIPG.

DIPG-22. DISSECTING THE ONCOGENIC ROLE OF *FOXR2* IN DIFFUSE INTRINSIC PONTINE GLIOMA

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BACKGROUND: Diffuse intrinsic pontine gliomas (DIPGs) pose particular challenges for treatment. We recently completed a genomic analysis of close to 200 DIPGs and high-grade gliomas. We identified that nearly 10% of all DIPGs have increased expression of the fork head domain transcription factor *FOXR2*. We hypothesize that *FOXR2* accelerates gliomagenesis in histone mutant DIPGs and represents a previously unexplored therapeutic target. METHODS: To determine whether *FOXR2* is sufficient to mediate gliomagenesis, we applied an integrative genomics approach using both *in vitro* and *in vivo* DIPG models: mouse neural stem cell models expressing *FOXR2*, *in vivo* mouse models using *in utero* brainstem electroporation, patient-derived DIPG cell lines, and RNA sequencing analysis of human and mouse tumors expressing *FOXR2*. RESULTS: Our data shows that *FOXR2* indeed is an oncogene that rapidly accelerates gliomagenesis using an *in vivo* brainstem *in utero* electroporation model of DIPG. In human tumors, increased *FOXR2* expression is mutually exclusive with *MYC* amplification suggesting functional redundancy. *In vivo*, *FOXR2* results in large brainstem gliomas and rapid neurologic decline of animals. Transcriptional profiling of these tumors demonstrates activation of *MYC* signaling pathways. *In vitro*, we have further identified patient-derived cell lines with increased expression of *FOXR2*. CONCLUSION: *FOXR2* is sufficient to enhance gliomagenesis and represents a previously understudied therapeutic target for patients with the devastating disease DIPG.

DIPG-23. SINGLE CASE REPORT OF LOW DOSE RADIOTHERAPY AND CHEMOTHERAPY IN THE TREATMENT OF DIPG

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A 3 year-old girl, was noted to have progressive gait problem since Nov. 2017 and brought to hospital for checkup. Brain MRI on Jan. 2018 showed T2 hyperintensity infiltrative pontine lesion, favoring diffuse infiltrative pontine glioma and mild obstructive hydrocephalus, received VP-shunting on Jan. 15, 2018. Due to the refusal of surgical biopsy for tissue proof, we started the radiotherapy from Jan. 24, 2018, using Rapidarc technique with 6MV photon energy to treat the brain stem lesion, ended on Feb. 24, 2018 with total dose of 25.5Gy in 17 fractions as our usual practice. Following the completion of radiotherapy, we started the adjuvant chemotherapy using 1-week on, 1-week off regimen of temozolomide using dosage of 75 mg/sq-m/day, and this patient's general condition returned back to nearly normal. Serial follow-up images of brain MRI on 04/30/2018, 08/01/2018, 11/30/2018, 02/26/2019, 05/30/2019, 08/28/2019 showed slow progression of the pontine lesion, without the development of contrast enhanced new lesion. She maintained the functional independent until Sep. 2019, she was noted to have symptoms of ataxic gait, esotropia and choking on drinking liquid. We started the retreatment of radiotherapy from Oct.7, 2019, using same technique, ended on Nov. 5, 2019 with total dose of 30Gy in 20 fractions. The symptoms improved partially after the treatment, with residual weakness over left extremity. We are still treating the patient with adjuvant temozolomide, and she has survived most of time functionally independent in these 2 years.

DIPG-25. KETOGENIC DIET IN DIFFUSE INTRINSIC PONTINE GLIOMA IN CHILDREN: A RETROSPECTIVE STUDY INVESTIGATING THE FEASIBILITY

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PURPOSE: Diffuse Intrinsic Pontine Glioma (DIPG) is one of the most devastating diseases amongst children with cancer, thus novel strategies are urgently needed. We aimed to retrospectively evaluate the feasibility of the carbohydrate restricted ketogenic diet (KD) in DIPG patients. METHODS: Searches of MEDLINE and Embase identified four publications meeting the inclusion criteria (diagnosis of DIPG and exposition to a KD ≥ 3 months). One additional case was identified by contact with experts. The minimal feasibility criteria were defined as the ability to use the KD for ≥ 3 months. Individual patient data were extracted from the publications or obtained from investigators. RESULTS: Five patients (males, n=3; median age 4.4 years; range, 2.5–17 years) met the inclusion criteria (one

patient – identified and not included - was on KD < 3 months due to disease progression). Further feasibility analyses showed a duration of the KD of ≥ 3 months and less than 7 months (n=2), > 7 months and less than 1 year (n= 2), and two years (n=1), respectively. CONCLUSION: These results – based on a small patient population – suggest that the KD appears to be a feasible treatment option for children with DIPG. The potential duration of the KD is limited by the aggressive clinical behavior of DIPG. The safety analysis is currently being retrospectively assessed. These data should encourage further studies on a larger scale; ideally assessing the impact of the KD in DIPG patients in a randomized controlled trial.

DIPG-26. THERAPEUTIC EFFECTS OF RADIOTHERAPY WITH CONCOMITANT AND ADJUVANT TEMOZOLOMIDE VERSUS RADIOTHERAPY WITH CONCOMITANT TEMOZOLOMIDE ALONE IN CHILDREN WITH DIPG: A SINGLE-CENTER EXPERIENCE WITH 82 CASES

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OBJECTIVE: To retrospectively analyze the therapeutic effects of radiotherapy with concomitant and adjuvant temozolomide *versus* radiotherapy with concomitant temozolomide alone for pediatric diffuse intrinsic pontine glioma (DIPG), and to evaluate the value of temozolomide in the treatment of pediatric DIPG. METHODS: The clinical data of children with confirmed DIPG in Guangdong Sanjiu Brain Hospital between January 1, 2010 and December 30, 2019 were collected. The inclusive criteria included (1) receiving a total radiotherapy dose of 54 Gy in 27 fractions, (2) treated with concomitant temozolomide chemotherapy, and (3) with or without adjuvant temozolomide chemotherapy. RESULTS: A total of 82 pediatric patients were eligible for the study, with a median age of 7 years (range 2–16 years). The median follow-up was 8.6 months (range 2–28 months) and the median survival time was 9.4 months. The median survival time of 66 patients treated with radiotherapy with concomitant and adjuvant temozolomide was 9.8 months, longer than 7.5 months of the other 16 patients treated with radiotherapy with concomitant temozolomide alone, with statistical differences *(P*=0.010). Moreover, bevacizumab and nimotuzumab didn't bring survival benefits to patients with disease recurrence or progression. Hematological toxicity (Grade IV) was not found. CONCLUSION: Radiotherapy with concomitant and adjuvant temozolomide prolongs the survival time of children with DIPG.

DIPG-27. TARGETING FACILITATES CHROMATIN TRANSCRIPTION (FACT) AS A NOVEL STRATEGY FOR DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) THAT ENHANCES RESPONSE TO HISTONE DEACETYLASE (HDAC) INHIBITION

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Diffuse intrinsic pontine glioma (DIPG) is an aggressive and incurable childhood brain tumour for which new treatments are needed. A high throughput drug screen of 3500 pharmaceutical compounds identified anti-malarials, including quinacrine as having potent activity against DIPG neurospheres. CBL0137, a compound modelled on quinacrine, is an anti-cancer compound which targets Facilitates Chromatin Transcription (FACT), a chromatin remodelling complex involved in transcription, replication, and DNA repair. CBL0137 effectively crosses the blood-brain barrier and is currently in Phase I trials in adult cancer. CBL0137 induced apoptosis in DIPG neurospheres *in vitro* and had profound cytotoxic activity against a panel of DIPG cultures. In a DIPG orthotopic model, treatment with CBL0137 significantly improved survival. We found that treatment with CBL0137 up-regulated TP53 and increased histone H3.3 acetylation and tri-methylation in DIPG cells. We therefore examined the interaction between CBL0137 and the HDAC inhibitor, panobinostat. *In vitro* experiments showed that the two agents had profound synergistic activity against DIPG neurospheres in clonogenic assays and enhanced apoptosis. Transcriptomic analysis and immunoblotting indicated that combination treatment activated signalling pathways controlled by Retinoblastoma (RB)/E2F1 and subsequently increased phosphorylation and enzymatic activity of enhancer of zeste homolog 2 (EZH2). Consistent with the *in vitro* results, the combination of CBL0137 and panobinostat significantly prolonged the survival of two orthotopic models of DIPG, while histological analysis showed increased H3K27me3 and decreased Ki67 positive cells. Given these promising results, a paediatric trial of CBL0137 is planned to open through the Children's Oncology Group with an expansion cohort for DIPG patients.

DIPG-28. REPEATED LOW DOSE RT FOR PEDIATRIC DIPG – LESS DISEASE BURDEN WITH COMPARABLE OUTCOMES

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PURPOSE: Pediatric diffuse intrinsic pontine glioma (DIPG) is the most dismal prognosis pediatric brain tumor. Six weeks radiation therapy (RT) remains the mainstay of treatment. The aim of the current study was to compare the results of firstly reported repeated low dose RT (rLRT) with conventional RT (CRT). METHODS AND MATERIALS: This retrospective review included 24 children with DIPG, aged 3 -18 years, underwent CRT (52- 60.0 Gy in 1.8- 2.0 Gy, n = 16) or rLRT (18 - 30 Gy in 1.5–2.0 Gy per cycle for 1–3 cycles, n = 8). All children had typical symptoms and MRI features of DIPG, or biopsy-proven DIPG. RESULTS: The median overall survival (OS) was 12.6 months in rLRT group and 11.4 months in CRT group (p =0.347), progression-free survival (PFS) was 3.6 months in rLRT group and 6.5 months in CRT group (p = 0.821), no significant survival difference was observed between two groups. Temporary discontinuation or tapering of steroids rate was significantly higher in rLRT group (100% vs 60%, p = 0.028). Although not statistically significant, mean non-hospitalized days were longer in the rLRT group, 403 days versus 305 days in the CRT group, as were mean cumulative progression-free days, 276 days versus 163 days and 1-year free from CSF diversion rate was higher, 100% versus 64.9%. CONCLUSIONS: For patients with newly diagnosed DIPG, repeated low dose RT, given over 3 to 4 weeks per cycle for 1 to 3 cycles, offers comparable survival outcome with less disease burden compared with conventional RT.

DIPG-29. PHOSPHATIDYLINOSITOL-4,5-BISPHOSPHATE 3-KINASE (PI3K) INHIBITION DRIVES PROTEIN KINASE C ACTIVATION (PKC) IN DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

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Recurring somatic mutations and gene amplifications to members of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) signaling axis are overarching contributors to the aggressive growth and survival of diffuse intrinsic pontine gliomas (DIPG). However, targeting PI3K has thus far failed to improve outcomes for patients in the clinic. To identify the mechanisms underpinning PI3K/AKT/mTOR treatment failure in DIPG, we have employed high-resolution quantitative phosphoproteomic profiling in patient-derived DIPG cell lines harboring H3K27M and PI3K mutations, +/- the blood-brain barrier permeable PI3K inhibitor, paxalisib (previously "GDC-0084", currently in Phase I trials - NCT03696355) and rapamycin. Paxalisib was significantly more potent than rapamycin at inducing PI3K/AKT/mTOR inhibition, however, both simultaneously activated protein kinase C signaling (^{pT500}PKCβ +8.2 and +4.5 fold, respectively). PKC lies directly upstream of myristoylated alanine-rich C-kinase substrate (MARCKs), which was phosphorylated at Ser170 by +9.4 and +4.7 fold, respectively; promoting actin cytoskeletal remodeling and cellular migration. Indeed, activation of PKC signaling using phorbol 12-myristate 13-acetate (PMA), increased DIPG cell growth and migration by >3 fold. Targeting PKC using midostaurin (FDA-approved for acute myeloid leukemia), and enzastaurin (blood-brain barrier penetrant inhibitor of PKCβ), in combination with paxalisib was highly synergistic (CI=<0.9), reducing proliferation and driving apoptosis. Mechanistically, compensatory activation of PKC signaling following PI3K inhibition was regulated by the accumulation of Ca^{+2} ions, as chelation using

BAPTA-AM significantly reduced PKC activity following PI3K inhibition. These data highlight the power of phosphoproteomic profiling for the rational design of drug combination strategies, which need to be tested *in vivo* prior to clinical trials for DIPG.

DIPG-31. MOLECULAR MECHANISMS AND FUNCTIONAL IMPACT OF ABERRANT SPLICING IN DIFFUSE MIDLINE GLIOMAS

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Fewer than 1% of children diagnosed with diffuse-midline glioma (DMG) survive for more than 5 years, because no effective therapies exist for these patients. Here, we sought to identify and characterize mechanisms of aberrant splicing (AS) in primary DMG tumors. We observed transcriptome-wide AS (9,805 differential splicing variations in 4,734 genes), and identified a DMG-specific splicing signature, that included known cancer genes. We hypothesize that AS of cancer genes play a role in DMG tumor formation. Assessing whether splicing factor dysregulation impacted known cancer transcripts, we discovered several splicing factors, including *SRRM4*, *SRRM3* and *RBFOX3* to be down-regulated in DMG. Additionally, we found an enrichment of binding motifs for these proteins within flanking regions of these mis-spliced exons. We also observed recurrent significant exon inclusion in tumor suppressor *SMARCA4*, an integral member of the SWI/SNF family of proteins involved in chromatin remodeling. Further, we identified AS in 16 of the 27 members of the SWI/SNF complex, including increased skipping of exon 7 in *DPF2*, representing a complete mRNA transcript switch in DMG. Since *SRRM4, SRRM3 and RBFOX3* are known regulators for neural-specific microexons, we focused on microexon splicing changes, hypothesizing that these regulators may be driving microexon mis-splicing in these tumors. We identified 245 known microexons lost or gained in DMG. Moreover, a quarter of which were observed in known cancer genes, with the most frequent splice event causing gain of a clathrin-binding site in the tumor suppressor *BIN1* with a concurrent loss of an out-of-frame microexon in the oncogene *BAK1,* presumably activating it. Altogether, our results suggest that aberrant splicing may be an alternative mechanism driving DMG tumorigenesis and we are currently molecularly validating a subset of these events with the overall goal of identifying novel therapeutic targets for DMG tumors.

DIPG-32. AKT SIGNALING DRIVES RESISTANCE TO ONC201 IN DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

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Diffuse intrinsic pontine glioma (DIPG) is a highly aggressive, childhood brainstem cancer with a median overall survival of 10 months post diagnosis. Remarkably, 80–90% of patients harbor recurring point mutation in histone H3, which induces a lysine for methionine substitution at amino acid 27 (H3K27M) in either H3.1 (*HIST1H3B* ~25%) or H3.3 (*H3F3A* ~65%) variants. Using the blood-brain barrier (BBB) permeable DRD2 antagonist, ONC201 (in clinical trials for DIPG and H3K27M-mutant gliomas – NCT03416530), we hypothesized that DRD2 antagonism would induce TRAIL expression via indirect inhibition of AKT and ERK signaling, to drive apoptosis in both H3.1K27M and H3.3K27M patient-derived DIPG cell lines alike. For the first time, we reveal that ONC201 shows efficacy in 100% of WT-H3 and H3.1K27M mutant DIPG cell lines (n=5), compared to 50% of H3.3K27M mutant DIPGs (n=6). Investigations to identify the mechanisms of resistance to ONC201, revealed that cell lines with decreased sensitivity upregulated the PI3K/AKT/MTOR signaling axis to drive phosphorylation of AKT and increase metabolic activity. Combined administration of ONC201 and the BBB-permeable PI3K/AKT inhibitor, paxalisib (previously GDC-0084, in clinical trials for newly diagnosed DIPG – NCT03696355), showed synergistic cytotoxicity, reduced PI3K/AKT signaling and metabolic reprogramming to drive apoptosis in all DIPG cell lines tested. This combination was used to treat a 3-year-old DIPG patient, commencing 14 weeks post disease progression, completing 40 weeks of therapy prior to her passing, December 2019. These studies highlight the potential of combined administration of two safe, BBB penetrant, oral targeted therapies and supports testing under clinical trial conditions.

DIPG-33. CHARACTERIZING THE NEURO-VASCULAR UNIT IN DIFFUSE INTRINSIC PONTINE GLIOMA

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Diffuse intrinsic pontine glioma (DIPG) is a childhood brainstem tumor with a median overall survival of eleven months. Lack of chemotherapy efficacy may be related to an intact blood-brain-barrier (BBB). In this study we aim to compare the neuro-vascular unit (NVU) of DIPG to healthy pons tissue. End-stage DIPG autopsy samples (n=5) and age-matched healthy pons samples (n=22), obtained from the NIH NeuroBioBank, were immunohistochemically stained for tight-junction proteins claudin-5 and zonula occludens-1 (ZO-1), basement membrane component laminin, and pericyte marker PDGFRβ. Claudin-5 stains were also used to determine vascular density and diameters. In DIPG, expression of claudin-5 and ZO-1 was reduced, and claudin-5 was dislocated to the abluminal side of endothelial cells. Laminin expression at the glia limitans was reduced in both pre-existent vessels and neovascular proliferation. In contrast to healthy pons, no PDGFRβ expression was detected. The number of blood vessels in DIPG was significantly reduced compared to healthy pons, 13.9±11.8/mm^2 versus 26.3±14.2/mm^2, respectively (P<0.01). Especially the number of smaller blood vessels (<10μm) was significantly lower (P<0.01). Distribution of larger blood vessels (≥10μm) did not differ between groups (P=0.223). Mean vascular diameter was 9.3±9.9μm for DIPG versus 7.7±9.0μm in healthy pons (P=0.016). Our study demonstrates evidence of structural changes in the NVU in end-stage DIPG. Chemotherapeutic inefficacy could be the result of reduced vascular density. However, further research is needed to determine meaning and extent of these changes and to determine whether these observations are caused by the tumor or the result of treatment.

DIPG-34. SUPER ELONGATION COMPLEX AS A TARGETABLE DEPENDENCY IN H3K27M+ DIFFUSE MIDLINE GLIOMA

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Mutations in the histone 3 gene (H3K27M) are the eponymous driver in diffuse intrinsic pontine gliomas (DIPGs) and other diffuse midline gliomas (DMGs), aggressive pediatric brain tumors for which no curative therapy currently exists. To identify specific epigenetic dependencies within the context of the H3K27M mutation, we performed an shRNA screen targeting 408 genes classified as epigenetic/chromatin-associated molecules in patient-derived DMG cultures. This identified AFF4, a component of the super elongation complex (SEC), as necessary for DMG cells to maintain growth and self-renewal. We hypothesized that aberrant SEC expression occurs as a consequence of the H3K27M mutation and that this dysregulated SEC signaling overcomes repressive transcriptional regulation in order to suppresses differentiation and promote self-renewal of DMG tumor stem cells. We interrogated the role of AFF4 in DMG using an shRNA lentiviral approach. We demonstrate a significant decrease in *in vitro* clonogenicity and stem cell maintenance following AFF4 depletion. We employed RNA-seq-based gene set enrichment analysis to delineate differentiation programs under SEC regulatory control. Finally, we sought to determine whether CDK9, the catalytic subunit of the SEC, represents a therapeutic vulnerability in DMG. Using RNA polymerase II ChIP-seq, we demonstrate that CDK9 pharmacologic inhibition restores regulatory Pol II pausing, promotes cellular differentiation, and leads to potent anti-tumor effect both in vitro and in patient-derived xenograft models. These studies present a biologic rationale for the translational exploration of CDK9 inhibition as a promising therapeutic approach.

DIPG-35. BIOLOGICAL MEDICINE FOR DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) ERADICATION: RESULTS OF THE THREE ARM BIOMARKER-DRIVEN RANDOMIZED BIOMEDE 1.0 TRIAL

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Despite 50 years of clinical trials, no improvement of survival has been observed in DIPG and most children die within 2 years of diagnosis. Only radiotherapy transiently controls disease progression. The study was conceived as a randomized multi-arm multi-stage program. It started with an open-label phase-II trial comparing three drugs (everolimus, dasatinib, erlotinib) combined with irradiation, allocated according to the presence of their specific targets (PTEN-loss, EGFR-overexpression) defined with a stereotactic biopsy after central confirmation of the diagnosis (presence of histone H3K27M mutation or loss of K27 trimethylation). Targeted therapies were started concomitantly with radiotherapy and were continued until disease progression. No biopsy-related death was reported and diagnostic yield was excellent, with only 5 non-informative biopsies. Biopsy excluded the diagnosisof DIPG in 8% of the cases. At the 3rd interim analysis, based on 193 randomized patients, the IDMC concluded that the study was unlikely to show a difference of OS between the 3 drugs even if 250 patients would be randomized. The median OS from the time of diagnosis was 11.9, 10.5 and 10 months for everolimus, dasatinib and erlotinib. Treatment was discontinued due to toxicity in 2%, 13%, and 15%, respectively. BIOMEDE shows the feasibility of biologically-driven treatment in DIPG on a large international scale. Based on the better toxicity profile and the slightly better efficacy, although not statistically significant, the steering committee proposed that everolimus should be used as the control arm for the next BIOMEDE 2.0 trial.

DIPG-37. PREDICTING OUTCOME IN CHILDHOOD DIFFUSE MIDLINE GLIOMAS USING MAGNETIC RESONANCE IMAGING BASED TEXTURE ANALYSIS

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BACKGROUND: Diffuse midline gliomas (DMG) are aggressive brain tumours with 10% overall survival (OS) at 18 months. Predicting OS will help refine treatment strategy in this patient group. MRI based texture analysis (MRTA) is a novel technique that provides objective information about spatial arrangement of MRI signal intensity and has potential as an imaging biomarker. OBJECTIVES: To investigate MRTA in predicting OS in childhood DMG. METHODS: Retrospective study of patients diagnosed with DMG, based on radiological features, treated at our institution 2007–2017. MRIs were accomplished at diagnosis and 6 weeks after radiotherapy (54Gy in 30 fractions). MRTA, performed using TexRAD software, on T2W sequence and Apparent Diffusion Coefficient (ADC) maps encapsulated tumour in the largest single axial plane. MRTA comprised filtration-histogram technique using statistical and histogram metrics for quantification of texture. Kaplan-Meier analysis determined association of MRI texture parameters with OS. RESULTS: 32 children 2–14 years (median 7 years) were included. MRTA was undertaken on T2W (n=32) and ADC (n=22). MRTA on T2W was better at prognosticating than on ADC maps. Children with homogenous tumour texture, at medium scale on baseline T2W MRI, had worse prognosis (mean p=0.0098, SD p=0.0115, entropy p=0.0422, mean of positive pixels (MPP) p=0.0051, kurtosis p=0.0374). MPP was the most significant texture parameter. Median survival in this group as identified by MRTA (medium texture, MPP) was 7.5 months versus 17.5 months. CONCLUSIONS: DMG with more homogeneous texture on diagnostic MRI is associated with worse prognosis. MPP texture parameter is the most predictive of OS in childhood DMG.

DIPG-38. ADDITION OF MULTIMODAL IMMUNOTHERAPY TO COMBINATION TREATMENT STRATEGIES FOR CHILDREN WITH DIPG: FINAL RESULTS OF A COHORT OF CHILDREN

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The prognosis of children with Diffuse Intrinsic Pontine Glioma (DIPG) remains dismal in spite of radio- and chemotherapy or therapies based on molecular biology diagnostics. Immunotherapy is a powerful and promising approach for improving the overall survival (OS). A retrospective analysis for feasibility, immune responsiveness and OS was performed on 41 children treated in compassionate use with Newcastle Disease Virus, hyperthermia and autologous dendritic cell vaccines as part of an individualized combined treatment approach for DIPG patients at diagnosis (n=28), or at time of progression (n=13). All except one patient had reduced values of at least one immune test before starting immunotherapy. In all patients at least one PanTum Detect test was outside the normal range. Ten patients had PDL1 mRNA expression in circulating tumor cells at diagnosis. Multimodal immunotherapy was feasible as scheduled, until progression, in all patients without major toxicity. When immunotherapy was part of primary treatment, median PFS and OS were 8.4m and 14.4m respectively with a 2-year OS of 10.7%. When immunotherapy was given at the time of progression, median PFS and OS calculated from diagnosis were 6.5m and 9.1m respectively. Th1 shift and rise in PanTum Detect test scores were linked with longer OS. Multimodal immunotherapy is feasible without major toxicity, and its value as part of a combination treatment for primary diagnosed DIPG should be elaborated in clinical trials.

DIPG-39. NOVEL PROTEOMIC ANALYSIS REVEALS EPIGENETIC THERAPEUTIC TARGETS IN PEDIATRIC GLIOMA

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INTRODUCTION: Diffuse midline glioma is a highly morbid pediatric cancer. Up to 80% harbor Histone H3K27M mutation, which alters Histone H3 post-translational modifications (PTMs) and genomic enrichment patterns, affecting chromatin structure and transcription. We previously identified tumorigenic patterns of H3K27Ac/bromodomain co-enrichment and pre-clinical efficacy of bromodomain inhibition (JQ1) in DMG. Here, we employ a novel proteomics approach developed at our institution to further elucidate the impact of H3K27M mutation on glioma epigenetic signatures and treatment response. METHODS: Epiproteomic analysis was performed on pediatric glioma cells (H3K27 WT n=2, H3K27M n=2) to characterize 95 distinct Histone H3 N-terminal tail modification states. Cells were treated with JQ1 or DMSO, and collected at 0h, 24h, 48h, Histones extracted from isolated nuclei and immunopurified, then analyzed by LC-MS/MS. Results were integrated with RNA-Seq and ChIP Seq (H3.3K27M, H3.3, H3K27Ac, H3K27me3, H3K4me1, H3K4me3) from the same cell lines. Pediatric glioma tissues (H3K27M WT n=3, H3K27M n= 9) were similarly analyzed to validate cell line results. RESULTS: Cell PTM profiles cluster by H3 mutation status on unsupervised analysis. Significant differential PTM abundance and genomic enrichment H3K27M, H3.3 WT, H3K27Me3 and H3K27Ac was observed between mutant and wild type cell lines with epigenetic-targeted therapy, correlating with cell transcriptomes. CONCLUSIONS: Histone H3 tail analysis reveals the effects of H3K27M mutation and bromodomain inhibition on the tumor epigenetic landscape, providing insight into mechanisms of tumorigenesis and therapy response. Further investigation of the utility of these signatures as biomarkers for diagnosis and monitoring treatment response are therefore underway.

DIPG-40. TARGETING MASTER REGULATOR DEPENDENCIES IN DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

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Diffuse intrinsic pontine glioma (DIPG) remains a fatal disease with no effective drugs to date. Mutation-based precision oncology approaches are limited by lack of targetable mutations and genetic heterogeneity. We leveraged systems biology methodologies to discover common targetable disease drivers—master regulator proteins (MRs)—in DIPG to expand treatment options. Using the metaVIPER algorithm, we interrogated an integrated low grade glioma and GBM gene regulatory network with 31 DIPG-gene expression signatures to identify tumor-specific MRs by differential expression of their transcriptional targets. Unsupervised clustering identified MR signatures of upregulated activity in RRM2/TOP2A in 13 patients, CD3D in 5 patients, and MMP7, TACSTD2, RAC2 and SLC15A1/SLC34A2 in individual patients, all of which can be targeted. Notably, intratumoral administration of etoposide by convection enhanced delivery was effective in murine proneural gliomas in which TOP2 was identified as a MR while RRM2—targetable by drugs such as cladribine—has been shown to be a positive regulator of glioma progression whose knock-down inhibits tumor growth. We also prioritized drugs by their ability to reverse MR-activity signatures using a large drug-perturbation database. Patients clustered by

predicted drug sensitivities with distinct groups of tumors predicted to respond to proteasome inhibitors, Thiotepa or Volasertib all of which have early evidence in treating gliomas. We will refine this analysis in a multi-institutional study of >100 patient gene expression profiles to define MR signatures driving known biological/molecular disease subtypes, use DIPG cell lines recapitulating common MR architectures to optimize therapy prioritization, and validate our findings *in vivo*.

DIPG-41. DISSECTING THE MECHANISTIC BASIS FOR *ACVR1* AND *PIK3CA* MUTATION CO-OCCURRENCE IN DIFFUSE MIDLINE GLIOMAS USING GENETICALLY ENGINEERED MOUSE MODELS

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Diffuse midline gliomas (DMGs) are aggressive childhood brain tumors with a dismal prognosis. Most of these tumors carry K27M mutations in histone H3-encoding genes, particularly *H3F3A* and *HIST1H3B*. In addition, activating mutations in *ACVR1* and *PIK3CA* co-occur in a subset of DMGs. To understand how these lesions drive the development of DMGs, we generated genetically engineered mouse models in which *Acvr1G328V*, *Hist1h3bK27M*, and *Pik3caH1047R* are targeted to the OLIG2-expressing cell lineage. Animals carrying *Acvr1G328V* and *Pik3caH1047R*, with ("AHPO") or without ("APO") *Hist1h3bK27M*, developed high-grade diffuse gliomas involving midline and forebrain regions. Neither *Acvr1G328V* nor *Pik3caH1047R* drove tumorigenesis by themselves, but *Acvr1G328V* was sufficient to cause oligodendroglial differentiation arrest, pointing to a role in the earliest stages of gliomas formation. Transcriptomic analyses of AHPO and APO tumors indicated a predominantly proneural and oligodendrocyte precursor-like gene expression signature, consistent with the corresponding human pathology. Genes encoding transcription factors (TFs) with dual roles in controlling glial and neuronal differentiation were upregulated in tumors. Some of these genes were mildly induced by *Acvr1G328V* alone. Functional experiments using CRISPR/Cas9-mediated gene editing in patient-derived cell lines confirmed a role for some of these TFs in controlling DMG cell fitness. Overall, our results suggest that *Pik3caH1047R* consolidates *Acvr1G328V*-induced glial differentiation arrest to drive DMG development and progression.

DIPG-42. TOWARD MULTIMODALITY THERAPY FOR DIPG/DMG: DEVELOPMENT AND INVESTIGATION OF CRANIOSPINAL IRRADIATION AND CONVECTION-ENHANCED DELIVERY PDX MODELS

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BACKGROUND: Diffuse intrinsic pontine glioma (DIPG) and diffuse midline glioma (DMG) are metastatic diseases, as demonstrated by early convection-enhanced delivery (CED) clinical trials in which prolonged local tumor control can sometimes be achieved, but fatal disseminated disease then develops. We hypothesize that improvements in treatment of both focal disease and the entire neuraxis are necessary for long-term survival, and patient-derived xenograft (PDX) models can help advance these efforts. METHODS: We used a BT245 murine orthotopic DIPG PDX model for this work. We developed a protocol and specialized platform to deliver craniospinal irradiation (CSI) with a pontine boost. We separately compared intratumoral drug concentration by CED and intraperitoneal delivery. In our CED model, mice receive gemcitabine 60 ug x1 in 15 ul at 0.5 ul/minute through a stepped catheter design with silica tubing extending 2mm beyond a 27G needle. RESULTS: Mice receiving CSI (4 Gy x2d) plus boost (4 Gy x2d) showed minimal spinal and brain leptomeningeal metastatic disease by bioluminescence, MRI, and pathology compared to mice receiving radiation to the pons only (4 Gy x4d) or no radiation. CED achieved an intratumoral gemcitabine concentration 50-fold greater than intraperitoneal dosing when controlled for dose. CONCLUSIONS: In a DIPG PDX model, CSI+boost minimizes tumor dissemination compared to focal radiation, and CED achieves clinically significant improvements in intratumoral chemotherapy concentration compared to systemic delivery. Adding these modalities to current treatment could improve both focal and metastatic tumor control, leading to meaningful improvements in survival.

DIPG-43. CAN WE REPROGRAM DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)? EXPLORING THE ROLE OF DISTALLESS/DLX HOMEOBOX GENE REGULATION OF OLIGODENDROGLIAL PROGENITOR CELLS (OPC) IN THE DEVELOPING VERTEBRATE NERVOUS SYSTEM

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BACKGROUND: The identification of H3.3/H3.1K27M in most DIPG has changed our understanding of this disease. H3K27M mutations usually demonstrate global loss of H3K27 trimethylation (me^3) with gain of H3K27 acetylation (ac). Single cell RNAseq has identified the putative cell of origin as oligodendroglial progenitor cells (OPC). The *distalless* gene family is necessary for the differentiation and tangential migration of committed neural progenitors to become GABAergic interneurons. *Dlx1/Dlx2* double knockout (DKO) cells from the ganglionic eminences (GE) transplanted into a wild-type environment become oligodendrocytes. RESULTS: We identified DLX2 occupancy of early (*Olig2, Nkx2.2*) and late (*Myt1, Plp1*) genes required for OPC differentiation *in vivo* and confirmed direct DLX2 protein-promoter DNA binding *in vitro*. Co-expression of *Dlx2* with target sequences reduced reporter gene expression *in vitro*. There was increased expression of OLIG2, NKX2.2 and PLP-1 expression *in vivo*, consistent with de-repression in the absence of *Dlx1/Dlx2* function. Transient overexpression of a *Dlx2*-GFP construct into murine DIPG cells from a GEMM that develops DIPG resulted in significant increases in expression of *Gad* isoforms with concomitant decreases in *Olig2* and *Nkx2.2*. *Dlx2*-transfected mDIPG cells also demonstrated reduced migration, invasion and colony formation *in vitro*. Of significance, there was global restoration of $H3K27me^3$ with corresponding loss of H3K27ac expression in transfected cells compared to controls. CONCLUSIONS: DLX2 promotes GABAergic differentiation and migration while concomitantly repressing OPC differentiation *in vivo*. Developmental reprogramming of mDIPG cells by DLX2 demonstrates the potential role for directed differentiation strategies towards improving patient outcomes for this devastating pediatric cancer.

DIPG-44. A GAIN OF FUNCTION EZH2 MUTATION DELAYS DIFFUSE INTRINSIC PONTINE GLIOMA PROGRESSION

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BACKGROUND: Diffuse Intrinsic Pontine Glioma (DIPG) remains an incurable pediatric brain cancer. The oncohistone H3K27M implicated in 80% of the cases, is also predicted to target Enhancer of Zeste Homolog 2 (Ezh2), the catalytic component of the Polycomb Repressor Complex 2 (PRC2). There are no reported mutations of Ezh2 and its function in DIPG is not fully determined. This work aims to address the role of Ezh2 in DIPG. METHODS: Brainstem tumors were established by intracranial injections of *Nestin*;Tv-a; $Ezh2^{Y641F/+}$ (NTv-a; $Ezh2^{Y641F/+}$) neonatal pups using Replication Competent Avian Sarcoma leucosis virus long terminal repeat with splice acceptor (RCAS) viruses, expressing PDGF-B, p53 shRNA, and RCAS-CRE/Y. Immunohistochemical staining for Ki-67 and H3K27me3 were performed on the Discovery ULTRA (Ventana). RESULTS: Ezh2 overexpression ($Ezh2^{Y641F/+}$, RCAS CRE) conferred a survival advantage of approximately 10 days (n=20 mice/group, $p<0.001$). H3K27me3 levels were significantly upregulated in RCAS CRE group (50% vs 20% in RCAS Y, n=4 tumors/group, $p<0.03$), with a concomitant lower Ki-67 staining (30% vs. 55% in RCAS Y, n=3 tumors/group, $p<0.05$). Interestingly, pathological review categorized more RCAS-CRE tumors as 'atypical'. RNA-sequencing of virus-infected neural precursor cells revealed a suppression of inflammatory/interferon gene signature in the Ezh2 overexpression group. CONCLUSIONS AND FUTURE DIRECTIONS: Enhanced Ezh2 activity appears to delay DIPG pathogenesis. Ongoing work aims to highlight the contribution of differentially expressed gene signatures that contribute to this phenotype.

DIPG-46. NON-DIPG PATIENTS ENROLLED IN THE INTERNATIONAL DIPG REGISTRY: HISTOPATHOLOGIC EVALUATION OF CENTRAL NEURO-IMAGING REVIEW

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INTRODUCTION: The role of diagnostic biopsy in diffuse intrinsic pontine glioma (DIPG) remains in question. Distinguishing radiographically between DIPG and other pontine tumors with more favorable prognosis and different therapy is critically important. METHODS: Cases submitted to the International DIPG registry with histopathologic data were analyzed. Central imaging review was performed by two neuro-radiologists; all cases with imaging features or histopathology suggestive of alternative diagnoses were re-reviewed. Imaging features suggestive of alternative diagnoses included non-pontine origin, <50% pontine involvement (without typical DIPG pattern on follow-up), focally exophytic morphology, sharply-defined margins, or marked diffusion restriction throughout. RESULTS: Among 297 patients with pathology from biopsy and/or autopsy available, 27 (9%) had histologic diagnoses not consistent with DIPG, commonly embryonal tumors (n=9) and pilocytic astrocytomas (n=11). 163 patients had diagnostic MRI available for central neuroimaging review. Among 81 patients classified as characteristic of DIPG, 80 (99%) had histopathology consistent with DIPG (diffuse midline glioma, H3K27M-mutant, glioblastoma, anaplastic astrocytoma, diffuse astrocytoma). Among 63 patients classified as likely DIPG, but with unusual imaging features, 59 (94%) had histopathology consistent with DIPG. 19 patients had imaging features suggestive of another diagnosis, including 13 with non-pontine tumor origin; the remaining 6 all had histopathology not consistent with DIPG. Association between central imaging review and histopathology was significant (p<0.001). CONCLUSIONS: The important role and accuracy of central neuroimaging review in diagnosing or excluding DIPG is demonstrated. In patients with pontine tumors for which DIPG is felt unlikely radiographically, biopsy may be considered to guide diagnosis and treatment.

DIPG-47. HISTONE MUTATIONS ENHANCE RAS MEDIATED ERK5 GROWTH SIGNALING IN DIFFUSE MIDLINE GLIOMAS

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Diffuse midline gliomas (DMGs) are incurable brain tumors with an aggressive onset. Apart from irradiation, there are currently no effective therapies available for patients with DMG, who have a median survival time of less than one year. Most DMG cells harbor mutations in genes encoding histone H3 (H3K27M) proteins, resulting in a global reduction of H3K27 trimethylation and activation of oncogenic signaling pathways. Here we show that the H3K27M mutations contribute to RAS pathway signaling, which is augmented by additional RAS activators including PDGFRA. H3K27M mutation led to increased expression of receptor tyrosine kinases (RTK). A RAS pathway functional screen identified ERK5, but not ERK1/2, as a RAS pathway effector important for DMG growth. Suppression of ERK5 decreased DMG cell proliferation and induced apoptosis *in vitro* and *in vivo*. In addition, depletion or inhibition of ERK5 significantly increased survival of mice intracranially engrafted with DMG cells. Mechanistically, ERK5 directly stabilized the proto-oncogene MYC at the protein level. Additionally, persistent ERK5 depletion does not result in complete growth inhibition and therefore we set out to determine potential adaptation or resistance mechanisms in response to ERK5 loss. Using RNA-sequencing and Immunoprecipitation (IP) mass spectrometry (IP-MS), we have identified several positive and negative feedbacks involved in ERK5 that are also targetable. These findings identify the H3K27M mutation as an enhancer of RAS activation in DMG with ERK5 and ERK5 regulated networks immediately actionable pathways.

DIPG-49. BRAINSTEM AND PONTINE VOLUMETRIC ANALYSIS AS A SURROGATE MEASURE OF LOCAL DISEASE CONTROL IN CHILDREN WITH DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

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INTRODUCTION: Response-assessment in pediatric neuro-oncology (RAPNO) criteria designed to describe treatment outcomes are poorly implemented in diffuse intrinsic pontine glioma (DIPG), due to inter-observer variability in measurement of tumor volume, lack of tumor enhancement, and undefined relationships between radiographic parameters and survival. Given these issues, this study assessed whether anatomically defined brainstem and pontine volumes can serve as surrogate measures of local disease burden and response to therapy in DIPG. METHODS: Thirty-two consecutive patients with newly diagnosed DIPG were treated with standard definitive radiation therapy (RT) between 2010 and 2016 at a single institution. MRI brain scans throughout treatment course were analyzed using iPlan® Flow software (Brainlab AG, Munich, Germany). Semi-automated 3D measurements of the brainstem and pons were calculated using a built-in knowledge-based segmentation approach and manually adjusted. RESULTS: Mean age at diagnosis was 6.5+/-0.5 years (range 2–12 years). Median follow up time was 317 days. Average brainstem volume at diagnosis (Vdiag) was 52.7+/-2.1mL with subsequent decrease at first post-RT MRI to 41.4+/-2.0mL ($p < 0.0001$). By time of last follow up, brainstem volume increased to 51.9+/-3.3, no longer significantly different as compared to Vdiag ($p=0.61$). The same relationships were found for pontine volume. CONCLUSIONS: Volumetric changes in the brainstem and pons occur in response to treatment and correlate with local disease burden and response to therapy. This surrogate may be a useful standardized measure in ongoing and future trials involving localized delivery of therapeutics in DIPG that require evaluation of local-regional disease control in addition to survival.

DIPG-50. A NOVEL ORTHOTOPIC PATIENT-DERIVED XENOGRAFT MODEL OF RADIATION-INDUCED GLIOMA

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Diffuse midline glioma (DMG) can arise as a primary tumour but also as a consequence of radiation therapy (RT) in survivors of other paediatric brain tumours. Radiation-associated gliomas are molecularly distinct from primary gliomas and have poorer overall survival. We report a case of radiation-associated DMG following treatment for medulloblastoma, and the development of a matched patient-derived xenograft (PDX) model. A four-year-old boy diagnosed with medulloblastoma was treated with surgical resection, RT and chemotherapy (COG:CCG-99701-Arm B). Eleven years post-diagnosis, the patient relapsed with radiation-associated DMG, participated in a Phase I clinical trial (COG:ACNS0927), and passed away eight months later. Tumour tissue collected at autopsy was intracranially implanted into immunodeficient mice and serially transplanted *in vivo*. Immunohistochemistry demonstrated both the primary DMG and PDXs expressed PDGFR-alpha and PTEN, were H3K27me3-positive, and had undetectable levels of p53. Sequencing revealed an activating mutation in PI3-kinase (H1047L) and variants of unknown significance in *GRK4*, *FLG*, *BAZ2A*, and *CRTC3*. DNA methylation array of the PDX demonstrated 1p loss, which is not typically associated with primary DMG, and broad deletion within 9p including *CDKN2A/B*, *MTAP* and multiple interferon genes. The methylation profile did not significantly classify with other tumours in the Molecular Neuropathology database (molecularneuropathology.org/mnp). We describe the first reported PDX model of radiation-associated DMG following medulloblastoma, which recapitulates the patient disease and is molecularly distinct from primary DMG. Interrogation of this model through RNA and whole genome sequencing presents a valuable opportunity to better understand and identify novel therapeutic vulnerabilities against this currently incurable disease.

DIPG-51. ACVR1 MUTATIONS PROMOTE TUMOR GROWTH IN MODELS OF DIFFUSE INTRINSIC PONTINE GLIOMA

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Mutations in the gene encoding activin A receptor type 1 (*ACVR1*) are found in approximately 25% of diffuse intrinsic pontine gliomas

(DIPGs), a pediatric glioma with 2-year survival rate of less than 10%. *ACVR1*mutations frequently coincide with activating *PIK3CA* or *PIK3R1* mutations, indicating a potential cooperative effect of BMP and PI3K signaling in gliomagenesis. We used genetically engineered mice with inducible knock-in of *Acvr1*^{R206H} or *Pik3ca*^{E545K} alleles, such that cre-mediated recombination resulted in expression of the gain of function mutated genes from their endogenous promoters at physiological levels. Cre-mediated deletion in *GFAP-CreER;Pik3caE545K/+;p53cKO* mice (*Pik3ca;p53*) mediated *Trp53* deletion and expression of *Pik3caE545K* in glial progenitors, and spontaneously induced high-grade glioma (HGG) in mice with complete penetrance. Heterozygous knock-in of the *Acvr1R206H* allele accelerated tumorigenesis and impaired survival in *Pik3ca;p53* mice (*Acvr1;Pik3ca;p53*). Transcriptomic analysis of *Acvr1;Pik3ca;p53* tumors compared to *Pik3ca;p53* littermate controls, as in patient-derived tumors, revealed broad molecular signatures associated with cell fate commitment and chromosome maintenance. Pharmacologic inhibition of ACVR1 was sufficient to impair growth in human patient-derived DIPG cell lines. Together, our studies show that ACVR1 activation promotes tumor growth in spontaneous mouse HGG and patient-derived DIPG cells, suggesting that ACVR1 inhibition may produce a clinically significant therapeutic effect in DIPG.

DIPG-52. PHASE I CLINICAL TRIAL OF ONC201 IN PEDIATRIC H3 K27M-MUTANT GLIOMA OR NEWLY DIAGNOSED DIPG

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H3 K27M-mutant gliomas often manifest as midline gliomas, have a dismal prognosis, and have no effective treatments. ONC201 efficacy has been shown in high-grade glioma preclinical models and durable responses with single agent ONC201 have been reported in adults with recurrent H3 K27M-mutant gliomas. These observations led to a Phase I pediatric clinical trial of ONC201 dosed by body weight. This multicenter, open-label, 3 + 3 dose-escalation and dose-expansion clinical trial (NCT03416530) for H3 K27M-mutant glioma or non-biopsied DIPG has 6 arms: arms A and E determine the RP2D in pediatric post-radiation (recurrent or not-recurrent) H3 K27M-mutant glioma patients with ONC201 administered as an oral capsule as well as a liquid formulation, respectively. Both arms have completed accrual. The study is currently enrolling newly diagnosed DIPG patients to determine the RP2D for ONC201 in combination with radiation (arm B). Dedicated assessment of intratumoral ONC201 concentrations in midline gliomas patients (arm C) and the effects of ONC201 in H3K27M DNA levels in circulating CSF (arm D) are currently enrolling patients. ONC201 as a single agent in patients with progressive H3K27M mutant tumors following irradiation (excluding DIPG/spinal cord tumors) was recently opened (arm F). Once the RP2D is confirmed, there is a dose-expansion cohort to confirm the safety, radiographic efficacy and survival with ONC201. The primary endpoints of arms A, B, and E have been established with the RP2D of 625mg scaled by body weight as a capsule or liquid formulation administered alone or in combination with radiation without incidence of dose-limiting toxicity.

DIPG-53. CHARACTERIZING THE ROLE OF PPM1D MUTATIONS IN THE PATHOGENESIS OF DIFFUSE INTRINSIC PONTINE GLIOMAS (DIPGS)

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INTRODUCTION: We have previously found that up to 15% of all DIPGs harbor mutations in *PPM1D*, resulting in the expression of an activated and truncated *PPM1D (PPM1Dtr)*. Here we evaluate the mechanisms through which *PPM1Dtr* enhances glioma formation and identify its associated therapeutic vulnerabilities. METHODS: We have developed multiple in vitro and in vivo models of *PPM1D*-mutant DIPGs and applied quantitative proteomic and functional genomic approaches to identify pathways altered by *PPM1Dtr* and associated dependencies. RESULTS: *PPM1D* mutations are clonal events that are anti-correlated to *TP53* mutations. We find ectopic expression of *PPM1Dtr* to be sufficient to enhance glioma formation and to be necessary in *PPM1D*-mutant DIPG cells. In addition, endogenous truncation of *PPM1D* is sufficient to enhance glioma formation in the presence of mutant *H3F3A* and *PDGFRA*. *PPM1Dtr* overexpression attenuates g-H2AX formation and suppresses apoptosis and cell-cycle arrest in response to radiation treatment. Deep scale phosphoproteomics analyses reveal DNA-damage and cell cycle pathways to be most significantly associated with *PPM1Dtr*. Furthermore, preliminary analysis of genome-wide loss-of-function CRISPR/Cas9 screens in isogenic GFP and *PPM1Dtr* overexpressing mouse neural stem cells reveal differential dependency on DNA-damage response genes in the *PPM1Dtr* overexpressing cells. Consistent with *PPM1D*'s role in stabilizing *MDM2*, *PPM1D*-mutant DIPG models are sensitive to a panel of *MDM2* inhibitors (Nutlin-3a, RG7388, and AMG232). CONCLUSION: Our study shows that *PPM1Dtr* is both an oncogene and a dependency in *PPM1D*- mutant DIPG, and there are novel therapeutic vulnerabilities associated with PPM1D that may be exploited.

DIPG-54. A NON-INVASIVE PROGNOSTIC CIRCULATING MIRNAS SIGNATURE IN DIFFUSE INTRINSIC PONTINE GLIOMAS

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Diffuse intrinsic pontine gliomas (DIPG) are the most common brainstem tumors of childhood and represent one of the most challenging paediatric tumours to treat. A non-randomized, open label phase II pilot study was conducted at Fondazione IRCCS Istituto Nazionale Tumori (Milan) to assess the efficacy in terms of objective response rate according to the RECIST criteria of combining nimotuzumab and vinorelbine with radiation in newly-diagnosed DIPG. Serum specimens were collected at baseline. microRNA expression profiling was performed using Agilent platform and Human miRNA SureSelect 8x60K containing 2006 miRNAs annotated on miRBase19.0. Primary data analysis yielded a matrix containing 330 detectable miRNA. Association with PFS allowed us to disclose a signature of 10 miRNAs able to stratify high and low risk patients (HR=4.33, 95%CI 1.49–12.54; p=4.27E-05). To test the 10 ct-miRNA model performance, we collected an independent cohort of the same sample size (n=24) and we derived the index values and risk stratification. The distribution of index values covers a range similar to the discovery cohort. Imposing the signature threshold patients were divided in high/low risk and Kaplan-Meier curves confirmed the different PFS time for the two groups with HR=3.5 (95%CI: 1.8–8.01, p-value=0.0002) for the high-risk patients, reaching AUC=0.833. Our signature is a biomarker based on non-invasive procedures for prognosis able to enter into clinical practice. Further validation on multicenter case series is warranted.

DIPG-55. PATTERNS OF CEREBROSPINAL FLUID DIVERSION AND SURVIVAL IN CHILDREN WITH DIFFUSE INTRINSIC PONTINE GLIOMA: A REPORT FROM THE INTERNATIONAL DIPG REGISTRY

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There is no standard of care for cerebrospinal (CSF) diversion in children with diffuse intrinsic pontine glioma (DIPG), nor understanding of survival impact. We evaluated CSF diversion characteristics in children with DIPG to determine incidence, indications and potential impact on survival. Data was extracted from subjects registered in the International DIPG registry (IDIPGR). IDIPGR team personnel obtained clinical and radiographic data from the registry database and when appropriate, abstracted additional data from individual medical records. Univariable analyses were performed using the Fisher's exact test or Wilcoxon rank sum test. Survival was estimated using the Kaplan-Meier method. Evaluable patients (n=457) met criteria for DIPG diagnosis by central radiology review. Ninety-two patients (20%) had permanent CSF diversion. Indications for permanent diversion were hydrocephalus (41%), hydrocephalus and clinical symptoms (35%), and clinical symptoms alone (3%). Those with permanent diversion were significantly younger at diagnosis than those without diversion (median 5.3 years vs 6.9 years, p=0.0002), otherwise no significant differences in gender, race, or treatment were found. The progression-free and overall survival of those with permanent CSF diversion compared to those without permanent diversion was 4.5 and 10.9 months vs 6.9 and 11.2 months, respectively (p=0.001, p= 0.4). There was no significant difference in overall survival in patients with or without permanent CSF diversion among a large cohort of DIPG patients. Patients without permanent diversion had significantly prolonged progression free survival compared to those with permanent diversion. The qualitative risks and benefits of permanent CSF diversion need to be further evaluated.

DIPG-56. EXPLORATION OF TUMOR/STROMA INTERACTIONS IN DIPG XENOGRAFT BY SPECIES-SPECIFIC RNA-SEQ DECONVOLUTION INDICATES A ROLE OF MICROGLIA CELL IN DIPG DEVELOPMENT

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Diffuse Intrinsic Pontine Glioma (DIPG) and more largely Diffuse Midline Gliomas H3 K27M-mutant (DMG) harbor a unique property of infiltration. Our objective is to elucidate/describe the cellular and molecular determinants of micro-environmental modifications resulting from the tumour/stroma dialogue as it might provide pro-invasive conditions that favour the development of the disease. To this end, we performed RNA-seq analyses to characterize exhaustively the bidirectional molecular modifications of the stroma/tumour in DIPG xenograft models. Gene expression changes in murine microenvironment compartment were investigated as continuous or semi-continuous traits of tumor load by measuring transcriptome in zone with high *vs*. low infiltration. We observed substantial modulations in gene expression in the microenvironment associated with increasing tumor cell content, pointing to a modification of the macrophage/microglial infiltrate. The expression or overexpression of several modulated genes was validated by IHC in the stroma of DMG primary tumors. Among them, overexpression of the cytokine CCL3 was confirmed, reflecting the activation status of microglial cells. Moreover, we observed in patients that the density of IBA-1 positive microglial cells increases according to the extent of tumor infiltration and that a significant part of them harbor a mitotic status, supporting their interaction with DMG cells. The involvement of this interaction in DMG development needs further evaluation and might represent opportunity to slow down DIPG extension.

DIPG-57. TRANSCRIPTOMIC AND PROTEOMIC ANALYSES OF DIPG RESPONSE TO ONC201

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Diffuse Intrinsic Pontine Glioma (DIPG) is an incurable pediatric brain tumor. Current standard of care has shown no improvements in survival. Here, we report our study of ONC201, a first-in-class small molecule developed by Oncoceutics, Inc., against a panel of DIPG cells *in vitro* and in mouse orthotopic models. ONC201 inhibits signaling through dopamine receptor D2 (DRD2), a G protein-coupled receptor (GPCR). MTT assays revealed a delayed but more robust response to ONC201, as measured by IC50 values, in DIPGs with histone H3.3-*K27M* expression compared to cells expressing wildtype (WT) or *K27M* mutant histone H3.1. Interestingly, transcriptomic profiling identified an association of this response delay with an elevation of genes controlling the cellular unfolded protein response, lysosomal and vacuole organization, and a decline in nucleic acid biosynthetic genes. These cells were also more committed to neuronal and oligodendrocytic lineage specification. By contrast, WT-H3 DIPGs that survived ONC201 treatment were stem-like and exhibited altered expression of genes controlling cell proliferation and apoptosis induction, respectively. Single cell proteomics validated the increase in anti-apoptotic proteins in these cells. Intraperitoneal administration of ONC201 for 7-weeks in mice bearing pontine xenografts of histone H3.1-*K27M* mutant DIPGs, caused a complete blockade of tumor growth relative to untreated controls. However, identical treatment of animals with forebrain tumors resulted only in a partial reduction in tumor burden, suggesting that the tumor microenvironment may be involved in the differential effect. These data indicate that tumor intrinsic and extrinsic factors may contribute to the response of DIPG tumors to ONC201.

DIPG-58. HISTONE H3 WILD-TYPE DIPG/DMG OVEREXPRESSING EZHIP EXTEND THE SPECTRUM OF DIFFUSE MIDLINE GLIOMAS WITH PRC2 INHIBITION BEYOND H3-K27M MUTATION

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Diffuse midline gliomas (DMG) H3 K27M-mutant were introduced in the 2016 WHO Classification unifying diffuse intrinsic pontine gliomas (DIPG) and gliomas from the thalamus and spinal cord harboring a histone H3-K27M mutation leading to Polycomb Repressor Complex 2 (PRC2) inhibition. However, few cases of DMG tumors presenting a H3K27 trimethylation loss, but lacking an H3-K27M mutation were reported. To address this question, we combined a retrospective cohort of 10 patients biopsied for a DIPG at the Necker Hospital or included in the BIOMEDE trial (NCT02233049) and extended our analysis to H3-wildtype (WT) diffuse gliomas from other midline locations presenting either H3K27 trimethylation loss or *ACVR1* mutation from Necker, ICR, the HERBY trial, the INFORM registry study and the St. Jude PCGP representing 9 additional cases. Genomic profiling identified alterations frequently found in DMG, but none could explain the observed loss of H3K27 trimethylation. Similar observations were previously made in the PF-A subgroup of ependymoma, where the H3K27me3 loss resulted from *EZHIP*/*CXorf67* overexpression rather than H3-K27M mutations. We thus analyzed *EZHIP* expression and observed its overexpression in all but one H3-WT DMGs compared to H3-K27M mutated tumors (EZHIP negative). Strikingly, based on their DNA methylation profiles, all H3-WT DMG samples analyzed clustered close to H3-K27M DIPG, rather than *EZHIP* overexpressing PF-A ependymomas. To conclude, we described a new subgroup of DMG lacking H3-K27M mutation, defined by H3K27 trimethylation loss and EZHIP overexpression that can be detected by IHC. We propose that these EZHIP/H3-WT DMGs extend the spectrum of DMG with PRC2 inhibition beyond H3-K27M mutation.

DIPG-59. UPREGULATION OF PRENATAL PONTINE ID1 SIGNALING IN DIPG

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BACKGROUND: Diffuse intrinsic pontine gliomas (DIPGs) are lethal pediatric brain tumors with no curative therapies. Inhibitor of DNA binding (ID) proteins are key regulators of gene differentiation during embryogenesis. Previous work has shown that *H3F3A* and *ACVR1* mutations increase ID1 expression in cultured astrocytes, but this has not been validated in human DIPG, nor has the regulation and targetability of ID1 been explored in DIPG. RESULTS: Analysis of post-mortem tissue and multiple human datasets showed ID1 to be elevated in DIPG, and to correlate with reduced survival. In a multi-focal autopsy of a DIPG case, we also found ID1 expression to be heterogeneous and to correlate with tumor invasion. Chromatin immunoprecipitation qPCR (ChIP-qPCR) revealed elevated H3K27ac and low H3K27me3 at ID1 regulatory regions (enhancers/promoters) in DIPG tissue compared to normal brain, regardless of H3 or *ACVR1* mutation status. Analysis of publicly-available ISH and ChIP-sequencing data of developing murine brains revealed H3K27ac at ID1 enhancers to be elevated in the prenatal hindbrain compared to prenatal forebrain and midbrain, and all postnatal brain regions. ID1 shRNA-mediated knockdown of primary human H3K27M DIPG cells (DIPG007) significantly reduced invasion and migration. We also treated DIPG007 cells with cannabidiol (CBD) and found reduced viability at clinically relevant dosing (IC50=2.4 uM) with dose-dependent reduction in ID1 protein. CONCLUSIONS: These findings indicate that a multifactorial (genetic and regionally-based) epigenetic upregulation of *ID1* drives DIPG invasiveness and is targetable with CBD. ID1 knockdown and CBD treatment experiments in murine models of DIPG are ongoing.

DIPG-60. PILOT STUDY OF CIRCULATING TUMOR CELLS IN PEDIATRIC HIGH GRADE BRAIN TUMORS

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BACKGROUND: Despite its increasing use, circulating tumor cells (CTCs) have not been studied in pediatric brain tumors. METHODS: Cell surface vimentin (CSV) is a marker for CTC detection. We developed an automated CSV-based CTC capture method for pediatric brain tumor using the Abnova Cytoquest platform. PBMCs isolated from blood samples from 52 brain tumor patients were processed to isolate CSV^+ CTCs. Captured cells were then stained for CSV and CD45 and scanned to determine the number of CTCs. DIPG samples were additionally examined for H3K27M expression on CSV^+ cells. Long term cancer survivors were used as a control cohort. RESULTS: 86.4% of all the samples exhibited between 1–13 CSV+ CTCs, with a median of 2 CSV+ CTCs per sample. Using a value of ≥ 1 CTC as a positive result, the sensitivity and specificity of this test was 83.05% and 60.0% respectively. 19 DIPG samples were analyzed and 70% (13 samples) were positive for 1–5 CTCs. Five of these 7 positive CSV+ CTCs DIPG samples were also positive for H3K27M mutations by immunohistochemistry (71%). Mean survival in days for the CTC positive and negative DIPG samples were 114 and 211 days, respectively (p= 0.13). CONCLUSION: This is the first study of CTCs in pediatric CNS tumors using an automated approach. Patients with brain tumors can exhibit CSV+ CTCs within peripheral blood. The use of specific molecular markers such as H3K27M can improve the diagnostic capability of liquid biopsies and may enable future disease assessment for personalized therapy.

DIPG-61. RESCUE REGIMENS AFTER BIOMEDE: POSSIBLE INFLUENCE ON OS ASSESSMENT

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BIOMEDE is a multicentric randomized phase II trial to evaluate in DIPG the OS of patients treated with dasatinib, erlotinib or everolimus. The OS is the result of the first line treatment but it could also be affected by re-irradiation and the second line treatment received after progression, especially in case of a possible crossover outside of the trial. This preliminary analysis focuses on the first patients enrolled at Gustave Roussy (n=37). The median age at diagnosis was 7 years, median interval from diagnosis to progression and median survival after progression were 7 (1–20) and 2 (0–13) months respectively. Initial treatment was everolimus for 13, dasatinib for 20, erlotinib for 4 patients. The most frequent targetable molecular alterations were mTOR pathway in 6, PDGRFA in 4, ACVR1 in 3 patients. Out of the 31 patients who relapsed and were evaluable, 18 and 13 had a median survival < 3 and > 3 months respectively. At relapse patients have received different types of therapies, in 6 cases matching the molecular profile of the tumour obtained by sequencing. At progression, seven patients switched from dasatinib to mTOR inhibitors and 2 patients switched from everolimus to dasatinib. Patients with OS after progression > 3 months had higher rate of reirradiation (77% vs 5%), steroid weaning (69% vs 33%) and Lansky/Karnowsky > 50% (85 vs 67%). Extended results on the entire cohort will be presented. It will be important to consider the distribution of reirradiation to interpret the results of the randomisation on OS.

DIPG-62. PRECLINICAL EVALUATION OF IMIPRIDONE-BASED COMBINATION THERAPIES IN PEDIATRIC H3K27M MUTANT DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

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Imipridones induce apoptosis in cancer via p53 independent upregulation of TNF-related apoptosis inducing ligand (TRAIL) pathway and its proapoptotic receptor DR5. ONC201, a first-in-class imipridone, is being evaluated alone and with radiotherapy for children with H3K27M mutant diffuse glioma. We sought to determine if ONC201 and its imipridone analogs (ONC206, ONC212) are synergistic with other chemotherapy agents. Seven patient-derived DIPG cell lines, six H3.3K27M mutant (SU-DIPG-IV, SU-DIPG-13, SU-DIPG-25, SU-DIPG-27, SU-DIPG-29, SF8628) and one H3.1K27M mutant (SU-DIPG-36) were grown in culture and exposed to ONC201, ONC206, and ONC212 alone and in combination with histone de-acetylase inhibitors (HDACi) or etoposide. A dose-dependent response to ONC201, ONC206, and ONC212 was demonstrated in all cell lines, with mean IC50 values of 1.46 μM, 0.11 μM, and 0.03 μM respectively. ONC206 and ONC212 induced apoptosis measured by increased expression of cleaved PARP and ISR by increased expression ATF4. In two cell lines, synergy studies revealed combination indices (CI) < 1 for ONC206 and etoposide, with a best CI of 0.62 in SU-DIPG-IV and 0.46 in SU-DIPG-25. Synergy was also observed between ONC201 and etoposide (CI 0.46) and ONC201 and panobinostat (CI 0.01). Imipridones and analogs were superior to panobinostat and etoposide in triggering apoptosis as measured by sub-G1 phase content. Additional synergy and mechanistic analyses are ongoing and will be reported. Our results suggest that H3K27M mutant DIPG cells demonstrate increased sensitivity to imipridone analogs (ONC206 and ONC212) when compared to ONC201. Combinational strategies with etoposide or HDACi should be considered for clinical translation.

DIPG-63. LOSS OF THE H4 LYSINE METHYLTRANSFERASE KMT5B DRIVES INVASION / MIGRATION BY DEPLETING H3K27ME3 AT LOCI OTHERWISE RETAINED IN H3K27M MUTANT DIPG CELLS

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Diffuse intrinsic pontine glioma (DIPG) and other diffuse midline glioma (DMG) are characterised by K27M mutations in histone H3 variants. The major functional consequence is a global loss of the repressive mark H3K27me3, causing a raft of transcriptional changes promoting tumorigenesis, although certain key loci retain trimethylation, such as *CDKN2A/B*. We recently identified subclonal loss-of-function mutations in the H4 lysine methyltransferase *KMT5B* to be associated with an enhanced invasion/migration, but the mechanism by which this occurred was unclear. Here we show by ChIP-seq using patient-derived subclonal DIPG models and CRISPR-Cas9 depletion that loss of KMT5B (or KMT5C) causes a paradoxical increase in global levels of H4K20me3 in promoters and regulatory regions, only ablated by knocking out both enzymes. Loss of KMT5B alone further causes loss of the majority of otherwise retained H3K27me3 loci in DIPG cells, although *CDKN2A/B* itself was spared. De-repression occurred at bivalent loci marked by H3K4me3 and had elevated gene expression by RNAseq; these were significantly enriched for genes involved in chromatin remodelling and invasion/migration, the latter including *MMP9/MMP24*.

Phenotypic assessment of the models *in vitro* by high-throughput imaging demonstrated significantly increased invasion and migration in association with either KMT5B or KMT5C loss, but not both. Quantitative proteomic assessment of the secretome identified factors by which a minority of KMT5B-deficient cells may signal to promote motility of the neighbouring populations. These data suggest a previously unrecognised trans-histone (H4/H3) interaction in DIPG cells with a potentially profound effect on their diffusely infiltrating phenotype.

DIPG-64. INTERNATIONAL PRECLINICAL DRUG DISCOVERY AND BIOMARKER PROGRAM INFORMING AN ADOPTIVE COMBINATORIAL TRIAL FOR DIFFUSE MIDLINE GLIOMAS

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INTRODUCTION: DMG-ACT (DMG- multi-arm **A**daptive and **C**ombinatorial **T**rial) aims to implement a highly innovative clinical trial design of combinatorial arms for patients with diffuse midline gliomas (DMGs) at all disease stages that is adaptive to pre-clinical data generated in eight collaborating institutions. The goals of the team are to: i) rapidly identify and validate promising drugs for clinical use, and ii) predict biomarkers for promising drugs. METHODS: In vitro (n=15) and in vivo (n=8) models of DMGs across seven institutions were used to assess single and combination treatments with ONC201, ONC206, marizomib, panobinostat, Val-083, and TAK228. In vivo pharmacokinetic assays using clinically relevant dosing of ONC201, ONC206, and panobinostat were performed. Predictive biomarkers for ONC201 and ONC206 were identified using extensive molecular assays including CRISPR, RNAseq, ELISA, FACS, and IHC. RESULTS: Inhibitory concentrations (IC_{50}) were established and validated across participating sites. In vivo validation of single and combination drug assays confirmed drug efficacy as increased survival for: ONC201 (p=0.01), ONC206 (p=0.01), ONC201+ONC206 (p=0.02), and ONC201+panobinostat (p=0.01). Marizomib showed toxicity in murine/zebrafish PDXs models. Murine pharmacokinetic analysis showed peak brain levels of ONC201 and ONC206 above pre-clinical IC_{50}. Molecular testing and analyses of existing drug screen across 537 cancer cell lines validated mitochondrial stress and ATF4 as the main targets induced by ONC201/6. CONCLUSION: Thorough preclinical testing in a multi-site laboratory setting is feasible and identified ONC201 in combination with ONC206 as promising therapeutics for DMGs. Preclinical and correlative-clinical studies are ongoing.

DIPG-66. FEASIBILITY AND APPLICABILITY OF MOLECULAR GUIDED THERAPY IN HIGH GRADE GLIOMA/DIFFUSE MIDLINE GLIOMA: RESULTS FROM BEAT CHILDHOOD CANCER NMTRC-009 MOLECULAR GUIDED THERAPY STUDY

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High grade gliomas/diffuse midline gliomas (HGG/DMG) historically have a poor prognosis with an overall survival of less than 20% at 5 years. The pathophysiology is under close investigation across the world in efforts to understand this tumor type with aims of increasing effective treatment options. We present our results on the feasibility and outcomes of patients treated on our Molecular Guided Therapy study. Tumor samples were analyzed with whole exome (DNA) and RNA sequencing. Three drug matching algorithms were utilized to generate a report that was reviewed at a multi-institutional tumor board meeting, culminating in a proposed treatment protocol. Eleven patients enrolled, but one did not complete cycle 1 of therapy due to progression of disease, thus ten patients (6-HGG, 4-DMG) were evaluable and received at least 2 cycles of therapy. Time to reports generated and tumor board assembly was (median) 18 and 24 days, respectively. Secondary goals included evaluation of efficacy. Responses showed 50% of patients with stable disease or better at 2 cycles of therapy, but these were temporary with median time to progression of 81 days. In conclusion, we determined that it is feasible to collect individual biological DNA and RNA sequencing information to offer patients individualized treatment plans for this devastating group of diseases. Though data is not statistically significant, we show that there is a suggestion of efficacy in this approach to treatment for patients, indicating a need to expand on this treatment approach with individualized medicine.

DIPG-68. ALPHA-THALASSEMIA X-LINKED MENTAL RETARDATION PROTEIN (ATRX) LOSS-OF-FUNCTION IN A MOUSE MODEL OF DIFFUSE INTRINSIC PONTINE GLIOMA

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Diffuse Intrinsic Potine Glioma (DIPG) is a rare pediatric brain tumor for which no cure or efficacious therapies exist. Previous discoveries have revealed that, DIPG harbors distinct genetic alterations, when compared with adult high-grade glioma (HGG) or even with non-DIPG pediatric HGGs. ATRX alteration is found in 9% of clinical cases of DIPG, and significantly overlaps with H3.3K27M mutation and p53 loss, the two most common genetic changes in DIPG, found in 80% and 77% clinical cases, respectively. Here we developed genetically engineered mouse model of brainstem glioma using the RCAS-Tv-a system by targeting PDGF-B overexpression, p53 loss, H3.3K27M mutation and ATRX loss-of function to Nestin-expression brainstem progenitor cells of the neonatal mouse. Specifically, we used Nestin-Tv-a; p53 floxed; ATRX heterozygous female and Nestin-Tv-a; p53 floxed; ATRX floxed male breeders, generated offsprings with ATRX loss of function (n=18), ATRX heterozygous females (n=6), and ATRX WT (n=10). Median survial of the three groups are 65 days, 88 days and 51 days, respectively. Also, ATRX null mice is lower in tumor incidence (44.4%), compared with ATRX WT (80%). We evaluated the pathological features of DIPG with or without ATRX alteration, RNA-seq is performed to identify differentially expressed genes between ATRX WT and loss-of-function. In conclution, this study generated the first genetically modified mouse model studying ATRX loss-of-function in DIPG, and suggested that ATRX loss-of-function in DIPG may slow down tumorigenesis and decrease tumor incidence.

DIPG-70. DISORDERED DNA METHYLATION IN DIPG UNDERLIES PHENOTYPIC PLASTICITY

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Diffuse intrinsic pontine glioma (DIPG) is a childhood brainstem tumor with a dismal prognosis and no effective treatment. Recent studies point to a critical role for epigenetic dysregulation in this disease. Nearly 80% of DIPGs harbor mutations in histone H3 encoding replacement of lysine 27 with methionine (K27M), leading to global loss of the repressive histone H3K27 trimethylation mark, global DNA hypomethylation, and a distinct gene expression profile. However, a static view of the epigenome fails to capture the plasticity of cancer cells and their gene expression states. Recent studies across diverse cancers have highlighted the role of epigenetic variability as a driving force in tumor evolution. Epigenetic variability may underlie the heterogeneity and phenotypic plasticity of DIPG cells and allow for the selection of cellular traits that promote survival and resistance to therapy. We have recently formalized a novel framework for analyzing variability of DNA methylation directly from whole-genome bisulfite sequencing data, allowing computation of DNA methylation entropy at precise genomic locations. Using these methods, we have shown that DIPG exhibits a markedly disordered epigenome, with increased stochasticity of DNA methylation localizing to specific regulatory elements and genes. We evaluate the responsiveness of the DIPG epigenetic landscape to pharmacologic modulation in order to modify proliferation, differentiation state, and immune signaling in DIPG cells.

DIPG-71. SELECTIVE HDAC INHIBITOR RG2833 INDUCES DIPG CELL DEATH VIA DOWNREGULATION OF THE NFκB PATHWAY

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Histone deacetylase (HDAC) inhibitor panobinostat demonstrated activity against diffuse intrinsic pontine glioma (DIPG) *in vitro*, but its efficacy *in vivo* was limited by toxicity and poor blood brain barrier penetration. RG2833 (RGFP109) is a selective HDAC1/3 inhibitor that has established brain penetration. In clinical trials, the Cmax (plasma) of RG2833 was 32uM. RG2833 demonstrated cytotoxicity against temozolomide-resistant

glioblastoma and downregulated the NFκB pathway. Because this pathway is overexpressed in DIPG and may play a role in DIPG cell growth and survival, we hypothesized that RG2833 would kill DIPG cells. Treatment of DIPG cell lines with RG2833 as a single agent suppresses cell proliferation in the 5–10μM range (MTS assay for HSJD007 p=0.0004 10μM vs DMSO, JHH-DIPG1 p=0.001 10μM vs DMSO, SF-7761 p=0.04 10μM vs DMSO, SU-DIPG13 p=0.01 10μM vs DMSO by *t-test*). RG2833 induces apoptosis by 48 hours as measured by Western blot for cPARP and cleaved caspase 3 immunofluorescence (HSJD007 p<0.003 8μM vs DMSO, JHH-DIPG1 p=0.0026 10μM vs DMSO by *t-test*). RG2833 also slows cell proliferation as measured by Western blot for pRb and immunofluorescence for BrdU (HSJD007 p=0.008 8μM vs DMSO, JHH-DIPG1 p=0.0002 10μM vs DMSO by *t-test*). Western blot confirmed a dose-dependent increase in histone 3 acetylation with RG2833 treatment at 5 hours. We detected increased acetylated p65 and decreased expression of the NFκB regulated pro-survival genes BCL2, BCL-xL, and XIAP with RG2833 treatment. Together, this data shows that HDAC inhibitor RG2833 may be a promising therapeutic candidate for DIPG via downregulation of the NFκB pathway.

DIPG-72. LONG-TERM SURVIVAL OF A CLASSIC DIFFUSE INTRINSIC PONTINE GLIOMA TREATED WITH NIMOTUZUMAB

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BACKGROUND: Long-term survival in diffuse intrinsic pontine glioma is rare, and typically associated with atypical imaging and/or atypical clinical course. Although most patients harbor hotspot mutations in H3.1/3-K27M, a proportion of patients have alternate mutations, despite a typical clinicoradiological course. Herein we describe a long-term survivor with a classical presentation, treated with nimotuzumab, highlighting the challenges associated with such cases. CASE REPORT: A 5 year old male, diagnose in 2012 with a 10 day history multiple cranial neuropathies and a right hemiparesis. Cranial MRI revealed a poorly delimited diffuse pontine tumor and secondary hydrocephalus. Tumor biopsy was not performed due to the classic clinical presentation, and he received 54Gy/30 of radiation plus concomitant weekly nimotuzumab 150mg/m2. Initial tumor dimensions were 43x31x28mm. Nimotuzumab 150mg/m2 was continued every 2 weeks. Image assessment at week 12 of treatment revealed 16.9% volume increase, 4 weeks after radiotherapy completion. Nevertheless, subsequent neuroimaging at 24th, 36th, 60th, 96th and 108th weeks of nimotuzumab therapy showed a sustained and progressive tumor cytoreduction of 47.5%, 59%, 62.2%, 63.8% and 67%, respectively, when compared with post-radiotherapy dimensions. Currently, the patient is 13y old, good school performance, no neurologic disabilities. The last MRI at 394 weeks of nimotuzumab revealed dimensions of 21x19x14mm which corresponds to 70% of reduction compared with initial volume. CONCLUSIONS: Our case of progressive cytoreduction over two years of a classic DIPG, diagnosed in the era prior to the discovery of the K27M mutation, highlights the challenges associated with long-term survival of this devastating entity.

DIPG-73. SENESCENCE ASSOCIATED SECRETORY PHENOTYPE AS A MECHANISM OF RESISTANCE AND THERAPEUTIC VULNERABILITY IN BMI1 INHIBITOR TREATED DIPG

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BACKGROUND: Diffuse intrinsic pontine gliomas (DIPGs) driven by mutations in the histone 3 (H3) gene (H3K27M) are aggressive pediatric brain tumors for which there is no curative therapy. METHODS: To identify novel therapeutic targets we performed a high throughput drug screen combined with an epigenetically targeted RNAi screen using H3K27M and H3.3 WT DIPG cells. RESULTS: Chemical and genetic depletion of BMI1 *in vitro* resulted in inhibition of clonogenicity and cell self-renewal consistent with previous studies. We show for the first time that clinically relevant BMI1 inhibitors attenuates growth of orthotopic DIPG xenografts as measured by MRI and prolong survival *in vivo*. We found that BMI1 inhibition drives phenotypic cellular senescence and that the senescent cells were able reactivate to form new neurospheres *in vitro* and tumor growth *in vivo*. RNA-seq, ChIP-Seq and immuno-proteomic analysis revealed that the senescent cells induced the expression of the Senescence Associated Secretory Phenotype (SASP) cytokines by increasing occupancy of activated histone marks at SASP factor promoters. The SASP results in increased expression of anti-apoptotic BH3 proteins including BCLxl, and BCL2. Treatment of the PTC028 treated senescent DIPG cells with BH3 mimetics induces apoptosis and clears the senescent cells. Combining BH3 mimetics with BMI1 inhibition attenuates tumor growth *in vivo* synergistically and significantly prolongs survival of DIPG bearing mice compared to BMI1 inhibition alone. CONCLUSION: These data inform the current trial of BMI1 inhibition as a monotherapy and predict the need for adding BH3 mimetics to achieve efficacy.

DIPG-74. RE-IRRADIATION OF DIPG: DATA FROM THE INTERNATIONAL DIPG REGISTRY

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PURPOSE: To review data from DIPG Registry patients recorded to have received a second course of radiation therapy (rRT). METHODS: The International DIPG Registry was searched for patients with DIPG who were treated with a known dose of rRT. Doses of rRT, timing from initial diagnosis and primary radiation therapy (pRT), radiographic response to rRT and survival from diagnosis (OS) were evaluated. RESULTS: Sixty (11.2%) of 535 Registry patients underwent rRT; dose was provided for 44 patients. Median (range) data from those 44 revealed that rRT was given at 12 (2–65) months from initial diagnosis of DIPG and at 9.6 (1–61) months from completion of pRT at a dose of 26.7 (1.8–74) Gy. After completion of rRT, MRI showed response, progression, stable disease or was not available in 19, 8, 3 and 14 patients, respectively. Median PFS and OS were 11 and 18.1 months, respectively. 475 Registry patients did not undergo rRT; their ages, duration of symptoms, and primary treatment with or without chemotherapy were not significantly different from the rRT cohort. Median PFS and OS for the non-rRT patients were 6.9 and 10 months, respectively. rRT patients were more likely to have had radiographic evidence of tumor necrosis at diagnosis than non-rRT patients. CONCLUSIONS: Administration of rRT to patients with DIPG has been inconsistent with respect to timing and dose. Toxicity,

response and quality of life data are incomplete, but survival appears to be lengthened with rRT. Prospective clinical trials will elucidate benefits and risks of rRT.

DIPG-75. PRECISION MEDICINE FOR PAEDIATRIC HIGH-GRADE DIFFUSE MIDLINE GLIOMAS - RESULTS FROM THE ZERO CHILDHOOD CANCER COMPREHENSIVE PRECISION MEDICINE PROGRAM

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The Australian Zero Childhood Cancer (ZERO) program aims to assess the feasibility of a comprehensive precision medicine approach to improve outcomes for patients with an expected survival <30%. ZERO combines molecular profiling (whole genome sequencing, whole transcriptome sequencing, DNA methylation profiling) with *in vitro* high-throughput drug screening (HTS) and patient-derived xenograft drug efficacy testing. We report on the cohort of patients with midline high-grade glioma (HGG), including H3-K27M DMG, enrolled on the pilot study (TARGET) and on the ongoing ZERO clinical trial (PRISM). We identified 48 patients with midline HGG. Fresh or cryopreserved samples were submitted in 37 cases and cell culture was attempted in 30/37 cases with 45% success rate. The most commonly mutated genes/pathways identified by molecular profiling include H3-K27M mutations, DNA repair pathway, and PI3K/mTOR pathway. Two targetable fusions (NTRK and FGFR1) were reported. Five patients with germline alterations were identified. Thirty-five (72%) patients received a therapeutic recommendation from the ZERO molecular tumour board and the main recommended therapies were mTOR inhibitors, PARP inhibitors or tyrosine kinase inhibitors. HTS added evidence for the recommended therapy (n=3) or identified novel potential therapy (n=1). Out of the 35 patients, 16 received a recommended drug. Response to treatment was complete response for five months (n=1), partial response for nine months (n=1), stable disease (n=4), and progressive disease (n=10). These results highlight the feasibility of the ZERO platform and the value of fresh biopsy, necessary for pre-clinical drug testing. Targetable alterations were identified leading to clinical benefit in six patients.

DIPG-76. HISTONE H3 PHOSPHORYLATION IN H3K27M MIDLINE GLIOMAS

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Diffuse midline gliomas (DMG) patients have a dire prognosis despite radiation therapy and there is an urgent need to develop more effective treatments. DMG are characterized by heterozygous mutations in select H3 genes resulting in the replacement of lysine 27 by methionine (K27M) that leads to global epigenetic reprogramming and drives tumorigenesis. We previously reported that pharmacological inhibition of aurora kinase (AKI) may represent a targeted approach for treating tumors with this mutation. Our analysis with both published dataset and patient samples showed that patients with higher aurora kinase A (AKA) expression were associated with worse survival. AKA phosphorylates H3S10 and H3S28 during mitosis. Intriguingly, phosphorylation of the H3S28 (H3S28ph) by AKA blocks PRC2 methyltransferase activity and decreases global H3K27me3 in certain stem cells. We propose that a similar mechanism occurs in H3K27M DMG tumors, where there is a reciprocal relationship between H3S28ph and H3K27me3. We found that AKI significantly decreases H3S28ph while increasing H3K27me3 specifically in H3K27M tumors. To further evaluate the link between the H3K27M mutation and H3 serine phosphorylation, we used CRISPR/Cas9-directed gene editing to silence H3S28ph by replacing serine with alanine (H3S28A) in DIPG cell lines. Ectopic expression of histone H3S28A leads to a prominent epigenetic changes in H3K27M tumors and is similar to AKA inhibition. Overall, this study highlights H3S28ph, one of the targets of AK, is a key driver of epigenetic changes in H3K27M tumors through both direct and indirect changes to H3K27me3 and H3K27ac across the genome.

DIPG-77. TREATMENT EXTENT AND THE EFFECT ON SURVIVAL IN DIFFUSE INTRINSIC PONTINE GLIOMA

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BACKGROUND: Front line radiotherapy for diffuse intrinsic pontine glioma (DIPG) remains the only standard of care. Is this still appropriate? PATIENTS AND METHODS: We examined survival outcomes across six treatment modalities including I) no treatment (n=19), II) radiotherapy alone (n=38), III) radio-chemotherapy (n=101), IV) radiotherapy and relapse chemotherapy (n=35), V) radio-chemotherapy and relapse chemotherapy (n=163), and VI) radio-chemotherapy and relapse chemotherapy, plus reirradiation (n=54). Data were collected retrospectively using the Society of Pediatric Oncology and Hematology (GPOH) and the SIOPE DIPG Registry. 410 patients were included with radiologically centrally reviewed DIPG, mostly unbiopsied. Of note, the untreated patients and radiotherapy only cohorts chose limited treatment voluntarily. RESULTS: Median overall survival (MOS) of the whole cohort was 11 months and progression free survival (PFS) 7 months. PFS was not significantly different between the treatment groups. OS and post-progression survival (PPS) were significantly different between cohorts. For the respective treatment groups, median OS was 3 months (I), 7 months (II), 8 months (III), 13 months (IV), 13 months (V), and 15 months (VI). For only front line vs at least one second line therapy, MOS was 8 months vs 14 months and PPS 2 months vs 5 months. CONCLUSIONS: Although subject to biases to some extent, it seems that additional therapies beyond radiation therapy are of benefit to extending survival in DIPG patients. This is at least partially caused by the introduction of reirradiation regimens. To what extent other therapies contribute to survival and quality of life is subject to further investigation.

DIPG-78. REVERTANCE OF THE H3K27M MUTATION RESCUES CHROMATIN MARKS NECESSARY FOR ONCOGENESIS IN DIFFUSE MIDLINE GLIOMA

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Diffuse midline glioma (DMG) is a lethal brain tumor that typically occurs in children. Numerous studies have demonstrated the central role of the H3K27M mutation and secondary loss of H3K27 trimethylation (H3K27me3) in DMG tumorigenesis. Understanding how the H3K27M mutation alters the epigenetic landscape of the cell is necessary for revealing molecular targets that are critical to tumorigenesis. To investigate the epigenetic effects of H3K27M mutation in DMG, we developed revertant DMG cell lines with the mutant methionine residue reverted to wildtype (i.e., M27K). Revertant cells were analyzed for epigenetic changes and phenotypic differences in vitro and in vivo. H3M27K DMG cells grew in culture but displayed diminished proliferative capacity. H3M27K cells demonstrated total loss of H3K27M expression and restored trimethylation of H3K27 and H3K4. Furthermore, consistent with the hypothesis that the H3K27M mutation impacts H3 phosphorylation via expression of Aurora Kinase during mitosis, H3M27K cells demonstrated reduced expression of both Aurora Kinase A and phosphorylation of H3 serine residues 10 and 28. In line with the critical role of H3S10 phosphorylation in chromatin segregation, H3M27K cells also demonstrated restored chromosome segregation compared to H3K27M cells. In vivo data will be discussed. Revertance of the H3K27M mutation reduces tumorigenesis in DMG tumors. Isogenic H3M27K cells display reversal of key epigenetic changes associated with oncogenesis in DMG. The revertant H3M27K DMG model is a useful tool to investigate the downstream epigenetic reprogramming specific to H3K27M mutation in these tumors.

DIPG-79. H3K27M INDUCES EPIGENETIC AND ONCOGENIC CHANGES THAT ARE PARTIALLY REVERSED BY SMALL MOLECULE AURORA KINASE B/C INHIBITION

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Diffuse intrinsic pontine glioma (DIPG) is a fatal pediatric brain tumor with no curative treatments. Approximately 80% of DIPGs contain an H3K27M mutation. The implications of the mutation and how they may be targeted are not fully understood. We established an H3K27M effect-isolating model by transducing H3K27-wildtype lines (HSJD-GBM-001, normal human astrocytes) with lentiviral-packaged H3K27M. We characterized H3K27M-related changes through western blot, phenotypic assays, and RNA-seq. Drug screening of H3K27-wildtype and matched H3K27M-transduced lines was used to identify targets more effective with H3K27M present. Patient-derived pediatric glioblastoma and DIPG lines (BT-245, SU-DIPG-IV, HSJD-DIPG-007, SU-DIPG-XIII*, SF7761) were used for validation. We observed increased H3K27ac and decreased H3K27me3, as well as increased proliferative and migratory abilities, with the addition of H3K27M to H3K27-wildtype lines. RNA-seq showed downregulation of cell cycle regulation and upregulation of epithelial-mesenchymal transition. GSK1070916, an Aurora kinase B/C inhibitor, was isolated from a synthetic lethality screen with H3K27M. GSK1070916 showed strong efficacy in native H3K27M lines (IC_{50}s=60nM-1250nM), superior to the Aurora kinase A inhibitor alisertib, to which all cell lines showed substantial resistance. Combination of both drugs was not synergistic. GSK1070916 treatment caused increased H3K27me3 and decreased H3S10ph and H3S28ph. GSK1070916 induced apoptosis and S-phase stall. The H3K27M mutation induces epigenetic, phenotypic, and cell cycle regulation changes resulting in relaxation of transcriptional controls and more aggressive growth. Aurora kinase B/C inhibition is a novel therapeutic modality for DIPG that appears capable of reversing some H3K27M-related epigenetic changes, inducing apoptosis, and repressing uncontrolled cellular division.

DIPG-80. CLINICAL AND RADIOGRAPHIC RESPONSE TO ONC201 IN A PEDIATRIC PATIENT WITH A THALAMIC H3K27M AND BRAFV600E MUTANT DIFFUSE MIDLINE HIGH GRADE GLIOMA

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Recent improved understanding of the molecular markers of high grade glioma has shifted the approach to these aggressive CNS tumors to increasingly use molecularly guided targeted therapies. Treatment of patients with BRAFV600E mutant high grade gliomas with BRAF inhibitors has shown efficacy, however the impact of concomitant H3K27M mutation is unknown. ONC201 targets dopamine receptor D2 (DRD2), which is shown to be broadly overexpressed in the thalamus as well as multiple tumor types; its antagonism has demonstrated anti-tumor efficacy and immunomodulatory properties in preclinical studies. ONC201 has also demonstrated clinical efficacy in patients with H3K27M mutant gliomas. We present the case of a 9-year-old male with a right thalamic H3.3K27M mutant diffuse midline glioma with a concomitant BRAFV600E mutation with an ongoing partial response to ONC201 treatment. The patient was diagnosed in May 2018. He underwent biopsy, followed by standard focal proton radiation therapy (54Gy) and subsequent treatment with dasatinib, bevacizumab and everolimus over the course of five months. After continued radiographic progression on serial imaging, in April 2019 he started ONC201 375mg orally once per week through an expanded access trial. He has tolerated the medication well with grade 1 nausea and fatigue. Over the next nine months, he demonstrated clinical and radiographic improvement with modest increased use of his left side and MRIs showing progressive decrease in size of the thalamic lesion with a 70 % decrease in the target lesion (measuring 53x62mm prior to treatment, decreased to 38x26mm in January 2020).

DIPG-82. CLINICAL EXPERIENCE OF CONVECTION ENHANCED DELIVERY (CED) OF CARBOPLATIN AND SODIUM VALPROATE INTO THE PONS FOR THE TREATMENT OF DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) IN CHILDREN AND YOUNG ADULTS AFTER RADIOTHERAPY

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PURPOSE: Effective treatment of diffuse intrinsic pontine glioma (DIPG) remains a formidable challenge due to inadequate penetration of the blood-brain barrier (BBB) by systemically administered chemotherapies. The BBB can be overcome by directly infusing drugs into pons using method of convection-enhanced delivery (CED). We describe our clinical experience and what we have learned about the safety and feasibility of treating DIPG with intermittent CED of carboplatin and sodium valproate to the pons through the Renishaw Drug Delivery System (RDDS). METHODS: Retrospective review (2017–2020) of children with DIPG, who following radiotherapy, received compassionate treatment commencing 3.3–10 months post diagnosis (median 4.9 months). They received up to 7 cycles of 3–6 weekly pontine infusions of carboplatin (0.12-0.18mg/ml) and sodium valproate (14.4- 28.8mg/ml). RESULTS: 13 children 3–19 years (mean 6.9 years) were treated. There were no surgical complications. With the exception of infusion channels blocking in one device there were no adverse device effects. Two patients developed persistent 6th nerve palsies, which led to drug concentration reduction in the combination therapy. Subsequently infusion/ drug related toxicities were transient. Tumour was controlled in pons in 11/13 patients. Median progression free survival (PFS) was 13.0 months, while median overall survival (OS) was 15.3 months. CONCLUSIONS: Use of the RDDS was safe and well tolerated in all 13 patients. Treatment improved control of pontine disease resulting in longer PFS and OS than reported for conventional therapy and merits further evaluation in a clinical trial.

DIPG-83. USING COPPER CHELATING AGENTS TO TARGET RECEPTOR TYROSINE KINASE SIGNALLING IN DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

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DIPG is a universally fatal pediatric brain cancer. Receptor tyrosine kinase (RTK) pathway alterations are among the defining characteristics in many patients. Copper is a transition metal essential for cellular signaling, known to impact PI3K/AKT and MAPK/ERK pathways. Copper chelating agents are clinically approved for use in children with Wilson's Disease, documented to reduce brain copper levels and are cited as potential cancer therapeutics. Due to copper's wide cellular integration, we propose that targeting copper in DIPG through use of copper chelators is a viable therapeutic strategy and are strong candidates for combination therapy. Cytotoxicity assays performed in a panel of DIPG cell lines using copper chelator tetraethylenepentamine (TEPA) demonstrated a millimolar range of efficacy. To identify copper integrated pathways, western blots were performed on DIPG cell lines dosed with sub-lethal copper concentrations, which increased phosphorylated expression of AKT, ERK1/2, ERK5 and STAT3. Conversely, western blots performed after TEPA treatment demonstrated reduced phosphorylated expression of all these proteins compared to controls. Western blots investigating TEPA in combination with Everolimus and Trametinib demonstrated synergistic targeting of these proteins. Our results indicate that adding copper in the culture media initiated two RTK-mediated downstream signal transductions, including AKT and ERK and additionally STAT signaling. The use of copper chelator TEPA affected copper homeostasis and reduced DIPG cell proliferation. Our study proposes copper plays an important role in RTK-mediated signaling promoting DIPG proliferation. This implies that reducing copper with clinically available chelation agents can represent a potential anti-cancer treatment for DIPG.

DIPG-84. COMPLEMENTARY AND ALTERNATIVE MEDICINE IN DIFFUSE INTRINSIC PONTINE GLIOMA

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INTRODUCTION: Diffuse intrinsic pontine glioma (DIPG) is a rare and aggressive childhood brainstem malignancy with a two-year survival rate of ≤10%. In this international survey study we aim to evaluate the use of complementary and alternative medicine (CAM) in this patient population. METHODS: Parents of-, and physicians treating DIPG patients were asked to participate in a retrospective online survey with questions regarding CAM use during time of illness. RESULTS: 120 parents and 75 physicians contributed to the online survey between January and May 2020. Physicians estimated that <50% of their patients used CAM, whereas 69% of the parents reported to have used CAM to treat their child during time of illness. Cannabis was the most widely used form of CAM, followed by vitamins and minerals, melatonin, curcumin and boswellic acid. CAM was mainly used to actively treat the tumor. Other motivations were to treat side effects of chemotherapy, or to comfort the child. Children diagnosed ≥2016 were more likely to use CAM ($\chi 2$=6.08, p=0.014). No significant difference was found between CAM users and non-users based on ethnicity ($\chi 2$=4.18, p=0.382) and country of residence ($\chi 2$=9.37, p=0.154). Almost 50% of the physicians do not frequently ask their patients about possible CAM use. CONCLUSION: This survey demonstrates that worldwide a considerable number of DIPG patients use CAM. Physicians should be more aware

of potential CAM use and more actively discuss the topic. More research is needed to gain knowledge about possible anticancer effects of CAM and their interactions with conventional therapies.

EARLY PHASE CLINICAL TRIALS

EPCT-01. PHASE I STUDY OF DAY101 (TAK580) IN CHILDREN AND YOUNG ADULTS WITH RADIOGRAPHICALLY RECURRENT OR PROGRESSIVE LOW-GRADE GLIOMA (LGG)

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BACKGROUND: We report a phase I study examining pharmacokinetics, safety and recommended dosage of the type 2 RAF inhibitor DAY101 in children/young adults with radiographically recurrent/progressive LGGs harboring MAPK pathway alterations. METHODS: Applying a 3 + 3 design, patients < 18 years of age with radiographically recurrent/progressive LGG received oral DAY101 weekly for 4-week cycles up to a maximum of 2 years, if deriving clinical benefit. The starting DAY101 dosage was 280 mg/m^2. Dose limiting toxicities were determined after one cycle. RESULTS: We treated nine eligible patients at 280, 350, and 420 mg/m^2. Eight patients had KIAA1549:BRAF fusions. One patient with NF1 did not have a biopsy. There were no DLTs. Weekly administration of DAY101 in children resulted in dose-proportional increases in C_{max} and AUC similar to that described in adults. A 2.2-fold mg/kg exposure difference was observed with respect to weight-based dosing and suggested a correlation to best radiographic RANO responses of 2 complete responses, 2 partial responses, 3 stable disease, and 2 progressive disease (independently-reviewed). Median time to response was 10.5 weeks (range: 8–32 weeks). CONCLUSION: The phase 1A data provide initial pharmacokinetic parameters to describe oral weekly dosing of DAY101 in pediatric patients with radiographically recurrent/progressive LGG. Plasma exposures of DAY101 achieved in adults can be reached in pediatric patients. Oral weekly DAY101 is well-tolerated and possesses anti-tumor activity. The amended protocol will explore additional dose levels and the potential for differential dosing to achieve similar responses across a variety of BSAs.

EPCT-02. PBTC-051: FIRST IN PEDIATRICS PHASE 1 STUDY OF CD40 AGONISTIC MONOCLONAL ANTIBODY APX005M IN PEDIATRIC SUBJECTS WITH RECURRENT/REFRACTORY BRAIN TUMORS

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BACKGROUND: CD40 is a co-stimulatory molecule expressed on antigen presenting cells (APCs). APX005M is a CD40 agonist monoclonal antibody which stimulates innate and adaptive anti-tumor immunity through activation of APCs, macrophages, and antigen-specific CD8$^+$T-cells. Pediatric Brain Tumor Consortium study PBTC-051 is the first investigation of APX005M in pediatric patients and is evaluating the safety, recommended phase 2 dose (RP2D), pharmacokinetics, and preliminary efficacy of APX005M in children with central nervous system (CNS) tumors. RESULTS: Accrual of patients with recurrent/refractory primary malignant CNS tumors (stratum 1) began in March 2018. 16 patients (2 ineligible) have enrolled on this stratum; 14 were treated. Dose escalation through 3 planned dose levels of APX005M was completed without excessive or unanticipated toxicities. The highest dose level (0.6 mg/kg q3 weeks) is the presumptive RP2D, and an expansion cohort is currently enrolling at this dose. 2 patients at dose level 3 have received >12 cycles of therapy. Grade 3 or higher adverse events at least possibly attributable to APX005M include 11 lymphopenia, 5 neutropenia, 5 leukopenia, 3 ALT elevations, 1 AST elevation, 1 thrombocytopenia, and 1 hypoalbuminemia. PK data will be available March 2020. Stratum 2 is now enrolling patients with post-radiation/pre-progression DIPG beginning at dose level 2, with 1 patient currently enrolled. CONCLUSION: The CD40 agonistic antibody APX005M has demonstrated preliminary safety in pediatric patients with recurrent/refractory primary malignant CNS tumors and has a likely RP2D of 0.6 mg/kg q3 weeks in this population. Preliminary efficacy data are pending.

EPCT-03. A PHASE I TRIAL OF 2-HYDROXYOLEIC ACID IN PEDIATRIC PATIENTS WITH ADVANCED CENTRAL NERVOUS SYSTEM TUMORS

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2-hydroxyoleic acid (2-OHOA) is the first potential anti-cancer drug to act by modification of cell membrane lipid content. The agent is a derivative of oleic acid, a naturally occurring component of olive oil. Through its unique mechanism of activating sphingomyelin synthase 1, 2-OHOA targets the membrane lipid composition of cancer cells. These lipid changes alter membrane-dependent signaling cascades, such as the Ras/MAPK pathway, that promote tumor cell proliferation. A comprehensive pre-clinical program has characterized the safety and effects of 2-OHOA across a host of animal models. A European phase I/IIa trial of 2-OHOA in adult patients has shown initial promising results with five refractory high-grade glioma patients demonstrating objective clinical benefit by RANO criteria for six or more months. The drug has been very well-tolerated in adult patients with minimal toxicity. This phase I study is the first pediatric investigation of 2-OHOA and focuses on the treatment of relapsed/refractory pediatric central nervous system (CNS) tumors. The trial consists of a dose-escalation phase in up to 18 patients using a standard "3 + 3" design, followed by an expanded safety cohort of up to 10 patients treated at the maximum tolerated dose to confirm the recommended phase II dose. Due to the promising clinical results in adult neuro-oncology patients and the widespread involvement of the Ras/MAPK pathway and other membrane-dependent signaling cascades in the development of pediatric malignancies, we hypothesize that 2-OHOA may be a safe and effective treatment for pediatric patients with several types of advanced CNS tumors.

EPCT-05. A PHASE I TRIAL OF THE CDK 4/6 INHIBITOR PALBOCICLIB IN PEDIATRIC PATIENTS WITH PROGRESSIVE OR REFRACTORY CNS TUMORS: A PEDIATRIC BRAIN TUMOR CONSORTIUM (PBTC) STUDY

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PBTC-042 was a phase I trial of palbociclib to determine the maximum tolerated dose (MTD) and describe toxicities in children. Palbociclib is an oral, selective cyclin dependent kinase 4/6 inhibitor. METHODS: A rolling-6 design was utilized. Eligible patients were children ≥4 and ≤21 years-old with a progressive/refractory CNS tumor with intact retinoblastoma protein, measurable disease, and ability to swallow capsules. Pharmacokinetic studies were performed during the first course. Here, we report on the heavily pretreated stratum, which included patients who received >4 prior treatment regimens (either chemotherapy or biologic agent), and/or craniospinal irradiation, and/or myeloablative chemotherapy plus stem cell rescue. Palbociclib was initiated at 50 mg/m^2/day for 21 consecutive days of a 28-day course. This was one dosage level below the MTD for the less heavily pretreated stratum (75 mg/m^2). RESULTS: Fourteen eligible patients were enrolled (median age 12.8 years; male 79%). Eleven patients (79%) had either ependymoma or medulloblastoma. Four eligible and evaluable patients were enrolled at 50 mg/m^2 with no DLTs. This prompted a dosage increase to 75 mg/m^2. Ten eligible subjects were enrolled and 7 were evaluable for DLT assessment. One of 7 evaluable patients experienced a DLT (grade 3 thrombocytopenia). This established 75 mg/m^2 as the MTD for more heavily pretreated patients. Mean ± SD palbociclib apparent oral clearance was 34.6 ± 18.4 L/h/m2. CONCLUSION: The MTD for palbociclib on a 3 week on/1 week off schedule in children with brain tumors is 75 mg/m^2 and does not appear to be influenced by the degree of prior therapy.

EPCT-06. A PHASE I STUDY OF MULTI-TARGETED THERAPY IN NEWLY DIAGNOSED OR PROGRESSIVE DIFFUSE INTRINSIC PONTINE GLIOMA

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BACKGROUND: Diffuse intrinsic pontine glioma (DIPG) constitutes 80% of pediatric brain stem tumors with a median survival of 12 months. The PI3K/AKT/mTOR pathway is a key oncogenic driver of this tumor. Targeting the chromatin dysregulation through HDAC inhibition, demonstrated benefit in vivo and vitro studies. We completed the first study as a multi-targeted therapy using SAHA and temsirolimus in pediatric DIPG. METHODS: After receiving institutional IRB approval, we enrolled 6 patients on this phase I study using a 3 + 3 statistical design. Patients were divided into stratum 1 and stratum 2, based on newly diagnosed or relapsed DIPG respectively. Stratum I patients received radiation therapy concurrently with vorinostat, followed by maintenance therapy with vorinostat and temsirolimus for 10 cycles (28 day cycle), while in stratum II patients received vorinostat and temsirolimus for 12 cycles. Neuroimaging including diffusion tensor imaging were evaluated where feasible. RESULTS: Three patients were enrolled in each of the stratum. One patient in stratum 1 completed therapy, 2 other demonstrated progressive disease (PD) after 4th and 1st cycle of maintenance therapy respectively. In stratum 2 all patients progressed 2 months after the start of therapy. However no dose-limiting toxicity (DLT) was noted. The patient in stratum 1 who completed therapy, remained free of PD 21 months after diagnosis with continued improvements in the volume of enhancing and T2 hyperintense disease. CONCLUSION: Although no significant benefit was seen as compared to historical controls during this study, no dose limiting toxicity was noticed with this treatment.

EPCT-07. DEBIO1347, AN ORAL FGFR INHIBITOR: RESULTS FROM A SINGLE CENTER STUDY IN RECURRENT/REFRACTORY FGFR ALTERED PEDIATRIC GLIOMAS

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BACKGROUND: Oncogenic driver alterations in FGFR are present in a subset of pediatric gliomas. Debio1347 is an orally available, highly selective FGFR 1–3 inhibitor that had a favorable safety profile and encouraging preliminary clinical activity in an adult phase 1 study. METHODS: Five children with progressive/refractory CNS tumors harboring an FGFR gene alteration following prior chemotherapy were treated with Debio1347 at Memorial Sloan Kettering Cancer Center on single patient use protocols. Patients were treated using the 20 mg tablet formulation at the adult recommended phase 2 dose (80 mg/1.73 m2 * BSA once daily). Toxicities were graded using CTCAEv5.0 and imaging response assessments were performed every 8–12 weeks. RESULTS: All AEs were grade 1–2. Most common treatment-related adverse events were ALT increased, hypoalbuminemia and hyperphosphatemia (4 patients). Two patients met criteria for partial response and two patients had stable disease. A 13 month-old patient with a spinal cord high-grade glioma harboring two FGFR1 mutations (V592M, K687) had tumor reduction of 91.7% maintained for 12 months. A 26-month-old patient with a pilomyxoid astrocytoma harboring an FGFR1-TACC1 fusion had a tumor reduction of 74.5% maintained for 9 months. Prolonged disease stabilization was noted in an eight year-old patient with metastatic suprasellar pilomyxoid astrocytoma harboring an FGFR1 mutation (9 months) and in a 14 year-old patient with posterior fossa glioneuronal tumor harboring an FGFR3-TACC3 fusion (18 months and ongoing). CONCLUSIONS: Debio1347 demonstrated tolerable toxicity and promising anti-tumor efficacy in pediatric patients with refractory FGFR altered gliomas. Further studies in this population are warranted.

EPCT-08. ACTIVITY OF LAROTRECTINIB IN PEDIATRIC TROPOMYOSIN RECEPTOR KINASE (TRK) FUSION CANCER PATIENTS WITH PRIMARY CENTRAL NERVOUS SYSTEM (CNS) TUMORS

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BACKGROUND: TRK fusions are oncogenic drivers in a variety of tumors, many involving the CNS. Larotrectinib, a selective FDA- and EMA-approved TRK inhibitor, demonstrated a 79% objective response rate (ORR) and a 35.2-month median duration of response (DoR) in adult and pediatric patients with various non-CNS solid tumors harboring *NTRK* gene fusions. We report the clinical activity of larotrectinib in pediatric patients with primary TRK fusion CNS tumors. METHODS: Patients aged <18 years with primary CNS tumors harboring an *NTRK* gene fusion detected by local molecular testing who were treated with larotrectinib in two clinical trials (NCT02637687, NCT02576431) were identified. Larotrectinib was administered until disease progression, withdrawal, or unacceptable toxicity. Disease status was investigator assessed (RANO). RESULTS: As of February 2019, 14 pediatric patients with primary TRK fusion CNS tumors were identified. Gene fusions involved *NTRK2* (n=10), *NTRK1* (n=2), and *NTRK3* (n=2). Median age was 7.0 years (range 1.3–16.7). ORR was 45% (95% CI 17–77%) among 11 evaluable patients. Two patients had complete responses (pending confirmation), three had confirmed partial responses, and six had stable disease. 24-week disease control rate was 73%. DoR ranged from 2.6+ to 5.5+ months and progression-free survival ranged from 0.03+ to 13.9+ months. Duration of treatment ranged from 0.03+ to 16.6+ months. Treatment-emergent adverse events were mainly grade 1–2. CONCLUSIONS: Larotrectinib resulted in objective responses and durable disease control in pediatric patients with primary TRK fusion CNS tumors. These results support expanded testing for *NTRK* gene fusions in patients with CNS tumors.

EPCT-09. CLR 131 IN PATIENTS WITH RELAPSED OR REFRACTORY PEDIATRIC MALIGNANCIES

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BACKGROUND: CLR 131 is a novel targeted radiotherapeutic that exploits the selective uptake and retention of phospholipid ethers by malignant cells. CLR 131 selectively delivers radiation to malignant tumor cells, thus minimizing radiation exposure to normal tissues. OBJECTIVE: CLR 131 is being examined in a Phase 1 trial, CLOVER-2 (NCT03478462), to determine the safety, tolerability, and initial efficacy of CLR 131 in children and adolescents with relapsed/refractory malignancies. METHODS: Eligibility criteria include children with relapsed or refractory solid tumors or malignant brain tumors for which there are no standard treatment options with curative potential. Subjects must be between ages 2 and 21 with no limit to the number of prior therapies. CLR 131 is administered as a single infusion in escalating doses beginning at 15 mCi/m^2. Adverse events (AEs) are graded by NCI-CTCAE v5. RESULTS: As of 10Jan2020, four subjects with brain tumors have received CLR 131; one at 15 mCi/m^2 and three at 30 mCi/m^2. Diagnoses included DIPG (2), glioblastoma (1), and medulloblastoma (1). Median age is 13 years (range 10–15) and patients received a median of two prior therapies (range 1 to 8). There were no treatment emergent AEs at the 15 mCi/m^2 dose level attributed to CLR 131 by the investigator. Assessment of the 30 mCi/m^2 dose level is ongoing. CONCLUSIONS: CLR 131 is a unique, first in class targeted radiotherapeutic for pediatric malignancies. Preliminary data shows an acceptable and expected safety profile in this patient population. Dose escalation to determine the highest tolerated dose is ongoing.

EPCT-11. PHASE 1 STUDY OF FLUVASTATIN-CELECOXIB COMBINATION IN CHILDREN WITH RELAPSING/REFRACTORY OPTICO-CHIASMATIC LOW-GRADE GLIOMA OR HIGH-GRADE GLIOMAS (FLUVABREX): FINAL RESULTS

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BACKGROUND: Preclinical data support the activity of celecoxib and fluvastatin in high grade (HGG) and low grade gliomas (LGG). A Phase I study was designed to evaluate this combination in children with re-

fractory/relapsed glioma. AIM: To assess the safety, pharmacokinetics (PK), maximum tolerated dose, Recommended Dose for Phase II (RDP2). METHOD: Multicenter phase I trial, including patients aged 6 to 21 year old. Fluvastatin starting dose was 2 mg/kg/day, 14/28 days, with fixed dose of celecoxib (200–800 mg /day). Four dose levels of fluvastatin (2, 4, 6, 8 mg/kg/day) were evaluated. A Continual Reassessment Method was used for dose escalation. Dose-limiting toxicities (DLT) were determined on the 1st cycle. PK samples were obtained at D1 and D14 of cycle 1, pre-dose of cycle 2. RESULTS: 20 patients were enrolled with a median age of 12 years (5.9–19). They previously received a median of 3 (1–7) lines of treatment. Ten patients were treated for LGG and 10 for HGG, receiving a median of 3.5 cycles (1–21). Patients with LGG received a median of 9 cycles (1–21). Among the 17 patients evaluable for DLT, 2 DLTs were reported: 1 grade 3 maculo-papular rash (4 mg/kg), and 1 grade 4 increase of CPK (6 mg/kg). The RP2D of fluvastatin is 6 mg/kg/day. CONCLUSION: In children with refractory/relapsed glioma, the RDP2 of fluvastatin associated with celecoxib is 6 mg/kg/day. This combination is well tolerated encouraging a phase 2 study in LGG.

EPCT-12. PNOC015: PHASE 1 STUDY OF MTX110 (AQUEOUS PANOBINOSTAT) DELIVERED BY CONVECTION ENHANCED DELIVERY (CED) IN CHILDREN WITH NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) PREVIOUSLY TREATED WITH RADIATION THERAPY

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OBJECTIVE: To determine safety and distribution of MTX110 delivered by CED in newly diagnosed DIPG patients. METHODS: DIPG patients (3–21 years) were enrolled after radiation. CED of MTX110 combined with gadoteridol was completed based on dose levels (DL) (30–90 μM with volumes ranging from 3 cc (single dose) to 2 consecutive doses of 6 cc; total number of DL=7). Catheter position was chosen to maximize tumor coverage. Distribution of infusate was monitored with real-time MR imaging. Repeat CED was performed every 4–8 weeks if tolerated. Quality of life (QOL) assessments using PedsQL Generic Core and Brain Tumor modules were obtained at baseline (n=5), 3-months (n=3), and end of therapy (n=2). Single-cell RNA sequencing and analysis of histone modifications was performed to assess pharmacodynamic effects on DIPG cells. RESULTS: Between May 2018-Dec 2019, 6 patients were enrolled (median age 8 years, range 5–21). Dose limiting toxicities included: grade 3 gait disturbance (DL7; cycle 1); grade 3 muscle weakness/vagus nerve disorder (DL5; cycle 4) and grade 2 intolerable dysphagia (DL7; cycle 4). Twelve CED procedures were completed at DL7 and repeated cycles ranged from 2 to 7. Infusion to distribution volume ratio was approximately 1:3.5. There were no significant changes in self-reported QOL. Parent ratings of patients' worry ($p = 0.04$) and overall QOL ($p = 0.03$) significantly decreased at 3-months. CONCLUSION: Repeat CED of MTX110 at the highest dose is tolerable. Tissue concentrations are likely to be substantially higher compared to oral dosing. Pharmacodynamic effects will be presented.

EPCT-13. CMV PP65 RNA-PULSED DENDRITIC CELL VACCINES FOR PEDIATRIC GLIOBLASTOMA AND MEDULLOBLASTOMA: PHASE I TRIAL RESULTS

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BACKGROUND: Recurrent medulloblastoma and malignant glioma are lethal tumors that are virtually incurable. The cytomegalovirus (CMV) antigen pp65 is ubiquitously expressed on medulloblastoma and malignant glioma but not on healthy brain. We evaluated autologous CMV pp65 RNA-pulsed dendritic cell (DC) vaccines in children and young adults in a phase I trial. METHODS: Circulating monocytes were harvested using leukapheresis, differentiated into DCs, matured, and pulsed with pp65 RNA using electroporation. DCs were packaged into vaccines ($2x10^7$DC/vaccine) and administered intradermally following tetanus-diphtheria toxoid site preconditioning every 2 weeks x3, then monthly. The primary objectives of the study were to establish the feasibility of generating at least 3 vaccines and safety. An exploratory objective was to evaluate the ability of vaccination to create and enhance patient pp65-specific T cell responses. RESULTS: Eleven patients were enrolled with medulloblastoma (n=3) or glioblastoma (n=8). Ages ranged from 9–30 years old (mean 15.5y). Ten of 11 patients (91%) generated at least 3 vaccines (mean 6.2). Eight patients received at least 3 vaccines. To date, 4 patients have received all generated vaccines without progression, 4 patients have progressed, and 2 patients are still receiving vaccines. There have not been any severe adverse events probably or definitely related to vaccines. More mature data will be presented at ISPNO. CONCLUSIONS: Leukapheresis and monocyte differentiation is a feasible strategy for generating adequate DCs for active immunization in children with malignant brain tumors. CMV pp65 RNA-pulsed DCs are well-tolerated and immunogenic. Efficacy endpoints will be evaluated in a subsequent phase II trial.

EPCT-15. THE REMIND TRIAL: MULTI-ANTIGEN TARGETED T CELLS FOR PEDIATRIC CNS TUMORS

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BACKGROUND: Patients with relapsed CNS malignancies or DIPG face terrible prognoses. We hypothesized that T cells specific for 3 tumor-associated antigens (TAA), WT1, PRAME and survivin, would be safe and elicit anti-tumor immunity. METHODS: Patients (n=9) have received autologous tumor antigen-associated T cells (TAAT) (up to $4x10^7/m^2$) for newly diagnosed DIPG (Group A) or recurrent CNS malignancies (Group B) on a Phase I dose-escalation study (NCT03652545) and were monitored for safety and response. RESULTS/DISCUSSION: 9/9 patients who received TAAT completed the 45-day safety monitoring phase with no dose-limiting toxicities. Infused cells were predominantly CD3+ T cells (median 96%; range: 87–99%), with CD4+ and CD8+ comprising 16% (range: 5–87%) and 40% (range: 4–67%) of the CD3+ cells, respectively. TAAT with specificity for 1–3 TAAs, at varying frequencies, was demonstrated in 8/9 TAAT by anti-IFN-γ ELISPOT. Plasma cytokine profiles demonstrated infusion-related immune cytokine responses. In summary, TAAT are safe and may elicit anti-tumor responses in vivo. To confirm TAAT-driven effects, we are evaluating plasma proteomic profiles for immune-response signatures and assessing unique T cell receptor rearrangements of infused TAAT. Response assessment and dose escalation are ongoing.

EPCT-16. A PHASE IB STUDY OF PTC596 IN CHILDREN WITH NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOMA AND HIGH GRADE GLIOMA

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BACKGROUND: BMI-1 is highly expressed in DIPG. Downregulation leads to inhibition of cell proliferation, cell cycle signaling, self-renewal, telomerase expression, activity, and suppression of DIPG cell migration. Targeted inhibition of BMI-1 sensitizes DIPG cells to radiation and drug-induced DNA damage. PTC596 (formulated by PTC Therapeutics, Inc.) is a novel, orally available drug that inhibits microtubule polymerization, resulting in G2/M cell cycle arrest and post-translational modification of BMI-1 protein and reduced BMI-1 protein levels. OBJECTIVES: To estimate the maximum tolerated dose and describe dose limiting toxicities, pharmacokinetics and pharmacodynamics of PTC596 in children 3–21 years of age with newly diagnosed diffuse intrinsic pontine glioma and high-grade gliomas. METHODS: PTC596 is administered twice per week orally during radiotherapy and as maintenance for up to two years. The starting dose of PTC596 was 200 mg/m^2, with a subsequent dose level of $260mg/m^2$/dose. Pharmacokinetics are performed in Cycles 1 and 2. RESULTS: This study is currently ongoing. Nine patients (7 with DIPG, 2 with HGG), 8 evaluable, have been enrolled. At dose level 1, 200 mg/m^2, three evaluable patients were enrolled and experienced no DLTs. At dose level 2, among 5 evaluable patients, 2 experienced dose-limiting grade 4 neutropenia. PTC596 has been otherwise well tolerated. Five patients remain in Cycles 2–11. CONCLUSION: This phase I trial is ongoing. PTC596 is tolerable at dose level 1. We

are amending the protocol to introduce tablets that can be dissolved in liquid to allow enrollment of younger patients and those unable to swallow whole tablets.

EPCT-17. A PHASE I AND SURGICAL STUDY OF RIBOCICLIB AND EVEROLIMUS IN CHILDREN WITH RECURRENT OR REFRACTORY MALIGNANT BRAIN TUMORS: PEDIATRIC BRAIN TUMOR CONSORTIUM INTERIM REPORT

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Genomic aberrations in the cell cycle and PI3K pathway are commonly observed in recurrent childhood brain tumors. Dual inhibition of CDK4/6 (ribociclib) and mTOR (everolimus) has strong biologic rationale, non-overlapping single-agent toxicities, and adult clinical experience. The maximum tolerated dosage (MTD) and/or recommended phase two dose (RP2D) of ribociclib and everolimus was determined in the Phase I study and ribociclib concentrations were characterized in plasma and tumor in children undergoing neurosurgical procedures. Following resection, eligible patients were enrolled in the Phase I study according to a rolling 6 design and received ribociclib and everolimus once daily for 21 days and 28 days, respectively. Patients undergoing surgery received ribociclib at the pediatric RP2D (350 mg/m^2/day) for 7–10 days pre-operatively. Pharmacokinetic samples were collected on both cohorts and analyzed in nine patients on phase I study. Sixteen eligible patients enrolled on phase I study (median age 10.3 years; range: 3.9–20.4) and 5 patients were enrolled on the surgical cohort (median age 11.4 years; range: 7.2–17.1). Six patients enrolled at dose level 1 without dose limiting toxicities (DLT). Two of the three patients at dose level 2 experienced DLT (grade 3 hypertension and grade 4 ALT). The most common grade 3/4 toxicities were lymphopenia, neutropenia, and leucopenia. Everolimus concentrations following administration of everolimus alone were lower than those following drug combination, suggesting an impact of ribociclib on everolimus pharmacokinetics. The MTD/RP2D of ribociclib and everolimus in recurrent CNS tumors is 120 mg/m^2 and 1.2 mg/ m^2 daily for 21 days and 28 days, respectively.

EPCT-18. PHASE 0/I STUDY OF GM-CSF AND INTRATHECAL TRASTUZUMAB IN CHILDREN WITH RECURRENT POSTERIOR FOSSA EPENDYMOMA

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BACKGROUND: Posterior fossa ependymoma (PF EPN) is a pediatric central nervous system malignancy that has a poor outcome to standard therapeutic approaches. The majority of PF EPN tumors have increased HER2 expression. Trastuzumab is a monoclonal antibody that targets HER2, and sargramostim (GM-CSF) stimulates hematopoietic progenitor cell proliferation. The combination of trastuzumab and GM-CSF has been shown to trigger antibody-dependent cell cytotoxicity in vitro in PF EPN cell lines. METHODS: Children aged 1–21 years with relapsed PF EPN and no ventriculoperitoneal shunt or CSF obstruction are eligible for the Phase 0/I institutional trial at Children's Hospital Colorado. Stratum 1 involves IT trastuzumab and subcutaneous (subQ) GM-CSF prior to standard-of-care surgical resection. Stratum 2 involves a 3 + 3 phase I design with serial IT trastuzumab doses, each preceded by three days of GM-CSF, to establish the MTD for IT trastuzumab. RESULTS: Trastuzumab was detected in a sufficient number of tumors after presurgical IT delivery in Stratum 1 to open Stratum 2. Four patients (75% female) have been enrolled in Stratum 2 at trastuzumab Dose Level 1. Median age at enrollment is 9.8 years (range, 3.5–20.2 years). Preliminary CSF pharmacokinetic analysis demonstrated detectable trastuzumab up to 14 days after IT doses. No dose-limiting toxicities have occurred. Two patients progressed on therapy (median, 4 cycles). One patient is progression-free at 18 months off therapy. One patient remains on study therapy. CONCLUSIONS: IT trastuzumab penetrates PF EPN tumor tissue. Stratum 2 remains open to accrual at Dose Level 2.

EPCT-19. A PHASE I STUDY OF RIBOCICLIB AND EVEROLIMUS FOLLOWING RADIATION THERAPY IN CHILDREN WITH NEWLY DIAGNOSED NON-BIOPSIED DIFFUSE PONTINE GLIOMAS (DIPG) AND RB+ BIOPSIED DIPG AND HIGH GRADE GLIOMAS (HGG)

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Genomic aberrations in the cell cycle and mTOR pathways have been reported in diffuse pontine gliomas (DIPG) and high-grade gliomas (HGG). Dual inhibition of CDK4/6 (ribociclib) and mTOR (everolimus) has strong biologic rationale, non-overlapping single-agent toxicities, and adult clinical experience. The maximum tolerated dose (MTD) and/or recommended phase two dose (RP2D) of ribociclib and everolimus administered during maintenance therapy following radiotherapy was determined in the phase I study as a rolling 6 design. Ribociclib and everolimus were administered once daily for 21 days and 28 days, respectively starting two-four weeks post completion of radiotherapy. All HGG patients and any DIPG patient who had undergone biopsy were screened for RB protein by immunohistochemistry. Eighteen eligible patients enrolled (median age 8 years; range: 2–18). Six patients enrolled at dose levels 1,2, and 3 without dose limiting toxicities (DLT). Currently, five patients are enrolled at dose level 3 expansion cohort. The median number of cycles are 4.5 (range: 1–20+). Among the expansion cohort, one dose limiting toxicity included a grade 3 infection and one patient required a dose reduction in course 3 due to grade 3 ALT and grade 4 hypokalemia. The most common grade 3/4 adverse events included neutropenia. Preliminary pharmacokinetic studies on 12 patients suggest an impact of ribociclib on everolimus pharmacokinetics. The MTD/RP2D of ribociclib and everolimus following radiotherapy in newly diagnosed DIPG and HGG is anticipated to be 170 mg/m^2/day x 21 days and 1.5 mg/ m^2/day every 28 days which is equivalent to the adult RP2D.

EPENDYMOMA

EPEN-01. MULTIDISCIPLINARY TREATMENT IN EPENDYMOMA

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BACKGROUND: In intracranial ependymoma, the effectiveness of chemotherapy and radiation therapy is unclear, and the degree of tumor removal contributes to the improvement of life prognosis. METHODS: We examined ependymoma cases treated in our institution from July 1998 to March 2017. RESULTS: There were 18 boys and 7 girls. The average age at the time of surgery is 5.3±3.6 years. The pathological diagnosis was Grade II for 8 cases and Grade III for 17 cases. Genetic analysis was performed in 16/25 cases (64%). Of the infratentorial cases, 10/11 cases (90.1%) were PFA and PFB were one case. Of the supratentorial cases, 3/5 cases (60%) were positive for RELA fusion. As chemotherapy, 19 patients were VCR + VP-16 + CDDP + CPA. Irradiation was performed in all cases, local irradiation (50.4–55.8Gy) in 22 cases (88%), and craniospinal irradiation in 2 cases (8%). The 7-year OS was 74.6±9% and the 7-year PFS was 59.7±10.5%. Grade III showed a short OS (p = 0.053). GTR and NTR were obtained in the first excision in 14 cases (56%), and OS and PFS were not significantly different from those in the STR group (p = 0.219, p = 0.248). GTR and NTR including 2nd-look surgery were obtained in 18 cases (72%), and significant improvement of OS was observed compared with STR group (p = 0.02). CONCLUSION: Even if it is not GTR or NTR at the first operation, improvement of OS is expected by total excision after chemotherapy.

EPEN-02. EVALUATION OF TREATMENT OUTCOMES AND EXPRESSION OF EMT-RELATED TRANSCRIPTION FACTORS AS NOVEL THERAPEUTIC TARGETS IN PEDIATRIC EPENDYMOMA

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OBJECTIVE: Intracranial ependymomas are common brain tumors in children. However, prognosis, especially in young children, remains poor because of the chemo- and radioresistant properties of intracranial ependymomas. Furthermore, effective treatments for intracranial ependymomas remain a challenge. The epithelial-to-mesenchymal transition

(EMT) is important for invasion and metastasis in many cancers. This study aimed to evaluate and compare treatment outcomes with the expression of EMT-related transcription factors in pediatric ependymomas. MATERIAL AND METHODS: Medical and radio-imaging data of 22 (11 boys, 11 girls) patients aged <15 years with intracranial ependymomas were reviewed from January 1983 to December 2018. Six cases were subdivided into clinicopathological-molecular subgroups and immunohistochemically analyzed for Slug and ZEB. RESULTS: The median age at the start of treatment was 5 years (range 8 months–15 years) (9 cases were aged <3 years). The median progression-free survival (PFS) was 25.6 (range, 0.8–383.5) months; the median overall survival (OS) was 81.9 (range, 2.9–383.5) months. Extent of resection and malignant histology were significant prognostic factors for OS and PFS in multivariate analysis. There were 6 cases (2 cases of PFA, 2 of PFB, 1 of ST and 1 case of ST-RELA). Nuclear expression of ZEB1 was found in all tumors; however, that of Slug increased only in PFA and PFB tumors, which were associated with a poor prognosis. CONCLUSION: Expression of EMT-related transcription factors was increased in pediatric ependymomas. These data suggest that EMT is a novel therapeutic target for treating pediatric intracranial ependymomas.

EPEN-03. LONG-TERM FOLLOW-UP OF AIEOP 2ND SERIES OF CHILDREN AND ADOLESCENT WITH PRIMARY INTRACRANIAL (ST:SUPRATENTORIAL; PF: POSTERIOR FOSSA) EPENDYMOMA AND METHYLATION GROUPS RE-ANALYSES

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BACKGROUND: This 2002–2014 Italian prospective study stratified 160 patients by surgical resection (complete=NED/incomplete=ED) and centrally-reviewed grade. Grade2/NED patients received focal radiotherapy (RT) up to 59.4Gy, Grade3/NED received 4 courses of VEC(vincristine,etoposide,cyclophosphamide) after RT.ED patients received 1–4 VEC courses, second-look surgery, 59.4 Gy+8Gy boost on measurable residue. METHODS: We re-analyzed data at 115 months follow-up including methylation profile on available samples. RESULTS: Global PFS/OS at 5/10 years were 66/59% and 80/74%, respectively. Of the 64 relapsers at median 20 months, 53 died at median 37/18 months after diagnosis/relapse, respectively.10/64 relapsed after 5 years (66–126 months); 4 died, relapse was local in 8/10, metastatic 1, combined 1;5/10 patients were below age 3, 5 females, 8 PF tumors. Their survival post-relapse was not longer than earlier relapsers'. At univariable analysis, age over 3 years, female sex, complete surgery, grade 2, no shunt confirmed better PFS/OS. 66/95 analyzed tumors received a score >0.80 through the DNA methylation-based central nervous system tumor classifier: 41/8 as PFA/PFB, respectively,14/17 ST as RELA-positive (3 scored for other molecular entities i.e. anaplastic PXA, LGG MYB, HGNET). Prognostic factors were equally distributed among PFA/PFB groups,1 only group B patient relapsed locally at 96 months. CONCLUSIONS: Already published prognostic factors remained at long-term follow-up;6.2% patients had late relapses. OS after relapse was not better in late relapsers. Group B confirmed better prognosis but all patients had received «at least» adjuvant RT. Modern ependymoma trials need long follow-up to draw firm conclusions.

EPEN-04. ONCOGENIC 3D TUMOR GENOME ORGANIZATION IDENTIFIES NEW THERAPEUTIC TARGETS IN EPENDYMOMA

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By profiling enhancers in primary ependymoma tumors, we have recently identified putative oncogenes, molecular targets, and functional pathways. Inhibition of selected targets diminished the proliferation of patient-derived neurospheres and increased survival in mouse models of ependymoma. While enhancers frequently regulate the nearest gene, identification of enhancer target genes remains to be a challenge in the absence of chromosome conformation information. Consequently, we have now used HiC to map the 3-dimensional organization of tumor chromatin in the two most common and aggressive ependymoma subgroups: posterior fossa group A (PF-EPN-A) and supratentorial ependymomas with gene fusions involving the NF-κB subunit gene RELA (ST-EPN-RELA). By an integrative analysis of enhancer and gene expression in the context of the newly derived HiC data, we find that a large number of the predicted enhancer target genes are enriched for strong physical interactions. Importantly, we also identify many new putative tumor-dependency genes activated by long-range promoter-enhancer interactions and complex tumor-specific chromatin clusters of regulatory elements. Complementary to the analysis of gene-enhancer interactions, we have also leveraged the HiC data for resolving structural rearrangements underlying copy number alterations. Copy number gains of the 1q arm of chromosome 1 are especially associated with poor survival. Our preliminary results in PFA relapse samples show complex structural variants underlying 1q gain that lead to inter-chromosomal rearrangements and affect several genes that potentially contribute to poor survival. In ongoing work we are testing the relevance of the novel candidate genes for tumor cell growth and proliferation in-patient derived ependymoma models.

EPEN-05. CLINICAL AND GENETIC EVOLUTION OF EPENDYMOMA EXPOSED FROM A MULTI-RECURRENCE GIRL CASE

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Ependymomas are glial brain tumors accounting for approximately 2~3% of all primary tumors of the central nervous system (CNS), and 12% of all pediatric intracranial tumors. To better understand the evolution process of ependymomas, we studied the clinical, pathological and genetic development of a rare girl case with repeatedly recurrent ependymoma. This girl was diagnosed as ependymoma at age of 9 years old, and experienced 7 times tumor relapse and received 9 times surgeries but finally ceased at 19 years old with multiregional recurrences. The pathological characteristics, radiographic images and therapeutic strategies of the patient were all retrieved. Molecular markers confirmed the diagnosis of anaplastic ependymoma based on the updated WHO guideline for CNS tumors. Whole-genome sequencing (WGS) was performed to elucidate the landscape of mutation signatures and to identify potential driver mutations along the tumor progression. The seven tumor specimens showed a highly branched evolutionary pattern. There were six gene mutations found in 5 of the 7 specimens (PCDHA4, PCDHA8, SEC14L6, SETD2, RIOK2, and SLCO2A1) and three

in 6 of 7 the samples (RYR1, SNX25, DSC2). Strikingly, there was one gene, ADGRL3, which was found to be consistently mutated in the entire disease progression process. Our findings therefore suggest that ADGRL3 might play roles in the disease progression of ependymoma patient.

EPEN-06. CHEMOTHERAPY OF RECURRENT EPENDYMOMA: LONG-TERM RESPONSE ONLY IN FEW CASES

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INTRODUCTION: The efficacy of chemotherapy in recurrent ependymoma is unclear. We present results from the German HIT-REZ-studies. METHODS: 137 patients were analyzed regarding the treatment with chemotherapy at first recurrence, the time from first relapse to progression (PFS) and to either time-point of death or last follow-up (OS). Tumor response evaluation was based on MRI and clinically; molecular data was available in 80. RESULTS: In our cohort, 96 patients (20 supratentorial, 73 infratentorial, 3 spinal) received chemotherapy during first recurrence: 49 (51.0%) temozolomide (TMZ) monotherapy, 12 (12.5%) HIT-SKK regime, 9 (9.4%) carboplatin/etoposide (CE) and 26 (27.1%) other combinations. In 19.8% (26.5% in TMZ), chemotherapy was administered prior to surgery (neoadjuvant), which resulted in tumor progression in 78% (85% in TMZ). Gross-total resection was achieved in 86% without neoadjuvant chemotherapy and in 74% (69% in TMZ) with neoadjuvant treatment. Switching to trofosfamide/etoposide (TE) after surgery and unresponsiveness to TMZ showed further progression in all cases of tumor-residuum after surgery. Regarding 1-year-PFS, treatment with HIT-SKK (50.0%±14.4%) or CE (55.6%±16.6%) was advantageous over TMZ (30.2%±6.7%). However, 5-y-OS was lower in CE (19.0% ±16.8%) than in TMZ (39.8%±7.7%) and HIT-SKK (42.9%±8.7%). Long-term control was seen in individual cases of TMZ, HIT-SKK and CE, with TMZ providing longest response of 72 months. CONCLUSION: Neoadjuvant TMZ has no significant advantage regarding PFS. However, in few cases chemotherapy prevented progression after incomplete resection. Difficulties in response evaluation and variability in therapies hinder conclusions. Supported by the German Children's Cancer Foundation

EPEN-07. PATTERNS OF EXTRANEURAL METASTASES IN PEDIATRIC SUPRATENTORIAL EPENDYMOMA: CASE SERIES AND REVIEW OF THE LITERATURE

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BACKGROUND: Ependymomas account for 10% of all malignant pediatric intracranial tumors. Standard therapy includes maximal safe surgical resection followed by involved-field radiation. Up to 50% of localized pediatric ependymomas recur. Extraneural metastases at time of recurrence are rarely reported. OBJECTIVE: To describe extraneural metastases of pediatric ependymomas. METHODS: Retrospective review of patients' medical records and literature review. RESULTS: Three patients with history of locally recurrent, supratentorial ependymoma developed extraneural metastases: one in a cervical lymph node, one with a scalp nodule, and one with a dural lesion. Each extraneural recurrence had similar histologic and molecular features as the initial diagnosis. The cervical lymph node recurrence was treated with multimodal therapy; she is without disease four years later. The isolated scalp nodule occurred at the exit site of a subgaleal drain placed during prior resection. Following nodule resection, he developed additional scalp and lymph node disease and is receiving palliative care. The isolated dural recurrence occurred at the exit site of a ventriculoperitoneal shunt placed following a previous resection. She died of progressive disease 18 months after dural lesion resection. Reports of lymph node, scalp, and dural metastases of ependymomas are exceedingly rare, and outcomes are poor. CONCLUSIONS: Extraneural manifestations of ependymoma are rare. Regional seeding from prior surgical procedures may play a role in metastatic spread. Extraneural metastases should be considered in children previously treated for ependymoma who develop local findings even in the absence of CNS relapse. Salvage therapy with curative intent should be considered using a multimodal approach.

EPEN-09. IMPACT OF MOLECULAR SUBGROUP ON OUTCOME FOR INFANTS <12 MONTHS WITH INTRACRANIAL EPENDYMOMA - GERMAN EXPERIENCE FROM HIT2000, INTERIM-2000-REGISTRY AND I-HIT-MED REGISTRY

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BACKGROUND: For infant ependymoma (EP), decision for radiotherapy during first-line therapy is a dilemma. We analyzed therapy outcomes of EP patients younger than 12 months at diagnosis according to molecular subgroup. PATIENTS AND METHODS: Between 2001 and 2017, 30 patients with histological diagnosis of intracranial EP <12 months at diagnosis with DNA-methylation profiling available were registered in HIT-MED-studies/-registries. RESULTS: In 3/30, DNA methylation-based CNS tumor classification suggested a diagnosis other than EP or could not be assigned to a reference class. Of the remaining 27 tumors, 16 were classified as PF-A, 8 as *RELA*-fusion positive and 3 as *YAP*-fusion positive. Median age at diagnosis was 0.73 (0.30–0.99) years. After a median follow-up time of 5.36 (0.20–12.90) years, 5y.3% experienced progressive disease (PD). 5y-PFS and -OS for the whole cohort were 38.2% and 73.1%. *RELA*- and *YAP*-fusion positive EP had significantly better OS than PF-A (5y-OS for PF-A: 55.9%; *RELA* 100%; *YAP* 100%; p=0.023). PFS was not significantly different. All but one patient with relapsed PF-A died despite multimodal salvage strategies. In contrast, patients with relapsing *RELA*- and *YAP*-fusion positive EP (n=5), survived with a combination of re-surgery and first or second local radiotherapy. CONCLUSION: In this cohort of infants <12 months, patients with PF-A had a significantly inferior OS compared to patients with *RELA*- and *YAP*-fusion positive EP. Salvage therapy was ineffective for patients with PF-A, whereas patients with can *RELA*- and *YAP*-fusion positive EP can be long-term survivors after PD. Therefore, subgroups-specific therapy should be discussed.

EPEN-10. SPINAL MYXOPAPILLARY EPENDYMOMA AND METHYLATION-PROFILING: THE MD ANDERSON CANCER CENTER (MDACC) EXPERIENCE

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INTRODUCTION: Spinal myxopapillary ependymoma (MPE) is a rare histological variant of ependymoma, classified as WHO grade I tumor. Further interrogation of the molecular and clinical profile is warranted,

to better understand the biology and clinical phenotype. We summarize our institutional experience with spinal MPE including methylation-profiling. METHODS: A retrospective analysis of charts during the period of 2001 to 2019 of histologically proven MPE was done. We performed methylation profiling for 12 patients by Infinium MethylationEPIC Kit. RESULTS: 26 patients with spinal MPE were identified, median age of diagnosis was 34.2 years with a range of 11 to 59.9 years. Ten patients were below 30 years of age, lumbar spine location was commonest and 6 had leptomeningeal spread at diagnosis. All the patients underwent surgery and 11 received radiation following surgery. Eight patients below the age of 30 received radiation due to residual disease or metastases. Methylation profiling revealed 11,752 CpGs differentially methylated between the younger and older patients ($p < 0.05$), however only one CpG cg22496254 associated with gene NCAPG/DCAF16 (role in promoting mitosis) was detectable with FDR < 0.25 that overly methylated in the younger age group. This is a new finding in MPE. CONCLUSIONS: Spinal MPE is a rare spinal tumor. Our study though limited by numbers, showed younger patients had aggressive phenotype, most requiring radiation. Methylation profiling reaffirmed this finding and trend in the younger patients. Prospective studies in a larger cohort of patients with methylation profiling are needed to identify prognostic variables and new targets for treatment.

EPEN-11. ONGOING RESPONSE IN A MULTIPLY RELAPSED METASTATIC POSTERIOR FOSSA EPENDYMOMA A AFTER VORINOSTAT AND CONCOMITANT IRRADIATION

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BACKGROUND: Among the nine molecular subgroups of ependymoma identified, posterior fossa ependymoma A (PF-EPN-A) confers the worst prognosis. These tumors often relapse despite aggressive resection and irradiation, resulting in limited therapeutic options. Although the genomic profile of PF-EPN-A does not typically show any recurrent alterations; they demonstrate distinct epigenetic changes which can be targeted with modulators such as histone deacetylase (HDAC) inhibitors. These inhibitors have shown efficacy in pre-clinical studies in both their anticancer and radiosensitizing properties. CASE: We describe a male diagnosed with a posterior fossa ependymoma at 3 years of age. After initial therapy with resection and focal irradiation, he went on to have a number of recurrences requiring multimodal therapy. Most recently, he developed diffuse intraventricular and leptomeningeal disease not amenable to surgical intervention. Genetic evaluation demonstrated a BCOR mutation and methylation profile was consistent with PF-EPN-A. He received 23.4 Gray craniospinal irradiation with a 30.6 Gray boost to the nodular lesions. Vorinostat was given concomitantly for radio-sensitization in 2 week intervals for a total of 6 weeks. Serial imaging after irradiation revealed decreased tumor burden with almost complete resolution of disease at 15 months. Unfortunately, MRI at 18 months exhibited mild interval growth of 2 lesions. CONCLUSIONS: To our knowledge, this is the first report of a clinical response in a pediatric patient with PF-EPN-A following irradiation administered concomitantly with vorinostat therapy. This response highlights the importance of further studies evaluating this combination therapy and its potential use in this population.

EPEN-13. PRIMARY EXTRADURAL SACROCOCCYGEAL SUBCUTANEOUS MYXOPAPILAR EPENDYMOMA MISDIAGNOSED AS PILONIDAL CYST IN A 7 YEAR-OLD BOY: A CASE REPORT

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BACKGROUND: Ependymomas occur in the brain or spinal cord and rarely as an extraspinal variety at the sacrococcygeal region, separated from the spinal cord. This rare presentation is thought to originate from a group of heterotopic ependymal cells called the coccygeal medullary vestige. There are few reports of this occurrence in children. CLINICAL CASE: A 7-year-old male presented with a history of a soft mass arising in the sacrococcygeal area 3 years earlier, diagnosed as pilonidal cyst at primary level and treated with surgery twice, as this mass recurred the boy was sent to our hospital, a 3rd surgery was performed, all tumoral tissue was removed, no attachment with dural space was founded, pathology revealed myxopapilar ependymoma with positivity for PS100, EMA and Vimentin. After surgery a Follow up MRI of cranium and spine showed absence of disease, no radiotherapy neither chemotherapy was implemented. He has been on surveillance from 3 years now without recurrence. CONCLUSION: This report highlights the fact that pediatric ependymoma can have an extradural presentation and can be confounded with pilonidal cyst, total resection is needed to control the disease. Potential for recurrence or metastatic disease can continue 20 years from the time of primary tumor, so prolonged surveillance is important.

EPEN-14. GENERATION OF A C11ORF95-RELA FUSION TARGETING ANTIBODY AS A DIAGNOSTIC TOOL FOR SUPRATENTORIAL EPENDYMOMA

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Ependymomas account for 10% of paediatric brain tumours and arise in the ventricular walls of the central nervous system. Ependymomas were previously classified as one tumour type and all patients received similar treatment. However, recent genomic studies have identified nine different molecular subgroups of the disease, including one supratentorial subtype characterized by a novel fusion gene C11ORF95-RELA. When introduced into neural stem cells, this fusion is a potent driver of tumorigenesis and its presence in patient samples has previously also been shown to negatively correlate with overall survival. Accurate diagnosis of this subgroup is currently limited to sophisticated approaches such as break-apart FISH or RNA sequencing. Here, we report the generation of a C11ORF95-RELA Fusion-specific antibody that can be used for routine immunohistochemistry (IHC). Candidate antibodies were first selected using phage display and favourable leads were subjected to affinity maturation using ribosome display after a screening process involving immunoblotting and IHC. Further IHC-based screening of affinity-matured candidates using fusion-positive and -negative mouse tissue as well as human fusion-negative ependymoma tumour tissue produced one lead antibody. The antibody detects fusion-specific nuclear staining pattern on fusion-positive tissue and does not react with fusion-negative tissues. This candidate antibody is currently being tested on human fusion-positive ependymoma tissue. This accurate diagnostic tool holds great promise to transform the management of patients with supratentorial ependymoma.

EPEN-16. TRANSCRIPTIONAL REGULATORY CIRCUITRIES AS MOLECULAR TARGETS IN EPENDYMOMA

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Genomic sequencing has driven precision-based oncology therapy; however, genetic drivers remain unknown or non-targetable for many malignancies, demanding alternative approaches to identify therapeutic leads. Ependymomas comprise histologically similar tumor entities driven by distinct molecular mechanisms, such as fusion oncoproteins, genome-wide chromosomal instability, or disruption of DNA methylation patterns. Despite these differences, ependymomas resist chemotherapy and lack available targeted agents for clinical trial development. Based on our previous findings, we hypothesized that mapping chromatin landscapes and super enhancers (SE) could uncover transcriptional dependencies as targets for therapy (Mack, Pajtler, Chavez et al., Nature, 2018). To functionally test the requirement of these SE genes for ependymoma cellular growth, we designed a pooled RNA interference screen against 267 SE associated genes. Our screen was performed in one *C11ORF95-RELA*-fusion model and two PF-EPN-A models as controls in biological triplicates. As an indication that our screen was successful, positive controls scored among lead hits including *KIF11, BUB1B, PHF5A and MYC*. Importantly, we identified many subtype specific dependencies in both *C11ORF95-RELA*-fusion and PF-EPN-A models, thus revealing novel pathways that potentially govern subgroup-specific ependymoma cell growth. Further, several candidates detected across all ependymoma lines were also identified as pan-cancer dependencies or glioma/glioblastoma specific essential genes from the DepMap Cancer Dependency Gene Resource. Our findings reveal novel targets and pathways that are essential for ependymoma cell growth, which may provide new insight into therapeutic strategies against these aggressive brain tumors.

EPEN-17. FAVORABLE OUTCOME TO INTENSIVE CHEMOTHERAPY WITHOUT IRRADIATION IN INFANTILE METASTATIC EPENDYMOMA WITH A NOVEL MOLECULAR PROFILE: A CASE REPORT

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Metastatic disease at initial presentation of intracranial ependymoma is an uncommon occurrence with only rare reports of survival and is reportedly more prevalent in the youngest of children. Clinical and molecular characteristics associated with metastatic presentation, their prognostic implications, as well as optimal treatment options for such patients, have not been identified. CASE REPORT: A seven months old child presented with posterior fossa anaplastic ependymoma; following sub-total resection of primary tumor, a spine MRI revealed leptomeningeal dissemination along the cervical spinal cord and nerve roots of the cauda equina. The patient was successfully treated with five cycles of intensive induction chemotherapy (as per Head Start with high-dose methotrexate) followed by three sequential cycles of marrow-ablative chemotherapy and autologous hematopoietic progenitor cell rescue (AuHPCR) without irradiation; he is currently without evidence of the disease now 60 months following initial diagnosis. MOLECULAR/GENOMIC RESULTS: The patient was enrolled on a patient-centric comprehensive molecular profiling protocol, which included paired tumor-normal whole-exome sequencing, RNA sequencing of the disease-involved tissue, and DNA methylation classification. The genomic profile of the tumor was relatively unremarkable, revealing only a terminal gain of chromosome 3p and a terminal deletion of chromosome 22q, suggestive of an unbalanced translocation. Using RNA sequencing, we identified a novel *SPECC1L-RAF1* gene fusion. The tumor harbors unique transcriptomic and DNA methylation profiles, failing to discretely classify with well-established ependymoma subgroups. CONCLUSION: Use of genomic profiling techniques provides meaningful information for disease characterization allowing for further expansion of the molecular spectrum associated with malignant disease.

EPEN-18. CROSS-SPECIES GENOMICS IDENTIFIES *GLI2* AS AN ONCOGENE OF *C11ORF95* FUSION-POSITIVE SUPRATENTORIAL EPENDYMOMA

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The majority of supratentorial ependymomas (ST-EPN) are driven by fusions between *RELA* and a zinc finger containing gene, *C11orf95*. Apart from fusions to the Hippo effector *YAP1,* which affects a small group of infant patients, the oncogenic mechanism of remaining ST-EPNs is unclear. Aiming at refining the molecular classification of ST-EPNs, we analyzed methylation profiles, RNA and DNA sequencing results as well as clinical data in a cohort of 617 ST-EPNs. Unsupervised clustering analysis of DNA methylation data revealed four distinct clusters that formed in addition to the known molecular groups ST-EPN-RELA and –YAP1. Tumors within these additional clusters were characterized by fusions of *C11orf95* to numerous fusion partners different from *RELA,* e.g. *MAML2*, *MAML3*, *NCOA2* and *SS18*, suggesting a general role of *C11orf95* in tumorigenesis of ST-EPN. Transforming capacity of newly identified fusion genes was validated using an electroporation-based *in vivo* gene transfer technology. All fusion genes were sufficient to drive malignant transformation in the cerebral cortex of mice and resulting tumors faithfully recapitulated molecular characteristics of their human counterparts. We found that both, the partner gene and the zinc finger DNA binding domain of *C11orf95,* were essential to exert tumorigenesis. When exploring genes commonly upregulated in *C11orf95* fusion-expressing tumors of human and murine origin, the Sonic Hedgehog effector gene *Gli2* was identified as a promising downstream target. Subsequent co-expression of *C11orf95:RELA* and a dominant negative form of *Gli2* indeed hampered tumorigenesis. We thus propose *GLI2* as a potential therapeutic downstream target of *C11orf95* fusion-dependent oncogenic signaling in ST-EPN.

EPEN-20. EZHIP/CATACOMB COOPERATES WITH PDGF-A AND P53 LOSS TO GENERATE A GENETICALLY ENGINEERED MOUSE MODEL FOR POSTERIOR FOSSA A EPENDYMOMA

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BACKGROUND: PFA ependymoma is a pediatric brain tumor with only 30% long-term survival. Recently a gene called *CXORF67/EZHIP/CATACOMB* (henceforward: *CATACOMB*) was found to be overexpressed in PFA ependymoma. CATACOMB's mechanism of action has been found to be analogous to that of the H3K27M mutation as its expression reduces H3K27me3 via inhibition of PRC2 catalytic activity. METHODS: We infected NESTIN- or GFAP-expressing neonatal hindbrain progenitors with wild-type *CATACOMB* or a loss of function (LOF) point mutant (M406K), alone, with PDGFA, and with and without p53 deletion. RESULTS: CATACOMB overexpression alone or with p53 loss was insufficient to induce tumorigenesis. CATACOMB overexpression with PDGFA and p53 loss was sufficient to induce tumorigenesis using either the LOF mutant (M406K) or the wild-type CATACOMB in both cells-of-origin. The histology appeared more ependymoma-like when CATACOMB was expressed in GFAP-expressing progenitors. Median survival for the model initiated in NESTIN progenitors was 99.5 days for the CATACOMB mutant (n=26) group and 61 days for the CATACOMB wild-type (n=28; log-rank test p=0.0033). Median survival for the model initiated in GFAP progenitors were 144 days for the CATACOMB mutant (n=19) group and 65 days for the CATACOMB wild-type (n=21; log-rank test is P<0.0013). Immunohistochemistry for H3K27me3 demonstrated that CATACOMB wild-type tumors had reduced H3K27me3 compared to CATACOMB mutant tumors. CONCLUSIONS: Disrupting CATACOMB inhibitory activity toward PRC2 significantly increases survival in mice in both models, suggesting this activity plays a critical role in accelerating tumorigenesis. Ependymoma-like histology was more commonly observed in the model initiated in the GFAP-expressing progenitors.

EPEN-21. IMPAIRED NEURONAL-GLIAL FATE SPECIFICATION IN PEDIATRIC EPENDYMOMA REVEALED BY SINGLE-CELL RNA-SEQ

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Ependymoma represents a heterogeneous disease affecting the entire neuraxis. Extensive molecular profiling efforts have identified molecular ependymoma subgroups based on DNA methylation. However, the intratumoral heterogeneity and developmental origins of these groups are only partially understood, and effective treatments are still lacking for about 50% of patients with high-risk tumors. We interrogated the cellular architecture of ependymoma using single cell/nucleus RNA-sequencing to analyze 24 tumor specimens across major molecular subgroups and anatomic locations. We additionally analyzed ten patient-derived ependymoma cell models and two patient-derived xenografts (PDXs). Interestingly, we identified an analogous cellular hierarchy across all ependymoma groups, originating from undifferentiated neural stem cell-like populations towards different degrees of impaired differentiation states comprising neuronal precursor-like, astroglial-like, and ependymal-like tumor cells. While prognostically favorable ependymoma groups predominantly harbored differentiated cell populations, aggressive groups were enriched for undifferentiated subpopulations. Projection of transcriptomic signatures onto an independent bulk RNA-seq cohort stratified patient survival even within known molecular groups, thus refining the prognostic power of DNA methylation-based profiling. Furthermore, we identified novel potentially druggable targets including IGF- and FGF-signaling within poorly prognostic transcriptional programs. Ependymoma-derived cell models/PDXs widely recapitulated the transcriptional programs identified within fresh tumors and are leveraged to validate identified target genes in functional follow-up analyses. Taken together, our analyses reveal a developmental hierarchy and transcriptomic context underlying the biologically and clinically distinct behavior of ependymoma groups. The newly characterized cellular states and underlying regulatory networks could serve as basis for future therapeutic target identification and reveal biomarkers for clinical trials.

EPEN-22. SINGLE-CELL RNA SEQUENCING IDENTIFIES UPREGULATION OF IKZF1 IN PFA2 MYELOID SUBPOPULATION DRIVING AN ANTI-TUMOR PHENOTYPE

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We have previously shown immune gene phenotype variations between posterior fossa ependymoma subgroups. PFA1 tumors chronically secrete IL-6, which pushes the infiltrating myeloid cells to an immune suppressive function. In contrast, PFA2 tumors have a more immune activated phenotype and have a better prognosis. The objective of this study was to use single-cell(sc) RNAseq to descriptively characterize the infiltrating myeloid cells. We analyzed approximately 8500 cells from 21 PFA patient samples and used advanced machine learning techniques to identify distinct myeloid and lymphoid subpopulations. The myeloid compartment was difficult to interrupt as the data shows a continuum of gene expression profiles exist within PFA1 and PFA2. Through lineage tracing, we were able to tease out that PFA2 myeloid cells expressed more genes associated with an antiviral response (MHC II, TNF-a, interferon-gamma signaling); while PFA1 myeloid cells had genes associated with an immune suppressive phenotype (angiogenesis, wound healing, IL-10). Specifically, we found expression of IKZF1 was upregulated in PFA2 myeloid cells. IKZF1 regulates differentiation of myeloid cells toward M1 or M2 phenotype through upregulation of either IRF5 or IRF4 respectively. IRF5 expression correlated with IKZF1, being predominately expressed in the PFA2 myeloid cell subset. IKZF1 is also involved in T-cell activation. While we have not completed our characterization of the T-cell subpopulation, we did find significantly more T-cell infiltration in PFA2 than PFA1. Moving forward these studies will provide us with valuable information regarding the molecular switches involved in the tumor-immune microenvironment and to better develop immunotherapy for PFA ependymoma.

EPEN-23. A COMPUTATIONAL ANALYSIS OF THE TUMOUR IMMUNE MICROENVIRONMENT IN PAEDIATRIC EPENDYMOMA

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Ependymoma is the third commonest childhood brain tumour. Relapse is frequent, often fatal and current therapeutic strategies are inadequate. Previous ependymoma research describes an immunosuppressive environment with T-cell exhaustion, indicating a lack of response to T-cell directed immunotherapy. Understanding the immune microenvironment is therefore critical. We present a computational analysis of ependymoma, gene expression derived, immune profiles. Using 465 ependymoma samples from gene expression datasets (GSE64415, GSE50385, GSE100240) and two RNA-seq databases from UK ependymomas, we applied bulk tumour deconvolution methods (CIBERSORT and xCell) to infer immune cell populations. Additionally, we measured checkpoint blockade related mRNAs and used immunohistochemistry to investigate cell populations in ependymoma sections. CIBERSORT indicated high proportions of M2-like macrophages and smaller proportions of activated natural killer (NK) cells, T follicular helper cells, $CD4^+$ memory T-cells and B-cells. xCell overlapped with the M2-like macrophage and CD4+ memory T-cell signatures seen in CIBERSORT. On immunohistochemistry, T and B cells were scarce, with small numbers of $CD8^+$, $CD4^+$ and $CD20^+$ cells in the parenchyma but greater numbers in surrounding regions. CD68 was more highly expressed in the parenchyma. Analysis of nine checkpoint ligands and receptors demonstrated only the *TIM3*/*GAL9* combination was reliably detectable. *GAL9* is implicated in tumour interactions with T-cells and macrophages elsewhere, possibly contributing to poorer outcomes. Our study supports the presence of myeloid cells being leading contributors to the ependymoma immune microenvironment. Further work will delineate the extent of myeloid contribution to immunosuppression across molecular subtypes. Modulation of tumour immunity may contribute to better clinical outcomes.

EPEN-24. SIOP EPENDYMOMA II: CENTRAL EPENDYMOMA MANAGEMENT ADVISORY GROUP – THE UK EXPERIENCE

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Paediatric Ependymoma is the second most common malignant brain tumour of childhood with approximately 50% of cases recurring. It has been described as a "surgical" disease since patients who have undergone a gross total surgical resection (GTR) have a better prognosis than those who have a subtotal resection (STR). Analysis of the UKCCSG/SIOP 1992 04 clinical trial has shown that only 49% of cases had a GTR, with 5-year survival rates for STR of 22–47% and GTR of 67–80%. As part of the SIOP II Ependymoma trial the UK established a panel of experts in the treatment of Ependymoma from Neuro-oncology, Neuro-radiology and Neuro-surgery. Meeting weekly, cases are discussed to provide a consensus on radiological review, ensuring central pathological review, trial stratification and whether further surgery should be advocated on any particular case. Evaluation of the first 68 UK patients has shown a GTR in 47/68 (69%) of patients and STR in 21/68 (31%) of patients. Following discussion at EMAG it was felt that 9/21 (43%) STR patients could be offered early second look surgery. Following this 2nd look surgery the number of cases with a GTR increased to 56/68 (82%). There has been a clear increase in the number of patients for whom a GTR has been achieved following discussion at EMAG and prior to them moving forwards with their oncological treatment. This can only have beneficial effects in decreasing their risk of tumour recurrence or CSF dissemination and also in reducing the target volume for radiotherapy.

EPEN-25. EXCEPTIONAL CLINICAL AND IMAGING RESPONSE TO TRK-INHIBITION IN A PATIENT WITH SUPRATENTORIAL EPENDYMOMA HARBORING NTRK2 GENE FUSION

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BACKGROUND: Patients with metastatic pediatric ependymoma have limited therapeutic options and poor outcomes. Approximately ¾ of supratentorial ependymomas are driven by *C11ORF95-RELA* fusions, and the remaining by a heterogeneous group of fusion events. We present a six year-old male diagnosed with supratentorial ependymoma with leptomeningeal carcinomatosis harboring an *NTRK2*-fusion. Local and distant multifocal, intracranial and intraspinal tumor recurrence occurred seven months following gross total resection of the primary lesion and proton beam craniospinal irradiation. METHODS: DNA and RNA from FFPE tumor were used for targeted sequencing using an 81-gene fusion panel and 124-gene mutation panel. Separately, capture transcriptome sequencing, exome sequencing, and copy number array were performed as part of the Texas KidsCanSeq study, an NHGRI/NCI-funded Clinical Sequencing Evidence-Generating Research (CSER) consortium project. All sequencing was carried out in CLIA-certified laboratories. RESULTS: An in-frame fusion between 5' exons 1–3 of *KANK1* and 3' exons 16–21 of *NTRK2*, predicted to retain the kinase domain, was identified. At tumor recurrence, therapy was initiated with Larotrectinib, an FDA-approved pan-TRK inhibitor. Clinical improvement in cognitive speed, motor strength, and coordination was observed at two weeks with significant tumor response on MRI at two and four months. CONCLUSION: TRK gene fusions have not previously been reported in ependymoma. Further tumor characterization by methylation profiling is underway and will be of diagnostic interest given the apparent discordance between tumor histology and molecular findings. This case highlights the potential impact of clinical genomic analysis for children with CNS tumors.

EPEN-26. NON-CANONICAL NF-ΚB SIGNALING DRIVES MESENCHYMAL EPENDYMAL CELL SUBPOPULATION IN PFA EPENDYMOMA

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NF-κB signaling is a hallmark of PFA1 ependymoma. Loss of LDOC1, through epigenetic silencing, leads to constitutively active NF-κB signaling and chronic IL-6 secretion. In this study, we investigate the loss of LDOC1 within the PFA tumor clusters. Using our PFA scRNAseq database, in which there are 5 clusters within the tumor cell compartment: mesenchymal (MEC), ciliated (CEC), transportive (TEC), and undifferentiated (UEC). LDOC1 expression was significantly reduced and had an inverse correlation with genes defining the unfavorable MEC subpopulation, predominate in PFA1. This is consistent with our findings that MEC was defined by an NF-κB2 signaling profile. In contrast, LDOC1 expression was higher and positively correlated with genes defining the favorable CEC subpopulation, mostly seen in PFA2. RELA expression, which we studied as a target of LDOC1, was not localized to MEC and was wide-spread throughout the PFA compartment. RELB, part of non-conical NF-κB signaling, was expressed only the MEC subpopulation correlating with IL-6 gene expression found only in this subpopulation. In MAF-811, a PFA cell line with more CEC-like gene phenotype, RELB co-immunoprecipates with the active form of NF-κB2 in both the nucleus and cytoplasm. IL-6 gene expression is almost completely lost when NF-κB2 is knock-down using shRNA. Additionally, loss of LDOC1 leads to over 3 fold increase in NF-κB2 expression. Combined with our previous work, this would suggest that NF-κB2 drives IL-6 expression by binding with RELB in MEC subpopulation and targeting loss of LDOC1 may shift the MEC subpopulation toward the more favorable CEC subpopulation.

EPEN-27. *CDKN2A* DELETION IN SUPRATENTORIAL EPENDYMOMA WITH *RELA* ALTERATION INDICATES A DISMAL PROGNOSIS – A RETROSPECTIVE ANALYSIS OF THE HIT EPENDYMOMA TRIAL COHORT

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INTRODUCTION: Since supratentorial *RELA*-fusion positive ependymomas are considered a biologically distinct disease, we aimed to identify histological and genetic predictors of outcome in a defined cohort of pediatric patients. MATERIALS AND METHODS: We analyzed 54 *RELA* ependymomas in pediatric patients treated according to HIT2000-E protocols. All cases underwent central neuropathological review. Genome-wide copy number alterations were assessed by molecular inversion probe or SNP array. *RELA* alterations were detected by RT-PCR, sequencing and assessment of nuclear p65-RelA protein. Copy number alteration of the *CDKN2A (cyclin dependent kinase inhibitor 2A)* locus and concordant p16 protein expression were analyzed. RESULTS: Fifty-two tumors were classified as WHO-grade III (96.3%) with high mitotic activity in 39 cases (72.2%), vascular proliferation in 47 (87.0%), necrosis in 43 (79.6%) and clear cell morphology in 19 (35.2%). All tumors harbored *RELA* alterations. Homo- or heterozygous *CDKN2A* deletions were detected in 9 (16.7%) and 14 (25.9%) cases, respectively. p16 protein expression was lost in all cases with homozygous deletion. Median follow-up was 5.4 years with 5-years EFS and OS of 74.1% and 92.6%. In Kaplan-Meier analysis high mitotic activity was related to shorter EFS (p=0.016) and clear cell morphology to longer OS (p=0.039); *CDKN2A* deletion was associated with shorter OS (homozygous deletion, p=0.009; homo-or heterozygous deletion, p=0.034). No correlation between *CDKN2A* deletion and high mitotic activity was found but with higher age at diagnosis (p=0.001). CONCLUSION: Deletion of *CDKN2A* occurred in 42.6% of supratentorial ependymomas with *RELA* alteration and represented a genetic predictor of worse overall outcome in pediatric patients.

EPEN-28. NOVEL ONCOGENE AMPLIFICATION IN SPINAL EPENDYMOMA INVOLVING THE MYC LOCUS (8Q24)

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BACKGROUND: We report a unique case of spinal ependymoma with classic histology and aggressive clinical behavior which harbored a focal *MYC* (8q24) amplification. CASE REPORT: A-12-year old male presented with a three months history of back pain and acute onset weakness with ataxia. A spine MRI revealed an avidly enhancing intradural, extramedullary mass occupying the dorsal spinal canal from C6 through T2. The tumor demonstrated mild diffusion restriction and was associated with severe cord compression and mild edema. He underwent gross total resection. Pathological diagnosis was classic grade II ependymoma. Eleven months later, he re-presented with acute onset lower extremity paresthesia and left-handed weakness. Spine MRI demonstrated tumor recurrence extending from C2 through T1-T2 with resultant severe cord compression, again demonstrating avid enhancement and restricted diffusion. He underwent subtotal resection of the mass and focal proton beam irradiation. MOLECULAR CHARACTERISTICS: The patient was enrolled on an institutional comprehensive genomic profiling protocol. The tumor's copy number profile was complex, including homozygous loss of 17p and notably, amplification of the *MYC*

oncogene. Using fluorescence *in situ* hybridization, we identified >20 copies of *MYC* in interphase cells, confirming the gene amplification, while two copies of *MYCN* (2p24) were seen. DNA methylation further classified this tumor as clustering near posterior fossa group A (score=0.6073) tumors. CONCLUSION: We report a unique case of an adolescent male with aggressive spinal ependymoma harboring focal *MYC* amplification. Testing for *MYC* amplification may be reasonable in newly-diagnosed spinal ependymomas to aid in characterization.

EPEN-30. C11ORF95-RELA FUSION PROTEIN ENGAGES NOVEL GENOMIC LOCI TO DRIVE MURINE EPENDYMOMA GROWTH

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RATIONALE: Over 70% of supratentorial (ST) ependymoma are characterized by an oncogenic fusion between C11ORF95 and RELA. C11ORF95-RELA fusion is frequently the sole genetic driver detected in ST ependymoma, thus ranking this genomic event as a lead target for therapeutic investigation. RELA is a transcription factor (TF) central to mediating NF-kB pathway activation in processes such as inflammation, cellular metabolism, and chemotaxis. HYPOTHESIS: We posited that C11ORF95-RELA acts as an oncogenic TF that aberrantly shapes the tumor epigenome to drive aberrant transcription. Approach: To this end we developed an *in utero* electroporation (IUE) mouse model of ependymoma to express C11ORF95-RELA during embryonic development. Our IUE approach allowed us to develop C11ORF95-RELA driven tumor models and cell lines. We comprehensively characterized the epigenome and transcriptome of C11ORF95-RELA fusion driven mouse cells by H3K27ac ChIP-seq, ATAC-seq, and RNA-seq. RESULTS: This data revealed that: 1) C11ORF95-RELA directly engages 'open' chromatin and is enriched at regions with known RELA TF binding sites as well as novel genomic loci/motifs, 2) C11ORF95-RELA preferentially binds to both H3K27ac (active) enhancers and promoters, and 3) Bound C11ORF95-RELA promoter loci are associated with increased transcription of genes shared with human ependymoma. CONCLUSION: Our findings shed light on the transcriptional mechanisms of C11ORF95-RELA, and reveal downstream targets that may represent cancer dependency genes and molecular targets.

EPEN-31. SINGLE-CELL RNASEQ OF CHILDHOOD EPENDYMOMA REVEALS DISTINCT NEOPLASTIC CELL SUBPOPULATIONS THAT IMPACT ETIOLOGY, MOLECULAR CLASSIFICATION AND OUTCOME

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Ependymoma (EPN) is a brain tumor commonly presenting in childhood that remains fatal in the majority of children. Intra-tumoral cellular heterogeneity in bulk-tumor samples significantly confounds our understanding of EPN biology, impeding development of effective therapy. We therefore used single-cell RNA sequencing to catalog cellular heterogeneity of 26 childhood EPN, predominantly from ST-RELA, PFA1 and PFA2 subgroups. ST-RELA and PFA subgroups clustered separately, with ST-RELA clustering largely according to individual sample-of-origin. PFA1 and PFA2 subgroup EPNs cells were intermixed and revealed 4 major subpopulations – 2 with characteristics of ependymal differentiation (transporter and ciliated phenotype subpopulations), an undifferentiated subpopulation and a mesenchymal phenotype. Pseudotime analysis showed the undifferentiated progenitor subpopulation either differentiating into ependymal differentiation subpopulations or transitioning into the mesenchymal subpopulation. Histological analysis revealed that undifferentiated and mesenchymal subpopulations cells colocalized to perinecrotic/perivascular zones, the putative ependymoma stem cell niche. Deconvolution of PFA bulk transcriptome data showed that undifferentiated and mesenchymal subpopulations were associated with a poor prognosis; whereas the ciliated ependymal cell-differentiated subpopulation was associated with a good prognosis. In conflict with current distinct classification paradigms, the ratio of mesenchymal and ciliated subpopulations determined bulk-tumor subgroups assignment to PFA1 and PFA2 respectively. This atlas of EPN cellular heterogeneity provides an important advance in our understanding of EPN biology, identifying high-risk associated subpopulations for therapeutic targeting.

EPEN-33. PHARMACOGENOMICS REVEALS SYNERGISTIC INHIBITION OF ERBB2 AND PI3K SIGNALING AS A THERAPEUTIC STRATEGY FOR EPENDYMOMA

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Subgroups of ependymoma, especially RELA fusion-positive and posterior fossa type A tumors, are associated with poor prognosis. Curative therapeutic strategies have not yet been identified. We set up a high-throughput drug screening (HTS) pipeline to evaluate clinically established compounds (n=196) in primary ependymoma cultures (n=12). As culturing ependymoma is challenging, assay miniaturization to 1536-well microplates emerged as a key feature to process HTS despite smallest cell numbers. DNA methylation profiling showed that entity and subgroup affiliation from primary diagnosis was maintained in primary cultures, as assessed through molecular neuropathology 2.0 based classification (MNP 2.0, Capper, D. et al., Nature, 2018). A comparison of HTS data of ependymoma and other pediatric brain tumor models (n=48) revealed a remarkable chemoresistance in vitro. However, we identified Neratinib, an irreversible ERBB2 inhibitor, as the most prominent candidate which was preferentially active in a subset of the investigated ependymoma cultures (n=5). Combinatory treatment with Copanlisib, a PI3K inhibitor, was able to overcome resistance to single agent treatment using Neratinib in established cell lines of ependymoma (n=3) and 2/4 primary cultures for which combinatory treatment could be tested. Finally, we validated efficacy of Neratinib combined with Copanlisib in mice bearing ependymoma xenografts which revealed significantly reduced tumor size compared to vehicle-treated animals. In summary, our study demonstrates that HTS may reveal targeted therapies for pediatric brain tumors. Specifically, we found a synergistic interaction of Neratinib and Copanlisib for treatment of ependymoma, thereby providing a novel therapeutic approach in an otherwise largely chemoresistant entity.

EPEN-34. THE CRISPR-CAS9 SYSTEM-MEDIATED ENDOGENOUS GENE REARRANGEMENT INDUCED C11ORF95-RELA FUSION IN VITRO AND IN VIVO THAT LED TO THE DEVELOPMENT OF EPENDYMOMA-LIKE TUMOR

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Recent large-scale genomic studies of ependymal tumors have identified recurrent RELA and YAP1 fusion genes in supratentorial ependymomas. The formation of the C11orf95-RELA fusion gene has been attributed to massive genomic rearrangement involving chromosome 11q termed Chromothripsis in many cases. However, the causal relationship has not been clarified experimentally. In this study, we developed a system to reproduce the oncogenic gene rearrangement using the CRISPR-Cas9 system and examined whether consequent endogenous ependymoma fusion genes are competent to form brain tumors in mice. Initially, to investigate whether C11orf95-RELA fusion can be formed by inducing the relevant gene rearrangement in vitro, we designed multiple guide RNAs on the human and mouse genomic loci and introduced them into cultured cells. RT-PCR and immunoblot analyses detected endogenous C11orf95-RELA fusion transcript and protein in both human and mouse cultured cells. Subsequently, we lentivirally introduced the gRNAs into a mouse brain. Brain tumor formation was observed from around 2 months after the lentivirus injection, thus indicating successful gene rearrangement followed by C11orf95-RELA fusion expression *in vivo*. Analysis of the tumor tissue con-

firmed the expression of the endogenous C11orf95-RELA fusion gene. These results suggested that a gene rearrangement is a primary mechanism to form the C11orf95-RELA fusion which is the direct driver of tumorigenesis. Our system to simulate a genomic event will provide significant insights into the understanding of the tumorigenic mechanism in ependymomas.

EPEN-35. PERITONEAL CARCINOMATOSIS OF ANAPLASTIC EPENDYMOMA: FIRST REPORTED CASE

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Peritoneal Carcinomatosis of anaplastic ependymoma is not a previously reported entity. The authors report on a child with multiple successfully treated brain and spine disease occurrences who subsequently develops carcinomatosis of the abdomen and no evidence of CNS recurrence. Ependymoma accounts for up to 10% of childhood CNS tumors diagnosed in the United States with a median age of 51–71 months. Typical locations are based on age. Disease is typically treated with surgical resection followed by radiation. The role of chemotherapy has not been proven but currently being examined with open clinical trials. We will describe patient's presentations, clinical treatment and recurrence with subsequent treatment and outcome at time of meeting.

EPEN-36. THE TREATMENT OUTCOME OF PAEDIATRIC SUPRATENTORIAL C11ORF95-RELA FUSED EPENDYMOMA: A COMBINED REPORT FROM E-HIT SERIES AND AUSTRALIAN NEW ZEALAND CHILDREN'S HAEMATOLOGY/ONCOLOGY GROUP

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AIM: Advances in molecular classification of paediatric ependymoma have been pivotal in improving risk stratification and understanding of this disease. *C11orf95-RELA* fused supratentorial ependymoma (ST-EPN) have been reported to have a poor outcome, with 10-year overall survival (OS) of 49% and progression free survival (PFS) of 19%. A cohort of patients from multiple international institutions with molecularly confirmed *C11orf95-RELA* fused ST-EPN were reviewed to assess their disease behaviour. METHOD: We reviewed patients with molecularly determined *C11orf95-RELA* supratentorial ependymoma diagnosed between 1999 – 2019. Demographic information, extent of surgical resection, use of radiotherapy and/or chemotherapy, disease recurrence, treatment at recurrence and clinical outcome data was collected. PFS and OS of all patients were estimated using Kaplan-Meier method. RESULTS: A total of 76 ST-EPN patients with *C11orf95-RELA fusion* were identified (median age: 7 years3 months, range: 5 months – 18 years7 months). 58 patients (76.3%) had complete surgical resection. 70 patients(92.1%) received radiotherapy. 55 patients(72.3%) received chemotherapy. The 10-year OS of *C11orf95-RELA* fused ST-EPN was 72.4% and PFS was 63.8%. In contrast, ST-EPN at a single institution with unconfirmed molecular status had an OS of 61.1% and PFS of 34.9%. CONCLUSION: Detailed molecular analysis identified distinct subgroups of patients with ST-EPN. Patients from this cohort with *C11orf95-RELA* methylation profiles had a significantly higher OS compared to previous reports and those with unconfirmed fusion status, emphasising the critical importance of complete molecular profiling to assist in treatment decision making. Complete molecular analysis in future prospective cohorts is essential for accurate risk stratification and treatment selection.

EPEN-37. TREATMENT OUTCOME OF RECURRENT EPENDYMOMA IN CHILDREN IN NORTHERN EGYPT

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INTRODUCTION: 1/3 of Ependymoma patients will develop recurrence with only 25% are long term survivors. Treatment is usually between surgery, radiotherapy or combinations. PATIENTS AND METHODS: Retrospective review of children with recurrent Ependymoma in northwest of Egypt between 2005 and 2019 in Alexandria School of medicine records. RESULTS: 27 patients were identified 19 of them after 2010. The median age is 9.7 years (1.5–19), with 16 males and 11 females. Pathology were 11 grade II Ependymoma and 16 anaplastic Ependymoma. 16 had gross residual disease after 1st surgery and 22 received radiotherapy initially at median dose of 53.5 Gy, 4 patients received suboptimal radiotherapy. The initial site was14 supratentorial tumors and 13 infratentorial. Median time to recurrence is 27.6 months(3–84), and recurrences were 17 local and 9 CSF disseminated, and one patient had recurrence at the scar with lung metastasis. At a median follow up of 56.6 months 14(51.8%) are still alive. Treatment was surgery only in 6(4 alive) radiotherapy alone in 2(1alive), combined in 15(9 alive) and 4 patients received neither. The best outcome were in patients with late local relapse treated with complete resection and CSI after 2010. Radiotherapy dose was between 54 to 57.3 Gy and one patient developed reirradiation injury at brain stem. 5 of the 14 living patients is having toxicity in form of hearing aids (4) and low TSH(1). CONCLUSION: Aggressive treatment of recurrent Ependymoma with surgery and radiotherapy is feasible and about half of the patients are salvageable.

EPEN-38. EZH2 INHIBITORY PROTEIN (EZHIP/CXORF67) EXPRESSION IS HIGHLY CONCORDANT WITH H3K27ME3 LOSS AND IS A PROMISING SURROGATE MARKER FOR POSTERIOR FOSSA TYPE A EPENDYMOMAS

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BACKGROUND: Gene expression and DNA methylation have identified 2 distinct clinicopathological subgroups among the WHO Grade II/III posterior fossa (PF) ependymomas (EPN), of which the PF-A molecular subgroup associates with poor outcome. OBJECTIVE: To analyse the utility of immunohistochemistry for H3K27me3, Tenascin C, EZHIP (Cxorf67), EZH2 and fluorescence-in-situ-hybridisation for chromosome 1q21 locus gain in the prognostic stratification of PF-EPNs. METHODS: All PF Grade II/III tumors were retrieved (2009–2019). Immunohistochemistry for H3K27me3, H3K27M-mutation-specific antibody, EZH2, EZHIP, Tenascin-C and fluorescence in-situ hybridisation for 1q21 locus was performed and compared with outcome. RESULTS: 71 PF-EPNs were included. H3K27me3 loss (PF-A) was seen in 65% (46/71) of cases, of which majority were positive for EZHIP (73%, 24/33) and Tenascin C (65%, 28/43). Minority showed chromosome 1q gain (19%, 8/42). An EZHIP negative PF-A tumor was immunopositive for H3K27M-mutant staining, while all others were negative. PF-A EPNs occurred at a median age of 4.5 years (range 1–53), were predominantly grade III (Grade III:II – 1.6:1), and 50% (10/20) of patients on follow-up experienced tumor progression. EPNs with retained H3K27me3 (PF-B) did not show EZHIP expression (0/20) or 1q gain; however, tenascin C expression was seen in 47% (8/25) of them. They occurred predominantly in adults, showed Grade II preponderance and only 2/11 patients on follow-up experienced progression. EZH2 expression did not correlate with H3K27me3 loss but positively correlated with EZHIP expression (p=0.015). CONCLUSION: H3K27me3 is a reliable surrogate for prognostic classification of PF-EPNs. EZHIP expression is highly concordant with H3K27me3 loss and is a valuable adjunct.

EPEN-39. CLINICAL STRATIFIED TREATMENT OF LOCALIZED PEDIATRIC INTRACRANIAL EPENDYMOMA WITH COMBINED LOCAL IRRADIATION AND CHEMOTHERAPY WITHIN THE PROSPECTIVE, MULTICENTER E-HIT TRIAL – THE MOLECULAR SUBGROUP MATTERS

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BACKGROUND: Pediatric ependymoma is a heterogenous disease. Subgroup-specific clinical information on prospectively treated patients will help to improve treatment stratification. METHODS: Within the population based, prospective, multicenter E-HIT-trial (2001–2011) patients with localized ependymoma confirmed by neuropathological central-review, received hyperfractionated local radiotherapy (68Gy, 2x1Gy/day) followed by chemotherapy (stratum-A), or chemotherapy followed by local radiotherapy (54Gy, 1.8Gy/day) (children < 4years, stratum-B), or age-adapted radiotherapy with pre-/post-irradiation chemotherapy (residual tumor, diagnosis after 2005, stratum-C). Retrospective classification of DNA-methylation was available for n=164 E-HIT-trial participants, and n=80 patients with comparable treatment and prospective registration in the subsequent HIT-interim-registry (2012–2014). FINDINGS: For 291 E-HIT-trial patients, 5-year progression-free (PFS) and overall survival (OS) were 61±3%, and 81±2%. Five-year PFS/OS after complete resection were 71±4% and 87±3% in stratum-A (n=127), and 64±5% and 86±4% in stratum-B (n=86). Outcome was poor after incomplete resection, irrespective of treatment-stratum (n=78, 5-year PFS/OS: 43±6%, 68±5%). In the pooled trial- and registry-cohort, there were 152 patients with PF-EPN-A (5-year PFS/OS: 44±4%, 77±4%), 40 of them with 1q-gain (5-year PFS/OS: 28±7%, 66±8%), 21 with PF-EPN-B (5-year PFS/OS: 90±7%, 100%), 59 with ST-EPN-RELA (5-year PFS/OS: 63±7%, 87±5%), and 4 with ST-EPN-YAP1 (2 progression/relapse, no death). CONCLUSION: Outcome differed between molecular subgroups and insufficient survival rates were achieved for patients with PF-EPN-A with 1q-gain, despite combined radio- and chemotherapy treatment. Treatment reduction in the context of a clinical trial may be considered for PF-EPN-B.

EPEN-41. C11ORF95-RELA FUSION REGULATES ABERRANT GENE EXPRESSION THROUGH THE UNIQUE GENOMIC BINDING SITES FOR EPENDYMOMA FORMATION

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A majority of supratentorial ependymoma is associated with recurrent C11orf95-RELA fusion ($RELA^{FUS}$). The presence of RELA as one component of the $RELA^{FUS}$ leads to the suggestion that NF-kB activity is involved in the ependymoma formation, thus being a viable therapeutic target in these tumors. However, the oncogenic role of another C11orf95 component in the tumorigenesis is not still determined. In this study, to clarify the molecular mechanism underlying tumorigenesis of $RELA^{FUS}$, we performed $RELA^{FUS}$-ChIP-Seq analysis in cultured cells expressing the $RELA^{FUS}$ protein. Genomic profiling of $RELA^{FUS}$ binding sites pinpointed the transcriptional target genes directly regulated by $RELA^{FUS}$. We then identified a unique DNA binding motif of the $RELA^{FUS}$ different from the canonical NF-kB motif in de novo motif discovery analysis. Significant responsiveness of $RELA^{FUS}$ but not RELA to the motif was confirmed in the reporter assay. An N-terminal portion of C11orf95 was sufficient to localize in the nucleus and recognizes the unique motif. Interestingly, the $RELA^{FUS}$ peaks concomitant with the unique motif were identified around the transcription start site in the $RELA^{FUS}$ target genes as previously reported. These observations suggested that C11orf95 might have served as a key determinant for the DNA binding sites of $RELA^{FUS}$, thereby induced aberrant gene expression necessary for ependymoma formation. Our results will give insights into the development of new ependymoma therapy.

EPEN-42. MOLECULAR PROFILING REVEALS DISTINCT SUBGROUPS OF PEDIATRIC SPINAL EPENDYMOMA

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Paediatric spinal ependymomas are important, albeit uncommon, malignant central nervous system tumours. Unlike adults, children with these tumours are likely to experience a more aggressive disease course, with a higher rate of local failure and a higher rate of metastases. The clinical and molecular factors underlying these differences remain poorly characterized. We analyzed spinal ependymoma (SEPN) tumour samples from 27 paediatric patients (female: 11, male: 15; age range: 4–18 years) using genome-wide DNA methylation profiling, copy-number analysis, as well as transcriptome profiling. Using DNA methylation profiles, two distinct unsupervised consensus-clustering approaches, hierarchical clustering and non-negative matrix factorization reliably identified two subgroups. These subgroups were designated as Myxopapillary ependymomas (SP-MPE) and spinal ependymomas (SP-EPN) based on the online Classifier tool (MNP2.0). The genome-wide copy-number analysis showed differences in numbers and pattern of copy-number alterations between these groups. The gain of chromosome 20 (39%) followed by loss of chromosomes 6 (28%), 10 (28%), and 13 (28%) were detected in the SP-MPE group, whereas loss of chromosome 22 was frequent (60%) in the SP-EPN group. Transcriptomics analysis showed that genes associated with oxidative phosphorylation, TCA cycle components, electron transport, and Interferon-gamma production characterize the SP-MPE group whereas potassium ion import and regulation of astrocyte differentiation characterize the SP-EPN group. Western blot analysis validated the increased protein expression of oxidative phosphorylation complexes in SP-MPE. With this study, we provide a foundation for further molecular characterization of pediatric SEPN subgroups. Our results suggest that mitochondrial oxidative phosphorylation may drive the regulation of energy metabolism of SP-MPE tumours.

EPEN-43. TARGETING INTRA-TUMOUR HETEROGENEITY IN PAEDIATRIC EPENDYMOMA: AN INTEGRATED OMICS STUDY TOWARDS PATIENT-TAILORED THERAPY

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Ependymoma (EPN) is the second most common malignant paediatric brain tumour, which despite extensive genomic sequencing, no novel therapeutic options have been discovered. Multi-omics are anticipated to reveal dysregulated pathways that may be predictive of patient-specific biomarkers. Given the close association between gene expression, active biochemical signaling and metabolism, there is an unmet scientific challenge to determine whether EPN gene expression correlates with aberrant metabolic pathways, thus presenting therapeutic vulnerabilities. We first compared two distinct subgroups of EPN, PF-A and ST-RELA, identifying 115 metabolites and 1580 upregulated genes between the two subgroups, therefore validating previously reported genetic clustering of these two subtypes. We next integrated transcriptomics and metabolomics, comparing 28 intra-tumour tissue regions from eight primary PF-A EPN patients. Polar metabolites and RNA were simultaneously extracted from the same population of cells. RNAseq identified dysregulated genes and liquid chromatography-mass spectrometry (LC-MS) detected 98 significantly altered metabolites between 18 multi-regions, the majority mapping onto the arginine and proline pathways. Integration of genes and metabolites using pathway-based network analysis revealed 124 aberrant gene-metabolite interactions between intra-tumour regions, with large numbers occurring in the glucogenesis and glycine metabolic pathways in 6/8 patients. These may represent ubiquitous and therapeutically relevant metabolic pathways critical for EPN survival. Additionally, patients presented at least one unique intra-tumour genomic-metabolomic interaction, applicable for patient-tailored therapy. This is the first exploration of EPN multi-omic integration and intra-tumour heterogeneity. Selected drug targets predicated on aberrant gene-metabolite networks will be validated in multi-region patient-derived cell lines and orthotopic models using repurposed therapeutics.

EPEN-44. EXTRACELLULAR VESICLES OF SUPRATENTORIAL EPENDYMOMA RELA MEDIATE INTERACTIONS WITH CELLS OF THE TUMOR MICROENVIRONMENT

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Ependymal tumors (EPNs) account for ~10% of all pediatric brain tumors. Supratentorial EPN characterized by RELA fusions (ST-EPN-RELA) and posterior fossa EPN group A (PF-EPN-A) form the two most frequent molecular groups, both of which are associated with poor prognosis and for which only limited therapeutic options are available. Since pediatric EPNs have a relatively low mutational burden, identification and characterization of tumor-associated pathways and molecular processes is of critical importance to inform potential therapeutic targets. Previous transcriptional studies implicated aberrant vesicular pathways in ST-EPN-RELA, prompting further investigation into their putative role in EPN pathogenesis. To this aim, we isolated extracellular vesicles (EVs) of ST-EPN-RELA patient derived cell lines and performed protein mass spectrometry. The specific ST-EPN-RELA EV protein content resembles the parental cells as well as primary tumors. Promising candidates to be transferred by ST-EPN-RELA EVs but not control EVs were associated with unfolded protein response and endoplasmic reticulum stress. When uptaken by recipient cells of the tumor microenvironment, brain endothelial cells or microglia, ST-EPN-RELA EVs induced proliferation and had a chemoattractant effect towards the tumor. ST-EPN-RELA EVs stimulated angiogenesis of brain endothelial cells potentially by the transfer of ER stress proteins. Uptake of ST-EPN-RELA EVs by microglia changed their activation status indicating a tumor promoting function through EV transfer. Therefore, we hypothesize that vesicular pathways play an important role in the pathogenesis of pediatric ST-EPN-RELAs and that an improved understanding may promote new therapeutic opportunities.

EPEN-45. NORMALIZING AND FACILITATING GENOMIC TESTING AT DIAGNOSIS IN PEDIATRIC EPENDYMOMA

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The current consensus is that diagnosis and treatment of ependymoma should be based upon clinical and molecular classification. As we move into this paradigm, it is important all ependymoma cases undergo tumor collection, preservation, and molecular profiling at diagnosis. Our group of 6 sites gathered data on a cohort of 72 ependymoma cases. Sites were asked to report known molecular findings; 60/68 eligible cases (88%) did not include genetic findings. The low number of cases with molecular findings was surprising and since cases were diagnosed from as early as 2004, we asked collaborators to share their current practice in profiling (e.g., how frequently; in what setting were ependymomas sent for testing) to try and better understand current practice at sites. Since the publication of ependymoma molecular data, sites with a neuro-oncology program report sending almost all newly diagnosed ependymomas for molecular testing, whereas current practices at sites without dedicated neuro-oncology were less consistent. Profiling in the setting of relapse was more frequently reported at all centers. The implementation of molecular testing at diagnosis may need support at sites without dedicated neuro-oncology. Lead investigators for upcoming ependymoma clinical trials will need to think carefully about the logistics of profiling at centers where this is not standard practice at diagnosis.

EPEN-46. DNA METHYLATION LANDSCAPE OF RECURRENT PEDIATRIC EPENDYMOMA IDENTIFIES KEY DRIVER EVENTS

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Pediatric ependymoma has a propensity of developing late and multiple relapses over many years. About 50% of patients will experience relapses and eventually succumb to their disease. Our study is aimed to understand the mechanism of resistance and drivers associated with pediatric ependymoma relapse. We developed 10 sets of patient-derived orthotopic xenograft (PDOX) models of recurrent pediatric ependymoma from both RELA and PFA tumors. Time from primary tumor to last recurrence ranges from 2.75 – 13 years. Number of recurrences per patient ranges from 1 – 7 times. We performed Reduced Representation Bisulfite Sequencing (RRBS) and Whole Genome Bisulfite Sequencing (WGBS) to map the DNA methylation landscape of total of 30 samples of matched primary and recurrent tumors. Molecular subtypes and DNA methylation profiles were maintained, and RELA/PFA signature genes showed similar expression pattern during serial relapses. RELA- and PFA-specific Differentially Methylated CpGs (DMCs) are identified from primary tumors. During the recurrent process, individual patients displayed consistent changes of DMCs and shared DMCs among patients became convergent. We then identified shared common specific DMCs in recurrent RELA and PFA tumors that emerged as the driver signatures. We found that these recurrent DNA methylation signatures could be identified from primary tumors. Our analysis of the PDOX models showed that they can mostly recapitulate humor tumors' DNA methylation and we were able to identify shared recurrent specific DMCs associated genes in PDOX models. Our comprehensive data is the first of its kind aimed to investigate the epigenetic mechanisms during pediatric ependymoma recurrence.

EPEN-47. PEDS: PEDIATRIC EPENDYMOMA DISCOVERY STUDY

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The prognosis for pediatric ependymoma remains unaffected by recent discovery. Upfront therapy is maximal surgical resection followed by radiation and the utility of histologic diagnosis remains unreliable. Nine molecular subgroups and possible genetic drivers of ependymoma have been identified, but the implementation of these findings into targeted therapy and stratified clinical trials has not occurred. It is imperative that researchers work collaboratively to move discovery towards clinical testing. Heterogeneity of ependymoma requires that we collect a large amount of data; progress in the field is dependent on deep analysis of this information. As we further subclassify ependymoma, it will be important to have a large patient population for enrollment onto clinical trials, which will maximize data collection and the amount of materials available for experimentation and analysis. Researchers in the United States, Europe, and Japan propose an international ependymoma research collaborative which aims to synthesize research across sites, foster drug discovery, and prove strategies to integrate clinical and molecular diagnostics into biology-based therapy. Our goal is to maximize information and materials from existing bio and data repositories and not to 're-create the wheel'. We envision PEDS as an open science platform and present this concept at ISPNO to invite our colleagues to harmonize efforts towards pediatric ependymoma discovery.

EPEN-49. RESPONSE OF RECURRENT EPENDYMOMA TO MEMMAT BASED METRONOMIC ANTIANGIOGENIC COMBINATION THERAPY UTILIZING TAPERED BEVACIZUMAB AND MAINTENANCE THERAPY WITH CELECOXIB AND FENOFIBRATE

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Recurrent ependymomas have a dismal prognosis (2 year survival rates 29% OS and 23% EFS) and are relatively resistant to conventional chemotherapy. We previously reported five relapsed ependymoma patients treated with a MEMMAT based metronomic antiangiogenic combination therapy. All patients are currently alive, including four patients who were multiply relapsed with at least three recurrences. These four patients received between 44–52 weeks of therapy with minimal toxicity. Three had recurrent disease within an average of 44 months (median 42 months) after discontinuation of therapy. One patient who received the following tapering bevacizumab schedule: q3 weeks x 3, q4 weeks x 4 and q5 weeks x 5 followed by maintenance therapy with fenofibrate and celecoxib is in complete remission 12 months post treatment. This regimen was well tolerated with good quality of life in this patient population. Our results suggest that the chosen anti-angiogenic drug combination prolonged the time to progression in these multiply relapsed patients and thus may be particularly beneficial for patients with recurrent ependymoma. Tapered bevacizumab and maintenance therapy with celecoxib and fenofibrate may be modifications worth further investigation for prolonged disease free survival in relapsed ependymoma patients.

EPEN-50. THE MANAGEMENT AND TREATMENT OF PEDIATRIC SPINAL CORD EPENDYMOMA: RESULTS FROM A COLLABORATIVE INTERNATIONAL MULTI-INSTITUTIONAL REVIEW

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PURPOSE: Pediatric Spinal cord ependymoma (SCE) is rare, and the management is often heterogeneous across centers. We evaluated the impact of clinical, pathologic, and treatment-related factors on outcomes in a multi-institutional, international cohort. METHODS: SCE patients age <21 years were reviewed across 5 institutions. We utilized nonparametric descriptive statistics, survival, and recursive partitioning analysis (RPA) to examine patient, tumor, histopathologic and treatment characteristics, failure pattern, and cause of death. RESULTS: 125 patients were identified, 18 (14.4%) with metastases. Initial surgery was GTR, and STR in 44, 56% of patients respectively. Histology was grade 1, 2, and 3 in 55, 17.7 and 23.2% respectively. 55 patients with initial GTR were observed (52.7%) or irradiated (43.6%); 60 patients had STR and were observed (40%) or irradiated (60%). The 7-year event-free (EFS) and overall survival (OS) was 60% (95% CI 51.5–71.4) and 79% (95% CI 71.1–87.8) respectively. STR and metastasis increased the hazard for death [HR 1.87, 95% CI 1.02–3.57, p=0.05 (vs. GTR)] and [HR 2.28, 95% CI 1.1–5.2, p=0.048 (vs. localized)] respectively. Across 43 failures, local failure predominated (48.8%). Distant and combined failure occurred in 30.2 and 13.9% respectively. Adjuvant RT offered a 20% absolute improvement (vs. observation) in EFS at 5 years regardless of extent of resection. RPA identified thoracic (vs. non-thoracic), grade (1 & 3 vs. 2), STR (vs. GTR) and metastases as determinants of inferior EFS. CONCLUSIONS: Tumor and treatment-related factors are predictive of EFS. OS is favorable despite diverse schema and frequent distant failures.

EPEN-51. CHILDHOOD INTRACRANIAL EPENDYMOMA: A MULTI-CENTER RETROSPECTIVE ANALYSIS

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Ependymoma is a heterogeneous disease which is resistant to improvement. Current challenges are the unreliability of histologic classification, the uncertain role of adjuvant chemotherapy, and a lack of clinical trials integrating molecular and clinical diagnostics into risk-guided therapy. Ependymoma can show surprising latency, reoccurring many years after the original diagnosis. In this study, we performed a retrospective analysis of ependymoma cases treated at six centers over a period of 12 years. A total of 73 cases were submitted from six sites; 68 cases were retained for review. Median age at diagnosis was 4.1 years and gender was reported as male (50%) and female (50%). Histologic grade was reported as Grade II (49%) and Grade III (50%)(not reported: 1). Anatomic location reported as supratentorial (27%) and infratentorial (73%). Metastatic disease was reported in 9% of patients. At diagnosis, gross total resection was achieved in 59% of cases. Twenty-eight percent of patients have died, 59% of patients are alive (with and without disease), and 13% of patients are lost to follow-up. Maximal safe surgical resection is currently the best predictor of long-term survival but was achieved in only 60% of cases. Biology-based therapy will be the next step towards improving the prognosis of pediatric ependymoma.

EPEN-52. METABOLIC REGULATION OF THE EPIGENOME DRIVES LETHAL INFANTILE EPENDYMOMA

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PFA ependymomas are a lethal glial malignancy of the hindbrain found in infants and toddlers. Lacking any highly recurrent somatic mutations, PFAs have been proposed to be a largely epigenetically driven entity, defined by hypomethylation at the histone 3 lysine 27 residue. Unfortunately, an almost complete lack of model systems has limited the discovery of novel PFA therapies. In this study, we have identified that the PFA hypoxic microenvironment controls the availability of specific metabolites, resulting in diminished H3K27 trimethylation and increased H3K27 acetylation *in vitro* and *in vivo*. Unique to PFA cells, transient exposure to ambient oxygen results in irreversible cellular toxicity. Furthermore, perturbation of key metabolic pathways is sufficient to inhibit growth of PFA primary cultures *in vitro*. Although PFA tumors exhibit a low basal level of H3K27me3, inhibition of H3K27 methylation paradoxically demonstrates significant and specific activity against PFA. Thus, we propose a "Goldilocks Model" of metabolic-epigenetic regulation in PFA ependymoma, whereby increased or decreased H3K27 trimethylation results in cell death. Mapping of PFA ependymoma tumours suggests a cell of origin arising in the first trimester of human development where there is a known hypoxic microenvironment. Therefore, targeting metabolism and/or the epigenome presents a unique opportunity for rational therapy for infants with PFA ependymoma.

EPEN-53. C11ORF95-RELA REPROGRAMS 3D EPIGENOME IN SUPRATENTORIAL EPENDYMOMA

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Ependymoma is the third most common malignant brain tumor in children. However, there is no effective chemotherapy identified and treatment is limited to surgery with or without adjuvant radiation therapy currently. Thus, to develop targeted therapy based on the underlying biology is an urgent need. Since 2014, *C11orf95-RELA* fusion was found to be the most recurrent structural variation in approximately 70% of supratentorial ependymomas (ST-EPN), but the molecular mechanisms of oncogenesis are unclear. Here we utilized HEK293T transgene models and a ST-EPN cell line to investigate the epigenomic changes and transcriptional regulations by C11orf95-RELA fusion. By applying ChIP-seq and HiChIP approaches, we found C11orf95-RELA is a novel transcription factor that recognizes a specific DNA motif dictated by the C11orf95 component while the RELA component is required for driving the expression of ependymoma-associated genes such as *CCND1* and *L1CAM*. Moreover, C11orf95-RELA modulates chromatin states and mediates chromatin interactions, leading to transcriptional reprogramming in ST-EPN cells. Multiple signaling pathways such as Notch signaling and G-protein signaling are identified to be involved in ST-EPN development. Our findings provide important characterization of the molecular underpinning of *C11orf95-RELA* fusion and shed light on potential therapeutic targets for *C11orf95-RELA* subtype ependymoma.

EPEN-54. ACNS0831, PHASE III RANDOMIZED TRIAL OF POST-RADIATION CHEMOTHERAPY IN PATIENTS WITH NEWLY DIAGNOSED EPENDYMOMA AGES 1 TO 21 YEARS

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PURPOSE: The primary objective of this study is to determine the EFS and OS of children with gross total and near totally resected ependymoma (EPN) treated with post-operative focal radiation therapy (RT) followed by randomization to either RT alone or RT + 4 cycles of maintenance chemotherapy with vincristine, cisplatin, cyclophosphamide and etoposide. Secondary objectives include estimating the EFS and OS of children not randomized, evaluation of neurobehavioral and quality of life (QoL) endpoints, and EPN biomarkers. RESULTS: 479 patients enrolled, 451 were eligible. Of 325 eligible randomized patients, 161 were randomized to RT alone and 164 to RT + maintenance chemotherapy. Age range (1–21 years, median 4.9 years). The planned primary analysis was based on intent-to-treat, irrespective of actual treatment received. Based on the data available as of 12/31/2019, estimated 3-year EFS in the RT + maintenance chemotherapy

vs. RT arms were 78% vs. 72%, respectively, which did not meet statistical criteria to establish the benefit of maintenance chemotherapy post RT (1-sided log-rank p-value=0.074). Due to significant noncompliance (30.5% in the RT + maintenance vs 4.3% in the RT arm), a planned secondary "as treated" analysis was performed. With median follow-up of 42.6 months among patients without events, the 3 year EFS estimates for patients who received any chemotherapy (n=114) vs. those who received RT only (n=196) were 80% vs. 71%, respectively (1-sided p-value = 0.0121). CONCLUSION: Early results in this randomized trial suggest that there may be some EPN patients who benefit from maintenance chemotherapy. Genomic analyses are ongoing.

EPIDEMIOLOGY

EPID-01. TRENDS OF INCIDENCE IN PEDIATRIC BRAIN TUMORS IN KUMAMOTO PREFECTURE, JAPAN

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BACKGROUND/PURPOSE: One of the most problematic issues Japan has is a declining birthrate resulting in an aging society. There are some reports on the trends of incidence in brain tumors in the elderly, whereas few reports on those in the children. The aim of this study is to investigate the trends of incidence in childhood primary brain tumors. METHODS: The population of children aged <15 years was available from Kumamoto Prefecture's annual census between 1990 and 2017. During the period 301 childhood primary brain tumors (124 gliomas, including astrocytic tumors and ependymomas, 35 embryonal tumors, 34 germ cell tumors, 22 craniopharyngioma, and 86 others) were registered with the Kumamoto Brain Tumor Data Bank, and investigated. RESULTS: The average of the annual incidence rate per 100,000 child populations was 3.90 for total brain tumors, 1.63 for gliomas, 0.44 for embryonal tumors, 0.42 for germ cell tumors, 0.26 for craniopharyngioma, and 1.15 for others. Divided into the first half from 1990 to 2003 and the second half from 2004 to 2017, there was no significant difference in the incidence of brain tumors aged <15 years between the two periods. However, the average of the annual incidence rate/100,000 child populations was 3.02 in the first half, while significantly increased in the second half of 4.78 (p=0.00075, t-test). DISCUSSION & CONCLUSIONS: The average number of children aged <15 years in Kumamoto Prefecture was 31,2737.9 from 1990 to 2003, while decreased remarkably to 251460.2 from 2004 to 2017. A decrease in the number of children may affect increasing the incidence rate of pediatric brain tumors.

EPID-03. COMPARISON OF SURVIVAL IN ADULT AND PEDIATRIC PATIENTS WITH MEDULLOBLASTOMA: A 2018 SEER BASED ANALYSIS

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Medulloblastoma (MB) is the most common high-grade primary brain malignancy in children and accounts for 1% of adult brain tumors. Previous studies have compared survival in pediatric and adult MB from the National Cancer Institute Surveillance Epidemiology and End Results (SEER) database finding no difference. However, diagnostic subgroup analyses are limited. We examined survival in children (age 0–19) and adults (20–79) coded as MB in the 2018 SEER database (2000–2016), using Kaplan Meier analysis, log-rank test and Cox proportional hazard ratios (HR) with 95% confidence intervals (CI).). MB in SEER-18 is defined as ICD-O-3 histology codes 9470–9474 (n=1,728). ICD 9473, supratentorial PNET (sPNET, n=97) is biologically distinct so was analyzed separately. 5-year survival for MB, excluding sPNET, was similar in children (n = 1,091, 75.3%) and adults (n= 488, 79.1%) (HR=0.97, CI: 0.79 – 1.17, p=0.50). Subtype analyses showed no survival difference comparing adults and children with desmoplastic nodular MB (n=222, p=0.09), large cell MB (n=73, p=0.46), or MB NOS (n=1330, p=0.10). In contrast, children with sPNET had improved survival (n=65, 72.3%) compared to adults (n=29, 51.7%) (HR = 2.0, CI: 1.10 – 3.92; p=0.02,). In conclusion, 2018 SEER data for MB continue to show no survival difference between adults and children, suggesting adult patients could appropriately be entered on pediatric MB treatment protocols. Further analyses of the 2018 data are ongoing adjusting for sex, race, and treatment. Comparison of adults and children with MB and sPNET will be re-evaluated using the new 2016 World Health Organization classification.

EPID-04. MORBIDITY IN PAEDIATRIC BRAIN TUMOURS: 17 YEARS' EXPERIENCE IN A TERTIARY NEUROSURGICAL UNIT

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The treatment of paediatric brain tumours has shown significant improvement over the last 2 decades. The aim of our study is to evaluate the prevalence of various effects among this population within our institution. 102 patients diagnosed with a brain tumour at the age of 0–18 years between 2002 and 2018 were identified within a single paediatric institution. Data was collected retrospectively based on electronic medical records. Medulloblastoma (20.6%) was the most common subtype followed by pilocytic astrocytoma (18.6%) and craniopharyngioma (11.8%). Overall, the 5-years survival rate was approximately 77%. Endocrine dysfunction was reported in 36% of the population, mainly due to tumour located in suprasellar region and irradiation causing progressive pituitary dysfunction. Neurological disorders such as epilepsy, weakness, cranial nerves palsy, visual and hearing impairment were present in 46% of the population. Importantly, 20.4% of patients who received chemotherapy had some degree of sensorineural hearing loss. 16% of the population suffered from impaired neurocognition which is likely an underestimation as screening could not be performed on all patients. Other significant complications are infections (12%) and ventriculoperitoneal shunt dysfunction (7%). Most of these effects can be attributed to direct injury to the developing brain caused by the tumour or related to its treatment during surgical excision and the long term side effects of chemotherapy and radiation therapy. Morbidities in various domains can pose significant challenges to survivors of paediatric brain tumours. Active screening and surveillance of these effects can help improve the health outcomes of survivors of paediatric brain tumours.

EPID-05. EVALUATION OF THE INCIDENCE OF CENTRAL NERVOUS SYSTEM TUMORS IN A CHILDHOOD CANCER TREATMENT CENTER AND THE CREATION OF A SPECIFIC GROUP

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Central Nervous System Tumors (CNST) are the main solid neoplasm of childhood, representing 20% diagnosis. Based on this information, a search was carried out at a reference treatment center for childhood cancer in the state of Sao Paulo, belonging to University of Sao Paulo- ITACI/HCFMUSP, and at between 2017 and 2019, 352 new patients, 116 of which were neoplasm of CNS (32.9%). Aiming at an incidence of new cases, in 2019, an institutional group was created, with a team composed of Pediatric Oncologists, Neurosurgeons, Radiologists, Radiotherapists and Pathologists. In this first year, 31,8% of the 132 new patients were diagnosed with CNS tumor. According to WHO 2016, 15 patients were classified as a group that includes Diffuse Astrocytomas, Oligodendrioglial Tumors and Other Astrocytic Tumors. Among the other patients, 14.2% were Medulloblastomas, 4.7% Embryonic Tumors and 2.3% ART / RT. Patients diagnosed with diffuse brainstem glioma accounted for 11.9% of the total. The institution had a diagnosis of Angiocentric Glioma, Craniopharyngioma, Plexiform Neurofibroma and Anaplastic Ependymoma. Neuronal-glial tumors accounted for 9.5% of cases. Choroid plexus tumors represents 5%. Among them, 4.72% had metastatic tumors: Neuroblastoma and Ewing's Sarcoma. Of the total of 42 patients, there were 5 deaths, 4 due to disease progression and one due to clinical complications. With the group, the discussions were carried out, allowing us to analyze that the presence of the Radiotherapy, Neurosurgery and Pathology team from the first moment, optimized the beginning of treatment and increased the patients' survival.

EPID-06. DIAGNOSTIC INTERVAL TIME OF PEDIATRIC CNS TUMORS: A REPORT OF THE CANCER IN YOUNG PEOPLE IN CANADA (CYP-C) DATABASE

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INTRODUCTION: CNS tumors are the second most common neoplasm in children and have historically been associated with longer time to diagnosis. Data on the time-to-diagnosis for Canadian children with CNS tumors

are limited and outdated. We aimed at evaluating the diagnostic interval time(DIT) for Canadian children, and identifying factors possibly associated with prolonged DIT. METHODS: Using the CYP-C database, we analyzed data from children <15 years, diagnosed with CNS tumors between 2001–2015. DIT was defined as time in weeks, elapsed from the first contact with a healthcare provider to confirming diagnosis. We described DIT according to patient's demographics, socioeconomic, geographic factors as well as tumor-related criteria. RESULTS: Patients from all Canadian provinces, except Ontario, had available timepoints to calculate DIT. The cohort included 842 patients. Mean DIT for all patients was 11.7 weeks(median 1.4). Gliomas had the longest mean DIT and embryonal tumors had the shortest(14.6 and 3.6 weeks *p<0.01*). ATRT and medulloblastoma had a mean DIT of 1.3 and 4.3 weeks respectively. DIT for HGG was shorter than for LGG (6.4 versus 16.1 weeks, *p<0.01*). Metastatic disease, infratentorial tumors, or age £36 months had significantly shorter DIT (5.6 vs 12.4 vs 18.4, 7.4 vs 13.1 and 8.6). Sex, annual income(QAIPPE), and distance from tertiary center did not influence DIT. CONCLUSION: The current diagnostic interval time for pediatric CNS tumors in Canada is 11.7 weeks(median 1.4weeks). These results only reflect the healthcare system's contribution toward diagnosis confirmation, but not the patient interval before seeking medical attention.

EPID-07. A GLOBAL PERSPECTIVE ON THE BURDEN OF PEDIATRIC CENTRAL NERVOUS SYSTEM TUMORS

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Although approximately 90% of pediatric cancer cases exist in low- and middle-income countries, the magnitude of the global burden of pediatric central nervous system (CNS) tumors remains poorly quantified. METHODS: Data from International Incidence of Childhood Cancer-3 and CONCORD-3, which include observed incidence and survival from population-based cancer registries (PBCR), and from GLOBOCAN 2018 and Global Burden of Disease 2016, which produce burden estimates from observed and modelled data, were used to analyze epidemiologic characteristics and correlations for CNS tumors globally. Data from The World Bank were used for national macroeconomic variables. RESULTS: The majority of countries are not covered by PBCR, with information on incidence and survival available for 37% and 27% of countries, respectively. Survival data is not available for any low-income country. The incidence of CNS tumors varies markedly, from 0.4 to 49 $x10^6$ person-years, the greatest variability in pediatric cancer subgroups. Modelled data suggests that approximately 40,000 incident cases and 19,000 deaths occur from CNS tumors worldwide. When country-level data are segregated based on World Bank groups, a difference in incidence and survival exists ($p<0.05$). A higher national health expenditure correlates with both an increased incidence and survival of CNS tumors, while the inverse is true for under-5 mortality ($p<0.05$). CONCLUSIONS: Scarce facts are available, but this analysis establishes a link between national income and epidemiologic parameters for CNS tumors. In this context, carefully designed initiatives, focusing on a health-systems approach are critical to meet the global challenge of pediatric CNS tumors.

EPID-08. FINDING THE NEEDLE IN THE HAY STACK – POPULATION-BASED STUDY OF PREDIAGNOSTIC SYMPTOMATIC INTERVAL IN CHILDREN WITH CNS TUMORS

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PURPOSE: Delay in diagnosis of central nervous system (CNS) tumors in children is well documented. The aims of this study were to characterize the symptomatology of CNS tumors and the time to diagnosis in a large pediatric hospital in Canada. METHODS: Retrospective chart review of children diagnosed with a CNS tumor between 2000 and 2016 in Vancouver, British Columbia, Canada was performed. Data collected included demographics, symptomatology, tumor type, age at diagnosis, known visits to healthcare professionals, neuroimaging, therapy and post treatment relapse or progression. RESULTS: 148 children with complete medical records were reviewed. The average age at diagnosis was 87.8 months (standard deviation (SD) = 59.7; median = 72). 50.7% of patients had posterior fossa tumors and 49.3% had supratentorial tumors. 30% of patients were diagnosed after a single visit to a health care provider. 7.7% of children needed more than 4 visits. Median total time to diagnosis (PSI) was 62 days (range = 0-2047 days). The longest prediagnostic interval was first symptom onset to first healthcare provider visit (PSI1, median 37 days). Patients with posterior fossa tumors, presence of metastases, and symptoms of ataxia and paresis were associated with shorter PSI. CONCLUSIONS: CNS tumors in children continue to pose a diagnostic challenge with significant variability in time to diagnosis. Our population-based study found that median time from symptoms to seeking medical advice by parents was over a month. It is essential to uncover the reasons for delay and address them where possible.

EPID-09. THE INCIDENCE OF PRIMARY BRAIN TUMORS IN CHILDREN IN JAPAN BASED ON 2016 NATIONAL CANCER REGISTRY IN JAPAN

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The national cancer registries began in January 2016 and the actual number of cancer patients in 2016 including primary brain tumors in Japan was released as a preliminary report in January 2019. According to the report, 667 incidence of pediatric brain tumors were reported in aged 0–14 years (boy: 382; girl: 285), of them 537 patients underwent surgery, chemotherapy, or radiation therapy (diagnosis: 516, undiagnosed: 21), and 130 patients were followed up without any treatments. The breakdown of tumor types was 279 Neuroepithelial tumors, 73 Embryonal tumors (61 Medulloblastomas), and 63 Germ Cell Tumors (GCTs). The crude rate per 100,000 population in 2016 was 4.23 for all pediatric brain tumors, 1.77 for Neuroepithelial tumor, 0.39 for Medulloblastoma, and 0.40 for GCTs. In comparison, the United States CBTRUS2019 (2012–2016) reported that the age-adjusted incidence rates per 100,000 population in the United States was 5.74 for all pediatric brain tumors, 4.15 for Neuroepithelial tumors, 0.48 for Medulloblastoma, and 0.22 for GCTs. The age-adjusted incidence in Japan based on the US population in 2000 was 4.21 for all pediatric brain tumors, Neuroepithelial tumor 1.77, Medulloblastoma 0.39, and GCTs 0.39, suggesting that the incidence of Neuroepithelial tumor and Medulloblastoma is lower whereas that of GCTs is approximately twice comparing to the US. By taking advantage of the national cancer registry data, which was publicly opened to researchers in 2019, we report the incidence of primary brain tumors and its comparison worldwide based on the re-classification criteria of primary brain tumors including benign tumor.

EPID-10. EPIDEMIOLOGY STUDY OF UNCOMMON CHILDHOOD BRAIN TUMOURS IN ASIAN CHILDREN

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Our local registry identified 656 brain tumours from Jan 1999 to Dec 2018, (incidence: 29.8/yr/million). Other from Glioma, Medulloblastoma/PNET, Germ Cell tumours, Ependymoma, the remaining rarer tumours accounted for 18% (n=118). The 7 more common groups are: craniopharyngioma(n=28); ATRT(n=18); choroid plexus papilloma/CA(n=12); Ganglioglioma(n=11); ETMR(n=7); DNET(n=7); meningioma(n=6). Their respective incidences are 1.27; 0.81; 0.55; 0.5; 0.32; 0.32 0.27/yr/million. For craniopharyngioma, M:F=15:13 and median age was 7.4yrs (2mons-16.5yrs). 12/28 children had surgery alone and 13/28 had focal RT post-surgery with better outcome. 3 underwent intra-cystic interferon-beta also stable. For ATRT, M:F=7:8 and median age was 2.3yrs (4mos-14.2yrs). 2 had metastatic disease and 7/18 patients remained alive. For choroid plexus tumours, there were 7 papilloma, 2 atypia and 3 carcinoma. M:F=5:6 and median age was 1.5yrs (4mos-14yrs). All papilloma, 1/2 atypia and 1/3 carcinoma survived. For ganglioglioma, M:F=7:4 with median age of 5.5yrs (5mos-13.2yrs). They commonly presented with seizure and only one died (brainstem primary). The ETMR includes ependymoblastoma and medulloepithelioma, they had quite different clinical characteristics and outcome. 6/7 DNET had convulsion and M:F=6:1. Median age was 11.5yrs (2.66-14yrs). They all survived even if incompletely resected. For meningioma, 1/6 had germline mutation of NF-2 gene. M:F=3:3 and onset was >8yrs except the NF-2 patient. All survived but the NF-2 had multiple recurrences. 4 patients developed secondary meningioma due to irradiation but they were >18yrs so excluded. In summary, rarer forms of childhood brain tumours only accounted for <20% of all brain tumours and they had diverse presenting features and outcome.

EPID-11. ESTABLISHING A BASELINE TIME-FRAME FOR SYMPTOM ONSET TO DEFINITIVE DIAGNOSIS FOR CHILDREN WITH NEWLY-DIAGNOSED CNS TUMORS: AN EXPANDED, MULTI-INSTITUTIONAL COLLABORATIVE STUDY

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BACKGROUND: We have previously documented the presence of diagnostic delays in children with central nervous system (CNS) tumors in the United States. This study serves to expand and validate the previously established baseline from symptom onset to definitive diagnosis in children with newly-diagnosed CNS tumors. DESIGN: The medical records of children with newly-diagnosed CNS tumors were retrospectively reviewed from January 2004 to December 2017 at Nationwide Children's Hospital, Akron Children's Hospital and Riley Hospital for Children at IU Health. Records were reviewed for age, gender, tumor type, presenting symptoms, number of healthcare visits prior to diagnosis, time interval (in months) from onset of symptoms to definitive diagnosis and any associated genetic syndromes. RESULTS: Of the 768 patients with newly-diagnosed CNS tumors, the median time interval from symptom onset to definitive diagnosis was *40.5 days* while the mean symptom interval was *144 days* (range < 1 to 5,475 days). The median age of diagnosis was 7 years, with a male predominance (57%). This expanded cohort continues to reveal that pediatric brain tumor patients most often seek care at the primary care level, although many patients were seen in various multiple subspecialty clinics prior to diagnosis. CONCLUSIONS: This multi-institutional cohort study updates our previously documented single state time interval and provides a consistent Midwest "benchmark" to improve awareness for children with brain tumors through the adaptation of the UK 'HeadSmart,' now renamed 'BrainFirst.' Additionally, future work could include a prospective registry to better examine potential risk factors for delays in diagnosis.

EPID-12. TEMPORAL AND GLOBAL GEOGRAPHIC VARIATION IN THE INCIDENCE OF PEDIATRIC CNS TUMORS, 1998–2012

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AIMS: To describe the temporal and geographic variation in the incidence of pediatric CNS malignancies worldwide, presenting analyses by sex, period, region, and histological subtype between 1998 and 2012. METHODS: Data were extracted from volumes IX to XI of the Cancer Incidence in 5 Continents, covering the periods 1998–2002 (1), 2003–2007 (2), and 2008–2012 (3). We pooled data from 44 countries, classifying them into 6 regions (Africa (AF), Asia (AS), Oceania (O), Europe (E), Central/South America (CSA), North America (NA)). Age-standardized incidence rates (ASIR per million, 0–19 years) were calculated and temporal variation was evaluated using incidence rate ratios (IRR) (95% CI). RESULTS: The highest incidence (Period 3) was observed in NA (34.0 and 30.2 for males and females, respectively). Astrocytic tumors were predominant in all regions, with percentages ranging between 24.5% (E, females) and 45.6% (NA, females). Increasing trends (Period 3 x 1) were observed in AS (IRR=1.15, 95% CI 1.06–1.25), CSA (IRR=1.25, 95% CI 1.01–1.55), and NA (IRR=1.05, 95% CI 1.03–1.07), for males and in AS (IRR=1.15, 95% CI 1.05–1.26) and NA (IRR=1.08, 95% CI 1.06–1.11) for females. Geographic discrepancies in time-trends were observed for astrocytomas, ependymomas, medulloblastomas, other embryonal tumors, and other specified tumors. Reductions in the incidence of unspecified tumors from period 1 to 3 were noted in E, AS, and NA, ranging from -20% (E, females) to -66% (AS, females). CONCLUSIONS: Heterogeneous trends and improvement in the registration of histological types were noted. Geographic variation can help to raise hypotheses to investigate etiologic factors.

EPID-13. A POPULATION-BASED ANALYSIS OF CNS TUMOR DIAGNOSES, TREATMENT, AND SURVIVAL IN CONGENITAL AND INFANT AGE GROUPS

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BACKGROUND: Congenital (<3 months) and infant (3 to 11 months) brain tumors are biologically different from tumors in older children, but epidemiology of these tumors has not been studied comprehensively. Insight into epidemiological differences could help tailor treatment recommendations by age and increase overall survival (OS). METHODS: Population-based data from the SEER 18 registries was obtained for 14,493 0-19-year-olds diagnosed with CNS tumors between 1990 and 2015. Incidence, treatment, and survival were analyzed using Chi-square and Kaplan-Meier analyses. RESULTS: Between the <3 month, 3–5 month, 6–11 month, and 1–19 year age groups, tumor type distribution differed significantly ($p<0.001$); high-grade glioma (HGG) was most common in the <3-month-olds, while low-grade glioma (LGG) was most common in the other groups. 5-year OS for all tumors was 36.7% (<3 months), 56.0% (<3–5 months), 63.8% (6–11 months), and 74.7% (1–19 years) (log rank $p<0.001$). OS by tumor type was worst for <3-month-olds with LGG, medulloblastoma, and other embryonal tumors; OS was worst for 3-5-month-olds with ependymoma, <1-year-olds collectively with atypical teratoid-rhabdoid tumor, and 1-19-year-olds with HGG (log rank $p<0.02$ for all tumor types). <3-month-olds were least likely to receive any treatment for each tumor type and least likely to undergo surgery for all except HGG. <1-year-olds were far less likely than 1-19-year-olds to undergo radiation for embryonal tumors, as expected, but were also less likely to undergo chemotherapy. CONCLUSIONS: Congenital/infant CNS tumors differ pathologically, therapeutically, and prognostically from those in older children. Treatment changes could help address poorer outcomes for these young patients.

EPID-14. GABRIELLA MILLER KIDS FIRST DATA RESOURCE CENTER: COLLABORATIVE PLATFORMS FOR ACCELERATING RESEARCH IN PEDIATRIC CANCERS & STRUCTURAL BIRTH DEFECTS

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Since launching to the public in September 2018, the Gabriella Miller Kids First Data Resource Center (DRC) has made an increasing number of pediatric genomic studies available to the research community. Currently, 1.3 PBs of genomic and clinical data drawn from 12,000 participants are available across a variety of pediatric cancer and structural birth defect studies. The DRC has architected a secure, cloud-based platform with over 1,300 users that supports the ability of researchers to not only find, access, and reuse data, but also integrate, collaborate, and analyze data quickly at scale. Users can use integrations with platforms such as Cavatica for bioinformatics workflows and PedcBioPortal for cancer genomic visualizations. Additionally, a set of framework services, powered by Gen3, provide a foundation for interoperability with other large-scale data sources, platforms, and a growing ecosystem of analysis and visualization applications. These integrations allow users to search across both TARGET and Kids First clinical data in one location while allowing data governance to be maintained by the original approvers. The new "explore data" feature allows users to search across all studies in order to identify virtual cohorts. Within the portal, these cohorts can be saved and shared with collaborators for iterative refinement and analysis. With appropriate approvals, the associated genomic data can be accessed and analyzed seamlessly in Cavatica or other platforms with interoperable framework services. Additionally, gene searching capabilities will be available in 2020. Data is free to download and cloud credits are available for analysis support.

EPID-15. THE INTERNATIONAL DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)/DIFFUSE MIDLINE GLIOMA (DMG) REGISTRY AND REPOSITORY (IDIPGR) EXPANSION

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Established in April 2012, the mission of the IDIPGR is to provide secure integrated data sets including clinical, pathologic, radiologic and molecular genomics to the research community to promote hypothesis driven research. Over 600 data points per patient are securely stored on a CCHMC constructed web resource and domain using the open-source data mart

development framework Harvest (PMID:24303304) ('Links'). Genomic data is stored in the cloud-enabled VIVA platform and accessed through cross-platform integration and standardization algorithms for comparison across datasets. Features include source identification, data wrangling, and standardization of molecular and phenotypic data (2017), a web-enabled data mart that provides phenotype-genotype query/exploration, along with raw and processed data file downloads to authorized investigators (Harvest, 2017), additional tools for filtering and analysis of genomic datasets at the level of a phenotype, sample, gene, and variant (VIVA, 2017–2018), and uploaded digitized slides (Aperio, 2019). The IDIPGR Repository stores abstracted datasets for >1020 patients with DIPG/DMG, of whom 366 have tumor tissue available through biopsy and/or autopsy, and centrally reviewed and digitized specimens from 124 patients. The Repository contains >5000 radiology studies from >700 patients, with >550 patients centrally reviewed, and genomics data from 80 patients. Currently 27 IDIPGR approved projects utilize these datasets. The DIPG/DMG Registry constructed a robust database platform and integration system that provides the infrastructure to promote highly collaborative, international, hypothesis-driven research. Broadening collaboration among investigators for hypothesis-driven research studies will lead to better classification and more effective treatment of patients with DIPG and DMG.

EPID-16. INTEGRATION OF EHR AND CANCER REGISTRY DATA TO CONSTRUCT A PEDIATRIC NEURO-ONCOLOGY SURVIVORSHIP COHORT AND IMPROVE LONG-TERM FOLLOW-UP CARE

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BACKGROUND: Pediatric neuro-oncology (PNO) survivors suffer long-term physical and neurocognitive morbidity. Comprehensive care addressing late effects of brain tumors and treatment in these patients is important. Clinical guidelines offer a framework for evaluating late effects, yet lack of extended follow-up is a significant barrier. The electronic health record (EHR) allows novel and impactful opportunities to construct, maintain, and leverage survivorship cohorts for health care delivery and as a platform for research. METHODS: This survivorship cohort includes all PNO cases ≤18-years-old reported to the state-mandated cancer registry by our institution. Data mining of the EHR for exposures, demographic, and clinical data identified patients with lack of extended follow-up (>1000 days since last visit). Explanatory variables included age, race/ethnicity, and language. Primary outcome included date of last clinic visit. RESULTS: Between January 1, 2013 and December 31, 2018, there were 324 PNO patients reported to our institutional registry with ongoing analysis to identify the specific survivorship cohort. Thirty patients died with an overall mortality of 9.3%. Two-hundred-and-sixteen patients were seen in PNO clinic, of which 18.5%% (n=40) did not receive extended follow-up. Patients without extended follow-up were an average of 3.5 years older up ($p<0.01$); however, there was no significant difference in preferred language ($p=0.97$) or race/ethnicity ($p=0.57$). CONCLUSION: Integration of EHR and cancer registry data represents a feasible, timely, and novel approach to construct a PNO survivorship cohort to identify and re-engage patients without extended follow-up. Future applications include analysis of exposures and complications during therapy on late effects outcomes.

EPID-17. A SINGLE INSTITUTE EXPERIENCE IN THE REGISTRATION STUDY OF PEDIATRIC SOLID TUMOR IN JAPAN CHILDREN'S CANCER GROUP

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A larger scale prospective registration study has been conducted nationwide in Japan since 2011, called as "registration study in pediatric solid tumor", in Japan Children's Cancer Group (JCCG). In this study, clinical data and surgical specimen are collected into the National Center for Child Health. Kyoto University Hospital has participated in this study since IRB approval in 2011. We reviewed our registered patients to the registration study and assessed the current status. 40 patients with pediatric brain tumors participated in this study from 2011 to 2020. There were 13 intracranial germ cell tumors, 9 medulloblastomas, 6 gliomas in 4 diffuse midline gliomas, 4 pilocytic astrocytoma, and 4 other types of tumor. The informed consent was obtained from 36 patients by pediatricians and 3 patients by neurosurgeons. Twenty-five surgical specimens were collected for central review. The reasons of no surgical specimens were nonsurgical management in 6 patients and no enough FFPE sample in 3 patients. There was no discrepancy between central review and institutional diagnosis. The status of clinical data entry was complete in 13 patients and uncomplete in 9 patients. These registration data including pathological diagnosis, molecular diagnosis, treatment, clinical information in patients with pediatric brain tumor are very important to realize current status. To conduct this study certainly, the collaboration among pediatrician, neurosurgeon, and supporting staff should be needed in collecting specimens and clinical data.

EPID-18. TRENDS IN INCIDENCE AND SURVIVAL OF MALIGNANT PEDIATRIC CENTRAL NERVOUS SYSTEM TUMORS IN THE NETHERLANDS

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BACKGROUND: Variation in survival of pediatric central nervous system (CNS) tumors is large between countries. Within Europe, the Netherlands had one of the worst reported survival rates of malignant CNS (mCNS) tumors during 2000–2007. METHODS: Using the Netherlands Cancer Registry, we evaluated trends in incidence and survival of pediatric mCNS tumors (behavior /3, 5th digit in the morphology code) diagnosed between 1990–2017. RESULTS: 839 newly-diagnosed mCNS tumor patients <18 years were registered between 1990–2017. Incidence of mCNS tumors remained stable (average incidence rate, 21.6 per million person-years). However, an increased incidence of malignant gliomas, NOS was found (Estimated Annual Percentage Change (EAPC) 11.6% $p<0.001$). This appears to be related to a registration shift between 1990–1999 and 2000–2009 as brainstem tumors increased (+25%, n=79) for astrocytomas and other gliomas but decreased (-31%, n=32) for unspecified intracranial and intraspinal neoplasms. Overall, 5-year observed survival (5Y-OS) of mCNS tumors increased from 51% in 1990–1999 to 61% in 2010–2017 (P-for-trend<0.001). This increase was not constant over time, as 5Y-OS for the period 2000–2009 was 47%. The only significant decrease in survival was found for malignant astrocytomas and other gliomas with a 5Y-OS of 56% in 1990–1999 decreasing to 48% in 2010–2017 (P-for-trend<0.001). CONCLUSION: Between 1990–2017 incidence of mCNS tumors in the Netherlands remained stable and survival increased. However, a decrease in survival was seen for malignant astrocytomas and other gliomas, which is partially explained by the registration shift of brainstem tumors. The impact of this shift on survival for all mCNS tumors is subject to further research.

ETMR AND OTHER EMBRYONAL TUMORS

ETMR-01. TREATMENT OUTCOME OF TWO CASES WITH HIGH-GRADE NEUROEPITHELIAL TUMOR WITH BCOR ALTERATION

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INTRODUCTION: High grade neuroepithelial tumor with BCOR exon 15 internal tandem duplication (HGNET BCOR) is a recently described tumor entity of the central nervous system (CNS) with a distinct methylation profile and characteristic genetic alteration. We report the outcome of two cases after 1st line multimodality therapy. MATERIAL AND METHOD: A 7 year old girl with a ventricular tumour and a 6 year old boy with a tumour in the occipital region with infiltration of the transverse and sigmoid sinus were both diagnosed based on histology and methylation with HGNET-BCOR. No spinal or liquor dissemination were found at diagnosis in both cases. Treatment consisted of radical resection of the tumour. In the case of the lesion with sinus infiltration residual tumour in the vessel could not be removed. Both children were postoperatively treated with radiotherapy (craniospinal 36 Gy and boost to 54 Gy), concomitant Vincristin and adjuvant Cisplatin, Lomustine and Vincristine. RESULTS: The girl developed a local recurrence at the primary tumour site 18 months after diagnosis. Reoperation showed the same histology. Start of 2nd line chemotherapy with Temozolomid and Irinotecan is being discussed. The boy with sinus infiltration developed seven months after diagnosis multiple liver, lung and bone metastasis. Biopsy of a liver lesion showed HGNET-BCOR. He was treated with Temozolomid, Irinotecan and died nine months after diagnosis. CONCLUSION: We report two cases with failure after 1st line treatment for HGNET-BCOR. To our knowledge HGNET-BCOR with development of hematological disease dissemination is a rare finding.

ETMR-02. NOVEL CIC-LEUTX FUSION IN CNS EMBRYONAL TUMOR: A CASE REPORT AND REVIEW OF THE LITERATURE

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INTRODUCTION: Central nervous system (CNS) embryonal tumor is a group of rare, poorly differentiated neuroepithelial malignant neoplasm predominantly occurs in pediatrics. Herein, we firstly report a CNS embryonal tumor harboring pathogenic CIC-LEUTX fusion. METHODS: Immunohistochemistry (IHC), Fluorescence in Situ Hybridization (FISH) and Next Generation sequencing (NGS). RESULTS: A 2-year-old male was found to have solid and cystic mass in left temporal lobe-basal ganglia and left parietal lobe (maximum diameter=75mm). The pathological diagnosis was CNS embryonal tumor (NEC) after totally resection. The tumor was poorly differentiated embryonal neoplasms of neuroectodermal origin that lacked the specific features and rosettes. IHC showed Syn was strongly/diffusely positive and Ki67 proliferation index was high (50%+), and copy number at the 19q13.42 C19MC locus showed no alterations. NGS showed pathogenic mutations including a brand new CIC-LEUTX fusion, heterozygous germline NBN c.C127T mutation and somatic TSC2 c.G2714A mutation. One month after operation, intracranial tumor recurred (maximum diameter=55mm) and spinal cord implantation metastasis occurred, and then the patient received chemotherapy (CTX+CBP+VCR/DDP+VP-16) and had significant improvement in symptoms and tumor shrinkage (maximum diameter=31mm). Literature review revealed CIC fusion predominantly presented in sarcomas, such as CIC-NUTM1 fusion in rare CNS sarcoma, CIC-LEUTX fusion in epithelioid angiosarcoma and CIC-DUX4 fusion in Ewing-like sarcoma. Hitherto, apart from this case, there were only two cases which had CIC-LEUTX fusion in CNS, including a case of CNS angiosarcoma and a case of anaplastic ganglioglioma. CONCLUSIONS: We firstly found a specific new type in CNS embryonal tumor with distinct molecular-pathological characteristics of CIC-LEUTX fusion.

ETMR-03. THE ROLE OF FOXR2 IN PEDIATRIC BRAIN CANCER

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Forkhead Box R2 (FOXR2) is a transcription factor of the Forkhead Box family that has been correlated with tumorigenesis, aberrant cell growth or tumor progression. Expression of *FOXR2* in pediatric brain tumors is, besides in subsets of medullo-, pineo- and glioblastoma, primarily present in CNS neuroblastoma with FOXR2 activation (CNS NB-FOXR2), a novel entity that we in 2016 identified from the former class of primitive neuroectodermal tumors of the central nervous system (CNS-PNET). Analyzing CNS-NB-FOXR2 tumors we found that *FOXR2* mRNA is expressed in an anti-correlative manner compared to the proto-oncogenes *MYC* and *MYCN*. With immunoprecipitation analyses we show that FOXR2 binds to MYC and MYCN and is thereby stabilizing these proteins. These observations on the interaction and the anti-correlative manner suggest that FOXR2 and MYC(N) may drive tumor formation in a molecularly similar fashion. To investigate this further we stably expressed *FOXR2*, *MYCN* and *MYC* and a combination of *FOXR2* with *MYC(N)* in human neural stem cells (hNSC) and injected these in the striatum of NSG mice. We could show that hNSC itself do not from a tumor, whereas the expression of *FOXR2* and/or *MYC(N)* in hNSC results in tumorigenesis. Tumors expressing both, *FOXR2* and *MYC(N)* were growing faster than tumors with *FOXR2* alone. In addition, tumors are currently being analyzed by ChIP-sequencing for FOXR2, MYC, and MYCN, to better understand the mechanisms how FOXR2 drives tumor formation compared to its interaction partners MYC and MYCN.

ETMR-04. EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES: THE MD ANDERSON CANCER CENTER EXPERIENCE

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BACKGROUND: Embryonal Tumor with Multilayered Rosettes (ETMR) are rare tumors that are molecularly diagnosed by C19MC amplification. Rarity of this tumor has precluded profiling uniform therapeutic strategy. METHODS: Retrospective review after institutional approval, identified 10 pediatric case of ETMR, treated at MD Anderson Cancer Center during the period of 2005 to 2019. RESULTS: Median age of at diagnosis was 4.6 years. Tumor sites include frontal or parietal lobes (3), spine (3) and posterior fossa involving the brainstem (4). All patients received a combination of chemotherapy and radiation. 4 patients had metastasis at the presentation. 9 patients received focal radiation but only 6 of them received Craniospinal irradiation (CSI). Average dose of radiation was 50 Gy. Surgical resection was performed in all cases except the brainstem tumors. 7 children had recurrence including all the patients with metastasis at diagnosis (median time: 9.4 months), 1 passed away secondary to hemorrhage in brainstem and data was not available for 2 patients. 5/6 patients who received CSI had recurrence. CONCLUSIONS: To-date no well-defined treatment regimens exists for these neoplasms, resulting in poor overall survival. Preclinical drug screen have shown the efficacy of topotecan, actinomycin D, and volasertib as potential new therapeutic candidates, though this has not translated successfully into the clinical arena. Given the limited success with current conventional therapeutic methods, molecular interrogation in addition to histopathological diagnosis are essential upfront, as it could provide clues to targeted therapy. Defining molecularly-based treatment with less toxicities and increased survival are warranted.

ETMR-05. SINGLE-CELL RNA-SEQ OF ETMR REVEALS CELL PROGRAMS OF DEVELOPMENTAL HIERARCHY AND CELLULAR DIVERSITY IN THE TUMOR MICROENVIRONMENT

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Embryonal tumors with multilayered rosettes (ETMR) are deadly brain malignancies affecting young children. No standard treatment is available and the median survival is less than 12 months. Molecularly, the disease is characterized by the miRNA C19MC cluster amplification, with the expression of multiples miRNAs related to a stem cell program. The discoveries on the purely molecular mechanisms of the disease did not help to create a bridge for new treatment strategies so far and the cellular diversity of ETMR remains poorly understood. In this study, we used single-cell RNA sequencing of murine and human tumors to describe ETMR cellular heterogeneity. Our findings support that intra-tumoral heterogeneity is mainly characterized by 4 cellular programs defining a developmental hierarchy related to different metabolic states: 1) Early quiescent NSC-like cells supported by fatty-acid oxidation 2) Late NSC and NP-like proliferative cells fueled by glycolytic metabolism; 3) Post-mitotic neuroblast-like cells, relying on oxidative-phosphorylation; 4) NSC-like proliferative cells, with metabolic plasticity and capable of performing the three types of metabolism. Tumor-specific ligand-receptor interaction analysis revealed that ETMR exchange with microglia and vascular mural cells (MC) signals related to extracellular matrix (ECM) organization (*Cxcl12-CxCr4*), stem cell signaling (BMPs-BMP receptors), anti-apoptosis and survival (*Ntf3-Ntrk*), not seen in the control brain. In addition, the vascular MC showed a cancer-associated fibroblast (CAF) phenotype, with potential prognostic implications, as previously demonstrated for other tumors. This study provides new findings to build up a more robust understanding of ETMR biology and opens space for further studies in the field.

ETMR-06. DISSECTING THE MOLECULAR AND DEVELOPMENTAL BASIS OF PINEOBLASTOMA THROUGH GENOMICS

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Pineoblastoma (PB) is an aggressive embryonal brain tumor comprising 1% of pediatric CNS tumors. The clinico-molecular heterogeneity and developmental origins underlying PB are poorly understood; therefore, we have assembled a molecular cohort of histologically defined PBs (n=43) with corresponding outcome data. Methylation profiling revealed four molecularly and clinically distinct PB subgroups, including two novel entities. Mutational and transcriptional analysis identified characteristic molecular features of each subgroup, such as mutations in the miRNA processing pathway or *FOXR2* proto-oncogene overexpression. Furthermore, subgroups exhibited differences in propensity for metastasis, cytogenetics, and clinical outcomes. To dissect PB developmental origins and resolve PB subgroup biology, we have employed a combination of single-cell genomics and genetically engineered mouse modeling. We created a single-cell transcriptional atlas of the developing murine pineal gland across 11 timepoints and are currently integrating these data with single nuclei RNA-seq data of human PB (n=25). Single-cell analysis of the developing pineal gland revealed three distinct populations of pinealocytes, referred to as early, mid and late pinealocytes, which segregate by developmental stage yet lie along a single developmental trajectory. Preliminary results implicate significant associations between PBs and the early pinealocyte population as well as subgroup-specific differences in intratumoral heterogeneity. Furthermore, this knowledge has informed the downstream generation of biologically faithful disease models, including a transgenic mouse model of the PB-RB subgroup. Remarkably, this model shows up-regulation of key markers of PB such as *Crx*, *Asmt* and *Otx2* and substantiates early pinealocytes as the probable cell-of-origin for this PB subgroup.

ETMR-07. ETANTR: A RARE TUMOR IN A RESOURCE-LIMITED SETTING

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INTRODUCTION: Embryonal tumor with abundant neuropil and true rosettes (ETANTR) is a rare aggressive brain tumor with low survival rates. There are about 80 cases reported in literature since 2000 when it was first described. There is no standard treatment scheme for ETANTR yet. CASE REPORT: A 2 years old boy presented with a month-long of headache and inability to hold his head. CT scan and MRI revealed a large mass in the right frontal lobe with midline shift. Subtotal tumor resection was done. Histological and immunohistochemical analyses was consistent with ETANTR in one laboratory and PNET in another. The second opinion suggested by the Center of Pediatric Oncology, Hematology and Immunology in Moscow the diagnosis ETANTR was confirmed. Taking into account certain similarities with medulloblastoma was decided to provide treatment according to HIT-2014 protocol. Control MRI done after 2 cycles of Block SKK Carboplatin/Etoposide found tumor progression and for that reason patient underwent second surgical resection. Considering the age of the child radiation therapy was not expedient and the decision was to continue treatment with HIT 2014 intensified regimen, which includes Cisplatin, Vincristine, Etoposide, Cyclophosphamide and intravenous High dose Methotrexate with intrathecal Methotrexate. Aiming to evaluate the effectiveness of treatment we are planning to perform MRI after this 2nd cycle of intensified regimen. DISCUSSION: There are difficulties in diagnosis of rare types of cancers in Armenia. Since there is no approved treatment for ETANTR, there is a need for ongoing research to improve its prognosis.

ETMR-08. INTERNATIONAL CONSENSUS PROTOCOL FOR EMBRYONAL TUMOR WITH MULTILAYER ROSETTES

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Embryonal tumors with multilayer rosettes (ETMR) are rare and highly-aggressive central nervous system (CNS) neoplasms which occur primarily in young children and carry a dismal prognosis. To date, no large clinical investigations have been conducted to determine the optimal therapy for ETMR. Data from retrospective case series suggest that our most aggressive standard therapies are not sufficient for cure in the majority of cases. New treatment approaches incorporating pre-clinical data and the known biology of ETMR are therefore urgently needed. A German drug screen using the patient-derived ETMR BT183 cell line and its xenograft revealed anti-tumor activity of topotecan, doxorubicin, and actinomycin D; three agents used infrequently for treating infant CNS tumors. Additional results from a small series of ETMR patients suggest that optimization of induction chemotherapy using these active agents may improve response and survival outcomes. In 2019, an international panel of pediatric neuro-oncology experts convened to advance therapy for ETMR. A consensus protocol was developed incorporating maximal safe surgical resection, induction chemotherapy with active pre-clinical agents, intrathecal chemotherapy, radiotherapy, and high-dose chemotherapy. This international consensus protocol represents the first prospective clinical investigation specific to ETMR and will be available through a treatment registry globally and as a clinical trial at select centers. The study aims to improve survival by providing aggressive, optimized therapy for ETMR and will serve as a platform to explore new biologically-promising agents. The investigation will also provide valuable prospective outcome data and correlative biological studies to serve as baseline comparators for future clinical trials.

ETMR-09. THE ROLE OF RADIATION FOR EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES

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BACKGROUND: Embryonal tumor with multilayered rosettes (ETMR) is a challenging tumor. The prognosis of the patients suffering from this tumor is extremely poor. We have survival cases of more than 12 months. However, the status of illness is different. In order to clarify the cause of this difference, we reviewed our treatments in this study. TREATMENT COURSE: We have two cases. Both have relapsed after the same chemotherapy after the same radiation therapy. After the recurrence we used protocols that were included extended resection, second radiation therapy with bevacizumab. METHODS: We compared molecular biological evaluations for the initial and recurrent tumors. The resection rate at the time of second removal and the intensity of radiation therapy intensity were compared. RESULTS: We succeeded to remove the tumors with the confirmation of intraoperative MRI. No apparent differences could be seen in molecular biological characters of tumors before and after treatment. There was a difference between the period until radiation therapy and the irradiation methods. CONCLUSIONS: This tumor is untreatable only by resection. We need the second radiation therapy with bevacizumab. It was presumed that tumor should be irradiated quickly with appropriate irradiation field and dose.

ETMR-10. EARLY FOCAL RADIOTHERAPY AND TEMOZOLOMIDE FOLLOWING COMPLETE RESECTION APPEAR SUPERIOR TO INTENSIVE CHEMOTHERAPY AND DELAYED RADIOTHERAPY IN CHILDREN WITH EMBRYONAL TUMORS WITH MULTILAYERED ROSETTES (ETMR)

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BACKGROUND: Embryonal tumor with multilayered rosettes (ETMR) is a rare, aggressive embryonal central nervous system tumor characterized

by LIN28A expression and alterations in the *C19MC* locus. ETMRs predominantly occur in young children, have a dismal prognosis, and no definitive treatment guidelines have been established. We report on our experience in nine consecutive patients. METHODS: Between 2006 and 2017, nine patients were diagnosed with ETMR. Median age was 25 months (5–38), seven were treated for primary diagnosis, two referred with progressing tumors, seven diagnosed prospectively, two retrospectively, five were located supratentorially, three pineal, one in the brainstem. RESULTS: Seven patients had a gross total resection, one a partial resection and one a biopsy at initial diagnosis, followed by second resections at progression. Six patients were treated with intensive chemotherapy regimens including high-dose chemotherapy in three patients and all recurred after a median of 6 months (range 2–11) and all except one patient who died after high-dose chemotherapy, succumbed to their disease after a median of 13 months (range 7–28). Two patients were treated with gross total tumor resection, early focal radiotherapy and concomitant temozolomide followed by temozolomide and intrathecal therapy for one year and both are in continuous complete remission 51 and 46 months after diagnosis. CONCLUSION: Gross total resection followed by early focal radiotherapy, temozolomide, and intrathecal chemotherapy seem to be superior to intensive chemotherapy including high-dose chemotherapy. Steady progression was observed in both patients with initial biopsy and PR only despite intensive therapy. Radiotherapy at recurrence/progression was not successful.

ETMR-11. A CASE OF PRIMARY DIFFUSE LEPTOMENINGEAL PRIMITIVE NEUROECTODERMAL TUMOR

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BACKGROUND: Primary diffuse leptomeningeal primitive neuroectodermal tumor (PDL PNET) is a rare embryonal brain tumor which arises primarily in the meninges without an intraparenchymal mass. Few previous reports of this condition exist, and the clinical outcomes are poor. We herein report a case of a child with PDL PNET and present a cursory review of the literature. CASE: A 3-year-old female patient was seen at a local clinic due to vomiting, headaches, and seizures. As a head MRI revealed hydrocephalus but no mass, acute encephalopathy was initially diagnosed. She received steroid pulse therapy, but the symptoms progressed to hallucination and lethargy. Another MRI at the 1-month follow-up revealed diffuse leptomeningeal enhancement. Thereafter she was transferred to our hospital. A spine MRI revealed spinal dissemination. She underwent a dura mater biopsy, and the pathological analysis led to the diagnosis of PDL PNET. She received chemotherapy consisting of vincristine, cyclophosphamide, etoposide, cisplatin, and intrathecal methotrexate injections two months after the initial presentation. The progressive hydrocephalus was managed with external ventricular drainage. Two weeks after the first cycle of chemotherapy the hydrocephalus resolved, and the external ventricular drainage was removed. A follow-up MRI showed that the leptomeningeal enhancement decreased during the four cycles of chemotherapy without radiotherapy. The patient is scheduled to receive high-dose chemotherapy as consolidation therapy. CONCLUSION: PDL PNET is extremely rare, and its diagnosis is often delayed. Treatment of PDL PNET is very difficult due to its aggressive course, and surgical resection is impossible. Early diagnosis may help improve outcomes.

ETMR-12. EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES: A SINGLE CENTER EXPERIENCE

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BACKGROUND: Embryonal tumor with multilayered rosettes (ETMR) is a rare, highly malignant tumor of the central nervous system and is usually diagnosed in children aged <2 years. Currently, because no defined treatment strategy has been reported, treatment regimens are often extrapolated from other embryonal tumors. Therefore, data collection of ETMR cases is important for further understanding EMTR. Here, we present our experience with four patients with ETMR. MATERIAL AND METHODS: Patients with a pathological diagnosis of ETMR from 1999 to 2016 at Saitama Children's Medical Center were included. Their clinical data were retrospectively analyzed. RESULTS: This study included four cases of ETMR (one male and three females). The mean age at diagnosis was 29.5 (range, 15–37) months. Presenting symptoms included seizure, hemiparesis, vomiting, and headache. The mean maximal tumor diameter was 42.5 mm. The tumor locations included frontal lobe, temporal lobe, occipital lobe, cerebellum, and brainstem. Gross total resection was achieved in two cases. Fluorescence in situ hybridization analysis demonstrated amplification of 19q13.42 chromosome region in all cases, and diffuse positive expression was observed in the immunohistochemical staining for LIN28A. Systemic postoperative chemotherapy was administered to all patients. Three patients received intrathecal therapy and three were irradiated. The mean overall survival and progression-free survival were 45.3 and 42 months, respectively. Two patients who underwent gross total resection are alive without recurrence. CONCLUSION: Complete surgical resection may be an important prognostic factor in patients with ETMR. Further prospective studies are needed to confirm these results.

ETMR-13. NFI GENES IN ETMR TUMORIGENESIS AND NEURODEVELOPMENT

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Embryonal tumors with multilayered rosettes (ETMRs) are aggressive pediatric embryonal brain tumors with a universally poor prognosis. These tumors are commonly characterized by amplification of *C19MC*, but other miRNA-related aberrations, such as *DICER* mutations or *MIR17HG* amplifications, are also observed. Nevertheless, it remains unknown how these aberrations are driving the tumorigenesis. We applied miRNA target prediction to investigate the downstream targets shared by these aberrations affecting normal brain development and tumorigenesis. The nuclear factor one (*NFI*) family of transcription factors were found to be top candidates shared by both miRNA clusters. These genes are expressed at very low levels in ETMRs, in contrast to other brain tumors. During normal brain development these genes are expressed in radial glial progenitors and are required for the transition of proliferation to differentiation. Since radial glial progenitors are the potential cell-of-origin of ETMRs, we hypothesize that downregulation of NFI is required for the proliferative, undifferentiated state of ETMRs. Indeed, mouse models with deletion of an *Nfi* family member display sustained proliferation and delayed differentiation of radial glial progenitors during development. This leads into brain overgrowth, which has also been observed in humans with intellectual disabilities caused by *NFI* haploinsufficiency. When multiple *Nfi* family members are simultaneously targeted in mice, the progenitors are retained and both neurogenesis and gliogenesis are inhibited, resulting in a neuropathology similar to that of human ETMR tumors. Hence, downregulation of *NFI* genes resulting from miRNA aberrations could contribute to the developmental state and possibly tumorigenesis of ETMRs.

ETMR-14. TREATMENT OF EMBRYONAL TUMOURS WITH MULTILAYERED ROSETTES (ETMR) WITH CARBOPLATIN-ETOPOSIDE INDUCTION AND TANDEM HIGH-DOSE CHEMOTHERAPY WITHIN THE PROSPECTIVE HIT-TRIALS AND REGISTRIES

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BACKGROUND: Embryonal tumours with multilayered rosettes (ETMR) are highly aggressive tumors, mostly occurring in infants. Published clinical data refer to retrospective cohorts of inhomogeneously treated patients. Here, we describe the outcome of patients, who were prospectively treated within the P-HIT2000-trial, the subsequent HIT2000-interim-registry and earlier HIT-trials. PATIENTS AND METHODS: Nineteen patients from the P-HIT2000-trial (2001–2011), 12 patients from the subsequent HIT2000-interim-registry (2012–2014) and 4 patients from earlier HIT-trials with centrally reviewed neuropathological and molecularly-confirmed diagnosis of ETMR were included. Outcome of 18 patients treated with carboplatin-etoposide-induction followed by tandem-high-dose chemotherapy ("CARBO-ETO+HDCT") with stage-stratified radiotherapy administered in case of persistant disease, relapse or progression were compared to patients treated with HIT-SKK chemotherapy ± radiotherapy (n=9) or other regimens (n=8). RESULTS: Median age at diagnosis was 2.9(1.0–5.3) years. Metastases at diagnosis were detected in 9 patients (26%). For the entire cohort of n=35, 5-year overall survival (OS) was 26.7%, and progression-free survival (PFS) was 18.5%. Five-year OS for patients with CARBO-ETO+HDCT, SKK chemotherapy or other regimens was 44.4%, 13.0% and 0%, respectively (p=0.006). Five-year PFS was 33.3%, 0% and 0%, respectively (p=0.119). Of 10 survivors, n=8 were treated with CARBO-ETO+HDCT; n=4 had craniospinal, n=2 local and n=4 no radiotherapy. Impact of initial gross-total-resection (p=0.231) and non-metastatic disease (p=0.097) was limited. CONCLUSIONS: We show improved survival with carboplatin-etoposide-induction followed by tandem-high-dose chemotherapy, indicating that a cure is possible for some patients. However, despite intensive treatment, outcome is unsatisfactory and innovative therapies urgently need to be included in an upfront setting.

ETMR-15. USE OF HIGH-DOSE CHEMOTHERAPY FOR TWO CHILDREN WITH EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES

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Embryonal tumor with multilayered rosettes (ETMR) is new entity defined in the 4th revised edition of the WHO classification of tumors of the central nervous system. Although radical resection, radiotherapy, and multiagent chemotherapy are considered to be necessary for ETMR, the efficacy of chemotherapy for ETMR in Japan has not been established. Here, we report different clinical courses for two children with localized ETMR treated with the St. Jude medulloblastoma-96 (SJMB96) regimen, which consists of four cycles of high-dose chemotherapy with autologous peripheral blood stem cell transplantation. For both children, the diagnosis of ETMR, C19MC-altered was confirmed after gross total tumor resection. Multiagent chemotherapy was administered following cranio-spinal irradiation with local boost. One month after completion of the treatment, one patient experienced local recurrence but has been in remission for over 2 years after tumor resection and stereotactic irradiation with a CyberKnife and treatment every three weeks with bevacizumab. The other patient also experienced local recurrence after the third cycle of chemotherapy and several times thereafter. Although she again underwent tumor resection and local irradiation, her tumor grew larger and invaded. Because her prognosis was very poor, her parents choose only palliative care. Based on our experience, we believe that continuous chemotherapy at conventional doses is preferred over intensive-dose chemotherapy such as SJMB96. However, the number of reports on chemotherapy for ETMR is still small, and a prospective multicenter trial is needed to establish effective chemotherapy for ETMR.

ETMR-17. SINGLE-CELL TRANSCRIPTOME ANALYSIS OF ETMR PATIENT SAMPLES

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Brain tumors are comprised of cells with heterogeneous genetic and transcriptional states, resulting in substantial phenotypic diversity. This diversity is particularly evident in embryonal tumor with multilayered rosettes (ETMR), which shows a striking bi-phasic pattern for which it is named. A better understanding of its underlying molecular makeup is urgently needed to develop more effective therapeutic strategies that eliminate all malignant cell types underlying ETMR initiation, maintenance, progression, and relapse. Furthermore, the cellular origin of ETMR is currently poorly understood. We used plate-based single-cell RNA sequencing to assess the intratumoral heterogeneity in 6 fresh and 4 snap-frozen surgical biopsies, following a workflow that we have previously established to study pediatric high grade gliomas, medulloblastomas, and ependymomas. Computational analyses conducted on >4,000 single cells identified cellular hierarchies ranging from a proliferative, undifferentiated cell population to more differentiated, predominantly neural-like progeny in all samples. Patient-derived cell line and xenograft models partially recapitulated this hierarchy. We further integrated transcriptional programs identified in single cells with available datasets of the developing normal brain, as well as with programs identified in other pediatric brain tumor entities, to inform both putative cellular origins and ETMR-specific oncogenic pathways. These timely results provide unparalleled insights into the molecular underpinnings of the phenotypic heterogeneity observed in ETMR. Analyses aimed at further integrating malignant cell type abundances with genetic alterations and clinical annotations, and therapeutical targeting of malignant cell populations using in-vitro models are currently ongoing.

ETMR-18. TARGETING LIN28 IN ETMR WITH ODC1 INHIBITOR DFMO

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Embryonal tumor with multilayered rosettes (ETMR), is an aggressive brain tumor primarily occurring in young patients (<4 years of age) and characterized by C19MC amplification and Lin28 overexpression. These genetic hallmarks have been shown to participate in driving ETMR in a C19MC-Lin28-MYCN circuit. Reducing Lin28 disrupts this circuit and reduces cell viability in ETMR models. Investigation of therapeutic agents targeting this pathway is required to provide new treatment options for this deadly disease. We present data showing the effect of DFMO (α-difluoromethylornithine) in ETMR, an ODC1 inhibitor known to reduce Lin28 in neuroblastoma. DFMO treatment of the ETMR cell line BT-183 resulted in a significant reduction of intracellular Lin28 protein levels ($P<0.05$) as indicated by flow cytometry. In concert with this reduction in Lin28, there was a as significant reduction in viable cells ($P<0.05$), and the number of CD133+ cells were reduced 2-fold ($P<0.05$). High throughput drug testing of BT-183 identified a number of additional therapeutic agents with potential therapeutic efficacy for ETMR and combining these with cytostatic agent DFMO demonstrated the potential use of these drugs in combination. These *in vitro* data were complemented by testing of DFMO in an *in vivo* stereotaxic xenograft ETMR model, with inhibition of tumor burden monitored by bioluminescent imaging of the tumors. Together this work shows that Lin28 targeting agents such as DFMO merit further examination and integrating these types of agents into treatment strategies for ETMR may lead to better outcomes.

ETMR-19. SINGLE CELL ANALYSES OF ETMRS REVEAL THAT C19MC+ POPULATION DRIVES CELL CYCLE PROGRESSION AND STEM CELL MAINTENANCE

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Embryonal tumors with multilayered rosettes (ETMRs) are highly fatal diseases characterized by recurrent amplification of *C19MC*, an oncogenic miRNA cluster. While *C19MC* was discovered as a major driver of ETMRs, its direct role in ETMRs remains unknown. As ETMRs exhibit significant heterogeneity in C19MC expression, we employed single cell transcriptomics to investigate features of C19MC+ population. We conducted single-nuclei RNAseq of 23,269 cells from 6 primary and 2 matched recurrent ETMRs. We also conducted single-cell RNAseq of human neural stem cells (hNSC-5miR) and ETMR cell line (A664-5miR) with stable expression of 5 C19MC miRNAs. Bulk RNAseq (n=27), H3K27Ac ChiP-seq (n=5) and ATAC-seq (n=5) corroborated scRNAseq data and identified core transcription factors (TFs) of C19MC+ population. C19MC+ population (24%) mapped to neuro-epithelial cells and exhibited signatures of cell cycle and stem cell maintenance, consistent with bulk-RNAseq data. The C19MC+ population overlaps with MKI67+ cycling (57%) and PROM1+ stem cell population (56%). Interestingly, interrogation of hNSC-5mir and A664-5miR showed a larger MKI67+/PROM1+ population compared to controls. Likewise, hNSC-5miR/A664-5miR *in vitro* and *in vivo* experiments showed increased proliferation/stemness. C19MC+ population is characterized by SHH, WNT, mTOR, Hippo and IGF-signalling and driven by MEIS1, SOX11, ZNF521, RFX4 and NR2F2 TFs. Recurrent ETMRs exhibit a persistent but smaller C19MC+ population. Intriguingly, recurrent tumors were more quiescent with a smaller proliferative population. C19MC is directly involved in driving cell cycle and stemness in ETMRs. Cellular and molecular features of primary and recurrent ETMRs were remarkably different, suggesting that C19MC plays a different role upon recurrence.

ETMR-20. IMPACT OF HIGH DOSE CHEMOTHERAPY WITH AND WITHOUT METHOTREXATE (MTX) ON OUTCOME OF PATIENTS WITH EMBRYONAL TUMORS WITH MULTI-LAYERED ROSETTES (ETMRS): A REPORT FROM CHILDREN'S ONCOLOGY GROUP PHASE III TRIAL ACNS0334

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Infant embryonal brain tumors comprise a spectrum of histologic and molecular entities including medulloblastoma (MB) and tumors collectively called CNS PNET's, including supratentorial PNET (sPNET), pineoblastoma and other less common histologic entities. Non-MB embryonal tumors, historically considered high risk disease, were included in ACNS0334, A Children's Oncology Group prospective phase III trial which compared efficacy of an induction regimen with and without methotrexate combined with high dose chemotherapy and stem cell rescue; no radiation was mandated. Molecular testing performed after ACNS0334 closure identified 14 patients with embryonal tumors with multi-layered rosettes (ETMRs), a new molecular entity previously classified under various diagnostic categories. ETMR patients made up 20% of the molecularly analyzed ACNS0334 cohort and were predominantly females. Tumors were largely non-metastatic (10/14 M0, 1 M1, 3 M2/M3) and originated in the cerebrum (8), cerebellum (3) and pineal gland (3). Gross total tumor resection was achieved in 5/11 patients with M0/M1 disease; 9/14 patients completed full treatment with 5 randomized to MTX induction and 9 to no-MTX. Five of 14 patients progressed on treatment, one had a toxic death. Disease progression was primarily local (88 %). No difference by methotrexate randomization was observed. Four patients are alive without progression 5–10+ years off therapy, none received radiation. No patients received radiation prior to progression. Four were irradiated after progression and died from disease within 3 to 13 months. Our study, a first report on ETMRs prospectively treated on a clinical trial, suggests high dose chemotherapy benefits a portion of ETMR patients.

ETMR-21. META-ANALYSIS OF PINEAL REGION TUMOURS DEMONSTRATES MOLECULAR SUBGROUPS WITH DISTINCT CLINICO-PATHOLOGICAL FEATURES: A CONSENSUS STUDY

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Pineoblastomas (PB) are rare, aggressive pineal gland tumours with poor global OS of 50–70% and only 15–49% OS for patients <4 years, despite intensive treatments. Recently, three independent groups (German Cancer Research Centre, Rare Brain Tumour Consortium/SickKids, St. Jude Children's Research Hospital) collectively analyzed large tumour cohorts and revealed molecular sub-groups of PB. To harmonize and better characterize clinico-pathologic associations of these sub-groups, we undertook a meta-analysis of molecular and clinical data of the combined cohorts. Unsupervised consensus cluster analyses of global methylation data from 227 unique cases identified five robust molecular sub-groups of pineal region tumours: PB_miRNA_1, PB_miRNA_2, PB_MYC/FOXR2, and PB_RB, mainly comprised of pediatric WHO grade 4 PBs and PNETs; and a fifth group: named PPTID, comprised of mainly pineal parenchymal tumours of intermediate differentiation, a WHO grade 2–3 tumour common in adults. PB_miRNA_1 and PB_miRNA_2 tumours, primarily arising in children (median ages 7.7, 11.4y, respectively), were characterized by alterations of miRNA biogenesis genes *DICER1*, *DROSHA,* and *DGCR8*. PB_MYC/FOXR2 and PB_RB groups, arising in infants/toddlers (median ages 1.4, 2.0y, respectively), were distinguished by recurrent *MYC* gain/amplification and *RB1* loss, respectively. The PPTID group affected mainly adults (median age 33y) and exhibited limited CNAs. Higher rates of metastasis were observed with PB_miRNA_1 (42%), PB_MYC/FOXR2 (38%), and PB_RB (75%) tumours, compared to PB_miRNA_2 (20%) and PPTID (25%). Results from ongoing integrative survival analyses of this large cohort will provide critical data for design of future clinical trials.

ETMR-22. TITLE: DEFINING THE CLINICAL AND PROGNOSTIC LANDSCAPE OF EMBRYONAL TUMORS WITH MULTI-LAYERED ROSETTES (ETMRS), A RARE BRAIN TUMOR REGISTRY (RBTC) STUDY

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ETMR, an aggressive disease characterised by *C19MC* alterations, were previously categorised as various histologic diagnoses. The clinical spectrum and impact of conventional multi-modal therapy on this new WHO diagnostic category remains poorly understood as a majority of ~200 cases reported to date lack molecular confirmation. We undertook comprehensive clinico-pathologic studies of a large molecularly confirmed cohort to improve disease recognition and treatment approaches. Amongst 623 CNS-PNETs patients enrolled in the RBTC registry, 159 primary ETMRs were confirmed based on a combination of FISH (125), methylation analysis (88), SNP and RNAseq (32) analyses; 91% had *C19MC* amplification/gains/fusions, 9% lacked C19MC alterations but had global methylation features of ETMR NOS. ETMRs arose in young patients (median age 26 months) predominantly as localized disease (M0-72%, M2-3 -18%) at multiple locations including cerebrum (60%) cerebellum (18%), midline structures (6%); notably 10% were brainstem primaries mimicking DIPG. Uni-and multivariate analyses of clinical and treatment details of curative regimens available for 110 patients identified metastatic disease (p=0.002), brainstem locations(p=0.005), extent of surgery, receipt of multi-modal therapy including high dose chemotherapy and radiation (P<0.001) as significant treatment prognosticators, while C19MC status, age and gender were non-significant risk factors. Analyses of events in all patients showed respective EFS at 3 and 12 months of 84%(95%CI:77–91) and 37%(95%CI:20–41) and 4yr OS of 27%(95%CI:18–37) indicating despite intensified therapies ETMR is a rapidly progressive and fatal disease. Our comprehensive data on the largest cohort of molecularly-confirmed ETMRs provides a critical framework to guide current clinical management and development of clinical trials.

GERM CELL TUMORS

GCT-02. THE LONG-TERM OUTCOMES AND SEQUELAE ANALYSIS OF INTRACRANIAL GERMINOMA FROM 187 PATIENTS IN THE SINGLE INSTITUTE: NECESSITY FOR THE ADAPTATION OF RADIOTHERAPY DOSE AND VOLUME

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PURPOSE: We aimed to refine the radiotherapy (RT) volume and dose determinant for disease failures and long-term sequelae in the intracranial germinoma. METHODS: The main treatment for intracranial germinoma was craniospinal RT only (n=51) during 1981–1992 and RT with upfront chemotherapy (CRT) (n=152) during 1992–2015 in Seoul National Uni-

versity Hospital. All 187 cases were confirmed histologically. RT fields included craniospinal, whole-ventricle (WV), whole-brain (WB), and focal radiotherapy. RT dose was dependent on the M status and combination of chemotherapy. The median follow-up duration was 115 months (range, 3–358). RESULTS: The 10-year overall and recurrence-free survival was 94.5% and 91.4%. The complete response rate after chemotherapy was 62.6%. For the patients with complete response, WV RT 16–20 Gy, and focal boost of 25–36 Gy after upfront chemotherapy showed no in-field recurrence. The causes of death were progression (n=3), 2nd malignancy (n=6), treatment-related complications (n=7), and others (n=8). For non-sellar tumors, the rate of hormonal replacement treatment was significantly related to WB RT and WB/WV RT dose ≥ 30 Gy (p=.030, and .026). After a latency of the median 20 years, ten patients (5.3%) developed 2nd malignancy. WB RT and WB/WV dose ≥ 30 Gy were significantly correlated with the 2nd malignancy (p=.024, and .004). The rate of severe neurocognitive dysfunction was significantly associated with WB/WV dose ≥ 30 Gy (p=.027). CONCLUSION: CONCLUSION: RT with or without upfront chemotherapy exhibits the excellent control rate of disease. However, the intensity and volume of RT are critical for managing treatment toxicities. Adaptation and further de-intensification of RT should be followed.

GCT-03. TREATMENT OUTCOMES, PHYSICAL DEVELOPMENT AND QUALITY OF LIFE OF PATIENTS WITH BIFOCAL GERM CELL TUMOURS

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BACKGROUND: The optimal radiation field in patients with bifocal germ cell tumours(GCTs) is controversial, especially in non-metastatic cases. Accordingly, we analysed the survival, growth, and health-related quality of life (HRQOL) data of patients with bifocal GCTs. METHODS: The data of 87 patients diagnosed with bifocal GCTs at our hospital during the last 10 years were collected. The WHO AnthroPlus software—used to monitor the growth of persons aged 5–19 years—was employed to calculate the Z-score of height (ZSOH) at diagnosis and the last follow-up. The absolute change in the ZSOH was defined as $|ZSOH_{last\ follow\text{-}up} - ZSOH_{diagnosis}|$. The Pediatric Quality of Life Inventory 4.0 was used to evaluate HRQOL. RESULTS: The median follow-up was 49 months (range,6–134 months). Among 49 patients with non-metastatic germinoma, those receiving cranial spinal irradiation(CSI; n=12) or whole-brain radiotherapy (WBRT; n=34) had comparable disease-free survival (DFS;p=0.54), but better DFS than those receiving focal radiotherapy(n=3;p=0.016). Furthermore, among 17 patients with non-metastatic non-germinomatous GCTs, DFS was not significantly different between those treated with CSI(n=4) and those receiving WBRT(n=13;p=0.11). Twenty-nine patients had paired ZSOH data at both diagnosis and the last follow-up. Patients receiving CSI(p=0.026) or >40Gy(p=0.048) experienced a significant decline of absolute change in the ZSOH. HRQOL analysis(n=35) did not reveal difference between patients receiving CSI and those not receiving CSI. CONCLUSIONS: Given the comparable DFS and HRQOL but negative impact on growth, CSI could be spared, especially in patients with non-metastatic bifocal germinoma.

GCT-06. DIAGNOSIS OF A RARE CASE OF RECURRENT GERM CELL TUMOR BY CSF PLACENTAL ALKALINE PHOSPHATASE PRESENTING WITH DIFFUSE INTRAAXIAL ABNORMALITY IN THE LOWER BRAINSTEM

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INTRODUCTION: Germ cell tumors in the central nervous system (CNS) typically arise either at suprasellar and/or pineal region, and occasionally at basal ganglia. We report a case of diagnostically challenging, recurrent germ cell tumor presented with diffuse intraaxial abnormality in and across the lower brainstem, which was diagnosed by the elevated placental alkaline phosphatase (PLAP) level in cerebrospinal fluid (CSF). CASE DESCRIPTION: A 28-year-old man had been treated by chemoradiotherapy at the previous hospital for bifocal suprasellar and pineal lesions with the provisional diagnosis of germinoma without histological confirmation. Three years later, he presented with progressive weakness of bilateral extremities for weeks. Magnetic resonance imaging showed a diffuse, bilaterally symmetric high intensity lesion on T2-weighted image with slight contrast enhancement across the ventral side of the medulla oblongata to the upper cervical spinal cord. Serum and CSF hCG, hCG-β, and AFP were all negative. Since the image findings were atypical for recurrent germ cell tumor, some kind of myelitis was initially suspected. Therefore, steroid pulse therapy was administered. However, the patient's symptom was still gradually progressing. Then, the CSF PLAP turned out to be positive, indicating the recurrence of germinoma. Accordingly, platinum-based chemotherapy was administered, and the imaging findings, patient's symptoms, and CSF PLAP began to improve. The patient is to be treated with radiotherapy following chemotherapy. CONCLUSION: We report a rare case of CNS germ cell tumor that presented with diffuse intraaxial lesion in the lower brainstem in which examination of CSF PLAP was extremely useful.

GCT-08. PROTON BEAM RADIOTHERAPY FOR PEDIATRIC AND YOUNG-ADULT PATIENTS WITH INTRACRANIAL GERM CELL TUMOR

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BACKGROUND: To reduce treatment-related adverse events in pediatric and young-adult patients with brain tumors, proton beam radiotherapy (PBT) has recently been performed instead of conventional X-ray radiotherapy. However, whether PBT is as effective as X-ray radiotherapy has not been sufficiently investigated, especially in patients receiving whole-ventricular irradiation. METHODS: We report a retrospective observation of 15 patients with intracranial germ cell tumors (GCT), who received PBT at our institution from April 2014 to September 2019. We evaluated their clinical course, short-term adverse events, and prognosis. RESULTS/CONCLUSION: Fifteen patients (9 males and 6 females; median age 13 years) who received PBT following induction chemotherapy were analyzed. Nine patients received 23.4–27.0 GyE of whole-ventricular irradiation due to GCT in the pituitary gland, pineal body, or hypothalamic area. Three patients received 23.4 GyE of whole-brain irradiation: one of them had boost irradiation for basal ganglia. Three patients received 30.6 GyE of craniospinal irradiation (CSI). Six of the 15 patients experienced nausea (grade 2, according to the CTCAE version 4.0). Four patients, including two who received CSI, showed myelosuppression: decrease in white blood cell count, lymphocyte cell count, and neutrophil count (grade 3). No other severe short-term adverse events of >grade 2 was observed in any of the patients. At a median follow-up of 21 months (2-62 months) after irradiation. all patients are alive without recurrence. Our results may be encouraging and further investigations with a larger scale is warranted.

GCT-09. HEALTH AND SOCIAL ISSUES IN THE LONG-TERM GERM-CELL TUMOR SURVIVORS

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Germ cell tumor (GCT) is a rare juvenile CNS tumor that is more frequent in eastern Asia. Most survivors require continuous medical care for hormone replacement, maintenance of shunting devices, and late radiation-induced effects. In the present study, we retrospectively analyzed medical records of long-term GCT survivors, and make the health and social issues clear. Ninety-two GCT patients were treated in our institute from 1982 to 2018, and 81 patients, of which medical records are available, are included. The median follow-up period is 12.2 years, and 47 patients (58.1%) are followed for more than ten years. The overall survival rate is gradually decreasing more than ten years follow-up, such as 10-, 15- and 25-years survival are 92.3, 87.7, and 73.3%, respectively. In the long-term follow-up, eight subsequent malignancy and seven cerebrovascular events are recorded. These events occurred 20 years or more after the treatments, and six CNS malignancies were observed in survivors irradiated with 50Gy or more. As social issues, forty-two of 50 adult survivors had been employed after the treatments, but only thirty-four (70.8%) are still working. Of note, only nine (18.8% of adults) survivors got married. All four married women require any hormone replacement, while only one of 4 men requires the replacement. Long-term follow-up of GCT survivors revealed subsequent malignancy and social problems. A recent attempt to decrease the dose of irradiation might overcome some issues. As a conclusion, GCT survivors require a supporting program for not only health but also social issues.

GCT-10. CAN HIGH LEVEL SERUM HCG-B BE CONSIDERED EQUIVALENT TO A DIAGNOSIS OF CHORIOCARCINOMA IN PRIMARY CENTRAL NERVOUS SYSTEM GERM-CELL TUMOR?

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BACKGROUND: Primary central nervous system(CNS) choriocarcinoma(CC) is very rare and has the poorest prognosis among germ cell tumor (GCT). CC usually has extremely high level (HL) of serum beta-human chorionic gonadotropin (bhCG) over than 1,000 mIU/ml. Some studies assign HL bhCG cases to poor prognosis group even without biopsy. The purpose of this study was to find out if there was a good prognosis subset in the HL bh group. MATERIALS AND METHODS: We analyzed 103 cases diagnosed with GCT from 1998 to 2019 in Hokkaido University Hospital and reviewed the literature of CNS CC and bhCG. Survival was assessed using Kaplan-Meier method and log-rank statistics between the group with CC component and that with no CC component but HL bhCG. RESULTS: One out of 103 our cases was diagnosed as a mixed GCT with CC component and did not respond to treatment and died 9 months later. Two cases were treated as CC because of HL bhCG (1,226 and 2,739 mIU/ml) despite that the biopsy showed only germinomas and survived(105 and 37 months), that is, no CC component. Combining our cases with 69 cases in the literature, all 7 cases with no CC component but HL bhCG survived but the median survival of the other 65 cases with CC component was 38.2 months (P=0.02). CONCLUSION: This study has a limitation of selection bias, however, it suggests that patients with no CC component but HL bhCG may have a better prognosis.

GCT-12. INTRACRANIAL GROWING TERATOMA SYNDROME: CLINICAL IMPLICATION FROM SINGLE UNIVERSITY EXPERIENCES

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In general, intracranial germ cell tumors (GCT) are sensitive to chemotherapy, radiation therapy, and have favorable outcomes. However, a rare chemotherapeutic retro conversion phenomenon, known as intracranial growing teratoma syndrome (iGTS), shown a poorer prognosis. We analyze the diagnostic characteristics and the result of treatment response for the patients with iGTS treated in our institutes (SNUH and SNUBH, from 1997 to 2019). The electronic medical records and PACS were used for reviewing the clinical information, follow-up MRI images, tumor markers (alpha-fetoprotein, human chorionic gonadotropin, in serum or cerebrospinal fluids), and pathological findings. Out of 328 intracranial GCT patients, seventeen were finally identified as iGTS. Sixteen out of 17 patients were non-germinomatous GCTs, and 1 were germinomas. Initial pathology was common in order of immature teratoma (26.7%), other than immature teratoma (11.5%), and germinoma (0.5%). All of the tumors showed typical 'honeycomb appearance' in their follow-up MRI images. Sixteen out of 17 tumors were surgically resected as 2nd look surgery. Among them, 13 tumors were gross totally resected. Twelve were alive without evidence of recurrences during follow-up periods, and the other was dead from the progression of the disease. Among the other than the gross total resection group (n=4), two patients were dead, one recurred the tumor, and the other is following up with stable disease after adjuvant radiation therapy. Early detection and total resection of the tumor as possible might be meaningful for favor prognosis, especially in non-germinomatous GCTs patients.

GCT-13. THE TREATMENT OUTCOMES OF INTRACRANIAL GERM CELL TUMORS WITH KSPNO PROTOCOL: SINGLE CENTER RETROSPECTIVE ANALYSIS

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Dho et al. (BTRT, 2017) reported that 1.1% (127/11,827) of primary brain tumors are intracranial germ cell tumors (iGCT) in Korea. We analyzed the epidemiology and treatment results of germ cell tumors in our institution. From 2004 to 2019, among 6494 patients with intracranial neoplasms the 61 (0.9%) patients with iGCTs were enrolled: histologically diagnosed in 50 patients and clinically in 11 respectively. Pediatric patients underwent treatment according to the KSPNO protocol, and adult patients were treated with bleomycin, etoposide, and cisplatin regimens. The median age was 20 years (range: 1–42) and the follow-up period was 7.7 months (range: 10.0–203.4 months), respectively. The tumors arise most frequently in the pineal area (n=30, 49.2%). There were no significant differences in outcomes between protocols, but in KSPNO protocol group showed lower tumor recurrence rate (11.5% vs. 20%, p=0.494) and mortality (0% vs. 5.2%, p=0.503). According to the pathological subtype, the outcomes showed statistically significant differences between germinoma and non-germinomatous germ cell tumor (NGGCT) groups. The 10-year progression-free survival was 93.2% and 67.1% in the germinoma and the NGGCT group, respectively (p=0.009). The NGGCT pathological type (p=0.021) was a significant recurrence associated factor in multivariate analysis. Significant adverse events (CTCAE version 5.0 grade≥3) were showed in 14 patients (7 patients in both KSPNO and other treatment protocol groups). Pure germinoma has a higher survival rate and a lower recurrence rate than NGGCT. And KSPNO protocol might be safe and effective. For appropriate treatment for iGTCs, a multidisciplinary approach might be needed.

GCT-14. SECOND-LOOK SURGERY FOR INTRACRANIAL GERM CELL TUMORS

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OBJECTIVE: The authors present their experiences of second-look surgery in patients with intracranial GCTs who showed less than complete response despite normalizing or decreasing tumor markers after chemotherapy. METHODS: Retrospective review of 14 patients who underwent second-look surgery for an intracranial GCT was performed. RESULTS: Of 40 consecutive patients with newly diagnosed intracranial GCTs treated between August 2003 and 2019, 14 patients (35%) underwent second-look surgery. The mean age was 9.2 years. The initial diagnoses were mixed germ cell tumor in 6, immature teratoma in 4, yolk sac tumor in 2, and germinoma 2. Second-look surgery was performed after 1–3 courses of chemotherapy. Magnetic resonance imaging (MRI) at the surgery demonstrated increasing residual tumor in 8 and stable residual tumor in 6. Tumor markers were normalized in 10 and nearly-normalized in 4. Gross total resection was achieved in 12 patients and near-total resection in 2. Histopatholgy at second-look surgery revealed mature teratoma in 6, immature teratoma in 3, fibrosis with atypical cells in 2, and fibrosis in 3. Eleven patients subsequently underwent additional chemo-radiation therapy according to the initial diagnosis. All patients are alive with no evidence of recurrence with a mean follow-up of 69 months. CONCLUSIONS: Second-look surgery plays an important role in the treatment of intracranial GCTs. Surgery may be encouraged at a relatively early phase after chemotherapy when the residual tumor increases or does not change the size despite normalized or nearly-normalized tumor markers in order to achieve complete resection and improve the outcome.

GCT-15. INTEGRATED CLINICAL, HISTOPATHOLOGICAL, AND MOLECULAR DATA ANALYSIS OF 190 CENTRAL NERVOUS SYSTEM GERM CELL TUMORS FROM THE IGCT CONSORTIUM

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BACKGROUND: We integrated clinical, histopathological, and molecular data of central nervous system germ cell tumors to provide insights into their management. METHODS: Data from the Intracranial Germ Cell Tumor Genome Analysis Consortium were reviewed. A total of 190 cases were classified as primary GCTs based on central pathological reviews. RESULTS: All but one of the cases that were bifocal (neurohypophysis and pineal glands) and cases with multiple lesions including neurohypophysis or pineal gland were germinomas (34 of 35). Age was significantly higher in patients with germinoma than other histologies. Comparison between tumor marker and histopathological diagnoses showed that 18.2% of histopathologically diagnosed germinomas were marker-positive and 6.1% of non-germinomatous GCTs were marker-negative, suggesting a limitation in the utility of markers or histopathology alone using small specimens for diagnosis. Comparison between local and central histopathological diagnoses revealed a discordance of 12.7%. Discordance was significantly less frequent in biopsy cases, implying difficulty in detecting all histopathological components of heterogeneous GCTs. Germinomas at the typical sites (neurohypophysis or pineal gland) showed a better PFS than those at atyp-

ical sites (p=0.03). A molecular-clinical association study revealed frequent MAPK pathway mutations in males (51.4 vs 14.3 %, p=0.007), and PI3K/mTOR pathway mutations in basal ganglia cases (p=0.004). Basal ganglia cases also had frequent chromosomal losses. Some chromosomal aberrations (2q, 8q gain, 5q, 9p/q, 13q, 15q loss) showed potential prognostic significance. CONCLUSIONS: These in-depth findings of this study regarding the clinical and molecular heterogeneity will increase our understanding of the pathogenesis of this enigmatic tumor.

GCT-16. LONG-TERM CLINICAL OUTCOMES OF GERM CELL TUMORS

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BACKGROUND: Intracranial germ cell tumors (GCT) are mainly arising in adolescent term and treated with chemotherapy concomitant with radiation therapy. There is accumulating evidence that the progress of treatment. Besides, long-term outcome and adverse effects are major problem in treatment. So, we must grasp the influence of these outcomes on daily and social life. Then we investigated in clinical outcome in cases of GCT treated in our institution. METHOD: We reviewed the clinical features and outcomes of 52 cases of intracranial GCT in 1975 to 2019. Ages on diagnosis are 5–35 years old (median 14 years old), consisted with 44 male cases. The pathological distributions are these: pure germinoma: 40 cases, non-germinomatous germ cell tumor (NGGCT): 10 cases (mature teratoma: 4, mixed germ cell tumors: 3, and one cases of choriocarcinoma, embryonal carcinoma, yolk sac tumor), unidentified pathology: 2 cases. Almost all cases have biopsied and treated by chemotherapy and radiation therapy. RESULTS: Chemotherapy with ICE regimen (ifosphamide, cisplatin, etoposide) or CARE regimen (carboplatin, etoposide) concomitant with radiation therapy (mainly, extended local irradiation) have done in almost cases by the era. Clinical outcomes are relatively well in our cases, but 10 cases experienced recurrence. 3 cases have dead. Some cases with suprasellar involvement have need hormone replacement in long term. There are 10 cases at work. CONCLUSION: Almost cases have gained better outcome and ADL. But there is slightly lower rate in work or marriage. Serial evaluation in outcome, and higher brain functions should be performed in follow up.

GCT-17. WHAT IS THE CLINICAL OUTCOME OF PROTON BEAM THERAPY FOR PATIENTS WITH INTRACRANIAL GERM CELL TUMOR IN KOREA?

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PURPOSE: To evaluate the clinical outcome of patients with intracranial germ cell tumor treated with proton beam therapy (PBT). MATERIALS AND METHODS: Fifty-seven patients with intracranial germ cell tumor treated with PBT between 2009 and 2016 were retrospectively analyzed. RESULTS: Median follow-up duration was 63.7 months (range, 5.6–204.5). Thirty-seven patients (64.9%) were pure germinoma and 20 patients (35.1%) were non-germinomatous germ cell tumor (NGGCT). All patients except 2 patients received chemotherapy before PBT. Twenty-one patients (36.8%) of localized germinoma were treated with whole ventricle irradiation (WVI), while 36 (63.2%) patients who were diagnosed as disseminated germinoma or NGGCT received cranio-spinal irradiation (CSI). Two patients with pure germinoma in basal ganglia showed disease relapse at 3.0 and 6.9 years after PBT at the primary site and pituitary gland, respectively. There was one patient with NGGCT who died of chemotherapy-related mortality at 4.7 years after PBT while her disease was complete remission. The 7-year progression-free survival and overall survival were 70.8% and 100% for focal germinoma, 100% and 100% for disseminated germinoma, 100% and 100% for focal NGGCTs, and 100% and 80.0% for disseminated NGGCTs, respectively. CONCLUSIONS: PBT of pure germinoma resulted in comparable clinical outcomes to that with photon radiotherapy. Our result for NGGCT is also excellent compared to other reports. Failure patterns of germ cell tumors originating in basal ganglia needs to be assessed in large pooled data.

GCT-18. CLINICAL FEATURES OF GERM CELL TUMORS IN CHILDREN

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INTRODUCTION: Here, we discuss the presentation, histology, therapy, and outcome of germ cell tumors in children. METHODS: Treatment outcome and management was assessed for children diagnosed with germ cell tumors from 2007 to 2017 at Kagoshima University. RESULTS: Twenty-six patients (20 boys, 6 girls) with a mean age of 11.5 ± 4.9 years were included in this study. Patient tumor types included: germinoma (n = 19); immature teratoma (n = 3); yolk sac tumor (n = 3); choriocarcinoma (n = 1); embryonal carcinoma (n = 1). The most common patient clinical features were headache and vomiting associated with hydrocephalus. The median follow-up period was 96.5 months. Tumor location was pineal (n=9), bifocal (n=6), suprasellar (n = 5), basal ganglia (n=2), frontal lobe (n=2), and cerebellum (n=2). Surgical procedures included stereotactic biopsy (n=13), endoscopic third ventriculostomy and biopsy (n=8), and tumor decompression (n=5). All patients with germ cell tumors underwent adjuvant chemotherapy and radiation therapy; patients with germinoma or immature teratoma were still alive, while patients with embryonal carcinoma, yolk sac tumor, or choriocarcinoma had poor prognosis with a median survival of 16 months. CONCLUSIONS: Patients with germinoma had a relatively good prognosis, while patients with embryonal carcinoma, yolk sac tumor, or choriocarcinoma had a poor prognosis. A multidisciplinary approach including surgical strategy based on location, appropriate radiation planning, and chemotherapy is needed for effective treatment and improved outcomes.

GCT-19. MODELING GERM CELL TUMORS WITH KIT MUTANT HIPSCS

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Central Nervous System Germ Cell Tumor (CNS GCT) is the second most common pediatric brain tumor in Japan, and within CNS GCT, germinoma is the most common subtype, accounting for 62.3%. Recent reports of transcriptome and methylome analysis suggested that germinoma highly resemble the state of gonocytes, the germ cells at around 5th to 7th week of human embryo development. It is also identified that 60% of germinoma harbored somatic mutations in *KIT/RAS* pathway. As the protocol to derive gonocytes from human iPSCs have been reported, we aimed to recapitulate tumorigenesis by generating human iPSCs bearing common genetic mutations and derive gonocytes from them. We first introduced the most common mutation *KITD816V* to human iPSCs using CRISPR/Cas9, and confirmed in iPSCs that mutated KIT was phosphorylated in the absence of ligand stimulation, and also found that KIT activation contribute to the phosphorylation of AKT but not of ERK. Upon differentiation towards primordial germ cell -like cells (PGCLCs), KIT mutant lines were efficiently induced into PGCLCs, however, by comparing conditions with or without KIT ligand (SCF), mutant lines exhibited less dependency to SCF compared to wildtype cells. Mutant cells were further differentiated to gonocytes following published protocol and the cells were collected for transcriptome analysis. By comparing with the transcriptome of germinoma, we confirmed that germinoma samples express germ cell genes similar to gonocytes. We are attempting to identify the molecular mechanism of tumorigenesis in relation to KIT activation using this system.

GCT-20. EVALUATION OF NEURORADIOLOGICAL RESPONSE TO INDUCTION CHEMOTHERAPY FOR PATIENTS WITH LOCALISED GERMINOMA IN THE SIOP CNS GCT II TRIAL

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INTRODUCTION: The SIOP-CNS-GCT-96 trial demonstrated excellent survival for patients with germinoma. Localised patients received either craniospinal irradiation (CSI) 24Gy plus tumour-bed-boost 16 Gy or 2xcarboPEI chemotherapy (carboplatin/etoposide alternating with etoposide/ifosfamide) and focal-radiotherapy 40 Gy. Following trial closure, whole-ventricular-irradiation (WVI) was delivered with focal-radiotherapy to avoid ventricular relapse. Accordingly, current research priorities focus on reducing treatment burden and long-term neurocognitive sequelae. METHODS: SIOP-CNS-GCT-II employed national central radiological review to assess whether dropping the 16Gy boost was safe for localized germinoma in complete-remission (CR) following 2xcarboPEI: i.e. no disease on clinical/marker/radiological assessment. Any abnormal

thickening/enhancement after chemotherapy was to be classified as partial-remission (PR). Patients with less than CR after chemotherapy received a boost. RESULTS: Shortly before trial closure (2018), it was noted that national CR rates were discrepant across the largest recruiting countries. For German patients, CR rates were ~80%, compared with ~30–40% for UK and France. A formal neuroradiology review was therefore convened. A total of 59 cases were randomly selected (UK, n=32; France, n=14 and Germany, n=13), including those deemed to be in CR and PR. Cases included those with disease at pituitary, pineal and bifocal sites. Both diagnostic scan and scan after induction chemotherapy were used for assessment. Detailed analysis is ongoing and will be presented. CONCLUSION: Residual changes at both pituitary and pineal sites of uncertain significance may remain after chemotherapy. This process should facilitate consensus to define the best response criteria allowing treatment reduction for CNS germinoma for future clinical trials.

GCT-21. CENTRAL NERVOUS SYSTEM GERMINOMA - PONDERING THE NEXT STEPS

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Central nervous system germinoma (CNS) represents one successful example where the introduction of chemotherapy into the treatment allowed significant and meaningful reductions in the volume and dose of radiation therapy while maintaining excellent outcomes. However, the long-term toxicities and morbidities of the current therapies, in addition to their substantial negative impact on the social wellbeing of germinoma patients, should clearly indicate that the current achievements are not enough. While stepwise cutback of the radiation therapy needs to be commended, real progress must be achieved in the exploration and investigation of biological and molecular markers. Furthermore, the differences that still exist between the several working groups around the globe in determining the tumor marker cut-offs that help diagnose these tumors illustrate their shortcomings, and therefore the need for newer and more reliable methods. Additionally, efforts should focus on the inclusion of metastatic and basal ganglia/thalamic germinomas in future prospective clinical trials given the lack of evidence on the best treatment strategy for these patients. A comprehensive review of all major CNS germinoma clinical trials will be presented aiming to lay a foundation for researchers and clinicians alike who are currently working on designing innovative approaches for this group of patients. This review also details the current issues of debate, and provides suggestions which may assist in the design of future prospective clinical trials for children with CNS germinomas.

GCT-22. PROTEIN DEUBIQUITINATION PATHWAY IS A NOVEL THERAPEUTIC TARGET AGAINST MALIGNANT NON-GERMINOMATOUS CNS GERM CELL TUMORS

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Central nervous system germ cell tumors (CNSGCTs) are rare intracranial neoplasm usually developed in adolescents and young adults. However, in East Asia including Japan, incidence of CNSGCTs is considerably higher compare with other regions of the world. Whereas germinomas generally respond to chemo-radiotherapy well, malignant subtypes of non-germinomatous germ cell tumors (NGGCT) are refractory, and development of novel therapy against NGGCTs is urgently needed. To develop a new therapeutic strategy against aggressive NGGCTs, we have investigated novel molecular targets for NGGCT treatment. We screened a total of 120 CNSGCT tumor tissues (including 55 NGGCT), which were registered to the Intracranial Germ Cell Tumor Consortium (iGCT), and discovered multiple mutations of a molecule that regulates protein ubiquitination and degradation specifically in NGGCT cases (5 of 55 cases; 1 immature teratoma, 3 mixed gem cell tumors, and 1 embryonal carcinoma). An in vitro ubiquitination assay revealed the mutations of this molecule discovered in NGGCT cases were loss of function mutations. Reduced expression of this molecule by knockdown in an established human seminoma cell line Tcam2 or a human yolk sac tumor cell line YST1, which was recently established in our institute, resulted in enhanced proliferation as well as upregulation of MEK-ERK activation. Importantly, treatment of these two GCT cell lines with reduced expression of this molecule by MEK inhibitor trametinib suppressed augmented proliferation of these cells. Taken together, these results suggest that protein ubiquitination-related pathways as well as MEK-ERK cascade may serve as a novel therapeutic target against NGGCTs.

GCT-23. MULTI-INSTITUTIONAL ANALYSIS OF TREATMENT MODALITIES IN BASAL GANGLIA AND THALAMIC GERMINOMA

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BACKGROUND: Central nervous system (CNS) germinomas are radiotherapy (RT)-sensitive tumors with excellent survival. Current treatment strategies combine chemotherapy with RT to reduce the field and dose of RT. There is no standard treatment for germinomas originating in the basal ganglia/thalami (BGTG) given their rarity and poorly-defined imaging characteristics. Craniospinal (CSI), whole brain (WBI), whole ventricle (WVI), and focal RT have been previously utilized; however, the optimal strategy remains unclear. METHODS: Retrospective multi-institutional analysis was conducted across 18 institutions in four countries. RESULTS: For 46 cases with non-metastatic BGTG, the event-free survival (EFS) was 86.9% at both 5 and 10 years, while overall survival (OS) was 100%, and 95.7% respectively at 5 and 10 years. Median RT dose and range for the various treatment volumes were as follows: CSI (n=10): 2340 cGy (1980–3060 cGy), WBI (n=8): 2340 (1800–3000 cGy), WVI (n=14): 2340 cGy (1800–2550 cGy), focal (n=9): 3600 cGy (3060–5400 cGy). There was no statistically significant difference in the EFS based on RT modality (p=0.57), but EFS for subjects with CSI and WBI were both 100%. The three subjects who received chemotherapy alone had significantly lower EFS than those who received chemotherapy and RT (p=0.001), but were salvageable with RT. CONCLUSION: In the largest study to date for BGTG, there were no significant differences in outcomes between patients who received CSI, WBI, WVI or focal RT. This group of patients should be included in future prospective clinical trials, and a more limited RT field may be considered.

GCT-24. RELAPSE PATTERN AND QUALITY OF LIFE IN PATIENTS WITH LOCALIZED GERMINOMA ORIGINATING FROM BASAL GANGLIA REGION

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BACKGROUND: The optimal radiation field in localized basal ganglia (BG) germinoma was not well defined, mostly due to unknown relapse patterns. In our institute, both focal radiotherapy (FR) and craniospinal irradiation (CSI) plus boost were considered in this population until whole-brain radiotherapy (WBRT) plus boost became an option in 2008. Thus, a retrospective study was conducted to address the issue. Furthermore, the health-related quality of life (HRQOL) was also evaluated. METHODS: Patients who were diagnosed as localized BG germinoma between 2000 and 2017 were studied. HRQOL was evaluated by PedsQL 4.0 (≤15 years) and SF-36 (>15 years) questionnaires based on the age at last follow-up. RESULTS: Among 161 patients included, 35 patients received FR, 109 patients

received WBRT plus boost, and 17 patients received CSI plus boost. After a median follow-up of 83 months (range, 13 to 214 months), 15 patients relapsed in FR group, 4 in WBRT group and 0 in CSI group. The 5-year DFS was 74.3%, 97.2%, and 100%, respectively (p<0.001). Among 15 patients who relapsed after FR, 14 had positive radiological findings, in which 6 (42.8%) had lesions documented at the periventricular area, and 7 (50.0%) in the frontal lobe. HRQOL data were available in 69 patients, which generally scored low. In 38 patients evaluated by SF-36, those receiving CSI had significantly lower mental component scores than those receiving WBRT (p=0.027) or FR (p=0.011). CONCLUSIONS: Patients with localized BG germinoma present a unique relapse pattern. WBRT, which covers at-risk areas, showed both better disease control and HRQOL.

GCT-25. INNOVATIVE, INTENSIVE IRRADIATION-AVOIDING/ MINIMIZING CHEMOTHERAPY FOR HIGH-RISK PRIMARY CENTRAL NERVOUS SYSTEM (CNS) MIXED MALIGNANT GERM CELL TUMORS (HR-MMGCT): A PILOT STUDY AND PROPOSED MULTI-NATIONAL PROSPECTIVE TRIAL

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BACKGROUND: About one-third of children with primary CNS MMGCT experience incomplete responses to initial induction chemotherapy prior to irradiation, many of whom will subsequently relapse. Such high-risk patients are variably defined as having initial alpha-fetoprotein (AFP) elevations exceeding 1,000ng/mL, predominant histopathologies of malignant non-germinomatous GCT and incomplete responses to induction chemotherapy. Drugs targeting GCT-specific molecular markers have been identified for non-germinomatous GCT elements but have yet to be incorporated into prospective clinical trials. Four children with clearly identified HR-MMGCT characteristics have been treated on an innovative pilot regimen incorporating intensified chemotherapy and molecularly targeted agents, with avoidance or minimization of irradiation. METHODS: Four children (two with pure suprasellar embryonal carcinoma (EC) - one with Down syndrome and the other with pre-diagnosis cognitive dysfunction; one with initial serum AFP exceeding 7,000ng/mL and yolk sac tumor (YST)+EC+Teratoma pathology; one with initial serum AFP exceeding 1,000ng/mL) were treated with 3 cycles of "standard" induction chemotherapy (ACNS1123), followed by 1–3 transplant cycles (thiotepa/carboplatin) each with complete radiographic and tumor marker responses. Two children with pure EC subsequently received six cycles of brentuximab-vedotin without irradiation and remain disease-free off therapy for 2–4 years. One child with YST+EC+Teratoma has subsequently received reduced dose craniospinal irradiation and pineal region boost, and will receive oral everolimus, erlotinib, palbocyclib and intravenous brentuximab-vedotin. The fourth child with YST+MT will commence everolimus, erlotinib and palbocyclib without irradiation. CONCLUSION: This treatment strategy for HR-MMGCT patients provides preliminary tolerance and response data justifying extension to a multi-center trial.

GCT-26. PROGNOSTIC FACTORS IN PATIENTS WITH BASAL GANGLIA GERM-CELL TUMORS: A RETROSPECTIVE ANALYSIS OF THE SINGLE CHINESE INSTITUTE EXPERIENCE FROM 2009 TO 2019

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OBJECTIVE: To evaluate the clinical factors related to the prognosis of basal ganglia germ cell tumors. METHODS: A retrospective analysis of 52 cases of the basal ganglia germ cell tumors treated from January 2009 to January 2019 in the department of oncology of Guangdong Sanjiu Brain Hospital. The median age: 12 years (range: 5–32), The median course of disease: 11.7 months (range: 1–54). Thirteen cases were diagnosed by biopsy and 39 cases were diagnosed by elevated tumor markers. There were 31 patients (59.6%) diagnosed with germinomas and 21 patients (40.4%) with non-germ germ cell tumors. Univariate and multivariate survival analysis was performed. RESULTS: To October 15, 2019, the median follow-up time was 30.4 months (range 2–124 months). The 5-year survival rate was 85%, and the 5-year progression-free survival rate was 84%. Multivariate analysis found whether serum AFP was greater than 100mIU / ml, (with HR: 11.441,95% CI: 2.09–47.66, P = 0.005),the degree of surgical resection(with HR 5.323 (1.19–23.812), P = 0.029), PD as the effect of radiotherapy (HR: 16.53, (1.19–23.81), P = 0.001) were independent prognostic factor affecting survival. CONCLUSION: The pathological type, degree of surgical resection, and response to initial treatment can all affect survival.

GCT-27. CLINICAL FEATURES AND PROGNOSTIC FACTORS OF NONGERMINOMATOUS GERM CELL TUMORS IN 111 CONSECUTIVE PATIENTS IN A SINGLE INSTITUTION: IMPACT OF IRRADIATION AND CHEMOTHERAPY CYCLES ON SURVIVAL

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BACKGROUND: Limited data is available in intracranial nongerminomatous germ cell tumors (NGGCTs) in Chinese population. Here we aimed to retrospectively assess the clinical-pathological and prognostic factors of NGGCTs in a single large institution in China. METHODS: From June 2003 to December 2018, 111 consecutive NGGCTs were treated in Guangdong Sanjiu Brain Hospital, China. RESULTS: The median follow-up was 36.2 months (range, 1.2 to 131.2 months). Three-year EFS and OS for 111 NGGCTs patients were 78.5%±4.5% and 82.8%±4.0%, respectively. 98 patients received CSI plus boost yielded better survival than those who received reduced-volume radiotherapy or no radiotherapy (3y OS, 86.7% vs. 51.4%, p=0.007). Patients had at least four cycles of chemotherapy were strongly associated with improved 3-year OS, compared to those received less than 4 cycles (94.1% vs. 63.6%, $p < 0.001$). There was no significant difference in survival of patients stratified by age, surgery, hydrocephalus, as well as tumor diameter. Multivariate analysis identified chemotherapy cycles less than 4 was the only prognostic factor that conferring a worse OS (p=0.003). Patients both received CSI and at least 4 courses of chemotherapy were correlated with lower incidence of relapse (p=0.044). CONCLUSIONS: Multimodal approach including CSI and enough courses of chemotherapy was effective and should be recommended for the treatment of newly diagnosed NGGCTs in Chinese population.

GCT-28. RECURRENCE PATTERN AND SURVIVAL FOR RELAPSED INTRACRANIAL NON-GERMINOMATOUS GERM CELL TUMORS: A SINGLE-INSTITUTION EXPERIENCE

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PURPOSE: Intracranial non-germinomatous germ cell tumors (NGGCTs) have lower overall survival than germinoma because relatively higher recurrence usually occurs after first line therapy. METHODS: Between January 2003 and December 2018, 111 consecutive patients diagnosed with NGGCTs reviewed. Those who progressed after first line therapy were included in this study. Data of first line treatment, salvage treatment, clinicopathological features and survival were collected and analyzed. RESULTS: Totally, thirty patients (30/111, 27.0%) relapsed in our cohort, including 19 patients with accurate relapse information detail, and 11 patients who died of disease progression during follow up but without exact time and site of relapse. The median OS from diagnosis of the disease was 49.2 months (95% CI: 14.1 to 84.3 months) and 3-year OS was 54.3%. Patients who received both CSI and chemotherapy relapsed less than those who received reduced volume of radiotherapy or only CSI or only chemotherapy (22.5% vs. 45.5%, p=0.034). Of 19 patients who had detail information of recurrence time and site, the median time from diagnosis of disease to relapse was 9.5 months (2.2 to 72.1 months). Regarding to recurrence site, most patients relapsed in primary site (10/19, 52.6%) or distant intracranial (6/19, 31.6%). The recurrence site of other 3 patients were spinal (n=1), ventricular (n=1) and peritoneal (n=1). CONCLUSION: Protracted follow-up is recommended because late recurrence is not uncommon. Primary tumor site and distant intracranial are the most prevalent relapsed location. Patients who relapsed could benefited from both CSI and salvage chemotherapy.

GCT-29. DOES TUMOUR MARKER DECLINE PREDICT OUTCOME IN INTRACRANIAL NON-GERMINOMATOUS GERM CELL TUMOURS (NGGCTS)?

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INTRODUCTION: The prognostic impact of tumour marker (TM) decline rate has been demonstrated for extracranial poor prognostic non-seminomatous/germinomatous germ cell tumours (NGGCT). The current series aimed to assess if this finding can be applied to intracranial primaries. METHODS: Patients were retrieved from the SIOP-CNS-GCT-96 database. They were selected if they had i/assessable values of serum alpha-fetoprotein (AFP) and/or human chorionic gonadotropin (HCG) before and 18 to 28 days after the first course of chemotherapy and ii/ available data for outcome. Decline rate was calculated using a logarithmic transformation and expressed as time to normalization (TTN) as published by Fizazi (JCO 2004). TTN≤ 9 weeks for AFP and ≤ 6 weeks for HCG were considered as favourable decline rate. Prognostic impact of TTN on outcomes was assessed using the log-rank test. RESULTS: Out of 149 patients with NGGCT, 59 were evaluable for both HCG and AFP TTN of whom 44 (74%) had a favourable decline rate. After a median follow-up of 88 months (2–251), 20 relapses and 15 deaths occurred. The 5-year PFS rates were 72% and 60% in patients who had a favourable and an unfavourable TTN, respectively (p=0.15). The 5-year OS rates were 77 % and 69%, respectively (p=0.66). Separate analysis of TTN based only on AFP or only on HCG gave similar results. CONCLUSION: Despite the use of a methodology similar to that used in extracranial NGGCT, no significant impact of serum TM decline on prognosis was observed, but insufficient statistical power cannot be ruled out.

GCT-30. TREATMENT OF PRIMARY INTRACRANIAL GERM CELL TUMORS: SINGLE INSTITUTION EXPERIENCE OF 74 CASES WITHOUT HISTOLOGICAL CONFIRMATION

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BACKGROUND AND OBJECTIVE: Primary intracranial germ cell tumors (PIGCTs) are a group of heterogeneous tumors. It is very difficult to treat those patients without pathological diagnosis. This study retrospectively analyzed the clinical data and outcomes of patients with clinically diagnosed (without histologically confirmed) PIGCTs in SunYat-sen University Cancer Center. METHODS: Patients who were clinically diagnosed as PIGCTs without histological diagnosis through surgical resection or biopsy were included in this study. Patients were analyzed for clinical characteristics, treatment patterns, outcomes and adverse effects. RESULTS: From May 2002 to July 2014, 74 patients clinically diagnosed with PIGCTs received chemotherapy and/or radiotherapy at the Sun Yat-sen University Cancer Center. The median age was 16.5 years old (4–45 years old, majority was teenagers). The most of tumors were found in male, and located in the pineal and suprasellar regions. When the patients were grouped into diagnostic chemotherapy group (57 cases), diagnostic radiotherapy group (5 cases) and gamma knife radiosurgery group (12 cases) based on their initial anti-tumor therapy. The 5-year survival rates were 84.3%, 75.0% and 75.0%, respectively. There was a trend that the chemotherapy group got a better survival. Patients were allocated to secretory tumor group (49 cases) and non-secretory tumor group (25 cases) based on their levels of tumor makers (α-FP and β-hCG). The 5- year survival rates were 80% and 77.8% (P value = 0.966), respectively. CONCLUSION: Clinical diagnosed PIGCT (without histological confirmation) patients may obtain good responses when receiving comprehensive treatments of chemotherapy combined with radiotherapy.

GCT-31. DIAGNOSTIC CAPABILITY OF CSF-PLAP ON INTRACRANIAL GERM CELL TUMOR

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BACKGROUND: Since the majority of intracranial germ cell tumor(GCT) is sensitive for chemoradiation, biopsy specimens are usually tiny and not enough for accurate pathological diagnosis. To supply complementary diagnostic information, a-fetoprotein or human chorionic gonadotropin-b are important biomarkers. Recently CSF-placental alkaline-phosphatase(PLAP) is also reported as an additional biomarker in intracranial GCT. This study's purpose is to evaluate the significance of CSF-PLAP. METHODS: CSF-PLAP was obtained from the patients with the intraventricular and periventricular tumor before any adjuvant therapy. Definitive diagnoses were made by histopathological information and/or their clinical courses; GCT(germinoma or non-germinomatous GCT(NGGCT)) or other tumors. In GCT, the relationship between CSF-PLAP and tumor reduction volume was evaluated. Tumor volumes were calculated on gadolinium-enhanced T1-weighted magnetic resonance imaging before and after initial chemoradiotherapy. RESULTS: Between 2005 and 2019, 42 patients were studied: 24 with GCT and 18 with others. CSF-PLAP value in patients with GCT was significantly higher than those with others: the Specificity was 88% and the sensitivity was 95% at the cutoff value of 8.0 pg/ml. For GCT patients, CSF-PLAP value tended to be higher in germinoma(n=12, mean 4756 pg/ml), compared to the value in NGGCT(n=7, mean 332 pg/ml), although there was no statistical difference. There was a significant positive correlation between initial CSF-PLAP value and tumor reduction volume. CONCLUSION: CSF-PLAP is a useful tumor marker for GCT differentiating from the other tumors located in intraventricular and periventricular region and CSF-PLAP value might correlate with the volume of germinomatous component of the tumor.

GCT-33. A PHASE 2 TRIAL OF RESPONSE-BASED RADIATION THERAPY FOR PATIENTS WITH LOCALIZED CENTRAL NERVOUS SYSTEM GERM CELL TUMORS: A CHILDREN'S ONCOLOGY GROUP (COG) STUDY. IMPACT OF RAPID CENTRAL RADIOTHERAPY REVIEW ON RADIOTHERAPY QUALITY AND PATTERN OF FAILURE FOR NON-GERMINOMATOUS GERM CELL TUMORS

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BACKGROUND: COG ACNS 1123 tested reduced radiotherapy (RT) for non-metastatic, non-germinomatous germ cell tumor (NGGCT) patients. The impact of central review on quality of RT and pattern of failure for NGGCT patients is evaluated. METHODS: Patients who achieved a complete response (CR) or partial response (PR) to induction chemotherapy were eligible for reduced dose and field RT of 30.6 Gy whole ventricular field (WVI) and 54 Gy tumor-bed total dose. An online contouring atlas was available. Within three days of RT start, WVI plans were submitted for rapid central review. Within one week of RT completion, the complete RT record was submitted. Brain and spine MRIs of relapsed patients were centrally reviewed. RESULTS: Between 5/2012–9/2016, 107 eligible patients were accrued and 70 met reduced RT criteria. Rapid RT review was performed for 49 (70%) of 70 patients. Forty-four (89.8%) required no modification. All modifications were completed and plans became compliant. Final central review was performed for 66 evaluable patients: 62 (94%) were per protocol; there were 2 major (1 dose and 1 target) and 2 minor deviations. Eight patients progressed; none had deviations. Median time to progression was 3.54 months (range: 1.7–19.1) from RT start. All failures had a spine component; two also had cranial component: one local progression (within the RT boost volume) and one leptomeningeal disease. CONCLUSION: Providing an online contouring atlas and performing a rapid central review lead to high quality radiotherapy on this prospective trial. The deviations did not contribute to the pattern of failure.

GCT-34. ELUCIDATION OF THE MECHANISMS OF TUMORIGENESIS IN INTRACRANIAL GERM CELL TUMOR BY WHOLE GENOME SEQUENCE

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Intracranial germ cell tumors (iGCT) are heterogenous group of primary brain tumors that consist of various subtype, and driver genetic alterations in iGCTs remain largely unknown. We have previously reported in a study

of whole exome sequence that iGCTs frequently harbored mutations in the KIT gene and its downstream MAPK/PI3K pathway, regardless of tumor subtype. However, no mutations were detected in about one-quarter of germinomas and half of non-germinomatous germ cell tumors. A genome-wide methylation profiling revealed that only germinomas exhibited extreme DNA hypomethylation among iGCTs. Moreover, in mixed iGCT tumors which contained more than one tumor subtypes, each component exhibited distinct methylation status depending on the subtype, while they shared the same mutations. These data suggested that not only mutations in the coding region as previously reported, but also genetic alterations in regulatory regions including promoters and enhancers as well as non-coding RNA genes may be involved in the tumorigenesis of iGCTs. In order to comprehensively search for driver gene alterations, we performed whole genome sequence in 18 paired tumor blood samples from iGCT tumors (16germinomas and two yolk sac tumors (YST)) registered in the Intracranial Germ Cell Tumor Genome Analysis Consortium. In a preliminary analysis of four cases, YSTs harbored a significantly higher number of structural abnormalities, compared with germinomas. Of note, 62 structural abnormalities were clustered within the small genomic region of 95Mb at 1q21-44 in one YST case, suggesting a possibility of chromothripsis. A full analysis of somatic alterations is underway and will be reported.

GCT-35. SALVAGE CRANIOSPINAL IRRADIATION FOR RECURRENT GERMINOMAS

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BACKGROUND: The treatment strategies for recurrence has not been established. PURPOSE: To clarify the tumor control and complications of salvage craniospinal irradiation (CSI) for recurrent germinoma. METHODS: We retrospectively reviewed the medical record. Among 153 germinomas treated in Tohoku University Hospital since 1983, 22 had recurrence of germinoma. At first recurrence, 7 cases received CSI, whereas 15 cases did chemotherapy and/or radiation therapy other than craniospinal field (non- CSI). CSI was performed at 24 Gy/ 12 fractions or 30 Gy/ 25 fractions. RESULTS: CSI had statistically significant better recurrence-free survival rate after recurrence than non-CSI (100% vs 33%, $p<0.001$: log-rank test). In addition, tumor control was obtained in all of four cases with the failure after non- CSI treatments for recurrence. The late complications of these 11 cases were examined. The local dose before CSI was 24- 50 Gy, and the median interval from last irradiation to CSI was 33 months. Median follow- up period after CSI was 126 months. Three patients developed newly developed visual or cognitive deficits. These patients received high-dose irradiation at initial treatment or multiple treatment before CSI. There were no late complications in the cases which had prior chemotherapy and 24 Gy of irradiation to whole ventricle only before CSI. CONCLUSION: Low dose CSI for the first recurrence of germinoma is effective and safe in the cases treated by chemotherapy and low dose irradiation to whole ventricle only.

GCT-36. TREATMENT RESULTS AND RADIATION-INDUCED TUMORS IN CASES OF CENTRAL NERVOUS SYSTEM GERM CELL TUMOR: A LONG-TERM FOLLOW-UP STUDY IN KUMAMOTO PREFECTURE

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INTRODUCTION: Central nervous system germ cell tumor (GCT) is one of the pediatric brain tumors. Although there have been epidemiological studies in the past, long-term prognosis and the late effects remained unclear. In this study, we examined GCT over the past 41 years in Kumamoto prefecture. METHODS: Epidemiological features and complications with radiation-induced tumors were searched in patients diagnosed with GCT in the 41-year period from 1977 to 2018. RESULTS: There were 93 patients diagnosed with GCT. These cases were divided into 14-year periods before and after incorporation of chemotherapy into the treatment, and the results for germinomas were compared. An improvement in the 10-year survival rate from 12 of 23 cases (52.2%) between 1977 and 1991 to 19 of 28 cases (67.9%) between 1992 and 2006 was observed. The 10-year survival rate for germinoma cases that received medical treatment during a more recent 5-year period between 2004 and 2009 increased to over 90%. However, 10.3% of all long-term survivors of GCT developed radiation-induced glioblastoma. The examination results showed that regardless of the tumor type, patients who received a high dose of radiation during their initial treatment developed the complication of radiation-induced glioblastoma within 10 to 25 years after their initial treatment. CONCLUSION: This study suggests that the long-term survival rates for GCT are improving but the rate of radiation-induced glioblastoma in these cases are too high to be ignored. Long-term follow-up of at least 10 years is essential to effectively evaluate the details of treatment for pediatric brain tumors.

GCT-37. PREVALENCE OF AUTISM SPECTRUM DISORDER AND OTHER NEURODEVELOPMENTAL DISORDERS IN PEDIATRIC PATIENTS WITH INTRACRANIAL GERM CELL TUMORS

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PURPOSE/OBJECTIVE(s): Intracranial germ cell tumors (IGCTs) are rare tumors of the central nervous system with peak incidence around puberty. Due to the developmental origins of IGCTs, we investigated the prevalence of neurodevelopmental disorders (NDDs), including autism spectrum disorder (ASD), in our retrospective institutional cohort of patients diagnosed with IGCTs. MATERIALS/METHODS: A retrospective review of medical records was conducted for 105 patients who were diagnosed with IGCTs and treated at Massachusetts General Hospital between 1998 and 2016. All patients with ASD had thorough neuropsychological assessment at the time of radiotherapy that confirmed their diagnoses. RESULTS: Median age at diagnosis was 12.8 years (range: 4.3–21.6) and median follow-up time was 4.7 years (range: 0.4–15.8). Seventeen patients with IGCTs were diagnosed with NDDs prior to cancer diagnoses, including five patients with ASD, and three patients with chromosomal abnormalities, including one patient with Down syndrome. Interestingly, four of five patients with ASD developed pure germinomas, giving an ASD prevalence rate of 6.5% and 2.3% in the pure germinoma and NGGCT cohorts, respectively. All other patients had no known diagnoses of NDDs. CONCLUSIONS: Our study found 17 patients with IGCTs were diagnosed with NDDs prior to their cancer diagnoses. An ASD prevalence of 6.5% in the pure germinoma cohort is more than three-fold greater than the national prevalence, suggesting there may be an association between ASD and pure germinomas. Future prospective studies with larger cohorts are still needed to examine associations between NDDs and ASD and IGCTs.

GCT-38. RELAPSE PATTERNS OF INTRACRANIAL GERMINOMAS BEFORE AND AFTER ENDOSCOPIC ERA

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PURPOSE: We evaluated the relapse patterns of CNS germinomas before and after introducing neuroendoscopic biopsy in 2000. METHODS: We retrospectively assessed the relapse patterns of 57 patients treated as pure germinoma or germinoma with STGC between 1980 and 2019 at University of Tsukuba, partially containing the patients of the previous report (Takano S et al., World Neurosurg, 2015). Median age was 15 y.o.(7y.o.~38y.o.), and men was 80.7%. Tumor locations were pineal 35, sellar 19, basal ganglia 3, others 11. Group A;1980~1999 was 20, and group B;2000~2019 was 37. From 1980 to 1994, whole brain irradiation(WB) 30.6 Gy plus whole ventricle irradiation(WV) 19.8 Gy. From 1995 to 1999, WV 26~30.6 Gy with Chemotherapy(Chem) or Chem alone. Since 2000, Chem for 3 kurr with WV 24~30.6 Gy, and 6–19.8 Gy as local boost to residual lesion. RESULTS: Follow up periods were median 121 M(4.5M~386M; group A), and median 89 M(4 M~231 M; group B). Six patients(30%) recurred in the group A, as ex field 4(1;brain and extramedullary, 1;brain and paranasal sinus, 1;LV & third ventricle, 1;extramedullary), in field 1(LV). Chem only 1(LV & third ventricle). Two patients(5.4%) recurred in the group B, as ex field 2(1;intramedullary, 1;extramedullary). The group A showed CR;18, PR;1, Dead;1(Dissemination), and the group B showed CR;35, PR;1 Dead;1(Encephalopathy). CONCLUSION: WV and Chem prevented extrafield recurrence keeping good quality of life. Neuroendscopy biopsy with ETV did not increase CSF seeding.

GCT-40. PROGNOSTIC FACTORS FOR PATIENTS WITH RELAPSED CENTRAL NERVOUS SYSTEM (CNS) NON-GERMINOMATOUS GERM CELL TUMORS (NGGCTS)

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BACKGROUND: Patients with relapsed CNS NGGCTs experience poor outcomes. Our aim to explore prognostic factors that may guide future clinical trials. METHODS: A review of clinical trials that included patients with relapsed CNS NGGCTs was performed. RESULTS: Seventy-four patients were identified; only 14 patients (19%) were long-term survivors. Patients who relapsed >24 months after initial diagnosis had a survival rate of 47% compared with 15% of patients who relapsed in <24 months after initial diagnosis (p= 0.015). Patient with serum/cerebrospinal fluid (CSF) alpha-fetoprotein (AFP) level <25 ng/ml at relapse had a survival rate of 40% compared with 0% among patients with serum/CSF AFP level >25 ng/ml at relapse (p= 0.0015). Patients who achieved complete response/continued complete response (CR/CCR) by the end of therapy had a survival rate of 59% compared with 3% among patients who had less than CR/CCR by the end of therapy (p= 0.0001). Patients who received marrow-ablative chemotherapy followed by autologous hematopoietic cell rescue (HDCx/AuHCR) at relapse had a survival rate of 33% compared with 9% of patients who did not receive HDCx/AuHCR at relapse (p=0.056). The extent of surgical resection, receiving radiotherapy, and beta-human chorionic gonadotropin levels at relapse were not statistically associated with improved outcomes. CONCLUSION: Timing of relapse (>24 months after initial diagnosis), serum/CSF AFP <25 ng/ml at relapse, achieving CR/CCR after treatment were associated with a positive impact on survival. Receiving HDCx/AuHCR at relapse was associated with an improved outcome trend among the patients.

GCT-41. RESPONSE-BASED RADIATION THERAPY IN PATIENTS WITH NEWLY DIAGNOSED CENTRAL NERVOUS SYSTEM LOCALIZED GERMINOMA: A CHILDREN'S ONCOLOGY GROUP (COG) PROSPECTIVE PHASE 2 CLINICAL TRIAL

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BACKGROUND: The objective of stratum 2 of COG ACNS1123 was to evaluate children and young adults (3–21 years) with localized central nervous system (CNS) germinoma and investigate whether simplified pre-irradiation chemotherapy followed by response based dose-reduced whole ventricular irradiation (WVI) would maintain a high progression-free survival (PFS) while reducing long term treatment burden. METHODS: Pre-irradiation chemotherapy consisted of 4 cycles of carboplatin and etoposide every 21 days followed by response-based irradiation (XRT). Patients with a complete response (CR) to pre-XRT chemotherapy received 18Gy WVI + 12Gy boost to the tumor bed. Patients with partial response (PR) but less than 1.5 cm residual proceeded to 24Gy WVI + 12Gy boost. All patients were also enrolled on COG ALTE07C1 to prospectively evaluate and longitudinally model the cognitive, social and behavioral functioning. RESULTS: During a total accrual time of 45.5 months from 05/2012 to 06/2018, 137 eligible patients were enrolled. Median age was 14.09 years (4.95–21.46), 73% were male, and 45.26% had elevated βhCG in serum and/or cerebrospinal fluid. Twenty-nine patients (21.17%) did not have tissue biopsy. Eleven patients underwent second-look surgery; 7 had mature teratoma and 4 had non-viable tumor. Eighty-one patients (59.13%) had a CR. There were 4 relapses in patients receiving 18Gy WVI + boost, but no deaths. No unexpected treatment-related events were observed. The estimated 3-year PFS was 94.4 ±2.7% among 74 evaluable subjects. CONCLUSION: This study shows promise in XRT reduction for patients with localized CNS germinoma and CR. Long-term survival outcomes and ALTE07C1 data are being evaluated.

GCT-42. CLINICAL CHARACTERISTICS OF LOCALIZED CENTRAL NERVOUS SYSTEM NON-GERMINOMATOUS GERM CELL TUMORS (NGGCT) PATIENTS ENROLLED ON ACNS1123 WITH RELAPSE: A CHILDREN'S ONCOLOGY GROUP (COG) STUDY

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ACNS1123 was a Children's Oncology Group Phase 2 study that was undertaken to determine whether irradiation could be safely reduced without impacting survival in a subgroup of NGGCT patients. Between May 2012-Jan 2017, 107 eligible patients were accrued to Stratum 1 (NGGCT stratum). Sixty-six (61.7%) patients achieved a complete/partial response (CR/PR) to induction chemotherapy and received 30.6Gy whole ventricular field irradiation followed by 54Gy tumor-bed boost achieving a 2-year progression-free survival rate of 89% (95% CI:81%-97%) and overall survival rate of 92% (95% CI:86%- 99%). Eight patients progressed; 6 had a spinal relapse and 2 patients had a local plus spinal relapse. Seven of eight patients had marker elevation at relapse and data was not available in one patient. At diagnosis, location was pineal in six cases, suprasellar in one, and bifocal in one case. Four patients had beta HCGβ and AFP elevation and two each had HCGβ and AFP elevation alone at diagnosis. Only two patients had HCGβ or AFP >1000 (HCGβ 3550 in one patient and AFP of 1340 in another). All eight patients were CR by markers; four had radiographic CR and four had a PR. Five patients had surgery at diagnosis: two had embryonal carcinoma, one germinoma, and two mixed germ cell tumor with malignant elements on histology. A consistent significant risk factor could not be identified to explain excess of spinal failures seen in our cohort.

GCT-43. GAIN OF SHORT ARM OF CHROMOSOME 12 IS A MOLECULAR MARKER TO PREDICT PROGNOSIS AND REPRESENTS AN EARLY EVENT IN TUMORIGENESIS IN INTRACRANIAL GERM CELL TUMORS

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Gain of short arm of chromosome 12 (12p) is commonly observed in testicular germ cell tumors (tGCTs) and also seen in intracranial GCTs (iGCTs). However, little is known about the clinical significance of 12p gain in iGCTs. We have collected over 200 fresh frozen tissue samples of iGCTs through the Intracranial Germ Cell Tumor Genome Analysis Consortium in Japan. Firstly, we analyzed DNA methylation profile in 83 iGCTs, 3 tGCTs (seminomas) and 6 normal control samples using Infinium Human Methylation 450K BeadChip array (Illumina, CA, USA) in order to determine 12p gain status. Then, fluorescence in situ hybridization (FISH) study was carried out on 3 mixed iGCT cases using 12p/CEP12 probe (Abbott Molecular, Abbott park, IL, USA). Lastly, 58 iGCTs with clinicopathological information were analyzed for progression-free survival (PFS) and overall survival (OS). Gain of 12p was observed in 100% (3/3) of seminoma, 14% (3/22) of germinoma, 17% (1/6) of mature teratoma, 25% (1/4) of immature teratoma, 55% (11/20) of mixed germ cell tumor, 100% (4/4) of yolk sac tumor, 100% (1/1) of embryonal carcinoma, and 100% (1/1) of choriocarcinoma. In total, 45% (37/83) of iGCT showed 12p gain. Different histological components in each mixed GCT shared the same 12p copy number status within each mixed GCT case. Both PFS and OS were significantly worse in iGCTs with 12p gain (PFS: P=0.027, OS: P=0.0012). Gain of 12p can be a molecular marker to predict prognosis and represents an early event in tumorigenesis prior to histological differentiation in iGCTs.

GCT-44. A CASE OF INTRACRANIAL GERMINOMA WHICH RECURRED IN THE SPINAL CORD 13 YEARS AFTER THE INITIAL TREATMENT

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BACKGROUND: Central nervous system germinoma occurs most often in early teens, accounting for 15% of childhood brain tumors. Here, we report a case of germinoma which recurred in the spinal cord 13 years after complete remission. CASE DESCRIPTION: A 15-year-old boy presented with diabetes insipidus (DI). MRI showed a pineal gland tumor and ventriculomegaly. Biopsy was performed and the histological examinations revealed PLAP and c-kit positive pure germinoma. Ki67 LI was 64.4%. Gamma knife radiosurgery and 3 courses of ICE chemotherapy brought disappearance of the tumor. However, it recurred in lateral ventricles. Forty-Gray whole brain radiation resulted in complete remission of the tumor. For the sake of DI treatment and MRI examinations, he kept periodical visit to our hospital. Thirteen years later, when he was 28y/o, he complained paresthesia in the right upper extremity. MRI demonstrated gadolinium-enhance mass lesion in the cervical spinal cord. Recurrence of the tumor and multiple sclerosis were the principal differential diagnosis. Pulse steroid therapy did not make any change, and radiation therapy to the cervical spinal cord led to tumor disappearance. Nevertheless, the tumor recurred on the dorsal medulla oblongata one and a half years later. Biopsy of the tumor clarified that the tumor was germinoma. ICE chemotherapy which was limited to three courses due to severe bone marrow suppression was carried out. MRI proved no enhanced mass lesion in the central nervous system. DISCUSSION: Germinoma may recur even after long period of remission, demonstrating that long-term follow-up is indispensable.

GCT-45. YOLK SAC TUMOR IN THE CEREBELLAR VERMIS - A CASE REPORT

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Yolk sac tumor (YST) is a non-germinomatous malignant germ cell tumor in a young child. It usually arises along a midline axis, mostly pineal region or suprasellar compartment, and it is exceedingly rare to locate in a cerebellar vermis. In the present report, we describe a case of a pure YST located in the cerebellar vermis and review the previous literature. A three-year-old boy visited a local clinic for gait disturbance and frequent vomiting. Gadolinium-enhanced magnetic resonance imaging (MRI) showed a homogeneously-enhanced mass with a cystic component in his cerebellar vermis, and it resulted in hydrocephalus. By its location and his age, our preoperative diagnosis was a medulloblastoma, and we performed a total resection of the tumor with ventricular drainage. Unexpectedly, the histological investigation revealed it to be a YST. We confirmed that the serum levels of α-fetoprotein (AFP) had elevated at 3176.4 ng/ml in his preserved sample, obtained before the surgery, and it was consistent with the pathological diagnosis. He is receiving chemotherapy consisting of ifosfamide, cisplatin, and etoposide, followed by radiation therapy. In this case, pre-operative MRI revealed that the tumor did not grow into the IVth ventricle in spite of midline location, which was not typical for medulloblastoma. Of note, serum AFP levels had increased, and they might contribute to a precise pre-operative diagnosis and be able to propose an alternative treatment plan, such as neoadjuvant chemotherapy to reduce surgical risk. As a conclusion, a YST should be considered even if it locates in a cerebellar vermis.

GCT-46. MULTI-KINASE INHIBITORS AS NOVEL THERAPEUTIC AGENTS AGAINST INTRACRANIAL NON-GERMINOMATOUS GERM CELL TUMORS

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Central nervous system germ cell tumors (CNS GCTs) are rare intracranial malignancies developing in adolescents and young adults which relatively frequently occur in East Asia region of the world including Japan. However, among CNS GCTs, non-germinomatous germ cell tumors (NGGCTs) are highly resistant to the current chemoradiotherapies, and the prognosis of CNS NGGCTs is still extremely poor. Therefore, development of novel therapeutic strategy against CNS NGGCTs is urgently needed. In this study, we screened small molecule inhibitors of kinases specifically targeting cell membrane receptors, such as receptor tyrosine kinases, and their related molecular signaling, which could effectively exert antitumor effects against NGGCT cells. As the NGGCT model cells, the Tcam2 cell, a mixed germ cell tumor cell line composed of germinoma and embryonal carcinoma components, and the YST1 cell, a novel yolk sac tumor cell line established in our institute, were used. As a result, effective induction of cell death in both cell lines was confirmed only by treatment with two multi-kinase inhibitors. Immunoblotting revealed these multi-kinase inhibitors suppressed activation of various kinases concurrently. Furthermore, these multi-kinase inhibitors also triggered cell death in the Tcam2 cell stably expressing mutant KIT, the most common oncogenic driver genes of CNS GCTs, suggesting that these inhibitors would be also effective against CNS GCTs harboring activated KIT mutants. In vivo studies of these multi-kinase inhibitors using CNS GCT xenografts are currently on going.

GCT-47. TREATMENT STRATEGIES FOR GIANT IMMATURE TERATOMAS IN INFANTS

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INTRODUCTION: Immature teratomas are the most frequent fetal brain tumors and show a poor prognosis. At onset, the tumor is often already giant with deep origins such as suprasellar or pineal region, and easy bleeding is also considered to be a cause of poor prognosis. On the other hand, it is also known that the prognosis is improved in total removal cases. METHODS: We investigated the best treatment strategy based on two cases of total removal of giant immature teratomas in infants. RESULTS: 1.5 month after birth at onset (median), maximum diameter of 75 mm (median). A giant tumor centered around the third ventricle with hydrocephalus. First, biopsy (+septostomy) was performed using an endoscope. The tumor showed easily bleeding. In addition, external ventricular drainage was taken out of the lower abdomen subcutaneously by long tract. After chemotherapy (carboplatin and etoposide), tumor removal was performed by using drainage tract. Both cases showed not easily bleeding at that time and the tumor was safely removed. Regarding the deep blind spot, using a flexible endoscope was effective. They showed no recurrence after total removal (median 50 months). DISCUSSION: There have been reports of cases in which chemotherapy for immature teratomas suppressed tumor growth and reduced bleeding and safely removed totally. In infants giant immature teratomas, chemotherapy before tumor removal can be expected to reduce bleeding, and further increase body weight during that period. In addition, long-term placement of ventricular drainage by long tract during the chemotherapy can prevent brain development delay due to hydrocephalus.

GCT-48. OUTCOME OF CNS MALIGNANT NON-GERMINOMATOUS GERM CELL TUMORS (GCT) WITH AFP > 1000 NG/ML AT DIAGNOSIS TREATED ACCORDING TO SIOP CNS GCT 96

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Analysis of CNS MMGCT with AFP >1000 ng/ml (serum and/or CSF) at diagnosis, treated on trial in SIOP-CNS-GCT-96, revealed an inferior prognosis (32% 5-year progression-free survival) compared with AFP <1000 ng/ml (76%). As this patient group is small, to evaluate a bigger cohort, we revisited all patients treated according to SIOP-CNS-GCT-96, who were registered in the database until July 2015. Between October 1996 and July 2015, 373 patients with CNS MMGCT were registered. 48 patients (13%)

presented with an AFP >1000 ng/ml at diagnosis. 41 patients were evaluable with a median observation time of 2.4 years; 6/41 received chemotherapy alone. Primary site, histological components (if available), metastatic status and outcome were evaluated. Primary site was pineal in 29/41, suprasellar in 6/41, bifocal 1/41 and other in 5/41 patients. 10/41 patients were metastatic at diagnosis. Four to five courses of standard PEI and radiotherapy (RT) or 2 standard and two intensified PEI (as for SIOP CNS GCT II) were administered in 32 patients. Two received less then 4x PEI and RT, 6 patients <6 years were treated with PEI (either standard or intensified) alone. 16/34 patients with PEI and RT are alive in CR; 2/6 patients without RT survived. Overall, 18/40 (45%) survived. 10–15% of CNS MGGCT are high-risk patients by diagnostic AFP, with the pineal as the main tumour site. Outcome of <50% survival is unsatisfactory. Further research, international cooperation and common data analysis is needed to identify additional risk factors and develop alternative treatment strategies.

GCT-49. EVALUATION OF THE PERIOPERATIVE AND POSTOPERATIVE COURSE OF SURGERY OF PINEAL GERMINOMA ACCORDING TO THE SIOP CNS GCT 96 TRIAL

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INTRODUCTION: CNS germinoma, being marker-negative, are diagnosed by surgical biopsy. Here we evaluate the perioperative status and postoperative complications of patients with pineal germinoma who underwent a primary biopsy or resection, treated according to SIOP CNS GCT 96. METHODS: 235 patients with histologically confirmed germinoma were registered, of which 113 were pineal: 55 were biopsied and 58 underwent primary resection. Initial symptoms, tumour size, complications and neurological status were assessed. 111 patients were evaluable. RESULTS: Pure germinoma was present in 101 patients; 10 had additional teratoma components. The main clinical symptoms at diagnosis were headache (n=98), hydrocephalus (n=93), double vision (n=62), Parinaud syndrome (n=57) and papilloedema (n=44). Tumour size was documented in 81 patients (<2cm, n=14; 2-3cm, n=35; ≥3cm, n=32). 17 patients underwent primary total resection, 14 subtotal resection >50%, 26 subtotal resection <50%, 39 stereotactic biopsy, 11 endoscopic biopsy, 2 open biopsy and 2 not documented. The postoperative neurological status after resection was improved in 23 patients, unchanged in 27, deteriorated in 6 and not documented in one. Clinical status after biopsy improved in 26 patients, was unchanged in 15, deteriorated in 2 and not documented in 11. Postoperatively, 16/57 patients after resection and 5/54 after biopsy developed complications (Parinaud syndrome, double vision and hydrocephalus). CONCLUSION: Although surgical techniques have improved within recent decades, these results support the practice of biopsy over resection for histological confirmation of germinoma arising at the pineal site. Supported in part by German Cancer Aid.

GCT-50. LONG-TERM OUTCOMES OF INTRACRANIAL GERMINOMA IN A SINGLE INSTITUTION

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The treatment for intracranial germinoma has been well-established. Complete removal is not necessary, but radiation therapy is important. As the prognosis of patients with germinoma has become better, side effect of radiotherapy and chemotherapy must be well considered. The aim of this study was to evaluate the outcome of intracranial germinomas at Kyoto University Hospital from 1979 to 2019. 64 patients were diagnosed as intracranial germinoma. Patients with hCG > 100 IU/l and/or AFP > 10 ng/ml were excluded. Patients, who were histologically diagnosed as germinoma without information of hCG and AFP, were included. Follow-up time was from 2 to 486 months (median 136 months). Recently, germinoma patients were diagnosed with biopsy and received low dose whole-ventricle irradiation with intensity modulated radiation therapy (IMRT) (total 24-30Gy) and chemotherapy dominated by platinating agent. 10-year PFS was 80.21% (high dose radiation alone), 86.36% (high dose radiation with chemotherapy) and 100% (low dose radiation with chemotherapy). Many recurrent sites were out of irradiation areas. Late cognitive dysfunction was identified in 6 patients, and 5 of them were treated with high dose radiation. Patients with intracranial germinoma can obtain long-term survival. It is important to prevent recurrence without increasing late iatrogenic complications. Low dose radiotherapy and chemotherapy is highly effective, and it potentially reduces late adverse effects.

GCT-51. IMMUNE CHECKPOINT MOLECULES AND TUMOR INFILTRATING LEUKOCYTES IN THE TUMOR MICROENVIRONMENT ARE ASSOCIATED WITH THE GROWTH OF INTRACRANIAL GERMINOMAS

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The role of immune checkpoint molecules and the tumor immune microenvironment in the development of intracranial germ cell tumors remains unclear. In the present study, we investigated the expression of immune checkpoint molecules, as well as the number of tumor-infiltrating lymphocytes (TILs), in intracranial germinomas to determine whether there were any correlations between the statuses of these immune-related molecules/cells and clinical manifestations in patients with germinoma. The 8 patients were categorized based on the duration between symptom onset and pathological diagnosis into the long-term onset (LTO) group (> 1 year of symptoms, 3 patients) and the short-term onset (STO) group (< 1 year of symptoms, 5 patients). Compared with STO tumors, LTO tumors were significantly associated with a lower ratio of programed cell death ligand-1 (PD-L1)–positive tumor cells ($p = 0.012$), higher number of infiltrating CD3- and CD8-positive lymphocytes ($p = 0.016$, 0.003, respectively), and lower ratio of programed cell death-1 (PD-1)–positive cells per CD8–positive lymphocytes ($p = 0.047$). LTO germinomas were significantly smaller in size than STO tumors and tended to be present in patients with atypical tumor location. Our data suggest that the tumor immune microenvironment, including PD-1/PD-L1 signaling, is associated with the growth of intracranial germinomas. Immune checkpoint inhibitors might be a reasonable treatment option for recurrent germinomas or as replacement for radiotherapy in patients with intracranial germinomas.

GCT-52. TRANSCRIPTOME OF CENTRAL NERVOUS SYSTEM GERM CELL TUMOR REVEALS ITS PATHOGENESIS AND CONTRASTS WITH TESTICULAR COUNTERPARTS IN INTEGRATED OMICS ANALYSIS

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Germ cell tumors (GCTs) are unique neoplasms in that they arise from the migrated cells which were supposed to be directed to gonads. They occur in the central nervous system (CNS), as well as gonadal organs such as testis and ovary. Our genomic analysis revealed that they are characterized by mutations in MAPK and PI3K pathways, chromosomal instability and global

hypomethylation in germinoma. However, there were plenty of cases which lacked driver alterations and their pathogenesis is yet to be fully unraveled. Here we aimed to uncover CNSGCT's pathogenesis from a transcriptomic perspective. Genome-wide transcriptional analysis was performed for 58 CNS and 3 testicular GCTs. This demonstrated that germinoma had a transcriptional profile characteristic to primordial germ cells (PGCs) at early embryogenesis, whereas non-germinomatous germ cell tumors (NGGCTs) showed that with differentiation into various tissues. Integration of transcriptome and methylome corroborated the above finding that pluripotency/meiosis-genes were unmethylated and highly expressed in germinoma compared with NGGCT. Co-analysis with transcriptome of various developmental stages of embryonic cells revealed germinoma and NGGCT had similarities in expression to PGC and embryonic stem cells, respectively. Multi-omics analysis with testicular GCTs (n=134) from TCGA showed shared genomic backgrounds between germinoma-seminoma and NGGCT-nonseminomatous GCT (NSGCT) in mutation and methylation profiles, and contrast in the chromosomal instability, which was more highlighted in testicular GCTs. These new insights into molecular profiles of GCTs lead to a better understanding of the complex pathogenesis of GCTs, and will hopefully provide a clue to future development of new treatments.

GCT-53. CASE OF INTRACRANIAL GROWING TERATOMA SYNDROME WITH DIFFICULTY IN TIMING OF RESECTION

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BACKGROUND: Intracranial Growing teratoma syndrome(iGTS) is a phenomenon in which a tumor with a teratoma component grows during treatment, and its pathological tissue is often a mature teratoma. Here we report a case of iGTS in which the timing of surgery was determined by tumor markers and changes in tumor size on MRI images. CASE-REPORT: 11-year-old boy with a short stature. He developed a headache and we found a pineal gland tumor on MRI. Due to obstructive hydrocephalus, an endoscopic third ventriculostomy and biopsy were performed. The pathological diagnosis was mature teratoma, but AFP was elevated at 104.2 ng/mL. Considering NGGCT, we started chemoradiation immediately. Despite the declining AFP, it gradually increased, at which point we suspected iGTS. Resection was considered, but at some point tumor growth had stopped, so radiation therapy and a second course of ICE therapy preceded the resection. Thereafter, the tumor was completely removed, and a third course of ICE therapy was performed. DISCUSSION: The onset mechanism of iGTS has not been elucidated, and its prediction is difficult. Early resection of the tumor is required, but discontinuation of radiation therapy and side effects of chemotherapy also need to be considered. In our case, resection was performed after normalization of AFP and recovery of myelosuppression. The patient followed an uneventful course, but the timing of resection was controversial. CONCLUSION: We experienced a case of iGTS in NGGCT, a mixed tumor with mature teratoma. The optimal timing of the resection was discussed and literature was reviewed.

GCT-55. INTRACRANIAL GERMINOMA ORIGINATING FROM ATYPICAL LOCATION WITH SUBCLINICAL ADH INSUFFICIENCY

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INTRODUCTION: Intracranial germinomas are rare tumors which usually develop in the midline structures and affect in 90% of cases the pineal gland and suprasellar regions. Sometimes they involve basal ganglia, septum pellucidum, and other regions. We report a very unusual presentation of an intracranial germinoma originating from the lateral ventricle. METHODS: A 10-year-old boy presented with a 1-year history of polydipsia and polyuria. During the hypertonic saline test, a low ADH was detected and established the diagnosis of subclinical ADH insufficiency. MRI showed a heterogeneously enhancing periventricular lesion in the lateral ventricle, but no other abnormal findings, including hypophyseal stalk. Initially, the correlation of imaging findings and clinical symptoms were not clear. With suspected subependymoma, tumor removal was performed by small craniotomy. Since the intra-operative pathological diagnosis was germinoma, we performed only partial removal of the tumor. After establishing the histological diagnosis of germinoma, the patient received chemotherapy using carboplatin and etoposide, followed by radiation therapy. MRI showed no recurrence for five years after treatment. RESULTS/CONCLUSION: Our case presents two atypical features. First, intracranial germinoma originating from the lateral ventricle is quite rare. Though the cases with intracranial germinoma originating from septum pellucidum and corpus callosum have been reported, this case is even different. Second, imaging findings did not match clinical symptoms. The cause of subclinical ADH deficiency may be the occult hypophyseal germinoma. In conclusion, we report a 10-year-old case with a very unusual presentation of an intracranial germinoma originating from the lateral ventricle.

GCT-56. ACUTE MYELOID LEUKEMIA FOLLOWING CHEMORADIOTHERAPY FOR INTRACRANIAL GERMINOMA: A CASE REPORT

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INTRODUCTION: Therapy-related acute myeloid leukemia (t-AML) is known as possible complication of chemotherapy, especially topoisomerase II inhibitor, alkylating agents, and platinum agents. Although there are many reports of therapy-related leukemia associated with gonadal germ cell tumor, few cases have been reported on central nervous system (CNS) germ cell tumor. CASE REPORT: A 35-year old gentleman presented with diplopia. CT and MR imaging showed enhancing nodules on his right hypothalamus and around fourth ventricle, and differential diagnoses included sarcoidosis and germinoma. Biopsy for fourth ventricle lesion was performed via transvermian approach, and histopathological diagnosis was germinoma. He was treated by 3 cycles of CARE chemotherapy (carboplatin and etoposide) followed by craniospinal irradiation (CSI, 24Gy). After completion of chemoradiotherapy, he was followed up every half year by MRI, and there had been no evidence of tumor recurrence. Two years after chemoradiotherapy, however, the patient presented with bleeding tendency, which led to the diagnosis of AML. Based on the history of chemoradiotherapy and the presence of t(16;21)(q24; q22), t-AML was diagnosed. Complete remission was successfully achieved by chemotherapy consisting of idarubicin and cytarabine. DISCUSSION: t-AML was diagnosed after chemoradiotherapy in a patient with CNS germinoma probably due to the administration of topoisomerase II inhibitor, etoposide. The prognosis of t-AML is known to be poorer as compared with de novo AML. Therefore, intensive therapy such as allogeneic stem cell transplantation should be considered in younger patients. CONCLUSION: A possibility of t-AML should be kept in mind following chemotherapy for CNS germ cell tumors.

GCT-57. ARE MELATONIN LEVELS A RELIABLE MARKER FOR INTRACRANIAL GERM CELL TUMORS POST TREATMENT DEFICIENCY?

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BACKGROUND: Pineal is the melatonin-producing gland, with this hormone importantly acting as a central and peripheral chronobiotic, antioxidant and in energy metabolism. The urinary dosage of 6-sulfatoxymelatonin (aMT6s), a melatonin metabolite, is an indirect marker to estimate the total melatonin nocturnal production, ranging in clinically normal individuals from 10–50 micrograms(ug). The purpose of this study was to evaluate aMT6s in patients with diagnosis of intracranial germ cell tumors (iGCT) treated at IOP/GRAACC/UNIFESP. METHODS: After an interview to collect data about therapies employed and medications, night urine samples (from 8:00pm to first void in the morning) were collected and analyzed by ELISA. RESULTS: Twenty patients between 5–42 years old (mean 20.9 years), all male, were analyzed. Thirteen patients had diagnosis of Germinoma, 1 with Imature Teratoma, 5 NGGCT and 2 Mature Teratoma. The first site was pineal (N=15) and bifocal (N=5). The treatment was surgery/biopsy/2º look surgery in 17 patients associated with chemotherapy/ radiotherapy, except in 2 (pure teratoma-surgery only) and 1 (chemo only). Three patients had diagnosis by tumor markers treated with chemo only (N=1) and chemotherapy/radiotherapy (N=2). The levels of aMT6s were between 0.2–3.2ug in all participants, except in one (14.8ug-biopsy, chemo and RT). CONCLUSION: aMT6s levels found in most patients are below the expected for the general population suggesting that this is an appropriate marker for pineal tumors with melatonin deficiency. It may contribute to support future studies in this area and adoption of follow-up protocols, with eventual hormone supplementation and consequently improved quality of life.

GCT-58. BRAZILIAN CENTRAL NERVOUS SYSTEM GERM CELL TUMOR CONSORTIUM PROTOCOL

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INTRODUCTION: Primary central nervous system (CNS) germ cell tumors (GCT) account for 2–3% brain tumors children/adolescents in Western hemisphere. The report aim is to present the results of a Brazilian CNSGCT consortium protocol. METHODS: Since 2013, 45 patients with histologic and/or tumor marker (TM) diagnosis of germinoma with/without HCGβ levels≤200mIU/ml (n=33), four between 100-200mIU/ml and NGGCT (n=12), received carboplatin/etoposide/cyclophosphamide (4–6 cycles), followed by 18Gy ventricular field irradiation and primary site(s) boost. Autologous bone marrow transplant (ABMT) was conducted for NGGCT low responders. RESULTS: Mean age 12.9 years (4.7-20y), 34 males. Diagnosis was made by TM (n=9), surgery (n=19), both (n=15). Two bifocal cases, (-)TM were treated as germinoma. Primary tumor location was pineal (n=20), suprasellar (n=13), bifocal (n=11) and basal ganglia/thalamus (n=1). Fourteen had ventricular/spinal spread. Second-look surgery occurred in 5 patients. For the germinoma group, 26 achieved complete response (CR) after chemotherapy, seven showed residual teratoma/scar. For the NGGCT after 2/4 cycles, four patients showed CR, 2 failure/progression and 6 partial response (4 (-)TM). Two were submitted to ABMT. Radiotherapy was performed as described, except in three. One recurrence to date. Two patients died (endocrinologic complications/progression). Toxicity was mostly grade ¾ neutropenia/thrombocytopenia during chemotherapy. At a median follow-up of 38 months, OS was 100% for Germinoma and 85% NGGCT. CONCLUSION: The treatment is tolerable and VFI dose reduction to 18Gy seems to preserve efficacy. Further follow-up is warranted to assess the NG group and the slow-responder patients.

GCT-59. EPIDEMIOLOGY OF PEDIATRIC INTRA-CRANIAL GERM CELL TUMORS: COMPARING THE INCIDENCE OF INTRA-CRANIAL GERM CELL TUMORS IN THE NATIVE JAPANESE POPULATION AND IMMIGRANT JAPANESE POPULATIONS ABROAD

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Pediatric intra-cranial germ cell tumors (iGCTs) occur at an incidence of 0.6–1.2 cases/million/year in Western countries. The incidence is reported up to 5 times higher in the Japan. It is unknown whether this increased incidence is due to tumor biology or environment. The incidence of iGCTs in children ages 0–19 years was evaluated from 12/1/96-12/1/2016 in stable Japanese immigrant populations living abroad compared to current native Japanese registry data. Medulloblastoma incidence was used as a control to account for assumptions in the data. A review of the Brain Tumor Registry of Japan from 1984–2004 revealed an incidence of 2.5 cases/million/year and a lower incidence of medulloblastoma at 1.1 cases/million/year. Sites outside of Japan included Vancouver, Canada, Lima, Peru, and San Paolo, Brazil and together included a population of 853,174 Japanese persons. Within this population, 0 cases of iGCT were identified over a 20-years. The ratio of medulloblastoma to iGCT cases in Japan was identified as 1:2 while the ratio was 2:1, 6.5:1, and 5:1, respectively, in the other three locations. The data suggests increased incidence in the native Japan may not translate to higher incidence in immigrant Japanese populations abroad and a clear genetic component was not found in this preliminary data set. A more precise and comprehensive study is needed to determine the cause of this difference in incidence. This study also emphasizes the importance of national and state registries and is a call to collaborate on state and country level epidemiology studies.

GCT-60. DEVELOPMENT OF MICROBLEEDING AFTER PROTON THERAPY FOR PATIENTS WITH GERM CELL TUMOR

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BACKGROUND: Proton therapy has been increasingly used to treat pediatric brain tumor. However, there were few reports about radiation-induced cerebral microbleeds(CMBs) and cavernous malformation among these patients. Here we evaluate the incidence and risk factor of CMBs with MR imaging. MATERIAL AND METHOD: We retrospectively identified patients with germ cell tumor treated with whole ventricle irradiation of 30.6 Gy using proton therapy at the Tsukuba University Hospital between 2004 and 2017. CMBs were characterized by examination of MR imaging scan including susceptibility-weighted imaging and T2* weighed gradient-recalled echo sequence. RESULT: The mean age at the time of proton therapy was 14.5 years. The median follow-up duration was 62.3 months. Three patients were treated by local boost in addition to whole ventricle irradiation. CMBs were found in 78% at 5 years, and 88% at 10 years from irradiation. Over 80% of CMBs occurred in area of the brain exposed to 30 Gy. CONCLUSION: This study indicated over 30 Gy irradiation may become a risk factor for development of CMBs. Although the correlation between development of CMBs and cognitive function, proton therapy might have an advantage to reduce late sequelae with decreasing irradiating dose to surrounding normal brain tissue.

GCT-61. CORRELATION OF PATTERNS OF DISEASE RECURRENCE WITH RADIOTHERAPY TECHNIQUES AND DOSE IN INTRACRANIAL GERM CELL TUMOURS (ICGCT): LESSONS FROM THE UK COHORT OF SIOP GCT96 STUDY

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BACKGROUND: There are global variations in radiotherapy approaches for icGCT. An understanding of patterns of disease recurrence correlated with radiation techniques and doses is important in standardising and improving the quality of radiotherapy using high-precision techniques. METHODS AND RESULTS: Data from 20 patients with tumour recurrence after treatment within the SIOP GCT96 study in the UK were analysed. Seven (35%) patients had germinoma and 13 (65%) had non-germinoma. Twelve patients had local recurrence, 5 had metastatic and 3 had local and metastatic disease. Radiotherapy details were retrieved in only 8 patients (40%). Six patients had received focal radiotherapy and two craniospinal radiotherapy. Of the patients who received focal radiotherapy, 4 had recurrence within the radiation portal, one had periventricular recurrence and one had marker-positive recurrence with no radiological lesions. Both patients who received CSI recurred within the CSF space. The main reasons for poor retrieval of treatment details were difficulty in retrieving archived information and that the study was conducted during a period before PACS or electronic radiotherapy records. CONCLUSION: This study highlights the importance prospective data collection and analysis to understand the patterns of recurrence in icGCT. Even within a prospective study, radiotherapy techniques varied between centres. There is therefore an urgent need for centralised radiological review and prospective radiotherapy quality assurance measures in future clinical trials.

GCT-62. DISSECTING INTRATUMORAL HETEROGENEITY OF CENTRAL NERVOUS SYSTEM GERM CELL TUMORS BY SINGLE-CELL RNA-SEQUENCING

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BACKGROUND: Central nervous system germ cell tumor (CNSGCT) is a rare pediatric brain tumor. However, they are found at a relatively high incidence in East Asia. Germinoma is sensitive toward radiotherapy and chemotherapy; however, non-germinoma GCTs (NGGCT) often show poor response. Some cases are a mixture of germinoma and NGGCT (mixed GCT), and they sometimes change histological subtypes at recurrence. Previous report demonstrated that a germinoma and NGGCT component within the same mixed GCT tissue shared the same gene mutation, whereas the genome-wide methylation profiles were distinct from each other. The methylation profiles of germinoma was similar to the primordial germ cells (PGC) at the migration phase, supporting a model that PGC is the cell of origin for CNSGCT. However, tumor heterogeneity hinder information of the mixed bulk RNA-sequence data, causing difficulty in elucidating the mechanism of tumor development. The purpose of this study was to investigate the tumor cells subpopulations at the resolution of individual cells by single-cell RNA-seq. RESULTS: Fresh surgical tumor tissue was immediately dissociated mechanically and enzymatically. Tumor cells are separated from CD45-labelled lymphocytes by FACS, and libraries were generated by Chromium Single cell 3' Reagent Kit. Total of 11 tumor samples were collected and sequenced. Unsupervised Clustering showed individual clusters. One of the clusters had high expression of Oct-4, which is a marker of germinoma. The other clusters showed different subtypes of cells representing the heterogeneity of CNSGCT. Further analysis including a pseudo-time course analysis is underway to identify the lineage of tumor cell development.

GCT-63. STEREOTACTIC RADIOSURGERY FOR RESIDUAL LESIONS OF PINEAL NON-GERMINOMATOUS GERM CELL TUMORS AFTER CONVENTIONAL RADIOTHERAPY: A RETROSPECTIVE STUDY

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OBJECTIVE: To explore the efficacy and safety of SRS for residual lesions of NGGCTs after conventional RT. METHODS: The clinical data of patients with iGCT who were admitted to Department of Oncology, Guangdong Sanjiu Brain Hospital between January 1, 2008 and December 30, 2019 were gathered. Those who were pathologically or clinically diagnosed with NGGCTs, with lesions located at pineal region, limited stage and residual lesions (with a maximum diameter>10mm) of pineal NGGCTs after RT with a total dose of 50-54Gy/25-30f, were eligible for the study. Several indexes such as local control rate, PFS, OS and treatment-related toxicity were analyzed. RESULTS: A total of 27 patients were included; all were male, with a median age of 16 years (range 8–31 years). The patients were followed-up to December 30, 2019, but there were 2 cases lost to follow-up. The median follow-up time was 34 months (range 8–142 months). After a month of treatment with SRS, the ORR and DCR were 71.4% and 95.2%, respectively. During follow-up, 5 cases had radiographic progressions, including 3 cases combined with increased AFP which were diagnosed with local recurrence and 2 cases diagnosed with GTS ; The 3y-PFS and OS were 85.2% and 88.0%.no acute radiation response was found after treatment with SRS, and only one patient had brain neurotoxicity. CONCLUSION: SRS for residual lesions of NGGCTs after RT is proved to be safe and feasible, with well tolerance, which is beneficial for the improvement of local control and the prolongation of survival.

GCT-64. TREATMENT RESULTS IN CHILDREN WITH LOCALIZED CNS NGGCT

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BACKGROUND/OBJECTIVES: Treatment of children with CNS NGGCT remains challenge: 5y OS is 60 – 80%; relapses are very aggressive. DESIGN/METHODS: Between 2003 and 2019, 14 children (median age 10.5, range 4 – 16 years) with localized intracranial NGGCT were treated with RT after induction chemotherapy (focal – 4, WVI+boost – 6, WBI+boost – 3, CSI+boost – 1). Tumor markers were elevated in 13 patients: 6 – AFP, 5 – HCG, 2 – both. One patient with level of HCG 72049 IU/l in serum and 121451 IU/l in CSF received 4 cycles of PEI + CSI 30 Gy with boost 54Gy. RESULTS: At a median follow-up of 4,7 years (range 1 – 16,25 years), 12 patients are alive. 5-year PFS and OS are 77,1% and 85,7%, respectively. Two patients (both AFP and HCG) progressed during RT (1 – focal, 1 – WBI+boost), both died. Two patients with high level of HCG recurred after therapy (WVI+boost – 1, focal – 1), both are alive. The first of them at recurrence (mts of lateral ventricle) received 4 cycles of PEI and RT (WBI+boost). The second patient had level of HCG 620IU/l and initially received focal irradiation 54Gy. At recurrence with distant spinal mts he received HD-CHT with auto-SCT, surgical resection of residual tumor and CSI with boost. CONCLUSIONS: Good results of treatment of localized CNS NGGCT with CSI, WBI or WVI in compare with focal RT show advantages of extended irradiation field. CSI should be considered for patients with extremely high levels of tumor markers and respectively poor prognostic histology.

GCT-65. INCIDENCE AND OUTCOME OF INTRACRANIAL MALIGNANT GERM CELL TUMOURS DIAGNOSED IN WESTERN DENMARK IN THE LAST DECADE

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INTRODUCTION: Intracranial malignant germ cell tumours (iGCT) are rare brain tumours mainly diagnosed in children and younger adults. MATERIAL AND METHODS: A retrospective analysis was performed by chart review of patients treated for iGCT in the northern and central region of Denmark. Teratoma only patients were not included in the study. RESULTS: 20 patients with iGCT were diagnosed from 2008–2019 in Western Denmark. The cumulative incidence was 1.05 per 100.000. The yearly incidence was 0.1 per 100.000. Mean age at diagnosis was 18 years (range 8–36 years), 17 were males and 3 were females. 13 patients presented with germinoma and 7 patients with non germinomateous germ cell tumours (NGGCT). Three patients had disseminated disease, two with germinoma and one with NGGCT. All patients had received radiotherapy and 18 patients were treated with multidrug chemotherapy including platinum and etoposide before irradiation. Two patients experienced recurrent disease, both non disseminated at diagnosis, one patient with germinoma and one patient with NGGCT. Both received salvage treatment including high dose chemotherapy with stem cell transplantation and reirradiation. Two NGGCT patients died, one patient after development of an anaplastic astrocytoma in the radiation field five years after radiotherapy and one patient after intracranial hemorraghe 18 months after salvage treatment for recurrent disease. Overall survival was 90%, 100% for GCT and 71% for NGGCT. CONCLUSION: The outcome of patients with iGCT in Western Denmark was comparable to the literature. A nationwide study of epidemiology and outcome of iGCT in Denmark is planned.

GCT-66. FINAL REPORT OF THE PROSPECTIVE NEXT/CNS-GCT-4 CONSORTIUM TRIAL (GEMPOX FOLLOWED BY MARROW-ABLATIVE CHEMOTHERAPY) IN PATIENTS WITH REFRACTORY/RECURRENT CNS GERM CELL TUMORS

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BACKGROUND: We report the responses, toxicities and long-term outcomes of gemcitabine, paclitaxel and oxaliplatin (GemPOx) regimen administered, in responsive patients, prior to single cycle marrow-ablative chemotherapy (thiotepa, etoposide and carboplatin) with autologous hematopoietic progenitor cell rescue (HDCx+AuHPCR). METHODS: Since De-

cember 2009, 11 recurrent/refractory patients (10 MMGCT, 1 germinoma; 10 males; mean age 16.5 years, range 7–46 years) have been treated with up to four cycles of gemcitabine (800mg/M2), paclitaxel (170mg/M2) and oxaliplatin (100mg/M2) administered on one day at 14 days intervals. RESULTS: All 11 patients were enrolled on a prospective multicenter trial, which was closed in October 2019. Three patients achieved complete remissions (tumor marker and/or imaging studies), five achieved partial remissions, two developed disease progression (PD), and one was withdrawn after one cycle for severe paclitaxel neurotoxicity followed by rapid tumor progression and death. One patient with PD after one cycle had pathologically-confirmed metastatic transformation to pure embryonal rhabdomyosarcoma, and rapidly expired. A second patient, with pure pineal choriocarcinoma, progressed after the second GemPOx cycle, ultimately died of tumor progression. Eight of the 11 responsive patients subsequently underwent HDCx+AuHPCR; five of these received some form of radiotherapy. Seven patients (six MMGCT, one germinoma) are alive and disease-free without recurrence for a mean of 94 months (range 74–118 months) since completion of therapy. CONCLUSION: GemPOx is an effective re-induction regimen for patient with recurrent CNS germ cell tumors, with acceptable toxicities; when followed by marrow-ablative chemotherapy and subsequent irradiation/re-irradiation, the regimen produces encouraging long-term disease-free survival.

GCT-67. CENTRAL NERVOUS SYSTEM GERMINOMA IN TWO CAUCASIAN AMERICAN SIBLINGS WITH AUTISM SPECTRUM DISORDER

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BACKGROUND: Central nervous system germ cell tumors (CNS-GCT) account for approximately 5% of all pediatric brain tumors. These tumors are pathologically heterogeneous, but have recurrent somatic mutations in KIT and rare germline variants in a Japanese cohort. Chromosomal abnormalities, specifically Klinefelter Syndrome, are associated with increased tumor development and familial cases have been reported, but no germline tumor syndromes are known. We describe a pair of siblings, both with autism spectrum disorder (ASD) that developed CNS-GCT, which previously has not been described outside of Japan. CASES: We report two siblings with ASD who developed CNS germinomas within two months of each other. The older brother, with basal ganglia and hypothalamic tumors, underwent surgical resection followed by treatment per ACNS0232 with chemotherapy and whole-ventricular irradiation (WVI). The younger sibling, with a midbrain tumor, also received ACNS0232, but due to poor response required additional chemotherapy and WVI. Both siblings are without evidence of disease 7 years after end of therapy. Genetic testing, including chromosomal microarray, karyotyping, and whole genome sequencing did not elucidate any variant identified as causative at that time. CONCLUSIONS: CNS-GCT are rare tumors, diverse in both histopathologic diagnosis and clinical outcomes. Currently there are known somatic alterations and germline chromosomal disorders associated with increased tumor development, but no known inheritable causes. Despite this, familial CNS-GCT have been reported in patients of Japanese descent. The description of two Caucasian American siblings with ASD and CNS-GCT is novel, refuting that familial CNS-GCT are limited to the Japanese population.

GCT-69. VOLUMETRIC CHANGE BEFORE CHEMORADIOTHERAPY AND INFLUENCE OF DIAGNOSTIC RADIATION EXPOSURE IN INTRACRANIAL GERMINOMAS

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BACKGROUND: Spontaneous regression in intracranial germ cell tumors has been reported in some literatures, but the mechanism has not been well known. We retrospectively measured the tumor volume before chemoradiotherapy and analyzed factors that influence reduction of tumor volume. PATIENTS AND METHODS: Plural MRI scans were done before the first course of chemotherapy regimen in 27 patients with primary intracranial germinomas. Their age ranged from 8 to 31 years. 35 lesions from them were enrolled and included 13 pineal, 4 neurohypophyseal, 4 basal ganglia, 4 bifocal type, and 2 multiple lesions. All regions were verified as pure germinoma or HCG-producing germinoma by histopathological examination. Tumor volume of 35 lesions was analyzed by volumetric assessment based on MRI. Ratio of volumetric change between the first MRI and the scan immediately before chemotherapy was defined as shrinking rate (%). Period between disease onset and the first chemotherapy was 20 to 47 days. Diagnostic radiation dose was calculated in each case. RESULTS: Initial tumor volume ranged from 0.962 to 72.356 cubic centimeters (mean: 8.27). Diagnostic radiation dose: 40.5 to 910.1 mGy. Shrinking rate ranged from -57.8 to 85.4% (mean: 30.8). In 10 regions, shrinking rate was within 30%. Shrinking rate was significant positively influenced by diagnostic radiation dose ($p<0.05$) and negatively influenced by initial volume ($p<0.05$). But, other factors such as age, sex, histopathological parameters did not influence tumor shrinkage. CONCLUSION: This study shows that the volume of intracranial germ cell tumors is changing dynamically before chemoradiotherapy in many cases. Diagnostic exposure to low-dose radiation influences tumor shrinkage of intracranial germinomas.

GCT-70. INTRACRANIAL GROWING TERATOMA SYNDROME IN CHILDREN

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Germ cell tumors account for less than 5% of all intracranial malignancies in children. Intracranial growing teratoma syndrome (GTS) is a rare pathophysiologic process characterized by growth of mature teratoma elements of a non-germinomatous germ cell tumor (NGGCT) during or following treatment with chemotherapy, in addition to normalization of or declining AFP/βHCG of the cerebral spinal fluid (CSF)/serum. A 13-year-old male presented with headache, emesis, and diplopia. MRI of the brain/spine revealed a localized 3.1 x 3.1 x 3.2 cm pineal tumor. Biopsy confirmed NGGCT (germinoma, immature and mature teratoma). Serum AFP (227ng/ul) and βHCG (12 IU/L) and CSF AFP (21ng/ul) and βHCG (31 IU/L) were elevated. Prior to cycle two of chemotherapy, he developed unstable gait and moderate hearing loss. Repeat MRI brain demonstrated tumor enlargement (4.4 x 5.2 x 5.1 cm) and obstructive hydrocephalus, although serum AFP/βHCG had normalized. Gross total resection of tumor confirmed GTS, without residual immature/malignant elements. Following six cycles of multiagent chemotherapy (carboplatin, etoposide, ifosfamide) and proton beam craniospinal irradiation (36 Gy with 18 Gy boost), he remains free of disease at eleven months since diagnosis. The pathogenesis of GTS remains unclear. Care must be taken to avoid misdiagnosing GTS as progressive NGGCT, as treatment and prognosis differ significantly. Second-look surgery, with a goal of complete resection, should be considered in cases of NGGCT when residual tumor grows during or following therapy, as this may represent GTS. Although histologically benign, GTS can be fatal. In patients with GTS, complete resection is usually curative.

GCT-71. SIOP STRATEGY TREATMENT FOR CENTRAL NERVOUS SYSTEM GERM CELL TUMORS IN A MIDDLE INCOME COUNTRY

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BACKGROUND/OBJECTIVES: Central nervous system (CNS) germ cell tumors (GCTs) represent 3% of primary paediatric brain tumours in occident. They can be divided into major groups including germinomas and nongerminomatous GCTs (NGGCTs). The aim is to describe demographic characteristics, Event Free Survival (EFS) and Overall Survival (OS) in patients with GCTs treated at Oncology Unit of Garrahan Hospital (HG). DESIGN/METHODS: Retrospective analysis of patients with GCTs admitted between September 1st,2000 to September 1st,2019. Variables analysed: age, localization, treatment, relapse and death. Patients were treated per SIOP-CNSGCTs protocol. For statically analysis SPSS (IBM), for EFS/OS Kaplan-Meyer, Long-rank for significance. RESULTS: Fifty-seven patients were included, comprising 38 Germinomas and 19 NGGCTS. Median age was 146 months (range 11–228). Primary site in localized Germinomas were pineal (16p), suprasellar (7p) and bifocal (7p). Five-year EFS and OS of 100% and 88.5%, respectively. Four patients presented metastatic disease, with an EFS and OS of 60.9% and 66.6%. Tumor site in localized NGGCT were pineal(8p) and suprasellar(5p). Five-year EFS was 81.8% and OS was 80.2%. No patients presented metastatic disease. All patients with high-risk tumor markers at diagnosis relapsed. No significative differences were found in OS neither EFS between groups (Germinomas OS5y 90% vs NGGCTs 74.6%p=0.19[CI95%0.0786–1.689]), (Germinomas EFS5y 78.9% vs NGGCTs5y 81.8%p=0.85[CI95%0.3046–4.230). Global OS and EFS5y was 83% and 72.9%. CONCLUSION: OS of our cohort is lower than what has been shown in current literature. This result may be related to the lack of resources and lower social economic status in our population.

GCT-72. ANALYSIS OF MICRORNA EXPRESSION PROFILE OF INTRACRANIAL GERM CELL TUMORS: A PROMISING TOOL FOR DIFFERENTIAL DIAGNOSIS

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INTRODUCTION: One of the major limitations of pathological diagnosis for intracranial germ cell tumors (iGCTs) is tumor heterogeneity, which cannot be evaluated using limited amount of tumor tissues. In this study, we performed comprehensive analysis of microRNA (miRNA) of iGCTs to identify miRNAs profile to help determine tumor diagnosis. METHODS: RNA was extracted from frozen samples of 16 germinoma and 14 NGGCTs. Five non-iGCT pediatric brain tumor tissues were used as control. miRNA expression analysis was performed using a 3D-Gene Human miRNA Oligo Chip ver.22 (Toray Industries, Inc) which was designed to detect 2565 miRNAs. The miRNA expression profile was analyzed using t-SNE dimensionality reduction and weighted average difference method (WAD). RESULTS: Different histological subtypes of the iGCTs and control samples were clustered into distinct classes. Furthermore, we found that the germinoma, NGGCTs and control samples may be readily distinguished by expression patterns of miR-200 and miR-371a-3p: a high expression of miR-200 was observed in the NGGCTs, whereas a high expression of miR-371a-3p was observed in all cases of germinoma and some of NGGCTs. Neither of miR-200 nor miR371-3p was highly expressed in control samples. CONCLUSION: Our data indicated that germ cell tumor and other pediatric brain tumors, and also germinoma and NGGCT can be distinguished by expression patterns of 2 micro RNA, miR-200 and miR-371a-3p. These 2 microRNA may serve as a useful tool for supporting the pathological diagnosis of iGCTs.

GCT-73. EXPRESSION PROFILING OF INTRACRANIAL GERM CELL TUMORS REVEALS UPREGULATION OF RAS THROUGH MRNA-MICRORNA SIGNALING PATHWAY

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Intracranial germ cell tumors (IGCTs) account for 3% of CNS tumors in children in the U.S. and 11% in Japan and East Asian countries. IGCTs are separated into two distinct subtypes based on histology: germinomas and non-germinomatous germ cell tumors (NGGCTs). The deep central location of IGCTs makes surgical resection and therefore molecular subtype classification difficult, and previous gene expression studies are limited. We performed mRNA expression profiling (Human Genome U133 Plus 2.0) and microRNA expression profiling (ABI TaqMan) with 36 and 49 IGCTs, respectively. Sample stratification using non-negative matrix factorization clustering of gene expression revealed two distinct subgroups that delineated germinomas from NGGCTs. Employing stepwise model building in each data set separately, we were able to separate these groups using only mRNA probes for the LIN28B and L1TD1 genes, and two microRNA, microRNA-26a and microRNA-373. MicroRNA26a suppresses the LIN28B gene and is down-regulated in germinoma. LIN28B directly binds and suppresses the let-7 microRNA family, which suppress the KRAS oncogene, previously found to be mutated in ~19% of IGCTs. L1TD1 is required for human stem cell renewal and directly interacts with LIN28B for its RNA binding function. LIN28B and L1TD1 are both known to be upregulated in other systemic germ cell tumors, but this has not yet been documented in IGCTs. In conclusion, these results show that intracranial germinomas have similar gene expression compared to systemic seminoma, and suggest a mechanism by which activation of LIN28B and L1TD1 downregulates the let-7 microRNA and subsequently upregulates KRAS.

GCT-74. RETROSPECTIVE LITERATURE REVIEW OF CENTRAL NERVOUS SYSTEM (CNS) GERM CELL TUMORS (GCTS) IN PATIENTS WITH DOWN SYNDROME (DS)

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BACKGROUND: A standard-of-care has not been established for the management of DS patients who develop primary CNS GCTs – the most common CNS neoplasm in DS – despite being more susceptible to treatment-related adverse events. METHODS: A review of the English-language medical literature between 1960 and 2020 was conducted. RESULTS: Thirty-one cases of CNS GCTs in DS patients (median nine-years-old; 21 males) were reported; the majority (23/31) originated from East Asia. Twelve had germinomas (39%), 12 had non-germinomatous germ cell tumors (NGGCTs) (39%), and seven had teratomas (22%). Four patients (13%) died from tumor progression (one germinoma *versus* three teratoma). Seven patients (23%) died from treatment-related complications (four germinoma *versus* three NGGCT). Of the germinoma patients, two died from chemotherapy-related sepsis, one from post-surgery cardiopulmonary failure, and one from Moyamoya following radiation-therapy (RT) only. Of the NGGCT patients, one died from chemotherapy-related sepsis, one from post-surgical infection, and one from pneumonia following surgery/chemotherapy/RT. Three-year overall survival (OS) was 58.1% for all patients, 52.5% for germinoma, 64.8% for NGGCT, and 60% for teratoma. Three-year OS for patients who received RT or chemotherapy was 63.6% and 59.6% respectively. Twenty patients (65%) remain alive (seven germinoma *versus* nine NGCCT *versus* four teratoma). Ten patients (32%) experienced serious treatment-related complications (five germinoma *versus* five NGGCT). CONCLUSIONS: Patients with DS and CNS GCTs are at an increased risk of treatment-related complications. Therefore, a different therapeutic approach may need to be considered for this patient population in order to mitigate the treatment-related complications and long-term neurocognitive sequelae.

GCT-75. ISOLATED PITUITARY STALK THICKENING

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OBJECTIVES: Only few studies have examined the predictive factors and outcome of isolated pituitary stalk thickening (PST) in children. We aim to describe our institutional cohort to determine predictors of future malignancy. METHODS: A search of the radiology, endocrinology and neuro-oncology databases was performed to identify patients with isolated PST diagnosed between January 2000 and June 2019. Clinical data was collected. A detailed radiology review of baseline and follow up magnetic resonance imaging (MRI) was undertaken in a blinded fashion by two examiners. RESULTS: Forty-four patients were identified, with 37 meeting criteria for isolated PST and adequate imaging. Median age of baseline MRI was 9.9 years (range 0.9–17.5). Twenty-three were female (62%). Median follow up time was 5 (0.31–18.6) years. Indication for MRI was symptoms of diabetes insipidus (DI) in 28 patients with the remainder having other concerns for endocrine disturbance (7), headache (1) or visual impairment (1). Thirty-five subjects had pituitary dysfunction (95%), including 30 with diabetes insipidus (81%). Nine patients developed a malignancy (24%), with germinoma (5), Langerhans cell histiocytosis (3) and lymphoma (1) at a median of 0.36 years, 0.63 years and 1.1 years respectively. Elevated white blood cell count (>5 x 10^6/L) in initial cerebrospinal fluid analysis was predictive of future diagnosis of germinoma or lymphoma (p=0.027). CONCLUSION: In this cohort 24% of children with PST were eventually diagnosed with a neoplasia after a median of 0.63 years. Pleocytosis in initial CSF samples was predictive for future development of germinoma or lymphoma.

GCT-76. 24GY WHOLE VENTRICULAR RADIOTHERAPY ALONE IS SUFFICIENT FOR DISEASE CONTROL IN LOCALISED GERMINOMA IN CR AFTER INITIAL CHEMOTHERAPY – EARLY RESULTS OF THE SIOP CNS GCT II STUDY

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SIOP CNS GCT II aimed to establish if 24Gy Whole Ventricular Radiotherapy (WVRT) in localised germinoma is sufficient for tumour control. After central review of radiological response after 'CarboPEI' chemotherapy, patients in complete remission (CR) were consolidated with 24Gy WVRT. Between 2/2012 and 7/2018, 182 patients from 8 European countries with histologically-confirmed fully-staged localised germinoma were registered. 70 patients were in CR after chemotherapy, 98 in partial remission (PR), seven had stable disease, two progressive disease, and in five no response data were documented. Of the 70 patients in CR, 58 received 24Gy WVRT alone; two of these relapsed, one local and one disseminated, two and six years after diagnosis. Of the 98 patients in PR after chemotherapy, 86 received 24Gy WVRT and 16Gy boost, of which five relapsed (three local, two distant) 12–24 months from diagnosis. Twelve patients in each of the CR/PR groups received non-protocol or undocumented radiotherapy fields/doses. Median follow-up was 3.7 years. Event-free survival (EFS) for patients in CR and with WVRT only (n=58) was 98% at 4 years. 4-years EFS of patients with PR and WVRT 24Gy and 16Gy tumor boost (n=86) was 95%. Localised germinoma in CR after chemotherapy had an excellent outcome with 24Gy WVRT alone; 24GY WVRT can therefore be considered standard consolidation treatment in this group. International consensus on radiological response criteria is of utmost importance to avoid over- and undertreatment of such patients and to pave the way for further treatment reduction in this group of patients.

HIGH GRADE GLIOMA

HGG-01. ENTRECTINIB IN RECURRENT OR REFRACTORY SOLID TUMORS INCLUDING PRIMARY CNS TUMORS: UPDATED DATA IN CHILDREN AND ADOLESCENTS

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STARTRK-NG (phase 1/2) is evaluating entrectinib, a CNS-penetrant oral, TRK/ROS1/ALK tyrosine kinase inhibitor, in patients <21 years with recurrent/refractory solid tumors, including primary CNS tumors. After determining the recommended dose, 550mg/m^2/day, in all-comers, expansion cohorts with gene-fusion-positive CNS/solid tumors (*NTRK1/2/3*, *ROS1*) are being enrolled. As of 5Nov2019 (data cut-off), 39 patients (4.9m–20y; median 7y) have been evaluated for response, classified as complete (CR) or partial response (PR), stable (SD) or progressive disease (PD) using RANO (CNS), RECIST (solid tumors), or Curie score (neuroblastoma). Responses in patients with fusion-positive tumors were Investigator-assessed (BICR assessments are ongoing) and occurred at doses ≥400mg/m^2. Best responses in fusion-positive CNS tumors (n=14) were: 4 CR (*GKAP1-NTRK2, ETV6-NTRK3* [n=2], *EML1-NTRK2*); 5 PR (*KANK1-NTRK2, GOPC-ROS1, ETV6-NTRK3, TPR-NTRK1, EEF1G-ROS1*); 3 SD (*BCR-NTRK2, ARHGEF2-NTRK1, KIF21B-NTRK1*); 2 PD (*PARP6-NTRK3, EML4-ALK*); and in fusion-positive solid tumors (n=8) were: 3 CR (*ETV6-NTRK3* [n=2], *DCTN1-ALK*); 5 PR (*EML4-NTRK3, TFG-ROS1* [n=3], *KIF5B-ALK*). Responses (Investigator-assessed) in non-fusion tumors (n=17) were: 1 CR (*ALK F1174L* mutation), 3 SD, 10 PD, 3 no data/unevaluable. The objective response rate (CR+PR/total) in patients with fusion-positive tumors was 77% (17/22) versus 6% (1/17) in those with non-fusion tumors. All 39 patients experienced ≥1 adverse event (AE); the most frequent AEs included weight gain and anemia (both 48.7%); increased ALT, increased AST, cough and pyrexia (all 46.2%); increased creatinine and vomiting (both 43.6%); and bone fractures (n=10, in 9 patients). Entrectinib has produced striking, rapid, and durable responses in solid tumors with target gene fusions, especially high-grade CNS neoplasms.

HGG-02. ADOLESCENT AND YOUNG ADULT (AYA) GLIOMA WITH BRAF V600E-MUTANTATION

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BACKGROUND: Biological features of pediatric glioma differ significantly from those of adult glioma, and limited data are available on those of AYA patients. Here, we focused on AYA patients with glioma, especially those harboring BRAF V600E mutation, and investigated their clinical and genetic features. METHOD: We retrospectively analyzed AYA patients with brain tumors harboring BRAF V600E, who were treated in two hospitals in Japan. RESULTS: Clinical information was available for 14 patients. The median age at diagnosis was 25 years (range: 15–38). Five patients were diagnosed with glioblastoma (GBM), including one epithelioid type. These patients were over 25. Although one patient with GBM died of the disease 6.9 years after initial diagnosis, the remaining patients were alive. Two patients were alive without recurrence at 38 and 51 months after the treatment. The patient with epithelioid glioblastoma experienced early recurrence. The remaining nine patients (64%) were diagnosed with low-grade glioma, including ganglioglioma, pilocytic astrocytoma, diffuse astrocytoma, oligodendroglioma, pleomorphic xanthoastrocytoma, and polymorphous low-grade neuroepithelial tumor of the young. No patients died of the disease, and four patients are alive without recurrence after initial operation without adjuvant treatment. Two patients are (epithelioid glioblastoma and ganglioglioma) currently undergoing treatment with a BRAF inhibitor for recurrent tumors. DISCUSSION: Although the number of this study is limited, our study suggested that the prognosis of AYA patients with BRAF-V600E positive GBM may not be as dismal as that of children or adults.

HGG-04. ZINC ENHANCES TEMOZOLOMIDE CYTOTOXICITY IN PEDIATRIC GLIOBLASTOMA MULTIFORME MODEL SYSTEM

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BACKGROUND: Temozolomide (TMZ) is an alkylating agent that has become the mainstay treatment of the most malignant brain cancer, glioblastoma multiforme (GBM). Unfortunately only a limited number of patients respond to it positively. We have shown that zinc metal reestablishes chemosensitivity in adult GBM in vitro and also in vivo but this effect has not been tested with pediatric GBM. METHODS: Using Human pediatric glioblastoma cell lines- KNS42 (mutant p53/ MGMT [+]) and SF188 (mutant p53/ MGMT [-]), we investigated whether addition of zinc to TMZ enhances its cytotoxicity against GBM. RESULTS: *In vitro* cell viability analysis showed that the cytotoxic activity of TMZ was substantially increased with addition of zinc and this response was accompanied by an elevation of p21, PUMA, BAX and a decrease in growth fraction as manifested by low ki67. Beta gal analysis showed that most of the remaining cells after the combination therapy are in senescence state. In order to eliminate the senescent population created as a result of the combined treatment of TMZ and Zinc, we decided to use a senolytic agent Navitoclax (ABT-263) that was demonstrated to be effective in reducing senescent cells by specific in-

hibition of Bcl-2, Bcl-XL and Bcl-w. Following the addition of Navitoclax to the combined treatment, SF188 cells, but not KNS42, show a significance reduction in viability compare to the combination treatment. CONCLUSIONS: Our results suggest that zinc may serve as a potentiator of TMZ therapy in pediatric GBM patients and using a second hit with senolytic drug in some cases may be even more beneficial.

HGG-05. REGRESSION OF RECURRENT GLIOBLASTOMA AFTER BORON NEUTRON CAPTURE THERAPY AND CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY IN A CHILD

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A 6 y/o girl with recurrent multifocal glioblastoma received 3 times of boron neutron capture therapy (BNCT) and chimeric antigen receptor (CAR)–engineered T cells targeting the tumor-associated antigen HER2. Multiple infusions of CAR T cells were administered over 30 days through intraventricular delivery routes. It was not associated with any toxic effects of grade 3 or higher. After BNCT and CAR T-cell treatment, regression of all existing intracranial lesions were observed, along with corresponding increases in levels of cytokines and immune cells in the cerebrospinal fluid, but new lesions recurred soon after the treatment. This clinical response continued for 14 months after the initiation of first recurrence.

HGG-06. REMARKABLE RESPONSE TO BRAF INHIBITOR IN AN INFANT WITH DISSEMINATED DIFFUSE LEPTOMENINGEAL GLIONEURONAL TUMOR (DLGNT)

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INTRODUCTION: Diffuse Leptomeningeal Glioneuronal Tumor (DLGNT) are rare CNS tumors and in infants, they can be lethal. There are several anecdotal reports in infants with low grade gliomas (LGG) with treated with BRAF inhibitors. METHODS: A six-month old baby girl presented with a 2-week history of absent visual contact and vomiting. Imaging revealed a large 4.7 X 4.2 X 2.8 cm suprasellar charismatic region mass and multiple small extra-axial plaques in spinal canal. The child developed significant ascites post VP shunt requiring shunt externalization, extensive protein infusion support and hospitalization for six weeks. Immunohistochemical staining revealed Olig-2 and S-100, GFAP and synaptophysin positive. EMA showed patchy cytroplasmic reactivity in stromal cells and CD99 showed diffuse reactivity in stromal and lesional cells. INI-1, IDH-1, and CD117 were negative. Ki-67 proliferation index was 8–10%. PCR for BRAF V600E/E2/D was detected and KIAA1549-BRAF fusion as negative. This was confirmed by Genome Wide Next Generation Sequencing. While waiting for GNS testing results, the baby received one dose of Vinblastine. However, within seven days of initiating Debrafenib, significant clinical and radiological responses were observed. CONCLUSION: The baby continues safely on Debrafenib with continued dramatic radiological response. This suggest that there may be a role in early initiation of targeted therapy such as *BRAF* inhibitors rather than giving standard chemotherapy such as Vinblastine or Carboplatin-Vincristine in extremely ill infants with low grade gliomas.

HGG-07. CYCLIN-DEPENDENT KINASES AS TARGET STRUCTURES FOR CANCER THERAPY – A COMPARATIVE IN VITRO ANALYSIS ON PATIENT-DERIVED GLIOBLASTOMA CELL CULTURE MODELS

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INTRODUCTION: Current therapeutic approaches have limited clinical success for Glioblastoma patients, making novel strategies urgent. Cyclin-dependent kinases (CDK) are crucial in cell cycle, oncogenic transcription, DNA repair, and stem-cell renewal. Glioma cells frequently show genomic alterations in CDKs. Here, we evaluated the antitumoral activity of selective CDK inhibitors (CDKI) abemaciclib (CDK4/6), palbociclib (CDK4/6), and dinaciclib (CDK1/2/5/9) alone and in combination with chemo-/radiotherapy. MATERIALS/METHODS: Low passage glioblastoma cell lines (N=5) with different molecular characteristics were cultured in 2D and 3D (neurospheroids (NSPs), glioma stem-cells (GSCs). The impact of CDKI alone or in combination with TMZ and radiation (2Gy) was examined. Viability was measured using Calcein-AM and 3D-Glo assays; DNA double-strand breaks by γ-H2AX immunofluorescence. Functional analyses were performed from a 2D culture (72h treatment). RESULTS: Dinaciclib significantly affected viability of GBM cell lines even shortly after low-dose treatment. CDK 4/6 inhibitors were less effective. Abemaciclib and dinaciclib acted radio-sensitizing. Dinaciclib combined with different substances (72h, dose: IC_{20}), synergistically potentiated antitumoral effects. In a scratch assay, abemaciclib decelerated wound healing; dinaciclib even induced cell death. Microarray analysis revealed altered gene expression: Genes mediating cell adhesion, division, DNA-binding, apoptosis (*Casp3,Casp8*), senescence (*ASF1A,CENPA,FBXO31*), and autophagy (*ATG4D,ATG2A,SOGA1*) were upregulated. Chemotaxis-mediating *(CXCL8,CCL20)* and proto-oncogenes like *JUNB* and *FOS* were strongly down-regulated. Long-term treatment induced dinaciclib resistance in 1/5 cases, and none abemaciclib-treated cells. This was reversed when dinaciclib was combined with TMZ. CONCLUSION: Our results demonstrate strong anti-GBM activity of dinaciclib and abemaciclib, with additive effects of chemotherapy and radiosensitization, encouraging to move forward this strategy.

HGG-09. FIRST LINE THERAPY OF PEDIATRIC GLIOBLASTOMA WITH LAROTRECTINIB

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PURPOSE: In this case report, we document new recommendations for the treatment of pediatric glioblastoma based on a genetic understanding of the disease. PATIENTS AND METHODS: A Saudi girl aged 18 months presented with a history of right sided weakness and partial seizures. MRI revealed the presence of large complex left frontal tumor. Craniotomy and gross total resection were performed. post-operatively The patient showed excellent recovery with no neurological deficits. Pathology reports confirmed glioblastoma (GBM). Due to the expected poor survival, the patient's family declined standard therapy, including chemotherapy and/or radiation therapy. RESULTS: Molecular analysis showed positive fusion mutations for ETV6-NTRK3 making the patient an ideal candidate for larotrectinib, an oral tyrosine kinase (TRK) inhibitor. Unfortunately, follow-up MRI showed local tumor recurrence at 3-months post-surgery. The family agreed to the initiation of oral larotrectinib as a less invasive therapy. The patient tolerated Larotrectinib very well with no reported side effects. Follow up MRI was performed 8-weeks post-larotrectinib treatment and showed significant tumor regression, indicating an excellent treatment response. CONCLUSION: This case highlights how TRK-inhibitors can be integrated as a first-line therapy for pediatric high grade GBMs harboring TRK-fusions. We also highlight the need for the integration of genomic profiling and molecular analysis into the routine histopathologic analyses of pediatric patients with malignant primary intracranial tumors, to detect any genetic mutations that can be targeted with available therapies to avoid the morbidity associated with non-precision conventional therapies.

HGG-11. HIGH-GRADE GLIOMAS IN ADOLESCENTS AND YOUNG ADULTS HIGHLIGHT HISTOMOLECULAR DIFFERENCES WITH THEIR ADULT AND PAEDIATRIC COUNTERPARTS

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BACKGROUND: Considering that paediatric high-grade gliomas (HGGs) are biologically distinct from their adult counterparts, the objective of this study was to define the landscape of HGGs in adolescents and young adults (AYAs). METHODS: We performed a multicentric retrospective study of 112 AYAs from adult and paediatric Ile-de-France neurosurgical units, treated between 1998 and 2013 to analyse their clinicoradiological and histomolecular profiles. The inclusion criteria were age between 15 and 25-years, histopathological HGG diagnosis, available clinical data, pre-operative and follow-up MRI. MRI and tumoral samples were centrally reviewed. Immunohistochemistry and complementary molecular techniques such as targeted/next generation sequencing, whole exome sequencing and DNA-methylation analyses were performed to achieve an integrated diagnosis according to the 2016 WHO classification. RESULTS: Based on 80 documented AYA patients, HGGs constitute heterogeneous clinicopathological and molecular groups, with a predominant representation of paediatric-subtypes (Histone H3-mutants, 40%) but also adult-subtypes (*IDH*-mutants, 28%) characterized by the rarity of oligodendrogliomas, *IDH*-mutant and 1p/19q co-deleted and the relative high frequency of "rare adult *IDH* mutations" (20%). H3G34-mutants (14%) represent the most specific subgroup in AYAs. In the H3K27-mutant subgroup, the non-brainstem diffuse midline gliomas are more frequent (66.7%) than diffuse intrinsic pontine gliomas (23.8%), contrary to children. We found that WHO grade has no prognostic value, but molecular subgrouping has major prognostic importance. CONCLUSIONS: HGGs in AYAs could benefit from a more personalized neuro-oncological management, driven by molecular subtyping rather than age group. Collaborative efforts are needed from paediatric and adult neuro-oncology teams to improve the management of HGGs in AYAs.

HGG-12. A CASE OF PEDIATRIC SPINAL HIGH-GRADE GLIOMA WITH NTRK1 GENE FUSION

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INTRODUCTION: Tumors arising from the spinal cord are uncommon, especially high-grade tumors in pediatric patients. We report a case of high-grade glioma in the spinal cord harboring *NTRK1* gene fusion, who received effective entrectinib therapy. CASE REPORT: A 5-year-old boy presented right hemiparesis and MR imaging revealed an intramedullary enhancing mass at the vertebral body level between C3 and Th1. He underwent microsurgical partial resection and the histological diagnosis was low-grade astrocytoma. After the first-line chemotherapy with vincristine and carboplatin, his right hemiparesis deteriorated and recurrent MR imaging showed growth of the tumor. He underwent microsurgical partial resection again and the histological examination was high-grade glioma with endothelial proliferation and necrosis. The chemoradiotherapy with temozolomide and focal irradiation of 50.4 Gy were given, and his neurological symptom slightly improved. One month later, he presented respiratory disturbance and required assisted ventilation with tracheostomy. MR imaging showed tumor progression invading upward to medulla oblongata. *NTRK1* gene fusion was detected in the previous surgical specimen by a gene panel testing, and he received entrectinib, a potent inhibitor of tropomyosin receptor kinase (TRK). Since then, no tumor progression has been demonstrated for several months by MRI and he has been stable neurologically. CONCLUSION: High-grade spinal cord tumors are rare and effective treatment strategies have not been addressed. Although the frequency of the gene fusion is very low in pediatric gliomas, identification of the driver gene aberration like in this case by a gene panel can provide potential targeted therapies for selected patients.

HGG-14. TREATMENT AND PROGNOSTIC FACTORS FOR PEDIATRIC GLIOBLASTOMAS--THE 10 YEARS EXPERIENCE FROM ONE SINGLE CENTER

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OBJECTIVE: We retrospectively analyzed the clinical features of pediatric glioblastoma patients in our center in the past 10 years. METHODS: From November 2009 to December 2018, patients with glioblastoma under 18 years were admitted to Guangdong Sanjiu Brain Hospital. Clinical and pathological features were summarized, and the curative effect was evaluated. RESULTS: A total of 31 pediatric patients were enrolled. The median age is 13.8 years (range 0.8–18), including 19 males and 12 females. To Sep, 2019, the median follow-up time was 18 months(Range 4–80 months). Among them,2 were lost to follow-up,13 died, 16 still survived, and the longest survivor survived for 80 months. The median survival time was 16.4 months, the 2-year survival rate was 38%. In the prognostic factor analysis, the median survival time of patients with surgical resection ≥90% was 18 months (95% CI 15.9–20 months), and for children with resection 90% was 11 months (95% CI 9.9–12 months), P=0.027, with significantly statistically difference. Multivariate analysis showed that tumor resection rate was an independent prognostic factor for survival. CONCLUSION: The prognosis of pediatric glioblastoma is still dismal. This study demonstrates that prognosis of such patients with GTR or near GTR is better.

HGG-16. EXOSOME-MEDIATED INTER-CLONAL INTERACTIONS IN PEDIATRIC GBM AND DIPG

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Pediatric Glioblastoma (pGBM) and Diffuse Intrinsic Pontine Glioma (DIPG) are highly heterogeneous brain tumors which we demonstrated are comprised by distinct sub-clones interacting in a functional network. Exosomes are known to mediate the crosstalk between tumor and its microenvironment. Based on this, we aimed to investigate the role of exosomes in mediating pGBM and DIPG inter-clonal communication. By using *optical barcoding* for single cell-tracking, we generated two bulk multicolor patient derived-cell lines (one DIPG H3.3K27M and one pGBM histone WT) from which we obtained two and five single cell-derived clones respectively. The sub-clones demonstrated significantly phenotypic differences in terms of morphology, growth, adhesion, migration and invasion properties. In particular, co-culture experiments, with the two most different clones for both cell-lines, confirmed the cell-cell interaction key role in driving their more aggressive phenotype. Furthermore, we found that pGBM and DIPG subclones release exosomes which are actively and differentially up-taken by individual clones. Analysis of the exosomal microRNAs showed a different profile between the two selected clones in each cell-line. In particular, we found a pool of five upregulated microRNAs in 1C5 clone (DIPG cell-line) strongly associated to Wnt-signaling and PI3K-AKT pathway. Similarly, a pool of five upregulated microRNAs for 5E2 clone (pGBM cell-line) were found associated with focal adhesion and PI3K-AKT pathway. Our study may provide novel therapeutic strategies by interfering with the exosome-mediated inter-clonal communication in pGBM and DIPG.

HGG-17. HIGH-GRADE GLIOMA IN VERY YOUNG CHILDREN; A SINGLE-CENTER 11-YEAR-EXPERIENCE

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BACKGROUND: Data about high-grade glioma (HGG) in very young children (≤3 years old at diagnosis) is scarce. METHODS: 180 pediatric HGG patients were treated at the Children Cancer Hospital - Egypt (CCHE-57357) between July 2007 and June 2018, with 17 patients aged ≤3 years at diagnosis. Medical records were retrospectively reviewed for clinical, radiological and histopathological data, treatment received and survival outcome. RESULTS: Median age was 29.2 months (range: 2.4 – 35.8 months; males = 9). Most frequent pathological diagnosis was Glioblastoma, WHO grade-IV (n = 11, 64.7%) and one patient had H3-mutant diffuse midline glioma. All patients underwent surgery (gross-total resection, n = 6, 35.3%; subtotal-resection, n = 5, 29.4%; biopsy, n = 6, 35.3%). One patient (age = 7 months) progressed and died before starting adjuvant therapy. All patients ≤1 year of age (n = 5) received adjuvant chemotherapy (CT) only, older children (n = 11) received adjuvant radiotherapy (RT) (total dose range: 54 – 60 Gy) and CT (CCG-945 protocol). The 1-year overall survival (OS) rate was 47.1%; and event-free survival (EFS) rate was 35.3%. EFS differed between those who received RT and those who did not (1-year EFS 54.5% and 0% respectively, p = 0.001). Compared to older children, anatomical distribution of tumors was significantly different with non-midline locations being the commonest in patients ≤3 years old (88.2% vs 46.4%, p=0.01). CONCLUSIONS: HGG in very young children arise predominantly in non-midline locations and usually lack the H3-mutation. RT seems crucial in the management of pHGG regardless of age subgroup.

HGG-18. CLINICAL EFFICACY OF ONC201 IN THALAMIC H3 K27M-MUTANT GLIOMA

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ONC201, a bitopic DRD2 antagonist and allosteric ClpP agonist, has shown encouraging efficacy in H3 K27M-mutant glioma. Given that the thalamus has the highest extra-striatal expression of DRD2, we performed an integrated preclinical and clinical analysis of ONC201 in thalamic H3 K27M-mutant glioma. ONC201 was effective in mouse intra-uterine electroporation (IUE)-generated H3 K27M-mutant gliomas, with an *in vitro* IC_{50} of 500 nM and 50% prolongation of median survival *in vivo* (p=0.02, n=14). We analyzed thalamic H3 K27M-mutant glioma patients treated with ONC201 on active clinical trials as of 5/22/19 enrollment (n=19 recurrent and 10 post-radiation, non-recurrent; 5–70 years old). As of 12/18/2019, PFS6 and OS12 are 26.3% and 36.8%, respectively, in the recurrent group. For non-recurrent patients, with median follow up of 21.9 months (8.6–26.6) from diagnosis, median PFS or OS have not been reached. This surpasses historical OS of 13.5 months. Best response by RANO includes 1 CR, 3 PR, 4 SD, 8 PD for recurrent patients and 2 PR, 4 SD, 1 PD for non-recurrent patients (4 on-trial patients experienced regressions that are yet unconfirmed responses). Median duration of response for recurrent patients is 14.0 months (2.0–33.1). Furthermore, H3 K27M cell-free tumor DNA in plasma and CSF correlated with MRI response. In summary, single agent ONC201 administered at recurrence, or adjuvantly following radiation, demonstrates promising clinical efficacy in thalamic H3 K27M-mutant glioma patients who currently have no effective treatments following radiation. Investigations are ongoing to assess whether micro-environmental DRD2 expression explains the early exceptional responses in thalamic H3 K27M-mutant glioma.

HGG-19. IDENTIFICATION OF NOVEL SUBGROUP-SPECIFIC MIRNA EXOSOMAL BIOMARKERS IN PEDIATRIC HIGH-GRADE GLIOMAS

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Pediatric high-grade gliomas (pHGG) are heterogeneous brain tumors for which new specific diagnostic/prognostic biomarkers are needed. In this study, we aimed to identify new pHGG subgroup specific biomarkers by exploiting exosomes, known vehicles of oncogenic signals. We used plasma from 23 patients (including 6 controls) and conditioned medium from 12 patient-derived cell-lines, representing all locational and molecular subgroups. Upon exosome isolation, total RNA was extracted and miRNAs were assessed using a PCR Panel. Analysis of plasma miRNome showed that tumor exosomal samples were largely clustered together, independently from their locational and/or molecular subgroup. We identified 20 significantly upregulated and 25 downregulated miRNAs compared to controls. Interestingly, 27 miRNAs were expressed only in tumors. Furthermore, the unsupervised clustering showed a clear separation based on locational (hemispheric *vs* pontine) and mutational (WT *vs* H3.3G34R or H3.3G34R *vs* H3K27M) subgroup comparisons, with the identification of distinct miRNomes underlying the key role of location and mutations in defining the pHGG exosomal miRNA profile. This was further confirmed analyzing the miRNOme from cell-line derived exosomes. Moreover, we identified a pool of significantly differentially regulated miRNAs in diagnose *vs* relapse and biopsy *vs* autopsy cell-lines. Most importantly, when comparing hemispheric *vs* pontine and H3.3G34R *vs* H3.3K27M, we identified respectively four and three miRNas equally dysregulated and in common between plasma and cell-lines. Those were strongly associated mainly to transcriptional regulation and targeting *TTC9*, linked to cancer invasion and metastasis. Based on this, we suggest exosomal miRNAs as a powerful new pHGG diagnostic/prognostic tool.

HGG-20. DIAGNOSTIC AND BIOLOGICAL ROLE OF METHYLATION PATTERNS IN REPLICATION REPAIR DEFICIENT HIGH GRADE GLIOMAS

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Replication repair deficiency (RRD) is an important driving mechanism of pediatric high grade glioma (pHGG) occurring predominantly in the context of germline mutations in RRD-associated genes. Although pHGG present specific patterns of DNA methylation corresponding to driving oncogenic processes, methylation patterns have not been well studied in RRD tumors. We analyzed 52 RRD pHGG using either 450k or 850k methylation arrays. These arrays were compared with 234 PHGG driven by other genetic or epigenetic mechanisms and 10 additional pHGG samples known to be hypermutant. RRD pHGG displayed a methylation pattern corresponding to specific secondary mutations such as IDH1 and H3K27M. Strikingly, RRD pHGG lacking these known secondary mutations largely clustered together with a poorly described group previously labelled Wild type-C. Most of the hypermutant tumors clustered in a similar location suggesting undiagnosed RRD may be a driving force for tumors clustering in this location. Analysis of methylation patterns revealed that RRD pHGG displayed a unique CpG Island Demethylator Phenotype in contrast to the Methylator Phenotype described in other cancers. This effect was most concentrated at gene promotors. Prominent demethylation was observed in genes and pathways critical to cellular survival including cell cycle, gene expression, cellular metabolism and cellular organization. These data suggest that methylation profiles may provide diagnostic information for the detection of RRD pHGG. Furthermore, our findings highlight the unique natural selection pressures in these highly dysregulated, hypermutant cancers and provide novel impact of hypermutation and RRD on the cancer epigenome.

HGG-21. GERMLINE MUTATIONS IN *MSH2* GENE IN PEDIATRIC PATIENTS WITH CONGENITAL AND SPORADIC GLIOBLASTOMA

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INTRODUCTION: Glioblastoma (GBM) remains one of the biggest therapeutic challenges in neuro-oncology. In spite of multimodal treatment approaches the prognosis of GBM is extremely poor, median survival is estimated about 12–16 months. Although GBM is one of the most common and malignant primary brain tumors, pediatric glioblastoma, including congenital is a very rare tumor, with an incidence of about 1.1–3.4 per million live births. Moreover, the mode of presentation, behavior, response to therapy and molecular background of pediatric glioblastomas differs from adult type of GBM. Until now, about ten patients with congenital glioblastoma have been described and in none of them germline markers were examined. Here we report two patients with GBM, one with congenital tumor with germline mutations in *MSH2* gene. METHODS: Targeted Next-Generation Sequencing (NGS) of the probands DNA extracted from leucocytes was performed using the TruSight One sequencing panel on an Illumina HiSeq 1500. Applied gene panel investigated the coding sequence and splice sites of 4813 genes associated with known disease phenotypes. The NGS data were analyzed using an in-house procedure. Identified variants were validated by Sanger sequencing. RESULTS: NGS analysis of patients constitutional DNA revealed know, pathogenic variants c.940C>T and c.942 + 3A>T in *MSH2* gene (NM_000251.3) associated with MMR-dependent hereditary cancer syndromes. CONCLUSION: Molecular analysis are heavily needed for better understanding of pediatric GBM etiology and new treatment modality implementation. Identification of this oncogenic driver may provide insight into the pathogenesis of GBM, including congenital cases. Funded by National Science Centre, Poland (2016/23/B/NZ2/03064 and 2016/21/B/NZ2/01785).

HGG-24. HIGH-GRADE GLIOMA WITH A NOVEL FUSION GENE OF VCL-ALK

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A previously healthy 2-year-old boy presented with status epilepticus following intermittent vomiting. Computed tomography scan showed a 7 cm mass on the left occipital lobe with midline shift, inferior cerebellar herniation, and diffuse cerebral edema. The extensive dissemination to bilateral cerebral hemispheres, brain stem, and optic nerve was also observed. He underwent brain biopsy from the lesion on his left occipital lobe. The histopathological diagnosis determined the diffuse or epithelial proliferation of astrocytic tumor cells with high mitotic rate, positive for p53 and glial fibrillary acidic protein positive staining consistent with high-grade glioma. The progressive tumor led to communicating hydrocephalus, that was favorably controlled by cerebrospinal fluid shunting. The data from the FoundationOne CDx cancer genome profile disclosed a novel VCL-anaplastic lymphoma kinase (ALK) fusion in the tumor cells of the patient. ALK rearrangement was determined to be positive for the tumor cells assessed by fluorescence *in situ* hybridization. Only 4 pediatric cases of glioma with ALK-rearrangement have ever been reported. All of them received subtotal or gross total resections and then survived with or without chemotherapy. This is the first case of glioma harboring *VCL* as a novel partner of ALK fusion gene. After the favorable response to the first-line chemotherapy, subsequent irradiation therapy has now been scheduled. The molecular classification of high-grade glioma may help to expand the targeted therapy for unresectable advanced brain tumor.

HGG-26. H3G34V MUTATION AFFECTS GENOMIC H3K36 METHYLATION IN PEDIATRIC GLIOMA

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BACKGROUND: Histone H3.3 mutation (*H3F3A*) occurs in 50% of cortical pediatric high-grade gliomas. This mutation replaces glycine 34 with arginine or valine (G34R/V), impairing SETD2 activity (H3K36-specific trimethyltransferase), resulting in reduced H3K36me on H3G34V nucleosomes relative to wild-type. This contributes to genomic instability and drives distinct gene expressions associated with tumorigenesis. However, it is not known if this differential H3K36me3 enrichment is due to H3G34V mutant protein alone. Therefore, we set to elucidate the effect of H3G34V on genomic H3K36me3 enrichment *in vitro*. METHODS: Doxycycline-inducible short hairpin RNA (shRNA) against *H3F3A* was delivered via lentivirus to established H3G34V mutant pediatric glioma cell line KNS42, and H3G34V introduced into H3.3 wild type normal human astrocytes (NHA). Transfections were confirmed by western blot, fluorescent imaging, and flow cytometry, with resulting H3.3WT and H3K36me3 expression determined by western blot. H3.3WT, H3K36me3, and H3G34V ChIP-Seq was performed to evaluate genomic enrichment. RESULTS: Complete knockdown of H3G34V was achieved with DOX-induced shRNA, with no change in total H3.3, suggesting disproportionate allelic frequency of genes encoding H3.3 (*H3F3A* and *H3F3B)*. Modest increase in H3K36me3 occurred after *H3F3A*-knockdown from KNS42, suggesting H3G34V alone impacts observed H3K36me3 levels. Distinct H3K36me3 genomic enrichment was observed with H3G34V knock-in. CONCLUSIONS: We demonstrate that DOX-inducible knockdown of *H3F3A* in an H3G34V mutant pediatric glioma cells and H3G34V mutation transduction in wild-type astrocytes affects H3K36me3 expression. Further evaluation by ChIP-Seq analysis for restoration of wild-type genomic H3K36me3 enrichment patterns with H3G34V knockdown, and mutant H3K36me3 patterns with H3G34V transduction, is currently underway.

HGG-27. ANTI-CANCER POTENTIAL OF ARGINASE FOR HIGH-GRADE GLIOMA *IN VITRO* & *IN-VIVO*

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BACKGROUND: High-grade glioma is currently incurable. It was reported that glioma may be auxotrophic to arginine due to the lack of urea cycle genes expressions, suggesting arginase may be a potential agent for high grade glioma. AIM: We investigated the efficacy of pegylated arginase I (pegArg-I) or in combination with other anti-cancer drugs for high-grade glioma *in vitro* and *in vivo*. METHODS: 4 high-grade glioma cell lines (U87, U373, U138, D54) were treated with pegArg-I *in vitro*. The molecular mechanism of pegArg-I-induced cytotoxicity was tested in U87. The ultramorphological changes of pegArg-I-treated U87 was investigated by both scanning and transmission electron microscopy. Orthotopic glioma xenograft model with luciferase-transfected U87 cell line was tested for anti-cancer efficacy of peg-Arg I *in vivo*. RESULTS: We showed that pegArg-I

induced significant cell death in all 4 cell lines *in vitro*. Temozolomide, difluoromethyornithine and chloroquine (CQ) were then tested together with pegArg-I in U87 *in vitro*. We found that only CQ showed additive effect with pegArg-I against glioma *in vitro*. Such additive cytotoxic effect may be associated with enhanced autophagy and necrosis as shown in transmission electron microscopy and autophagy markers' expression by Western blotting. PegArg-I prolonged the survival of glioma mice, suggesting its possible anti-glioma efficacy. However, CQ+pegArg-I didn't show further significant anti-cancer efficacy *in vivo*. CONCLUSION: PegArg-I may be useful in slowing the progression of glioma, but additional drug candidate which works synergistically with pegArg-I remains to be explored.

HGG-29. A CASE OF CIRCUMSCRIBED HIGH-GRADE ASTROCYTOMA WITH ATRX AND CDKN2A/B ALTERNATIONS WHO WAS INITIALLY DIAGNOSED AS GLIOBLASTOMA AND HAS 20 YEARS SURVIVAL

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Pediatric high-grade gliomas are rare and often hard to classify, which grow locally and show longer survival than diffuse high-grade gliomas in adults. We report a case of circumscribed high-grade astrocytoma who was initially diagnosed as glioblastoma and has 20 years survival. A 7-year-old girl suffered from epileptic seizure due to a left occipital lobe tumor. The tumor was resected in another hospital and diagnosed as glioblastoma. The tumor disappeared after extended local irradiation and chemotherapy using nimustine hydrochloride (ACNU) and cisplatin (CDDP). Eighteen years after initial onset, first recurrence was confirmed as the intra-tumoral hemorrhage. The tumor was resected and diagnosed as anaplastic oligoastrocytoma. After 6 courses of temozolomide (TMZ), the tumor disappeared. Twenty years after initial onset, the second local recurrence was confirmed. Although gamma knife and TMZ was performed, the tumor did not disappear. The tumor was surgically resected. Histopathology showed localized growth with some infiltration and mitosis but lacked pseudopallisading and microvascular proliferation. The tumor was diagnosed as circumscribed high-grade astrocytoma. Immunostaining revealed ATRX nuclear loss and CDKN2A / B homozygous deletion. After 10 courses of TMZ, the third local recurrence was confirmed. The tumor was completely removed and has not occurred recurrence more than 3 months after the last operation. Circumscribed high-grade glioma is expected to survive longer than invasive glioma. Pediatric gliomas should differ from adult gliomas in the genes of tumorigenesis. Care should be taken for its diagnosis and treatments. We also need a new classification based on histology and gene profile. HGG-30, ANALYSIS OF PEDIATRIC GLIOMAS IN OUR INSTITUTE *Kaoru Tamura*, Mai Fujioka, Masae Kuroha, Motoki Inaji, Yoji Tanaka, Tadashi Nariai, and Taketoshi Maehara; Tokyo Medical and Dental University, Tokyo, Japan. PURPOSE: Recent advances in genetic interrogation of pediatric glioma increase the importance of molecular diagnosis using surgical specimen. However, surgical resection may be avoided to preserve quality of life, especially in brain stem glioma cases. We retrospectively examined diagnosis and treatment of pediatric gliomas in our hospital. METHODS: This study includes 14 consecutive glioma patients under the age of 18 who underwent initial treatment at our hospital from 2000 to 2019. Histopathological diagnosis, clinical course and molecular status such as IDH, H3F3A and BRAF were analyzed. RESULTS: 5 patients (1 pilocytic astrocytoma (PA), 3 diffuse astrocytomas, 1 oligodendroglioma were treated only by surgical resection (group A). 7 patients (1 PA, 1 anaplastic oligodendroglioma, 2 diffuse midline gliomas and 3 glioblastomas (GBM)) received radiation and/or chemotherapy after surgical resection (group B). 2 diffuse intrinsic pontine gliomas (DIPG) received radiation and chemotherapy without surgical resection (Group C). No IDH mutation was observed in all pathological specimen obtained cases. BRAF alteration was observed in all PA cases. 1 case of GBM had *BRAF V600E*mutation and the other had H3K27M mutation. During a median of 7.7 years of follow-up, group A patients have no recurrence. Group B includes various diagnosis and prognosis. 2 group C patients diagnosed DIPG by MRI showed different clinical courses. CONCLUSION: Pediatric gliomas include diverse biological subgroups and show broad range of clinical behavior. Since pediatric glioma has a low incidence and a wide variety of genetic mutations, multicenter study is important to improve the treatment of pediatric glioma.

HGG-31. UNIQUE BIOLOGICAL CHARACTERISTICS OF RADIATION-INDUCED GLIOMAS

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Radiation-induced gliomas (RIGs) are the most common secondary solid tumours with very unfavourable prognosis. We aimed to describe different clinical and molecular biological characteristic of RIGs from primary gliomas. We reviewed clinical data of ten patients with RIGs. In patients with available samples, we used the whole genome methylation array and performed targeted sequencing for specific mutations. Between 2000–2018, we diagnosed RIG in 10 patients (M/F 2/8) aged 5–12 years at primary diagnosis of different solid tumours and acute leukaemia. These patients developed RIG with a median 9.5 years (ranging 3–31) after primary diagnosis. Eight patients died within 1 year after diagnosis of RIG and 2 patients are still alive more than 4 years from this diagnosis. According to Heidelberg DNA methylation-based classification, most RIGs belong to the IDH-wild type glioblastoma subclass midline which biologically corresponds to diffuse midline glioma (DMG). However, compared to primary DMGs they do not carry the characteristic H3K27M mutation. One patient developed anaplastic ganglioglioma with BRAF-V600E mutation and methylation profile identical to pleomorphic xanthoastrocytoma (alive for 4 years after diagnosis of RIG). In half of the patients from the group DMGs IDH wild type, examined by methylation array, PDGFRA amplification was found. Our data shows that most RIGs are midline IDH-wild type glioblastomas with poor prognosis that are biologically different from primary DMGs. PDGFRA amplifications are potentially targetable by kinase inhibitors in order to order to prognosis of these patients.

HGG-32. UNCOVERING THERAPEUTIC VULNERABILITIES IN MISMATCH REPAIR-DEFICIENT GLIOMAS

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INTRODUCTION: We have observed that approximately 26% of recurrent gliomas acquire hypermutation following treatment with temozolomide (TMZ). Intriguingly, 91% of these tumors harbor mutations in mismatch repair (MMR) genes. Strategies to target MMR-deficient gliomas thus stand to impact a large number of patients. METHODS: We ablated the MMR genes *MSH2, MSH6, MLH1, and PMS2* using an all-in-one sgRNA-CRISPR/Cas9 expression vector to generate panels of isogenic MMR knockouts in patient-derived glioma cell lines. We have characterized the phenotype of these MMR-deficient glioma cells, and leveraged high-throughput drug screens to identify therapeutic vulnerabilities induced by loss of MMR. RESULTS: We demonstrate that sgRNA-CRISPR/Cas9 targeting of either *MSH2* or *MLH1* – the two obligatory components of the MutSα and MutLα complexes, respectively – also results in loss of protein expression of their respective binding partner MSH6 or PMS2. Moreover, we show that loss of each MMR component confers resistance to TMZ while maintaining sensitivity to the alkylating nitrosourea CCNU. Furthermore, we show that long-term TMZ treatment of *MSH2* and *MSH6* knockouts in an *MGMT*-methylated line induces hypermutation with enrichment of C > T mutations but not in MMR wild-type controls. Lastly, loss of MSH2 or MLH1 confers differential dependencies to small molecule inhibitors. CONCLUSIONS: CRISPR/Cas9 knockout of individual MMR pathway members allows us to systematically study the response of MMR-deficient cells to alkylating agents in an isogenic context. MMR deficiencies in glioma confer dependencies to small molecule treatment, which may inform future therapies for MMR-deficient tumors.

HGG-34. DETECTION OF ONCOGENIC FUSION EVENTS IN SUPRATENTORIAL GLIOBLASTOMAS OF YOUNG CHILDREN

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INTRODUCTION: Glioblastoma in infancy and early childhood is characterized by a more favorable outcome compared to older children, a stable genome, and the occurrence of tyrosine kinase gene fusions that may represent therapeutic targets. METHODS: 50 glioblastomas (GBM) with supratentorial location occurring in children younger than four years were

retrieved from the archives of the Brain Tumor Reference Center, Institute of Neuropathology, University of Bonn. DNA and RNA were extracted from FFPE tumor samples. Gene fusions were identified by FISH using break-apart probes for *ALK, NTRK1, -2, -3, ROS1* and *MET*, Molecular Inversion Probe (MIP) methodology, and targeted RNA sequencing. RESULTS: 37 supratentorial GBM occurred in the first year of life, 13 GBM between one and four years. 18 cases showed fusions of *ALK* to different fusion partners; all occurred in the first year of life (18/37 cases, 48.6%). Fusions of *ROS1* were found in 5, *MET* in 3, *NTRK1*, -2, -3 in 10 cases. 12 cases showed no and two novel fusions. The different methods led to comparable results; targeted RNA sequencing was not successful in a fraction of cases. Break-apart FISH led to reliable results on the next day, MIP technology represented the most sensitive method for analysis of FFPE samples. CONCLUSIONS: Gene fusions involving the tyrosine kinase genes *ALK, MET, ROS1* and *NTRK1, -2, -3* occurred in 72% of glioblastomas of children younger than four years; the most frequent were *ALK* fusions occurring in infant GBM. DNA based MIP technology represented the most robust and sensitive assay.

HGG-35. PEDIATRIC PLEOMORPHIC XANTHOASTROCYTOMA WITH ANAPLASIA TREATED WITH SURGERY AND ADJUVANT CHEMOTHERAPY: A CASE SERIES OF 3 LONG-TERM SURVIVORS

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OBJECTIVE: Pleomorphic xanthoastrocytoma (PXA) with anaplasia is a rare histological subtype of central nervous system astrocytoma and generally treated as high grade gliomas. The optimal extent of therapy required is unknown. Here we report on 3 pediatric cases of PXA with anaplasia. We also describe molecular features and methylation profile of PXA with anaplasia compared to age-matched PXA without anaplasia. METHODS: Our institutional database was queried for cases of PXA since 1998 and 3 cases with anaplasia were identified and records reviewed. RESULTS: 2/3 patients were male and all were aged 12 at diagnosis. All underwent a gross total resection (GTR), where the diagnosis of PXA with anaplasia was made. Immunohistochemistry demonstrated that two cases were BRAF V600E positive and two were CD34 positive. Methylation profiling revealed unique pattern of CpG methylation/unmethylation. All patients underwent 5400cGy radiation to the surgical bed. 2/3 patients received concurrent temozolamide with radiation followed by maintenance chemotherapy with temozolamide and lomustine for 6 cycles as per the Children's Oncology Group Protocol ACNS0423. These two patients had a continued complete response. The third patient received temozolamide following radiation and subsequently had recurrent disease at the end of treatment and went on to have a re-resection GTR and achieved complete response after 6 cycles of lomustine, vincristine and procarbazine. All are alive with no evidence of disease at more than 2 years post treatment completion (OS=100%,EFS=67%). CONCLUSIONS: This rare pediatric tumor is not well understood. The genetic landscape may be informative for optimizing treatment and prognosis.

HGG-36. HIF-2: A NEW DRUG TARGET IN PEDIATRIC HIGH-GRADE GLIOMA WITH PROMISING PRECLINICAL RESULTS

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Pediatric high-grade gliomas (pHGGs) have a very dismal prognosis and need new innovative strategy for treatment. Despite the past discovery of histone H3 driver mutations, we are not able for instance to stop this induced epigenetic remodulation. Therefore, proactive translational studies wish to go further discovering new targetable proteins in pHGG. In our past clinical work, we were able to link significantly HIF-2alpha to a worse pHGG outcome and to their treatment resistance. We designed this new work to determine in several patient-derived cell lines (6 PDCLs) with or without H3.3 mutation the variation of HIF-2alpha, its role, its induction in normoxic and hypoxic microenvironment and its transcriptional targets using RNAseq, metabolomics and ChipSeq analyses. Complementary functional analyses were performed using siRNA strategy during cultures and migration assays. Finally, preclinical drug testing involving commercialized and non-commercialized HIF-2alpha specific inhibitors in the same PDCLs were evaluating their antiproliferative and pro-apoptotic effect. Our results confirmed the central role of HIF-2alpha in cell resistance to treatment, in pHGG stemness features and its direct link with metabolism adaptation and histone interaction. After the confirmation of its frequent presence in multiple PDCLs initiated from thalamic pHGGs and DIPG, we were using inhibitors in a single and combinatorial strategy targeting HIF-2alpha plus another hypoxia biomarker (mTor). This preclinical targeting was highly effective to favor cell arrest, apoptosis and to stop cell migration. In conclusion, HIF-2alpha seem to be a major biomarker in pHGGs that might be targeted giving a useful new opportunity for pHGG treatments.

HGG-37. PAEDIATRIC GLIOBLASTOMA CELLS SHOW CRITICAL DEPENDENCIES ON EPIGENOMIC AND EPITRANSCRIPTOMIC CONTROL OF GENE EXPRESSION BY H3.3G34R/V MUTATIONS

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H3.3G34R/V mutations are restricted to glioblastomas of the cerebral hemispheres, and occur predominantly in adolescents and young adults. We had previously shown these mutations to result in a global re-organisation of the activating mark H3K36me3 to drive transcription of key developmental transcription factors and oncogenes such as MYCN, however the precise mechanism was unclear. Using multiple H3G34R/V samples and ChIP-seq with antibodies specific to both wild-type and mutant histone H3.3, we show a high degree of incorporation of mutant histone into nucleosomes, with only a minority (<15%) remaining wild-type only. Heterogenous G34-mutant nucleosomes displayed significantly elevated H3K36me3 binding, the majority apparently in *trans* to the mutation on the wild-type H3.3, and expression signatures associated with chromatin modification, cell cycle progression, DNA repair and gene transcription. Super-enhancer analysis by H3K27ac ChIP-Seq highlighted lineage-dependent transcription factors and previously identified targets MYCN and NOTCH1 (both stabilised by FBXW7, down-regulated by loss of chromosome 4q), as well as specific H3K36 lysine demethylases and splicing factors. Whole-genome CRISPR-Cas9 screening of patient-derived H3.3G34R/V cells identified critical dependencies on these latter targets, in addition to a general essentiality for genes involved in RNA processing. Assessment of RNA methylation by MeRIP-seq revealed a strong concordance of m6A-modified RNA and H3K36me3 binding, with differentially modified transcripts in mutant cellsassociated with the 3'-UTR but also the promoter and gene bodies. These data highlight the critical nature of the epitranscriptome in H3.3G34R/V-mutant paediatric glioblastoma, and highlight novel targets for therapeutic intervention.

HGG-38. A COMPARATIVE PROTEOMIC-ANALYSIS OF THE CELL MEMBRANE FRACTIONS OF HISTONE 3 MUTATED BRAIN TUMOURS TO IDENTIFY NOVEL THERAPEUTICS

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Improvements in the treatments for childhood and adolescent brain tumours, High-Grade Glioma (pHGG) and Diffuse Intrinsic Pontine Glioblastoma (DIPG), have not advanced much and they continue to carry a very poor prognosis. These brain tumours are now defined by mutations affecting histone 3 proteins, indeed 80% of DIPGs harbour histone H3.1 and H3.3 K27M somatic mutations whilst 30% of pHGGs exhibit H3.3 G34R or G34V mutations. We hypothesized that the histone 3 mutant tumours will have distinct mutation specific surfactome. We therefore analysed the cell surface proteomics of pHGG and DIPG, in order to identify novel targets for therapy. We have at first isolated the cell membrane fractions from a range of patient cells carrying different histone 3 mutations (G34R, G34V, K27M), relative to wild type histone 3. A comparative quantitative mass-spectrometry analyses of these cell surface membrane fractions is then performed to identify specific targetable factors, which can be then be used for tumour specific precision-therapy. Results of these experiments will be presented.

HGG-39. CLINICAL CHARACTERISTICS AND OUTCOME OF PATIENTS WITH RADIATION-INDUCED GLIOMA

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The development of gliomas subsequent to therapeutic cranial irradiation is a rare but serious complication. The purpose of this study is to understand the clinical characteristics and outcome of patients with radiation-induced glioma (RIG). Between 2001 and 2018, we identified 10 patients with RIG, which satisfied the Cahan's criteria in our data base. There was no sex predominance (M: 5, F: 5), and the median age of the primary diseased was 13.5 years (range: 1–39). The primary diseases included 2 germinoma, 2 acute lymphoblastic lymphoma, 2 medulloblastoma, 1 diffuse astrocytoma, 1 pilocytic astrocytoma, 1 pituitary adenoma and 1 metastatic tumor from

lung cancer. All the patients received cranial radiation (range: 12–60 Gy). The median latency time between primary disease and RIG was 16 years (range: 9–30 years), which was not correlated with age at the time of primary disease (r^2= 0.014, p=0.74). Radiation-induced gliomas included 8 glioblastoma and 2 grade III glioma based on histological diagnosis. After surgical removal or biopsy of the RIG, 4 patients underwent chemotherapy alone (nimustine, temozolomide (TMZ), carboplatin and etoposide), and 6 received chemotherapy (nimustine, TMZ, bevacizumab) combined with radiotherapy (range: 40-66Gy). The median progression free survival and survival time from RIG were 10.1 and 27.5 months, respectively. In summary, RIG may occur many years after successful initial treatment using radiotherapy, and the outcome of our patients with RIG supports the use of radiotherapy and/or chemotherapy after surgical resection.

HGG-40. EXCEPTIONAL SYNCHRONOUS OCCURENCE OF A BRAF V600E MUTANT GLIOBLASTOMA AND A H3.3K27M MUTANT DIFFUSE INTRINSIC PONTINE GLIOMA: A CASE REPORT

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We report herein the case of a 17-year-old female who presented with intracranial hypertension and diplopia. Magnetic resonance imaging showed a large left cystic and solid temporoparietal lesion, associated with an infiltrating lesion of the brainstem, hypointense in T1 and hyperintense in FLAIR sequences, without enhancement after injection of gadolinium. Complete resection of the parietal mass and biopsy of the brainstem lesion were performed. Histopathological analysis of the parietal mass showed glioblastoma (WHO grade IV) with no IDH1/2 or H3.3/H3.1 gene mutation detected by Sanger sequencing. Immunohistochemistry found the expression of the proteins of mismatch repair system. Whole exome and RNA sequencing identified a BRAF-V600E mutation. The brainstem lesion was a diffuse midline glioma, H3K27M-mutant (grade IV) according to the 2016 WHO classification. Pan-genomic SNP arrays of the 2 tumors showed distinct genetic alterations. The parietal glioblastoma displayed complex genomic alterations whereas the brainstem glioma harbored chromosome 7q gain, chromosome 9p and 10 losses, and RB, TP53 and CDKN2A homozygous deletions. The patient was treated by concomitant radiochemotherapy (according to Stupp protocol). After 12 cycles of temozolomide, there was complete remission persistant in the parietal lobe. The brainstem tumor was stable but progressed after 3 months of temozolomide discontinuation. Treatment with mTOR inhibitors was initiated. At 21-month follow-up, the patient remains with few symptoms. No predisposition syndrome was identified in the patient or her family. Concurrent glioblastomas with distinct driver gene mutations are exceptional.

HGG-41. STRUCTURAL VARIANT DRIVERS IN PEDIATRIC HIGH-GRADE GLIOMA

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BACKGROUND: Driver single nucleotide variants (SNV) and somatic copy number aberrations (SCNA) of pediatric high-grade glioma (pHGGs), including Diffuse Midline Gliomas (DMGs) are characterized. However, structural variants (SVs) in pHGGs and the mechanisms through which they contribute to glioma formation have not been systematically analyzed genome-wide. METHODS: Using SvABA for SVs as well as the latest pipelines for SCNAs and SNVs we analyzed whole-genome sequencing from 174 patients. This includes 60 previously unpublished samples, 43 of which are DMGs. Signature analysis allowed us to define pHGG groups with shared SV characteristics. Significantly recurring SV breakpoints and juxtapositions were identified with algorithms we recently developed and the findings were correlated with RNAseq and H3K27ac ChIPseq. RESULTS: The SV characteristics in pHGG showed three groups defined by either complex, intermediate or simple signature activities. These associated with distinct combinations of known driver oncogenes. Our statistical analysis revealed recurring SVs in the topologically associating domains of MYCN, MYC, EGFR, PDGFRA & MET. These correlated with increased mRNA expression and amplification of H3K27ac peaks. Complex recurring amplifications showed characteristics of extrachromosomal amplicons and were enriched in coding SVs splitting protein regulatory from effector domains. Integrative analysis of all SCNAs, SNVs & SVs revealed patterns of characteristic combinations between potential drivers and signatures. This included two distinct groups of H3K27M DMGs with either complex or simple signatures and different combinations of associated variants. CONCLUSION: Recurrent SVs associate with signatures shaped by an underlying process, which can lead to distinct mechanisms to activate the same oncogene.

HGG-42. CLINICAL FEATURES AND TREATMENT OUTCOME OF MALIGNANT GLIOMAS IN CHILDREN AND ADOLESCENTS

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INTRODUCTION: Malignant gliomas in children and adolescents are rare. They are difficult to treat and are associated with an extremely poor prognosis. SUBJECTS AND METHODS: The treatment and outcomes of WHO grade IV -gliomas and diffuse intrinsic pontine gliomas (DIPG) in children and adolescents (Age 4–39, median 28) treated at our institute since 2001 were retrospectively reviewed. Thirty-five cases were included in this study. Nine cases were located in their brain stem and 2 of them were diagnosed as DIPG clinically without biopsy. Three (brain stem -2, thalamus-1) cases were diffuse midline glioma H3 K27 M mutant. Remaining 30 cases were diagnosed histologically as glioblastoma. Expect for 2 cases, all were irradiated. Twenty-four cases were treated with temozolomide (TMZ). Bevacizumab (BEV) was administrated as an initial therapy in 10 cases (concomitant with TMZ in 9 cases) and was administrated at the time of relapse in 9 cases. In summary, 19 cases were treated with BEV. RESULTS: Median survival time (MST) of all cases was 16.8 (4.4 -152.3) months. In total, BEV did not prolonged overall survival (OS), MST 16.02 vs 14.44, (p=0.498). Among adolescents (age 15–39), patients treated with BEV had a trend of longer OS but did not reached statistical significance, MST 19.64 vs 10.76 (p=0.167). An extent of resection and KPS =>70 at discharge from hospital were beneficial factors associated with prolonged OS. CONCLUSION: As well as in elderly cases, multidisciplinary treatment including resection, radiation and chemotherapy including BEV improves outcomes.

HGG-43. CONGENITAL GLIOBLASTOMA MULTIFORME: A CASE REPORT OF A RARE PEDIATRIC BRAIN TUMOR, MOLECULAR ANALYSIS, AND REVIEW OF THE LITERATURE

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Congenital brain tumors are rare, accounting for less than 4% of all pediatric brain tumors. Congenital glioblastoma multiforme (GBM) is rarer still, accounting for 3–15% of congenital brain tumors. There is literature to suggest that these tumors differ from pediatric and adult GBM clinically and molecularly, and as such should be treated as their own distinct entity. Our case is a 4 week old male who initially presented to his pediatrician for enlarging head circumference and upward gaze palsy. An MRI was obtained revealing a right parietal mass. He underwent gross total resection the following day with pathology revealing glioblastoma, WHO grade IV. Further analysis revealed ATRX retained, p53 immunoreactivity in 15–20% of nuclei, IDH1 and IDH2 wildtype, MGMT promoter not methylated, H3K27M wildtype, no 1p and/or 19q deletion/codeletion. Interestingly, RNA analysis of his tumor detected the PPP1CB-ALK fusion transcript as well as amplification of the ALK gene. Co-occurrence of these mutations has been reported in a small number of pediatric glioblastoma patients and PPP1CB-ALK fusions are one of the most common receptor tyrosine kinase fusions in infantile gliomas. ALK rearrangements and amplifications suggest a potential therapeutic target with tyrosine kinase inhibitors in glioblastoma. This patient serves as an example of a rare congenital glioblastoma with unique molecular features that may suggest novel treatment opportunities. We present his clinical course along with a pertinent review of the literature.

HGG-44. DEFECTS OF MISMATCH REPAIR PROTEINS IN PEDIATRIC HIGH GRADE GLIOMAS

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Hetero- and homozygous germline mutations of the mismatch repair genes MLH1, PMS2, MSH2 and MSH6 cause Lynch and constitutional mismatch repair (CMMRD) cancer predisposition syndrome, respectively. Affected CMMRD individuals are at risk to develop a variety of neoplasms including CNS tumors, particularly high grade gliomas (HGG), during childhood. Currently, few data exist on the prevalence of CMMRD in children with pediatric HGG. We screened a consecutive series of 79 supratentorial HGGs. Tumor tissue was available in 42 patients, 5 were reclassified as non-HGGs. Immunohistochemistry with antibodies against MLH1, PMS2, MSH2 and MSH6 was performed in 37 tumors. Four patients (3 families) with known CMMRD were included. The evaluation of the slides was performed blinded to the CMMRD status. All four patients with known CMMRD (3 patients with PMS2, one with MSH6 mutation) were identified, showing loss of PMS2 and MSH2/MSH6, respectively. Additionally, we identified 6 patients with loss of MSH2/MSH6 staining in tumor cells, but retained staining in preexisting cells, indicating a pattern like in Lynch syndrome. NGS sequencing of these tumor tissues revealed in 2 patients *MSH2* mutations and in one patient a hypermutator phenotype with *MSH2* and *MSH6* mutations. In 3/6 patients no mutations in the MMR genes were detectable. In summary, we found a low prevalence of CMMRD among HGGs, but identified also 2 patients with probable Lynch syndrome. Immunhistochemistry is an effective tool to screen for patients with MMR defects and should be performed in HGGs to optimize treatment and offer affected families genetic counseling.

HGG-45. PROTEOMIC ANALYSIS OF PEDIATRIC DIFFUSE ASTROCYTOMAS YIELDS PATHWAYS ASSOCIATED WITH BOTH PROGRESSION-FREE AND OVERALL SURVIVAL

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Brain tumors are now responsible for more deaths each year than any other childhood cancer. Current studies aim to discover key molecular drivers that can explain prognosis and serve as targets for new therapeutic approaches, reducing morbidity. In this study, we performed LC-MS/MS proteomics on a cohort of 28 primary diffuse astrocytoma formalin-fixed paraffin embedded samples (WHO Grades II-IV) from patients at Nationwide Children's Hospital with a median follow-up time of 2.3 (0.6–20.2) years. Ingenuity Pathway Analysis was used to analyze the proteomic data after using both age and grade as covariates and only including proteins with p-values less than 0.05. The upregulation of a well-known oncogenic pathway, the Protein Kinase A signaling pathway, was significantly associated with greater risk of progression and death (P=5.5E-07 and P=4.6E-04). Integrin signaling, a pathway commonly suppressed in cancer, was similarly downregulated in those with greater risk of progression and death (P=3.3E-04 and P=1.7E-07). A global upstream analysis of the proteomic data also predicted activation of the oncogene MYCN in those who performed poorly, supporting previous studies. When comparing grade II (n=10) to grade III (n=8) and IV (n=10) primary tumors, the pathway most upregulated in higher histopathological grades was EIF2 Signaling (P=4.9E-49). This pathway has previously been associated with resistance in adult glioblastoma. These pathways, and the proteins detected within, may provide novel means by which to better understand and treat pediatric diffuse gliomas. Ongoing studies are in progress to understand how these pathways drive aggressiveness and differ from adult astrocytomas.

HGG-47. DECREASED GROWTH VELOCITY WITH LONG TERM USE OF BRAFV600E AND MEK INHIBITION IN A PATIENT WITH ANAPLASTIC GANGLIOGLIOMA

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PURPOSE: To describe decreased growth velocity with long term use of BRAFV600e and MEK inhibition in a patient with anaplastic ganglioglioma. RESULTS: 4-year-old patient was found to have a 6 x 4.6 x 5 cm mass in the hypothalamus. Pathology consistent with anaplastic ganglioglioma and chromosomal microarray revealed a BRAFV600e mutation. Patient started on dabrafenib and trametinib and tumor decreased 85% after 3 months. She is stable without significant toxicities 39 months on therapy, and is now 8 years old. Patient had been growing at the 25% for weight and 12% for height but is now 65% for weight and 0.5% for height. It is difficult to tease out the relationship between the tumor, the location of the tumor, and the BRAF and MEK inhibitors and their effect on growth. Discussions with the family and endocrinology are ongoing but being <1% for height will lead to decrease in quality of life. CONCLUSIONS: Further follow-up study is needed to determine if this is truly a long-term toxicity, or if this may just be a direct result of the location of the tumor. Would supplementation with growth hormone in this patient lead to losing control of a high grade tumor, or would it simply replace a hormone that is not produced?

HGG-48. ROS1 INHIBITOR ENTRECTINIB USE IN RELAPSE/ REFRACTORY INFANTILE GLIOBLASTOMA WITH POSITIVE ROS1 FUSION - A CASE REPORT WITH PROMISING RESPONSE

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INTRODUCTION: Infantile glioblastoma is rare with poor prognosis. Recent molecular study for infantile hemispheric high grade glioma found its association with ALK/ROS1/NTRK/MET pathway. This suggested the potential use of targeted therapy for refractory / relapse patients. CASE: A newborn presented with apnea, CT brain showed intracranial haemorrhage. MRI then showed a left parietal tumour with bleeding and mass effect. Craniotomy achieved subtotal resection. Chemotherapy VCR/CPM alternating with CDDP/VP-16 was given for one year. Patient was stable with static residual tumour during chemotherapy. However patient developed status epilepticus two weeks after off treatment. MRI showed significant tumour progression which required 2nd & 3rd debulking surgery. Molecular assay by nanostring panel showed BRAF-KIAA1549 fusion. MEK inhibitor Trametinib was tried for 3 months and stopped as disease progression. Further molecular assay by RNASeq showed presence of ROS1 fusion (ZCCHC8-ROS1) while absent of BRAF fusion. Patient underwent 4th debulking surgery as impending herniation while waiting for the targeted therapy. It was complicated with right hemiplegia and facial nerve palsy postoperatively. Finally, ROS1 inhibitor Entrectinib was started 2 weeks later. It was well tolerated without significant adverse reaction. Patient made dramatic neurological recovery including improved facial nerve palsy, able to walk unaided and self feed. MRI brain 1 and 3 months after Entrectinib showed interval reduction in residual tumour. Patient is currently progression-free for 6 months. CONCLUSION: Early molecular study for infantile glioblastoma is useful to guide novel therapy. Molecular result may varies between different panels or change over time, to be interpreted with caution.

HGG-49. A PEDIATRIC THALAMIC HIGH-GRADE GLIOMA WITH *H3F3A* K27M AND *BRAF* V600E DOUBLE MUTATIONS

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CASE: A 18-month-old boy presented with approximately 2 months history of progressive left hemiparesis and left exotropia. MRI study showed a 3–4 cm T1-iso, T2-high tumor at right thalamus to midbrain with little contrast enhancement. The patient underwent endoscopic biopsy of the tumor, which showed relatively dense proliferation of small cells with round nuclei, mitosis of the tumor cell, but no necrosis. Immunohistochemical showed positive stain of GFAP and Olig2. Ki-67 was 34%. The histopathological diagnosis was compatible with high grade glioma. Chemotherapy with vincristine, cyclophosphamide, cisplatin and etoposide was initiated. Molecular testing of the tumor revealed *H3F3A* K27M and *BRAF* V600E double mutations in DNA from frozen tumor tissue. DISCUSSION: The concurrent mutation of *H3F3A* K27M and *BRAF* V600E in pediatric glioma is very rare, but there are several cases previously reported in literature. Interestingly those cases are heterogenous in age, location, histopathological subtypes and clinical outcome.

HGG-50. TWO CASES OF H3 K27M-MUTANT DIFFUSE MIDLINE GLIOMA OF CERVICAL SPINAL CORD

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BACKGROUND: "Diffuse midline glioma, H3 K27M-mutant' was newly categorized as a separate pathological entity in the 2016 WHO classification, based on recently discovered mutation. Spinal cord glioma with H3 K27M-mutant is rare, so we reported the clinical course of two cases. CASE 1: A 17-year-old male presented with posterior headache and right limbs paralysis. MRI showed cervical spinal cord with expansion, T2-weighted high intensity and a part of enhancement. The biopsy revealed a diffuse midline glioma, H3 K27M-mutant. He received bevacizumab plus radiotherapy-temozolomide. In a few months, he had quadriplegia and cranial nerve paralysis and needed respirator. There was not expansion of mass, but intracranial dissemination. CASE 2: A 16-year-old male presented with posterior neck pain and right limbs paralysis. On brain stem and cervical spine, MRI findings were same to case 1. The biopsy was undergone and revealed H3 K27M mutation. He received bevacizumab in addition to radiotherapy-temozolomide. Although he also had quadriplegia, the progression of tumor has stopped. He has received chemotherapy with respirator at home. DISCUSSION: It was previously reported that the prognostic factors for diffuse midline glioma were tumor location, H3 K27M-mutation and age, but there are few relevant studies. The consensus on the treatment is also not clearly determined. Because the cervical spinal cord gliomas are rapidly advanced miserably, we added bevacizumab to standard radiotherapy-temozolomide for initial treatment. In addition, whole brain and spine radiation may be considered to avoid dissemination. Multicenter study is important to collect information and improve treatment of H3 K27M-mutant glioma.

HGG-51. PAIRED EPITHELIOID GLIOBLASTOMA PATIENT DERIVED XENOGRAFT MODELS WITH/WITHOUT MOLECULAR TARGET THERAPY

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Epithelioid glioblastoma (E-GBM) predominantly arises at younger age and promotes dismal prognosis. Because of its rare etiology, pathological and genetical characterization of E-GBM remains elusive. Herein, we report 2 patient-derived E-GBM xenograft (PDX) models from young adult patients (YMG62 and YMG89) with *BRAFV600E* and *TERT* promoter mutation. The YMG62 patient received dabrafenib with trametinib, while YMG89 patient received dabrafenib monotherapy after recurrence with Stupp regimen. These molecular target therapies were initially responded, but gradually became resistant (YMG62R and YMG89R) and resulted in lethal. Treatment resistant cells were collected from CSF. These primary cells were propagated at multiple passage *in vitro*. Paired PDX models were established from initial and recurrent cells. All PDX tumors were preferentially disseminated and negative expression of GFAP, which were recapitulated to the patient characteristics. BRAF and MEK inhibitor moderately suppressed cell viability of YMG62 and YMG89 *in vitro*. However, BRAF and MEK inhibitor became resistant at recurrence *in vitro*. Western blotting indicated retained phospho-MEK expression after BRAF/MEK inhibitor treatment in recurrent cells, which implies crucial role of MEK activation for tumor maintenance in *BRAFV600E* mutant E-GBM. Together, paired E-GBM PDX models with/without molecular target therapy recapitulate patient characteristics, which may contribute to elucidate tumor biology and establish novel therapeutic target in E-GBM.

HGG-52. SUSTAINED RESPONSE TO CRIZOTINIB MONOTHERAPY IN AN INFANT WITH GOPC-ROS1 FUSED CONGENITAL HEMISPHERIC GLIOMA

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Recent studies identified the presence of *ALK/ROS/NTRK/MET* alterations in a subset of infantile hemispheric gliomas. We report a case of GOPC-ROS1 fused congenital hemispheric glioma with a sustained response to crizotinib. An infant born at 28 weeks gestation was diagnosed with a large hemispheric mass at 2 weeks of life. The tumor was partially resected at 7 weeks of life. Histological evaluation confirmed a neoplasm with a spindle cell growth pattern, hypercellularity, nuclear pleomorphism, endothelial proliferation and necrosis consistent with glioblastoma. Fresh tissue was submitted for targeted panel sequencing (Oncopanel) which identified the presence of a GOPC-ROS1 fusion (exon 36:intron 4). This was confirmed by copy number analysis which showed a focal intragenic deletion with a breakpoint in ROS1 on 6q22. Given the lack of preclinical native models for ROS1 and other congenital kinase-driven gliomas, live cells were utilized to attempt to establish a patient derived cell line (organoid/neurosphere model) and intracranial patient derived xenograft model, the results of which are pending and will be reported. The GOPC-ROS1 rearrangement was structurally predicted to respond to kinase inhibitors with activity against ROS1 and crizotinib was started at 280 mg/m2/dose twice daily at 6 months of life with progressive tumor noted on imaging. Three months after initiating therapy, a 56% reduction in the tumor size and subsequent imaging revealed additional response. Our report is the first to demonstrate clinical response to crizotinib in a GPOC-ROS1 fused congenital glioblastoma and describe the development of a renewable resources for future analysis.

HGG-53. PROJECT HOPE: "PEDIATRIC AND AYA HIGH-GRADE GLIOMA OMICS PROJECT"- A LONGITUDINAL MOLECULAR LANDSCAPE OF HIGH-GRADE GLIOMAS RESOLVED AT SINGLE-CELL LEVEL

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High-grade gliomas (HGG) are among the most prevalent and fatal cancers in pediatric, adolescent, and young adult (AYA) patients. Especially understudied are older children and young adults, aged 16–39 years. Previously, we profiled primary pediatric HGGs through single-cell transcriptomics and identified the genetic, epigenetic and developmental programs that drive their malignant progression. However, the questions of how these programs compare to those in older HGG patients, what the mechanisms are by which these tumors ultimately evolve to drive recurrence and treatment resistance, and how distinct tumor cell subpopulations bidirectionally communicate with their microenvironment remain to be elucidated. Here, we use single-nucleus RNA sequencing to compare 11 paired, matched high-grade gliomas at diagnosis and recurrence and 15 additional H3K27M primary and recurrent DMG samples in pediatric and AYA patients. In all tumors, we find both undifferentiated and differentiated tumor cells recapitulating distinct glial lineages, as well as diverse microenvironmental cell populations. When longitudinally comparing this tumor architecture within matched pairs, we find substantial differences in transcriptional program expressions. Diagnostic samples include more differentiated, astrocyte-like tumor cells, while cells from recurrent samples more highly express ribosomal and heat-shock protein genes, suggesting tumor progression- and treatment-related shifts. Ongoing sequencing and analysis will allow for unprecedented insight into the evolutionary dynamics of pediatric and AYA high-grade gliomas as well as delineate differences in the biology of DMGs occurring in different age groups. This multi-institutional project was funded by the National Institute of Health.

HGG-54. HISTOLOGICAL AND MOLECULAR CHARACTERIZATION OF HIGH-GRADE BRAIN TUMORS SECONDARY TO TOTAL BODY IRRADIATION FOR HEMATOLOGICAL MALIGNANCIES

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INTRODUCTION: Hematopoietic stem cell transplantation (HSCT) is increasingly used in the treatment of acute leukemias (AL), non-Hodgkin lymphomas and other primary malignancies. However, a growing number of neoplasms secondary to HSCT are reported. The combination of total body irradiation (TBI) and high dose chemotherapy (HD-CT) as conditioning regimen is considered a risk factor. We present four children who survived AL, treated with HSCT and conditioning regimens including TBI/HD-CT. These patients developed a high-grade-brain tumor. We analyzed histological and molecular characteristics of neoplasms. METHODS: Histologically, tumors were assessed for: presence of mitosis, necrosis and vascular proliferation; expression of ki67; expression of neuronal and glial markers, p53 and therapeutic targets. We analyzed the DNA methylation profile (DMP)

of all tumors using IlluminaEPICarrays and compared it to the brain tumor classifier which allowed to generate the CNVs. RESULTS: Morphologically two cases were defined as anaplastic astrocytoma, two cases as glioblastoma. Based on the DMP, all cases were found to belong to the methylation class "glioblastoma, IDH wildtype, subclass midline", hypermutants, with gain of chromosome 1q and loss of 1p. Two cases showed PDGFRA amplification. All patients were treated with Temozolomide combination therapy +/- Bevacizumab and radiation therapy. At progression three patients were treated with checkpoint inhibitors. CONCLUSIONS: The improvement of the precision medicine is fundamental in the therapeutic decision of brain tumors and even more in neoplasms secondary to antiblastic treatments. DMP and CNV have proven to be useful tools to complement the histological characterization of the reported cases.

HGG-56. EXTENSIVE MOLECULAR HETEROGENEITY WITHIN H3-/IDH-WILDTYPE PEDIATRIC GLIOBLASTOMA

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About half of all pediatric high-grade gliomas (HGG) harbor mutations in histone 3 or IDH genes. The remaining HGG are currently broadly classified as H3-/IDH-wild-type. Since the introduction of a uniform approach to DNA methylation-based classification of CNS tumors in 2018, DNA methylation data from over 45,000 CNS tumor samples have been generated. From this large cohort, a number of smaller yet distinct subgroups start to emerge within H3-/IDH-wild-type HGG. Three such subgroups are enriched for focal gene amplifications and have been provisionally termed pedGBM_MYCN, pedGBM_RTK1 and pedGBM_RTK2. Since a significant subset of samples in each subgroup is lacking characteristic alterations, we further investigated the molecular and transcriptional composition of H3-/IDH-wild-type HGG. We evaluated DNA methylation and copy-number profiles in >1000 tumors classified as H3-/IDH-wild-type HGG. Tumors classified pedGBM_MYCN showed a focal *MYCN* amplification in 25%, with a similar fraction showing amplification of *EGFR* (8% of samples harbored both alterations) compared to 4% and 4% in pedGBM_RTK1 and 14% and 22% in pedGBM_RTK2. Deletion of *CDKN2A/B* was much more prevalent in the pedGBM_RTK2 subgroup (~50% compared to 27% in pedGBM_RTK1 and <10% in the pedGBM_MYCN group). We defined a pedGBM_MYCN transcriptional signature, which will be helpful in identifying subgroup-defining mechanisms and alterations. Initial results suggest an involvement of the sonic hedgehog pathway and genes controlling stem-cell pluripotency. Patient-derived xenograft models and murine neural stem cells are now being used for functional characterization and pre-clinical testing of potential drug targets in these molecularly defined subgroups.

HGG-57. WHOLE-GENOME SEQUENCING, METHYLATION ANALYSIS, AND SINGLE-CELL RNA-SEQ DEFINE UNIQUE CHARACTERISTICS OF PEDIATRIC TREATMENT-INDUCED HIGH-GRADE GLIOMA AND SUGGEST ONCOGENIC MECHANISMS

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BACKGROUND: Pediatric treatment-induced high-grade glioma (TIHGG) is among the most severe late effects observed in childhood cancer survivors and is uniformly fatal. We previously showed that TIHGG are divergent from de novo pediatric high-grade glioma (pHGG) and cluster into two gene expression subgroups, one stemlike and the other inflammatory. Here we systematically compared TIHGG molecular profiles to pHGG and evaluated expression and single cell sequencing profiles in order to identify oncogenic mechanisms and the cellular basis for the observed TIHGG gene expression subgroups. MATERIALS/METHODS: 450/850K methylation and mutational signature analysis was conducted in 36 TIHGG samples. Resultant data were analyzed for the presence of chromothripsis, distinct molecular alterations, and mutational signatures in a subset of 10 samples with whole genome sequencing data. Five TIHGGs underwent single-cell RNA-Seq analysis (scRNAseq). RESULTS: 26/36 TIHGG clustered with the pedRTK1 methylation class. TIHGG were characterized by an increased frequency of chromothripsis relative to pHGG (67% vs. 31%, p=0.036). FISH and WGS revealed frequent PDGFRA amplification secondary to enrichment in ecDNA. TIHGG were enriched for COSMIC mutational signatures 5 and 19 (p=0.0003) relative to pHGG. scRNAseq data showed that TIHGG tumors are composed of stem-like, neuronal, and inflammatory cell populations which may contribute to the previously described dominant expression profiles. CONCLUSIONS: TIHGG represents a distinct molecular subtype of pHGG. Chromothripsis, leading to enriched expression of genes in extrachromosomal DNA, likely contribute to TIHGG oncogenesis. The dominant cell type (stem-like vs. inflammatory) may define the expression subgroup derived from bulk RNA-seq in heterogeneous tumors.

IMAGING

IMG-01. DWI RATIO OF HISTOLOGICAL MOLECULAR SUBTYPES OF PAEDIATRIC MEDULLOBLASTOMAS

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AIM: To evaluate if diffusion weighted imaging (DWI) ratio on MRI is able to distinguish between the histological molecular subtypes of paediatric medulloblastomas. MATERIALS AND METHODS: From 2002 to 2017, 38 cases of medulloblastoma with preoperative MRI available had histological subtyping performed with NanoString nCounter technology. The medulloblastomas were classified into 4 subtypes. There were 3 Sonic Hedgehog (SHH), 9 Wingless (WNT), 12 Group 3 and 14 Group 4 subtypes. Single operator manually outlined solid non-haemorrhagic component of the tumour on DWI images with largest axial tumour cross sectional diameter, correlating with the other MRI images (T1 pre and post contrast, SWI/GRE, FLAIR) to identify areas of haemorrhage. The same operator also drew region of interest to identify normal cerebellar tissue on the same axial images on which the tumour was outlined. All MRI images were obtained from the department's Radiological Information System Picture Archiving and Communicating System (RIS PACS). DWI ratio for each case was obtained by dividing the values obtained from tumour by normal cerebellar tissue seen on the same axial image. RESULTS: DWI ratio of all medullloblastomas is 1.34 +/- 0.18. DWI ratio of SHH subtype is 1.43 +/- 0.07. DWI ratio of WNT subtype is 1.40 +/- 0.07. DWI ratio of Group 3 subtype is 1.31 +/- 0.25. DWI ratio of Group 4 subtype is 1.30 +/- 0.17. There is no significant statistical differences in the DWI ratio between the various subtypes. CONCLUSION: DWI ratio of medulloblastoma is unable to distinguish between the 4 medulloblastoma subtypes.

IMG-02. USEFUL DIAGNOSIS OF PEDIATRIC CYSTIC BRAIN TUMORS USING MULTIPLE POSITRON EMISSION TOMOGRAPHY STUDIES

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OBJECTIVE: Pediatric brain tumors are primarily diagnosed using MRI or CT examination; however, determining the correct diagnosis using only morphological MRI can sometimes be challenging. Positron emission tomography (PET) uses radiotracers for metabolic and molecular imaging. We examined the accumulation of multiple PET (FDG, MET, FLT, and FMISO) studies for diagnosing pediatric cystic brain tumors. METHODS: We performed PET scans for eight pediatric patients (five pilocytic astrocytoma, one pleomorphic xanthoastrocytoma, one diffuse astrocytoma with IDH1 mutation, one ganglioglioma) from April 2010 to December 2019. The resulting studies were compared by measuring the tumor-to-normal lesion (T/N) ratio of FDG, MET, and FLT and the tumor-to-blood value (T/B) ratio of FMISO between each pediatric cystic brain tumor. RESULTS: All pediatric brain tumors showed tumor uptake of FDG, MET, and FLT. We could not examine FMISO PET for one diffuse astrocytoma with IDH1 mutation. The T/N ratios of FDG, MET, and FLT and the T/B ratio of FMISO were 1.07, 2.76, 4.6, and 1.12 for pilocytic astrocytoma; 0.65, 4.6, 7.67, and 1.38 for pleomorphic xanthoastrocytoma; 0.61, 2.14, and 3.82 for diffuse astrocytoma with IDH1 mutation; and 0.79, 1.78, 5, and 1.49 for ganglioglioma, respectively. The T/N ratios of MET and FLT for pleo-

morphic xanthoastrocytoma were high, but the Ki-67 labeling index was 1%. In the ganglioglioma, the T/N ratio of FLT was high, but the T/N ratio of MET was low. CONCLUSION: Specialized multiple PET accumulation patterns for tumors are useful for discriminating each tumor.

IMG-03. RESPONSE ASSESSMENT IN PEDIATRIC LOW-GRADE GLIOMA: RECOMMENDATIONS FROM THE RESPONSE ASSESSMENT IN PEDIATRIC NEURO-ONCOLOGY (RAPNO) WORKING GROUP

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INTRODUCTION: Pediatric low-grade gliomas (pLGG) show clinical and biological features that are distinct from their adult counterparts. Consequently, additional considerations are needed for response assessment in children compared to the established adult Response Assessment in Neuro-Oncology (RANO) criteria. Standardized response criteria in pediatric clinical trials are lacking, complicating comparisons of responses across studies. We therefore established an international committee of the Radiologic Assessment in Pediatric Neuro-Oncology (RAPNO) working group to develop consensus recommendations for response assessment in pLGG. METHODS: The committee consisted of 25 international experts in the areas of Pediatric Neuro-Oncology, Neuroradiology and Neurosurgery. The committee first developed a set of agreed upon topics they deemed necessary to understand the controversies of imaging utilization and assessment in pLGG. These topics were divided up among the committee members who presented all available literature to the entire RAPNO committee via web teleconference. Once presented, the group discussed these data and developed consensus statements and recommendations based on available literature, committee expertise and clinical experience. Each topic was discussed until a consensus was reached. RESULTS: Final consensus included recommendations about the following topics: specific imaging sequences, advanced imaging techniques, NF1-associated pLGG, molecular and histologic classification, assessment of cysts, vision and other functional outcomes as well as overall radiologic response assessment. CONCLUSIONS: The RAPNO pLGG consensus establishes systemic recommendations that represent an initial effort to uniformly collect and assess response in pLGG. These recommendations should now be evaluated internationally and prospectively in an effort to assess clinical utility, validate and modify as appropriate.

IMG-04. RESPONSE ASSESSMENT IN PEDIATRIC HIGH-GRADE GLIOMA: RECOMMENDATIONS FROM THE RESPONSE ASSESSMENT IN PEDIATRIC NEURO-ONCOLOGY WORKING GROUP

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INTRODUCTION: Response criteria for pediatric high-grade gliomas (pHGG) have varied historically and across clinical trials. Compared to adult HGG, pHGG response assessment has unique challenges. An international Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group was established to develop pHGG response assessment criteria. METHODS: Pediatric and adult neuro-oncologists, neuro-radiologists and experts in imaging informatics developed a consensus statement and established a unified response assessment for biopsy-proven pHGG, excluding DIPG. This was achieved by identifying major challenges, reviewing existing literature and current practices, and finally developing recommendations through an iterative process. RESULTS: Categories for response assessment include complete response, partial response, minor response, stable disease and progressive disease. Refractory disease is excluded. Criteria used to determine response assessment include quantitative evaluation of measurable disease, qualitative assessment of diffusion imaging, presence or absence of new lesions, clinical status using performance score, and vascular endothelial growth factor inhibitor and/or corticosteroid use. Response is determined over 2-time points ≥ 8 weeks apart, and when progressive disease is unclear, guidance for repeat MRI imaging and/or utility of repeat biopsy is described. A number of recommendations are also given to standardize response assessment across clinical trials including MRI protocol sequence recommendations for brain and spine, definitions for measurable and non-measurable disease, and imaging time points with post-operative considerations. In addition, guidance is given for differentiating vasogenic edema versus tumor invasion in non-enhancing disease. CONCLUSION: Consensus recommendations and response definitions have been established and, similar to other RAPNO recommendations, prospective validation in clinical trials is warranted.

IMG-05. INITIAL RADIOGRAPHIC ASSESSMENT OF DWI AND ADC VALUES IN CHILDREN AND YOUNG ADULTS TREATED WITH DAY101 (TAK-580) FOR RECURRENT LOW-GRADE GLIOMAS (LGG) HARBORING MAPK ALTERATIONS

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BACKGROUND: Apparent diffusion coefficient (ADC) is a quantitative measure reflecting observed net movement of water calculated from a diffusion-weighted image (DWI), correlating with tumor cellularity. The higher cellularity of high-grade gliomas results in diffusion restriction and reduced ADC values, whereas the lower cellularity of low-grade gliomas (LGGs) gives higher ADC values. Here we examine changes in ADC values in patients with LGGs treated with the type 2 RAF inhibitor DAY101 (formerly TAK580). METHODS: Historical, baseline, and on-treatment brain MRIs for 9 patients enrolled on a phase 1 study of DAY101 in children and young adults with radiographically recurrent or progressive LGG harboring MAPK pathway alterations were obtained, de-identified and independently evaluated for ADC changes. Time points included baseline, first follow-up, and best response. Data processing of ADC estimates was performed using pmod molecular image software package. ADC changes were displayed as a histogram with mean values. Results were based upon a single read paradigm. RESULTS: There was a clear shift to lower ADC values for the solid component of tumors, reflecting changes in cellularity and tissue organization, while necrosis correlated with a shift toward higher ADC values. DWI

reveals reduced ADCs in responding tumors, with the percent change in ADC from baseline correlating with deeper RANO responses. CONCLUSION: DWI analysis reveals reductions in ADC values that correlates with treatment response and a shift toward more normal cellularity in tumors treated with DAY101. Changes in ADC may represent a novel imaging biomarker, reflecting biological response to DAY101 treatment.

IMG-06. PREDICTING SURVIVAL FROM PERFUSION AND DIFFUSION MRI BY MACHINE LEARNING

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INTRODUCTION: Magnetic Resonance Imaging (MRI) is routinely used in the assessment of children's brain tumours. Reduced diffusion and increased perfusion on MRI are commonly associated with higher grade but there is a lack of quantitative data linking these parameters to survival. Machine learning is increasingly being used to develop diagnostic tools but its use in survival analysis is rare. In this study we combine quantitative parameters from diffusion and perfusion MRI with machine learning to develop a model of survival for paediatric brain tumours. METHOD: 69 children from 4 centres (Birmingham, Liverpool, Nottingham, Newcastle) underwent MRI with diffusion and perfusion (dynamic susceptibility contrast) at diagnosis. Images were processed to form ADC, cerebral blood volume (CBV) and vessel leakage correction (K2) parameter maps. Parameter mean, standard deviation and heterogeneity measures (skewness and kurtosis) were calculated from tumour and whole brain and used in iterative Bayesian survival analysis. The features selected were used for k-means clustering and differences in survival between clusters assessed by Kaplan-Meier and Cox-regression. RESULTS: Bayesian analysis revealed the 5 top features determining survival to be tumour volume, ADC kurtosis, CBV mean, K2 mean and whole brain CBV mean. K-means clustering using these features showed two distinct clusters (high- and low-risk) which bore significantly different survival characteristics (Hazard Ratio = 5.6). DISCUSSION AND CONCLUSION: Diffusion and perfusion MRI can be used to aid the prediction of survival in children's brain tumours. Tumour perfusion played a particularly important role in predicting survival despite being less routinely measured than diffusion.

IMG-07. GADOLINIUM IS NOT NECESSARY FOR SURVEILLANCE MR IMAGING IN CHILDREN WITH CHIASMATIC-HYPOTHALAMIC LOW GRADE GLIOMA

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BACKGROUND: Patients with chiasmatic-hypothalamic low grade glioma (CHLGG) have frequent MRIs with gadolinium based contrast agents (GBCA) for disease monitoring. Cumulative gadolinium deposition in children is a potential concern. The purpose of this research is to establish whether MRI with GBCA is necessary for determining tumor progression in children with CHLGG. METHODS: Children with progressive CHLGG were identified from Texas Children's Cancer Center between 2005–2019. Pre- and post-contrast MRI sequences were separately reviewed by one neuroradiologist who was blinded to the clinical course. Three dimensional measurements and tumor characteristics were collected. Radiographic progression was defined as a 25% increase in size (product of two largest dimensions) compared to baseline or best response after initiation of therapy. RESULTS: A total of 28 patients with progressive CHLGG including 683 MRIs with GBCA (mean 24 MRIs/patient; range: 10–43 MRIs) were reviewed. No patients had a diagnosis of NF1. Progression was observed 92 times, 91 (98.9%) on noncontrast and 90 (97.8%) on contrast imaging. Sixty-seven radiographic and/or clinical progressions *necessitating management changes* were identified in all (100%) noncontrast sequences and 66 (98.5%) contrast sequences. Tumor growth >2 mm in any dimension was identified in 184/187(98.4%) on noncontrast and 181/187(96.8%) with contrast imaging. Non primary metastatic disease was seen in seven patients (25%), which were better visualized on contrast imaging in 4 (57%). CONCLUSION: MRI without GBCA effectively identifies patients with progressive disease. One should consider eliminating contrast in imaging of children with CHLGG with GBCA reserved for monitoring those with metastatic disease.

IMG-08. UNUSUAL IMAGING FINDINGS IN TWO CASES OF PAEDIATRIC LOW GRADE GLIOMA

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Low grade gliomas (LGG), including pilocytic astrocytoma (PCA), are the commonest paediatric brain tumours and their behaviour is well understood, typically following a benign course. BRAF fusion is common, particularly in PCA of the cerebellum and optic pathway. Here we present two patients whose LGG behaved in an unusual fashion. The first patient who was treated 6 years previously on LGG2 with vincristine and carboplatin for a tectal plate lesion was identified on routine imaging to have local tumour progression and underwent completion staging. This showed a new enhancing soft tissue abnormality within the spinal cord at the level of L2. Due to radiological dubiety both lesions were biopsied for histological and molecular analysis, confirming LGG of the tectal plate and finding the spinal lesion to be a myxopapillary ependymoma. The second patient presented with acute hydrocephalus following a 2 year history of neurocognitive impairments. He was found to have a large, complex tumour centred in and expanding the bodies of both lateral ventricles with significant mass effect. Radiologically this was most in keeping with a central neurocytoma but histological analysis confirmed it to be a PCA with KIAA1549-BRAF fusion. The first case demonstrates the utility of molecular analysis in confirming two distinct tumour types in one patient, in a situation where metastasis would not be expected and would significantly alter treatment and prognosis. The second is an example of how imaging can be misleading in a KIAA1549-BRAF fused PCA presenting as an intraventricular mass.

IMG-09. RESPONSE ASSESSMENT IN DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG): RECOMMENDATIONS FROM THE RESPONSE ASSESSMENT IN PEDIATRIC NEURO-ONCOLOGY COMMITTEE

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Optimizing the conduct of clinical trials for diffuse intrinsic pontine glioma (DIPG) involves use of consistent, objective disease assessments and standardized response criteria. The Response Assessment in Pediatric Neuro-Oncology (RAPNO) committee, an international panel of pediatric and adult neuro-oncologists, clinicians, radiologists, radiation oncologists, and neurosurgeons, was established to address unique challenges in assessing response in children with CNS tumors. A subcommittee of RAPNO was formed to specifically address response assessment in children and young adults with DIPG and to develop a consensus on recommendations for response assessment. Distinct issues related to the response assessment of DIPG include its definition and recent molecular classifications, dearth of imaging response data, the phenomena of pseudoprogression, and measuring response in the era of focal drug delivery. The committee has recommended response be assessed using magnetic resonance imaging (MRI) of brain and spine, neurologic examination, and use of supportive medication, i.e. steroids and anti-angiogenic agents. Clinical imaging standards and imaging quality control

are defined. Unique recommendations for DIPG response include an eight-week response duration, a twenty-five percent decrease for partial response, and the distinction of pontine and extra-pontine response for trials that use focal drug delivery. The recommendations presented here represent an initial effort to uniformly collect and evaluate response assessment criteria; these recommendations can now be incorporated into clinical trials to assess feasibility and corroboration with patient outcomes.

IMG-10. MRI-BASED RADIOMIC PROGNOSTIC MARKERS OF DIFFUSE MIDLINE GLIOMA

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BACKGROUND: Diffuse midline gliomas (DMG) are lethal pediatric brain tumors with dismal prognoses. Presently, MRI is the mainstay of disease diagnosis and surveillance. We aimed to identify prognostic image-based radiomics markers of DMG and compare its performance to clinical variables at presentation. METHODS: 104 treatment-naïve DMG MRIs from five centers were used (median age=6.5yrs; 18 males, median OS=11mos). We isolated tumor volumes of T1-post-contrast (T1gad) and T2-weighted (T2) MRI for PyRadiomics high-dimensional feature extraction. 900 features were extracted on each image, including first order statistics, 2D/3D Shape, Gray Level Co-occurrence Matrix, Gray Level Run Length Matrix, Gray Level Size Zone Matrix, Neighboring Gray tone Difference Matrix, and Gray Level Dependence Matrix, as defined by Imaging Biomarker Standardization Initiative. Overall survival (OS) served as outcome. 10-fold cross-validation of LASSO Cox regression was used to predict OS. We analyzed model performance using clinical variable (age at diagnosis and sex) only, radiomics only, and radiomics plus clinical variable. Concordance metric was used to assess the Cox model. RESULTS: Nine radiomic features were selected from T1gad (2 texture wavelet) and T2 (5 first-order features (1 original, 4 wavelet), 2 texture features (1 wavelet, 1 log-sigma). This model demonstrated significantly higher performance than a clinical model alone (C: 0.68 vs 0.59, p<0.001). Adding clinical features to radiomic features slightly improved prediction, but was not significant (C=0.70, p=0.06). CONCLUSION: Our pilot study shows a potential role for MRI-based radiomics and machine learning for DMG risk stratification and as image-based biomarkers for clinical therapy trials.

IMG-12. CHARACTERISATION OF MODELS OF *H3F3A*_G34R/V MUTANT PAEDIATRIC GLIOBLASTOMA *IN VIVO* USING MAGNETIC RESONANCE IMAGING

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Approximately 15% of paediatric/young adult cerebral hemispheric glioblastomas (pGBM) harbour G34R/V mutations in *H3F3A*, encoding the histone H3.3 variant. Development of novel therapeutic interventions demands models that accurately recapitulate this subset of disease and sensitive imaging methods with which to study tumours *in situ*. Three *H3F3A*_G34R primary-patient-derived cultures, alongside established cell-line KNS42 (*H3F3A*_G34V), were implanted orthotopically in immunocompromised mice. KNS42 (*TP53*_R342*) tumours were clearly detectable using T_2-weighted (T_2w)-MRI, enhanced following contrast agent administration, indicating impaired blood-brain barrier (BBB) integrity, and demonstrated minimal invasion. OPBG_GBM_001 cells (*TP53*_89-90X,*ATRX*_II2133-2144X) formed infiltrative tumours that were hyperintense on T_2w-MRI and demonstrated contrast-enhancement suggestive of heterogeneous BBB integrity. HSJD_GBM_002 cells (*TP53*_P278T,*ATRX*_R666*) spread diffusely throughout the brain with their full extent typically not discernible by T_2w-MRI, the BBB also remaining intact. No evidence of CHOP_GBM_001 tumour was detected by MRI 11months post-implantation. Immunocompetent syngeneic models using tumour cells induced by mutations modelling hemispheric pGBM (NRAS/shP53/shATRX±H3.3G34R) are being explored. Fast growing heterogeneous lesions with variable contrast-enhancement were identified; the H3.3G34R mutation conferred longer median survival (2 clones:25/28days, control:14days). These models have the advantage of an intact immune system and short latency for initial efficacy studies. Primary pGBM cells yield tumours that are more representative of the spectrum of clinical disease; variable hyperintensity on T_2w-MRI corresponding to cellular density, with diffusely infiltrative disease less clearly definable, a paucity of oedema and a range of contrast-enhancement. Pathological features including giant multinucleated cells, and mitotic figures were also evident.

IMG-13. MRI-BASED RADIOMICS PROGNOSTIC MARKERS OF POSTERIOR FOSSA EPENDYMOMA

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PURPOSE: Posterior fossa ependymomas (PFE) are common pediatric brain tumors often assessed with MRI before surgery. Advanced radiomic analysis show promise in stratifying risk and outcome in other pediatric brain tumors. Here, we extracted high-dimensional MRI features to identify prognostic, image-based, radiomics markers of PFE and compared its performance to clinical variables. METHODS: 93 children from five centers (median age=3.3yrs; 59 males; mean PFS=50mos) were included. Tumor volumes were manually contoured on T1-post contrast and T2-weighted MRI for PyRadiomics feature extraction. Features include first-order statistics, size, shape, and texture metrics calculated on the original, log-sigma, and wavelet transformed images. Progression free survival (PFS) served as outcome. 10-fold cross-validation of a LASSO Cox regression was used to predict PFS. Model performance was analyzed and concordance metric (C) was determined using clinical variable (age at diagnosis and sex) only, radiomics only, and radiomics plus clinical variable. RESULTS: Six radiomic features were selected (all T1): 1 first-order kurtosis (log-sigma) and 5 texture features (3 wavelet, 2 original). This model demonstrated significantly higher performance than a clinical model alone (C: 0.69 vs 0.58, p<0.001). Adding clinical features to the radiomic features didn't improve prediction (p=0.67). For patients with molecular subtyping (n=48), adding this feature to the clinical plus radiomics models significantly improved performance over clinical features alone (C = 0.79 vs. 0.66, p=0.02). Further validation and model refinement with additional datasets are ongoing. CONCLUSION: Our pilot study shows potential role for MRI-based radiomics and machine learning for PFE risk stratification and as radiographic biomarkers.

IMG-14. DEVELOPING A PREDICTIVE GRADING MODEL FOR CHILDREN WITH GLIOMAS BASED ON DIFFUSION KURTOSIS IMAGING METRICS: ACCURACY AND CLINICAL CORRELATIONS WITH SURVIVAL

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PURPOSE: To develop a predictive grading model based on diffusion kurtosis imaging (DKI) metrics in children affected by gliomas, and to investigate the clinical impact of the model via correlations with overall survival and progression-free survival. MATERIALS AND METHODS: We retrospectively studied 59 children (33M, 26F, median age 7.2 years) affected by gliomas on a 3T magnet. Patients with tumor locations other than infratentorial midline were included. Conventional and DKI sequences were obtained. Mean kurtosis (MK), axial kurtosis (AK), radial kurtosis (RK), fractional anisotropy (FA) and apparent diffusion coefficient (ADC) maps were obtained. Whole tumor volumes (VOIs) were segmented semiautomatically. Mean DKI values were calculated for each metric. The quantitative values from DKI-derived metrics were used to develop a predictive grading model with penalized logistic regression (glmnet package, R). Elasticnet regularization was used to avoid model overfitting. Fitted model coefficients from each metric were used to develop a probability prediction of a high-grade glioma (HGG). Grading accuracy of the resulting probabilities was tested with ROC analysis. Finally, model predictions were correlated to progression-free survival (PFS) with a Kaplan-Meier analysis. RESULTS: The cohort included 46 patients with low-grade gliomas (LGG) and 13 patients with HGG. The developed model predictions yielded an AUC of 0.946 (95%CI: 0.890–1). Model predictions were significantly correlated with PFS (23.1 months for HGG vs 34.7 months for LGG, p<0.004). CONCLUSION: In our cohort, a DKI-based predictive model was highly accurate for pediatric glioma

grading. DKI-based model predictions were significantly correlated with progression-free survival.

IMG-15. PEDIATRIC GLIOBLASTOMAS CONTRAST ENHANCEMENT PATTERN IS PREDICTIVE OF SURVIVAL

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BACKGROUND: Pediatric GBMs are rare, accounting for 3% of all pediatric CNS tumors. Despite advances in treatment, the outcomes for pediatric glioblastomas (GBM) have not significantly improved. Research suggests a link between enhancement patterns and survival in adult patients with glial tumors. We sought to study this relationship in a cohort of pediatric GBMs. METHODS: A radiology database was searched for cases < 22 years, pathology proven brain glioblastoma, and pre-surgical MR imaging available for review. Based on pre-treatment, T1-contrast enhanced MR images, size, and contrast enhancement patterns were characterized as focal, diffuse, or ring-like. The extent of resection was assessed by comparing pre- and post-surgery T2 hyperintensity and contrast enhancement. RESULTS: 64 eligible patients (age 2-21y, 14.6 + 5.4) were identified. The majority of lesions demonstrated enhancement on gadolinium-enhanced T1 imaging. (n=58/64; 90%). The lesions were categorized into six (9.4%) cases with focal enhancement, 37 (57.8%) cases with diffuse enhancement, and 15 (23.4%) with ring-like enhancement. Patients who received GTR/subtotal resection (STR) and had focal-enhanced GBMs had a significantly longer progression-free survival (PFS) – 14.1 months (p = 0.0308), comparing to diffuse and ring-like enhancing glioblastomas which had respectively 13.9 and 5.5 months of PFS. DISCUSSION: Our data suggests that the contrast enhancement pattern is a significant prognostic factor for survival in pediatric GBM. Patients with GTR/STR who had focal-enhancing GBMs had a significantly longer progression-free survival (p=0.03) comparing to other enhancement patterns.

IMG-16. WHOLE TUMOR DIFFUSION KURTOSIS IMAGING ANALYSIS FOR DISCRIMINATING PEDIATRIC POSTERIOR FOSSA TUMORS: ACCURACY AND REPEATABILITY

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PURPOSE: Diffusion kurtosis imaging (DKI) has not yet been tested for pediatric brain tumors. Estimating diffusion values from whole-tumor based (VOI) segmentations may improve diffusion measurement repeatability compared to conventional region-of-interest (ROI) approaches. Our purpose was to compare repeatability between ROI and VOI DKI-derived diffusion measurements and to assess VOI-based DKI accuracy in discriminating among pediatric posterior fossa tumors. MATERIALS AND METHODS: We retrospectively analyzed 34 children (19 M, 15F, mean age 7.48 years) with posterior fossa tumors who underwent preoperative 3T MRI including DKI. For each patient, two neuroradiologists independently segmented the whole solid tumor (VOI), the area of maximum tumor diameter and a smallROI.Inter-observer variability was assessed with coefficient of variation (COV) and Bland-Altman plots. VOI-based DKI metrics accuracy in discriminating among tumor histology and for tumor grading were assessed with MANOVA and ROC analyses respectively. Correlation between grading accuracy and inter-observer variability was assessed with Spearman's rho. RESULTS: Tumor histology included medulloblastoma (15), pilocytic astrocytoma (14) and ependymoma (5). VOI-based measurements presented lower variability than ROI-based measurements across all DKI metrics. DKI-derived metrics could accurately discriminate between tumor subtypes (Pillai's trace: p<0.001) and were accurate for tumor grading (AUCs of 0.919, 0.986, 0.996, 0.842 and 0.926 for RK, MK, AK, FA and MD respectively). VOI-based COV was significantly correlated to AUC values (R=-0.900, p<0.037). CONCLUSIONS: DKI-derived metrics are useful for pediatric posterior fossa tumor discrimination and grading. VOI-based diffusion measurements present improved repeatability compared to ROI-based measurements and are significantly correlated to diagnostic accuracy.

IMG-17. RADIOMICS CHARACTERIZATION OF FOUR PEDIATRIC BRAIN TUMOR SUBTYPES IN PDX MOUSE MODELS

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BACKGROUND: Previously, we have reported on the development of advanced magnetic resonance imaging (MRI) protocols for mouse brain tumors. The goal of this follow-up pre-clinical study was to develop a machine-learning MRI classifier (radiomics) for four subtypes of childhood brain tumor in patient-derived xenograft (PDX) mice. METHODS: MRI scans on orthotopic medulloblastoma, ependymoma, ATRT and DIPG PDX (each n=12 animals) were performed on the animal 9.4 Tesla scanner with an in-plane resolution of 47 microns. Image segmentation, as well as shape and texture based radiomics descriptors were modeled using a modified COLIAGE software for tumor classification and to characterize tumor habitat of each tumor subtype. RESULTS: The mean tumor volumes were 11.2 mm^3. Each MRI scan was segmented into three regions: (i) well defined tumor (including distant metastases); (ii) peritumoral edema; (iii) tumor necrosis. 360 radiomics features (capturing co-occurrence, grey-level dependence and directional gradients) were obtained for each region. The model classified four subtypes with high accuracy while achieving sufficient segmentation accuracy despite the small lesion size. A subset of fourteen tumoral, six peritumoral and five distant MRI radiomics features were found to be predictive of the tumor sub-type (p=0.0017) independently of tumor anatomical location. CONCLUSIONS: MRI protocols followed by radiomics feature analysis discriminated among specific radiological features for four distinct orthotopic PDX models: medulloblastomas exhibit low ADC values, high angiogenesis and cortical metastases as compared to ependymomas (high levels of edema and olfactory bulb metastases), ATRT (the highest level of necrosis) and DIPG (highest T2 signal intensities and spinal metastases).

IMG-18. ASSESSMENT OF SUSPECTED DISEASE PROGRESSION USING MULTIPARAMETRIC 18F-CHOLINE PET/MRI IN CHILDHOOD AND TEENAGE-YOUNG ADULT GLIOMAS

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OBJECTIVES: Evaluation of post-treatment glioma burden remains a significant challenge in children, teenagers and young adults (TYA). The aim of this study was to evaluate the utility of ChoPET/MRI for evaluation of suspected disease progression in childhood and TYA gliomas. METHODS: 27 patients (mean age 14 years, range 6–21 years) with suspected glioma disease progression were evaluated with ChoPET/MRI (n=59). Relative cerebral blood volume (rCBV), apparent diffusion coefficient (ADC) and maximum standardised uptake values (SUV_{max}) in enhancing (enh) and non-enhancing (ne) tumour and normal-appearing white matter (wm) were calculated ($rCBV_{enh}$, $rCBV_{ne}$, $rCBV_{wm}$, ADC_{enh}, ADC_{ne}, ADC_{wm}, SUV_{enh}, SUV_{ne}, SUV_{wm}). 2 blinded radiologists scored tumour probability (1 = unlikely; 5 = definitely). Sensitivity and specificity calculated with gold standard histopathology or clinical follow-up. RESULTS: Accuracy for the detection of residual/recurrent tumour on conventional MRI was 96.3% (91.7% ≤14 years, 100% ≥15 years) and ChoPET was 73.1% (66.7% ≤14 years, 80.0% ≥15 years). Lack of agreement was observed in 9/27 patients, with ChoPET superior to MRI in 1 case of a posterior fossa tumour. Tumour component analysis demonstrated significantly higher SUV_{enh} and SUV_{ne} than SUV_{wm} (SUV_{enh}: p<0.001; SUV_{ne}: p=0.004, equivalent to results were observed for ADV and rCBV (ADC_{enh}, ADC_{ne}: p<0.001 vs ADC_{wm}; $rCBV_{enh}$, $rCBV_{ne}$: p<0.001 vs $rCBV_{wm}$). CONCLUSIONS: MRI is more sensitive than ChoPET in the evaluation of suspected disease progression in TYA gliomas. However, quanititative ChoPET is able to detect enhancing and non-enhancing tumour and may be helpful in evaluating posterior fossa disease where MRI is equivocal.

IMG-19. RADIOMICS AND SUPERVISED DEEP LEARNING TO PREDICT MOLECULAR SUBGROUPS IN MEDULLOBLASTOMA BASED ON WHOLE TUMOR VOLUME LABELING: A SINGLE CENTER MULTIPARAMETRIC MR ANALYSIS

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PURPOSE: Medulloblastoma (MB) is a complex pathology. Four molecular subgroups have been unveiled (Wingless-WNT, Sonic Hedgehog-SHH, Group 3-G3 and Group 4-G4), characterized by significant differences in patient clinical outcome. We investigated the utility of a radiomic analysis to predict molecular subgroups in patients with MB. MATERIALS

AND METHODS: We retrospectively evaluated 42 patients with histological diagnosis of MB, known molecular subgroup, and diagnostic MRI scan performed in our Institution on a 3 Tesla magnet. For each patient, FLAIR, ADC, T2 and contrast-enhanced MPRAGE sequences were analysed. Solid tumor volumes were segmented semiautomatically. 107 features were extracted for each sequence (Pyradiomics, Python). Features were tested for stability against labelling variations, selecting those presenting Intraclass Correlation Coefficient (ICC)>0.9 across all labelling variations and all sequences. Among the remaining features, relevant features were selected with an all-relevant wrapper algorithm (Boruta, R). Remaining features were used to predict MB subgroup with a Random Forest algorithm(R). The most relevant features were ranked based on Gini index (R). RESULTS: 83/107 features presented ICC >0.9 for all sequences. Boruta selected 10 features. Classification analysis yielded an out-of-bag (OOB) error rate of 0.6%, (99.4% accuracy). The most relevant features for classification were "simple" first-order features such as volume, major axis or shape. CONCLUSION: This radiomic study yielded robust features, which showed high accuracy in predicting the molecular MB subgroups. Random forest algorithms are ideal for multiclass classification (eg. MB subgroups) and are intrinsically suited against overfitting. The most relevant for molecular classification were first-order features.

IMG-20. RADIOMIC FEATURES IMPROVE PROGNOSTICATION OVER CONVENTIONAL MR DERIVED QUALITATIVE DESCRIPTORS IN PEDIATRIC SUPRATENTORIAL HIGH GRADE GLIOMA: COMPARISON OF MACHINE LEARNING TECHNIQUES

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PURPOSE/OBJECTIVES: Pediatric supratentorial high-grade glioma (stHGG) is a biologically heterogeneous disease defined by unique mutations, natural history and prognosis. Prior work by our group outlined a role for qualitative imaging features in aiding prognostication. We build on that work by evaluating the prognostic utility of radiomic features (RM) when paired with clinical factors. MATERIALS/METHODS: Ninety-one patients age < 21 years with stHGG treated between 1980–2007 were retrospectively reviewed. Prognostic clinical, qualitative imaging (Visually AcceSAble Rembrandt Images, VASARI), and treatment characteristics were evaluated in concert with manual and automatically segmented (DeepMedic), tumor-derived semi-quantitative radiomic features (Pyradiomics) extracted from MR images. Prognostic RM were limited to stable imaging features which were subsequently selected using bootstrapped least absolute shrinkage and selection operator (LASSO). Nonparametric descriptive statistics and prognostication model evaluation, incorporating RM and clinical variables, were developed using random forest (RF), Cox proportional hazards (CPH), and deep learning (deepsurv) algorithms and assessed for goodness of fit using (c-index). RESULTS: A subset (N=80) of 386 intensity, shape, and texture derived RM were stable between pre-treatment MR. 28 RM features were independently predictive of survival when compared to models utilizing combinations of clinical, VASARI and had comparable model fit statistics. CPH, RF and deepsurv showed comparable utility in modelling RM features. Combined modelling of clinical, VASARI and RM features using CPH, RF, and deepsurv resulted in c-indices of 0.68, 0.67, 0.68, respectively. CONCLUSION: RM features are stable and independently prognostic. Combined modelling of clinical, VASARI, and RM features improves prognostication in stHGG.

IMG-21. PROSPECTIVE PREOPERATIVE DETERMINATION OF ISOCITRATE DEHYDROGENASE MUTATION IN GLIOMAS USING SPECTRAL EDITING MAGNETIC RESONANCE SPECTROSCOPY

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BACKGROUND: Gliomas are the most common malignant brain tumors in children and adults. A subset of these tumors harbour mutations in the enzyme isocitrate dehydrogenase (IDH) which produces the novel oncometabolite *2-hydroxyglutarate* (2HG). In general, patients with an IDH mutant glioma have a longer survival—often necessitating more re-treatment sessions over the span of a patient's life and surveillance monitoring for tumor recurrence. The need to non-invasively detect early evidence of tumor recurrence is therefore heightened in this unique subset of patients with extended survival. As magnetic resonance spectroscopy (MRS) has been demonstrated to measure biochemical components of intracranial tumors using MRI, we conducted a study in 58 pre-operative adult patients to determine if a diagnosis of IDH mutant glioma could be made confidently using imaging data. METHODS: Patients underwent neuroimaging for diagnosis or preoperative planning on a 3 tesla MR scanner. A MEGA-PRESS spectral editing technique was employed. Imaging findings were directly compared to post-operative histopathologic diagnosis. RESUTLS: For all patients with gliomas from grade II to IV, detection of 2-HG with MEGA-PRESS sequence had a sensitivity between 48% and 81%, specificity between 60% and 100%, PPV between 53% and 100% and NPV between 77% and 85% depending on the CRLB threshold. Among the different metabolite ratios, a 2-HG/NAA ratio >0.034 had the highest sensitivity and specificity, 86% and 73% respectively. DISCUSSION: Magnetic resonance spectroscopy (MRS) is an underused advanced MR technique that deserves consideration in pediatric neuro-oncology given its utility in non-invasively detecting malignant gliomas.

IMG-22. A DEEP LEARNING MODEL FOR AUTOMATIC POSTERIOR FOSSA PEDIATRIC BRAIN TUMOR SEGMENTATION: A MULTI-INSTITUTIONAL STUDY

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BACKGROUND: Brain tumors are the most common solid malignancies in childhood, many of which develop in the posterior fossa (PF). Manual tumor measurements are frequently required to optimize registration into surgical navigation systems or for surveillance of nonresectable tumors after therapy. With recent advances in artificial intelligence (AI), automated MRI-based tumor segmentation is now feasible without requiring manual measurements. Our goal was to create a deep learning model for automated PF tumor segmentation that can register into navigation systems and provide volume output. METHODS: 720 pre-surgical MRI scans from five pediatric centers were divided into training, validation, and testing datasets. The study cohort comprised of four PF tumor types: medulloblastoma, diffuse midline glioma, ependymoma, and brainstem or cerebellar pilocytic astrocytoma. Manual segmentation of the tumors by an attending neuroradiologist served as "ground truth" labels for model training and evaluation. We used 2D Unet, an encoder-decoder convolutional neural network architecture, with a pre-trained ResNet50 encoder. We assessed ventricle segmentation accuracy on a held-out test set using Dice similarity coefficient (0–1) and compared ventricular volume calculation between manual and model-derived segmentations using linear regression. RESULTS: Compared to the ground truth expert human segmentation, overall Dice score for model performance accuracy was 0.83 for automatic delineation of the 4 tumor types. CONCLUSIONS: In this multi-institutional study, we present a deep learning algorithm that automatically delineates PF tumors and outputs volumetric information. Our results demonstrate applied AI that is clinically applicable, potentially augmenting radiologists, neuro-oncologists, and neurosurgeons for tumor evaluation, surveillance, and surgical planning.

IMMUNOTHERAPY

IMMU-01. IMMUNE CHECKPOINT INHIBITION FOR PEDIATRIC CNS TUMORS: A SINGLE INSTITUTION EXPERIENCE

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INTRODUCTION: Immune checkpoint inhibition through PD-1 and CTLA-4 blockade has shown efficacy in some adult malignancies and is being investigated in pediatrics. We describe our institutional experience with immune checkpoint inhibition in pediatric CNS tumors. METHODS: We performed a retrospective chart review of patients with recurrent, progressive, or refractory pediatric CNS tumors treated with immunotherapy at Dana-Farber/Boston Children's Hospital between 2018–2019. RESULTS: Eleven patients were identified, with median age of 11 years (range:3–9). Diagnoses included DIPG (n=3), HGG (n=4), ependymoma (n=1), craniopharyngioma (n=1), HGNET (n=1) and NGGCT (n=1). Eight patients had recurrent disease (5 local; 3 disseminated); three had refractory disease (non-recurrent). Nine patients were treated with combination

therapy (ipilimumab/nivolumab); two patients received monotherapy with either nivolumab or pembrolizumab. Median time from initial diagnosis-to-treatment was 8 months (range 0.8–156). Ten patients received radiation therapy (RT) prior to immunotherapy, with one receiving concurrent RT. Median duration of treatment was 6.1 months (range:1–19). Therapy was discontinued in nine patients: seven due to disease progression and two due to adverse events (colitis, transaminitis). Other pertinent toxicities included type 1 diabetes, hypothyroidism and skin toxicity. Based on iRANO criteria, best responses included partial (n=4), stable (n=6) and progressive disease (n=1). Durable response (>12months) was noted in two patients (HGG and progressive NGGCT). CONCLUSION: Immune checkpoint inhibition appears to have clinical benefit and is relatively well tolerated in this cohort of patients. Results from recently completed prospective clinical trials will be critical to inform clinical decisions.

IMMU-02. CHIMERIC ANTIGEN RECEPTOR (CAR) T CELL NEUROTOXICITY CORRELATES WITH PRETREATMENT AND ACUTE CSF NEUROFILAMENT LIGHT CHAIN (NFL) LEVELS

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OBJECTIVE: Immunotherapy for hematologic malignancies with CD19-directed CAR T cells is complicated by neurotoxicity in approximately 40% of patients. We have previously reported evidence of glial injury in pediatric patients with CAR T neurotoxicity by elevated CSF levels of GFAP and S100b. We now hypothesize that NFL is also a useful biomarker of neuronal injury related to abnormal blood-brain-barrier and glial function. METHODS: We used the Mesoscale Discovery platform to measure CSF and serum NFL levels in a consecutive cohort of 43 pediatric patients with B cell ALL who received CD19-directed CAR T cells. In addition, we will present expansion cohort measurements of NFL and GFAP (N=95). RESULTS: CSF NFL levels prior to CAR T cell infusion positively correlated with the risk of subsequently developing severe neurotoxicity (no neurotoxicity, median 275pg/mL, mild 378pg/mL, severe 951pg/mL, P=0.0182 for severe vs none, P=0.0458 for severe vs mild). During neurotoxicity, mean CSF NFL levels increased to 1179pg/mL (mild neurotoxicity, P=0.0338) and 1345 pg/mL (severe neurotoxicity, P=0.0148), respectively. In serum, pretreatment NFL levels were highly abnormal in many patients (median 368pg/mL, range 10–56,321pg/mL; healthy control median 4pg/mL, range 1–7.5pg/mL). However, there was no correlation with neurotoxicity, history of CNS radiation, peripheral neuropathy, stem cell transplant, or number of prior chemotherapies. Day 7 serum NFL levels did not change significantly (median 439pg/mL, range 5–17,439pg/mL, P=0.3254). CONCLUSION: We conclude that CSF NFL is promising biomarker of CAR T neurotoxicity risk and severity. The abnormal baseline serum NFL concentrations remain unexplained and require further study.

IMMU-03. UPDATES ON BRAINCHILD-01, -02, AND -03: PHASE 1 LOCOREGIONAL CAR T CELL TRIALS TARGETING HER2, EGFR, AND B7-H3 FOR CHILDREN WITH RECURRENT CNS TUMORS AND DIPG

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We report preliminary results of three Phase 1 trials of repetitively dosed locoregional CAR T cells for children with recurrent/refractory CNS tumors, targeting HER2 (BrainChild-01), EGFR (BrainChild-02), and B7-H3 (BrainChild-03). Cells are delivered into the tumor cavity (Arm A) or ventricular system (Arm B and BrainChild-03's DIPG-specific Arm C). Primary endpoints are feasibility and safety. Successful CAR T cell manufacture occurred in 2/2 subjects (BrainChild-01) and 2/3 (BrainChild-02). All subjects tolerated intra-patient dose escalation from $1x10^7$ to $2.5x10^7$ cells/dose without DLTs. Two subjects were evaluable on BrainChild-01 (S-001: glioblastoma, Arm A, survival 173 days post-first infusion, received 6 infusions; S-002: ependymoma, Arm B, survival 111 days, 9 infusions). One subject was evaluable on BrainChild-02 (glioblastoma, Arm A, withdrew from trial at 49 days, 5 infusions). One enrolled patient on BrainChild-03 has not begun treatment. None of the subjects developed new neurologic toxicities, although transient worsening of baseline tumor-related signs and symptoms were seen. Secondary endpoints are efficacy and disease response. No objective radiographic responses have been observed. Both BrainChild-01 subjects had transient systemic CRP elevations following infusions (S-001: peak of 3.9 post Course 1 Week 1; S-002: peak of 2.3 post Course 2 Week 1), possibly indicating an inflammatory response. Both subjects had post-infusion CSF cytokine elevations (CXCL10, GCSF, GM-CSF, IFNa2, IFNg, IL-10, IL12-p40, IL12-p70, IL-15, IL-1a, IL-3, IL-6, IL-7, TNFa, VEGF) without concurrent systemic changes. In summary, we provide preliminary evidence of safety and feasibility of intracranial delivery of CAR T cells for pediatric CNS tumors.

IMMU-05. B7-H3-SPECIFIC CAR T CELLS HAVE POTENT ANTI-TUMOR ACTIVITY IN THE GL261 IMMUNE-COMPETENT MURINE BRAIN TUMOR MODEL

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BACKGROUND: We and others have identified B7-H3 (CD276) as a promising target for CAR-based immunotherapies for pediatric brain tumors. So far, B7-H3-CAR T cells have only been studied in xenograft models for brain tumors, which do not recapitulate the immunosuppressive tumor microenvironment (TME). To overcome this obstacle, we decided to adapt the immune-competent GL261 murine glioma model which mimics human disease and host immune barriers. METHODS: To evaluate the safety and efficacy of antigen-specific CAR T cells, murine B7-H3-CAR T cells were generated using retroviral particles encoding 2nd generation B7-H3-specific CD28.z CAR. Expansion, persistence, and anti-tumor activity were evaluated *in vitro* and *in vivo*. Components of the brain TME were then evaluated using flow cytometry and immunostaining. RESULTS: B7-H3-CAR T cells only killed B7-H3+ tumor cells, secreted significant levels of IFNγ and IL-2 in an antigen-dependent manner and expanded an average of 33-fold in repeat stimulation assay with B7-H3+ tumor cells in contrast to control CAR T cells. *In vivo*, intratumoral injection of B7-H3-CAR T cells into orthotopic GL261 glioma induced complete regression in 60% of treated mice. Preliminary studies show numerous infiltration of suppressive tumor-associated macrophages within the tumor and its periphery. CONCLUSIONS: In summary, we successfully generated murine B7-H3-CAR T cells and have demonstrated that these cells have potent anti-tumor activity in the immune-competent GL261 glioma model. However, it is likely that the tumor-associated macrophages are mediating immunosuppressive effects on B7-H3-CAR T cells. Therefore, studies focusing on TME/CAR T cell interactions are in progress.

IMMU-06. T-CELL IMMUNOTHERAPY FOR PEDIATRIC BRAIN TUMORS: DIVERSITY IN CELL SURFACE ANTIGEN AND HLA EXPRESSION NECESSITATES A MULTI-PRONGED APPROACH

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Cell surface or intracellular antigens expressed in pediatric brain tumors are potential targets for chimeric antigen receptor (CAR) or ab (T-cell receptor) TCR T-cell immunotherapy. At present it remains unknown what cell surface antigens are suitable CAR targets for pediatric brain tumors; in addition, cell surface expression of HLA class I, a molecule critical for ab TCR T-cell recognition, has not been systemically studied in these tumors. Therefore, we set out to assess expression of five CAR targets (IL13Ra2, HER2, EphA2, B7-H3, GD2) and HLA class I. We established and validated a flow cytometry-based method to profile CAR targets and HLA class I expression from pediatric patient-derived xenograft (PDX) samples. To date, we profiled 53 PDX samples, including medulloblastoma, HGG, DIPG, ATRT, and ependymoma. We found that antigen expression has high intra- and inter-PDX sample variability with B7-H3 and IL13Ra2 being most consistently expressed. We confirmed these findings using conventional IHC for B7-H3 with PDX samples and patient tissue microarrays. HLA class I was present on the cell surface of HGGs and DIPGs, however significantly down-regulated in 26 out of 36 other brain tumor types. Finally, matched fresh tissue and PDX sample analysis revealed that cells derived from PDX models are indeed representative of fresh tissue. Our results indicate that more than one antigen needs to be targeted to achieve a more complete tumor clearance. In addition, variable expression

of HLA class I suggests that pediatric brain tumors have developed immune evasion strategies to prevent recognition by conventional T cells.

IMMU-07. IMMUNE EFFECTOR CELL ASSOCIATED NEUROTOXICITY (ICANS) AMONG PEDIATRIC AND AYA PATIENTS: MD ANDERSON CANCER CENTER EXPERIENCE

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INTRODUCTION: Immune effector cell associated neurotoxicity (ICANS) and cytokine release syndrome (CRS) are potentially life-threatening complications associated with immune effector cell (IEC) therapies. We characterize ICANS in pediatric and adult young adolescent (AYA) patients receiving IEC therapy at our institution. METHODS: We reviewed clinical characteristics and severity (based on ASTCT Consensus Criteria) in pediatric and AYA patients with IEC products from 2018–2019 at MDACC. RESULTS: Nine patients, median age 15.5 (range: 3–25) years received chimeric antigen receptor (CART) IEC therapy. Four (44%) developed ICANS within median of 8 (range: 3–27) days of CAR T cell infusion and median 6 (range: 2–7) days after CRS. Primary diagnoses were pre-B cell acute lymphoblastic leukemia (8) and mediastinal large B-cell lymphoma (1). Median CRS and ICANS severity grade was 2 (range 1–4). Symptoms included altered mental status (AMS) (5), seizure (1), aphasia (2), impaired ability to write a standard sentence (4). Neuroimaging did not correlate to ICANS symptoms or severity. EEG was performed in 3 and 1 had background slowing correlating with aphasia. CSF was obtained in two revealing lymphocytosis. All received prophylactic anti-epileptic medication and tocilizumab for concomitant CRS. Three received steroids. CONCLUSION: ICANS may present in almost half of pediatric patients within one week of receiving CART products associated with CRS. CAR-T trafficking into the CSF may explain pleocytosis in the CSF. Prospective studies may clarify. Impaired ability to write a standard sentence and the Cornell Assessment of Pediatric Delirium (CAPD) may be early indicators of ICANS in pediatric/AYA patients.

IMMU-08. REMATCH PROTOCOL: PHASE II STUDY OF EX-VIVO EXPANDED AUTOLOGOUS TUMOR SPECIFIC LYMPHOCYTE TRANSFER (X-ALT) + TOTAL TUMOR RNA DC VACCINE (TT-RNA DC) DURING RECOVERY FROM MYELOABLATIVE CHEMOTHERAPY (MAC) AND PERIPHERAL BLOOD STEM CELL (PBSC) RESCUE OR NON-MYELOABLATIVE CHEMOTHERAPY (NMAC) AND PBSC IN PATIENTS (PTS) WITH RECURRENT PNET (R-PNET)

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A phase II study was performed to assess vaccine-related toxicities and efficacy of x-ALT+tt-RNA DC following MAC +PBSC (group A) or NMAC +PBSC (group B) in pts with r-PNET. METHODS: Eligible pts underwent biopsy to confirm r-PNET and obtain tumor for vaccine preparation. Pts with local (group A) or metastatic (group B) disease received cytoreductive induction chemotherapy prior to either MAC (carboplatin+ thiotepa+ etoposide) or NMAC (cyclophosphamide + fludarabine) respectively and then received one dose of x-ALT (3 x 10^7cells/kg), PBSC, and 3 doses of bi-weekly intradermal tt-RNA DCs (10^7cells each). Patients were followed for survival and vaccine-related toxicities. Correlative studies included TCR RNA sequencing and measurement of serum cytokines RESULTS: 20 evaluable pts (75% males) [Medulloblastoma 17, PNET 3; unifocal 40%] were treated on protocol (group A 7, group B 13). There were no significant vaccine-related toxicities. At a median follow-up of 8.5 months, 5 patients (all with medulloblastoma) are alive following vaccine therapy; 2 pts with SD (3.5+ and 6.5+ months) and 3 pts with PD that stabilized with salvage therapies (26+, 31+, and 46+ months respectively). One patient with medulloblastoma and bone marrow involvement who had PD despite MAC, had an almost complete response one month following x-ALT + tt-RNA DCs and TCR RNA sequencing demonstrated massive clonal expansion of T cells. Correlative studies are ongoing CONCLUSIONS: x-ALT+tt-RNA DC following either MAC or NMAC is safe and shows signs of biologic and possible clinical activity in some pts with r-PNET.

IMMU-09. NIVOLUMAB THERAPY FOR A PEDIATRIC-ONSET PRIMARY INTRACRANIAL MELANOMA

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Primary intracranial malignant melanoma (PIMM) is an uncommon cancer in childhood, that accounts for approximately 1% of melanoma, and 0.07% of brain tumors even in all age group. Because extracranial malignant melanoma usually occurs as a cutaneous lesion, affected patients have a chance to receive the early diagnosis and curable resection of the isolated tumor. However, unresectable metastatic cases have a poor prognosis with a median overall survival of 8 months. We report a 12-year-old girl with PIMM who received nivolumab therapy after an administration of dacarbazine. The tumor harbored no *BRAF* mutation. After the intravenous administration of nivolumab, cerebrospinal fluid 5-S-cysteinyldopa levels declined and circulating $CD8^+HLA\text{-}DR^+$T cells increased, indicating the initial effect of nivolumab on PIMM. However, multiple lesions progressed for two month-immunotherapy, during which cerebrospinal fluid nivolumab concentrations attained to 1.2% of serum ones. The present case demonstrated the safety and modest effect of nivolumab for CNS melanoma. Nivolumab is a tolerable first-line therapy for diffuse PIMM, but pediatric patients need a more intensified CNS-specific immunotherapy.

IMMU-10. INTERIM ANALYSIS OF THE HIT-HGG REZ IMMUNVAC STUDY - DENDRITIC CELL VACCINATION WITH PARTIAL TREG DEPLETION IN CHILDREN, ADOLESCENTS, AND ADULTS WITH RELAPSED HIGH-GRADE GLIOMAS

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Efficacy of therapeutic dendritic cell vaccines (DCV) can be limited by immunosuppressive mechanisms in the micromilieu of high-grade gliomas. In the HIT-HGG-Rez Immunovac trial (Eudra-CT 2013-000419-26), we investigate whether a reduction of Treg with metronomic cyclophosphamide (metrCyc) might be a feasible option to improve vaccine efficacy. 10 pediatric (mean age 11.4±4.2y) and 5 adult patients (mean age 39.5±19.9y) with relapsed glioblastoma were treated according to the HIT-HGG-Rez Immunovac protocol so far. 2 children were treated within the trial, the other 13 in the pilot phase. Patients received upfront oral metrCyc for 2–4 weeks. After reoperation and monocyte-apheresis, patients received 4 weekly intradermal doses of autologous, TNFa/IL-1ß matured DCs pulsed with tumor lysate in imiquimod-prepared skin. Thereafter, tumor lysate boosts were given. All patients received at least 5 vaccines (4xDCs, 1xlysate boosts). MetrCyc was well tolerated and led to a reduction in Treg-frequency of 35.6±17.8% followed by a rebound after cessation of metrCyc. Importantly, 13/14 analyzed patients showed a positive IFNg-T-cell response against autologous tumor lysate with a tendency to decrease over time. 6-month overall survival was 100%, compared to 65% in a historical control. Mean PFS and OS were 5.7 and 21.1 months with no difference between adults and children. We conclude that DCV in combination with partial Treg depletion is feasible, safe, and related with a high rate of tumor-specific IFNg-responses. As the clinically and immunologically beneficial effects seem to diminish over time, we aim to combine our approach with checkpoint inhibition in the next amendment.

IMMU-11. LOCOREGIONAL DELIVERY OF TRANSIENT GD2 CAR T CELLS FOR SAFE AND EFFECTIVE TREATMENT OF DIPG

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Diffuse intrinsic pontine glioma (DIPG) is a universally fatal pediatric brain tumor with a median survival of one year. Recently Mount et al (Nat Med 2018) discovered the disialoganglioside GD2 is present at high levels on the surface of DIPG and can be targeted using GD2-directed CAR T cells. However, permanently expressed CAR T cells created by lentiviral transduction resulted in a significant number of deaths from tumor swelling with uncontrolled T cell proliferation. We hypothesized that using mRNA to create transient GD2-directed CAR T cells delivered locally with repeated dosing would result in a safer yet equally effective way to treat DIPG using CAR T cell therapy. In vitro studies using mRNA GD2-directed CAR T cells resulted in robust tumor cytotoxicity and T cell degranulation across a panel of six DIPG cell lines. Using an orthotopic murine model of SU-DIPGXIIIP*, an extremely aggres-

sive model, we delivered of a single dose of two million mRNA GD2-directed CAR T cells locoregionally to the pons via stereotactic injection. The mRNA GD2-directed CAR T cells resulted in no toxic deaths of the mice. In addition, a single dose of mRNA CAR T cells targeting GD2 prolonged survival of the mice by a median of six days ($p<0.05$). Ongoing studies using an indwelling catheter for repeated dosing of mRNA CAR T cells are currently underway and results expected at the time of presentation. This work will form of the basis of an mRNA CAR T cell trial targeting GD2 for patients with DIPG.

IMMU-12. PHASE I/II TRIAL OF IMMUNOTHERAPY WITH FUSIONS OF DENDRITIC CELLS AND TUMOR CELLS FOR RELAPSED OR REFRACTORY BRAIN TUMORS IN CHILDREN AND YOUNG ADULTS

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BACKGROUND/OBJECTIVES: Relapsed or refractory brain tumors in childhood continue to have a dismal prognosis in spite of intensive multidisciplinary treatment. Cancer immunotherapy is newly developed to be expected as next promising treatment for highly aggressive pediatric cancer. This trial was designed to evaluate the safety and effectiveness of an immunotherapy with fusions of dendritic cells (DCs) and tumor cells in patients with malignant brain tumors. METHODS: Patients with histopathologically confirmed malignant and recurrent/refractory brain tumor were eligible for this immunotherapy trial. Autologous cultured tumor cells obtained from surgical specimens were fused with autologous DCs using polyethylene glycol. The fusion cells (FC) were inoculated intradermally in the cervical region and repeated 3–10 times in each 28–84 days cycle. Treatment-related toxicity, progression-free survival (PFS), and overall survival (OS) were evaluated. RESULTS: Six patients were enrolled, three with high grade glioma and three with ependymoma. Median age at first course of immunotherapy was 10 years (range 8–25 years) and median follow-up time from the first course of immunotherapy was 13.5 months (range 3–33 months). All patients with immunotherapy were well tolerated to this treatment with no adverse events except local erythema in injected site. Median progression free survival and overall survival were 18 months and 18.5 months, respectively. CONCLUSIONS: FC immunotherapy with autologous DCs and tumor cells for brain tumor in children and young adults were extremely well tolerated and showed encouraging responses in this series. Further phase II study of FC immunotherapy is planned to improve survival and reduce treatment related morbidity.

IMMU-13. DUAL IGF1R/IR INHIBITOR IN COMBINATION WITH GD2-CAR T-CELLS AS A POTENT THERAPEUTIC STRATEGY FOR H3K27M-MUTANT DIFFUSE MIDLINE GLIOMAS

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Diffuse midline gliomas (DMG) are aggressive paediatric brain tumors for which there is no effective treatment. Recent pre-clinical studies suggest that adoptive transfer of chimeric antigen receptor (CAR) T-cells targeting the disialoganglioside antigen GD2 (GD2-CAR) has a significant therapeutic potential for H3K27M-mutant DMG. Still, some tumor cells resist to treatment suggesting that a multimodal approach may be necessary to treat more efficiently the disease. Our aim was to identify chemical compounds that, in combination with CAR T-cells, would enhance anti-tumor efficacy. After having confirmed the GD2 expression in tissue samples and patient-derived H3K27M-mutant DMG cells, we developed a high throughput cell-based assay to screen 40 kinase inhibitors in combination with T-cells expressing the GD2-CAR.CD28.4-1BB.z construct. The screening led to the identification of the dual IGF1R/IR antagonists, BMS-754807 and linsitinib, which, in combination with GD2-CAR T-cells, improved antitumor activity by 25% ($p<0.0001$) and 20% ($p<0.0001$) respectively, compared to GD2-CAR T-cells alone. The two compounds inhibited tumor cell proliferation through IGF1R/IR dependent mechanisms at a concentration which did not affect CAR T-cell expansion. Linsitinib, but not BMS-754807, decreased GD2-CAR T-cells exhaustion and increased their memory profile. Furthermore, linsitinib attenuated the expression of 10 out of 71 DMG genes involved in immunomodulation (*e.g.* IL33, VEGFC, STAT5A) and regulated upon tumor/CAR T-cells co-culture. Finally, we confirmed the anti-tumor activity of the new linsitinib/GD2-CAR T-cells combination strategy in a DMG H3K27M-mutant 3D culture model. Our work supports the development of IGF1R/IR inhibitors to be used in combination with GD2-CAR T-cells for H3K27M-mutant DMG therapy.

IMMU-14. IMMUNE CHECKPOINT INHIBITOR THERAPY FOR TREATMENT OF SYNCHRONOUS CANCERS IN PAEDIATRIC PATIENTS WITH CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY

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Constitutional mismatch repair deficiency (CMMRD) is an autosomal recessive condition in which affected patients carry biallelic germline mutations in the MMR genes. This highly penetrant syndrome results in nearly universal development of malignant neoplasms at a young age, most commonly pediatric brain tumors. Importantly, in addition to brain tumors, patients frequently develop multiple metachronous or even synchronous tumors making it impossible to treat these cancers with current chemotherapeutic approaches due to the complexity of different chemoradiation regimens required, resulting in excess toxicity and lack of efficacy. We first, assessed the metachronous (defined here as serial tumors diagnosed >1 year apart or after completion of definitive treatment for the initial tumor) or synchronous cancers (defined here as tumors diagnosed within a year of each other or during the definitive treatment for the initial tumor) in all patients within the consortium. Strikingly, 47% developed synchronous and/or metachronous cancers leading to patient demise. Molecular analysis revealed that all synchronous tumors (n=26) harbored a hypermutational burden accompanied by high genomic microsatellite instability and the relevant signatures. We therefore treated two patients with glioblastomas who had synchronous solid tumors with checkpoint inhibitors. In both patients, objective tumor response was associated with clinical benefit and prolonged survival. Biomarker analysis revealed increased tumor mutational burden, microsatellite instability and immune cell infiltration. These cases highlight the role of universal, mechanism based and tumor-agnostic approach to treat patients with brain tumors with additional synchronous cancers in the setting of cancer predisposition.

IMMU-15. PROTEOGENOMIC DISCOVERY OF NOVEL TUMOR PEPTIDES AS NEOANTIGENS FOR PERSONALIZED T CELL IMMUNOTHERAPY IN MEDULLOBLASTOMA

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T cell immunotherapies are promising new tools to combat high-risk subgroups of medulloblastoma without increasing the late effects burden. The ideal target antigen of an effective antitumor T-cell response is abundantly expressed by tumor cells but not by normal tissues, in order to limit off-target effects. Tumors translate a host of highly novel transcripts that are the result of aberrations in tumor DNA and the unmasking of alternative or novel exons. We developed a novel proteogenomic approach to identify tumor-restricted peptides and used them to select and expand T cells capable of mounting a tumor-specific cytotoxic immune response. Using RNA-seq and WGS data, we created personalized custom searchable databases containing predicted novel proteins from somatic mutations, novel junctions and fusion transcripts from 56 medulloblastoma tumors. By searching these databases with raw mass spectrometry data from paired medulloblastoma tumors, we identified tens of neoantigen peptides arising from the translation of tumor-specific transcripts; novel isoforms being the predominant source. We tested these peptides for their ability to select and expand autologous polyclonal populations of T cells and tested the immunogenicity of each individual peptide. Flow cytometry revealed populations of CD4+ and CD8+ cells with an activation profile marked by IFN-γ and TNF-α. Immunosuppressive marker profiles were also characterized. Using cytotoxicity assays, we demonstrated that tumor specific T cells can eliminate neoantigen bearing tumor cells. Thus, proteogenomics can identify immunogenic tumor

specific peptides that can be used to create a personalized, targeted T cell therapy for children with high risk medulloblastoma.

IMMU-16. INTRA-TUMOURAL IL-12 DELIVERY ENABLES CAR T-CELL IMMUNOTHERAPY FOR HIGH-GRADE GLIOMA

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Treatment with T-cells redirected to tumour specificity with a chimeric antigen receptor (CAR) may be well suited to treat intracranial tumours due to the ability of T-cells to access the central nervous system and migrate to infiltrative sites of disease. In adult glioblastoma, a case report of local and distant eradication of intracranial and spinal tumour deposits following intraventricular infusion of IL13Ra2-CAR T-cells indicates the potential of this approach. However, in contrast to the sustained complete remissions observed in haematological malignancies, in the majority of patients with glioblastoma CAR T-cell therapy has not resulted in clinical benefit. Tumour heterogeneity and the highly immune inhibitory tumour microenvironment (TME) are likely key barriers to achieving durable anti-tumour immunity. Here use intra-tumoural administration of IL-12 to enable CAR T-cell immunity. We employed CAR-T cells targeting the tumour-specific epidermal growth factor variant III (EGFRvIII). In an immunocompetent orthotopic mouse model of high-grade glioma, we show that CAR-T cells alone failed to control fully established tumour, but when combined with a single, locally delivered dose of IL-12, durable antitumor responses were achieved. IL-12 not only boosted cytotoxicity of CAR T-cells, but also reshaped the TME driving increased infiltration of proinflammatory CD4+ T-cells, decreased numbers of regulatory T-cells (Tregs) and activation of the myeloid compartment. Critically, immunotherapy enabling benefits of IL-12 were achieved with minimal systemic effects. Our findings show that local delivery of IL-12 is an effective adjuvant for CAR-T cell therapy for high-grade glioma. Assessment of application in high-risk childhood brain tumours is ongoing.

IMMU-17. CAR T CELLS TARGETING THE INTEGRIN ALPHA$_V$BETA$_3$ EXHIBIT ROBUST ANTI-TUMOR RESPONSES AGAINST DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) AND GLIOBLASTOMA (GBM)

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Effective therapies for DIPG and GBM are lacking. CD19 chimeric antigen receptor (CAR) T cells are highly effective in patients with refractory B-cell malignancies. We aim to develop novel CARs for high-grade gliomas. The integrin complex alpha$_v$beta$_3$ was selected as a CAR-T cell target due to its expression on gliomas and their vasculature, yet with minimal expression throughout normal tissues, vessels and organs. Indeed, a majority of DIPG and GBM cell lines express surface $\alpha_v\beta_3$. Second-generation CAR-T cells expressing an anti-$\alpha_v\beta_3$ scFv and either a CD28 or 4-1BB co-stimulatory domain and CD3zeta were constructed. Transduced healthy, donor-derived T cells exhibited high level CAR expression, efficient expansion, and representative populations of memory subsets including central, effector, and stem cell-like memory CAR-T cells. $\alpha_v\beta_3$.28z and $\alpha_v\beta_3$.BBz CAR-T cells exhibited antigen-specific *in vitro* cytotoxicity and cytokine production against DIPG and GBM cell lines. Both CARs mediated rapid and robust anti-tumor responses in NSG mice bearing orthotopic DIPG or GBM tumors. 5/13 $\alpha_v\beta_3$.28z and 0/14 $\alpha_v\beta_3$.BBz treated animals died without detectable disease within 2 weeks of infusion suggesting different toxicity profiles and is consistent with faster CAR-T cell expansion in CD28-versus 4-1BB-containing CD19 CAR-T cells seen clinically. Our results demonstrate that $\alpha_v\beta_3$.BBz CAR-T cell therapy may be both highly effective and safe in DIPG and GBM patients. Due to the restricted nature of $\alpha_v\beta_3$ expression in normal tissues, the robust responses seen in tumor-bearing mice, and the slower kinetics of $\alpha_v\beta_3$.BBz CAR-T cell expansion, a first-in-human clinical trial is being planned.

IMMU-18. FAVORABLE OUTCOME IN REPLICATION REPAIR DEFICIENT HYPERMUTANT BRAIN TUMORS TO IMMUNE CHECKPOINT INHIBITION: AN INTERNATIONAL RRD CONSORTIUM REGISTRY STUDY

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Pediatric brain tumors with replication repair deficiency (RRD) are hypermutant and may respond to immune checkpoint inhibition (ICI). We performed a consortium registry study of ICI in recurrent RRD cancers. Clinical and companion biomarkers were collected longitudinally on all patients. Biomarkers included tumor mutational burden (TMB), neoantigens and genetic signatures obtained from whole genome and exome sequencing. Immune inference was obtained by RNAseq and T cell rearrangement was collected in the tumor and in blood throughout treatment. Of the 46 tumors on the study, 32 were brain tumors with glioblastoma in 96%. Rapid, objective responses (>50%) were observed in 50% of glioblastomas. Three year overall survival for the whole cohort was 48+/-8% which compares favorably with historical controls. Brain tumors fared worse with OS of 39+/-10% and late recurrences observed even after 2 years of therapy (p=0.02). Tumor size and acute "flare" constitute poor outcome throughout all cancers. While all tumors are hypermutant, TMB and predicted neoantigens correlated with response to ICI (p=0.02). Specific signatures extracted from SNVs and total mutations predicted response to ICI and favorable outcome (p=0.005). RNA inference and TCR reveal that the FLARE phenotype is mostly acute nonspecific immune response and not true progression. Finally, glioblastomas (n=8) which failed single agent ICI had favorable responses to combinational immunotherapies with prolonged survival of 65%+/-8% at one year after failure vs 0 for other patients (p=0.01). RRD glioblastomas exhibit favorable outcome and responses to ICI. Combinational therapies based on tumor and immune signatures of these cancers are necessary.

IMMU-19. HDAC INHIBITORS SENSITIZE MYC-AMPLIFIED MEDULLOBLASTOMA TO IMMUNOTHERAPY BY ACTIVATING THE NF-KB PATHWAYS

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Medulloblastoma is the most common malignant brain tumor in childhood and comprises four distinct molecular subgroups with further layers of intertumoral heterogeneity. Amplification of the oncogene MYC drives tumorigenesis and constitutes a hallmark feature underlying Group 3 biology. Employing our in-house drug screening pipeline, we evaluated a library of epigenetic inhibitors (n=78) in various brain tumor cell lines followed by a secondary HDACi library (n=20) screen, we identified the clinically established, class I selective HDACi CI-994 as the compound with the most preferential antitumoral effect in MYC-driven medulloblastoma. We confirmed that the inhibitor response was in part MYC-dependent as our lentiviral-based MYC-overexpression model showed higher sensitivity towards CI-994 treatment as compared to the isogenic control with low endogenous MYC expression. CI-994 showed significant antitumoral effects at the primary site and at the metastatic compartment in two orthotopic mouse models of MYC-driven medulloblastoma. RNA sequencing profiling of tumor cells treated with CI-994 at IC50 revealed an up-regulation of multiple innate inflammatory pathways like NFκB, TLR4, Interferon-gamma, and TGFbeta. Flow cytometry analysis revealed an increased surface expression of MHC-I. We combined CI-994 with an anti-body against the innate checkpoint CD47 which acts as a "don't eat me" signal previously shown by us to have significant anti-tumor activity against MYC-driven MB. Combining CI-994 with anti-CD47 shows a significant increase in macrophage-mediated phagocytosis of tumor cells and a significant increase in the survival of tumor-bearing mice.

IMMU-20. EVALUATION OF CAR T CELLS IN EPENDYMOMA

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BACKGROUND: Ependymoma is the third most common pediatric brain tumor and current treatment still results in a 10-year relapse rate of over 70% in the highest risk groups. The treatment refractory nature of ependymoma to standard therapies strongly supports the development of novel interventions. Ependymoma tumor cells express HER2 and there are active clinical trials treating children with ependymoma using local delivery of second-generation HER2 CAR T cells. METHODS: Two high-risk patient-derived ependymoma cell lines, MAF811 and MAF928, that display HER2 surface expression are used for testing. We tested second-generation HER2-BBz CAR T cells in vitro and in vivo. RESULTS: HER2 CAR T cells effectively kill ependymoma tumor cells in culture, but this strategy cannot eradicate the same tumor cells in mice when implanted in the fourth ventricle of the brain. HER2 CAR T cells proliferate and traffic into the tumor, but this causes a dramatic influx of immune cells, tumor swelling and lethal toxicity in a subset of mice. Mice that survive this initial tumor swelling, display significant tumor shrinkage but all tumors eventually start growing again. Ependymoma tumor cells release high amounts of inflammatory chemokines that strongly attract neutrophils and monocytes to the tumor, compared to other brain tumors, and can downregulate HER2 expression to escape recognition by CAR T cells. CONCLUSION: The immunosuppressive microenvironment as well as tumor heterogeneity make HER2 CAR T cells ineffective in ependymoma. Studying these two hurdles in CAR T cell therapy is critical to effectively treat brain tumors with CAR T cells.

IMMU-21. INVESTIGATION OF WHITE BLOOD CELL CHARACTERISTICS IN CSF SAMPLES AT PEDIATRIC BRAIN TUMOR DIAGNOSIS

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BACKGROUND: There has been a recent surge in investigation of immunity and immunotherapy, but their role in pediatric brain tumors is incompletely defined. We hypothesized that investigating an understudied dataset, WBC and differential results in CSF drawn at the time of pediatric brain tumor diagnosis to look for microscopic metastases, would provide insight into the role of immunology and potential for immunotherapy in these diseases and correlate with prognosis and/or metastasis. METHODS: We conducted a retrospective comparison analysis of CSF values in 349 patients at our institution from samples drawn within 60 days of initial CNS tumor diagnosis from 1998–2018. We examined total nucleated cell count, absolute counts and percentages for WBC subtypes. We compared CSF values by tumor cell presence, patient vital status, and disease group: atypical teratoid rhabdoid tumor, ependymoma, germinoma, high-grade glioma (HGG), low-grade glioma (LGG), medulloblastoma, non-germinomatous germ cell tumor, and other embryonal tumors (OET). We used Wilcoxon and Kruskal-Wallis tests for comparisons. RESULTS: Overall, higher lymphocyte percentage (p=0.002) and lower monocyte percentage (p=0.007) were associated with survival. WBC characteristics did not differ significantly based on tumor cell presence. Compared to medulloblastoma, ependymoma showed a more active CSF immune response, while LGG, HGG, and OET showed a less active response, based on total WBC and/or absolute neutrophil count (p=0.001–0.007). CONCLUSIONS: Higher lymphocyte and lower monocyte percentages in CSF correlated with better prognosis overall; causality requires further investigation. Tumor subtypes varied in their immune stimulation, offering potential insight into which will be amenable to immunotherapy.

IMMU-22. PHASE IB IMMUNOTHERAPY CLINICAL TRIAL WITH THE USE OF AUTOLOGOUS DENDRITIC CELLS PULSED WITH AN ALLOGENIC TUMORAL CELL LINES LYSATE IN PATIENTS WITH NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

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BACKGROUND: Diffuse intrinsic pontine glioma (DIPG) is a lethal condition, and therefore novel approaches are needed. Monocyte-derived dendritic cells (mDCs) pulsed with tumor antigens, as professional antigen-presenting cells, are a promising strategy for immunotherapy of invasive brain tumors. METHODS: Our Ib pilot study explored the use of immunotherapy with mDCs for the treatment of newly diagnosed DIPG. Patient´s mDCs were extracted after irradiation and were primed with an allogenic tumor lysate from five patients with K27M-mutated DIPGs. The principal goal of this study was to establish the feasibility and safety of the intradermic administration of these mDC vaccines in patients with DIPG. In the absence of progression, patients received maintenance boosts of tumor lysate. Additionally, we evaluated the non-specific and antitumoral immune response generated in peripheral blood mononuclear cells (PBMC) and in cerebrospinal fluid (CSF) cells. RESULTS: Nine patients were included in the study (2016–2018). Vaccines fabrication was feasible and administered in all cases without grade 3 or 4 toxicities. KLH (9/9 patients) and antitumor (8/9 patients) specific responses were identified in PBMC. Immunological responses were also confirmed in T-lymphocytes from the CSF of two patients. Twenty-four month overall survival and progression free survival was 33.3% (95 % CI 13.2% to 84.0 %) and zero, respectively. DISCUSSION: These results demonstrate that mDC vaccination is feasible, safe, and generates a DIPG-specific immune response detected in PBMC and CSF. There was a trend in improved OS when compared to historic controls. This strategy shows a promising immunotherapy backbone for future combination schemas.

IMMU-23. A NOVEL MASS CYTOMETRY-BASED MULTI-PARAMETER CHARACTERIZATION OF NEOANTIGEN-REACTIVE CD8+ T-CELLS IN PATIENTS PARTICIPATING IN PNOC007 H3.3K27M PEPTIDE VACCINE CLINICAL TRIAL

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BACKGROUND: We have identified an HLA-A*02:01-restricted neoantigen epitope encompassing the H3.3K27M mutation and implemented a multi-center clinical trial of the peptide vaccine through the Pacific Pediatric Neuro-Oncology Consortium (PNOC007) for patients with diffuse midline glioma (DMG), including diffuse intrinsic pontine glioma (DIPG). We sought to characterize vaccine-reactive CD8+T-cells subpopulations using their precise activation and developmental status to find their associations with clinical outcomes. METHODS: Mass cytometry (CyTOF) analysis was performed on patient-derived peripheral blood mononuclear cells collected at baseline as well as pre-specified time points throughout the study. Each cell subtype was characterized via tSNE-clustering based on their expression profiles and quantified as a fraction of total CD45+cells. H3.3K27M-reactive CD8+T-cells were evaluated using an H3.3K27M-

HLA-A2 dextramer along with a panel of T-cell and myeloid markers. RESULTS: Among all 29 patients enrolled, we analyzed samples from all 19 DIPG and 9 of 10 non-brainstem DMG cases, of which 18 had longitudinal samples available (range: 2–5). Utilizing a novel CyTOF-based immunomonitoring platform, the expansion of H3.3K27M-reactive CD8+T-cells, defined as a 25% increase at any time-point relative to baseline, was observed in 7 of these 18 patients. Survival analyses indicated that the expansion of H3.3K27M-reactive CD8+T-cells, particularly the effector-memory phenotype, positively correlated with longer overall survival (OS) (median: 16.1 vs 9.7 months, p=0.03), whereas an abundance of early and monocytic myeloid-derived suppressor cells at baseline correlated with shorter OS among DIPG patients (9.5 vs 14.3 months, p=0.002). CONCLUSION: Our novel immuno-monitoring approach offers insight into how vaccine-induced immune responses impact clinical outcomes.

IMMU-26. DISEASE CONTROL IN A PEDIATRIC PATIENT WITH NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME (GBM) AND SOMATIC HIGH MICROSATELLITE INSTABILITY (MSI-H) WITH PD-1 INHIBITOR NIVOLUMAB (NIVO) ONLY AND NO FOCAL RADIOTHERAPY (RT)

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Immune checkpoint inhibitors that target programmed death receptor-1 (PD-1) have recently been shown to be a promising option for the management of recurrent mismatch repair (MMR) deficient GBM following radiotherapy. We report a case of a 9-year-old boy who presented with a 6 week history of frontal headaches and was found to have a left frontal lobe mass. Pathology obtained from a gross total resection (GTR) was consistent with classic GBM, WHO Grade IV. Neuroimaging four weeks following initial resection was remarkable for local recurrence. The patient underwent another GTR of the tumor at our center. While pathology again confirmed GBM, GlioSequencing of tumor tissue from second resection showed MSI-H, *NF2* mutation p.R338H, *NF1* mutations p.R2450* and pI193Yfs*11, *TP53* mutations p.R213* and p.R273C, *EGFR* mutation, and multiple variants of uncertain significance. Germline testing was negative for MMR deficiency or other deleterious mutations. Parents opted to defer radiotherapy and consented to monotherapy treatment with Nivolumab (Opdivo, BMS pharmaceuticals, USA), a PD-1 inhibitor, at a dose of 3 mg/kg administered every two weeks. Our patient is now 22 months post-second resection and continues to receive Nivolumab without evidence of recurrent disease or adverse autoimmune effects from PD-1 blockade. He has remained in school with good academic performance and has exhibited no regression of functional status during the entirety of his treatment course. This case provides evidence of possible efficacy of PD-1 blockade without focal radiotherapy in this child with GBM and somatic MSI instability.

IMMU-27. ANALYSIS OF IMMUNE SIGNATURES IN PEDIATRIC GLIOBLASTOMAS FOR PATIENT STRATIFICATION TO IMMUNOTHERAPY

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BACKGROUND: Pediatric glioblastoma (pGBM), despite being relatively rare (incidence rate: 0.5/100,000), are a leading cause of cancer deaths in children with a median overall survival of 9–15 months. In recent years, immunotherapy has emerged as one of the more promising advances in oncology, with impressive response rates reported in several malignancies. Effective application of immunotherapy in brain tumors depends upon a better understanding of the immune cell phenotype and mechanisms of immunosuppression in these tumors. This understanding will allow for the selection of patient population who are most likely to benefit from immunotherapeutic approaches. MATERIAL AND METHODS: In order to determine the frequency, distribution, and phenotype of tumor-infiltrating immune cells in pGBMs, we undertook an immunohistochemical survey on 19 recurrent pGBMs for CD3, CD8, CD4, CD163, PD-1, PD-L1, and FoxP3; RNA-Seq was also performed on a subset of 9 cases. Distribution of lymphocytes (LYMPHS) was recorded as intratumoral (IT) or perivascular (PV). RESULTS: The analysis indicates intratumoral CD3+ LYMPHS are commonly <5% of tumor cell mass; however, approximately half (10/19) of these recurrent pGBM have infiltrates that range from 5 to 30% CD3+ LYMPHS. Of these, 4/10 CD3+ tumors exhibit brisk CD8+ infiltrates that are associated with PD-L1+ tumor cells. These tumors with brisk CD3+/CD8+ LYMPHS and PD-L1+ tumor cells were associated with longer survivals. The data were confirmed by RNA-seq analysis. CONCLUSION: PD-L1+ pGBMs associated with CD3+/CD8+ LYMPH infiltrates deserve further investigation as candidates for immunotherapy.

IMMU-28. IMMUNOGENOMIC ANALYSIS REVEALS LGALS1 CONTRIBUTES TO THE IMMUNE HETEROGENEITY AND IMMUNOSUPPRESSION IN GLIOMA

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Mutualistic and dynamic communication between tumour cells and the surrounding microenvironment accelerates the initiation, progression, chemoresistance and immune evasion of glioblastoma (GBM). However, the immunosuppressive mechanisms of GBM has not been thoroughly elucidated to date. We enrolled six microenvironmental signatures to identify glioma microenvironmental genes. The functional enrichment analysis such as ssGSEA, ESTIMATE algorithm, Gene Ontology, Pathway analysis is conducted to discover the potential function of microenvironmental genes. In vivo and in vitro experiments are used to verify the immunologic function of LGALS1 in GBM. We screen eight glioma microenvironmental genes from glioma databases, and discover a key immunosuppressive gene (LGALS1 encoding Galectin-1) exhibiting obviously prognostic significance among glioma microenvironmental genes. Gliomas with different LGALS1 expression have specific genomic variation spectrums. Immunosuppression is a predominate characteristic in GBMs with high expression of LGALS1. Knockdown of LGALS1 remodels the GBM immunosuppressive microenvironment by down regulating M2 macrophages and myeloid-derived suppressor cells (MDSCs), and inhibiting immunosuppressive cytokines. Our results thus implied an important role of microenvironmental regulation in glioma malignancy and provided evidences of LGALS1 contributing to immunosuppressive environment in glioma and that targeting LGALS1 could remodel immunosuppressive microenvironment of glioma.

IMMU-29. AIF1 IS A PROGNOSTIC BIOMARKER AND CORRELATED WITH IMMUNE INFILTRATES IN GLIOMAS

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Gliomas remain highly variable clinical behaviors, leading to emerging studies to identify prognostic factors. AIF1 (Allograft Inflammatory Factor 1) is critical for promoting both macrophage- and dendritic cells (DCs)-mediated inflammatory response and growth of vascular smooth muscle cells and T-lymphocytes. Through comparative analyses of primary LGG patients from The Cancer Genome Atlas (TCGA) dataset and Chinese Glioma Genome Atlas(CGGA) dataset, we reported that the expression level and methylation level of AIF1 gene vary among glioma patients and AIF1 expression or gene body methylation is significantly associated with glioma patient survival. Cox regression results confirmed that AIF1 played an independent predictor of survival in lower-grade glioma(LGG), with a cox coefficient of 0.251 indicating a worse prognosis. Moreover, AIF1 expression was positively correlated with infiltrating levels of CD4+ T and B cells, macrophages, neutrophils, and DCs in LGG and glioblastoma(GBM). AIF1 expression also showed strong correlations with specific immune cell markers in LGG and GBM. In addition, AIF1 expression potentially contributed to the regulation of glioma-associated macrophages and microglia. In conclusion, our findings suggested that AIF1 was correlated with prognosis and immune infiltrating levels, and it can be used as a prognostic factor in gliomas.

IMMU-30. UPREGULATED T CELL AND INTERFERON-Γ-RELATED GENE EXPRESSION IS ASSOCIATED WITH INCREASED SURVIVAL IN RECURRENT PEDIATRIC HIGH-GRADE GLIOMA

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Recurrent pediatric high-grade glioma (pHGG) is the leading cause of cancer-related mortality in children. Immunotherapy is a successful treatment approach for a growing number of cancers and is being investigated as a treatment strategy for pHGG. Immunotherapy has shown the most benefit in tumors with increased infiltrating T cells at baseline. Our recently published results revealed that neoadjuvant checkpoint inhibition in recurrent adult glioblastoma was associated with upregulation of a T cell and interferon-γ-related gene expression signature (Tcell-IFNγGES) and was correlated with a significantly extended overall survival (OS). In this study, we examined the immune landscape in recurrent pHGG and the association of Tcell-IFNγGES in the tumor with survival. We analyzed tumor RNAseq data collected at time of recurrence from a historical cohort of 42 pHGG patients from the Children's Brain Tumor Tissue Consortium. We found a significant transcriptional enrichment of Tcell-IFNγGES in 54% of the tumors. The survival of patients with high Tcell-IFNγGES was observed to be significantly higher than patients with low Tcell-IFNγGES, (log-rank p=0.05). The 3-year OS for patients with low *versus* high Tcell-IFNγGE was 28.5% (95%, CI:13.7%-59.5%) compared to 50.2% (95%, CI:33.1%-76.1%). When patients were stratified by age, gender and race, low Tcell-IFNγGES was found to be a poor OS prognostic factor (hazard ratio=2.4 (1.14–5.14), p=0.02). This indicates a strong relationship of decreased Tcell-IFNγGES and increased risk of death. Future investigations are necessary to validate these findings, and to explore the value of Tcell-IFNγGES as a predictive biomarker for response to immunotherapy in pHGG.

IMMU-31. PNOC007: H3.3K27M SPECIFIC PEPTIDE VACCINE COMBINED WITH POLY-ICLC FOR THE TREATMENT OF NEWLY DIAGNOSED HLA-A2+ H3.3K27M DIFFUSE MIDLINE GLIOMAS (DMG)

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OBJECTIVE: To assess safety and efficacy within a multi-center trial the H3.3K27M specific peptide vaccine with poly-ICLC in HLA-A02.01$^+$ patients diagnosed with H3.3K27M$^+$ DMGs. METHODS: After focal radiation therapy, participants 3–21 years of age were enrolled into two strata. Stratum A: newly diagnosed diffuse intrinsic pontine glioma (DIPG); Stratum B: other DMGs. H3.3K27M vaccine was administered with poly-ICLC IM every 3 weeks for 8 doses followed by every 6 weeks for a total of 96 weeks. Immuno-monitoring of peripheral blood mononuclear cell (PBMC) and imaging occurred every 3 months. Modified iRANO criteria were applied. PBMC samples were evaluated by mass cytometry. RESULTS: From November 2016 until March 2019, 19 eligible patients (median age 11, range 5–17 yrs; 53 % female) were enrolled in Stratum A and 10 eligible patients (median age 13, range 7–18 yrs; 60 % female) in Stratum B. Treatment was well tolerated (7 grade 3; 0 grade 4 related toxicities). Median number of vaccines per participant was 6 (range 1–11). Overall survival at 12 months was 40% (95% CI 22–73%) for Stratum A and 39% (95% CI 16–93%) for Stratum B. Among the 19 subjects with longitudinal immune cell assessments, 7 exhibited an expansion of K27M-reactive CD8+ effector memory T-cells correlating with prolonged survival (p=0.028). CONCLUSION: H3.3K27M specific vaccine in combination with poly-ICLC is well tolerated. CyTOF-based immune monitoring of PBMCs facilitates sensitive high-throughput analysis. Further investigation is warranted to determine if this may be predictive of clinical outcomes.

LOW GRADE GLIOMA

LGG-01. CLINICAL MANAGEMENT AND GENOMIC PROFILING OF PEDIATRIC LOW-GRADE GLIOMAS IN SAUDI ARABIA

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Pediatric Low Grade Gliomas (PLGGs) display heterogeneity regarding morphology, genomic drivers and clinical outcomes. The treatment modality dictates the outcome and optimizing patient management can be challenging. In this study, we profiled a targeted panel of cancer-related genes in 37 Saudi Arabian patients with pLGGs to identify genetic abnormalities that can inform prognostic and therapeutic decision-making. We detected genetic alterations (GAs) in 97% (36/37) of cases, averaging 2.51 single nucleotide variations (SNVs) and 0.91 gene fusions per patient. The *KIAA1549-BRAF* fusion was the most common alteration (21/37 patients) followed by *AFAP1-NTRK2* (2/37) and *TBLXR-PI3KCA* (2/37) fusions that were observed at much lower frequencies. The most frequently mutated) genes were NOTCH*1 3* (7/37), *ATM* (4/37), *RAD51C* (3/37), *RNF43* (3/37), *SLX4* (3/37) and *NF1* (3/37). BRAF V600E mutations were observed in only 2/37 patients, while H3F3A (K27M) histone mutations were not detected. Interestingly, we identified a GOPC-*ROS1* fusion in an 8-year-old patient whose tumor lacked *BRAF* alterations and histologically classified as low grade glioma. The patient underwent gross total resection (GTR) currently he is disease free. To our knowledge this is the first report of *GOPC-ROS1* fusion in PLGG which may represent a genomically-distinct subgroup of pLGGs that could be targeted with oral target therapy crizotinib. Taken together, we reveal the genetic characteristics of pLGG Saudi patients can enhance diagnostics and therapeutic decisions. In addition, we identified a GOPC-*ROS1* fusion that may be a biomarker for pLGG. Our study proves the possibility of using genetic profiling to guide optimal treatment strategies for pLGG in Saudi population

LGG-02. A BRAIN TUMOR DIAGNOSED AFTER TRANSITION TO THE DEPARTMENT OF ADULT NEUROSURGERY FROM THE DEPARTMENT OF PEDIATRICS

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The patient was a 17-year-old boy with a history of 4 non-febrile convulsions at 15 and 16 years of age. He visited the Department of Pediatrics at a pediatric hospital. An electroencephalogram showed right frontal spike discharge. MRI was performed and judged to show no abnormality. The pediatric doctor diagnosed him with epilepsy. At 17 years old, he was referred to our Department of Adult Neurosurgery for transition. Physical and neurological examinations showed no abnormalities. Brain MRI showed right frontal cortical small tumor, with T1 low, T2 high, diffusion-weighted imaging low, and partial contrast enhancement. We diagnosed him with a brain tumor and symptomatic epilepsy. We surgically removed a right frontal cortical tumor. A pathological examination finalized the diagnosis of dysembryoplastic neuroepithelial tumor. MRI confirmed the total removal of the tumor. Anticonvulsant was started before surgery. No epileptic seizure was observed, so the anticonvulsant medication was gradually tapered and stopped at two years after the surgery. No epilepsy nor recurrence has been observed thus far. The problem with the initial management of this case at the Department of Pediatrics in the pediatric hospital was that the brain tumor was missed despite an MRI examination. Had the transition not happened, this brain tumor might not have been diagnosed. A brain tumor is a rare disease, and epilepsy is a common disease. However, in cases of non-febrile convulsion, a brain tumor should be considered. Collaboration within a single department, hospital and local area should be established.

LGG-03. INCIDENCE AND OUTCOME OF PEDIATRIC IDH-MUTANT GLIOMA

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INTRODUCTION: The incidence of *IDH* mutations in pediatric glioma is unclear. Recent publications suggest rates ranging between 0–20%.

Therapy poses challenges as it is unclear if the biology and prognosis of pediatric *IDH*-mutant gliomas are identical to adults. METHODS: We performed an IRB approved, systematic retrospective search for *IDH*-mutant gliomas in the Dana-Farber Cancer Institute/Boston Children's Hospital database between 2009–2018, analyzing incidence, demographics, histology, co-occurring genetic alterations and outcome. RESULTS: We identified 575 patients with glioma, ages 0–21 years. Of these, 394 underwent biopsy/resection (0–9 years:n=204; 10–21 years:n=190), with 294 genetic testing. Fifteen of 294 tumors (5%) were *IDH1*-mutant. Among patients 0–9 years and 10–21 years, 1/156 (0.6%) and 14/138 (10%) had *IDH1*-mutant tumors, respectively. Among patients 10–21 year old, 13/115 low-grade gliomas were *IDH1*-mutant (11%). High-grade gliomas accounted for the remaining 23, with one *IDH1*-mutant glioma (4%). Most common co-occurring genetic alterations for diffuse astrocytoma (n=12) were *TP53* (n=9) and *ATRX* (n=2). Three patients with *IDH1*-mutant oligodendrogliomas had 1p/19q deletion. Eleven *IDH1*-mutant patients were evaluable for outcomes with median follow-up of five years. Five-year radiation-free, progression-free and overall survival for patients with low-grade histology were 76% and 100%, respectively. One patient with high-grade glioma recurred 1.2 years after upfront chemo-radiation and died soon after recurrence. CONCLUSION: *IDH*-mutant gliomas comprise a small proportion of pediatric gliomas. Incidence rate is higher in the second decade of life. Comparative analyses between pediatric *IDH*-mutant gliomas and adult historical cohorts are currently underway, evaluating outcomes, radiation therapy and frequency of malignant transformation.

LGG-04. A PHASE II RE-TREATMENT STUDY OF SELUMETINIB FOR RECURRENT OR PROGRESSIVE PEDIATRIC LOW-GRADE GLIOMA (PLGG): A PEDIATRIC BRAIN TUMOR CONSORTIUM (PBTC) STUDY

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The PBTC conducted a re-treatment study (NCT01089101) evaluating selumetinib (AZD6244, ARRY-142886), a MEK I/II inhibitor, in children with recurrent/progressive pLGG. Eligible patients must have previously enrolled on PBTC-029 or PBTC-029B and progressed after coming off treatment with selumetinib. Patients must have maintained stable disease (SD) for ≥12 courses or had a sustained radiographic response (partial or complete) during their first exposure to selumetinib. Thirty-five eligible patients (median age: 13.11 years [range 7.96–25.33]) were enrolled, 57% of whom had optic pathway or hypothalamic target lesions. At the time of submission, median duration of treatment was 18 courses (range 2–48) and 21 subjects remained on therapy. Best responses reported to date are 6/35 (17%) partial response, 22/35 (63%) SD and 7/35 (20%) progressive disease with a 2-year progression-free survival of 75.7 + 8.3%, which met the design parameters for success. The most common attributable toxicities were grade 1 diarrhea, elevated AST, hypoalbuminemia, elevated CPK, maculo-papular rash, fatigue, paronychia, ALT elevation, acneiform rash and grade 2 CPK elevation. Rare grade 3 toxicities included CPK elevation (3), lymphopenia (2), paronychia (2) and ALT elevation (2). There was only one grade 4 CPK elevation. Five patients (14%) required dose reductions due to toxicity. There does not appear to be a notable difference in toxicities observed during initial selumetinib therapy versus re-treatment. In pLGG that has recurred/progressed following treatment with selumetinib, re-treatment with selumetinib appears to be effective with 80% of patients again achieving response or prolonged stable disease. Long-term follow-up is ongoing.

LGG-05. MOLECULAR GUIDED THERAPY FOR A PEDIATRIC LOW GRADE GLIOMA: A CASE REPORT

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Low grade gliomas are the most common type of central nervous system tumors among children. Despite the fact that they are not typically life threatening, low grade gliomas remain a significant clinical challenge. Case Study: Patient is a 4-year-old male who presented at 20 months of age with several weeks of ataxia, emesis, and head tilt. Imaging revealed a right temporal lobe lesion; he was subsequently taken to surgery, where a gross total resection was achieved. Imaging 9 months post resection revealed recurrent disease within the right temporal region with leptomeningeal involvement. Four months later imaging revealed progression of multifocal disease and new growth within the sella. At this time the patient started standard treatment, Carboplatin and Vincristine, per CCG 9952A. Persistent slow progression was observed despite receiving standard therapy. The patient developed a grade 3 reaction to carboplatin, worsening with each subsequent dose. At this time, he was referred to our Precision Genomics Neuro Oncology program for tumor molecular characterization. Somatic tumor testing revealed an ETV6-NTRK3 fusion, at which time standard treatment was stopped, and patient began targeted therapy, Larotrectinib. Imaging was preformed 2 months post start of targeted therapy and revealed interval decrease in size of previously enhancing nodular lesions; findings consistent with treatment response. Disease burden continues to decrease with therapy. This case illustrates a clear benefit of using molecular guided therapy in low grade gliomas.

LGG-06. LONG-TERM OUTCOME OF NEWLY DIAGNOSED LOW GRADE GLIOMA

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INTRODUCTION: Low grade glioma (LGG) is the most common central nervous system (CNS) tumor in children accounted for 30–50%. Regarding benign characteristic of disease, surgical management remains the mainstay of treatment. However, surgical approach is limited in some conditions such as location at brainstem or infiltrative tumor. Chemotherapy and radiation treatments have been included in order to control tumor progression. The 5-years survival rate is approach 90% especially in patients who receive complete resection. However, the outcome of children with LGG in low to middle income is limited. Therefore, the aim of the study was to determine long-term outcome of children with newly diagnosed LGG. METHODS: A retrospective study enrolled children aged <18 years who were newly diagnosed LGG during January 2006- December 2019. Diagnosis of LGG was confirmed by histological findings of grade I and II according to WHO criteria. RESULTS: A total of 40 patients, female to male ratio was 1:1.35 and mean (SD) for age was 6.7 (4.0) years. The most common location was optic chiasmatic pathway (42.5%), followed by suprasellar region (25.0%). Sixty percent of patients received at least partial tumor removal. Chemotherapy and radiation had been used in 70% and 10.0% respectively. The 10-year progression free survival was 74.1±11.4% and overall survival was 96.2±3.8%. SUMMARY: Treatment of Pediatric LGG mainly required surgical management, however, chemotherapy and radiation had been used in progressive disease. The outcome was excellent.

LGG-09. CORRELATING GENETIC SIGNATURE OF PILOMYXOID ASTROCYTOMAS AND PILOCYTIC ASTROCYTOMAS WITH QUALITATIVE AND QUANTITATIVE MR IMAGING CHARACTERISTICS

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PURPOSE: Pilomyxoid astrocytomas are predominantly located in supra-chiasmatic region and are more clinically aggressive than pilocytic astrocytomas, although recent WHO 2016 classification placed them into the grade I/II category. In our study, we describe imaging correlation of PMA to their genetic signature. MATERIALS AND METHODS: We identified 12 pediatric patients with pathologically proven PMA, PA, and PA with myxoid features in an IRB approved study. Three of the tumors had whole exome somatic and germline sequencing. Qualitative MRI characteristics of location, size, enhancement, edema, T2 and T1 intensity, and multifocality were assessed. RESULTS: Among the PMA, 3 cases were found to have *KIAA1549-BRAF* fusion, 1 case *BRAF* V600E mutation, and 2 cases had wildtype *BRAF*. The *BRAF* wildtype tumors had atypical imaging features with intraventricular extension of tumor, involvement of frontal lobe parenchyma and one tumor demonstrating increase in size and development of enhancement at 5 years. Whole exome sequencing of *BRAF* wildtype tumors identified somatic truncation mutations in *NF1* R1534X and R1513X with wildtype germline *NF1* and missense mutations in KMT2C and GLTSCR1. Among PAM, one was *BRAF* wildtype with mutations i *PTCH1* M956V and *PTPN1* (A72V) and demonstrated atypical features of intratumoral hemorrhage on presentation. Among PA, one was positive for *KIAA1549-BRAF*, one was *BRAF* wildtype. CONCLUSIONS: *BRAF* wildtype PMA and PA demonstrate atypical tumor localization and are associated with atypical genetic mutations on whole exome sequencing. On the contrary, presence

of *KIAA1549-BRAF* fusion or *BRAF* V600E mutation within PMA and PA correlates with classic qualitative imaging characteristics.

LGG-11. INSTITUTIONAL EXPERIENCE OF BRAF TARGETING THERAPY

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BACKGROUND: The use of BRAF inhibitors is widely accepted in adult oncology as treatment for BRAF mutated cancers. BRAF alterations are frequently found in both pediatric low grade and high-grade gliomas, which has opened a new door to targeted therapies for pediatric gliomas. Targeted therapy drugs are associated with predictable patterns of adverse events. However treating in children may potentiate unique challenges. We present our institutional experience of targeted therapy with a focus on adverse events. METHODS: We conducted a retrospective chart review of patients treated with BRAF and/or MEK inhibitors between 2015–2019. RESULTS: There are nine patients treated with either MEK inhibitor(n=) or the combination therapy(n=). The most common diagnosis was Pilocytic astrocytoma. Targeted therapy was chosen as salvage therapy in all patients. The most common side effect was a pruritic erythematous rash, observed in 8 out of 9 patients. Cardiac toxicity (Grade 2, n=1) and GI toxicity (Grade 3, n=1) were found in patients treated with MEK inhibitor. Both cases resulted in cessation of therapy or significant decreased dose respectively. While two patients died due to progression of disease and two other continued to progress, 5 patients have demonstrated stable disease while on therapy. CONCLUSIONS: Our study revealed the incidence of severe adverse events in two patients with BRAF targeted therapy. Due to the potential life-long use of targeted therapy, it is important to follow guidelines of adverse event monitoring and to develop a prevention and management strategy for severe adverse events.

LGG-12. TRAMETINIB FOR PEDIATRIC LOW GRADE GLIOMAS: A SINGLE INSTITUTION EXPERIENCE

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INTRODUCTION: Low grade gliomas (LGG) are the most common pediatric brain tumors. Tumors not amenable to resection can recur or progress despite treatment with chemotherapy and/or radiation. Recent discovery of the activation of the mitogen-activated-protein-kinase (MAPK) pathway as the primary oncogenic driver for this group of tumors has led to a shift towards the use of BRAF and MEK inhibitors. METHODS: Herein we performed a chart review of seven pediatric LGG treated with trametinib, a MEK inhibitor. While most were treated in the relapse setting, one patient was treated for de novo LGG as a result of experiencing multiple severe adverse effects to conventional agents. RESULTS: Median age was 14 years old (range: 5 to 17 years). Six of seven patients had tissue for molecular characterization. The 2 patients with Neurofibromatosis Type 1 (NF-1) carried no other molecular aberrations. Two had the BRAF V600e mutation (1 had a concurrent PTPN11 mutation) and 2 were positive for the KIAA1549-BRAF fusion. Average duration on treatment was 8 months (range: 3 to 31 months). Disease control was achieved in 6 of 7 subjects, with one PR as best response. One patient with concurrent BRAF V600e and PTPN11 mutations progressed on trametinib and was switched to dual BRAF and MEK inhibitor therapy. Most common toxicities were acne (57.1%), oral mucositis (42.9%), skin rash, and paronychia (both 28.6%). Three patients required dose reduction and/or intermittent dose interruption. CONCLUSION: Our data supports the use of trametinib for both upfront and relapsed/refractory pediatric LGG.

LGG-13. THE CLINICAL AND MOLECULAR LANDSCAPE OF GLIOMAS IN ADOLESCENTS AND YOUNG ADULTS

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OBJECTIVE: Pediatric low grade gliomas are typically driven by MAPK upregulation with excellent long-term survival. In contrast, adult lower grade gliomas commonly harbor IDH-1 mutations and undergo malignant transformation. Gliomas in adolescents and young adults (AYA) are an orphan group of tumors that have been poorly described. We aim to determine the clinical and molecular landscape of AYA gliomas. METHODS: A multi-institutional population based cohort of 839 patients diagnosed with glioma between 15–40 years has been identified. Complete molecular analysis, long term outcome and therapeutic data are being collected. RESULTS: Of 364 AYA gliomas analyzed, the prevalence of WHO grade I tumors was highest in those <21 years (54%), while the prevalence of higher grade tumors increased with age. Interestingly, only 38% harbor IDH-1 mutations while 23% harbor pediatric mutations, including 8% with BRAF p.V600E, and 4% with *KIAA1549:BRAF* fusion. The median age for IDH-1 mutation is 32 years, with highest frequency in WHO grade II and III tumors. In contrast, BRAF alterations were most frequently observed in WHO grade I and II tumors and enriched in those less than 20 years. Five-year progression-free survival for BRAF fusion, p.V600E and IDH-1 p.R132H were 81%, 78% and 26% respectively. No survivors were observed in H3 p.K27M and p.G34R gliomas ($p<0.0001$). CONCLUSIONS: Gliomas in AYA overlap pediatric and adult classification and exhibit enrichment for pediatric alterations. As the latter are associated with improved PFS and are amenable to targeted therapies, this should be considered in the work up of these tumors.

LGG-14. MULTI-OMIC ANALYSIS OF MAPK ACTIVATION IN PEDIATRIC PILOCYTIC ASTROCYTOMA

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Pilocytic astrocytomas (PA) are low-grade gliomas (pLGG) and are the most frequent childhood brain tumors. They are characterized by oncogene-induced senescence (OIS) initiated and sustained by senescence-associated secretory phenotype (SASP) factors. OIS and SASP in PA are thought to be driven by aberrations of the mitogen-activated protein kinase (MAPK) pathway (e.g. KIAA1549:BRAF fusion, $BRAF^{V600E}$ mutation, for the most common MAPK alterations occuring in PA), leading to its sustained activation. The MAPK pathway cascade is activated in a sequential manner: 1) ERK activation, which phosphorylates downstream partners in both cytoplasm and nucleus. 2) ERK-mediated induction of immediate early genes encoding transcription factors. 3) Induction of MAPK target genes expression. 4) Activation of downstream pathways. Our aim is to unravel the molecular partners involved at each level of the sustained MAPK pathway activation in pLGG with different genetic backgrounds (KIAA1549:BRAF fusion and $BRAF^{V600E}$ mutation), and leading to the induction of OIS and SASP factors expression. pLGG cell lines DKFZ-BT66 (KIAA1549:BRAF) and BT-40 ($BRAF^{V600E}$) were treated with the MEK inhibitor trametinib at key time points, and gene expression profile analysis was performed, allowing transcriptome analysis at each step of the MAPK cascade. This will be combined with a whole proteomic and phospho-proteomic analysis. Combination of the transcriptome and proteome data layers will allow the identification of a) downstream targetable partners activated by the MAPK pathway involved in PA senescence, b) new putative targets that might bring benefit in combination with MAPK inhibitors.

LGG-15. PEDIATRIC LOW-GRADE GLIOMAS IN SAUDI ARABIA: RETROSPECTIVE ANALYSIS OF CHILDREN WITH LOW-GRADE GLIOMAS TREATED IN KING FAHAD MEDICAL CITY KFMC-SINGLE INSTITUTIONAL EXPERIENCE

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Pediatric Low-grade gliomas (PLGGs) are extremely heterogeneous tumors and account for approximately 35% of childhood brain tumors. This retrospective study on 55 newly diagnosed children (<14 ys) with pathologically confirmed LGG from 2006 to 2016 aimed to review demographic data, clinical and therapeutic aspects and treatment outcome of PLGGs in children in Saudi Arabia. RESULTS: 33 (60.0%) males,22 (40.0%) females, median age at diagnosis 68 months. Pilocytic astrocytoma was the most common pathological diagnosis 42 (76.4%) location of tumor was Infratentorial in 30 patients (54.0%) and Supratentorial in 24 patients (43.2%), 19 patients (34.6%) had total surgical excision, 10 (18.2%) subtotal resection, 20 (36.4%) partial excision and 6 (10.9%) had biopsy only; After initial Surgery 30 patients (54.5%) required adjuvant chemotherapy of whom 14 patients (46.7%) experienced a treatment failure event, 25 patients (45.5%) who were initially observed post surgery 6 patients (24%) of them had relapse /progression and required further therapy. Only 2 patients (3.6%) received radiotherapy due to uncontrolled progression first line chemotherapy carboplatin and vincristine (CV) regimen was tolerated, Carboplatin allergic reactions developed in 21.1% of patients. Median follow-up of 6.49 years, the median time of relapse/ progression was 2.85 years The 5-year overall survival (OS) rates and progression free survival for all patients were 92.2 %, and 63.3% respectively. This study was to document the outcome of pediatric LGG in Saudi Arabia and to serve as a guideline for the future management with incorporation of molecular studies on pediatric LGGs which may help improve the outcome for Saudi children with LGG.

LGG-16. PILOMYXOID ASTROCYTOMA OF THE CERVICAL SPINAL CORD IN A 7-YEAR-OLD ARMENIAN BOY: A CASE REPORT

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BACKGROUND: Pilomyxoid astrocytoma (PMA) is a glial tumor that occurs predominantly in the hypothalamic-chiasmatic region and rarely in spinal cord. It has similar features as pilocytic astrocytomas, with some distinct histological characteristics and worse prognosis. The 2007 WHO recognized PMA as a Grade II glioma due to its aggressive behavior and dissemination tendency, but according to 2016 version grading of the pilomyxoid variant is under research. Here we report a case with a rare location, aggressive behavior and rapid progression. CASE PRESENTATION: A 7-year-old boy presented with headache, nausea, vomiting. Imaging revealed an intramedullary tumor extending from C2 to C6 with hydrocephalus. A ventriculo-peritoneal shunt and complete surgical resection were performed with significant improvement in the patient's condition. Histopathological findings were consistent with pilomyxoid variant of pilocytic astrocytoma, with negative BRAF V600E and MGMT. Three months later, the follow-up imaging revealed disease recurrence with leptomeningeal metastases, for which the patient received standard-dose craniospinal irradiation 35.2 Gy with boosts to tumor bed and metastatic sites 49.6 Gy and 54 Gy respectively. 11 months later tumor progression was revealed with new metastatic lesions in the bones. Patient received 6 cycles of chemotherapy with TMZ and Avastin, but continued to suffer disease progression on therapy and he succumbed to his disease at 24 months from diagnosis. CONCLUSION: Given the rarity of documented patients with spinal pilomyxoid astrocytoma with rapid progression, as well as the lack of certain WHO classification and treatment guidelines, this case report might be useful for development of more efficient treatment strategies.

LGG-17. SYNERGISTIC ACTIVITY OF MAPK INHIBITOR CLASSES REVEALED BY A NOVEL CELL-BASED MAPK ACTIVITY PEDIATRIC LOW-GRADE GLIOMA ASSAY

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Pilocytic astrocytomas (PAs) and other pediatric low-grade gliomas (pLGGs) exhibit aberrant activation of the MAPK signaling pathway caused by genetic alterations, most commonly KIAA1549:BRAF fusions, BRAF V600E and NF1 mutations. In such a single-pathway disease, novel drugs targeting the MAPK pathway (MAPKi) are prime candidates for treatment. We developed an assay suitable for pre-clinical testing of MAPKi in pLGGs, aiming at the identification of novel MAPK pathway suppressing synergistic drug combinations. We generated a reporter plasmid (pDIPZ) expressing destabilized firefly luciferase driven by a MAPK-responsive ELK-1-binding element, packaged in a lentiviral vector system. We stably transfected pediatric glioma cell lines with a BRAF fusion (DKFZ-BT66) and a BRAFV600E mutation (BT-40) background, respectively. Measurement of MAPK pathway activity was performed using the luciferase reporter. pERK protein levels were detected for validation. We performed a screen of a MAPKi library and calculated Combination Indices of selected combinations. The MAPKi library screen revealed MEK inhibitors as the class inhibiting the pathway with the lowest IC50s, followed by ERK and second generation RAF inhibitors. Synergistic effects in both BRAF-fusion and BRAFV600E mutation backgrounds were observed following combination treatments with different MAPKi classes (RAFi/MEKi, > RAFi/ERKi > MEKi/ERKi). We have generated a novel reporter assay for medium- to high-throughput pre-clinical drug testing of MAPKi in pLGG cell lines. MEK, ERK and next-generation RAF inhibitors were confirmed as potential treatment approaches for KIAA1549:BRAF and BRAFV600E mutated pLGGs. Synergistic suppression of MAPK pathway activity upon combination treatments was revealed using our assay in addition.

LGG-18. EVEROLIMUS TREATMENT IN PEDIATRIC PATIENTS AFFECTED BY LOW-GRADE GLIOMAS (PLGG) NON-TSC, BRAF V600-WT

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BACKGROUND: MAPK pathway is the hallmark of pediatric low grade gliomas (pLGGs); hyperactivation of mTOR (mammalian target of rapamycin) might be a suitable biomarker for therapeutic response. We investigated the feasibility of Everolimus, mTOR inhibitor, in patients affected by pLGGs. METHODS: Patients 1 to 18 years old, diagnosed with pLGG, with a positive tumor biopsy for mTOR/phospho-mTOR and radiological and / or clinical disease progression, treated at Bambino Gesù Children's Hospital in Rome were evaluated. Tumor DNA methylation analysis was performed in 10 cases. Exclusion criteria included: Tuberous Sclerosis patients, Sub Ependymal Giant Astrocytoma. Everolimus was administered orally at a dose of 2.5 mg or 5 mg daily based on body weight. Patients were evaluated with brain MRI every 4, 8 and 12 months after treatment start and every six months thereafter. RESULTS: 16 patients were enrolled from September 2014 and 2019. The median age was 7.5 years old. All patients had at least one adverse event. Events rated as severe (grade 3/4) were reported in 6 patients. Stomatitis was the most frequent adverse event. One patient discontinued treatment due to grade 4 toxicity (ulcerative stomatitis and fatigue). The median duration of treatment was 21 months (4–57 months). Brain MRI evaluations have showed disease stability in 11 patients, partial response in 2 patients and disease progression in 3 patients. CONCLUSIONS: Everolimus has proven to be well tolerated and effective treatment in terms of disease stability in patients with pLGGs. It's also an excellent example of chemo-free personalized approach.

LGG-19. SPINAL LOW-GRADE GLIOMAS IN CANADIAN CHILDREN: A MULTI-CENTRE RETROSPECTIVE REVIEW

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PURPOSE: Primary spinal low-grade gliomas (LGGs) are rare, can be difficult to treat, and can result in significant morbidity. The management of pediatric spinal LGGs remains controversial. METHODS: A national multi-centre retrospective review of spinal LGGs diagnosed in children less than 18 years of age between 1990–2015 was undertaken to examine the clinical features, pathological subtypes, and treatment outcomes. RESULTS: Forty-three patients from five institutions were included. The median age of diagnosis was 5.2 years. All patients were symptomatic at diagnosis. Forty-four percent of patients were diagnosed at least 6 months after symptoms developed. Two patients had metastatic disease at diagnosis. The most common histology was pilocytic astrocytoma (48.8%). Molecular information was available for 15/43 patients: 6 patients had *BRAF* fusions and 4 patients had *BRAF* V600E mutations. Gross-total resection was achievable in only 6 patients. Twenty-seven patients were treated with surgery-only and the others received chemotherapy and/or focal radiation. Eleven patients were irradiated. No patients were registered in clinical trials for first-line therapy. Twenty-three patients experienced relapse or progression. Patients were followed for a median of 8.3 years (range, 0.5–20.4 years). Five-year progression-free survival (PFS) and overall survival (OS) rates were 48.3% (95% CI, 32.3% to 62.5%) and 89.7% (95% CI, 74.6% to 96.1%) respectively. CONCLUSION: There is significant heterogeneity in surgical outcomes and treatment modalities of pediatric spinal LGGs. The PFS and OS rates remain suboptimal, likely due to tumor location. The low clinical trial enrollment rate highlights the paucity of available trials for spinal LGGs.

LGG-20. CLINICAL FEATURES AND TREATMENT RESULTS FOR PEDIATRIC OPTICO-HYPOTHALAMIC ASTROCYTOMA

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Current consensus for the treatment of optico-hypothalamic astrocytoma (OHA) is a chemotherapy-first policy, limiting the role of surgery for histopathological diagnosis and partial decompression. However, a subgroup of OHA patients show resistance to chemotherapy and have a worse prognosis. In this study, we retrospectively analyzed our clinical experiences of the treatment of patients with OHA in two university hospitals. We have extracted and analyzed the medical charts of 15 pediatric OHA patients treated in two university hospitals since 1990. NF-1-associated OHA patients were excluded. Patient ages ranged from 10 months to 21 years (median 7 years). Out of 15 cases, 12 patients had a tumor larger than 3 cm and classified as Dodge 3. The final histopathological diagnosis was pilocytic astrocytoma in 13 cases. Three patients with tumors classified as Dodge 1 or 2 show good prognosis only by biopsy or partial resection. However, regarding Dodge 3 tumor, patient prognosis is worse regardless of chemotherapy and radiotherapy. After the initial surgery, chemotherapy was administered in 11 cases and radiotherapy in 5 cases. Multiple surgeries are needed for tumor control in 7 patients. Four patients died of tumor progression or treatment-associated complications. When the initial tumor is large enough to cause neurological deterioration, a chemotherapeutic tumor suppressive effect might be limited in a subset of large OHA cases. Therefore, it is important to consider the proper timing of safe surgical decompression in the early phase when a large tumor does not respond to chemotherapy.

LGG-21. MR-GUIDED LASER INTERSTITIAL THERMAL THERAPY FOR UNRESECTABLE AND SYMPTOMATIC PEDIATRIC LOW GRADE GLIOMA

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BACKGROUND: Pediatric low-grade gliomas (LGG) not amenable to resection, while often indolent, represent a significant source of cancer-related morbidity and an unmet therapeutic need. Standardly, these patients are treated with sequential lines of chemotherapy, while delaying as long as possible radiation. Magnetic resonance-guided laser interstitial therapy (LITT) is a minimally invasive procedure that utilizes real-time MR thermography to ablate brain lesions. METHODS: A 15-year-old girl was diagnosed with a suprasellar, hypothalamic LGG, BRAF V600E mutation positive. The tumor was unresectable, and due to progressive vision loss and headaches, the patient underwent treatment. Despite sequential trials of thioguanine/procarbazine/lomustine/vincristine, carboplatin/vincristine, dabrafenib, and combination dabrafenib/trametinib, the patient continued to experience debilitating headaches, malnutrition, school absenteeism, and overall poor quality-of-life. Using real-time, sequential MRI-thermometry and the Neuroblate cooled directional laser catheter, the bulk of the enhancing tumor was heated to a killing temperature. RESULTS: At 1-year post LITT, the patient's symptoms were dramatically improved, including greatly improved headaches, malnutrition, school absenteeism, and overall quality of life. LITT was generally well tolerated, though the patient had slight progressive left homonymous hemianopia, thought secondary to LITT impact on the optic tracts. The tumor progressively shrank over the year post-LITT to a peak of 42% volume reduction. CONCLUSION: We report a case of a pediatric patient with an unresectable low grade glioma who underwent LITT with excellent clinical and radiographic effects. LITT should be considered for children with unresectable and morbid LGGs that fail to respond to more conventional therapies.

LGG-22. EVALUATION OF IMMUNE AND GENOMIC CHARACTERISTICS IN PEDIATRIC OPTIC NERVE GLIOMA (ONG)

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Pediatric optic nerve glioma (ONG) is a rare, sight-threatening tumor. We previously reported clinical, radiologic, histopathologic, and molecular characteristics of pediatric ONG patients treated at Columbia University Medical Center between 2000–2017. Here we evaluate this cohort and one additional patient using quantitative multiple immunofluorescence (qmIF) and next generation sequencing (NGS) using the Columbia Combined Cancer Panel (CCCP). For qmIF, 4 micron immuno-blank slides were stained for CD3, CD8, CD68, CD163, HLA-DR, and Olig2. QmIF images were analyzed and data were processed in R studio and compared based on tumor mutation and treatment history. QmIF failed in 1 case and CCCP failed in 2 cases. CCCP confirmed KIAA1549:BRAF fusions in 2 patients, identified NF1 in 2 patients, and demonstrated both a KIAA1549:BRAF fusion and SETD2 mutation in the added case. Qualitative analysis showed immune infiltrate across cases included macrophages (CD68+, 1.6–6.5% of all cells) and T cells (CD3+, 0.4% to 1.5%). Non-cytotoxic T cells (CD3+CD8-) comprised 60.7–100% of the T cell compartment. There was no difference when comparing mutation groups. However, patients who previously received radiation had increased CD3+, specifically CD3+CD8- cells compared to non-irradiated patients ($p=0.01$ and $p<0.01$, respectively) while CD3+CD8+ and CD68+ cells were not different between groups ($p=0.49$ and $p=0.27$, respectively). In summary, qmIF analysis showed increased tumor infiltration by non-cytotoxic T cells in previously irradiated pediatric ONG patients compared to non-irradiated patients, while there was no difference in macrophages of cytotoxic T cells. This type of analysis may be useful in designing immunotherapeutic strategies for pediatric ONG.

LGG-23. EXCELLENT CLINICAL / RADIOLOGICAL RESPONSE TO BRAF INHIBITION IN A YOUNG CHILD WITH IN-OPERABLE SUPRA-SELLAR PILOCYTIC ASTROCYTOMA

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In-operable low grade gliomas (LGG) in the pediatric population continue to present a treatment dilemma. Due to the low-grade nature of these tumors, and variable response to chemotherapy / radiation, the choice of adjuvant treatment is difficult. Overall survival is directly related to the degree of surgical resection, adding complexity to these inoperable tumors. Current chemotherapeutic regimen for these inoperable tumors includes vincristine (VCR) and carboplatin (Carbo). With advancements in the molecular characterization of gliomas, the role of targeted therapy has come into question. We present a 2-year-old female with biopsy proven Pilocytic Astrocytoma (positive BRAF-V600E mutation) involving the hypothalamic/optic chiasm region. She presented with ataxic gait, bi-temporal hemianopia, obstructive hydrocephalus and central hypothyroidism, which progressed to altered consciousness, and right hemiparesis due to location/mass effect of the tumor. She was initially treated with chemotherapy (VCR/Carbo) but her tumor progressed at 6 weeks of treatment. As her tumor was positive for BRAF-V600E mutation, she was started on Dabrafenib monotherapy, resulting in dramatic improvement in her clinical symptoms (able to stand, improved vision), and a 60% reduction in tumor size at 3-months. At 6-months, follow up MRI showed slight increase in the solid portion of the tumor, with no clinical symptoms. We plan to add MEK inhibitor (Trametinib) and continue with Dabrafenib. Our experience and literature review suggests that LGG with

BRAF-V600E mutations may benefit from upfront targeted therapy. Prospective clinical trials comparing the efficacy of BRAF inhibitors versus standard chemotherapy in LGG with BRAF mutations are urgently needed.

LGG-24. CARBOPLATIN-INDUCED HEMATURIA IN A PEDIATRIC PATIENT WITH LOW-GRADE GLIOMA AND REVIEW OF LITERATURE

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OBJECTIVE: In this case report, we present a pediatric patient with gross hematuria and hydroureteronephrosis associated with high dose carboplatin. Given the paucity of literature on the subject, we also conduct and present a review of cases. CASE PRESENTATION: A 6-year-old Caucasian female with history of Type 1 neurofibromatosis was undergoing treatment for a low-grade glioma with monthly high dose carboplatin (560 mg/m^2). After 8th dose out of 13, the patient developed severe nausea and vomiting and was admitted for dehydration. She was noted to have microscopic hematuria. After 9th dose, the patient again developed severe nausea, vomiting and gross hematuria with clots. She was admitted and treated with IV hydration. Renal ultrasound showed newly developed bilateral hydroureteronephrosis. Coagulation studies were normal. Multiple cultures and viral studies were negative. Hematuria cleared spontaneously after 4 days of aggressive hydration. RESULTS: Subsequent carboplatin was given with aggressive hydration and minimized nausea/vomiting and no hematuria was observed. Literature review revealed only 4 reported cases of carboplatin-induced hematuria, including only one pediatric case that occurred in a patient with concurrent thrombocytopenia. Carboplatin may exhibit toxicity to the transitional epithelial cells of the urogenital tract causing hemorrhage from the renal pelvis and ureters. If untreated, this may lead to urinary outflow obstruction and subsequent obstructive nephropathy. CONCLUSION: We present a rare toxicity, gross hematuria caused by high-dose carboplatin treatment. Providers should be aware of this rare toxicity and provide timely hydration and supportive care to prevent development of obstructive kidney injury and/or renal failure.

LGG-25. A PHASE 2 STUDY OF TRAMETINIB FOR PATIENTS WITH PEDIATRIC GLIOMA WITH ACTIVATION OF THE MAPK/ERK PATHWAY. TRAM-01

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BACKGROUND: Pediatric low-grade gliomas (PLGG) are the most frequent brain tumors in children. It is now known that the majority of PLGG have activation of the MAPK/ERK pathway. We hypothesize that we will observe responses in recurrent/refractory PLGG treated with trametinib. METHODS: This is a multicenter phase II including three progressing/refractory PLGG groups: NF1 patients, KIAA1549-BRAF fusion patients and patients with other activation of the MAPK/ERK pathway (excluding V600E). Patients will receive daily oral trametinib for a total of 18 cycles of 28 days. A total of 104 patients will be enrolled in seven Canadian centers. Secondary objectives include the assessment of progression-free survival, tolerability of trametinib, serum levels of trametinib and evaluation of quality of life during treatment. RESULTS: As of January 7 2020, 28 patients have been enrolled (NF1: 6 patients, KIAA1549-BRAF fusion: 17, other: 5 including 3 patients FGFR1 alteration). Median age is 8.5 years (range 2.5–25.4 years). Median follow-up is currently 4.6 months (range 0.16–14.7 months). Twenty patients are currently evaluable. Best response includes: 1 complete response (5%), 3 partial response (15%), 4 minor response (20%), 8 stable disease (40%), 4 progressive disease (20%). 8 patients (28,5%) discontinued treatment: 4 for progressive disease, 3 adverse event (alanine aminotransferase increase), 1 withdrew. CONCLUSION: Trametinib is potential effective targeted therapy for patients with recurrent/refractory PLGG. Overall treatment is well tolerated. This ongoing trial will continue to gather data on response rate, duration of response and safety of trametinib for PLGG.

LGG-26. DIFFUSE LEPTOMENINGEAL GLIONEURONAL TUMOR (DLGNT) IN CHILDREN: DIFFERENT CLINICAL PRESENTATIONS AND OUTCOMES

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Diffuse leptomeningeal glioneuronal tumor (DLGNT) is an extremely rare disease, newly recognized in the 2016 WHO classification of tumors of the CNS. Most DLGNTs are low-grade neuroepithelial tumors with variable elements of neuronal/neurocytic and glial differentiation, have diffuse leptomeningeal enhancement on MRI, and typically harbor *KIAA1549-BRAF* fusions. Other alterations, such as the *BRAF* V600E substitution, are less common. Here, we present three cases of DLGNT with different presentations and outcomes. The first patient is a 2yr-old male with KIAA1549-BRAF fusion, and was treated with Carbo/VCR chemotherapy after a biopsy, with resultant ongoing stable disease for 3.5 years. The second patient, an 8yr-old male had the *BRAF* V600E point mutation and was treated with conventional chemotherapy (VCR/carboplatin). On progression, he received the BRAF inhibitor vemurafenib, achieving a complete response which last 14 month. The third patient, a 27 month old male, harbored a KIAA1549-BRAF fusion and was treated at diagnosis with the MEK inhibitor trametinib. The tumor has been radiographically stable in the context of clinical improvement for 21 months since the treatment initiation, ongoing 24 month. In summary, we present further evidence of MAPK pathway alterations in children with DLGNT. We describe a range of molecular presentations and clinical outcomes, including one patient treated with conventional chemotherapy with further stabilization of disease during 3.5 years and two patients who were successfully treated with targeted therapy.

LGG-27. TARGETED THERAPY FOR PEDIATRIC LOW-GRADE GLIOMAS AND PLEXIFORM NEUROFIBROMAS WITH TRAMETINIB

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BACKGROUND: Targeted therapy aimed at modulating the RAS/RAF/MEK/ERK pathway is of increasing interest for patients with plexiform neurofibromas and low-grade gliomas. Trametinib is an FDA-approved MEK inhibitor that has little published pediatric experience to date. METHODS: A retrospective chart review of patients treated with trametinib for low-grade gliomas (LGG) and/or plexiform neurofibromas (PN) between 2015–2018 was conducted at Children's Hospital Colorado. Data collected included patient demographics, lesion location, Neurofibromatosis type 1 (NF1) status, best response of PN/LGG to trametinib, duration of trametinib therapy, and reported toxicities at least possibly attributed to trametinib. RESULTS: Thirty (57% male; 73% NF1) patients were identified. Sixteen (53%) patients had PN only, 12 (40%) had LGG only, and two (7%) patients had both PN and LGG. The most common LGG location was the optic pathway/hypothalamus (72%). The most common location of PN was the face (63%). Two-thirds (8/12) of patients with LGG had a BRAF alteration or NF1 mutation. The median age at start of trametinib therapy was 9.9 years (range, 2.0 – 18.8 years). The median duration of trametinib therapy was 0.8 years (range 0.1 – 2.9 years). The most commonly reported adverse event was rash. No patients developed retinal toxicity or cardiotoxicity. Only two (7%) patients discontinued for toxicity and one (3%) for progressive disease. CONCLUSIONS: Trametinib can be administered without significant toxicity to children with PN or LGG. Clinical benefit is noted in this cohort; however, prospective clinical trials are necessary to characterize efficacy formally.

LGG-28. NOVEL BRAF INTRAGENIC DELETION IN A GLIOMA: A CASE REPORT OF A PEDIATRIC PATIENT

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BACKGROUND: Numerous variant BRAF genetic alterations have been associated with malignancies. BRAF activating fusions/mutations are frequently present in low grade gliomas. BRAF intragenic deletions have been reported in melanoma, but have not previously been reported in gliomas. OBJECTIVE: To report a BRAF intragenic deletion in a pediatric patient with recurrent low-grade glioma. RESULTS: A 3-year-old female underwent a complete resection of a posterior fossa pilocytic astrocytoma. She had recurrences at age 4, and then at age 9; pathology was consistent with pilocytic astrocytoma. Microarray analysis on sample from the first recurrence showed one region of loss encompassing 86 Kbp within the BRAF gene. The deletion breakpoints are within intron 1 and 9, resulting in loss of exons 2 through 9, inclusive. This has been previously described melanoma, but appears to be a novel finding in glioma. It is hypothesized that, since the loss retains the kinase and ATP binding pocket domains but deletes the N-terminal conserved region 1 and 2 (CR1, CR2) of the BRAF gene, it is likely functionally similar to the loss and activation resulting from the more usually described KIAA1549 and BRAF gene fusion. CONCLUSION: This is the first BRAF intragenic deletion involving exons 2–9 reported in a glioma. Although 86kbp is small using whole genome microarray technology, it is large using sequencing strategies, and a targeted sequencing approach to investigate the BRAF gene would not readily identify this deletion. It is speculated that the deletion may be under ascertained in the pediatric population.

LGG-29. TREATMENT FOR RECURRENT OPTIC PATHWAY PILOCYTIC ASTROCYTOMA

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Chemotherapy after biopsy or partial resection of the tumor is widely accepted as first-line therapy for optic pathway pilocytic astrocytoma. However, there is no standard of care for recurred tumors. We investigated our cases which showed recurrence after initial therapy. Retrospective analysis of four recurrent optic pathway pilocytic astrocytoma cases was performed. All patients underwent partial resection or biopsy of the tumor, and all received carboplatin and etoposide- based chemotherapy as initial treatment. Mean age at first therapy was 2.3 years old, and mean time from initial therapy to recurrence of the tumor was 5.6 years. Two patients were totally blind at the time of recurrence, and other two had partial visual field losses. One patient underwent total resection of the tumor, and other three patients underwent partial resection followed by chemotherapy. Visual function in patients with visual acuity did not deteriorate after removal of the recurrent tumor. There was no recurrence of the tumor who underwent total resection. All of the three patients who had partial resection followed by chemotherapy recurred. Mean time from first recurrence to second recurrence was 1.8 years. After second recurrence, all patients underwent radiation therapy. One patient died due to malignant transformation of the tumor. For recurrent optic pathway pilocytic astrocytoma, prognosis may be better if total resection of the tumor without deteriorating the vision is possible.

LGG-30. TRAMETINIB-ASSOCIATED HYPONATREMIA IN A CHILD WITH LOW GRADE GLIOMA IS NOT SEEN FOLLOWING TREATMENT WITH ALTERNATIVE MEK INHIBITOR

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Molecularly targeted therapy with MEK inhibitors is increasingly being incorporated into the treatment of pediatric low-grade gliomas (LGGs). Trametinib is an orally available MEK1/2 inhibitor that has demonstrated tumor control in LGGs with BRAF alterations. Safe expansion of MEK inhibitor therapy within the pediatric patient population demands adequate understanding of and surveillance for potential MEK-inhibitor specific toxicities, especially among young children. Hyponatremia has been reported in adult patients receiving BRAF/MEK inhibitor combination treatment as well as in two pediatric patients with known diabetes insipidus treated with trametinib monotherapy. To our knowledge, single-agent trametinib has not previously been reported to be associated with hyponatremia in children in the absence of an underlying endocrinopathy. We present a case of hyponatremia associated with trametinib use in an infant with progressive LGG without known endocrine dysfunction, which recurred after significant dose reduction. Therapy with an alternative MEK1/2 inhibitor, binimetinib, provided excellent tumor response without hyponatremia. Hyponatremia is a rare but serious side effect of trametinib, even without underlying pituitary dysfunction. Infants and patients lacking the ability to quickly regulate fluid intake in response to osmolality changes are at particular risk of suffering severe consequences from hyponatremia and should be monitored closely with initiation of trametinib. Switching to a different drug within the same class may offer an alternative to significant dose reduction or discontinuation due to this toxicity.

LGG-31. CHARACTERIZING TEMPORAL GENOMIC HETEROGENEITY IN PEDIATRIC LOW GRADE GLIOMAS: ANALYSIS OF AN EXPANDED MULTI-INSTITUTIONAL COHORT WITH 101 PAIRED TUMOR SAMPLES

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INTRODUCTION: Recent discoveries have provided valuable insight into the genomic landscape of pediatric low grade gliomas (LGGs) at diagnosis, facilitating molecularly targeted treatment. However, little is known about their temporal and therapy-related genomic heterogeneity. An adequate understanding of the evolution of pediatric LGGs' genomic profiles over time is critically important in guiding decisions about targeted therapeutics and diagnostic biopsy at recurrence. METHODS: Fluorescence in situ hybridization, mutation-specific immunohistochemistry, and exome analyses were performed on paired tumor samples from primary diagnostic and subsequent surgeries. RESULTS: 101 tumor samples from 48 patients (43 with 2 specimens, 5 with 3 specimens) from 3 institutions underwent testing. *BRAF* fusion and $BRAF^{V600E}$ status were conserved in 100% and 97% of paired specimens, respectively. No loss or gain of *IDH1* mutations or *FGFR1*, *NTRK2*, *MYB*, or *MYBL1* rearrangements were detected over time. Histologic diagnosis remained the same in all tumors, with no acquired H3K27M mutations or malignant transformation. *CDKN2A* deletions were acquired in 7 patients (including 3 who received chemotherapy [2 with temozolomide] and 1 who received radiation), and were associated with a trend toward shorter time to progression (median: 5.5 vs. 13.0 months [p=0.08]). CONCLUSIONS: Most targetable genetic alterations in pediatric LGGs, including *BRAF* alterations, are conserved at recurrence and following chemotherapy or radiation. However, *CDKN2A* deletion acquisition was demonstrated and may define a higher risk group. Given potential for targeted therapies for tumors acquiring *CDKN2A* deletions, performing a biopsy at recurrence may be indicated in certain patients, especially those with rapid progression.

LGG-32. CLINICAL OUTCOME OF PEDIATRIC GLIOMAS IN SINGLE INSTITUTION

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Gliomas in children are rarer than in adult, then treatment strategies might vary from facility to facility. We report clinical features and outcome of pediatric glioma in our institution. Twenty-nine patients diagnosed with glioma, exclude ependymoma, 14 boys and 15 girls, among 98 pediatric brain tumor patients treated at Kagoshima University Hospital since 2006 were reviewed histopathology, extent of resection, adjuvant therapy and outcome, etc. Mean age at surgery was 10.4 (S.D. 5.6) years. Median follow-up period was 19.1 months. Histopathological diagnosis comprised 8 pilocytic astrocytoma, 3 ganglioglioma, 2 subependymal giant cell astrocytoma, 5 WHO grade II astrocytoma, 8 glioblastoma, and desmoplastic infantile astrocytoma, anaplastic astrocytoma and astroblastoma were one case each. Tumor resection was performed in 24 cases, and 5 cases underwent biopsy. Chemotherapy was performed in 15 cases and irradiation was performed in 9 cases. Out of 5 WHO grade II astrocytoma cases, 2 cases underwent biopsy following chemotherapy, 1 case underwent biopsy only and other 1 case underwent total resection. The four cases show long survival ranged from 71 to 136 months without irradiation. All of eight glioblastoma cases show poor prognosis ranged from 8.6 to 26.7 months regardless of chemoradiotherapy. In management for pediatric brain tumor patients, irradiation is often laid over until recurrence. In WHO grade II astrocytoma, the treatment strategy might be reasonable using appropriate chemotherapy even though biopsy cases.

LGG-33. ISOMORPHIC DIFFUSE GLIOMA HAS RECURRENT GENE FUSIONS OF *MYBL1* OR *MYB* AND CAN BE DISTINGUISHED FROM OTHER *MYB/MYBL1* ALTERED GLIOMAS BASED ON A DISTINCT MORPHOLOGY AND DNA METHYLATION PROFILE

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Isomorphic diffuse glioma (IDG) was first described in 2004 as an epilepsy-associated supratentorial diffuse glioma with low cellularity, low proliferation and very monomorphic tumour cells. Most patients had seizures since childhood but were operated on as adults. To study the position of these lesions among brain tumours we histologically, molecularly and clinically analysed 26 histologically typical IDGs. Tumour cells were GFAP-positive, MAP2-, OLIG2- and CD34-negative and the nuclear ATRX-expression was retained. Proliferation was very low. Sequencing of 24 cases revealed an IDH-wildtype status. Cluster analyses of DNA methylation data showed that IDG has a DNA methylation profile distinct from those of different glial/glio-neuronal brain tumours and normal hemispheric tissue. About half of IDGs had copy number alterations of *MYBL1* or *MYB* (13/25) and half of the cases analysed by RNA-sequencing had gene fusions of *MYBL1* or *MYB* with various gene partners (11/22), often associated with an increased RNA-expression of the respective *MYB*-family gene. Integrating all data available, 77% of IDGs had either *MYBL1* (54%) or *MYB* (23%) alterations. All patients had a good outcome and most were seizure-free after surgery. In summary, we show that isomorphic diffuse glioma is a distinct benign tumour in the family of *MYB/MYBL1*-altered gliomas. DNA methylation analysis is very helpful for their identification. More recent analyses of a large cohort of *MYB/MYBL1*-altered brain tumours suggest the presence of a third methylation group that primarily contains paediatric cases and seems to be distinct from IDG and angiocentric gliomas. Further histological, molecular and clinical analyses are ongoing.

LGG-34. CLINICAL AND MOLECULAR CHARACTERIZATION OF A MULTI-INSTITUTIONAL COHORT OF PEDIATRIC SPINAL CORD LOW-GRADE GLIOMAS

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BACKGROUND: The MAPK/ERK pathway is involved in cell growth and proliferation, and mutations in the *BRAF* paralog of this pathway have made it an oncogene of interest in pediatric cancer. Previous studies have identified that *BRAF* mutations as well as *BRAF-KIAA1549* fusions are common in intracranial low-grade gliomas (LGGs). Fewer studies have tested for the presence of these genetic aberrations in spinal LGGs. The aim of this study was to better understand the prevalence of BRAF and other genetic aberrations in spinal LGG. METHODS: We analyzed 46 spinal LGGs from children age 1–25 years from two institutions, Children's Hospital Colorado (CHCO) and The Hospital for Sick Children (Sick Kids) for the presence of *BRAF* fusions or mutations. Data was correlated with clinical information. A 67 gene panel additionally screened for other possible genetic abnormalities of interest in the patient cohort from CHCO. In the Sick Kids cohort, $BRAF^{V600E}$ was tested for by ddPCR and IHC while BRAF fusions where detected by FISH, RT-PCR or Nanostring platform. RESULTS: Of the 31 patient samples who underwent fusion analysis, 13 (42%) harbored the *BRAF-KIAA1549* fusion. Overall survival (OS) for patients confirmed positive for *BRAF-KIAA1549* was 100% compared to 76% for fusion negative patients. Other mutations of interest were also identified in this patient cohort including *BRAFV600E, STK11*, *PTPN11*, *H3F3A*, *APC*, *TP53*, *PIK3CA* (polymorphism), *FGFR1,* and *CDKN2A* deletion. CONCLUSION: *BRAF-KIAA1549* was seen in higher frequency than *BRAFV600E* or other genetic aberrations in pediatric spinal LGGs and trends towards longer OS although not statistically significant.

LGG-35. FUNCTIONAL GENOMIC APPROACHES TO IDENTIFY THERAPEUTIC TARGETS IN *MYB* AND *MYBL1* EXPRESSING PEDIATRIC LOW-GRADE GLIOMAS

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AIM: Recurrent structural variants involving *MYB* and *MYBL1* transcription factors were recently identified in pediatric low-grade gliomas (pLGGs), such as the *MYB-QKI* rearrangement in Angiocentric Gliomas and truncations of *MYBL1* (*MYBL1tr*) in Diffuse Astrocytomas. However, therapeutic dependencies induced by these alterations remain unexplored. METHODOLOGY: We have generated *in vitro* pLGG mouse neural stem cell (NSCs) models engineered to harbor distinct *MYB/MYBL1* genomic alterations. We used single cell RNA sequencing approaches to determine the transcriptional profile and dissect the central regulatory networks of our *in vitro* pLGG models over time. To identify specific genetic dependencies associated with *MYB/MYBL1* mutations, we employed the Brie genome-wide mouse CRISPR lentiviral knockout pooled library, consisting of 78,637 single guide RNAs (sgRNAs) targeting 19,674 mouse genes. RESULTS: *MYB/MYBL1* expression in neural stem cells induced activation of cell-cycle related, glioma-related and senescence-related pathways that are involved in normal development, including activation of MAPK and mTOR signaling which are also activated in human pLGG samples. Genome-scale CRISPR-cas9 screens in isogenic NSCs expressing *MYB-QKI* or *MYBL1tr* identified differential genetic dependencies relative to GFP controls. These included regulators of cell-cycle progression and several modulators of the ubiquitin-proteasome degradation pathway. Analysis of RNA-sequencing data from human tumors revealed several of these dependencies identified in the cell line model to be differentially expressed in *MYB*-altered pLGG tumors relative to normal brain. CONCLUSION: Expression of *MYB* family alterations induces expression of key developmental and oncogenic pathways and genetic dependencies that represent potential therapeutic targets for *MYB* or *MYBL1* rearranged pLGGs.

LGG-36. DESMOPLASTIC INFANTILE GANGLIOGLIOMA (DIG) WITH A PPP1CB-ALK FUSION IN A 6-YEAR-OLD GIRL

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Desmoplastic infantile astrocytoma (DIA) and desmoplastic infantile ganglioglioma (DIG) are benign glioneuronal tumors that typically occur in infants, involve the superficial cerebral cortex, and have an excellent prognosis. DIA/DIG are a distinct molecular entity based on DNA methylation profiling. BRAF600 mutations are frequently reported in DIG/DIA. A recent comprehensive genetic analysis of infantile hemispheric gliomas identified 2 unique groups: group 1 harbored alterations in the receptor tyrosine kinase (RTK) genes ALK, ROS1, NTRK, and MET and group 2 harbored alterations in the RAS/MAPK pathway. We report a case of a 6.5-year-old girl who presented with seizures and right homonymous hemianopia. MRI of her brain demonstrated a large cystic/solid left hemispheric mass with remodelling of the overlying skull, consistent with a long-standing process. She underwent a gross total resection (GTR) and pathology demonstrated a DIG with a PPP1CB-ALK gene fusion (exon 5 to exon 20) identified by RNA sequencing. She remains disease free 12 months following GTR. A literature review identified 4 reported cases of pediatric brain tumors with PPP1CB-ALK gene fusions including: a 3-month-old with a hemispheric high-grade glioma which recurred 4 years later and pathology showed mature ganglioglioma, with both tumors showing the identical PPP1CB-ALK gene fusion; a 10-month-old infant with a hemispheric low-grade glioma; an infant with a "congenital" hemispheric high-grade glioma; and a child with an astrocytoma with no further clinical data. PPP1CB-ALK gene fusion appears to be a rare oncogenic driver in gliomas of infancy, including DIG.

LGG-38. GENETIC ANALYSIS OF NEUROEPITHELIAL TUMORS IN THE PEDIATRIC AND ADOLESCENT AND YOUNG ADULT AGE IN A SINGLE INSTITUTE

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Molecular diagnosis in brain tumors has been widely spread after the publication of WHO 2016 classification. But it become a major problem that there are some tumors not to be classified on its criteria, especially in pediatric neuroepithelial tumors. To clarify the characteristics of gliomas in pediatric and adolescent and young adult age (AYA), we picked up 131 neuroepithelial tumors under 30-year-old at Kyoto University and analyze their molecular profiles. Hot spot mutations in *IDH1/2*, *H3F3A*, *HIST1H3B*, *TERT* promoter, and *BRAF* were analyzed by Sanger sequencing, and 1p/19q codeletion was examined by FISH or MLPA. With the pathohistological diagnosis and genetic information, all tumors were classified based on WHO 2016 classification. The terms "not otherwise specified" (NOS) and "not elsewhere classified" (NEC) were used based on cIMPACT-NOW. There were 25 glioblastomas and 34 pilocytic astrocytomas, which accounted for a larger percentage than in adult tumors. IDH-wild type gliomas accounted for 55% in diffuse astrocytomas and 69% in anaplastic astrocytomas. The percentages of gliomas with NEC were 50% of oligodendrogliomas and 20% in anaplastic oligodendrogliomas, respectively. Most pilocytic astrocytomas were under 20-year-old (27 patients) and located in infratentorial area (21 patients). Based on WHO 2016 classification, not a few neuroepithelial tumors in pediatric and AYA ages could be classified clearly. These tumors had more different genetic abnormalities than those in adult. Therefore, it may be important to evaluate these tumors with comprehensive genetic analysis.

LGG-40. NATURAL COURSE AND MANAGEMENT OF SMALL ASYMPTOMATIC LESION SUSPECTED OF LOW-GRADE GLIOMA IN CHILDREN

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OBJECTIVE: The natural course of incidentally discovered small intracranial lesions has not been well discussed. Surgical intervention, including resection and biopsy, could be achieved if the lesion is growing. We present 13 cases with incidentally found, small non-enhancing lesions without related symptoms. METHODS: We retrospectively reviewed a series of 13 children with T1 hypointense and T2 hyperintense intracranial lesions less than 20 mm in diameter without enhancement. We excluded the patients with NF-1 or Tuberous sclerosis. RESULTS: Most patients underwent MRI for headache unrelated to the lesions. All cases were located supratentorially. The median age of the patients at the initial examination was 8.9 years (range, 2.2–14.6). Of these children, 2 patients (15.3%) underwent surgery because of progression on follow-up MR images. The pathological diagnosis was compatible with diffuse astrocytoma. Patients were followed for a median of 55 months (range, 11–87) and the overall survival rate was 100%. No patient experienced increase in size after 3 years of follow-up. CONCLUSIONS: In most patients with small intracranial lesions, the lesions remained stable and conservative management was appropriate. However, in a few cases, the lesions changed in size or quality and surgical intervention was necessary. Long-term follow-up at least 3 years is mandatory.

LGG-42. BEVACIZUMAB-ASSOCIATED SECONDARY AMENORRHEA AND PREMATURE OVARIAN FAILURE IN ADOLESCENT FEMALE PATIENTS WITH LOW-GRADE CNS DISEASE

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Compelling body of evidence exists to use bevacizumab, a humanized monoclonal anti-VEGF antibody, in selected paediatric patients with low-grade CNS tumours. Common toxicities of bevacizumab, hypertension, proteinuria, epistaxis, mucosal perforation, decreased wound healing are well reported. However, the effect of bevacizumab on female ovarian function and long-term fertility is still being documented. Current evidence for bevacizumab-associated decline in ovarian function is largely from breast and colon cancer cohorts where exposure to multimodal chemotherapy confounds causative relationships. Fertility counseling and oocyte cryopreservation is currently offered as standard of care to post-pubertal females at high risk of infertility due to high-dose radiation and chemotherapy. Adolescent females with low-grade CNS tumours on bevacizumab represent a unique population which could potentially be at high risk for infertility. We report 2 cases of adolescent girls treated with bevacizumab as a single agent and in combination with vinblastine for NF2-associated vestibular schwannomas and brainstem glioma respectively. Both patients were post-pubertal with established menstrual cycles and normal baseline FSH/LH/oestradiol/AMH values prior to commencement of therapy. They became amenorrhoeic shortly after starting of therapy with levels of FSH/LH/oestradiol suggestive of premature ovarian failure. One patient has remained asymptomatic, whereas the other has developed profound post-menopausal symptoms interfering with quality of life which necessitated commencement of hormone-replacement therapy. Appropriate pretreatment fertility investigation and consultation should be offered to all post-pubertal females starting on bevacizumab. Further research into the long-term effects of gonadal toxicity in both females and males with drugs inhibiting angiogenesis is needed.

LGG-44. PROGNOSTIC SIGNIFICANCE OF IMAGING CHARACTERISTICS IN PEDIATRIC LOW GRADE GLIOMAS

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Pediatric low-grade gliomas (pLGG) account for one third of all central nervous system (CNS) tumors. MRI is the preferred imaging modality for diagnosis and response evaluation. This study aims to evaluate if radiographic characteristics of pLGG at diagnosis are prognostic. Medical records of 700 pLGG patients were reviewed who were seen between 1998- 2019 at our institution. Summary statistics were provided to describe patient demographic and clinical characteristics. 603 patients were not eligible because incomplete records, 97 patients were identified and eligible for the review. There were 45 females and 52 males with the mean age of 6.5 years at diagnosis. Patients were categorized based on contrast enhancement to 2 groups; none/mild versus moderate/high with 65 and 32 patients respectively. 31 patients had infiltrative glioma (32.3%) with more than one lobe involved at diagnosis. Fifteen patients (15.46%) had hydrocephalous at initial diagnosis. 32 patients (32.9%) did not have any treatment and remained stable while 65(67.0%) had either surgery, chemotherapy or radiation or combination. 21 patients had neurofibromatosis type-1(NF-1) with better outcome comparing to non-NF1 as previously reported. No statistically significant difference in outcome was found based on the imaging characteristics at diagnosis including contrast enhancement, hydrocephalus, tumor size, presence of cyst or infiltrative tumors. The 5 years PFS rate for the entire cohort was 47%. Our study results are limited by low patient number, hence collaborative multi-institutional studies are warranted to delineate consensus and investigate prognostic factors to improve the outcome of pLGG.

LGG-45. A REPORT OF IDH-MUTANT BRAINSTEM ASTROCYTOMAS IN YOUNG ADULTS

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IDH-mutant astrocytomas are well-recognized in the adult population and while increasingly identified, are rare in children and young adults. These tumors typically arise in cortical locations, however cases of these tumors occurring in the brainstem have been reported in the adult literature. Here we present two cases of young adults with IDH-mutant astrocytomas of the brainstem. Patient 1 was initially diagnosed with an infiltrative low grade glioma (LGG) of the brainstem at 19 years of age based on conventional magnetic resonance imaging and magnetic resonance spectroscopy characteristics. She was treated with LGG therapy and had stable disease for over three years. At the time of disease progression she underwent biopsy and pathology was consistent with an anaplastic astrocytoma, IDH1 R132S mutant. Despite treatment she experienced rapid disease progression and died six months later. Patient 2 is a 17-year-old male who underwent up-front biopsy of an infiltrating brainstem lesion; pathology was consistent with diffuse astrocytoma, IDH1 R132H mutant. He was treated with focal irradiation and chemotherapy and continues to have stable disease 26 months post diagnosis. To our knowledge, this is the first report of IDH-mutant astrocytomas occurring the brainstem in young adult patients. Both patients' tumors harbored accompanying TP53 mutations, but not ATRX mutations. These two cases reveal the importance of obtaining biopsies for brainstem tumors to perform molecular characterization and appropriate prognostication.

LGG-46. MOLECULAR CHARACTERIZATION OF HEMISPHERIC LOW-GRADE GLIOMAS IN CHILDREN

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BACKGROUND: Heterogeneous pathology in hemispheric low-grade gliomas (hemLGG) stress the importance of molecular testing in terms of prognosis prediction and targeted therapy options. METHODS: Demographic data was collected and targeted genomic approach was employed in the single institutional study. RT-PCR was used to screen for KIAA1549-BRAF fusion and FGFR1 tyrosine-kinase domain duplication (FGFR1-ITD). Direct sequencing evaluated point mutations (BRAF ex15 and ex11, FGFR1 ex12 and ex14). Samples with no detected alteration were subjected to panel RNA-sequencing (FusionPlex Archer Diagnostics). RESULTS: Within 2000–2019 were diagnosed 76 patients with hemLGG (median age 11.1y, range 0.0y–18.5y) comprising predominantly of ganglioglioma, dysembryoplastic neuroepithelial tumors, and diffuse astrocytoma. 40 % of hemLGG were characterized by BRAF alterations with over 2/3 of those cases harboring BRAF point mutations (two BRAFex11, 12 BRAFV600E). Notably, BRAF fusions were uncommon and detected only in six patients (two KIAA-BRAF fusion, two minor oncogenic BRAF variants, two non-KIAA BRAF fusion). 25 % of alterations were found in genes for receptor tyrosine kinases, consisting of seven patients with FGFR1-ITD, three FGFR2/3 fusions, two FGFR1 mutations, two ALK fusions, and one ROS fusion. Out of MAP kinase pathway, the most frequent alteration was IDH1 mutations (n=9). Two angiocentric gliomas were characterized by MYB-QKI fusion. CONCLUSION: Targeted sequencing combined with RNA-sequencing is feasible to establish molecular diagnosis in majority of cases and reveal new and rare alterations. Significant prevalence of non-BRAF alterations explains heterogeneity among hemLGG.

LGG-47. SYSTEMIC THERAPY OF ROSETTE-FORMING GLIONEURONAL TUMOR OF THE FOURTH VENTRICLE INAN ADOLESCENT

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An 11 y.o. female presented to a GI specialist with complaints of morning vomiting and periumbilical abdominal pain for several months. Had progressing symptoms with GI work-up for ~1 year. She developed diplopia and worsening headaches. Imaging revealed a T2/FLAIR hyperintense mass in the 4th ventricle with heterogeneous enhancement and obstructive hydrocephalus. Three T2 bright, non-enhancing, subcentimeter masses identified in the right cerebellum. Due to poor differentiation between tumor and normal tissue at brainstem, only partial resection (PR) was feasible. Pathology initially called pilocytic astrocytoma (PA). All symptoms resolved after PR. Slow progression in the tumor and "satellite" lesions noted over two years. Second opinion and molecular typing reclassified the tumor as rosette-forming glioneuronal tumor (RFGNT) with a mutation in *PIK3CA*. Therapy started with vinblastine and carboplatin with stable disease x 7 months, discontinued due to allergic reaction to carboplatin. Initiated therapy with everolimus, an mTOR inhibitor. The tumor's characteristics on imaging changed with initial growth and increase in peripheral enhancement in one satellite and the primary tumor. Nevertheless, we persevered. When comparing pre-treatment MRI to most recent 7 months later, there has been an overall decrease in volume of expansile heterogenous tumor along the margins of the fourth ventricle. The degree of peripheral enhancement associated with the mass has increased. RFGNT is a rare tumor included in WHO classification since 2007. Ellezam et al identified recurrent *PIK3CA* mutations. To our knowledge, this is the only report of treatment targeting the mutation. We report a radiographic response despite initial growth.

LGG-48. PROLIFIC GROWTH OF BRAF V600E MUTANT PILOCYTIC ASTROCYTOMA WHILE ON KETOGENIC DIET: CASE REPORT

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Epilepsy is a common diagnosis among pediatric patients with supratentorial tumors, particularly infiltrating gliomas. The ketogenic diet can be a successful antiepileptic therapy for patients with medically intractable epilepsy. Acetoacetate, a main ketone released during ketosis, has been shown to increase $BRAF^{V600E}$ binding to MEK1 and MEK1 phosphorylation in $BRAF^{V600E}$ mutant melanoma cells, thereby promoting proliferation and tumor growth (Kang et al, 2015, Xia et al, 2017). $BRAF^{V600E}$ mutation is common in pediatric low-grade gliomas. Therefore, use of a ketogenic diet to manage coincident epilepsy could, in theory, promote tumor growth. However, this has not been previously reported in a human patient. We present a 3 year-old male with a non-NF1 optic pathway $BRAF^{V600E}$ mutant pilocytic astrocytoma and medically intractable epilepsy. He was treated with carboplatin and bevacizumab for 1 year, with good tumor response and vision recovery. He showed stable, non-progressive disease for several months. He was placed on a ketogenic diet 9 months into treatment and became seizure free. Tumor recurrence occurred at 8 months off therapy, at which time a biopsy demonstrated $BRAF^{V600E}$ mutation. The tumor progressed rapidly despite treatment with Trametinib and Dabrafenib, leading to salvage therapy with carboplatin, vinblastine, bevacizumab, and XRT, without tumor control. We discuss the potential effect of the ketogenic diet on this patient's outcome.

LGG-49. SAFETY AND EFFICACY OF TRAMETINIB (T) MONOTHERAPY AND DABRAFENIB + TRAMETINIB (D+T) COMBINATION THERAPY IN PEDIATRIC PATIENTS WITH *BRAF* V600-MUTANT LOW-GRADE GLIOMA (LGG)

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BACKGROUND: Children with *BRAF* V600-mutant LGG have suboptimal response to standard chemotherapy. Previously, D (*BRAF* V600 inhibitor) monotherapy has demonstrated clinical benefit in this population. We report interim analysis results of pediatric patients with recurrent/refractory *BRAF* V600-mutant LGG treated with either T (MEK1/2 inhibitor) monotherapy or D+T combination therapy. METHODS: This is a 4-part, open-label, multicenter, phase I/II study (NCT02124772) in pediatric patients (<18 y) with refractory/recurrent tumors. The dose-finding phase, including dose confirmation stratified by age, was followed by disease-specific cohorts at recommended dose levels. Efficacy was determined by both investigator and independent review using RANO criteria. Adverse events (AEs) were assessed per NCI-CTCAE v4.03. RESULTS: Of 49 pediatric patients with *BRAF* V600-mutant LGG (T, n=13; D+T, n=36) enrolled, pooled efficacy data was available for both treatments while safety data was available for 30 patients (T, n=10; D+T, n=20). Most patients (n=8/10) receiving T monotherapy withdrew/discontinued the treatment in contrast to 3/20 in the D+T group. Pyrexia occurred in 50% of patients (n=5/10) in the monotherapy group and was a frequent AE in the combination group (75%; n=15/20). Objective response rate per independent review was 15% (95% CI, 2%–45%) with T monotherapy and 25% (95% CI, 12%–42%) with D+T combination therapy. Seven patients (54%) on monotherapy and 33 patients (92%) on combination therapy had stable disease or better. CONCLUSION: In pediatric patients with previously treated *BRAF* V600-mutant LGG, T monotherapy and D+T combination therapy demonstrated clinical activity, with pyrexia being a common AE.

LGG-50. INTEGRATED MOLECULAR AND CLINICAL ANALYSIS OF 1,000 PEDIATRIC LOW-GRADE GLIOMAS UNCOVERS NOVEL SUBGROUPS FOR CLINICAL RISK STRATIFICATION

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Pediatric low-grade gliomas (pLGG) are primarily driven by genetic alterations in the RAS/MAPK pathway, most commonly involving BRAF of NF1. Despite their molecular convergence, pLGG often show unexplained variability in their clinical outcome. To address this, we molecularly characterized a cohort of >1,000 clinically annotated pLGG. 84% of cases harbored a detectable driver mutation. The remaining 16% of patients nonetheless showed RAS/MAPK pathway up-regulation at the RNA level. The clinical presentation and outcome of pLGG appeared highly variable and linked to the alteration type: re-arrangement or SNV. Re-arrangement-driven tumors were diagnosed at a younger age (6.6 versus 10.9 years, p<0.0001),

enriched for WHO grade I histology (88% versus 66%, p<0.0001), infrequently progressed (27% versus 46%, p<0.0001), and rarely resulted in death (3 versus 13%, p<0.0001) as compared to SNV-driven tumors. These included the rarest molecular drivers of pLGG, for which we now have the clinicopathologic features of including MYB, MYBL1, FGFR2 fusions, FGFR1-TACC1, FGFR1 SNVs, IDH1 p.R132H, and H3.3 p.K27M. Utilizing this information, we suggest novel risk categories of pLGG that effectively predicted patient outcome. Low-risk tumors progressed infrequently and rarely succumbed to their disease (10-year PFS of 71% and OS of 98%). Intermediate-risk pLGG had a 10-year PFS and OS of 35% and 90%, respectively. High risk pLGG almost invariably progressed (10-year PFS of 0%) and these patients often succumbed to their disease (10-year OS of 41%). These data highlight the biological and clinical differences between pLGG subtypes and offers molecular based risk stratification to these cancers.

LGG-51. BRAF ALTERATIONS IN PEDIATRIC LOW-GRADE GLIOMAS: RESULTS FROM A BRAZILIAN COHORT

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BACKGROUND: Pediatric low grade gliomas (PLGG) are the most common central nervous system neoplasms in children. These are driven almost exclusively by alterations in the RAS/MAPK pathway. Specifically, alterations in the BRAF gene have emerged as an important target for therapy. This study aimed to identify the frequency of BRAF alterations in a Brazilian cohort of PLGGs. RESULTS: Forty-one patients diagnosed between 2001 and 2017 had enough FFPE tissue available for analysis. Real-time PCR test (n=35) was used to assess for BRAFV600E mutations, while BRAF fusions were detected by break-apart fluorescence *in situ* hybridization (n=30). The histologic distribution was as follows: 73% pilocytic astrocytoma, 12% ganglioglioma, 3% diffuse astrocytoma, 5% pleomorphic xanthoastrocytomas (PXA) and 7% NOS (n = 41). BRAF fusions were present in 21 patients (51%): 17 pilocytic astrocytomas, 2 xanthoastrocytoma, 1 pilomyxoid astrocytoma and 1 diffuse astrocytoma. BRAFV600E was detected in 4 cases (10%): 2 pilocytic astrocytomas, 1 ganglioglioma and 1 PXA. As expected, BRAF translocations were more frequent in pilocytic astrocytomas (p<0.001). From 22 patients treated in our institution, 59% were male with a mean age of 9.7 years, 50% occurred in the posterior fossa and 77% treated by surgery only. One patient relapsed and died from disease (BRAF V600E positive) (follow-up median=44.7 months). These are the first results using a CLIA method showing the frequency of BRAF abnormalities in a Brazilian population. Although preliminary, BRAF alterations are present in 61% of the cases emphasizing the importance of incorporating this analysis in the current work-up guidelines.

LGG-52. BINIMETINIB IN CHILDREN WITH PROGRESSIVE OR RECURRENT LOW-GRADE GLIOMA NOT ASSOCIATED WITH NEUROFIBROMATOSIS TYPE 1: INITIAL RESULTS FROM A MULTI-INSTITUTIONAL PHASE II STUDY

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BACKGROUND: RAS/RAF/MEK/ERK pathway activation is the primary driver for most pediatric low-grade gliomas (LGG). Binimetinib is an orally bioavailable MEK1/2 inhibitor found to have significant central nervous system penetration in a preclinical model. OBJECTIVE: The primary objective of this multi-institutional open-label phase II study was to assess preliminary efficacy of binimetinib in progressive pediatric LGG. The study included strata for both neurofibromatosis type I (NF1) and non-NF1 associated tumors, as well as a target validation (surgical) stratum. NF1 and surgical strata remain open to enrollment and will be reported separately. METHODS: Children aged 1–18 years with previously treated recurrent or progressive LGG were eligible. The dose of binimetinib was 32 mg/m^2/dose twice daily. Partial and minor responses were defined, respectively, as 50% and 25% decrease in maximal two-dimensional measurements. RESULTS: Fifty-seven eligible patients without NF1, median age 8 years, were enrolled and began treatment; 26 were female; 28 had documented KIAA1549-BRAF fusion. Eleven patients discontinued drug in the first year due to toxicity, and an additional 27 required dose reduction. The most common drug-attributable grade 3 toxicities included creatine kinase elevation (n=9 patients), rash (n=8), and truncal weakness (n=8). Truncal weakness improved or resolved with dose reduction or cessation. Grade 4 toxicities included creatine kinase elevation (n=2) and transient colitis (n=1). Of 44 patients with preliminary response data available, 22 (50%) showed a minor (n=7) or partial (n=15) response. CONCLUSION: Binimetinib is active, with manageable toxicities, in children without NF1 with progressive LGG.

LGG-53. PNOC001 (NCT01734512): A PHASE II STUDY OF EVEROLIMUS FOR RECURRENT OR PROGRESSIVE PEDIATRIC LOW-GRADE GLIOMAS (PLGG)

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OBJECTIVE: To estimate the 6-month Progression Free Survival (PFS6) associated with everolimus for progressive/recurrent pLGGs and to determine if activated PI3K/Akt/mTOR pathway as measured by positive phosphorylated-ribosomal protein S6 (p-RPS6) status was associated with response. METHOD: Patients 3–21 years of age with recurrent or progressive pLGG were enrolled. Everolimus was administered orally at 5 mg/m^2 daily. Tissue availability for molecular analysis was mandatory. Immunohistochemistry (IHC) for p-RPS6 was performed centrally. An adaptive Simon two-stage design was employed based on p-RPS6 status. Based on results of the first stage, enrollment in the second stage was either limited to pathway activated patients or open to all subjects. RESULTS: From December 2012 to July 2019 a total of 65 subjects enrolled [median age 9 years (range 3–19); 43% female]. As of December 15, 2019 median number of treatment cycle is 8 (range 1–24); 7 patients remain on treatment. Toxicity profile is similar to published reports with rash and elevated lipid profiles as most common adverse events. PFS6 for the entire cohort is 63%; PFS6 is 64% for the activated and 61% for the non-activated patients. Central imaging review (n=52) revealed 1 partial response, 1 complete response, 33 stable disease, and 17 progressive disease at the end of study treatment. Initial molecular analysis identified BRAF alterations in 35/65 patients. CONCLUSION: Everolimus is well tolerated and active in a subset of pLGGs. Ongoing analyses will assess predictive biomarkers of response and will be reported at the meeting.

LGG-54. DETECTION OF THE KIAA1549-BRAF FUSION GENE IN CELLS FORMING MICROVASCULAR PROLIFERATIONS IN PILOCYTIC ASTROCYTOMA

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Microvascular proliferation (MVP), an aberrant vascular structure is a histopathological hallmark of glioblastoma multiforme (GBM). Although MVP tends to be associated with high-grade glioma, it has also been detected in WHO grade I pilocytic astrocytoma (PA). However, little is known about the mechanism underlying its formation. Using TP53 point mutations as a marker for tumor-derived cells, we earlier reported that MVP was partially converted from tumor cells via mesenchymal transition. In the current study we used the KIAA1549-BRAF fusion gene as a marker to assess whether MVPs in PA contained tumor-derived cells and/or phenotypically

distinct tumor cells expressing vascular markers. Samples from three PA patients harbored the KIAA1549 exon 15, BRAF exon 9 fusion gene. In two patient samples with abundant MVP, RT-PCR assay detected strong bands arising from the KIAA1549-BRAF fusion gene in both tumor cells and cellular components of MVP. Digital PCR showed that vis-à-vis tumor tissue, its relative expression in cellular components of MVP was 42% in one- and 76% in another sample. FISH revealed amplified signals in both tumor cells and cellular components of MVP indicative of tandem duplication. Our findings suggest that in patients with PA, some cellular components of MVP contained tumor derived cell and/or phenotypically distinct tumor cells expressing vascular markers.

LGG-55. OUTCOME OF BRAF V600E PEDIATRIC GLIOMAS TREATED WITH TARGETED BRAF INHIBITION

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Children with pediatric gliomas harboring BRAF V600E mutation have a poor outcome with current chemoradiation strategies. Our aim was to study the role of targeted BRAF inhibition in these tumors. We collected clinical, imaging, molecular and outcome information from BRAF V600E glioma patients treated with BRAFi across 29 centers from multiple countries. Sixty-seven patients were treated with BRAFi (56 pediatric low grade gliomas, PLGG and 11 pediatric high grade gliomas, PHGG) for up to 5.6 years. Objective responses were observed in 80% of PLGGs compared to 28% with conventional chemotherapy ($p<0.001$). These responses were rapid (median, 4 months), and sustained in 86% of tumors up to 5 years while on therapy. PLGG which discontinued BRAFi, 76.5% (13/17) progressed rapidly after discontinuation (median 2.3 months). However, upon re-challenge with BRAFi therapy, 90% achieved an objective response. Poor prognostic factors to conventional therapies, such as concomitant homozygous deletion of *CDKN2A,* were not associated with a lack of response to BRAFi. In contrast, only 36% of PHGG responded to BRAFi with all but one tumor progressing within 18 months. In PLGG, responses translated to 3-year progression-free survival of 49.6% (95%CI, 35.3% to 69.5%) vs 29.8% (95% CI, 20% to 44.4%) for BRAFi vs chemotherapy respectively ($p=0.02$). The use of BRAFi results in robust and durable responses while on therapy in BRAF V600E PLGG. Prospective studies are required to determine long-term survival and functional outcomes with BRAFi therapy in childhood gliomas.

LGG-56. INFANTILE HEMISPHERIC BRAIN TUMOR WITH A GOPC-ROS1 FUSION GENE: A CASE REPORT

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INTRODUCTION: Infantile hemispheric gliomas with *ROS1* fusion genes have been reported to have a relatively poor prognosis. Treatment using *a ROS1* inhibitor is expected to generate less toxicity and effective for brain tumors with *ROS1* fusion genes. CASE PRESENTATION: A one-month-old female presented with a seizure, and a large hypervascular mass in the right hemisphere was found on MRI. The tumor was not biopsied over concerns of an increased risk for bleeding. The mass was clinically diagnosed as an atypical teratoid rhabdoid tumor. She received neoadjuvant chemotherapy using the modified EU-RHAB protocol. The tumor gradually decreased to 70% of its original size with a reduction of vascularity. A near-total resection (> 95%) was performed at eight months of age. Pathological examination revealed the unusual histology with immunostaining positive for INI-1, GFAP, synaptophysin, neurofilament, and slightly positive for NeuN. MIB-1 labeling index was 6%. The pathological diagnosis was a glioneuronal tumor with desmoplastic infantile ganglioglioma-like features, suggestive of low grade. She received adjuvant chemotherapy with carboplatin and vincristine, which is the standard treatment for low-grade gliomas, and achieved a partial response. The *GOPC-ROS1* fusion gene was detected in the tumor by FoundationOne® CDx. CONCLUSION: Chemotherapy may effectively reduce the size of an infant's brain tumor which is initially considered to be inoperable. A gene profile should be performed as soon as possible in order to direct appropriate management.

LGG-57. SIGNALLING MECHANISMS IN PAEDIATRIC LOW-GRADE GLIOMA

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Paediatric low-grade gliomas (pLGGs) constitute the largest group of childhood CNS tumours. They often cause significant disability and morbidity, despite their indolent growth and the good survival rate of patients. The most common genetic alterations in these tumours, *KIAA1549:BRAF* fusion and *BRAFV600E* mutation, lead to abnormal activation of MAPK signalling. The central role of this pathway in pLGG development is emphasized by the occasional presence of other MAPK-activating alterations such as RTK mutations. It is not known how these different aberrations can induce the variety of clinical phenotypes seen in pLGG. Here, we compared pilocytic astrocytomas (PAs) containing the *KIAA1549:BRAF* fusion with glioneuronal tumours (GNTs) containing the *BRAFV600E* mutation, to identify differentially activated downstream targets of the MAPK pathway. Liquid chromatography tandem mass spectrometry (LC-MS/MS) was used as a multi-proteomic approach. Kinase Set Enrichment Analysis (KSEA) using PhosphositePlus and NetworkIN was used to determine relative enrichment of kinase activity in the tumours compared to healthy control brain tissue. Significant similarities and differences were found in the two tumour types. For example, more robust MAPK activation was found in the GNTs than in PAs. However, while PI3K/AKT1/mTOR signalling was active in both PAs and GNTs, there was statistically higher activation in the PAs. In both tumour types, there was significant reduction in casein kinase 2 activity, which likely affects nuclear translocation of ERK and, in turn, alters the range of its phosphorylated substrates. We will present these data together with transcriptomics to further characterise the downstream targets of these genetic alterations.

PEDIATRIC NEURO-ONCOLOGY IN ASIA AND OTHER LOW/ MIDDLE INCOME COUNTRIES

LINC-01. COMPLIANCE TO FOLLOW UP IN PEDIATRIC PATIENTS WHO HAVE RECEIVED CRANIOSPINAL IRRADIATION

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OBJECTIVE: Attendance to follow-up after completion of cancer treatment is understudied area. Pediatric cancer patients have sequelae of illness or treatment. Many have no symptom immediately after completion of treatment. Long term follow-up is important to access disease control, early diagnosis of recurrence, second cancer and treatment-related morbidities. Purpose of this study was to evaluate the compliance to follow-up in pediatric patients treated with craniospinal irradiation (CSI). METHODS: This was retrospective review of follow-up in pediatric neuro-oncology patients who received (CSI) from January 2017 to June 2018 in the Radiotherapy Department of Yangon General Hospital, Myanmar. RESULT: Twenty-three patients received CSI; majority (43%) were medulloblastoma. Median age was 7.5 years (3–17 years). Only seven patients (30.4%) were attended to follow-up more than 6 months after completion of treatment. More than two-thirds of patients (n=16,69.6%) were lost to follow-up. Patients in active follow-up were diagnosed and treated at earlier age below 10years (n=5,21.7%). Demographically, 5 patients (22%) were living in the region around tertiary hospital. Sixteen patients (69.6%) from rural area had limited transportation and difficulty for accommodation in which they were treated. In socioeconomic points, 18 parents (78.2%) had poor education and financial status, lack of understanding about disease, treatment, long-term effects and follow-up. CONCLUSION: Although this was limited data in CSI patients only, loss to follow-up after 6 months was high. We need to evaluate in all pediatric cancer patients and collaborate to provide financial support, childcare centres for lodging, transportation and health education to promote compliance to follow-up.

LINC-02. IMPLEMENTATION OF AN INTEGRATED NEURO-ONCOLOGY SERVICE: CLINICIANS' PERSPECTIVE ON CONDUCT OF NEURO-ONCOLOGY MULTIDISCIPLINARY TEAM MEETING FROM A SINGLE-INSTITUTION IN MALAYSIA

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INTRODUCTION: Multidisciplinary Team (MDT) meetings are essential in the management of complex cancer cases. There are limited data regarding clinicians' perception on conduct of neuro-oncology MDT meetings and its impact on clinical management. In University Malaya Medical Centre (UMMC), weekly neuro-oncology MDT meeting was established since 2013 to discuss adult and paediatric complex central nervous system tumour cases. OBJECTIVE: To determine clinicians' perception and level of satisfaction of neuro-oncology MDT meeting. METHODOLOGY: Web-based questionnaire was distributed via e-mail to all neuro-oncology MDT clinicians at UMMC in April 2019. RESULT: Eighteen out of 20 clinicians responded to the survey. Respondents were: neurosurgeons (n=5), adult oncologists (n=4), paediatric oncologists (n=3), radiologists (n=2), radiation oncologists (n=2) and pathologists (n=2). Majority of clinicians (65%) agreed at current weekly MDT meeting with maximum length of one hour duration and 75% of them suggested to discuss 5 to 10 cases during each meeting. Almost all of them (94.4%) preferred e-mail as method of communication to disseminate information before and after the meetings. MDT members expected 100% attendance from neurosurgeons. Fourteen (70%) clinicians agreed that patients/ parents/ carers do not receive copy of MDT meeting plans and only seven (35%) clinicians document MDT meeting plans in patients' medical record. Overall, all clinicians felt that MDT meeting improved decision-making process, enhanced continuity of coordinated care and promoted good communication among team members. CONCLUSION: The structure and logistics of neuro-oncology MDT meeting in UMMC are generally agreed upon. However, documentation of post-meeting plan and notification to patients need uniformity.

LINC-03. MOLECULAR CLASSIFICATION OF PAEDIATRIC MEDULLOBLASTOMA FROM FOUR TERTIARY CENTRES IN MALAYSIA: DIAGNOSTIC DILEMMA WITH CONVENTIONAL METHODS

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OBJECTIVE: To determine the prognostic significance of the four molecular subgroups of medulloblastoma (MB) among children in Malaysia. METHODS: We assembled MB samples of children < 18 years between January 1999 and July 2017 in University Malaya Medical Centre, Penang General Hospital, Sarawak General Hospital and Sabah Woman and Children's Hospital. MB was sub-grouped using 850k DNA methylation profiling. RESULTS: Fifty-one tumour samples were retrieved. Histopathological subtypes were classic (n=12), MB extensive nodularity/desmoplastic (n=9) and 30 MB results without subtypes. Thirteen patients were M1-M4. Fourteen patients were stratified as standard-risk (SR,27.4%), 22 as high-risk (HR,43.2%) and 15 as high-risk children ≤ 3 years old (iHR,29.4%). Molecular subgrouping revealed 16 Group4, 11 SHH, 10 Group3 and 4 Wnt. In 8 patients, DNA methylation profiling identified a diagnosis other than MB and in 2 samples the DNA was inadequate. For patients >3 years old, the 5-year event-free survival (EFS) was 35.7%±13% in HR and 39.7%±20% in SR. The 5-year overall survival (OS) in these two groups was 43.4%±14% and 41.7±30% respectively. iHR had 5-year EFS and OS of 48.0%±16% and 60.0%±16% respectively. WNT tumours had the best 5y-OS of 66.7±22% of the cohort, albeit significantly lower than other reports, followed by SHH (56.8±17%), Group4 (44.3±17.6%) and Group3 (41.7±18%). Treatment abandonment rate was 20%. CONCLUSION: The discrepancy in the histological diagnoses highlights the importance of DNA methylation profiling technique for accurate diagnosis. We observed poor OS across all the subgroups, in part due to treatment abandonment.

LINC-04. POSSIBLE ROLE OF NEOADJUVANT CHEMOTHERAPY IN METASTATIC PURE GERMINOMA IN LOW AND MIDDLE INCOME COUNTRIES. A PRO POS OF A CASE

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BACKGROUND: CNS germ cell tumors represent about 3–5 % of pediatric brain tumors, 60% are pure germinomas. Germinomas are very sensitive to chemotherapy which has helped to reduce volume and dose of radiotherapy in localized disease while maintaining excellent survival. In metastatic disease the SIOP GCT-96 trial showed no benefit with addition of chemotherapy to craniospinal irradiation alone. Radiotherapy maybe not readily available in Low/Middle Income Countries (LMIC). METHOD: We describe a patient in which the use of neoadjuvant chemotherapy helped to rescue vision. The patient is a 9 year old female with a 3 months history of morning headaches and vomits. Visual decline was noticed a month before admission when the child had completely loss vision of the right eye and left eye was partially affected. MRI showed a large suprasellar mass with ventricular nodules. Beta-hGC in CSF was mildly elevated. Patient received 2 cycles of carboplatin/etoposide. After first cycle there was a complete vision recovery in both eyes. After the second course the MRI showed complete response in primary and metastatic disease. Patient received CSI (24Gy + 16 Gy Boost) after 2 cycles of chemotherapy. Chemotherapy was very well tolerated without side effects. Patient vision is 20/20 in both eyes without deficit in visual fields. CONCLUSION: Although the addition of chemotherapy in metastatic germinoma has no clear role in reducing radiotherapy it could possible help selected patients in attempt to rescue vision when radiotherapy is not readily available.

LINC-05. PRIMARY CENTRAL NERVOUS SYSTEM EWING SARCOMA IN PEDIATRIC AND AYA PATIENTS: 2 INSTITUTIONS EXPERIENCE IN BUENOS AIRES ARGENTINA

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INTRODUCTION: Ewing Sarcoma (ES) is defined by molecular markers, being t(11;22)(q24;q12) the most frequent. Intracranial ES usually shows as metastases from extracranial sites. Primary central nervous system (CNS) lesions are extremely rare. MATERIAL AND METHODS: Retrospective review of clinical records from patients with primary CNS ES, assessed at 2

institutions in Argentina between 2007–2019. Translocation was evidenced in all cases through molecular testing. Clinical characteristics, imaging, histopathology, and treatment response were evaluated. Extracranial and osseous lesions were excluded. RESULTS: 15 patients. Median age at beginning of symptoms: 8 yo (2–20). Most patients had intracranial hypertension syndrome (14/15). In brain MRI, 5/15 supratentorial lesions, 4/15 posterior fosa, 1/15 medullary, 2/15 supra and infratentorial, and 3/15 lesions diffuse leptomeningeal infiltration. Histopathologic findings showed diffuse pattern with small round blue cells in most cases, other patterns were also described. CD99 marked positive in all cases. Misdiagnosis with glial tumors (4/15), medulloblastoma (6/15) and infectious diseases (3/15); led to median delay to accurate diagnosis of 3 months (range 0–67). After correct diagnosis patients were treated with standard ES treatment (6 VIDE cycles plus radiotherapy) in 14/15 patients. Vincristine, irinotecan and temozolamide was used as second line treatment in all relapse cases whenever possible. EFS was 22 months (2- 65). OS at 5 years of follow-up was 46,67% (mean OS 31 mo). CONCLUSION: Even though molecular assessment led to accurate diagnosis in all cases, treatment response and outcome showed two different groups of patients with long and very short survival. Adaptative therapy should be considered.

LINC-06. OBSERVATION ONLY IN A PATIENT WITH SUSPECTED LOW GRADE GLIOMA. SHOULD NEUROSURGERY ALWAYS BE THE FIRST STEP IN LOW AND MIDDLE INCOME COUNTRIES?

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BACKGROUND: Low grade gliomas (LGGs) are the most frequent pediatric brain tumor and they comprise a variety of histologies. Complete surgery is curative but sometimes its location makes it difficult. Recent publications highlight the excellent long-term outcomes of patients with LGGs with complete and incomplete resected tumors. Current strategies are focused on reducing risks of treatment related sequelae. METHOD: We describe a patient with a suspected LGG managed by close observation. We describe the case of a 6 year old female with 5 months history of focal onset seizures. During this time a brain MRI was requested and tumor was evidenced. After "tumor diagnosis" was made family visited a handful of private neurosurgeons with a uniformly dismal prognosis and high risk morbidity from procedures offered. When first seen at our Hospital, the clinical history seemed compatible with a LGG and seizures well controlled with antiepileptic drugs. Neurological examination was completely normal. MRI showed a large tumor (7x5x5 cm) hypointense on T1, hyperintense on T2, without contrast enhancement, involving the right temporal lobe white matter, insula, internal capsule, hipoccampus, thalamus and mesencephalus with middle cerebral artery encasement. Interval imaging was proposed and after 4.5 years since diagnosis the tumor has been stable and patient clinically excellent. CONCLUSION: Overall survival in pediatric LGGs is excellent and risk of sequelae should always be part of multidisciplinary team considerations. In centers with significant neurosurgical morbidity, biopsy of large tumors that are compatible with LGG may not be required in selected cases.

LINC-07. PREVALENCE AND SPECTRUM OF EARLY ENDOCRINE DISORDERS IN SURVIVORS OF PEDIATRIC EMBRYONAL BRAIN TUMORS (PEBT): EXPERIENCE FROM INDIA

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BACKGROUND: Survivors of pediatric brain tumors are at high risk of developing endocrine disorders, potentially impacting growth,development and quality of life. METHODS: etrospective audit of 2-year survivors of PEBT(3-18years at diagnosis)viz. medulloblastoma(MB),Central nervous system Primitive neuro-ectodermal tumors(CNS-PNET) and atypical teratoid/rhabdoid tumor(ATRT) treated January 2006-December 2017 at Tata Memorial Centre,Mumbai, with surgery, cranio-spinal irradiation(CSI; 35Gy in high-risk MB,CNS-PNET,ATRT and 23.4Gy in average-risk MB with tumor boost 19.8Gy)and six cycles of adjuvant chemotherapy(cycloph osphamide,cisplatin and vincristine).Patients were followed up by a paediatric endocrinology team specialized in management of PEBT. RESULTS: Of 249 PEBT treated during this period,88 are alive in remission >2 years (69-MB, 15-CNS PNET,4-ATRT),median age at diagnosis 6 years. At a median follow-up of 5.6 years (range 3- 12.5years),63 patients(72%) had at least one endocrine disorder,26(29.%)≥2 hormonal deficiencies. The most common endocrine disorders were central hypothyroidism(57%),growth hormone deficiency(40%), central hypogonadism(5%)and central hypoadrenalism (3.5%).The median time to develop hypothyroidism was 2.8 years(range 5months to 8.5 years) from CSI. Growth hormone replacement therapy began after a median period of 4.2 years(range-1.5 to 11.5years) from CSI. Higher dose of CSI was associated with development of endocrine disorder (odds ratio [OR] 2.71; 95% CI, 1.03 to 7.04,p-0.04). CONCLUSIONS: The high incidence of endocrine deficits in survivors of PEBT necessitates early and lifelong monitoring. Early and appropriate management is crucial to achieve full growth potential.

LINC-08. INCREASED TREATMENT TOXICITIES AND INFERIOR OUTCOMES IN UNDERNOURISHED CHILDREN WITH BRAIN TUMOURS

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BACKGROUND: Children on treatment for brain tumours are known to be at high risk of undernutrition, the impact on outcome and toxicity is not well understood. METHODS: Retrospective audit of children(<18 years) diagnosed January 2017-December 2018 with embryonal brain tumours (medulloblastoma, primitive neuro-ectodermal tumors, pinealoblastoma, atypical teratoid/rhabdoid tumour) and treated at our centre. Data was retrieved from case records and electronic medical records. Nutritional status(NS) was defined as per World Health Organization (WHO) into severe malnutrition (SAM),moderate malnutrition (MAM),well nourished (WN) and overweight. Undernutrition(UN) was defined as SAM/MAM.Toxicity was documented till end of treatment,defined as treatment delay>1week,significant infection or toxic death. RESULTS: Of 124 eligible patients who received entire chemotherapy at our centre, NS data was available in 73 at diagnosis and 58 at follow-up. At diagnosis-29,16,26 and 2 and at follow-up-20,16,22 and 0 were SAM,MAM,WN and overweight. During treatment, weight gain was documented in 26%, stable weight in 55% and weight loss in 19%. Those UN at diagnosis had worse outcomes at follow-up with 70% alive in remission compared to 88% of WN(p-0.14). There was increased toxicity in UN group(50%) compared to WN(24%),p-0.04.All 3 toxic deaths were in UN. Those who lost weight during treatment had higher toxicities(70%) compared to those with stable weight (30%)or weight gain(20%),p-0.02. CONCLUSIONS: In spite of nutritional intervention, children on treatment for brain tumours tend to lose weight. Increased treatment toxicities and inferior outcomes in undernourished children with brain tumours necessitates proactive and aggressive nutritional monitoring and intervention.

LINC-09. TREATMENT AND OUTCOME IN CHILDREN WITH LOW-GRADE GLIOMAS IN WESTERN MEXICO: EXPERIENCE AT HOSPITAL CIVIL DE GUADALAJARA

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BACKGROUND: Brain tumors are the most common solid tumors in childhood, 35% of them being low-grade gliomas (LGGs). Few data is available regard LGGs in low-and-middle-income countries. This study evaluates LGGs in a tertiary center in Mexico. DESIGN: A retrospective review of clinical files of 105 children diagnosed with LGG other than optic nerve glioma from 2007 to 2019 was done. RESULTS: Median age at diagnosis was 7.2 years (from 5 months to 18 years). Male to female ratio was 0.75:1. WHO Grade I represented 68% of the cases. Anatomic sites were: posterior fossa (41%), supratentorial (43.5 %), spinal (8.5%), subependymal (6 %) and pineal (1%). Ten percent of patients had a diagnosed phacomatosis. Treatment was observation without surgery in 3.8%, surgery followed by observation in 49.5%, only chemotherapy in 2.8%, only radiotherapy in 6.7%, and surgery combined with chemotherapy or radiotherapy in 37.2% of cases. Among patients who had surgical intervention, 40% achieved gross total resection, 44% subtotal resection and 16% only biopsy. One or more recurrences were found in 20 % of patients. The 5 and 10-year overall survival (OS) was 83% and 73% respectively. The 5 and 10-year progression-free survival (PFS) was 66 % and 44 % respectively. CONCLUSIONS: In this series the OS were lower compared with countries with high income, reflecting the need to improve surgery, since only 40% achieved complete resection that is a determining factor for the prognosis. We observed a decrease in OS until 10-year follow and the PFS was even lower due to recurrence/progression.

LINC-10. SIOP PODC ADAPTED TREATMENT GUIDELINES FOR CRANIOPHARYNGIOMA IN LOW- AND MIDDLE-INCOME SETTINGS

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Pediatric craniopharyngioma is a rare tumor with excellent survival but significant long-term morbidities due to the loco-regional tumor growth or secondary to its treatment. Visual impairment, panhypopituitarism, hypothalamic damage and behavioral changes are amongst the main challenges. This tumor should be managed under the care of a multidisciplinary team to determine the optimum treatment within the available resources. This is particularly important for low middle-income countries (LMICs) where resources are variable. We provide a risk-stratified management guideline for children diagnosed with craniopharyngioma in a resource limited setting based on the service levels describing the facilities and personnel required for management as previously specified by the Pediatric Oncology in Developing Countries (PODC) committee of The International Society of Pediatric Oncology (SIOP). A multi-disciplinary group of neurosurgeons, radiation and pediatric oncologists, radiologists, pediatric endocrinologists and an ophthalmologist with experience in managing children with craniopharyngioma in LMIC setting was formed and carried online meetings to form a consensus guideline. The clinical characteristics (including the visual and endocrine presentations), suggestive radiological features as well as potential treatment options including surgery, radiotherapy and intra-cystic therapies were discussed in depth and in relation to available resources. In addition, hormonal management, pre- and post-operative PICU care and expected future complications related to craniopharyngioma and to follow up these children were discussed and documented in the guideline. We believe this guideline is a useful reference for health care providers in LMIC.

LINC-11. NEUROPATHOLOGY REVIEW OF LATIN AMERICAN CHILDHOOD AND ADOLESCENT BRAIN TUMOR PATIENTS: A MULTI-NATIONAL, MULTI-DISCIPLINARY PEDIATRIC NEURO-ONCOLOGY TELECONFERENCE EXPERIENCE

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BACKGROUND: Pediatric brain tumor classification has undergone significant evolution over the last decade requiring a high-level of expertise and diagnostic techniques. Such advances have created challenges for pathologists particularly in low-to-middle income countries (LMIC). We conduct weekly pediatric neuro-oncology teleconferences linking global pediatric neuro-oncologists from high-income countries (HIC) to review patients with pediatric subspecialists from Latin America. METHODS: Three to five patients are discussed weekly and second neuropathology review is offered when a high-level of suspicion emerges of a questionable diagnosis based on clinical and radiographical information. Nationwide Children's Hospital (NCH) provides second neuropathology review at no cost to institutions in Latin America that fulfill these criteria. RESULTS: From July 2015 to December 2019 NCH reviewed 54 pathology samples from eleven Latin American countries. Of these, 33 (61.1%) cases resulted in diagnostic changes, of which 28 (51.8%) were significant, impacting treatment plans and overall patient outcomes. The remaining 21 (38.9%) confirmed institutional diagnosis; however, in eight of these 21 cases additional molecular information and/or further tumor subtyping unavailable in their home country at the time (eg: BRAF, RELA-fusion, medulloblastoma subtyping) was provided. CONCLUSIONS: This study highlights the importance of centralized pathology review by institutions with the proper equipment, infrastructure and expertise in pediatric neuropathology. Furthermore, this documents the beneficial impact of teleconferencing for subspecialists in LMIC who must treat a wide variety of pediatric cancers with few resources and support. Additionally, our findings underscore the need for pediatric subspecialty training in LMIC.

LINC-12. COMBINED ADULT AND PAEDIATRIC NEURO-ONCOLOGY LONG-TERM SURVIVOR CLINIC EXPERIENCE FROM A TERTIARY CANCER CENTRE IN A LOW-MIDDLE-INCOME COUNTRY

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NeuroOncology survivor clinics (NOS) is uncommon in low-middle-income countries. We started combined (paediatric and adult) NOS clinic in our tertiary a cancer centre (Jan-2017) and review here the demographic, clinical-pathological and treatment spectrum for our paediatric (0-18years) and adult (>18years) survivors (>5years since their initial diagnosis) till date. Of total 312 patients registered, 198 (63.5%) were adults while 114 (36.5%) were paediatric at-diagnosis with median age (IQR) at presentation: 34 (23–41) and 9(6 – 13) years respectively. In both groups, only 33% were females. The median (IQR) time since diagnosis was 9 (9–14) and 8 (6–12) years respectively with 60% of paediatric turning into adult survivors. The commonest paediatric tumours were glioma (52, 45.6%), embryonal (34, 29.8%), and ependymoma (12, 10.5%) versus gliomas (114, 57.6%) and benign tumours (42, 21.2%) in adults. The low-grade-glioma comprised 90.4% of all pediatric gliomas and intermediate-grade (90%) in adults. The primary treatment consisted of radiotherapy and chemotherapy in 95% and 43% versus 99% and 36% in adults versus paediatric patients respectively. Temozolomide and multi-drug combinations were the commonest chemotherapy used in adults and paediatrics respectively. Relapse and retreatments were seen in 16.6 and 14% of adults and paediatric patients. There were two deaths each in each group since registration (median 12 months). Although the baseline diagnosis/treatment characteristics are different, survivors of both group had a similar number of retreatments and deaths. Combined survivor clinics may present an interesting and unique opportunity to learn and provide challenging service in this part of the world.

LINC-13. THE STATE OF PEDIATRIC NEURO-ONCOLOGY IN ARMENIA

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BACKGROUND: Every year in Armenia we have approximately 80–90 new pediatric cancer cases from which 10–15 are brain tumors (PBT). Here we try to summarize the current state of pediatric neuro-oncology in Armenia. DISCUSSION: In Armenia pediatric neuro-oncology is still in its first steps. Surgical treatment of PBTs is performed only in one medical center – "Sourb Astvatsamayr" Medical Center, with 7 practicing pediatric neurosurgeons. Radiation therapy service with two linear accelerators is located at the "National Oncology Center", however there are no dedicated pediatric radiation neuro-oncologists, and 2 specialists are treating pediatric tumors. Chemotherapy for all pediatric cancers currently is performed at the Pediatric Cancer and Blood Disorders Center of Armenia, established in

February 2019 as a result of merging of all pediatric oncology units in the country. Among the 11 practicing pediatric hematologist/oncologists no one is dedicated specifically to PBTs. Since September 2017 we have started discussing all PBT cases (up to now 18 cases) through the telemedicine with St. Jude Children's Research Hospital (SJCRH). In Sept 2019 neuro-oncology multidisciplinary team was created with the involvement of local and foreign specialists. On a weekly basis the multidisciplinary team discusses all new and problematic cases. The team also concentrates on adaptation of diagnostic and treatment guidelines for pediatric CNS tumors, creation of educational materials for different stakeholders, and identification of current problems and their possible solutions. CONCLUSION: To the best of our knowledge this is the first report summarizing the current state of pediatric neuro-oncology in Armenia.

LINC-14. TREATMENT OF PEDIATRIC CNS TUMORS IN ARMENIA. 10 YEARS OF EXPERIENCE IN A 29 YEARS OLD RESOURCE-LIMITED SETTING

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BACKGROUND: Pediatric CNS tumors are the most common solid childhood malignancies with many challenges facing optimal outcome due to multimodality complex therapies, abandonment, and long-term morbidity. In our three-decades young, country the field of neuro-oncology is in its infancy. MATERIALS: The aim of our study is to assess incidence, epidemiology and treatment outcomes of children diagnosed and treated with CNS tumors within the last 10 years (2009–2019) in the Chemotherapy Clinic of "Muratsan" Hospital Complex of Yerevan State Medical University. RESULTS: During these periods 20 patients with CNS tumors were treated in our clinic. 13 patients (65%) were diagnosed with medulloblastoma (2 patients were infants), two patients (10%) with optic pathway glioma, and 5 patients each with pilocytic astrocytoma, ATRT, ETANTR, DIPG, and glioblastoma. Five patients (3 patients with medulloblastoma, 1 patient with pilocytic astrocytoma, 1 patient with ATRT) had metastatic disease at the time of diagnosis. Seventeen patients (80%) had undergone surgery, 8 patients with medulloblastoma received chemo-RT with vincristine. Median follow up time was 15.5 months (range 5–94). Twelve patients (60%) are alive without evidence of disease. 5 patients had disease progression and three patients relapsed. From them, 3 patients died. Long-term survivors are mainly standard risk medulloblastoma patients. All medulloblastoma patients were treated according to HIT-MED guidelines. CONCLUSION: Here we report about the pediatric brain tumors of one of the main pediatric oncology units in Armenia for a period of 10 years. The numbers are quite small for firm conclusions, but it shows the emerging need for further research.

LINC-15. OUTCOME OF CHINESE CHILDREN WITH MEDULLOBLASTOMA: A MULTI-CENTER EXPERIENCE WITH RISK-ADAPTED THERAPY

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BACKGROUND: Medulloblastoma is the commonest brain tumor in young children but literature on Chinese is scarce. We hereby present the outcome of children with medulloblastoma managed according to a risk- and age-stratified guideline from ten institutions across China. METHODS: Patients <18 years of age diagnosed with medulloblastoma between January 2016 and April 2019 were reviewed. Patients ≥3 years, stratified into average-risk (≤1.5cm^2 residual tumor, non-metastatic, non-anaplastic histology) and high-risk (others) groups, were treated with risk-adapted craniospinal irradiation (average-risk: 23.4Gy, high-risk: 36Gy), tumor boost, and chemotherapy (lomustine/cisplatin/vincristine). Patients <3 years (considered high-risk, other than patients with localized and desmoplastic/nodular histology) received chemotherapy (cyclophosphamide/vincristine, high-dose methotrexate, carboplatin/etoposide) with/without delayed irradiation. RESULTS: 112 patients were included with a median age at diagnosis of 6.5 years (range: 0.5–16.7). 16 patients (14.3%) had residual tumor >1.5cm^2 and 36 (32%) had metastasis. Available data on histological subtype (n=87) were classic in 56 (64%), desmoplastic/nodular or extensive nodularity in 23 (26%), and large cell/anaplastic in 8 (9%). Molecular subgrouping (n=55) assigned tumors as WNT-activated (n=8, 15%), SHH-activated (n=17, 31%), Group 3 (n=12, 22%) and Group 4 (n=18, 33%). Respective 2-year EFS/OS for patients ≥3 and <3 years were 86.0±4.0%/96.4±2.1% and 57.8±12.6%/81.4±9.8% (EFS/OS p<0.001/p=0.009). Significant difference in outcome was also observed between patients with average-risk and high-risk disease (EFS/OS p=0.006/p=0.018). CONCLUSION: We demonstrated feasibility in protocolizing the inter-disciplinary treatment for medulloblastoma in China. This will serve as a prototype for the standardization of pediatric neuro-oncology care in the country.

LINC-16. MEDULLOBLASTOMA IN A BOY WITH RUBINSTEIN-TAYBI SYNDROME: A CASE REPORT

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BACKGROUND: Rubinstein–Taybi syndrome (RTS) is characterized by multiple congenital anomalies and associated with mutations in CREBBP (70%) and EP300 (5–10%). Previous reports have suggested an increased incidence of benign and possibly also malignant tumors, but the correlation remains unclear. Here we present a case of a patient with RTS and medulloblastoma. CLINICAL CASE: A 5-year-old male presented with increased intracranial pressure. An MRI revealed a 4.2 x 4.7 cm mass in the midline of cerebellum arising from the floor of 4th ventricle. The patient underwent a complete resection and pathology revealed medulloblastoma, classic histology. Staging established no disseminated disease. At diagnosis, a peculiar phenotype consisting in mild mental retardation, microcephaly, down-slanting palpebral fissures, broad nasal bridge, highly arched palate, mild micrognathia, screwdriver incisors and wide thumbs and toes was noted. Clinical genetics evaluation was consistent with RTS. Karyotype was performed and normal. Further genetics testing was not done. Treatment consisted in 8 cycles of chemotherapy and craniospinal radiation (2300 cGy to spine, 5500 cGy Total). At the end of treatment, there was no evidence of disease. He was under surveillance for 33 months free of disease, but relapsed with a supratentorial meningeal disease that ultimately resulted in death. CONCLUSION: This report highlights the fact that pediatric medulloblastoma can be associated to RTS, in this case associated to classical histology and recurrent disease.

LINC-17. SIROLIMUS AS AN ALTERNATIVE TO SURGICAL RESECTION OF PEDIATRIC TUBEROUS SCLEROSIS COMPLEX-ASSOCIATED BILATERAL SUBEPENDYMAL GIANT CELL ASTROCYTOMAS: AN AFFORDABLE OPTION FOR PATIENTS FROM LOW-MIDDLE INCOME COUNTRIES

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Subependymal giant cell astrocytomas (SEGA) may lead to significant neurological morbidity in children diagnosed with tuberous sclerosis complex (TSC). Surgical resection is warranted for SEGAs demonstrating continuous growth, causing hydrocephalus and increased intracranial pressure. mTOR inhibitors (sirolimus and everolimus) are alternatives to surgery and have shown efficacy in stabilizing and shrinking SEGAs. Everolimus showed stronger evidence in efficacy, but its cost poses a limitation for this treatment among patients from low-middle income countries. We explored sirolimus as a potentially more cost-effective alternative in our setting. We present a 10-year-old Filipino child with TSC admitted due to headache, vomiting, and increased sleeping time. Neuroimaging revealed large bilateral SEGAs involving the frontal horns and foramina of Monro, causing moderate obstructive hydrocephalus. Surgical excision was offered, but parents opted for medical treatment. Bilateral posterior parietal ventriculoperitoneal shunts were inserted to decrease intracranial pressure. Due to the cost of everolimus, the patient was started on sirolimus at 1mg/m^2/day. Imaging done 6 months after initiating therapy demonstrated significant decrease in size of both SEGAs (right: 82.5%, left: 64.1%). Sirolimus levels were maintained at 15.7ng/ml and minimal elevations on cholesterol and triglyceride levels were observed and treated with simvastatin. Results of this case and review of related data suggest that sirolimus can be used as a conservative approach in inducing regression of large bilateral SEGAs, and an affordable alternative to everolimus for pediatric TSC patients from low-middle income countries. Prospective studies and clinical trials are needed to further establish its efficacy, safety and cost-effectiveness in our setting.

LINC-18. FOLLOW-UP EVALUATION OF A WEB-BASED PEDIATRIC BRAIN TUMOR BOARD IN LATIN AMERICA

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BACKGROUND: Since 2013, pediatric oncologists from Latin America have discussed neuro-oncology cases with experts from North America and Europe in a web-based "Latin American Tumor Board" (LATB). This descriptive study evaluates the feasibility of the recommendations rendered during the Board. METHODS: An electronic questionnaire was distributed to physicians who received recommendations between October 2017 and October 2018, two months after their case presentation on the LATB. Physicians were asked regarding the feasibility of each recommendation given during the Board. Baseline case characteristics of all presented cases were obtained from anonymized minutes prepared after the presentations. RESULTS: 36 physicians from 15 countries answered 103 of 142 questionnaires (72.5%), containing 283 recommendations. Physicians followed 60% of diagnostic procedural recommendations and 70% of therapeutic recommendations. Overall, 96% of respondents considered the recommendations applicable and useful. The most difficult recommendations to follow were genetic and molecular testing, pathology review, locally adapted chemotherapy protocols administration, neurosurgical interventions and access to molecular targeted therapies. The most cited reasons for not implementing the recommendations were lack of resources, inapplicable recommendations to that low-to-middle income country (LMIC) setting, and lack of parental consent. CONCLUSION: The recommendations given on the LATB are frequently applicable and helpful for physicians in LMIC. Nevertheless, limitations in availability of both diagnostic procedures and treatment modalities affected the feasibility of some recommendations. Virtual tumor boards offer physicians from LMIC access to real time, high-level subspecialist expertise and provide a valuable platform for information exchange among physicians worldwide.

LINC-19. CURRENT SITUATION OF PEDIATRIC TUMORS OF CENTRAL NERVOUS SYSTEM IN CHINA - THE FIRST CNOG NATIONAL WIDE REPORT

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Tumors of Central Nervous System (CNS) are most seen solid tumor in childhood. Accounting approximate 25–30% of pediatric neoplasms, treatments on these tumors are complicated as they occur in different age ranges, have various types according to classification system and contain different characteristic molecular profiles. There are huge gaps of medical services for children with CNS tumors in different regions in China, which is blamed to limited medical resources and lack of epidemiology data for Chinese population. After the establishment of CNOG (Children's Neuro-Oncology Group) in China in 2017, national wide registry (CNOG-MC001) was conducted to collect data on the basic information about pediatric tumors of CNS. Results of 4059 cases from 37 centers providing medical services for pediatric CNS tumors in 25 provinces from 6 greater administrative areas in China showed distinct tumor ratio, compared to worldwide data by WHO classification. The mean of age was 8.01 ± 4.73, with a male vs. female ratio as 1.48 to 1. Embryonal tumor, astrocytic & oligodendroglial tumors, and other astrocytic tumors were three most common tumor types in CNS of children. The lost follow-up rate was surprisingly high as 53.07%. In all, this is the first national wide registry for pediatric CNS tumor in China and the results attracted public and government's attentions for further epidemic investigations.

LINC-20. INFANT BRAIN TUMOURS IN HONG KONG

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OBJECTIVES: To review the clinical features, pathology and survivals of infants with brain tumours. METHODS: A retrospective review of the clinical findings, pathology, treatment and survival outcome in infants with brain tumours. RESULTS: From 1999 to 2018, there were 507 children (<18 years) who were diagnosed to have brain tumours in Hong Kong. The patients were treated in five public hospitals. The clinical data were collected by the Hong Kong Paediatric Haematology and Oncology Study Group, and were cross-checked with the data of the Hong Kong Cancer Registry. In this group of patients, there were 36 infants (birth to 365 days of age) i.e. 7.1% of the whole group. Both benign and malignant brain tumours were included, while non-neoplastic lesions were excluded. On average, there was 1.89 cases per year. The pathology of the tumours were astrocytoma (n= 8), medulloblastoma (n=6), germ cell tumour (n=6), PNET (n=5), ATRT (n=4), choroid plexus tumours (n=3), ependymoma (n=2), craniopharyngioma (n= 1) and ganglioglioma (n= 1). These infants were treated according to their clinical conditions and prognosis, with operation, chemotherapy or both. Radiotherapy was withheld or postponed to older age. Some patients only received palliative care due to the poor neurological status or prognosis. The overall survivals of children younger than 18 years old vs infants were 67.3% (±2.3) vs 50.5%(±9.2) respectively, while the event free survivals were 64.4% (±2.4) and 43.5% (±8.8) at 10-years respectively. CONCLUSION: Infants with brain tumours have different pathology and inferior outcome.

LINC-21. SURVEY ON THE RESOURCES AVAILABLE FOR PEDIATRIC NEURO-ONCOLOGY IN CHILE, SOUTH AMERICA

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BACKGROUND: We report the human and material resources available in Chilean institutions providing pediatric neuro-oncology services. METHODS: A cross-sectional survey was distributed to 17 hospitals providing pediatric neuro-oncology services (Programa Infantil Nacional de Drogas Antineoplásicas (PINDA) centers=11, Private=6). RESULTS: Response rate was 71% (PINDA=8; Private=4). Pediatric neuro-oncology services were mainly provided within general hospitals (67%). Registries for pediatric central nervous system (CNS) tumors and chemotherapy-related toxicities were available in 100% and 67% of centers, respectively. Children with CNS tumors were treated by pediatric oncologists in 92% of institutions; none were formally trained in neuro-oncology. The most utilized treatment protocols were the national PINDA protocols followed by the Children's Oncology Group protocols. All World Health Organization essential medicines for childhood cancer were available in more than 80% of participating institutions except for gemcitabine, oxaliplatin, paclitaxel, and procarbazine. The median number of pediatric neurosurgeons per institution was two (range,0–8). General neuro-radiologists were available in 83% of institutions. Pathology specimens were sent to pediatric neuropathologists (33%), neuropathologists (25%), adult pathologists (25%), and pediatric pathologists (16.7%). In-house pediatric radiation oncologists were available in 25% of centers. Intensity-modulated radiotherapy, conformal radiotherapy and cobalt radiotherapy were utilized by 67%, 58% and 42% of hospitals, respectively. Only one center performed autologous hematopoietic cell transplant for pediatric CNS tumors. CONCLUSIONS: These results provide a glimpse into the pediatric neuro-oncology services available in Chile. A wide range of up-to-date treatment modalities is available for children with CNS tumors in Chile. Establishing formal pediatric neuro-oncology training may be beneficial.

LINC-23. PRE-OPERATIVE AND POST-OPERATIVE INTERVENTIONS REDUCE RATES OF VENTRICULITIS IN PEDIATRIC BRAIN TUMOR PATIENTS: A PILOT STUDY

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BACKGROUND: The Philippine General Hospital, a public national referral center, sees 60–80 pediatric brain tumor cases per year. Historically, the rate of post-operative ventriculitis has been high, resulting in

treatment delays and poor outcomes. Starting in July 2019, as a means to decrease infections, patients were provided standardized bathing and wound care kits and caregivers were trained to follow a bathing and wound care protocol. METHODS: This quality improvement study included patients younger than 18 years who underwent craniotomy at PGH were enrolled. The type of surgery, length of surgery, existence of post-operative CNS infection, length of stay and total cost of care was collected. The outcome of these interventions are analyzed 6 months after implementation. RESULTS: Thirty-two 32 patients were included, with mean age of 7 years (1–16). The surgeries performed were: tumor resection (n=20), ventriculoperitoneal shunt insertion (VPS) (n=3), endoscopic third ventriculostomy (n=3), resection with tube ventriculostomy (n=3), Ommaya reservoir placement (n=2), and resection with shunt (n=1). Median surgery time was 4 hours (1–10). Three patients (9.4%) developed ventriculitis. No surgical site infections occurred. Compared to historical controls, a lower rate of infections was noted (9.4% vs. 15.5%, runchart analysis). Patients without post-operative infections had a shorter length of stay (median 14 vs 48 days, $p<0.05$) and a lower cost of care (median $1098 vs. $2425 USD, $p<0.05$). CONCLUSION: Implementation of simple hygiene interventions effectively lowered post-operative CNS infections and hospital costs in a public hospital setting. Incorporation of these into standard clinical practices is urgently needed.

LINC-24. CHARACTERISTICS OF PEDIATRIC BRAIN TUMORS AT DEPARTMENT OF CHILD HEALTH FACULTY OF MEDICINE UNIVERSITAS INDONESIA-DR. CIPTO MANGUNKUSUMO TERTIARY GENERAL HOSPITAL, JAKARTA, INDONESIA

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Brain tumors are still the second leading cause of death among cancers in children. Based on data from National Brain Tumor Society (2019), in United States, there are 28.000 children living with brain tumor with varied clinical, radiological, and histopathological features. The most prevalent children's brain tumor types in US are gliomas (ependymal tumors, pilocytic astrocytomas) and embroyonal tumors, including medulloblastoma. From 1993–1994 at Department of Child Health Faculty of Medicine Universitas Indonesia-Dr. Cipto Mangunkusumo Tertiary General Hospital, Jakarta, Indonesia, there are 19 patients with brain tumors hospitalized with most of patients with astrocytoma 8 patients (42%), 4 patients (21%) medulloblastoma, 2 patients (11%) neuroblastoma, 2 patients (11%) ependymoma, 2 patients (11%) craniopharyngioma, and one patient (4%) meningioma. Retrospective cohort study (2010–2015) with subjects 100 children revealed that based on the radiographs, the brain tumors were located mostly in the cerebellum (24%) and the suprasellar region (10%); based on the histopathology, the most common types of brain tumor were astrocytomas (18%), medulloblastoma (21%), and gliomas (17%). The most common symptom of brain tumors was headache and impaired vision. Survival patients with brain tumors for 5 years in the age group aged 3 years and above was better than that in children aged under 3 years (60% vs 55% and 17% vs 14%). This report can serve as one of basic data for profile children's brain tumors in Indonesia. Keywords: brain; tumor; children; survival; Indonesia

LINC-25. BRAF ABERRATIONS IN PEDIATRIC PILOCYTIC ASTROCYTOMAS (PCAS): PREVALENCE AND IMPACT ON CLINICAL OUTCOME

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BACKGROUND: Increasing knowledge on pilocytic astrocytoma (PCA) biology now points towards an aberration in BRAF/MAPK/ERK pathway which has both diagnostic and therapeutic implications. This study was done to note the impact of BRAF aberrations on clinical outcome in childhood PCA. METHODS: FFPE tissues of all childhood PCA diagnosed during 2011–2017 were evaluated for BRAFV600E mutation by Sanger sequencing and KIAA1549 fusion transcripts (16–9;15–9;16-11) by reverse transcriptase polymerase chain reaction. Children undergoing gross tumor resection received no adjuvant treatment. Unresectable tumors (only biopsy) and NF-1 associated PCAs, were treated if clinically indicated. Only patients with documented therapy details/followup were included for analysis. STUDY RESULTS: Ninety-eight patients (median age-7.7yrs; boy:girl ratio-1.4) were included. Major sites were: Cerebellum-37(38%), 3rd Ventricle-26(27%), Cerebrum-15(15%). While BRAFV600E mutation was noted in 7/89(8%) specimens, BRAF-fusions were found in 34/85(40%). Following surgery/biopsy, 23(24%) and 21(22%) received adjuvant chemotherapy and radiotherapy respectively. The 1-year/3-year/5-year-EFS of the overall cohort was 90.7%/81.3%/67.4% respectively. Cerebellar tumors did better vis-à-vis other sites(5yr-EFS:74.3% v/s 66.4%;p=0.403). The 5yr-EFS of BRAF-fusion positive tumors (34), tumors without any BRAF aberration (40) and BRAFV600E mutant tumors (7) was 84.8%/ 69.6%/ 42.9% (p=0.215). CONCLUSIONS: BRAF-fusion and BRAFV600E mutation were associated with good and poor outcomes respectively. Lack of statistical significance could be attributed to use of radiation as planned therapy in patients from earlier years. Data on BRAF aberrations in PCAs aids decision making regarding adjuvant therapy and choosing appropriate salvage-therapy especially in relapsed/refractory PCAs.

LINC-26. ORAL VINORELBINE IN PROGRESSIVE UNRESECTABLE LOW-GRADE GLIOMA

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BACKGROUND: The management of progressive unresectable low-grade glioma (PULGG) remains controversial. Some series suggests that chemotherapy may delay or even avoid radiotherapy and/or surgery in a group of patients. Within this context, we performed at IOP/GRAACC/UNIFESP an institutional protocol with IV vinorelbine, a semi-synthetic vinca alkaloid that showed activity against PULGG. The objective of this study was to evaluate the response as long as the tolerability of oral vinorelbine in PULGG. PATIENTS AND METHODS: From April 2013 to Aug 2017, 17 patients with recurrent (n=5) and newly-diagnosed (n=12) optic-pathway glioma (OPG) were treated with oral vinorelbine in a dose of 90 mg/m² days 0, 8 and 22 for 18 cycles. Response criteria used a combination of magnetic resonance imaging, physical and visual evaluation. RESULTS: Mean age 8.6 years (4.8–17.9y). Three children with neurofibromatosis type 1. Eleven patients had neurosurgical intervention revealing grade I (n=8) and grade II astrocytoma (n=3). Twelve patients were assessable after 8 cycles of vinorelbine with 2 objective response (OR), 8 stable disease (SD) and 2 progressive disease (PD), one died after surgery and 1 alive in different protocol. After 18 cycles, eight patients were assessable to date for response with 1 OR, 7 SD. The most important toxicity was gastrointestinal observed in 12 patients- six of them switched to IV vinorelbine (3OR, 3SD). None of the patients showed neurotoxicity. CONCLUSION: These results suggest that oral vinorelbine, as the IV formulation, may show some activity in OPG. However, gastrointestinal toxicity should be considered.

LINC-27. PAEDIATRIC SUPRASELLAR TUMOURS: CLINICAL EXPERIENCE FROM A SINGLE TERTIARY CENTRE IN KUALA LUMPUR, MALAYSIA

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INTRODUCTION: The outcome of suprasellar tumours in children varies with the diagnosis and morbidity is significant. We herein report the clinical features of children with suprasellar tumours treated at our centre. METHODS: Clinical data were collected by retrospective review from January 2000 to December 2019. The patients were identified from the paediatric haematology and oncology unit registry. RESULTS: There was a total of 103 children with brain tumour and suprasellar tumours comprise of 14.6% (n=15). Median age at presentation was 7 years old. Male to female ratio was 3:2. Majority of cases was low grade glioma, 40% (n=6) and germ cell tumour(GCT) 33.3% (n=5) followed by craniopharyngioma, 13.3% (n=2) and Rathke cleft cyst, 6.7% (n=1). All patients had tissue diagnosis except one with secreting GCT and one with unsatisfactory tissue sample. Mean duration of follow up was 7.4 years. One patient with germinoma was lost to follow-up after radiotherapy. Three out of 13 (23%) patients died; 2 with GCT from disease progression; 1 craniopharyngioma after 11 years of unknown cause. All survivors have significant morbidity; 70% have moderate to severe visual impairment, 90% have at least two pituitary hormones deficiency, 20% have neurological deficit and 1 was surgically related. Two boys have precocious puberty not related to disease progression. Two with GCT with diabetes insipidus had history of thromboembolism (stroke and pulmonary embolism). CONCLUSIONS: Suprasellar tumours in children at our centre pose a significant long-term complications and multidisciplinary team management and follow up is required to improve the morbidity.

LINC-28. EPIDEMIOLOGICAL CHARACTERISTICS AND SURVIVAL OUTCOMES OF CHILDREN WITH MEDULLOBLASTOMA TREATED AT THE NATIONAL CANCER INSTITUTE (INCA) IN RIO DE JANEIRO, BRAZIL

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BACKGROUND: Medulloblastoma (MB), the most malignant brain tumor of childhood has survival outcomes exceeding 80% for standard risk and 60% for high risk patients in high-income countries (HIC). These results have not been replicated in low-to-middle income countries (LMIC), where 80% of children with cancer live. Brazil is an upper-middle income country according to World Bank, with features of LMIC and HIC. METHODS: We conducted a retrospective review of 126 children (0–18 years) diagnosed with MB from 1997 to 2016 at INCA. Data on patients, disease characteristics and treatment information were retrieved from the charts and summarized descriptively; overall survival (OS) and event-free survival (EFS) were calculated using the Kaplan-Meier Method. RESULTS: The male/female ratio was 1.42 and the median age at diagnosis was 7.9 years. Headache (79%) and nausea/vomiting (75%) were the most common presenting symptoms. The median time from onset of symptoms to surgery was 50 days. The OS for standard-risk patients was 69% and 53% for high-risk patients. Patients initiating radiation therapy within 42 days after surgery (70.6% *versus* 59.6% p=0.016) experienced better OS. Forty-five patients (35%) had metastatic disease at admission. Lower maternal education correlated with lower OS (71.3% *versus* 49% p=0.025). Patients who lived >40km from INCA fared better (OS= 68.2% *versus* 51.1% p=0.032). Almost 20% of families lived below the Brazilian minimum wage. CONCLUSIONS: These findings suggest that socioeconomic factors, education, early diagnosis and continuous data collection, besides oncological treatment must be adressed to improve the survival of children with MB.

LINC-29. IMPACT OF RELA FUSION ON OUTCOMES OF CHILDHOOD SUPRATENTORIAL EPENDYMOMAS (ST-EPEN)

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BACKGROUND: Ependymomas are heterogenous group of tumours with variable clinical course and diverse molecular features. RELA fusion status has been reported to have prognostic impact in ST-EPEN. Our retrospective study analysed the prevalence and clinical impact of RELA fusion in childhood ST-EPEN at our centre. STUDY METHODS: FFPE tissues of all childhood ST-EPEN diagnosed during 2011–2017 were evaluated for RELA fusion 1/2 by RT-PCR. Children were treated as per guidelines by the Neuro-oncology multidisciplinary team. Outcomes were correlated with RELA fusion, histological features and immunohistochemical parameters(L1CAM expression and Mib-1 index). Only patients with therapy details were included. RESULTS: A total of 37 patients(0–50 years) with ST-EPEN were included(median age-10.2 years; boy:girl ratio-1.4:1)for analysis. Histological grade II, II/III and III was seen in 4(11%),2(5%) and 31(84%) patients respectively. Mib-1 index was assessable in 33 patients of which, 9 patients (24%) had a Mib-1 index >20%. RELA fusion was detected in 13(35%)tumors. The 3-year and 5-year EFS/OS of the overall cohort was 64.2%/83.6% and 60.1%/73.1% respectively. The 3-year/5-year EFS of RELA-positive tumors was inferior compared to RELA-negative tumours (53.8%/36% v/s 62.6%/53.6%; p=0.391). The 3-year/5-year EFS of tumors expressing L1CAM versus negative-expression was comparable (61.1%/55%v/s59.8%/47.9%;p=0.44). Presence of Mib-1>20% correlated with inferior survival (5-year EFS:81.1%vs22.2%; p<0.01). CONCLUSIONS: ST-EPEN with RELA fusion had trend towards increased relapse/progression. High Mib-1 correlated with poor survival. RELA fusion status needs to be studied in a larger cohort prospectively to confirm its clinical impact.

LINC-30. A CLINICOPATHOLOGICAL STUDY OF IMMUNOGENICITY AND IMMUNE EVASION MECHANISMS AMONG MOLECULAR SUBGROUPS OF MEDULLOBLASTOMA

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INTRODUCTION: Medulloblastomas have been well characterised in terms of genomics, epigenomics, transcriptomics and recently proteomics. However, there is limited knowledge regarding immunogenicity, immune-microenvironment and immune evasion mechanisms in different molecular subgroups of medulloblastoma. It is important to analyze these parameters to understand tumor progression, prognostic stratification as well as treatment response to available immunotherapeutic drugs. MATERIALS AND METHODS: Molecular subgrouping performed by immunohistochemistry(IHC), Nanostring and 850k-methylation array. Immune profile by IHC for CD3, 20, CD8 [tumor infiltrating lymphocytes (TILs)], CD163 [tumor-associated macrophages (TAMs)], and PD-L1 and CTLA-4 [immune checkpoint proteins]. RESULTS: A total of 35 cases were analyzed with age-range from 1 to 54 years (77% pediatric and 23% adult). 82% cases were located in midline, while rest in cerebellar hemispheres. On molecular subgrouping, MBs were subdivided into 8 WNT, 10 SHH, 8 Group 3 and 9 Group 4. Twenty four cases had follow up, 12 with no evidence of disease while 12 with progressive disease or death. PD-L1 expression ranged from 0% to 20% and included 5SHH, 2WNT and 1Group 3. CTLA4 positive lymphocytes ranged from 0 to 33 in 4 cases: 1WNT, 3 SHH, 1Group4. TILs ranged from 0–220/mm^2 with a median of 3. TAMs ranged from 0–60/mm^2 with a median of 18. Both TILs and TAMs were significantly higher in SHH subgroup. CONCLUSION: PD-L1 positivity and number of TILs and TAMs were significantly more in SHH-subgroup tumors followed by WNT tumors. CTLA-4 expression did not correlate with subgroups. All parameters showed a positive trend with increasing age.

LINC-31. TREATMENT OUTCOME IN CHILDREN WITH MEDULLOBLASTOMA IN MEDIUM-INCOME COUNTRY: AN EXPERIENCE FROM A SINGLE TERTIARY CENTRE IN KUALA LUMPUR, MALAYSIA

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INTRODUCTION: Medulloblastoma is the most common malignant brain tumour in children. The overall outcome has improved however, this was not translated to developing nations. METHOD: This was a retrospective review of patients from January 2000 to December 2017. Treatment was given using modified SIOP PNET 4 protocol: cranio spinal irradiation (CSI), a total of 54G with vincristine followed by 8 cycles of adjuvant chemotherapy. Prior to year 2007, patients had CSI with or without adjuvant chemotherapy. Those <3 years old received modified UKCCSG/SIOP CNS protocol with 2 weekly chemotherapy for a duration of 392 days followed by CSI when required. All patients had MRI brain and spine, and tissue histopathological examination but without molecular subtype. RESULTS: Medulloblastoma comprised of 30% (n=31) out of total 103 brain tumour cases. Mean age at presentation was 7.6 years old (SD 4.4) with male to female ratio of 2:1. Average time of symptoms was 4.8 weeks. Majority, 77.4% was high risk and 19.4% was standard risk. There was high treatment abandonment rate (35.5%, n=11). Three patients returned and completed treatment after multiple surgeries in an average of 9 months. Three years OS and EF were 69.6% and 74.8%, respectively. Six patients aged < 3years; half had advance disease on palliative care post surgery. Other survivors had severe learning difficulty and two had second malignancy (meningioma and thyroid carcinoma) at average 15.5 years after diagnosis. CONCLUSION: Strategy to reduce treatment abandonment is crucial. Moreover, multidisciplinary management and molecular stratification are important in improving the outcome.

LINC-32. REPORT OF AN INITIAL SITE VISIT TO DETERMINE FEASIBILITY AND IMPLEMENTATION OF A COMPREHENSIVE NEURO-ONCOLOGY PROGRAM IN KENYA

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BACKGROUND: Pediatric central nervous system (CNS) tumors are the leading solid tumors in the United States, but vastly under-reported in the African population. There's limited data on childhood brain tumors as well as the histopathological distribution in Kenya. This report surveys as an initial site visit to determine the feasibility of a comprehensive neuro-oncology program at Kenyatta National Hospital (KNH) in Nairobi, Kenya. DESIGN: This collaboration began with a visit from the director of neuropathology at KNH to our neuro-Oncology program at Riley Hospital for Children at Indiana University Health in May 2019. This report includes recommendations from the May 2019 trip, as well as a reciprocal site visit to Kenya in January 2020. RESULTS: Building off the May 2019 trip, a brain tumor registry has been initiated and maintained. Additionally, the KNH program has many necessary components to forming a comprehensive neuro-oncology program, including capable neurosurgeons with a neurosurgical training program, radiology, intensive care unit, oncology ward, rehab, skilled nursing, and radiation oncology services. Currently, neurosurgery, radiology, and pathology meet weekly to review challenging cases. CONCLUSION: Kenyatta National

Hospital has the expertise to build a comprehensive neuro-oncology program. The program currently lacks a dedicated nurse coordinator and "specialist" in neuro-oncology. Ongoing discussions with local stakeholders are aimed to galvanize national support to improve awareness for children with brain tumors and to plan a multidisciplinary neuro-oncology symposium in 2021. In the meantime, telemedicine efforts can support nursing education and reiterate the multidisciplinary needs for children with brain tumors.

LINC-33. MULTIMODALITY MANAGEMENT OF PAEDIATRIC PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA- UPDATED EXPERIENCE FROM A REGIONAL CANCER CENTRE IN NORTH INDIA

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Paediatric primary central nervous system lymphoma(PCNSL) constitutes 1% of all PCNSLs. Data pertaining to paediatric PCNSL (2016–19) was abstracted by retrospective chart review. We identified 7 paediatric patients with PCNSL. None had congenital or acquired immunodeficiency. The median age at presentation was 13 years. The male to female ratio was 4:3. The median ECOG performance status was 2. On neuro-imaging, 3 patients had solitary and 4 patients had multiple lesions. CSF cytology showed atypical cells in 1 patient. None had ocular involvement. Systemic lymphoma work-up was negative in all. Biopsy and resection of tumour were done in 4 patients each. Histopathology revealed DLBCL in 6 and B-cell NHL in 1 patient. All patients underwent induction chemotherapy (median-5 cycles)- modified DeAngelis protocol (IV Methotrexate-2.5g/m^2,IT Methotrexate-12 mg,Vincristine,Procarbazine and Rituximab-375mg/m^2 every 2 weeks) in 6 and single agent Methotrexate -3.5g/m^2 every 3 weeks in 1 patient. Severe haematological toxicities included grade 3 neutropenia, leucopenia and febrile neutropenia in 2,1 and 1 patient respectively. Radiotherapy(RT) was administered in all-whole brain RT(36-45Gy/20-25fractions/4-5weeks) in 6 patients and craniospinal RT(36Gy/18fractions/3.5weeks) followed by whole brain RT(9Gy/5fractions/1week) in 1 patient(with positive CSF cytology). Subsequently consolidation chemotherapy with 2 cycles of Cytarabine(3g/m^2 IV D1-2 every 3 weeks) was administered in 5 patients. After a median follow-up of 14 months(mean-18.2 months), all patients are in complete radiological remission. Paediatric PCNSL is a rare tumour entity and multimodality management with high dose Methotrexate and Rituximab based chemo-immunotherapy and cranial radiotherapy leads to excellent early clinical outcome.

LINC-34. OPTIC NERVE INFILTRATION: RARE MANIFESTATION OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN REMISSION

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BACKGROUND: Optic nerve infiltration in acute lymphoblastic leukemia is a rare manifestation. This infiltration may appear months in advance as an isolated sign of extramedullary relapse and considered as one of the significant clinical findings of central nervous system leukemia. AIM: To describe a case of rapidly progressive optic nerve infiltration in a girl with ALL in remission. CASE: A 13-year-old girl in full remission following treatment for B-cell acute lymphoblastic leukemia presented with decreased vision and proptosis on the left eye. She completed the chemotherapy course two years before. On physical examination, we found the optic disc swelling in her left eyes. There were no signs of relapse from the hematological, cerebrospinal fluid analysis, and bone marrow aspiration. The orbital CT found a mass on the left retrobulbar (size 29x48x32 mm), suspected of optic nerve glioma. The mass has grown rapidly in a month, and she lost her left sight. The involved eye was exenterated (60x55x40 mm). The histopathology and immunohistochemistry showed the B-cell acute lymphoblastic lymphoma. Unfortunately, the patient could not come for further follow up due to the COVID-19 large-scale social distancing. Two months later, she came with pallor and pain in all of her body. The bone marrow aspiration showed leukemic relapse and she is undergoing chemotherapy. CONCLUSION: Optic nerve infiltration by leukemia requires both diagnostic certainty and urgent management. A routine ophthalmic assessment is recommended in patients with a history of acute lymphoblastic leukemia to diagnose optic nerve involvement due to leukemic infiltration.

LINC-35. THE ST. JUDE GLOBAL ACADEMY NEURO-ONCOLOGY TRAINING SEMINAR: A MULTIDISCIPLINARY, INTERNATIONAL EDUCATION PROGRAM

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The success of the treatment of children with central nervous system (CNS) tumors relies on an effective multidisciplinary team, with up-to-date and broad knowledge and skills. The St. Jude Global Academy Neuro-Oncology Training Seminar was launched as course in globally applicable content in pediatric neuro-oncology with a focus on multidisciplinary teams in low- and middle-income countries (LMICs). To identify the content that is most relevant for the learners, a needs assessment survey that included evaluation of team dynamics, treatment capacity, existing knowledge, and educational goals was designed. Survey questions in 11 domains were answered by 24 sites in LMICs across the world. This information was used to create the course that consists of two components: a 9-week online course and a 10-day workshop at the St. Jude campus. 72 participants from 11 institutions enrolled in the online portion and 20 participants were selected based on grades to attend the workshop. A retrospective post-test evaluation established that learners improved their understanding of the barriers to care, possible solutions to improve care, understanding of diagnosis and treatment, and methodology to implement projects ($p<0.01$). All participating teams developed projects that are locally implemented. Those present at the workshop formed a multidisciplinary, international collaborative group (Global Alliance in Pediatric Neuro-Oncology). This experience establishes that educational programs with systematically created curricula can not only improved knowledge but be a mechanism to share experiences and create collaborative networks. Ultimately, patient outcomes will be tracked to monitor the true impact of the course.

LINC-36. TRILATERAL RETINOBLASTOMA: A REPORT OF FOUR CASES

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Retinoblastoma is the most common primary malignant intraocular cancer that usually develops in early childhood. About 5% of those patients are at risk of developing trilateral retinoblastoma (TRB). In developing countries, most of them came in the late stage; therefore, ocular and patient survival rates are lower than in developed countries. From 2015–2019, we found four cases of trilateral retinoblastoma. Two of them had bilateral retinoblastoma, and two had unilateral retinoblastoma. They all presented with leukocoria and had no family history of retinoblastoma. The mean age was 13.8 months (range 9–24 months of age). The diagnosis of trilateral retinoblastoma was made from initial head CT/MRI. They were treated conservatively with high dose VEC chemotherapy, and three of them have died during treatment. Trilateral retinoblastoma is usually fatal and needs multidisciplinary treatment care. In developing countries, it is important to evaluate distant metastasis. Head CT or MRI from the initial diagnosis to exclude the trilateral retinoblastoma.

LINC-38. 500 CONSECUTIVE SURGICAL CASES FROM THE PEDIATRIC ONCOLOGY NEUROSURGERY GROUP: UNDERSTANDING THE PERSPECTIVE OF A TERTIARY CENTER IN BRAZIL

Felipe Hada Sanders, Hamilton Matushita, and Manoel Jacobsen Teixeira; USP, Sao Paulo, SP, Brazil

With this presentation we aim to present cases submitted to surgery by the same group of surgeons since 2010, presenting the physical structure, medical assistance, scientific production and the challenges that we need to overcome in the second decade of the twenty-first century, in a developing country.

LINC-39. PERFORMANCE STATUS OF PEDIATRIC PATIENTS WITH CENTRAL NERVOUS SYSTEM TUMORS TREATED IN MEXICO, A SINGLE-CENTER EXPERIENCE

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BACKGROUND: Central nervous system (CNS) tumors are the most common solid neoplasms in the pediatric age, they comprise about a quarter of all cancers at this age. Little is known about the specific epidemiology of this group in Mexico and there are no reports of results focused on the Performance Status of patients who are treated in a multidisciplinary setting. OBJECTIVE: To describe the Performance Status of CNS pediatric patients after being treated with a multidisciplinary approach in a tertiary center. METHODS: We report a retrospective chart review of all pediatric patients who presented to the Neuro-Oncology Clinic at Teleton Pediatric Oncology Hospital in Queretaro, Mexico, from December 2014 to January 2020. We analyzed age, gender, the extent of surgical resection and histopathology. Performance Status was assessed using ECOG and Karnofsky/Lansky scores during every patient's last follow-up visit. RESULTS: A total of 56 patients were treated, epidemiology and histopathology variants are similar to those described in the international literature. With a median follow-up of 33 months, 35 patients are alive (62.5%), 28 of them (74.2%)

have an excellent Performance Status (ECOG score 0 or Lansky/Karnofsky ≥ 90), 5 (14.2%) scored ECOG 1–2 and only 4 (11.4%) scored ECOG 3–4. CONCLUSIONS: A multidisciplinary approach with a focus on Performance Status and the potential for neurological recovery is essential in the management of pediatric patients with CNS tumors. Efforts should be aimed at reducing post-surgical morbidity and early rehabilitation to reintegrate patients into society in the long term.

LINC-40. VERY YOUNG PATIENTS AND CENTRAL NERVOUS SYSTEM TUMORS: A SINGLE-CENTER EXPERIENCE IN AN UPPER-MIDDLE-INCOME COUNTRY

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Tumors of the central nervous system comprise nearly a quarter of all childhood cancers and are the most frequent solid tumor in the pediatric population. Primary central nervous system tumors (PCNST) are a rare and heterogeneous group of tumors responsible for high mortality and morbidity. Around 10% of primary CNS tumors occur during the first year of life with almost half of them during the first six months. About 18% of these tumors appear before the age of two years. Very young children differ from older children and adolescents regarding the incidence and location of different histological entities of CNS tumors. We aimed at providing descriptive epidemiological data and report the outcome in a tertiary center from December 2013 to January 2020 for all histological subtypes of primary central nervous system tumors in very young patients, defined as patients younger than three years. We collect data from 19 patients treated in an oncology exclusive tertiary center in Mexico between 2013 and 2020. This study aims to relate factors such as age, radiotherapy, surgery, chemotherapy with Lansky Performance Scale and determine the impact, not only in the overall survival but also in the quality of life.

LINC-41. TREATMENT OF RECURRENT MEDULLOBLASTOMA IN CHILDREN IN LOW INCOME SETTINGS

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INTRODUCTION: Children with recurrent medulloblastoma after initial therapy have very poor prognosis due to limited second line treatment options and significant treatment-related morbidity. METHODS: A retrospective chart review of 18 children with recurrent or progressive medulloblastoma, treated initially with risk-adapted therapy in Western Ukrainian Specialized Pediatric Medical Centre from 2012 to 2019, was performed. RESULTS: All patients received first line multimodal treatment: surgery, distant beam radiotherapy and chemotherapy. Recurrent disease in 11 patients presented with metastatic dissemination and in 7 patients as local relapse. The median time to recurrence was 10 months. The median follow-up after diagnosis of recurrent disease diagnosed was 2 years and 2 months. Second line therapy included re-surgery (5 cases), radiation therapy (10 cases) and various cytostatic agents as monotherapy or combination - carboplatin, cisplatin, cyclophosphamide, etoposide, methotrexate, temozolomide, lomustine. Patients treated with radiotherapy for salvage had prolonged local control compared to those that received chemotherapy only. On follow-up 8 children are currently alive. CONCLUSION: Recurrent and progressive medulloblastoma had a poor prognosis with a 2-year overall survival (OS) of 28% on different salvage therapy. The variety in the treatment of all patients experiencing recurrence was observed due to low income country settings. The factors that influenced higher survival after recurrence of medulloblastoma were longer time to relapse, and local pattern of relapse/progression.

LINC-42. EPIDEMIOLOGICAL OVERVIEW OF CHILDHOOD CNS TUMORS IN THE NEUROSURGICAL UNIT IN YEREVAN, ARMENIA

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BACKGROUND: Central nervous system (CNS) tumors are the second most common malignant neoplasms among children worldwide. The current paper aims to analyze the situation in pediatric neuro-oncology in Armenia from the neurosurgical perspective. METHODS: We have collected data of pediatric patients with CNS tumors treated in the Neurosurgery department of "Surb Astvasamayr" Medical Center from 01.01.2010 till 01.12.2019. Incidence by gender, age at diagnosis, and histopathology results were calculated. Survival rates were calculated based on the follow-up results performed until 30.12.2019. RESULTS: Hospital-based data showed that during the previous 10 years 47 patients with CNS tumors received neurosurgical treatment in the unit, among them 66% were females. 38.3%, 31.9% and 29.8% of diagnosed patients were aged 0–4, 5–9, and 10–18 respectively. In 41 cases, the disease was not disseminated at diagnosis. The most common observed malignancies were low-grade gliomas (21.3%) and embryonal tumors (19.1%), followed by high-grade gliomas (14.9%) and ependymal tumors (8.5%). Follow-up information only for 33 patients is available. From them, 14 are dead and 19 alive. Survival rates in most common groups were 62.5%, 80%, 50%, and 50% respectively. The median follow-up time was 18 months (range 1–113 months). CONCLUSION: Similar to the data reported in the literature, low-grade gliomas, and embryonal tumors are the most frequent pediatric CNS tumors in Armenia. On the other hand, the pediatric CNS tumor survival rates are lower compared to those reported in developed countries.

LINC-43. FACTORS LEADING TO DIAGNOSTIC DELAY FOR CHILDREN WITH PRIMARY TUMORS OF CENTRAL NERVOUS SYSTEM (CNS) IN QATAR

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INTRODUCTION: Median time to diagnosis for primary CNS tumors for children in Qatar has been reported to be 28 days. However, a wide variation in diagnostic times is seen. This study was undertaken to analyze the factors leading to delay in diagnosis. METHODS: Data were retrospectively analyzed for children who had diagnostic delay (more than 28 days) from September 2006 to February 2020. Presenting symptoms, number and type of healthcare contacts and presenting symptom interval (PSI) were reviewed. Parental delay (PSI-1) was defined as the date of onset of first symptom to the date of first healthcare contact. Healthcare delay (PSI-2) was defined as date of first healthcare contact to the date of diagnostic scan. RESULTS: Twenty-four patients were identified with diagnostic delay. Median age at diagnosis was 48.2 (range 5.4–171.6) months with an equal sex distribution. Fifteen (62.5%) patients were older than 3 years, 13(54%) patients had low grade glioma, 16 (66.7%) had supratentorial tumors and 12 (50%) presented with raised intracranial pressure. Diagnosis was made after a median 3 (range 1–8) healthcare contacts. Nineteen (79%) patients presented to primary care. Median PSI was 132 (31–783) days. Parental delay (PSI-1) was 35 (0–496) days, while healthcare delay (PSI-2) was 41 (0–562) days. Endocrine (241 days) and oculo-visual (184 days) symptoms were associated with the longest PSI. CONCLUSIONS: There was no significant difference between parental and healthcare delay. Endocrine and oculo-visual symptoms were associated with longest PSI. Increased awareness is required for early recognition of signs suggestive of CNS tumors.

MEDULLOBLASTOMA (CLINICAL)

MBCL-01. METHYLATION PROFILING OF PEDIATRIC MEDULLOBLASTOMA IN SAUDI ARABIA IN A CLINICAL SETTING PERMITS SUB-CLASSIFICATION AND REVEALS NEW OUTCOME PREDICTIONS

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Medulloblastoma (MB) is the most common childhood malignant brain tumor. DNA methylation profiling has rapidly advanced our understanding of MB pathogenesis at the molecular level, MBs can be sub-grouped according to methylation patterns from FPPE samples into Wingless (WNT-MB), Sonic Hedgehog (SHH-MB), Group 3 (G3) and Group 4 (G4) WNT-MB and SHH-MB subgroups are characterized by gain-of function mutations that activate oncogenic cell signalling whilst G3/G4 tumors show recurrent chromosomal alterations. each subgroup has distinct clin-

ical outcomes, the ability to subgroup SA-FPPE samples holds significant prognostic and therapeutic value. We performed the first assessment of MB-DNA methylation patterns in Saudi Arabian SA cohort using archival biopsy materials (FPPE n=49). Of the 41 materials available for methylation assessments, 39 could be classified into the major DNA methylation subgroups (SHH, WNT, G3 and G4). Methylation analysis was able to reclassify tumors that could not be sub-grouped through NGS testing, highlighting its improved accuracy for MB molecular classifications. Independent assessments demonstrate clinical relationships of the subgroups, exemplified by the high survival rates observed for WNT tumors. Surprisingly, the G4 subgroup did not conform to previously identified phenotypes, with a high prevalence in females, high metastatic rates and a large number of tumor-associated deaths. DNA methylation profiling enables the robust sub-classification of four disease sub-groups in SA-MB patients. Moreover, the incorporation of DNA methylation biomarkers can significantly improve current disease-risk stratification schemes, particularly concerning the identification of aggressive G4 tumors. These findings have important implications for future clinical disease management in MB cases across the Arab world.

MBCL-02. ROLE OF PREOPERATIVE CHEMOTHERAPY IN METASTATIC MEDULLOBLASTOMA: A COMPARATIVE STUDY IN 92 CHILDREN

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BACKGROUND: Previous pilot studies have shown the feasibility of preoperative chemotherapy in patients with medulloblastoma, but benefits and risks compared with initial surgery have not been assessed. METHODS: Two therapeutic strategies were retrospectively compared in 92 patients with metastatic medulloblastoma treated at Gustave Roussy, France, between 2002 and 2015: surgery at diagnosis (n=54; group A) and surgery delayed after carboplatin and etoposide-based preoperative therapy (n=38; group B). Treatment strategies were similar in both groups. RESULTS: The rate of complete tumor excision was significantly higher in group B than in group A (93.3% versus 57.4%, p=0.0013). Post-operative complications, chemotherapy-associated side effects and local progressions were not increased in group B. Preoperative chemotherapy led to a decrease in the primary tumor size in all patients, 4/38 patients experiencing meanwhile a distant progression. The histological review of 19 matched tumor pairs (before and after chemotherapy) showed that proliferation was reduced and histological diagnosis feasible and accurate even after preoperative chemotherapy. The 5-year progression-free and overall survival rates were comparable between groups. Comparison of the longitudinal neuropsychological data showed that intellectual outcome tended to be better in group B (the mean predicted intellectual quotient value was 6 points higher throughout the follow-up). CONCLUSION: Preoperative chemotherapy is a safe and efficient strategy for metastatic medulloblastoma. It increases the rate of complete tumor excision and may improve the neuropsychological outcome without jeopardizing survival.

MBCL-03. RESULTS OF HIGH-DOSE THIOTEPA, CARBOPLATIN AND ETOPOSIDE WITH AUTOLOGOUS HEMATOPOIETIC STEM-CELL TRANSPLANTATION FOR PATIENTS WITH RECURRENT MEDULLOBLASTOMA

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AIM: Medulloblastoma is a highly lethal disease when it recurs. Very few patients survive with second line conventional treatment after relapse. This study evaluated the use of high-dose thiotepa, carboplatin and etoposide with autologous hematopoietic stem-cell transplantation (HSCT) in patients with recurrent medulloblastoma. METHODS: From 2010 to 2019, 60 patients at the age 4–32 years (median, 12) with recurrent medulloblastoma were received high-dose chemotherapy (HDCT) with auto-HSCT after induction second line chemotherapy. HDCT included thiotepa 150 mg/m^2 #4; carboplatin 500 mg/m^2 #4; etoposide 250 mg/m^2 #4 and +/- etoposide 1 mg intraventricular on days #5 if patient had Ommaya reservoir; followed by HSCT. At the moment of HDCT 24 patients were in complete response (CR), 31 patients were in partial response (PR) and 5 patients had stable disease (SD) after second line conventional chemotherapy. RESULTS: The median follow-up is 65 months (range, 24–227). The median time to engraftment after auto-HSCT was day +11 (range, 8–39). Five-year overall survival (OS) was 58% and disease free survival (DFS) was 46%. DFS was significantly better among patients in CR or PR 50% in compared to children in SD 20% at the moment of HDCT (p=0,002). Transplant related mortality were 12%, there were 7 patients died because of severe complications within 14 days after transplantation. CONCLUSIONS: HDCT with auto-HSCT in pediatric patients with recurrent medulloblastoma may be a feasible option for cases who had CR or PR after induction chemotherapy. It is ineffective as a salvage therapy in refractory patients.

MBCL-04. 5 – AZACYTIDINE IN TREATMENT OF CHILDREN WITH DE NOVO AND RELAPSED METASTATIC MEDULLOBLASTOMA: RESULTS OF INTERCENTER PILOT STUDY

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The aim of this study was to estimate treatment toxicity and event-free survival (EFS) according to therapeutic program, *MYC/MYC-N* gene amplification and MGMT/DNMT (1, 3a, 3b) proteins expression in tumor cells. From 2016 to 2018 twenty four patients were included in trial. Children underwent adjuvant therapy: craniospinal radiation (CSI) or local radiation therapy (RT) to the relapsed site up to 23.4Gy with 5-azacytidine, 2 cycles methotrexate/5-azacytidine/cisplatin/etoposide, 3 cycles 5-azacytidine/temozolomide - for relapsed group (arm A, n = 5); for patients with de novo medulloblastoma: arm B, n = 11 – vincristine/cyclophosphamide/cisplatin/etoposide (OPEC) - based induction, CSI 36Gy + local RT to the tumor bed up to 54Gy with 5-azacytidine, 1 cycle OPEC and 2 cycles thiophosphamide/carboplatin with auto stem cell transplantation (auto-SCT); arm C, n = 8 – cyclophosphamide/cisplatin - based induction, CSI 23.4 Gy followed by 2 cycles 5-azacytidine/thiophosphamide/carboplatin with auto-SCT, local RT with 5-azacytidine. The combination of 5-azacytidine with local RT or temozolomide was safety and tolerability. Arm C was discontinued due to severe gastrointestinal grade 3/4 toxicity, hemorrhagic syndrome after combination of 5-azacytidine with thiophosphamide/carboplatin. EFS was 0% in arm A, 53.0 ± 15.5%, 50.0 ± 17.7% in arms B and C, a median follow-up 8.8 ± 1.1 months (arm A), 18.8 ± 2.5 months (arm B), 25.0 ± 4.4 months (arm C). Addition of 5-azacytidine to RT or chemotherapy did not improve EFS of patients with *MYC/MYC-N* gene amplification positive tumor. There was not determined any prognostic significance of MGMT/DNMT (1, 3a, 3b) proteins expression in this cohort.

MBCL-05. TREATMENT OF CHILDREN WITH MEDULLOBLASTOMA WITHOUT METASTATIC INVOLVEMENT IN THE AGE GROUP OLDER THAN 3 YEARS: RESULTS OF INTERCENTER TRIAL

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The aim of this study was to identify a group of patients aged 3 to 7 years for whom there is the possibility for reducing of craniospinal radiation dose (CSI). From 2008 to 2018 fifty one pediatric patients with primary diagnosed medulloblastoma in the age group 3 - 18 years were included in trial, 38 in standard risk group, 13 in high risk group. Treatment program consisted of surgical removal of the primary tumor site with subsequent radiation therapy (with CSI of 23,4 Gy or 36 Gy, depending on the risk group) and high-dose chemotherapy (with high-dose cyclophosphamide or thiophosphamide). As a result of this study, sufficiently high rates of overall survival and progression/relapse - free survival (PFS) were achieved in standard and high-risk groups patients, which amounted to 76,0 ± 8,8% and 83,3 ± 10,8% with median follow-up 62,9 ± 6,2 months and 52,2 ± 7,8 months, respectively. There was revealed patients group in the age 3 - 7 years with 100% PFS and median follow-up 66,9 ± 8,9 months. Morphological and molecular biological factors of an unfavorable outcome of the

disease (large cell - anaplastic histology, *MYC/MYC-N* gene amplification, Iso17q and *TP53* gene mutation) were absent in this tumor samples. We have also achieved 100% PFS in patients with desmoplastic tumor histology and in patients, who were treated with thiphosphamide - based chemotherapy regimen. Molecular - biological characteristics analysis of tumor cells showed a negative effect on PFS of DNMT - positive status (Score 4 and>, by 3 markers) and presence of *MYC-N* gene amplification (SHH molecular subgroup).

MBCL-06. RISK STRATIFICATION IMPROVEMENT OF THE HIT2000 AND I-HIT-MED COHORTS USING MOLECULAR SUBTYPES I-VIII OF GROUP 3/4 MEDULLOBLASTOMAS

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OBJECTIVE: Molecular subtypes of Group 3/4 medulloblastoma have been identified by unsupervised clustering methods in different studies. We hypothesized that risk stratification using these subtypes I-VIII improves outcome prediction. PATIENTS AND METHODS: n=340 patients with Group 3 or Group 4 medulloblastoma defined by DNA methylation array profiling enrolled into the HIT2000 study and HIT-MED registries were subtyped by the Heidelberg Medulloblastoma Classifier. The discovery cohort consisted of n=162 previously published samples, the validation cohort of n=178 newly analyzed samples. RESULTS AND DISCUSSION: n=300/340 (88%) MBs could be assigned to one of the subtypes with confidence (score >0.8; Heidelberg Medulloblastoma classifier). Subtype II,III and V showed a poor PFS and OS and were classified as HR (discovery:5y-PFS 45%[95%-CI:33–62], 5y-OS 50%[37–67]; validation:5y-PFS 32%[20–50], 5y-OS 40%[27–61]). Subtypes I, IV, VI-VIII fared better (discovery:5y-PFS 67%[58–77], 5y_OS 84%[77–91]; Validation:5y-PFS 70%[58–83], 5y-OS 89%[81–99]). Survival prediction by subtype-based risk assessment was improved compared to Group 3 versus 4 differentiation in both cohorts in univariate and multivariable Cox regression models (PFS:Hazard ratio HR versus LR 2.474, p<0.001; Group 3 versus Group 4 1.842, p=0.003; adjustment for anaplasia, age and metastatic disease). Patients older than 4 with subtype IV tumors (mainly Group 3) treated with radiotherapy achieved a 100% PFS, while subtype V patients (mainly Group 4) had poor survival. CONCLUSION: We showed that molecular subtypes I-VIII improved risk stratification of Group 3/4 medulloblastomas. Group 3 subtype IV MB treated with RT had very high cure rates.

MBCL-07. NON-METASTATIC MEDULLOBLASTOMA OF EARLY CHILDHOOD: RESULTS FROM THE PROSPECTIVE CLINICAL TRIAL HIT-2000 AND AN EXTENDED VALIDATION COHORT

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OBJECTIVE: To avoid craniospinal irradiation (CSI) in children younger than four years with non-metastatic medulloblastoma by chemotherapy, intraventricular methotrexate and risk-adapted local radiotherapy. PATIENTS AND METHODS: Eighty-seven patients received systemic chemotherapy and intraventricular methotrexate. Until 2006, CSI was reserved for non-response or progression. After 2006, local radiotherapy was introduced for non-responders or classic (CMB), anaplastic or large-cell medulloblastoma (LCA). Infantile SHH-activated medulloblastomas (SHH_INF) were subdivided by DNA-methylation profiling. Survival in SHH_INF subtypes were also assessed in a val-

idation cohort (n=71). RESULTS: Patients with desmoplastic medulloblastoma (DMB) or medulloblastoma with extensive nodularity (MBEN) (n=42) had 93% 5-year PFS, 100% 5-year OS and 93% 5-year CSI-free survival. Patients with CMB/LCA (n=45) had 37% 5y-PFS, 62% 5y-OS and 39% 5y-CSI-free survival. Local radiotherapy did not improve survival in CMB/LCA patients. All DMB/MBEN assessed by DNA methylation profiling belonged to the SHH_INF subgroup. Group 3 patients (5y-PFS 36% [n=14]) relapsed more frequently than SHH_INF (5y-PFS 93% [n=28]) or Group 4 patients (5y-PFS 83% [n=6], p<0.001). SHH_INF split into iSHH-I and iSHH-II subtypes in HIT-2000-BIS4 and the validation cohort, without prognostic impact (5y-PFS: iSHH-I 73% vs. iSHH-II 83%, p=0.25, n=99). Mean IQ was 90 (radiotherapy-free survivors) vs. 74 (patients that received CSI) [p=0.012]. CONCLUSION: Systemic chemotherapy and intraventricular methotrexate led to favorable survival in both iSHH-subtypes of SHH-activated DMB/MBEN with acceptable neurotoxicity. Survival in non-WNT/non-SHH CMB/LCA patients was not improved by local radiotherapy. Survival was more favorable in patients with Group 4 than in patients with Group 3 medulloblastoma.

MBCL-08. INTEGRATIVE MOLECULAR ANALYSIS OF PATIENT-MATCHED DIAGNOSTIC AND RELAPSED MEDULLOBLASTOMAS

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INTRODUCTION: The next generation of clinical trials for relapsed medulloblastoma demands a thorough understanding of the clinical behavior of relapsed tumors as well as the molecular relationship to their diagnostic counterparts. METHODS: A multi-institutional molecular cohort of patient-matched (n=126 patients) diagnostic MBs and relapses/subsequent malignancies was profiled by DNA methylation array. Entity, subgroup classification, and genome-wide copy-number aberrations were assigned while parallel next-generation (whole-exome or targeted panel) sequencing on the majority of the cohort facilitated inference of somatic driver mutations. RESULTS: Comprised of WNT (2%), SHH (41%), Group 3 (18%), Group 4 (39%), primary tumors retained subgroup affiliation at relapse with the notable exception of 10% of cases. The majority (8/13) of discrepant classifications were determined to be secondary glioblastomas. Additionally, rare (n=3) subgroup-switching events of Group 4 primary tumors to Group 3 relapses were identified coincident with MYC/MYCN pathway alterations. Amongst truly relapsing MBs, copy-number analyses suggest somatic clonal divergence between primary MBs and their respective relapses with Group 3 (55% of alterations shared) and Group 4 tumors (63% alterations shared) sharing a larger proportion of cytogenetic alterations compared to SHH tumors (42% alterations shared; Chi-square p-value < 0.001). Subgroup- and gene-specific patterns of conservation and divergence amongst putative driver genes were also observed. CONCLUSION: Integrated molecular analysis of relapsed MB discloses potential mechanisms underlying treatment failure and disease recurrence while motivating rational implementation of relapse-specific therapies. The degree of genetic divergence between primary and relapsed MBs varied by subgroup but suggested considerably higher conservation than prior estimates.

MBCL-09. ISOLATED M1 METASTASES IN PEDIATRIC MEDULLOBLASTOMA: IS POSTOPERATIVE RADIOTHERAPY FOLLOWED BY MAINTENANCE CHEMOTHERAPY SUPERIOR TO POSTOPERATIVE SANDWICH-CHEMOTHERAPY AND RADIOTHERAPY?

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BACKGROUND: Impact of isolated spread into the cerebrospinal fluid (CSF) is still not investigated comprehensively for childhood medulloblastoma and the best therapeutic strategy is currently unclear. MATERIAL AND METHODS: Sixty-six patients with isolated M1-MB registered to the HIT-MED-database from 2000–2018 were identified. CSF and MRI were centrally reviewed for all patients. Patients were stratified by age and either treated with upfront craniospinal irradiation (CSI) followed by maintenance chemotherapy (CT) or with postoperative CT and delayed CSI. RESULTS: Forty-nine patients were non-infants ≥4 years and seventeen were infants <4 years. Median age was 7.3y (1.1–18.0). 83.3% were histologically classified as CMB, 12.1% as LCA-MB and 4.6% as DMB. Molecular subgroup was Gr.3 in 25.8%, Gr.4 in 28.8%, SHH in 4.5%, WNT in 1.5% and not evaluated for 39.4%. Lumbar puncture was performed on median postoperative day 19 (range: 14–77). Median follow-up for survivors was 7.6y (range: 1.2–15.9). The whole cohort showed a 3y- and 5y-PFS of 68.0(±6.0) and 60.0(±6.5)%, while OS was 79.1(±5.2) and 72.9(± 5.9)%. 10y-OS was 54.4(±7.5). Patients with upfront CSI had more favourable outcomes (5y-PFS 66.1 vs. 55.8% [p=0.119]; 5y-OS 90.6 vs. 64.5% [p=0.035]). The trend towards improved survival in patients with postoperative CSI was retained when only non-infants were considered (p_{PFS}=0.176, p_{OS}=0.055). M1-persistence occurred exclusively in patients with postoperative CT. CONCLUSION: Isolated M1-MB is rare. Patients without contraindication for CSI appear to benefit from treatment by upfront CSI followed by maintenance CT, while cumulative CT-doses would be reduced compared to sandwich strategies.

MBCL-10. LOCAL RECURRENCE AND SURVIVAL OUTCOMES OF MEDULLOBLASTOMA (MB) IN ADOLESCENT AND YOUNG ADULT PATIENTS (AYA)

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OBJECTIVE: The aim of this study is to evaluate the local recurrence-free survival (LRFS) and overall survival (OS) of MB in AYA patients at our institute. METHOD: Patients 15–39 years old with MB who was sent for post-operative radiation therapy (RT) in 2007 - 2017 at our institute were included. Kaplan-Meier statistics were used to estimate the LRFS and OS. RESULTS: Seven patients were included. The median age at RT was 18.3 years (16.7–28.6 years). Male was more common than female, 5 males vs. 2 females. NTR or GTR was achieved in 71.4% (5 in 7 patients). Only one patient had metastatic disease (M1) and received combined chemotherapy-RT. The rest 6 patients were received RT alone, all were M0. The median craniospinal irradiation (CSI) dose and total RT dose were 36Gy (23.4-46Gy) and 54Gy (54-56Gy), respectively. Five patients had available follow-up MRI brain. Local recurrence (LR) was found in one patient at 4.3 years after finished RT. Her initial treatment was subtotal resection (STR) followed by RT alone; CSI 36 Gy and posterior fossa boost to 55.8Gy. The 2-years and 5-years LRFS were 100% and 66.7%, respectively. Both 2-years and 5-years OS were 100%. The median follow-up time was 7.6 years (0.4–11.5 years). CONCLUSION: Our study shows high 2-years LRFS and OS of post-operative RT alone in AYA MB. Combined chemotherapy-RT should be considered in STR or M1. More number of patients and molecular histopathology subtype reports are still needed to confirm this report.

MBCL-11. TIME TO RADIOTHERAPY IMPACTS SURVIVAL IN PEDIATRIC AND ADOLESCENT NON-METASTATIC MEDULLOBLASTOMA TREATED BY UPFRONT RADIOTHERAPY – A REPORT FROM THE HIT 2000 TRIAL

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PURPOSE: To evaluate prognostic factors and impact of participation in a randomized trial in non-metastatic medulloblastoma. METHODS AND PATIENTS: 382 patients with non-metastatic medulloblastoma aged 4–21 years with primary neurosurgical resections between 2001 and 2011 were enrolled into the HIT 2000 trial and centrally reviewed. Between 2001 and 2006, 176 of these patients participated in the randomized trial HIT-SIOP PNET 4. Three different radiotherapy protocols were applied. Molecular subgroup was available for 157 patients. RESULTS: Median follow-up was 6.35 [0.09–13.86] years. The 5-year progression-free (PFS) and overall survival (OS) rates were 80.3 % ± 2.1 % and 86.5 % ± 1.8 %, respectively. On univariate analysis, there was no difference in PFS and OS according to radiotherapy protocols or in patients who participated in the HIT-SIOP PNET 4 trial or not, while histology, molecular subgroup and postoperative residual tumor influenced PFS significantly. Time interval between surgery and irradiation (≤48 days vs. ≥49 days) failed the significance level (p=0.052). On multivariate analyses, molecular subgroup (WNT activated vs. Group3 HR 5.49; p=0.014) and time interval between surgery and irradiation (HR 2.2; p=0.018) were confirmed as independent risk factors. CONCLUSION: Using a centralized review system, multiprofessional and multiinstitutional collaboration as established for pediatric brain tumor patients in Germany, and risk-stratified therapy, outcome for non-metastatic medulloblastoma treated within HIT-SIOP PNET4 could be maintained outside the randomized trial. Prolonged time to radiotherapy negatively influenced survival.

MBCL-12. MOLECULAR SIGNATURES AND TUMOR INFILTRATING IMMUNOLOGICAL CELLS ASSOCIATED WITH ASIAN MEDULLOBLASTOMA PATIENT SURVIVAL

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BACKGROUND: Medulloblastoma is an aggressive pediatric brain tumor with surgery and post-resection radiotherapy plus chemotherapy as the major type of treatment currently. METHODS: A cohort of 52 medulloblastoma patients were treated in Taipei Medical University Hospital and Taipei Veterans General Hospital. Among them, 28 (53.85%) are male. The average age at presentation is 7.21 ± 4.15. Genome-wide RNA profiling were performed on fresh-frozen surgical samples. Tumor infiltrating immune cell percentages were inferred by the cibersort immune deconvolution algorithm. RESULTS: A total of 13 leading genes, including DLL1, ASIC2, SLC22A17, TRPM3, RPS2P5 and KCNC3, were found to be significantly associated with overall survival (All P < 0.001). A risk score was constructed, which is indicative of overall survival (Hazard Ratio [HR] = 2.720, 95% confidence interval [CI] = 1.798 ~ 4.112, P < 0.001) and recurrence-free survival (HR = 1.645, CI = 1.337 ~ 2.025, P < 0.001). After adjustment of clinical factors, the score remained significantly associated with overall survival (HR = 2.781, CI = 1.762 ~ 4.390, P < 0.001) and recurrence-free survival (HR = 1.604, CI = 1.292 ~ 1.992, P < 0.001). The percentage of Natural Killer and T follicular helper (Tfh) cells were higher in patients with better overall survival (P = 0.046 and 0.001, respectively). Furthermore, the Tfh percentage is also positively associated with mutation burdens in the expressed exonic regions (P < 0.001). CONCLUSION: Higher mutation burdens are correlated with higher levels of tumor infiltrating Tfh cells, which is indicative of better post-surgery prognosis.

MBCL-13. CORRELATION OF HISTOPATHOLOGY, CHROMOSOMAL MICROARRAY, AND NANOSTRING BASED 22-GENE ASSAY FOR MEDULLOBLASTOMA SUBGROUP ASSIGNMENT ON "HEAD START" 4 CLINICAL TRIAL

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"Head Start" 4 (HS 4) is a prospective randomized clinical trial that tailors treatment based on medulloblastoma molecular subgroups and response to induction chemotherapy to compare efficacy of one versus three (tandem) cycles of myeloablative chemotherapy. Advances in RNA and DNA profiling have identified four molecular subgroups of medulloblastoma with prognostic significance: Sonic Hedgehog (SHH) subtype, WNT subtype, Group 3, and Group 4. In HS 4 trial, we utilize a combination of histopathology and immunohistochemistry (pathology/IHC), as well as chromosomal microarray analysis (CMA) utilizing OncoScan™ (Thermo Fisher) to classify medulloblastoma samples into either SHH, WNT, or non-WNT/non-SHH (Group 3/4) subgroups at the time of diagnosis. NanoString based 22-gene assay is performed retrospectively to test concordance. We have pathology/IHC, CMA, and NanoString data on 26 infants and young children with medulloblastoma enrolled on HS 4. Pathology/IHC was able to assign samples to SHH, WNT, and non-WNT/non-SHH subgroups in all but two cases: one case was classified as Group 3, and the second as SHH by both CMA and NanoString. CMA was indeterminate in six cases, of which, pathology/IHC was able to assign all six samples aforementioned three subgroups. NanoString was indeterminate in two cases: one case was classified as SHH by CMA and pathology/IHC, and the second case was indeterminate by CMA but was assigned as non-WNT/non-SHH on pathology/IHC. There is excellent correlation between NanoString and combination of histopathology and CMA for core medulloblastoma subgrouping on HS 4. Methylation studies are ongoing.

MBCL-14. A STUDY OF LOW-DOSE CRANIOSPINAL RADIATION THERAPY IN PATIENTS WITH NEWLY DIAGNOSED AVERAGE-RISK MEDULLOBLASTOMA

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INTRODUCTION: Medulloblastoma is one of the most common malignant brain tumors in children. To date, the treatment of average-risk (non-metastatic, completely resected) medulloblastoma includes craniospinal radiation therapy and adjuvant chemotherapy. Modern treatment modalities and now risk stratification of subgroups have extended the survival of these patients, exposing the long-term morbidities associated with radiation therapy. METHODS: We performed a single-arm, multi-institution study, seeking to reduce the late effects of treatment in patients with average-risk medulloblastoma prior to advances in molecular subgrouping. To do so, we

reduced the dose of craniospinal irradiation by 25% to 18 gray with the goal of maintaining the therapeutic efficacy as described in CCG 9892 with maintenance chemotherapy. RESULTS: 28 patients aged 3–30 years were enrolled across three institutions between April 2001 and December 2010. Median age at enrollment was 9 years with a median follow-up time of 11.7 years. The 3-year relapse-free (RFS) and overall survival (OS) were 78.6% (95% CI 58.4% to 89.8%) and 92.9% (95% CI 74.4% to 98.2%), respectively. The 5-year RFS and OS were 71.4% (95% CI 50.1% to 84.6%) and 85.7% (95% CI 66.3% to 94.4%), respectively. Toxicities were similar to those seen in other studies; there were no grade 5 toxicities. CONCLUSIONS: Given the known neurocognitive adverse effects associated with cranial radiation therapy, studies to evaluate the feasibility of dose reduction are needed. In this study, we demonstrate that select patients with average-risk medulloblastoma may benefit from reduced craniospinal radiation dose of 18 gray without impacting relapse-free or overall survival.

MBCL-15. IMPACT OF MOLECULAR SUBGROUPS ON OUTCOMES FOLLOWING RADIATION TREATMENT RANDOMIZATIONS FOR AVERAGE RISK MEDULLOBLASTOMA: A PLANNED ANALYSIS OF CHILDREN'S ONCOLOGY GROUP (COG) ACNS0331

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The COG conducted a randomized trial for average-risk medulloblastoma (AR-MB). Patients age 3–21 years were randomized to a radiation boost to the whole posterior fossa (PFRT) or an involved field volume (IFRT) after receiving CSI. Patients age 3–7 years were also randomized to standard dose CSI (23.4Gy, SDCSI) or low dose CSI (18Gy, LDCSI). 464 evaluable patients were available to compare PFRT vs. IFRT and 226 for SDCSI vs. LDCSI. 380 cases had sufficient tissue for DNA methylation-based molecular classification: 362 confirmed medulloblastoma; 6 non-medulloblastoma; 12 inconclusive. Molecular subgrouping confirmed the following representation amongst the evaluable cohort: 156 Group 4 (43.1%), 76 Group 3 (21.0%), 66 SHH (18.2%), 64 WNT (17.7%). Five-year event-free survival (EFS) estimates were 82.5±2.7% and 80.5±2.7% for IFRT and PFRT, respectively (p=0.44). Five-year EFS estimates were 71.4±4.4% and 82.9±3.7% for LDCSI and SDCSI, respectively (p=0.028). EFS distributions differed significantly by subgroup (p<0.0001). Group 3 had the worst outcome, while WNT had the best outcome. There was a significant difference in EFS by RT group among SHH patients; SHH patients receiving IFRT arm had better EFS compared to PFRT (p=0.018). There was a significant difference in EFS distributions by CSI group in Group 4 patients; young Group 4 patients treated with SDCSI had better EFS compared to LDCSI (p=0.047). As previously reported, IFRT is noninferior to PFRT in all patients with AR-MB but LDCSI is worse than SDCSI in younger children. Significant differences in outcome by study randomization and molecular subgroup are observed.

MBCL-16. EFFICACY OF CARBOPLATIN GIVEN CONCOMITANTLY WITH RADIATION AND ISOTRETINOIN AS A PRO-APOPTOTIC AGENT IN MAINTENANCE THERAPY IN HIGH-RISK MEDULLOBLASTOMA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

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BACKGROUND: Metastasis, residual disease, and diffuse anaplasia are high-risk features in medulloblastoma. METHODS: This was a randomized phase 3 study. Patients age 3–21 years with high-risk medulloblastoma received (+/-) daily carboplatin with 36Gy craniospinal radiation and weekly Vincristine followed by six cycles of maintenance chemotherapy with Cisplatin, Cyclophosphamide and Vincristine (+/) 12 cycles of isotretinoin during and following maintenance. The primary endpoint was event-free survival, with exact log-rank test to compare arms. Retrospective molecular analysis included DNA methylation and exome sequencing. RESULTS: Of 294 medulloblastoma patients enrolled, 261 were eligible by central review of radiology and pathology, median age 8.6 years (range 3.3–21.2), 70% male, 189 (72%) with metastatic disease, 58 (22%) with diffuse anaplasia, 14 (5%) with >1.5cm2 residual disease. The 5-year EFS and OS for all subjects was 63%+4 and 73%+3, respectively. Isotretinoin randomization was closed due to futility. 5-year EFS was 66 + 5 with carboplatin versus 59 + 5 without (p=0.11), with effect exclusively observed in Group 3 subtype: 73%+8 with carboplatin versus 54%+9 without (p<0.05). Overall survival differed by molecular subgroup (p=0.006): WNT 100%, SHH 54%+11, Group 3 74%+6, Group 4 77%+5 at 5 years. *MYC* amplification or isochromosome 17 were unfavorable in Group 3 (p=0.029). Chromosome 11 loss or chromosome 17 gain were favorable in group 4 (p<0.001). No survival difference was observed with *TP53* mutation in SHH subtype in this high-risk cohort. CONCLUSIONS: Therapy intensification with carboplatin improved survival for high-risk group 3 medulloblastoma. These findings further support an integrated clinical and molecular risk stratification for medulloblastoma.

MBCL-17. METASTATIC MEDULLOBLASTOMA CAN BE CURED WITHOUT EXCISION OF THE PRIMARY TUMOR: A SINGLE CENTER EXPERIENCE

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INTRODUCTION: Metastatic medulloblastoma is a challenging disease The current clinical approach advocates removal of the primary tumor in the posterior fossa despite evidence of metastatic disease and administer oncologic treatment within several weeks: Infants of 3–4 years are treated by tandem high dose chemotherapy with stem cell support (ACNS0334 protocol), while older children are given radiotherapy and tandem high dose chemotherapy with stem cell support (SJMB03 protocol). We postulate that a resection of the primary tumor is not obligatory, and a biopsy may suffice in order to enable prompt oncological treatment without affecting the long-term survival. PATIENTS AND METHODS: Between 2010-2019 7 patients with metastatic medulloblastoma (median age 4.5, age 1–10) were treated with biopsy only, five spinal and two from the primary tumor. Six children had a concurrent VP shunt. Four presented with cord compression, and two with neurological deterioration. Four needed emergency radiotherapy. Two infants received protocol ACNS0334, five patients received protocol SJMB03. RESULTS: Six patients (85%) survived; .3 patients are long term survivors (> 5 years), 2 patients are in remission for 2–3 years, one patient is on active therapy. Only 1 patient died after a late (4 years) metastatic relapse not in the posterior fossa. CONCLUSIONS: Metastatic medulloblastoma can be cured without excision of the primary tumor and without mutilating surgery. Long term prognosis is probably more attributable to disease subtype and prompt oncologic treatment. This approach merits further studies and may have implications on treatment of non-metastatic tumors.

MBCL-18. ANALYSIS OF DNA METHYLATION PROFILES OF PEDIATRIC MEDULLOBLASTOMAS: EXPERIENCE AT THE BAMBINO GESÙ CHILDREN'S HOSPITAL

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BACKGROUND: Medulloblastoma is the most frequent malignant brain tumor in children, still resulting fatal in about one third of affected patients. An accurate diagnosis is essential for correct therapeutic stratification. The DNA methylation profile (DMP) is a combination of changes in DNA methylation and genetic features that reflect the cell of tumor origin. DMP contributed to classify Medulloblastoma into four subgroups: WNT, SHH, Group 3/4 (the latter recently further subdivided into 8 subclasses). Each Methylation is associated with different genetic, demographic and clinical characteristics. We report our experience on Medulloblastoma molecular classification based on DMP. MATERIALS AND METHODS: 54 Medulloblastoma patients (28 males, 26 females) were selected. The DMP analysis was carried out via IlluminaEPICarrays. The results were obtained using the brain tumor classifier (Capper, 2018). RESULTS: In all cases the DMP allowed to classify the neoplasm, with an optimal score, in a defined methylation class. 10 WNTs, 15 SHHs, 10 Group 3, 19 Group 4 were found. Groups 3/4 were further re-

fined based on the new consensus (Sharma 2019) in group I (n = 1); group II (n = 5); group III (n = 2); group IV (n = 4); group V (n = 3); group VI (n = 2); group VII (n = 6); group VIII (n = 7). CONCLUSIONS: This study carried out the first classification of Medulloblastomas diagnosed in Italy through DMP, demonstrating its high reproducibility, precision and accuracy. The molecular classification improves diagnostic accuracy and provides further information that can guide personalized treatment.

MBCL-19. CHEMOTHERAPY STRATEGIES FOR YOUNG CHILDREN NEWLY DIAGNOSED WITH DESMOPLASTIC/ EXTENSIVE NODULAR MEDULLOBLASTOMA UP TO THE ERA OF MOLECULAR PROFILING – A COMPARATIVE OUTCOMES ANALYSIS OF PROSPECTIVE MULTI-CENTER EUROPEAN AND NORTH AMERICAN TRIALS

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BACKGROUND/OBJECTIVE: Survival has been poor in several multi-center/national trials since the 1980s, either delaying, avoiding or minimizing brain irradiation in young children with medulloblastoma. The introduction of German regimens incorporating both intravenous high-dose (HD-MTX) and intraventricular (IVENT-MTX) methotrexate, and North American regimens utilizing marrow-ablative chemotherapy with autologous hematopoietic cell rescue (HDCx+AuHCR), have reported encouraging outcomes. We performed a comparative outcomes analysis of these strategies for young children with desmoplastic/extensive nodular medulloblastoma (D/ENMB). DESIGN/ METHODS: Data from 12 trials reported between 2005 and 2019 for children <six-years-old with D/ENMB were reviewed; event-free (EFS) with standard errors were compared. RESULTS: The German HIT-SKK'92 and HIT-SKK'00 trials incorporating HD-MTX and IVENT-MTX reported 85+/-8% and 95+/-5% 5-10-year EFS respectively; a third trial (ACNS1221) incorporating HIT-SKK therapy but *without* IVENT-MTX reported 49+/-10% EFS. Three trials (Head Start I/II combined and CCG-99703) employing induction chemotherapy *without* HD-MTX, followed by 1/3 HDCx+AuHCR cycles, reported 3-5-year EFS of 67+/-16% and 79+/-11%. Two trials employing HD-MTX-containing induction chemotherapy (Head Start III and ACNS0334), followed by 1/3 HDCx+AuHCR cycles, reported 3-5-year EFS of 89+/-6% and 100%, respectively. Finally, four trials utilizing neither IVENT-MTX nor HDCx+AuHCR (UK-CNS-9204, CCG-9921, COG-P9934 and SJYC07) reported 2-5-year EFS of 35+/-11%, 77+/-9%, 58+/-8% and 53+/-9%. CONCLUSIONS: A trend towards better EFS for young children with D/ENMB is observed in trials including *either* HD-MTX as well as IVENT-MTX *or* including HD-MTX-containing induction chemotherapy and HDCx+AuHCR. Trials excluding HD-MTX, IVENT-MTX and HDCx+AuHCR have poorer outcomes.

MBCL-20. DETECTION OF SOMATIC MUTATIONS BY USING RNA-SEQ DATA IN CHILDHOOD MEDULLOBLASTOMA AND ITS POTENTIAL CLINICAL APPLICATION: A COHORT SERIES OF 52 CASES STUDY IN TAIWAN

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BACKGROUND: In 2016, a project was initiated in Taiwan to adopt molecular diagnosis of childhood medulloblastoma (MB). Part of our aim was to explore the clinical application for drug target identification and finding clues to genetic predisposition. METHODS: In total, 52 frozen tumor tissues of childhood MBs were collected. RNA-Seq and DNA methylation array data were generated. Molecular subgrouping was performed. We selected 51 clinically relevant genes for somatic variant calling using RNA-Seq data. Correlated clinical findings to genetic predisposition were defined. Potential drug targets and genetic predispositions were explored. RESULTS: Four core molecular subgroups (WNT, SHH, Group 3, and Group 4) were identified. Potential drug targets were detected in the pathways of DNA damage response. Five patients with relevant clinical findings to genetic predisposition clustered in SHH MBs. The corresponding somatic driver mutations involved TP53, MSH6, PTEN, PTCH1, and TERT promoter (suspicious). For validation, whole exome sequencing (WES) of blood and tumor tissue was used in 10 patients with SHH MBs in the cohort series. This study included the five patients with potential genetic predispositions. Four patients exhibited relevant germline mutations named as TP53, MSH6, PTEN, and SUFU. CONCLUSION: The findings of this study provide valuable information for personalized care of childhood MB in our cohort series and in Taiwan.

MBCL-21. GERMLINE ELONGATOR MUTATIONS IN SONIC HEDGEHOG MEDULLOBLASTOMA

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BACKGROUND: Our previous analysis of established cancer predisposition genes in medulloblastoma (MB) identified pathogenic germline variants in ~5% of all patients. Here, we extended our analysis to include all protein-coding genes. METHODS: Case-control analysis performed on 795 MB patients against >118,000 cancer-free children and adults was performed to identify an association between rare germline variants and MB. RESULTS: Germline loss-of-function variants of *Elongator Complex Protein 1* (*ELP1*; 9q31.3) were strongly associated with SHH subgroup (MB_{SHH}). *ELP1*-associated-MBs accounted for ~15% (29/202) of pediatric MB_{SHH} cases and were restricted to the SHHα subtype. *ELP1*-associated-MBs demonstrated biallelic inactivation of *ELP1* due to somatic chromosome 9q loss and most tumors exhibited co-occurring somatic *PTCH1* (9q22.32) alterations. Inheritance was verified by parent-offspring sequencing (n=3) and pedigree analysis identified two families with a history of pediatric MB. *ELP1*-associated-MB_{SHH} were characterized by desmoplastic/ nodular histology (76%; 13/17) and demonstrated a favorable clinical outcome when compared to *TP53*-associated-MB_{SHH} (5-yr OS 92% vs 20%; p-value=1.3e-6) despite both belonging to the SHHα subtype. *ELP1* is a subunit of the Elongator complex, that promotes efficient translational elongation through tRNA modifications at the wobble (U_{34}) position. Biochemical, transcriptional, and proteomic analyses revealed *ELP1*-associated-MBs exhibit destabilization of the core Elongator complex, loss of tRNA wobble modifications, codon-dependent translational reprogramming, and induction of the unfolded protein response. CONCLUSIONS: We identified *ELP1* as the most common MB predisposition gene, increasing the total gen-

etic predisposition for pediatric MB_{SHH} to 40%. These results mark MB_{SHH} as an overwhelmingly genetically-predisposed disease and implicate disruption of protein homeostasis in MB_{SHH} development.

MBCL-22. EFFICACY OF DOUBLE-CONDITIONING REGIMEN COMPRISING THIOTEPA AND MELPHALAN FOR RELAPSED MEDULLOBLASTOMA – A SINGLE INSTITUTION EXPERIENCE

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BACKGROUND: The prognosis of relapsed medulloblastoma was dismal. Recently, we published the promising outcome of metastatic medulloblastomas treated with a double-conditioning regimen comprising high-dose thiotepa and melphalan (HD-TM). Here, we report a single-center study of HD-TM for relapsed medulloblastomas. MATERIALS AND METHODS: From April 2006 to January 2019, 17 consecutive medulloblastoma patients with the first relapse were identified, and of which 10 received HD-TM were retrospectively reviewed. RESULTS: The median age at first relapse was 11.9 years (range 1.8–31.7). The median follow-up period was 23.5 months after 1st relapse. Four localized relapses at the posterior fossa and 6 metastatic relapses including 3 with multiple sites were observed. Surgical resection and re-irradiation were administered in 5 and 9 patients, respectively. Two-year PFS and OS after relapse were 21±18.1% and 60±21.9%, respectively, and significantly better than in patients who did not receive HD-TM. Among 7 evaluable patients, tumor shrinkage was observed in 6 after HD-TM administration including 3 patients who were resistant to prior chemotherapy. At the present time, 5 patients are alive with no evidence of disease (NED). The last 5 patients received re-irradiation including 12 Gy craniospinal irradiation (CSI), and 4 are alive with NED. In multivariate analysis for all patients, both HD-TM and re-irradiation were associated with improved OS and PFS, but disseminated relapse had no prognostic value (p=0.56). CONCLUSION: HD-TM contributes to prolonged survival when combined with re-irradiation. HD-TM might become a curative approach for relapsed medulloblastoma, especially when combined with CSI.

MBCL-23. PRELIMINARY ANALYSIS OF TREATMENT-RELATED TOXICITIES DURING INDUCTION CHEMOTHERAPY FOR PATIENTS ON THE HEAD START 4 TRIAL

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The currently active, prospective multi-center Head Start 4 (HS4) trial for CNS embryonal tumors differs from prior HS I-III trials by utilizing absolute phagocyte count (APC) as a measure of myeloid recovery instead of absolute neutrophil count. The aim of this study was to determine if utilization of APC resulted in unanticipated treatment-related toxicities during induction chemotherapy for patients enrolled on HS4. Review of the RedCap database was conducted for treatment-related CTCAE grade 3 and 4 toxicities. Data were summarized descriptively. Nonparametric statistical methods were used for comparisons. At the time of this most recent analysis, a total of 180 induction cycles were completed for the 57 patients enrolled. Of the 57 patients, nine voluntarily discontinued therapy after completing a median of three cycles each. These patients had a higher number of documented infections (59% *versus* 24%, p=0.0004). Veno-occlusive disease (VOD) occurred in five patients, three of whom voluntarily discontinued therapy. Since the protocol amendment utilizing milligram per kilogram dosing for patients less than six years of age, there have been no documented episodes of VOD. The overall toxicities for this cohort were comparable to those reported for induction chemotherapy in HS I-II trials. The toxic death rate is lower for HS4 compared to HS I-II (0.018% *versus* 4.7–6%) (Chi et al 2004). Other than the high rate of infection, possibly associated with shorter duration of the immediately prior cycles, the use of APC as part of a dose-compression strategy in HS4 does not appear associated with more significant toxicities.

MBCL-24. CAN YOUNG CHILDREN WITH RELAPSED MEDULLOBLASTOMA BE SALVAGED AFTER INITIAL IRRADIATION-SPARING APPROACHES?

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INTRODUCTION: Irradiation-sparing approaches are used in young children with medulloblastoma (MB) given the vulnerability of the developing brain to neurocognitive impairment. Limited data are available following relapse for these patients. We aimed to describe the management and outcomes of young children with MB who relapsed after initial treatment without craniospinal irradiation (CSI). METHODS: International retrospective study including patients with MB diagnosed between 1995–2017, ≤ 72 months old, initially treated without CSI, who subsequently relapsed. RESULTS: Data are available for 52 patients (32 male). Median age at initial diagnosis was 27 months (range, 6–72) with 24 being metastatic. Initial therapy included conventional chemotherapy alone or high-dose chemotherapy (HDC) in 21 and 31 subjects, respectively. Three received upfront focal irradiation. Molecular subgrouping, available for 24 tumors, included 9 SHH and 15 non-WNT/non-SHH. Median time to relapse was 13 months (range, 3–63). Relapse was local, disseminated or combined in 20, 15, and 16, respectively. Salvage therapy with curative intent was given in 42/52 patients, including CSI in 28 subjects (median dose 36Gy, 18–41.4) or focal irradiation in 5 others. Three received HDC only. At a median follow-up time of 46 months (range, 4–255), 25 (48%) were alive, including 7/9 SHH and 7/15 non-WNT/non-SHH. The 2- and 5-year OS was 67% and 56% (SE, 7%), respectively. Two of 3 patients with SHH who did not receive salvage radiotherapy are survivors. CONCLUSION: A substantial proportion of young children who relapse following irradiation-sparing strategies can be salvaged. Neurocognitive and ototoxicity outcomes are being evaluated.

MBCL-25. PILOT STUDY OF A SURGERY AND CHEMOTHERAPY-ONLY APPROACH IN THE UPFRONT THERAPY OF CHILDREN WITH WNT-POSITIVE STANDARD RISK MEDULLOBLASTOMA: UPDATED OUTCOMES

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BACKGROUND: Wnt+ medulloblastoma (WPM) is a favorable subtype with EFS > 90% when treating postoperatively with craniospinal irradiation and posterior fossa boost (CSI/XRT) followed by adjuvant chemotherapy. This pilot study explored the safety of omitting radiation in standard-risk WPM. METHODS: Subjects had to meet standard-risk criteria (< 1.5 cm2 residual tumor, no metastatic spread, no anaplasia) and have a WPM. Subjects received chemotherapy following the COGACNS0331 AAB-AAB-AAB (A=cisplatin/CCNU/VCR; B=cyclophosphamide/vincristine) backbone. RESULTS: Six children were enrolled on study treatment prior to early study closure. Subject #1 completed planned protocol therapy but relapsed 3 months following the completion of therapy. Subject #2 completed

planned protocol therapy but relapsed 6 months following the completion of therapy. In both cases, relapse was local and disseminated. Further accrual was halted. Both subjects were salvaged with CSI/XRT followed by adjuvant chemotherapy. Of the remaining 4 subjects, two had recently completed planned protocol therapy at the time of study closure and received CSI/XRT while in remission and remain in remission approximately one year from the completion of treatment. One subject aborted protocol therapy and transitioned to a Head Start regimen and remains in remission 10 months from completion of therapy. The final subject had just completed protocol therapy and had new areas of restricted diffusion concerning for early relapse. Went on to receive CSI/XRT but subsequently relapsed and is now receiving salvage chemotherapy. CONCLUSIONS: Chemotherapy following ACNS0331, omitting CSI/XRT, appears to be insufficient for the treatment of non-metastatic WPM.

MBCL-26. FACTORS ASSOCIATED WITH LONGER SURVIVAL AFTER FIRST RECURRENCE IN MEDULLOBLASTOMA BY MOLECULAR SUBGROUP AFTER RISK-BASED INITIAL THERAPY

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OBJECTIVE: To evaluate differences in time to recurrence among molecular subgroups of medulloblastoma treated on a single protocol and to identify factors associated with survival after first recurrence. METHODS: Time to recurrence following SJMB03 treatment was compared across methylation subgroups among relapsed patients. Therapies received subsequent to relapse were noted. Kaplan-Meier methods and log-rank tests were used for statistical analyses. RESULTS: 74 of 330 medulloblastoma patients developed recurrence after initial therapy. (38 Standard-Risk; 36 High-Risk). The 2- and 5-year survival after first recurrence was 30.4% and 14.6% respectively. DNA methylation-based subgroups from initial diagnosis were SHH (n=14), Group 3 (n=24), Group 4 (n=26), and unclassified (n=8). None of the pts with WNT MB had recurrent disease. Median time to first recurrence was 1.23, 0.91, and 3.09 years in SHH, Group3, and Group 4 respectively. Group 4 patients had longer post-recurrence survival than others (p-value=0.0169). Clinical risk at diagnosis (p-value=0.337), anaplasia (p-value=0.4032), *TP53* (p-value=0.1969), *MYC* (p-value=0.8967), and *MYCN* (p value = 0.9404) abnormalities were not associated with post progression survival. Patients who received any therapeutic modality (chemotherapy, re-radiation and second surgery) had longer survival and those who had all three (n=10) had the best outcome (p-value<0.0001). CONCLUSION: Outcome after recurrence in medulloblastoma is dismal, however, association with subgroups is still present. Group 4 patients had a longer time to recurrence and post progression survival. No other prognostic factor at initial diagnosis was associated with outcome after recurrence. Patients who received all 3 types of conventional therapy had better survival.

MBCL-27. ASSOCIATION OF MEDULLOBLASTOMA WITH CHARCOT-MARIE-TOOTH DISEASE

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Charcot-Marie-Tooth disease (CMT) is one of the most common hereditary neurological disorders and damages peripheral nerves that results in motor and sensory disturbance. Association of medulloblastoma (MBL) with CMT has been rarely reported. A one-year-old male was referred to our hospital because of cerebellar mass. He had partial resection of the tumor, and was pathologically diagnosed as having desmoplastic nodular medulloblastoma. He received chemotherapy according to the HIT protocol, however, developed severe peripheral neurotoxicity in the initial stage of the treatment. Reinvestigation of family history revealed his mother, grandmother, and aunt had muscle weakness. We suspected he had an inherited neurological disease including CMT, and discontinued administration of vincristine. Fluorescence in situ hybridization analysis detected duplication of PMP22 gene located on 17p11.2, confirming the diagnosis of CMT1A. He completed the rest of chemotherapy without vincristine, and remained in complete remission for four years from the end of treatment. In the literature, there are reports of patients with CMT who developed MBL and were complicated with severe peripheral neurotoxicity due to the use of vincristine. The present case, along with previous reports, suggests that medulloblastoma can develop in patients with CMT and reminds the importance of recalling the possibility of CMT when patients develop severe chemotherapy-induced peripheral neurotoxicity upon use of vincristine. Desmoplastic nodular medulloblastoma may be successfully treated by chemotherapy without vincristine.

MBCL-28. LONG-TERM FOLLOW-UP RESULTS OF REDUCED DOSE CRANIOSPINAL RADIOTHERAPY AND TANDEM HIGH-DOSE CHEMOTHERAPY IN PATIENTS WITH HIGH-RISK MEDULLOBLASTOMA

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BACKGROUND: In this study, we report the follow-up results of reduced-dose of craniospinal radiotherapy (CSRT) followed by tandem high-dose chemotherapy (HDCT) in patients with high-risk medulloblastoma (MB). METHODS: Newly diagnosed high-risk MB patients (metastatic disease, postoperative residual tumor > 1.5 cm^2 or large cell/anaplastic histology) over 3 years of age were enrolled in this study. Two cycles of pre-RT chemotherapy, RT including reduced-dose CSRT (23.4 or 30.6 Gy), 4 cycles of post-RT chemotherapy and tandem HDCT were given. NanoString and DNA sequencing were done with archival tissues. RESULTS: Forty patients were enrolled, and molecular subgrouping was possible in 21 patients (2 WNT, 3 SHH, 8 Group 3 and 8 group 4). All patients including two patients who experienced progression during the induction chemotherapy underwent HDCT. Relapse/progression occurred only in four patients (10-year cumulative incidence 10.4 ± 0.3%). However, six patients died from treatment-related mortality (TRM) (4 acute TRMs and 2 late TRMs) resulting in 18.5 ± 0.5% of 10-year cumulative incidence. Taken together, the 10-year event-free survival and overall survival were 71.1 ± 8.0% and 68.9 ± 8.5%, respectively. Late effects were evaluated in 25 patients and high-tone hearing loss, endocrine dysfunction, dyslipidemia, and growth retardation were common. CONCLUSIONS: Strategy using tandem HDCT following reduced-dose CSRT showed promising results in terms of low relapse/progression rate, however, the high TRM rate indicates that modification of HDCT regimen and careful selection of patients who can have benefit from HDCT will be needed in the future study.

MBCL-29. PHASE I/II STUDY OF SEQUENTIAL HIGH-DOSE CHEMOTHERAPY WITH STEM CELL SUPPORT IN CHILDREN YOUNGER THAN 5 YEARS OF AGE WITH HIGH-RISK MEDULLOBLASTOMA

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PURPOSE: To assess the 3-year EFS rate of children younger than 5 years of age with high-risk medulloblastoma (MB) treated according to the prospective multicenter trial HR MB-5. PATIENTS AND METHODS: After surgery, all children received 2 cycles of Etoposide- Carboplatine. If par-

tial (PR) or complete response (CR) was achieved after induction chemotherapy, children received 2 courses of thiotepa (600mg/m²) with stem cell rescue. For patients in CR after high-dose chemotherapy, they received one course of Cyclophosphamide – Busilvex with stem cell rescue (Phase I part). The others patients (not in PR after induction or in CR after thiotepa) were treated with 2 cycles of Temozolomide-Irinotecan followed by age-adapted craniospinal irradiation and maintenance treatment. RESULTS: 28 children (2 to 4 years; median: 3.0 years) were enrolled. Group 3 MB were most common (57%). The response rate to Etoposide-Carboplatine was 60.7%. Among 20 patients treated with Thiotepa, 13 children were in CR and received Cyclophosphamide – Busilvex without radiotherapy. Out of them, 9 patients (45%) are alive in CR without craniospinal irradiation (median follow-up 5 years). Among 15 patients treated with radiotherapy, 8 patients are alive (median follow-up 3.8 years). The study was prematurely stopped for an excess of events. The median follow-up was 4 years (range 1.5 - 6.1). The 3-year EFS and OS were 42.3% [25.9 - 60.6] and 71.3% [52.7 - 84.7], respectively. CONCLUSIONS: This risk-adapted strategy did not improve EFS in young children with high-risk MB. However, the study shows that good responders to chemotherapy can be cured without recourse to irradiation.

MBCL-30. NOVEL SMO MUTATION IN DESMOPLASTIC/NODULAR MEDULLOBLASTOMA: A CASE REPORT

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Smoothened (SMO) is a transmembrane protein which is regulated by SHH (Sonic hedgehog) protein binding to PTCH1. SMO activation controls GLI which then translocates into the nucleus and activates target genes. The SHH subtype of medulloblastoma has been extensively studied to have mutations within the SHH signaling pathway, often in PTCH1, SUFU, and SMO. We present a case of desmoplastic/nodular medulloblastoma with the mutation SMO c.1810G>A. The patient presented at 11 years old with a two-week history of headaches and morning vomiting. His neuroimaging revealed a T2 hyperintense, enhancing mass centered at the fourth ventricle. He underwent gross total resection and had no metastatic spread. There were no alterations in PTCH1, SUFU, Tp53, GLI2, MYC/MYCN, CTNNB1, or the WNT pathway. The SMO c.1810G>A alteration has not been previously identified as a somatic mutation in a CNS tumor. The functional effect of this mutation has not been studied. It is known that desmoplastic/nodular histology in medulloblastoma is associated with the SHH subtype and given the fact that SMO is regulated by SHH signaling, this patient was ultimately diagnosed with SHH subtype medulloblastoma. Findings of novel somatic mutations in patients raises the question of whether the mutation is in fact the driver of neoplasia.

MBCL-31. TREATMENT RESULTS AMONG 106 PATIENTS WITH MEDULLOBLASTOMA OF MOLECULAR SUBGROUP 3

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OBJECTIVE: To evaluate the treatment results among 106 patients of molecular subgroup 3 and to determine the factors affecting the prognosis. PATIENTS AND METHODS: In all the patients, initial removal of the tumor was performed. All the patients got chemoradiotherapy according to the HIT protocol. There were 34girls and 72boys. Most patients were over 3 years:74 compared to 32 younger than 3. The majority of the patients had stage M+: 65; in 38 stage M0 was determined; in 3patients, stage was not specified, Mx.MYC amplification was found in 20 patients; MYCN amplification, in 4 patients. Classic medulloblastoma was predominant: 65, and 41 patients had anaplastic/large cell medulloblastoma. RESULTS: The five-year progression-free survival was 0.51±0.05, the five-year overall survival was 0.52±0.04.The median survival was 82months,and the median progression-free survival was 37 months. There were no significant variations of PFS depending on the sex and age. The treatment results depended on the histological subtype: for classic medulloblastoma, the five-year PFS was 0.57; for the anaplastic/largecell,0.38(p = 0.02030). The presence of metastases significantly affected the survival: PFS for stage M0 was 0.77; for stage M+,0.35(p = 0.00062). Patients with MYC amplification had a significantly worse survival compared to MYCN patients and those without MYC amplification: 0.1, 0.75, and 0.58, respectively (p = 0.00002). Three patients with MYC amplification are alive: two patients had MGMT methylation detected. CONCLUSIONS: The results of treatment among the patients with molecular subgroup 3 depended on the tumor subtype, presence of metastases, MYC amplification and MGMT methylation. In the absence of unfavorable factors, the survival was the same as in molecular subgroup 4.

MBCL-32. HIGH-DOSE CHEMOTHERAPY WITH STEM CELL RESCUE FOR RECURRENT PREVIOUSLY IRRADIATED MEDULLOBLASTOMA

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BACKGROUND/OBJECTIVES: Relapse of medulloblastoma (MB) is highly lethal in previously irradiated patients. As one of therapeutic options for recurrence MB, high-dose chemotherapy with stem cell rescue (HDSCR) is suggested. The aim of our work was to evaluate the effectiveness of this therapy. DESIGN/METHODS: We retrospectively analyzed the data of 8 pts with previously irradiated relapse MB using HDSCR. Initially, M0-stage was verified in 4 cases. Histological diagnoses were desmoplastic (2 pts), classic (2 pts), anaplastic (2 pts) and MB NOS (2 pts). Molecular genetic analyses was performed in 6 cases: Group 3 was verified in 2 cases (1-classic, 1-anaplastic), Group 4 – in 3 cases (1-classic, 1-anaplastic, 1-desmoplastic). Time to first PD was from 15 to 86 months (median=29,4 months). Local relapse was revealed in 1 pt, metastatic – in 5 pts, mixed – in 2 pts. RESULTS: All pts were treated according HIT-REZ 2005 (3–5 cycles without/with intraventricular etoposide), with CR achieved in 3 pts and PR in 5 pts. HDCT regimens consisted of carboplatin, etoposide, thiotepa and temozolomide. 2 pts received re-irradiation – focal RT (1) and CSI (1). 7/8 patients died, 1 pt alive with PD. Time from HDCT to death was 5–15 months (median=9,6 months). CONCLUSIONS: HDSCR for recurrent previously irradiated MB is ineffective. Use of other methods should be considered in these cases.

MBCL-33. RARE PULMONARY TOXICITY IN THREE MEDULLOBLASTOMA PATIENTS UNDERGOING ANTIANGIOGENIC METRONOMIC COMBINATION THERAPY

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BACKGROUND: Metronomic and targeted anti-angiogenesis therapy (MEMMAT) has emerged as a promising treatment for recurrent/progressive medulloblastoma. This treatment includes bevacizumab, oral agents (thalidomide, celecoxib, fenofibrate, etoposide & cyclophosphamide) and intrathecal chemotherapy (etoposide & cytarabine). Common toxicities include myelosuppression, nausea, and infection. Mild respira-

tory toxicities can occur. We report three cases with significant respiratory toxicity. METHODS: An IRB approved chart review was performed of three children with recurrent medulloblastoma on MEMMAT treatment and meaningful pulmonary toxicity. Literature review found no reports of similar findings. RESULTS: Patient ages ranged from 3 to 11 years old. Patients completed a mean of 6.33 months on treatment. There was no history of chronic respiratory disease prior to starting MEMMAT. Patient #1 developed chronic cough requiring multiple respiratory and anti-infective treatments; CT scan demonstrated airspace opacities concerning for chronic inflammatory change. Each new viral infection led to significant respiratory distress. He eventually died from respiratory failure with large cystic lesions noted on CT. Patient #2 developed a chronic cough not responsive to antibiotics or respiratory treatments. Images reported airspace disease, bronchiectasis, and chronic inflammatory state. Patient #3 developed chronic cough without improvement despite antibiotics and inhaled respiratory treatments; images were suggestive of small airway disease. All three patients required numerous hospitalizations and additional treatment. CONCLUSION: With MEMMAT, many side effects are expected though respiratory symptoms have rarely been reported. Our cases highlight the possible important correlation of pulmonary toxicity while being treated on MEMMAT, and its impact on patients' overall health and quality of life.

MBCL-34. EFFICACY OF METHOTREXATE (MTX) ACCORDING TO MOLECULAR SUB-TYPE IN YOUNG CHILDREN WITH MEDULLOBLASTOMA (MB): A REPORT FROM CHILDREN'S ONCOLOGY GROUP PHASE III TRIAL ACNS0334

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ACNS0334, a Phase 3 trial, compared outcomes of children <36 months treated with intensive chemotherapy +/-high-dose methotrexate. Nodular-desmoplastic M0-stage MB were excluded. Treatment included 3 induction cycles (cyclophosphamide/etoposide/vincristine/cisplatin+/-mtx) and 3 consolidation cycles (carboplatin/thiotepa with stem cell rescue). Radiation (RT) was at physician discretion. Molecular sub-typing was by DNA-methylation. Log-rank testing was used to compare survival differences. Molecular subtyping of 38 MB identified 11 Sonic Hedgehog (SHH), 25 Group 3 (GP3), 2 Group 4 (GP4). Five-year survival (OS) was 100% for 5 SHH with MTX and 4 SHH without MTX; 80% for 10 GP3 with MTX, 40% for 15 GP3 without MTX (p=0.025). Only 6/14 survivors received RT: 4 for residual following therapy (1 SHH and 3 GP3) and 2 GP3 salvaged after progression. Two GP3 deaths were associated with toxicity; all others were due to disease. Histology among SHH was nodular-desmoplastic (8) or classic (3); GP3 histology was classic (17) or anaplastic (7). Whole-exome sequencing identified 6 somatic PTCH1 and 1 germline SUFU alteration(s) among 9 SHH. Among GP3, no p53 mutations were found; copy-number analysis identified 5/25 with myc-amplification, 5/25 iso17q, 11/25 with 8 loss, 14/25 with loss of 11. Among GP3, 14/19 had no significant germline mutation. ACNS0334 achieved 100% survival for metastatic SHH. Benefit of methotrexate was observed in GP3 MB supporting incorporation of methotrexate into standard therapy for GP3. Upfront central pathology review and molecular sub-typing are critical for future clinical trial risk stratification of young children with embryonal tumors.

MBCL-35. SALVAGE RADIATION THERAPY FOR PROGRESSIVE AND/OR RELAPSED PEDIATRIC MEDULLOBLASTOMA

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Medulloblastoma (MB) has a dismal prognosis after progression or relapse, and there is no standard of care for salvage therapy. Medical records of pediatric patients with progressive/relapsed MB were reviewed for clinical characteristics. We identified 23 patients with recurrent MB with median age at diagnosis of 3.8 years, 14 males (60%). At diagnosis, 16 patients had gross total resection, 1 near total, 5 subtotal, and 1 had biopsy alone. Fifteen patients (66%) had metastatic disease. Tumor histology was classic/nodular in 10, 4 desmoplastic, 8 anaplastic and 1 myogenic. Ten patients (43%) ages < 3 years, were treated with induction chemotherapy followed by high dose chemo and stem cell rescue. Other 13 patients were treated with chemoradiation (11 craniospinal and 2 posterior fossa radiation). Progression free survival after initial treatment was 11 months (range, 3–58 months); 8 patients (34%) had local recurrence, 10 patients (43%) had distant metastasis, 4 patients (17%) had local and distant, and one patient had CSF only recurrence. Salvage therapy was surgery followed by radiation in 12 patients (52%), radiation alone in 3 patients (13%), chemoradiation in 7 patients (30%), and chemotherapy alone in 1 patient. Thirteen patients (56%) received CSI, 6 (26%) received focal and 2 received spinal radiation only. Five year progression free survival and overall survival from the time of relapse were 25% and 45%, respectively. Multidisciplinary care is essential for patients with relapsed MB. Salvage radiation that accounts for the patient's initial treatment volumes should be considered for these patients.

MBCL-36. HOW TO INCREASE SURVIVAL IN 7 TO 10% OF PATIENTS WITH AVERAGE-RISK MEDULLOBLASTOMA WITHOUT NEW THERAPIES: EARLY PROSPECTIVE NEURORADIOLOGY SCREENING EXPERIENCE FROM THE CHILDREN'S ONCOLOGY GROUP

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BACKGROUND: Previous Children's Oncology Group (COG) average-risk medulloblastoma studies retrospectively identified that 7 to 10% of patients were wrongly staged; either due to the presence of unequivocal residual disease greater than 1.5cm^2 or metastatic disease. Notably, these patients had an inferior survival. The current COG front-line average-risk study for WNT-driven medulloblastoma patients, ACNS1422, is a reduced-intensity therapeutic protocol. Given the potentially devastating consequences of dose reduction in a wrongly staged patient, ACNS1422 is utilizing optimized MRI sequences, including thin slices with no gap and post contrast T2 FLAIR sequences, combined with a rapid central neuroradiology review. RESULTS: The study opened on October 2 2017. As of 31 December 2019, a total of 34 patients have undergone central neuroradiology review. In 27/34 (79%) repeat scans were requested due to technically inadequate sequences (majority due to missing post contrast T2 FLAIR, slice thickness and gap issues). Of 19 repeat scans received, four patients (12%) were wrongly staged as average-risk; three patients were identified with residual disease >1.5cm^2 (in 2 residual disease was confirmed at second resection) and one patient had widespread spinal metastases previously obscured by motion. In addition, metastatic disease was excluded in another patient, reported as having metastatic disease. CONCLUSION: Our data is consistent with previous reports revealing that approximately 10% of patients are wrongly staged as average-risk. The early experience of ACNS1422 reveals that the optimized MRI sequences combined with a rapid central neuroradiology review are very valuable in a cooperative group setting to more accurately stage patients.

MBCL-37. CHEMOTHERAPY STRATEGIES FOR YOUNG CHILDREN NEWLY DIAGNOSED WITH CLASSIC (CLMB) OR ANAPLASTIC/LARGE CELL (A/LCMB) MEDULLOBLASTOMA UP TO THE ERA OF MOLECULAR PROFILING – A COMPARATIVE OUTCOMES ANALYSIS

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BACKGROUND/OBJECTIVE: The introduction of German regimens, supplementing "standard" chemotherapy with both intravenous high-dose (HD-MTX) and intraventricular (IVENT-MTX) methotrexate, and North American regimens incorporating marrow-ablative chemotherapy with autologous hematopoietic cell rescue (HDCx+AuHCR), report encouraging outcomes for young children with medulloblastoma. We performed a comparative outcomes analysis of treatment strategies for young children with ClMB or A/LCMB. DESIGN/METHODS: Data from 12 prospective multi-center trials published between 2005 and 2019 for children <six-years-old with ClMB or A/LCMB were reviewed; survivals were compared. RESULTS: COG-9921, UKCCSG-CNS9204, COG-P9934 and SJYCO7 employing standard chemotherapy with either no or risk-based irradiation, reported 3-5-year event-free survival (EFS) of 17+/-5%, 33+/-28% (ClMB), 14+/-7% and 13.8+/-9% (ClMB) respectively, with reported EFS of 0% for A/LCMB in UKCCSG-CNS9204 and SJYCO7. HIT-SKK'87, HIT-SKK'92 and HIT-SKK'00 incorporating HD-MTX and IVENT-MTX reported 2-10-year EFS of 30–34+/-10–11% for ClMB and 33+/-27% (HIT-SSK'00) for A/LCMB. Head Start HS-I-II combined, CCG-99703 and HS-III employing induction chemotherapy, with or without HD-MTX, followed by single or tandem HDCx+AuHCR reported 3-5-year EFS of 42+/-14%, 50+/-11% and 27+/-6% for ClMB, with EFS for A/LCMB of 38+/-13% (HS-III). Finally, 5-year overall survivals for ACNS0334, without or with induction HD-MTX, are 39% and 69% respectively for ClMB and A/LCMB combined. CONCLUSIONS: A trend towards better outcomes for young children with ClMB and A/LCMB is observed in trials including *either* HD-MTX and IVENT-MTX *or* including HD-MTX-containing induction chemotherapy and HDCx+AuHCR. Trials excluding HD-MTX, IVENT-MTX and HDCx+AuHCR have poorer outcomes.

MBCL-38. UNUSUAL EXTRANEURAL METASTASIS OF PEDIATRIC EMBRYONAL TUMORS: TWO CASE REPORTS

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We report two cases of unusual extraneural metastasis in patients with embryonal tumors without central nervous system disease progression and prolonged survival. The first patient presented at 16 years of age with atypical teratoid rhabdoid tumor of the cervical spine. The tumor was confirmed to have loss of INI1, SMARCB1 deletion of exons 1–3, and heterozygous deletion of 22q11.2. The patient received treatment initially per ACNS0333 with high dose chemotherapy and tandem autologous transplants. The patient developed a biopsy-confirmed liver metastasis six months from diagnosis and, subsequently, had disease progression including liver metastases, bony lesions, muscle involvement, and lung nodules. Two and a half years from diagnosis the patient has still not had a relapse in the CNS. The second patient presented with medulloblastoma isolated to the posterior fossa at 11 years of age and was treated on SJMB03 protocol with craniospinal irradiation and high dose chemotherapy. He had his first recurrence in the temporal lobe three years post treatment. He had multiple recurrences in the brain over the next five years treated with re-resections, adjuvant chemotherapy, and gamma knife radiotherapy. He then developed cervical lymphadenopathy, bony lesions, liver lesions, and lung nodules. Cervical lymph node biopsy confirmed medulloblastoma. Next generation sequencing from recurrent tumor showed somatic mutations in *p53*, *KDM6A*, and *PPP2R1A*. Fourteen years from treatment, he has now developed a temporal lobe lesion. These cases are notable for prolonged survival despite widely metastatic disease and genomics predicting poor prognosis as well as metastatic disease disproportionate to CNS disease.

MBCL-41. LYMPHOHEMATOPOIETIC TOXICITY IDENTIFIED IN PATIENTS WITH MEDULLOBLASTOMA RECEIVING CRANIOSPINAL IRRADIATION

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BACKGROUND: Medulloblastoma (MB) is the most common malignant brain tumor of childhood. MB easily disseminates through the spinal fluid. Surgery followed by radiotherapy, applied to the entire craniospinal axis (CSI), and adjuvant chemotherapy, represent the treatment of choice for patients aged ≥3 years. Since the bone marrow of the skull and vertebral column are the major hematopoietic organs, we investigated the myelosuppressive effect of irradiation treatment in patients with MB retrospectively. METHODS: Medical records of newly diagnosed MB patients treated at our hospital from 2007–2019 were analyzed. Children <3 years old were excluded because they did not receive CSI to avoid potential neurotoxicity. RESULTS: Medical records of 18 patients (11 males and 7 females, aged 6–26, median 11 years) were reviewed. Eight patients were stratified as high-risk disease and 10 patients with standard risk. All patients received CSI (dosage range 23.4–39.6 Gy based on disease risk) and posterior fossa boost. All patients developed lymphocytopenia (<0.5×109/L) during irradiation, and for 11 of 18 patients, lymphocytopenia (<0.2×109/L) was severe. Although 13 patients recovered from the lymphocytopenia before the initiation of chemotherapy, five patients underwent chemotherapy without recovery. Conversely, only six patients developed neutropenia (<1.0×109/L), and five of the six patients were <10 years old. CONCLUSION: Although infectious episode associated with lymphocytopenia was not observed in this study, CSI treatment in children and adolescents may induce immunodeficient condition particularly in the lymphocytic system. Pediatric oncologists should pay attention to the impaired immunity of patients with MB who receive CSI.

MBCL-43. RECURRENT MEDULLOBLASTOMA – LONG-TERM SURVIVAL WITH A "MEMMAT" BASED ANTIANGIOGENIC APPROACH

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INTRODUCTION: Patients with recurrent medulloblastoma have a poor prognosis with only around 8% of patients surviving at 5 years irrespective of salvage therapy used. We report on 29 patients from four institutions treated with a "MEMMAT" based antiangiogenic combination therapy. PATIENTS AND METHODS: From 11/2006 to 06/2016, 29 patients were diagnosed with a recurrent medulloblastoma (19 first, 10 multiple recurrences). Median age at start of antiangiogenic therapy was 10 years (range 1–27). Subgroup of medulloblastoma was available in 18 patients and was group 3 or 4 in all except two (one WNT, one SHH-infant). For their current relapse patients received an antiangiogenic combination therapy consisting of bevacizumab, thalidomide, celecoxib, fenofibrate, and etoposide, alternating with cyclophosphamide and augmented with intraventricular therapy (etoposide and liposomal cytarabine). RESULTS: As of 01/2020, 8/29 patients are alive at a median of 44 months after recurrence. 6/8 surviving patients are currently in CCR between 66 and 134 months after recurrence that prompted MEMMAT therapy. Two patients are again in remission after intercurrent relapses 105 and 102 months after first starting MEMMAT therapy. Five patients died of another cause (accident, leukemia, septicemia). OS (median 44 months) was 44±10% at 5 years and 39±10% at 10 years, PFS was 33±10% at 5 years and 28 ±9% at 10 years. Therapy was well tolerated and toxicities were manageable. CONCLUSION: Our results suggest that antiangiogenic metronomic chemotherapy has clinical activity in recurrent medulloblastoma. Further investigation with an international phase II study is ongoing (MEMMAT; ClinicalTrials.gov Identifier: NCT01356290).

MBCL-46. TREATMENT OF RECURRENT WINGLESS-ACTIVATED MEDULLOBLASTOMA (WNT-MB) INCORPORATING MARROW-ABLATIVE THIOTEPA AND CARBOPLATIN CHEMOTHERAPY (HDCX) AND AUTOLOGOUS HEMATOPOIETIC PROGENITOR CELL RESCUE (AUHPCR): A DUAL REPORT

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BACKGROUND: Wnt-MB infers an excellent prognosis, and metastatic disease is rare. However, specific treatment strategies and patterns of failure for patients with recurrent Wnt-MB are unknown. We report two cases of

recurrent beta-catenin nucleopositive Wnt-MBs treated with an irradiation-sparing strategy, incorporating HDCx/AuHPCR. PATIENT 1: A nine-year-old female experienced local recurrence of a non-metastatic Wnt-MB nine months after gross total resection (GTR) followed by 18Gy craniospinal irradiation (CSI) with primary site boost to 54Gy, accompanied by weekly vincristine, followed by a maintenance regimen of nine cycles of cisplatin/lomustine/vincristine alternating with cyclophosphamide/vincristine every third cycle. GTR of the relapsed tumor was followed by three cycles of HDCx/AuHPCR. She is disease-free for over three years following relapse treatment. PATIENT 2: A 17-year-old male initially underwent GTR, followed by 23.4Gy CSI with 54Gy posterior fossa boost with concomitant weekly vincristine, followed by a maintenance regimen that included nine alternating cycles of vincristine/lomustine/cisplatin and cyclophosphamide/vincristine. Isolated right frontal horn metastatic recurrence developed 19 months post-treatment; three cycles of irinotecan/temozolomide/bevacizumab and gamma-knife radiosurgery produced complete response. A second isolated metastatic recurrence within the left frontal horn occurred 13 months post-treatment, which was treated with two cycles of cyclophosphamide/etoposide followed by two cycles of HDCx/AuHPCR. MRI of the brain showed no residual tumor one month post-treatment. He currently awaits follow-up stereotactic radiosurgery. CONCLUSION: Patients with recurrent Wnt-MB may be treated with curative intent using a multidisciplinary approach that includes HDCx/AuHPCR, and minimization or avoidance of re-irradiation.

MBCL-48. OUTCOMES OF TREATMENT BASED ON THE ST. JUDE MEDULLOBLASTOMA-96 REGIMEN FOR JAPANESE CHILDREN WITH MEDULLOBLASTOMA

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Medulloblastoma is a type of malignant embryonal tumor in childhood that is considered to require multiagent chemotherapy followed by radical resection and craniospinal irradiation (CSI). However, the outcomes of chemotherapy for this tumor in Japan are unclear. Here, we performed a multicenter retrospective study to determine the prognosis of pediatric medulloblastoma patients in Japan treated with the St. Jude medulloblastoma-96 (SJMB96) regimen. Thirty patients with newly diagnosed medulloblastoma received treatment with the SJMB96 regimen at Juntendo University Hospital in Tokyo (n=10), Saitama Medical University International Medical Center in Saitama (n=10), and Tohoku University Hospital in Miyagi (n=10) from 2011 to 2018. All patients underwent tumor resection and CSI, with radiation doses of 23.4Gy for standard-risk patients (n=11) and 39.6Gy for high-risk patients (n=19). Six weeks after radiation therapy, patients received four cycles of high-dose chemotherapy with autologous peripheral blood stem cell transplantation according to the SJMB96 regimen. We found that 5-year overall survival was 80.8% among standard-risk patients and 74.2% among high-risk patients. No treatment-related deaths occurred. Eight patients who experienced recurrence died within 80 months of diagnosis. As these treatment outcomes are comparable to those previously reported outside of Japan, our findings indicate that this regimen is a therapeutic option for medulloblastoma patients in Japan.

MBCL-50. DISMAL OUTCOME OF HIGH RISK MEDULLOBLASTOMA TREATED WITH CHEMOTHERAPY FIRST APPROACH IN MALAYSIA

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INTRODUCTION: Patients with high risk medulloblastoma are treated either with high dose chemotherapy or hyperfractionated radiotherapy. Both approaches are not feasible in resource-limited countries. POG9031 trial has reported favourable outcome for high risk medulloblastoma using standard chemotherapy and radiotherapy only. Hence, we have adopted the protocol using chemotherapy first approach due to logistical reasons. OBJECTIVE: To review the outcome of children diagnosed with high risk medulloblastoma in Hospital Kuala Lumpur. METHODS: Patients diagnosed with high risk medulloblastoma between January 2015 and June 2018 treated using the chemotherapy first approach as per POG9031 protocol were identified. Data was then extracted and analysed. RESULTS: Nine patients were identified, 3 boys and 9 girls. Median age was 9.3 years (range 2.6 – 15.9 years). Median follow up for survivors are 3.6 years. Five patients (55.6%) had macroscopic metastatic disease at diagnosis. All patients had significant residual disease post-op. Only 3 patients are disease free till last follow up, giving a 3 years event free survival of 16%. Of the 6 patients who had relapsed, 4 have died, giving a 3 years overall survival of 46%. Patients with no metastasis at diagnosis (M0) fared better with 3 years event free survival of 38%, but 3 years event free survival for patients with macroscopic metastatic disease (M+) was 0%. CONCLUSION: Outcome of children with high risk medulloblastoma treated with chemotherapy first approach was dismal.

MBCL-51. POST-AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION (AUHCT) PRACTICES FOR YOUNG CHILDREN WITH MALIGNANT BRAIN TUMORS

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BACKGROUND: "Head Start" protocols have used autologous hematopoietic stem cell transplant (AuHSCT) for infants and young children with malignant brain tumors in order to avoid cranial irradiation. The post-AuHSCT practice for children with a brain tumor diagnosis varies greatly. The goal of this research study is to explore practices and attitudes about post-AuHSCT care for children with brain tumors. DESIGN: An anonymous REDCap survey link was provided to all site primary investigators and additional support personnel at "Head Start" institutions. The survey questions defined the role of the medical provider completing the form and explored the various practices relating to transition, management, communication and overall satisfaction. RESULTS: Twenty-one individual replies have been received so far. The majority report that prophylactic medicines were discontinued upon WBC recovery; however, management of discontinuation was split evenly between the neuro-oncology and stem-cell transplant teams. Nearly half of responders follow T-cell recovery following transplant without immunology guidance. Post-AuHCT vaccination practices are highly variable, with no clear consensus. Lastly, most responders reported adequate ease of transition and communication between the neuro-oncology and transplant teams. CONCLUSIONS: This work underscores the need for both multidisciplinary communication for children with brain tumors in the post-AuHCT period and for the development of standardized vaccination and other prophylaxis practices.

MBCL-52. ENDOCRINE PROFILE AFTER MEDULLOBLASTOMA TREATMENT

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BACKGROUND: Treatment of medulloblastoma has evolved substantially with more chemotherapy, risk-adapted dosing of radiotherapy (RT) and new RT techniques. We present the endocrine profile for our patients treated over a 20-year period. METHODS: The charts of patients treated for medulloblastoma between 1/1/00 and 31/12/19 were reviewed. 105 were available. Group 1 received chemotherapy alone, Group 2 received 23.4 Gy whole CNS RT with a posterior fossa (PF) boost to 54 Gy, Group 3 received > 35 Gy whole CNS RT with PF boost to 54–59 Gy, Group 4 received PF RT to 54 Gy. All received chemotherapy according to national guidelines or clinical trials relevant at the time. RESULTS: Group 1 (M:F 11:6, 7 survivors mean age 2 years range 1–7) had no endocrinopathies. At 5 years from diagnosis Group 2 (M:F 15:13) and Group 3 (M:F 35:14) had the following % RESULTS: Survival 77:61; Growth Hormone deficiency 92:100; Thyroid deficiency 75:81; ACTH deficiency 42:33. Girls were more likely to need sex hormone replacement than boys. Group 4 (M:F 7:5 mean age 2) were all treated in the first decade. 3 survivors, one GH deficiency, one thyroxine deficiency, one both. CONCLUSIONS: There is a trend to earlier endocrinopathies in the group 3 vs group 2 patients, but it does not reach statistical significance. Girls are more likely to need sex hormone replacement than boys. This investigation provides a contemporary profile of

endocrinopathy after treatment for medulloblastoma that can be used for future comparisons.

MEDULLOBLASTOMA (RESEARCH)

MBRS-01. DISSECTING REGULATORS OF THE ABERRANT POST-TRANSCRIPTIONAL LANDSCAPE IN MYC-AMPLIFIED GROUP 3 MEDULLOBLASTOMA

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Medulloblastoma (MB) is the most common solid malignant pediatric brain neoplasm, with Group 3 (G3) MB representing the most aggressive subgroup. *MYC* amplification is an independent poor prognostic factor in G3 MB, however, therapeutic targeting of the MYC pathway remains limited and alternative therapies for G3 MB are urgently needed. Here we show that an RNA-binding protein, Musashi-1 (MSI1) is an essential mediator of G3 MB in both *MYC*-overexpressing mouse models and patient-derived xenografts. Unbiased integrative multi-omics analysis of MSI1 function in human G3 MB suggests a paradigm shift beyond traditional gene-based profiling of oncogenes. Here we identify MSI1 as an oncogene in G3 MB driving stem cell self-renewal through stabilization of HIPK1 mRNA, a downstream context-specific therapeutic target for drug discovery.

MBRS-02. BET BROMODOMAIN PROTEIN-KINASE INHIBITOR COMBINATIONS FOR THE TREATMENT OF MEDULLOBLASTOMA

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Recent sequencing studies have implicated many epigenetic regulators in medulloblastoma. The epigenetic reader protein Brd4 has been implicated in various cancers including medulloblastoma. Brd4 controls expression of the medulloblastoma essential genes *MYC* in G3 medulloblastomas, which have poor prognosis as well as *GLI1* and *GLI2* levels in Sonic hedgehog (SHH) driven medulloblastomas, which have intermediate prognosis. Highly selective Brd4 inhibitors have been developed that reduce *MYC*, *GLI1* and *GLI2* levels. These inhibitors have gone into clinical trials for multiple cancer indications including medulloblastoma. However, resistance is common for Brd4 inhibitors warranting combination therapies for improved clinical outcome. We have developed a computational pipeline termed SynergySeq that predicts patient specific combinations of Brd4 inhibitors along with kinase inhibitors. We demonstrate that Brd4-kinase inhibitors robustly reduce proliferation of Shh and MYC driven medulloblastoma cells. Improved efficacy is related to dampening the adaptive kinome reprogramming response that occurs after Brd4 inhibition. Our findings suggest that SynergySeq can be utilized to inform patient selection for clinical trials utilizing Brd4 inhibitors in medulloblastoma and other brain tumors.

MBRS-03. SINGLE NUCLEUS TRANSCRIPTOME PROFILES FROM HUMAN DEVELOPING CEREBELLUM REVEAL POTENTIAL CELLULAR ORIGINS OF MEDULLOBLASTOMA BRAIN TUMORS

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Medulloblastoma (MB) is a highly malignant pediatric brain tumor originating from the cerebellum and brainstem. Identification of molecular subgroups forming this heterogeneous tumor entity was initially achieved from transcriptome characterization and further strengthened using DNA methylation profiling. While subgroup classification improved clinical diagnosis and treatment options, the lack of knowledge of the cell-of-origin for some of the subgroups hinders further treatment improvements. In addition identification of the precise cells of origin for each subgroup could help to understand tumor cell biology. Single cell sequencing is the optimal way to solve this task; recently, there were attempts to uncover putative MB cell-of-origin by using such information obtained from mouse embryonic cerebellum. However, such a comparative strategy can miss important results due to the differences between mouse and human. To solve this issue, we performed global single nucleus sequencing on human cerebellum pre- and postnatal materials across several developmental time points and generated transcriptome profiles from ~200k single cells. We identified known cell types forming the human cerebellum and performed detailed comparison of normal cells to RNA-seq bulk data from MB brain tumors across all subgroups. By selecting an optimal analysis strategy, we verified granule neuron precursors as cells of origin for the SHH MB subgroup. Additionally, we also found other cell types in conjunction with the remaining MB subgroups, suggesting new potential targets for investigation. Notably, this strategy can be further applied to the examination of other brain tumors and has perspectives in medical application.

MBRS-04. MEDULLOBLASTOMA DETECTION BY BLOOD TEST

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INTRODUCTION: Long non coding RNAs (lincRNAs) are functionally defined as transcripts longer than 200 nucleotides in length with no protein coding potential. lincRNA involvement in human cancers etiology is being increasingly proved. Cancer-secreted long non-coding RNAs (lncRNAs) in exosomes are emerging mediators of cancer-host cross talk communication in tumor microenvironments. The ability to monitor and detect tumor markers in real time enables access to tumor biology and may allow highly personalized treatment for each patient. METHODS AND RESULTS: We analyzed RNA sequencing of 64 Medulloblastoma samples and quantified the genome wide long non coding RNAs (lincRNA) expression levels. We identified a lincRNA that is distinctively highly expressed in group 4 (MB4). MB4 expression was further examined in microarray analysis on a larger cohort of medulloblastoma patient samples and a large cohort (n=1405) of patient samples that include normal brain and different brain tumor samples. MB4 proved to be specific and highly expressed in group 4 Medulloblastoma. MB4 was detected in the plasma of medulloblastoma patients with active disease, or subtotal resection. MB4 was not detected in patients that their tumors were resected. MB4 expression is not detected in the serum of medulloblastoma type SHH, penioblastoma, ewing sarcoma and neuroblastoma patients. CONCLUSIONS: We have found that MB4 lncRNA is a highly specific medulloblastoma tumor biomarker and is sensitive and noninvasive biomarker that can be quantified from a blood test. MB4 can be a good diagnostic marker, and in future both may also be a good target for therapy.

MBRS-06. GLI3 INDUCES NEURONAL DIFFERENTIATION IN WNT- AND SHH- ACTIVATED MEDULLOBLASTOMA

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BACKGROUND: We have previously investigated the expression of Gli3, a downstream target of the Sonic Hedgehog pathway, which main function is to suppress Gli1/2 in medulloblastomas. We found that Gli3 is associated with neuronal and glial differentiation in desmoplastic / nodular (D/N) type medulloblastomas (Miyahara *et al*., Neuropathology, 2013). In the present study, we investigated the expression of Gli3 in molecular subgroups. METHOD: Thirty-one medulloblastomas treated at Niigata University between 1982 and 2013 were studied. Molecular classification into 4 subgroups (WNT-activated, SHH-activated, Group 3 and Group 4) using Nanostring and immunohistochemistry was performed. Furthermore, Gli3 and Gli1 expression in molecular subgroups was assessed using public data bases. RESULTS: Nanostring was considered reliable (confidence > 0.9) in 28 cases. Four cases were classified as WNT-, 5 cases as SHH-activated, 4 cases as Group 3 and 16 cases as Group 4. Gli3 was positive in 7 out of 9 (78%) WNT-/SHH- cases, but positive in only 8 out of 19 (42.1%) non-WNT-/SHH- subgroup cases ($p = 0.1145$, Fisher's exact test). R2 database analysis confirmed that Gli3 was significantly elevated in WNT- and SHH-activated medulloblastoma. Gli1 was elevated in SHH-activated cases but suppressed in WNT-activated cases. IHC analysis revealed that Gli3 was elevated inside nodules showing neuronal differentiation in D/N type

medulloblastoma. Results of single cell RNA analyses were consistent with those of IHC, Nanostring and R2. CONCLUSION: These results suggest that Gli3 is elevated inside the nodules of SHH-activated medulloblastoma, whereas in WNT-activated cases, Gli3 diffusely suppresses HH signaling.

MBRS-08. SONIC HEDGEHOG SIGNALING PRIMES CEREBELLAR GRANULE NEURON PROGENITORS, THE CELL OF ORIGIN FOR MEDULLOBLASTOMA, FOR APOPTOSIS BY INDUCING PRO APOPTOTIC BIM

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Medulloblastomas, unlike other malignant brain tumors, are typically sensitive to radiation therapy, but the mechanisms that mediate this sensitivity are unclear. Cerebellar granule neuron progenitors (CGNPs), the cell of origin for SHH-subgroup medulloblastoma, are also highly sensitive to radiation. In early life, CGNPs proliferate in response to Sonic Hedgehog (SHH) signaling, and hyperactivation of SHH signaling in CGNPs can lead to the development of SHH-subgroup medulloblastoma. We propose that SHH activation induces radiation sensitivity along with tumorigenesis. We have previously shown that the proapoptotic protein BAX is required for radiation sensitivity of both SHH-driven medulloblastomas and CGNPs in mice, and that BCL-xL supplies critical regulation of BAX, preventing spontaneous cell death. Here, we show that SHH signaling increases the radiation sensitivity of CGNPs by inducing the proapoptotic protein BIM. We found that BIM expression depends on SHH activity, and that genetic deletion of *Bim* decreases the radiation-sensitivity of CGNPs. Mechanistically, we show that BIM binds to anti-apoptotic proteins BCL-xL and MCL-1, where it may alter the balance of BAX and BCL-xL interactions. Consistent with our mechanistic model, human medulloblastoma patients with high BIM expression show a better prognosis. Based on these observations, we propose that SHH-induced BIM mediates the typical radiation sensitivity of SHH-driven medulloblastoma. Finding ways to enhance BIM activity may open new opportunities for targeted medulloblastoma therapy.

MBRS-10. QUIESCENT SOX9-POSITIVE CELLS BEHIND MYC DRIVEN MEDULLOBLASTOMA RECURRENCE

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Tumor recurrence is the leading cause of death in medulloblastoma, the most frequent malignant pediatric brain tumor. Recurrence occurs when subpopulations of cancer cells evade standard therapy by acquiring features of immune escape, metastatic spread, and treatment resistance. The transcription factor SOX9 correlated with treatment resistance and dissemination in aggressive Group 3 medulloblastoma. By studying paired primary-recurrent medulloblastoma samples and patient-derived xenograft models, we identified rare SOX9-positive slow-cycling, therapy-resistant tumor cells that accumulate in relapses and in metastases. In an inducible transgenic Group 3 tumor model, doxycycline treatment kills all tumor cells by turning MYC off. However, when MYC expression was redirected to the SOX9 promoter, recurrences from rare, dormant SOX9-positive cells developed with 100% penetrance. Expression profiling revealed that recurrences were more inflammatory, metastatic, and showed elevated MGMT methyltransferase levels which depleted recurrent cells when selectively inhibited. Our model explains how recurrences develop from SOX9-induced quiescence in MYC-driven brain cancer.

MBRS-12. A TRANSPOSON MUTAGENESIS SCREEN IDENTIFIES RREB1 AS A DRIVER FOR GROUP 3 MEDULLOBLASTOMA

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Medulloblastoma (MB) is the most common malignant childhood brain tumor. MB can be divided into four major subgroups – WNT, Sonic hedgehog (SHH), Group 3 (G3), and Group 4 (G4) – that exhibit distinct genetic alterations, gene expression profiles, and clinical outcomes. Patients with G3-MB have the worst prognosis, and a deeper understanding of this disease is critical for development of new therapies. Most G3-MBs express high levels of the MYC oncogene, suggesting that MYC plays an important role in tumorigenesis. To identify genes that cooperate with MYC to promote formation of G3-MB, we performed an in vivo mutagenesis screen using mice expressing the Sleeping Beauty (SB) transposon. Cerebellar stem cells from transposon/transposase-expressing mice were infected with viruses encoding Myc, and transplanted into the cerebellum of adult hosts. The resulting tumors were sequenced to identify transposon-targeted genes, and these genes were functionally analyzed to determine whether they could cooperate with Myc to drive G3-MB. These studies identified the transcription factor Ras-responsive element binding protein 1 (Rreb1) as a potent Myc-cooperating gene. Tumors driven by Myc and Rreb1 resemble G3-MB at a histological and molecular level. Moreover, RREB1 is overexpressed in human G3-MB, and knockdown of RREB1 impairs growth of G3-MB cell lines and patient-derived xenografts. Ongoing studies are aimed at identifying the mechanisms by which Rreb1 contributes to tumor growth. Our studies demonstrate an important role for RREB1 in G3-MB, and provide a new model that can be used to identify therapeutic targets and develop more effective therapies for medulloblastoma.

MBRS-13. MIR-1253 POTENTIATES CISPLATIN RESPONSE IN PEDIATRIC MEDULLOBLASTOMA BY REGULATING FERROPTOSIS

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Despite improvements in targeted therapies, few group 3 medulloblastoma patients survive long-term. Haploinsufficiency of 17p13.3 is a hallmark of these high-risk tumors; included within this locus is miR-1253, which has tumor suppressive properties in medulloblastoma. Therapeutic strategies capitalizing on the anti-neoplastic properties of miRNAs can provide promising adjuncts to chemotherapy. In this study, we explored the potentiation of miR-1253 on cisplatin cytotoxicity in group 3 MB. Overexpression of miR-1253 sensitized group 3 MB cell lines to cisplatin, leading to a pronounced downregulation in cell viability and induction of apoptosis. Cisplatin is reported as an inducer of both apoptosis and ferroptosis-mediated cancer cell death. *In silico* analysis revealed an upregulation of several ABC transporters in high-risk MB tumors. When compared to cell lines overexpressing miR-1253, the ABC transporter ABCB7, which regulates both apoptosis and ferroptosis, was revealed as a putative target of miR-1253 with poor survival that may facilitate its chemosensitizing effects by modulating mitochondrial ROS and HIF1α-driven NFκB signaling. We observed high expression of ABCB7 and GPX4, ferroptosis regulators, in MB patients with poor overall survival. MiR-1253 negatively regulated the expression of ABCB7 in Group 3 MB cell lines and induced cytoplasmic ROS and mitochondrial O_2-, suggesting ROS-mediated induction of ferroptosis through regulation of ABCB7 and GPX4. Treatment with ROS and ferroptosis inhibitors rescued miR-1253 transfected cells treated with cisplatin. We conclude that miR-1253 induced ROS and potentiated the ferroptotic effects of cisplatin via targeting miR-1253/ABCB7/GPX4/mtROS axis.

MBRS-14. INTEGRATING CLINICAL AND GENOMIC CHARACTERISTICS IN PEDIATRIC MEDULLOBLASTOMA SUBTYPES IN A SINGLE COHORT IN TAIWAN

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BACKGROUND: Medulloblastoma (MB) was classified to 4 molecular subgroups: WNT, SHH, group 3 (G3), and group 4 (G4) with the demographic and clinical differences. In 2017, The heterogeneity within MB was proposed, and 12 subtypes with distinct molecular and clinical characteristics. PATIENTS AND METHODS: PATIENTS AND METHODS: We retrieved 52 MBs in children to perform RNA-Seq and DNA methylation array. Subtype cluster analysis performed by similarity network fusion (SNF) method. With clinical results and molecular profiles, the characteristics including age, gender, histological variants, tumor location, metastasis status, survival, cytogenetic and genetic aberrations among MB subtypes were identified. RESULTS: In this cohort series, 52 childhood MBs were classified into 11 subtypes by SNF cluster analysis. WNT tumors shown no metastasis and 100% survival rate. All WNT tumors located on midline in 4th ventricle. Monosomy 6 presented in WNT α, but not in β subtype. SHH α and β occurred in children, while SHH γ in infant. Among SHH tumors, α subtype showed the worst outcome. G3 γ showed the highest metastatic rate and worst survival associated with MYC amplification. G4 α has the

highest metastatic rate, however G4 γ showed the worst survival. CONCLUSION: We identified molecular subgroups and subtypes of MBs based on gene expression and DNA methylation profile in children in our cohort series. The results may contribute to the establishment of nation-wide correlated optimal diagnosis and treatment strategies for MBs in infant and children.

MBRS-16. MYC REGULATED LONG NONCODING RNA LNC-HLX-2–7 IS A PUTATIVE MOLECULAR MARKER AND A THERAPEUTIC TARGET FOR GROUP 3 MEDULLOBLASTOMAS IN CHILDREN

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Medulloblastoma (MB), a central nervous system tumor that predominantly affects children, requires aggressive therapy. Recent advances in the noncoding RNA genome could contribute to the sub-classification of medulloblastoma. The focus of this study is to identify novel long noncoding RNAs (lncRNAs) as molecular markers and potential therapeutic targets within each subgroup of MBs, in particular within Group 3. We analyzed publicly available 175 RNA-seq datasets to identify a group of putative lncRNA signatures that may be able to differentiate medulloblastoma subgroups accurately. Among those, lncRNA *lnc-HLX-2–7* was highly upregulated in Group 3 MB cell lines, patient-derived xenografts, FFPE samples compared to other groups. CRISPR/Cas9 deletion of the *lnc-HLX-2–7* followed by the fluorescence-activated sorting and generating monoclonal Group 3 MB cells significantly reduced the cell growth and 3-D colony formation together with the induction of apoptosis. Intracranial injection to mouse cerebellum using *lnc-HLX-2–7* deleted cells resulted in reduced tumor growth compared to parental cells, and tumors were further characterized by single-cell sequencing. We identified that oncogene MYC regulates *lnc-HLX-2–7* and its expression can be controlled by the small molecule JQ1, a BET-bromodomain (BRD4) inhibitor that disrupts interactions with MYC. RNA-FISH analysis using FFPE, PDX, and tissue microarrays revealed that *lnc-HLX-2–7* expression is specific to Group 3 MB compared to other groups. We present supporting evidence that *lnc-HLX-2–7* is a novel molecular marker and a potential therapeutic target for Group 3 MBs in children.

MBRS-17. EXAMINING THE ROLE OF LHX9 IN GROUP 3 MEDULLOBLASTOMA

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Medulloblastoma (MB) is the most common malignant brain tumor of childhood. Despite major advances in our understanding of the biology of MB, novel treatments remain urgently needed. Using a chemical-genomics driven drug repositioning strategy, we identified the cardiac glycoside family of compounds as potential treatments for Group 3 MB. We subsequently demonstrated that single-agent treatment with digoxin prolongs survival in a patient-derived xenograft model (PDOX) of Group 3 MB to a degree comparable to radiation therapy, a mainstay in the treatment of MB. Finally, we examined the mechanism of digoxin-mediated cell killing using RNA-seq. This work identified LHX9, a member of the LIM homeobox family of transcription factors, as the gene most significantly down-regulated following treatment (Huang and Injac et al, *Sci Trans Medicine*, 2018). Homologs of LHX9 play key roles in cerebellar development via spatially and temporally restricted expression and LHX9 has been proposed as a core transcription factor (TF) in the regulatory circuitry of Group 3 tumors. Loss of function of other core TFs has been shown to impact MB growth. The role of LHX9 in MB, however, has not been previously experimentally evaluated. We now report that knockdown of LHX9 in MB-derived cell lines results in marked growth inhibition raising the possibility that loss of LHX9 plays a major role in digoxin-mediated cell killing and that LHX9 represents a key dependency required for the growth of Group 3 MB. Clinical targeting of core TFs would represent a novel approach to targeting this devastating disease.

MBRS-18. TUMOR SUPPRESSOR P53 DEFINES THE THERAPEUTIC RESPONSES IN TREATMENT OF MEDULLOBLASTOMA

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Medulloblastoma (MB) is the most common primary pediatric malignant brain tumor. Current molecular analysis classifies MB into 4 groups, classic (WNT), sonic hedgehog (Shh), group 3, and group 4. Furthermore, atypical p53 signaling is associated with disease progression and confers poor prognosis. This study investigated the correlation of mutational status of p53 and iSO17q with disease progression and metastatic potential. In addition, we used small molecule inhibitors of PI3K (Buparlisib; BKM120) and HDAC (LBH-589) on a p53-mutant MB cell line to find novel therapeutic targets. Efficacy of these drugs were assessed using functional assays (cell proliferation, migration, cell cycle and drug resistance). MB tumors (n=53) were evaluated for GLI-1, GAB-1, NPR, KV1, YAP expression and mutant p53 via immunohistochemistry and correlated to patient outcomes. Results demonstrated that: 1) high expression of GAB-1 and YAP were found in the Shh group, while KV1 expression was present in all subtypes; 2) mutant p53 expression was present in various subsets of MB with no apparent correlation with metastasis or disease progression; 3) patients displaying iSO17q (determined by fluorescence in situ hybridization (FISH) technique) exhibited metastatic disease; 4) LBH-589 and BKM120 caused both time and dose-dependent inhibition of MB cell proliferation and migration; 5) combined treatment of BKM120 and LBH-589 had a synergistic effect; 6) MB cells demonstrated drug-resistance to BKM120. In conclusion, these findings underscore use of Buparlisib and LBH-589 in treatment of MB. Further, the role of mutant p53 in disease progression remains elusive, whereas presence of iSO17q defines metastatic potential.

MBRS-19. SYNERGISM OF HDAC AND PARP INHIBITORS IN MYC-DRIVEN GROUP 3 MEDULLOBLASTOMA CELLS

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Patients with MYC-driven Group 3 medulloblastoma (MB) show particularly poor outcome. It was previously shown that MYC-driven MBs are highly sensitive to class I histone deacetylase inhibition (HDACi). We studied the molecular effects of the class I HDACi entinostat in MYC-driven MB cells to identify potentially synergistic drug combinations, prioritizing drug clinical availability to enable clinical translation. Gene expression profiles of the MYC-amplified group 3 MB cell line HD-MB03 treated with entinostat were analyzed using bioinformatic approaches, identifying 29 altered biomechanisms. Overlay with a translational drug library of n=76 compounds resulted in 44 compounds targeting 9 biomechanisms. Filtering for publications supporting each drug´s role in MYC-driven entities, or functional interaction with HDACs, without publication of this combination in MBs, resulted in 5 compounds (olaparib, idasanutlin, ribociclib, selinexor, vinblastine). Synergism testing identified olaparib as the drug with the strongest synergism. Validation of the combination olaparib and entinostat by p.H2AX and PI staining as well as trypan blue exclusion showed increased double strand breaks (DSBs), increased cell death, loss of viability and cell numbers. Selectivity of MYC-amplified MB cells was shown by comparison to MYC-non amplified cell lines, which showed higher IC50s, and reacted with cell cycle arrest as opposed to cell death to the combination treatment. The role of HDACis in DNA damage repair was confirmed by increased DSBs when entinostat was added to the combination of olaparib with doxorubicin. Our study identified olaparib as a potential combination partner with entinostat for the treatment of MYC-driven Group 3 MB.

MBRS-20. CSF-DERIVED CIRCULATING TUMOR DNA AS A BIOMARKER FOR DISEASE PROGRESSION AND TUMOR EVOLUTION IN MEDULLOBLASTOMA

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BACKGROUND: Cell-free DNA (cfDNA) profiling has been shown to carry utility as a clinically relevant biomarker in a variety of cancers, but studies in pediatric brain tumors, including medulloblastoma, are scarce. We hereby evaluated the actionability of profiling cfDNA from cerebrospinal fluid (CSF) based on a multi-institutional cohort of children with medulloblastoma. METHODS: 103 children aged ≥ 3 years with medulloblastoma harboring chromosomal aneuploidy enrolled on two prospective therapeutic trials were included. cfDNA was extracted from CSF obtained longitudinally, and profiled by low-coverage whole-genome sequencing (lcWGS) for annotating copy-number variants (CNVs). cfDNA-derived CNVs were compared against patient-matched primary tumor-derived CNVs and correlated with outcome. cfDNA profiles at diagnosis and relapse were compared to evaluate tumor evolution. RESULTS: Tumor-derived somatic CNVs were detected in 72% of baseline cfDNA samples, with higher detection rate in samples from patients with metastatic disease than those without (90% versus 50%, chi-square p=0.001). Longitudinal profiling of cfDNA revealed correlation between CNV detectability and clinical course, with detection of tumor-derived CNVs in cfDNA samples predating radiographic progression for ≥ 3 months in 62% of relapsing patients. Presence of cfDNA-derived CNVs in CSF collected during chemotherapy and at the end of therapy was significantly associated with inferior PFS (log-rank p<0.0001 for both time-points). Comparison of CNV profiles from cfDNA at baseline and relapse revealed molecular divergence in a subset of patients. CONCLUSION: These results carry major implications and supports the incorporation of cfDNA profiling in upcoming medulloblastoma protocols for more sensitive and accurate disease monitoring and personalization of treatment.

MBRS-21. CLINICAL AGGRESSIVENESS OF TP53-WILD TYPE SONIC HEDGEHOG MEDULLOBLASTOMA WITH MYCN AMPLIFICATION

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Clinical implication of MYCN amplification in sonic hedgehog (SHH) medulloblastoma may still be controversial due to the frequent co-occurrence with TP53 mutation, which is one of the poorest prognostic factors among the subgroup. We described two cases of TP53-wild type SHH medulloblastoma with MYCN amplification, showing dismal clinical course with rapid disseminated relapse just after the end of treatment. CASE 1: A 7-year-old boy developed a non-metastatic cerebellar tumor. Pathology of the tumor was consistent with classic medulloblastoma. The patient received treatment that involved reduced-dose (18 Gy) craniospinal irradiation (CSI), local irradiation, and chemotherapy. However, sudden respiratory arrest developed due to massive intracranial disseminated relapse 9 months after the initial surgery. CASE 2: A 6-year-old boy presented a large mass in his 4th ventricle without dissemination. He diagnosed with large cell/anaplastic medulloblastoma and underwent radiation therapy (24 Gy of CSI and local irradiation) and chemotherapy, followed by high-dose chemotherapy. However, dissemination through neuroaxis occurred 9 months after the diagnosis. Methylation data of the cases was entered into a recently published classifier and both tumors were classified as "medulloblastoma, subclass SHH A (children and adult)". Copy number analysis demonstrated MYCN amplification in both cases. TP53 mutation analysis from exon 2 to 10 indicated wild type in one case. Additionally, p53 immunochemistry in both cases also indicated wild type. The cases remind us of the clinical aggressiveness of SHH medulloblastoma with MYCN amplification, even if there is no TP53 mutation. The tumor should still be treated with the most intensified treatment.

MBRS-22. SIGNIFICANCE OF *RNF213* IN TUMORGENICITY OF MEDULLOBLASTOMA

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RNF213 gene, initially identified as a disease-causing gene for moyamoya cerebrovascular disease, has recently been recognized as a tumor regulator. The gene is known to be associated with WNT signaling, lipid metabolism, angiogenesis and genomic instability. The purpose of this study was to investigate the association of *RNF213* in tumorgenicity of medulloblastoma. Incidence of medulloblastoma and histopathological findings were compared among *ptch1*+/-, *ptch1*+/- *rnf213*+/-, and *ptch1*+/- rnf213-/- mice. Knockout of *rnf213* in *ptch1*+/- transgenic mouse model increased the incidence of spontaneous generation of medulloblastoma from 19.8% (*ptch1*+/-) to 76.5% (*rnf213*+/- *ptch1*+/-) at 9 months ($p < 0.001$). Heterozygous knockout was equivalent to homozygous knockout. Haploinsufficiency of *rnf213* seems to be associated with tumorgenicity in medulloblastoma. Molecular mechanism of medulloblastoma generation needs to be further investigated.

MBRS-23. SIGNIFICANCE OF MI-R33 IN GENERATION AND PROGRESSION OF MEDULLOBLASTOMA

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Lipid metabolism has been shown to be associated with tumorigenicity in various malignancies. The purpose of this study was to investigate the association of miR-33, a key regulator of lipid metabolism, in tumorigenicity and progression of medulloblastoma. miR-33a is an only isotype of miR-33 in rodents although miR-33b is also detected in human. Incidence of medulloblastoma and histopathological findings were compared between ptch1+/- mice and ptch1+/- miR-33a-/- mice. Effect of miR-33b upregulation by cordycepin was tested in DAOY medulloblastoma cells both in vitro and in vivo. Knockout of miR-33a in ptch1+/- transgenic mouse model increased the incidence of spontaneous generation of medulloblastoma from 19.8% to 49.5% ($p < 0.001$) at 10 months. Cordycepin, which upregulates miR-33b, prevented tumor growth in DAOY human medulloblastoma cell line, but the effect was not evident in an orthotopic mouse medulloblastoma model. Although miR-33 seems to be an important regulator of medulloblastoma, treatment efficacy of cordycepin was not enough. Combination treatment with immunotherapy or cytotoxic treatment needs to be tested to show survival benefit in preclinical models.

MBRS-24. FUNCTIONAL CHARACTERIZATION OF IKBKAP/ELP1 AS A NOVEL SHH MEDULLOBLASTOMA PREDISPOSITION GENE

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Medulloblastoma (MB), a common malignant pediatric brain tumor, comprises at least four distinct molecular entities: WNT, SHH, Group 3, and Group 4. SHH-MB is driven by aberrant activation of the Sonic hedgehog (SHH) pathway in granule neuron progenitors (GNPs) and is associated with hereditary cancer predisposition syndromes including Li Fraumeni and Gorlin. We recently identified germline loss of function (LoF) mutations affecting *IKBKAP/ELP1*, the primary scaffolding subunit of the Elongator complex in a subset of SHH-MB patients. Germline *ELP1* mutations account for ~15% of all pediatric SHH-MBs and position *ELP1* as the most prevalent hereditary predisposition gene in MB. We genetically engineered *Elp1* LoF in mouse GNPs to determine Elp1 function in cerebellar development and SHH-MB. Results of both mechanistic and phenotypic experiments demonstrate that GNPs harboring *Elp1* loss exhibit ribosome pausing and protein aggregation, reinforcing the critical role of Elp1 in translational elongation and protein homeostasis. Further, we generated new transgenic mouse models mimicking germline *ELP1* LoF mutations observed in SHH-MB patients. *Elp1*+/- transgenic mice exhibit purkinje cell

degeneration and an increased DNA damage response. These mice are currently being evaluated for their capacity to recapitulate *ELP1*-associated SHH-MB. Additional analyses carried out on SHH-MB patient-derived xenografts showed that *ELP1*-mutant tumor cells specifically exhibit defects in tRNA biogenesis. Therefore, the function of ELP1 as a translational regulator is severely impaired in *ELP1*-mutant SHH-MBs. Our ongoing molecular and functional studies will provide important insights into the most common MB predisposition gene and will lay the foundation for future preclinical studies.

MBRS-26. CDK7 MEDIATED TRANSCRIPTIONAL PROCESSIVITY OF DNA REPAIR NETWORKS REGULATES SENSITIVITY TO RADIATION IN MYC DRIVEN MEDULLOBLASTOMA

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Myc-driven Medulloblastoma remains a major therapeutic challenge due to frequent metastasis and a poor 5-year survival rate. Myc overexpression results in transcriptional dysregulation, proliferation, and survival of malignant cells. To identify therapeutic targets in Myc-amplified medulloblastoma we performed a CRISPR-Cas9 essentiality screen targeting 1140 genes annotated as the druggable genome. The cyclin-dependent kinase, CDK7, was identified as a top candidate. CDK7 phosphorylates the c-terminal domain of RNA Pol II facilitating transcriptional initiation and elongation. We subjected Myc-amplified cells treated with CDK7 inhibitors to whole transcriptomic analysis. The resultant data revealed gene networks mediating DNA repair were functionally repressed. Consistent with this data, ChIP-sequencing showed the most significant reduction in RNA Pol II and Myc promoter occupancy within a subset of DNA repair genes including BRCA2 and RAD51 but not across the whole genome. These data suggest that inhibition of CDK7 mechanistically limits Myc driven transcriptional processivity of DNA repair networks. Further, evaluation of genes mediating DNA repair show a muted response to DNA damage and increased cell death with CDK7 inhibition. We next evaluated Myc-amplified MB cell response to ionizing radiation *in vitro* and *in vivo* with CDK7 inhibition. Inhibition of CDK7 enhanced radiation sensitivity of Myc MB cells by potentiating DNA damage. Further, cotreatment produced decreased MRI T2 tumor volumes and enhanced survival benefit in orthotopic PDX xenografted mice compared to radiation alone. Our studies establish a mechanism for selective inhibition of Myc-driven MB by CDK7 inhibition combined with radiation as a viable therapeutic strategy for Myc-amplified medulloblastoma.

MBRS-27. EXOSOMES CARRY DISTINCT MIRNAS THAT DRIVE MEDULLOBLASTOMA PROGRESSION

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INTRODUCTION: Extracellular vesicles (EVs) represent an ideal source of functional biomarkers due to their role in intercellular communication and their ability to protect cargo, including RNA, from degradation. The most investigated EV's are exosomes, nanovesicles secreted by all cell types and able to cross the blood-brain-barrier. Here we characterised the RNA of exosomes isolated from medulloblastoma cell lines, with the aim of investigating exosomal RNA cargo as potential functional biomarkers for medulloblastoma. METHODS: Exosomes derived from a panel of matched (original tumour and metastasis) medulloblastoma cell lines were isolated and characterised by NanoSight, electron microscopy, western blotting and Nanoscale flow cytometry. Exosomal miRNA and mRNA from our matched cell lines and foetal neuronal stem cells, which were used as a normal control, were analysed by RNA-sequencing technology. RESULTS: Based on hierarchical clustering, malignant derived exosomes were distinctly separated from normal control exosomes. miRNA profiling revealed several established oncomiRs identified in our malignant derived exosomes compared to control samples. Using interaction pathway analysis, we identified that our malignant exosomes carry numerous miRNAs implicated in migration, proliferation, cellular adhesion and tumour growth. Several previously identified oncomiRs were also identified to be present at higher levels in metastatic exosomes compared to primary and normal, including hsa-miR-455-3p and hsa-miR-92a-3p. CONCLUSION: This study shows that exosomes from MB cells carry a distinct miRNA cargo which could enhance medulloblastoma progression. The use of circulating exosomes as markers of metastatic disease could be an innovative and powerful non-invasive tool.

MBRS-28. EXOSOMES DRIVE MEDULLOBLASTOMA METASTASIS IN A MMP2 AND EMMPRIN DEPENDENT MANNER

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INTRODUCTION: Recurrent/metastatic medulloblastoma (MB) is a devastating disease with an abysmal prognosis of less than 10% 5-year survival. The secretion of extracellular vesicles (EVs) has emerged as a pivotal mediator for communication in the tumour microenvironment during metastasis. The most investigated EV's are exosomes, nanovesicles secreted by all cell types and able to cross the blood-brain-barrier. Matrix metalloproteinases (MMPs) are enzymes secreted by tumour cells that can potentiate their dissemination by modification of the extracellular matrix. We hypothesise that exosomal MMP2 and its inducer EMMPRIN could enhance metastasis of MB. METHODS: Proliferation, invasion and migration assays were used to evaluate the phenotypic behaviour of primary cell lines pre-treated with metastatic tumour cell-derived exosomes. Gelatin zymography and western blotting were performed to confirm MMP2 functional activity in cell lines and exosomes. Nanoscale flow cytometry was used to measure surface exosomal EMMPRIN levels. Exosomal MMP2 and EMMPRIN were modulated at the RNA level. RESULTS: Number of exosomes is directly related to the migratory behaviour of parental MB cell lines ($p<0.01$). Notably, functional exosomal MMP2 and EMMPRIN levels also correlate with this. Furthermore, exosomes from metastatic cell lines conferred enhanced migration and invasion on their matched isogenic primary (non-metastatic) cell line pair by ~3.8-fold ($p<0.01$). Exosomes from metastatic cell lines also conferred increased migration on poorly migratory foetal neuronal stem cells. CONCLUSION: Together this data suggests that exosomal MMP2 and EMMPRIN may promote medulloblastoma metastasis and supports analysis of exosomal MMP2 and EMMPRIN levels in patient cerebral spinal fluid samples.

MBRS-29. PROSPECTIVE MOLECULAR PROFILING IN PEDIATRIC MEDULLOBLASTOMA PATIENTS ENROLLED ON THE "HEAD START 4" PROTOCOL

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Medulloblastoma is the most common malignant embryonal brain tumor in children with only modest improvements in outcomes achieved over the last 20 years. The implementation of irradiation-avoiding strategies, including trials by the "Head Start" consortium, have demonstrated improved cure rates along with enhanced quality of life. Simultaneously, the classification of medulloblastomas has undergone a dramatic shift as molecular testing has made it possible to divide these tumors into distinctive subtypes. Currently, the WHO recognizes four medulloblastoma molecular subgroups; however it remains unclear how patients within these subgroups respond to modern irradiation-avoiding therapies. This study aims to demonstrate the feasibility of prospective molecular profiling in medulloblastoma patients enrolled on the "Head Start 4" trial. Whole-exome sequencing (SureSelect Human All Exon *V6+COSMIC)* and DNA methylation (Illumina EPIC Array) profiling were performed on 10 paired tumor/blood samples and 4 tumor samples, respectively. High-quality mutational and copy number data were produced for each of the 10 subjects demonstrating well-described gene mutations (SUFU) and chromosomal losses (9q and 10q). Four subjects had methylation profiling which successfully separated them into the WHO subgroups (two SHH and two Group 3). These data showed the feasibility of prospective high-dimensional mutational and DNA methylation analysis using "Head Start 4" patients. Future work will focus on finalizing these profiling efforts, enabling the development of models that predict response to irradiation-avoiding treatment and, in general, a better understanding of the molecular mechanisms underlying treatment resistance and tumor progression, leading to more personalized approaches to treating children with medulloblastoma.

MBRS-31. COMBINING IRRADIATION AND ANTI-CD47 TO ENHANCE THE TREATMENT OF GROUP 3 MEDULLOBLASTOMA

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Medulloblastoma (MB) is the most common malignant primary pediatric brain tumor. The Group 3 molecular subgroup of Medulloblastoma

(Group 3 MB) is the deadliest with only 30% long term survival. Irradiation for Group 3 Medulloblastoma is required for long term survival of children. Methods to enhance the effect of irradiation against Group 3 MB are an active area of investigation. Immunotherapy using the anti-CD47 treatment has shown promise in treating Group 3 MB. We recently demonstrated that irradiation significantly enhanced anti-CD47-mediated phagocytosis of high-grade glioma cells *in vitro*. Furthermore, mice engrafted with human high-grade glioma that received anti-CD47 combined with irradiation showed a significant increase in the survival rate and a significant decrease in tumor growth than those that received a single treatment. We have now extended these studies to demonstrate the enhancement of anti-CD47-dependent phagocytosis of human Group 3 MB with irradiation. We also analyzed normal human neural stem cells exposed to the same treatments to assess for the potential toxicity that uniquely exists with this treatment combination.

MBRS-32. TOPOISOMERASE II B INDUCES NEURONAL, BUT NOT GLIAL, DIFFERENTIATION IN MEDULLOBLASTOMA

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BACKGROUND: We previously reported that Gli3, which was a downstream molecule of Sonic Hedgehog signal, induced neuronal and/or glial differentiation in some types of medulloblastoma (desmoplastic/nodular medulloblastoma and medulloblastoma with extensive nodularity), and patients of medulloblastoma with neuronal differentiation showed favorable prognosis, but those with glial differentiation tended to show miserable prognosis (Miyahara H, Neuropathology, 2013). This time, we focused on Topoisomerase II β (Top2β), which was reported to induce neuronal differentiation and inhibit glial differentiation, and examined the expression of Top2β in medulloblastomas with neuronal and glial differentiations. METHODS: We assessed the expression of Top2β, NeuN, and GFAP using triple fluorescent immunostaining method in medulloblastoma samples with both neuronal and glial differentiations. Furthermore, the expression of Top2β, H3K4me2, and H3K27me3 were also assessed, because Top2βwas positively or negatively regulated by H3K4me2 and H3K27me3, respectively. RESULTS: Many large nuclei in the nodules, in which differentiated cells were seen, was visualized by Top2β. The Top2β signals were seen in NeuN+ cells but not GFAP+ cells. H3K4me2 signals were visualized in Top2β+ large nuclei, but H3K27me3 and NeuN+ large nuclei were distributed independently. CONCLUSIONS: These results indicate that Top2β may be a molecule associated with neuronal, but not glial, differentiation of medulloblastoma cells. Drugs targeting histone modification enzymes such as EZH2 inhibitors are possible therapeutic targets as a differentiation-inducing therapy for medulloblastoma.

MBRS-33. TEMPORARY RESTORATION OF P53 ACTIVITY DURING FRACTIONATED RADIOTHERAPY IN A GROUP3 MEDULLOBLASTOMA GEMM REPRESENTS A POWERFUL TOOL FOR RADIOBIOLOGY STUDIES

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TP53 pathway alterations are well-described events in medulloblastoma (MB) and are predictive of poor clinical outcome. Alterations are rare at diagnosis in Group3 (Gr3) and Group4, but enriched in Sonic Hedgehog and WNT subgroups. However, *TP53* mutations are observed in all subgroups at relapse. Radiation therapy, along with surgery and chemotherapy, represents the standard of care treatment for MB. Loss of p53 function correlates with increased resistance to radiation in several cancers conferring poor survival for patients. In this study, we exposed the MYCN-driven/Trp53^{kiki} (with tamoxifen-inducible p53 activation) Gr3 MB GEMM to a clinically relevant fractionated radiation therapy (RT) regime, to assess the role of p53 in Gr3 radio-resistance and relapse. Mice exhibiting tumour progression (bioluminescence (BLI) signal >10^9 photons/second) were randomized to treatment groups. A small animal radiation research platform was used to deliver CT-guided cranio-spinal irradiation (CSI) and a cranial boost (CB). Mice were followed for survival and tumour burden tracked using BLI. Bodyweight was monitored to evaluate treatment tolerability. Full dose radiation therapy (54Gy CB, 36Gy CSI, α/β=10) or dose modulation (12Gy CB, 8Gy CSI) was performed. The results showed comparable primary tumour regression in response to RT in p53 inactive and active backgrounds, followed by imminent relapse or prolonged remission respectively. No significant acute toxicity was observed. Temporary activation of p53 during RT improved tumour-free survival and decreased the incidence of relapse. In conclusion, we developed a new model which will help improve understanding of the radiobiology of high-risk MB and future preclinical trials.

MBRS-37. RECURRENT ACTIVATING MUTATIONS OF AKT GENES IN WNT-ACTIVATED MEDULLOBLASTOMAS

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Medulloblastoma (MB) can be classified into four distinct molecular subgroups (WNT group, SHH group, group 3, and group 4). Medulloblastoma of the WNT subgroup (WNT-MB) are commonly associated with favorable prognosis. Prospective molecular analysis based on a combination of CGH-array, targeted NGS and Nanostring-based subgrouping on 272 MB was conducted. Our custom targeted NGS panel of 75 genes includes genes recurrently affected in MB together with actionable genes with therapeutic purpose including some involved in the PIK3/AKT signaling pathway. Among the 272 MB analyzed, 26 cases (9.6%) belonged to the WNT subgroup based on *CTNNB1* mutations, monosomy of chromosome 6 and Nanostring-based molecular subgrouping. Our targeted NGS revealed three hotspot activating mutations in *AKT3* in WNT-MB and only one cases in another MB subgroup (in a group 4 MB; among the 33 cases of confirmed group 4 MB in our cohort). We subsequently performed Sanger sequencing of the hotspot Glu17 codon of *AKT1*, *AKT2*, and *AKT3* in 42 additional WNT-MB. This analysis revealed six additional activating mutations of AKT genes (four *AKT3* and two *AKT1* hotspots mutations) in WNT-MB. Altogether, we report 9/68 (13.2%) cases of WNT-MB with AKT genes mutations (two mutations in *AKT1* and seven mutations in *AKT3*). Our molecular analysis revealed AKT hotspot mutations that presumably activate the PIK3/AKT signaling pathway in WNT-MB. Even though WNT-MB is the subgroup of MB with the most favorable prognosis, this result emphasizes a possibility of targeted therapy that need to be further explored *in vitro* and *in vivo*.

MBRS-38. MOLECULAR CLASSIFICATION AND CLINICAL CHARACTERISTICS OF 236 MEDULLOBLASTOMAS IN JAPAN

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Recent intensive genomic and molecular biological analyses have made a consensus that medulloblastomas (MBs) are at least classified into four core subgroups, and the new 2016 WHO brain tumor *classification* has introduced the *classification* of MBs genetically defined in addition to classical histopathological diagnosis. To establish a nationwide network of a molecular diagnosis system for pediatric brain tumors, the JPMNG co-organized by the Japan Society for Neuro-Oncology and the Japanese Society for Pediatric Neurosurgery have started the clinical researches in

2012, and we have summarized results of molecular analysis of Japanese MBs. Total 236 primary MBs have been subclassified by gene expression profile using the NanoString nCounter system or DNA methylation array, and their single nucleotide mutations and copy number aberrations have been also examined. Mean follow up time was 68.9 months. Proportion of four core subgroups were WNT (16.9%), SHH (25.4%), Group 3 (17.4%) and Group 4 (40.3%), respectively. In cases of less than 3 years old, no WNT have been found and 63.2% cases were SHH. In cases between 3 to 17 years old, Group 4 is the most (47%), and these trends is almost consistent with published references. *TP53* mutations were identified in 23.3% of SHH, and they were significantly poor prognosis. Metastatic or *MYC* gain Group 3 MBs were poor prognosis, while Group 4 MBs with loss of chromosome 11 or whole chromosomal aberration were good prognosis. These findings reveal molecular properties of Japanese MBs and will contribute to develop new therapeutic strategies.

MBRS-39. MAP4K4 CONTROLS PRO-INVASIVE SIGNALING IN MEDULLOBLASTOMA CELLS

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The molecular mechanisms contributing to distant dissemination and local recurrence of medulloblastoma, the most common malignant brain tumor in childhood, are poorly understood and no targeted anti-invasion therapies exist till date. We explored regulators and effectors of MAP4K4, a pro-invasive kinase overexpressed in MB and associated with metastatic progression in different solid malignancies. MAP4K4 is upregulated both at mRNA and protein levels in primary pediatric brain tumors compared to normal cerebellum. MAP4K4 is required for growth factor- and irradiation-induced migration and invasion of medulloblastoma cells. It furthermore promotes turnover and activation of the receptor tyrosine kinase c-Met and of the ß1 integrin adhesion receptor [1]. To characterize these clinically relevant consequences and to identify druggable targets of MAP4K4 function, we profiled the interactome of MAP4K4 in starved and growth factor stimulated medulloblastoma cells. To systematically address MAP4K4 impact on receptor expression and turnover, we determined the MAP4K4-dependent surface proteome in medulloblastoma cells. We found that MAP4K4 is part of the striatin-interacting phosphatase and kinase (STRIPAK) complex and that STRIPAK component striatin 4 is controlling cell motility and invasiveness in medulloblastoma cells. Invasiveness of medulloblastoma cells is abrogated by a truncation mutant of MAP4K4 lacking the striatin 4 interaction domain. We furthermore found that MAP4K4 mediates growth factor-induced surface expression of solute carriers and immunomodulatory proteins involved in chemoresistance and immune evasion. Thus, our study identified MAP4K4 as a missing link between pro-tumorigenic growth factor signaling and tumor cell functions relevant for disease progression. It may help identifying druggable vulnerabilities in medulloblastoma cells to restrict tumor growth and dissemination. 1. Tripolitsioti, D. *et al*., *Oncotarget* **9**, 23220–23236 (2018).

MBRS-42. YB-1 - A NOVEL THERAPEUTIC TARGET IN HIGH-RISK MEDULLOBLASTOMA?

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Medulloblastoma relapse occurs in 30–40% of patients and is typically fatal. The emergence of therapy resistant sub-clones likely plays a major role in a large proportion of recurrent medulloblastoma. Y-box binding protein 1 (YB-1) is a multifunctional transcription/translation factor and known onco-protein. Overexpression has been described in numerous cancers, where elevated expression and nuclear accumulation correlates with disease progression, metastasis and drug resistance. Genomic analysis of a large medulloblastoma cohort revealed YB-1 up-regulation across all subgroups of medulloblastoma, where elevated expression correlated with poor survival. Immunohistochemical staining of patient tissue microarrays displayed significant YB-1 expression, with a high proportion (83%) of patients exhibiting nuclear accumulation. High YB-1 expression was also observed at both protein and RNA level across medulloblastoma cell lines, with expression highest in Group 3 and 4. Hence, we hypothesised that YB-1 plays a role in medulloblastoma chemoresistance and progression. Treatment of Group 3 (HDMB-03 and D283MED) and SHH (DAOY) cell lines with vincristine and cisplatin and analysis of cellular localisation by nuclear/cytoplasmic fractionation and immunofluorescence demonstrated that YB-1 undergoes nuclear translocation in response to these standard medulloblastoma chemotherapy agents. Chromatin immunoprecipitation (ChIP) analysis of untreated Group 3 cell lines (D283MED and HDMB-03) demonstrated considerable YB-1 interaction with an inverted CCAAT box in the *ATP-binding cassette subfamily B member 1* (*ABCB1)* promoter. RT-PCR analysis of ABCB1 following vincristine and cisplatin treatment revealed differences in transcript expression, indicative of different YB-1 promoter interactions dependent on chemotherapeutic treatment. Our results highlight YB-1 as a novel candidate chemoresistance driver in medulloblastoma.

MBRS-43. ELUCIDATING HOW NOVEL EXTRACELLULAR MATRIX SUBTYPES DIFFERENTIALLY IMPACT THE SURVIVAL OF MEDULLOBLASTOMA SUBGROUPS

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Medulloblastoma (MB) is the most common malignant paediatric brain tumour and frequently exhibits metastasis and chemoresistance. MBs are categorised into four molecular subgroups (WNT, Sonic hedgehog, Group 3 and Group 4), each associated with different demographics and clinical features. We have shown that the expression of specific extracellular matrix proteins in the brain tumour microenvironment differ between subgroups. A prime example is laminin (an ECM glycoprotein) the expression of which correlates with good overall survival in the SHH subgroup and poor overall survival in Group 4. Our aim is to determine the cause of this difference in survival. Candidate laminin-responsive-genes (LRGs) were identified using the Cavalli data set and RNA-Seq analysis of MB cells grown on 3D hydrogels with and without laminin. The role of laminin in the regulation of MMPs and the other LRG candidates was investigated by qRT-PCR, western blotting and zymography in 2D and long-term 3D-hydrogel assays. Thus far we have shown that in CHLA-01-R (metastatic Group 4 cell line) three of our LRGs are upregulated in response to laminin in 2D, as well as in preliminary 3D studies. Additionally, we have observed a unique MMP9 secretion profile of SHH cells grown in 3D compared to 2D, suggesting that our 3D assay allows us to observe relevant phenotypes absent in 2D culture. We are now in the process of identifying which of these LRG candidates are involved in metastasis and chemoresistance. This will enable the elucidation of novel therapeutic targets and crucially increase our understanding of MB-microenvironment interactions.

MBRS-44. TIME, PATTERN AND OUTCOME OF MEDULLOBLASTOMA RELAPSE ARE ASSOCIATED WITH TUMOUR BIOLOGY AT DIAGNOSIS AND UPFRONT THERAPY: A COHORT STUDY

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Disease relapse occurs in ~30% of children with medulloblastoma, and is fatal in the majority. We sought to establish whether clinico-molecular characteristics at diagnosis are associated with the nature of relapse, subsequent disease-course, and whether these associations could inform clinical management. We surveyed the clinical features of medulloblastoma relapse (time-to-relapse, pattern-of-relapse, time-to-death and overall outcome) in 247 centrally-reviewed patients who relapsed following standard-upfront-therapies. We related these to clinico-molecular features at diagnosis, prognostic factors, and first-line/relapse treatment. Patients who received upfront craniospinal irradiation (CSI-treated) displayed prolonged time-to-relapse compared to CSI naïve patients ($p<0.001$). Similarly, in CSI naïve patients, CSI at relapse, alongside re-resection and desmoplastic/nodular histology, were associated with long-term survival. In CSI-treated patients, the nature of relapse was subgroup-dependent. Local-nodular relapse patterns were enriched in relapsed-MB_{SHH} patients ($p<0.001$), but a notable proportion (65%) also acquired distant-diffuse disease ($p=0.010$). MB_{Group3} relapsed quickly (median 1.3 years), MB_{Group4} slowly (median 2.1 years). Distant-disease was prevalent in MB_{Group3} and MB_{Group4} relapses (90%) but, in contrast to relapsed-MB_{SHH}, nodular and diffuse patterns of distant-disease were observed. Furthermore, nodular disease was associated with a prolonged time-to-death post-relapse ($p=0.006$). Investigation of second-generation $MB_{Group3/4}$ subtypes refined our understanding of heterogeneous relapse characteristics. Subtype VIII had prolonged time-to-relapse; subtype II a rapid time-to-death. Subtypes II/III/VIII developed a significantly higher incidence of distant-disease at relapse, whereas subtypes V/VII did not. The nature of medulloblastoma relapse are biology

and therapy-dependent, providing immediate translational opportunities for improved disease management through biology-directed surveillance, post-relapse prognostication and risk-stratified selection of second-line treatment.

MBRS-45. TWIST1 AND ABCB1 ARE FUNCTIONAL DETERMINANTS OF METASTASIS IN MEDULLOBLASTOMA

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Paediatric medulloblastomas (MB) are frequently metastatic, resulting in a poor prognosis for the patient. Of the four MB subgroups, group 3 patients present with the highest rates of metastasis and worst outcomes. The mechanisms behind the metastatic process are poorly understood, limiting our ability to develop novel therapeutic treatments. We hypothesised that the epithelial-mesenchymal transition (EMT) transcription factor TWIST1 and the multidrug efflux pump ABCB1 (ATP-binding cassette subfamily B member 1) synergistically drive MB metastasis. TWIST1 protein expression was analysed in patient tissue microarrays by immunohistochemistry. High TWIST1 expression was associated with metastatic patients (p=0.041). Physical and functional interactions between TWIST1 and ABCB1 were investigated using chromatin immunoprecipitation (ChIP) and a 3D migration and invasion model. ChIP analysis confirmed TWIST1 binding to the *ABCB1* promoter in SHH (ONS-76) and group 3 (D283MED and HD-MB03) metastatic cell lines. TWIST1 and ABCB1 were inhibited in HDMB03 cells with harmine and vardenafil respectively, resulting in attenuated cell migration in the 3D model. Western blot and qRT-PCR analysis of harmine treated cells confirmed a reduction in ABCB1 protein and gene expression. Overall our data reveals TWIST1 and ABCB1 to be key targets for MB metastatic disease. Using bioinformatics analysis and ChIP sequencing, additional TWIST1 downstream targets are now being identified and compared across the metastatic cell lines (ONS-76, D283MED and HD-MB03). This data will provide a deeper insight into the pathways associated with MB metastases, enabling personalised treatment approaches for patients with metastatic disease.

MBRS-46. CHARTING NEOPLASTIC AND IMMUNE CELL HETEROGENEITY IN HUMAN AND GEM MODELS OF MEDULLOBLASTOMA USING SCRNASEQ

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We explored cellular heterogeneity in medulloblastoma using single-cell RNA sequencing (scRNAseq), immunohistochemistry and deconvolution of bulk transcriptomic data. Over 45,000 cells from 31 patients from all main subgroups of medulloblastoma (2 WNT, 10 SHH, 9 GP3, 11 GP4 and 1 GP3/4) were clustered using Harmony alignment to identify conserved subpopulations. Each subgroup contained subpopulations exhibiting mitotic, undifferentiated and neuronal differentiated transcript profiles, corroborating other recent medulloblastoma scRNAseq studies. The magnitude of our present study builds on the findings of existing studies, providing further characterization of conserved neoplastic subpopulations, including identification of a photoreceptor-differentiated subpopulation that was predominantly, but not exclusively, found in GP3 medulloblastoma. Deconvolution of MAGIC transcriptomic cohort data showed that neoplastic subpopulations are associated with major and minor subgroup subdivisions, for example, photoreceptor subpopulation cells are more abundant in GP3-alpha. In both GP3 and GP4, higher proportions of undifferentiated subpopulations is associated with shorter survival and conversely, differentiated subpopulation is associated with longer survival. This scRNAseq dataset also afforded unique insights into the immune landscape of medulloblastoma, and revealed an M2-polarized myeloid subpopulation that was restricted to SHH medulloblastoma. Additionally, we performed scRNAseq on 16,000 cells from genetically engineered mouse (GEM) models of GP3 and SHH medulloblastoma. These models showed a level of fidelity with corresponding human subgroup-specific neoplastic and immune subpopulations. Collectively, our findings advance our understanding of the neoplastic and immune landscape of the main medulloblastoma subgroups in both humans and GEM models.

MBRS-47. RAPID MOLECULAR SUBGROUPING OF MEDULLOBLASTOMA BASED ON DNA METHYLATION BY NANOPORE SEQUENCING

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Medulloblastoma (MB) can be classified into four molecular subgroups (WNT group, SHH group, group 3, and group 4). The gold standard of assignment of molecular subgroup through DNA methylation profiling uses Illumina EPIC array. However, this tool has some limitation in terms of cost and timing, in order to get the results soon enough for clinical use. We present an alternative DNA methylation assay based on nanopore sequencing efficient for rapid, cheaper, and reliable subgrouping of clinical MB samples. Low-depth whole genome with long-read single-molecule nanopore sequencing was used to simultaneously assess copy number profile and MB subgrouping based on DNA methylation. The DNA methylation data generated by Nanopore sequencing were compared to a publicly available reference cohort comprising over 2,800 brain tumors including the four subgroups of MB (Capper et al. Nature; 2018) to generate a score that estimates a confidence with a tumor group assignment. Among the 24 MB analyzed with nanopore sequencing (six WNT, nine SHH, five group 3, and four group 4), all of them were classified in the appropriate subgroup established by expression-based Nanostring subgrouping. In addition to the subgrouping, we also examine the genomic profile. Furthermore, all previously identified clinically relevant genomic rearrangements (mostly *MYC* and *MYCN* amplifications) were also detected with our assay. In conclusion, we are confirming the full reliability of nanopore sequencing as a novel rapid and cheap assay for methylation-based MB subgrouping. We now plan to implement this technology to other embryonal tumors of the central nervous system.

MBRS-48. IDENTIFICATION OF NOVEL THERAPEUTIC APPROACHES FOR MYC-DRIVEN MEDULLOBLASTOMA

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Medulloblastoma (MB) is the most common malignant brain tumor in children and is frequently metastatic at diagnosis. Treatment with surgery, radiation and multi-agent chemotherapy may leave survivors of these brain tumors with long-term deficits as a consequence. One of the four consensus molecular subgroups of MB is the MYC-driven group 3 MB, which is the most malignant type and has a poor prognosis under current therapy. Thus, it is important to discover more effective targeted therapeutic approaches. We conducted a high-throughput drug screening to identify novel compounds showing efficiency in group 3 MB using both clinically established inhibitors (n=196) and clinically-applicable compounds (n=464). More than 20 compounds demonstrated a significantly higher anti-tumoral effect in MYC^{high} (n=7) compared to MYC^{low} (n=4) MB cell models. Among these compounds, Navitoclax and Clofarabine showed the strongest effect in inducing cell cycle arrest and apoptosis in MYC^{high} MB models. Furthermore, we show that Navitoclax, an orally bioavailable and blood-brain barrier passing anti-cancer drug, inhibits specifically Bcl-xL proteins. In line, we found a significant correlation between *BCL-xL* and *MYC* mRNA levels in 763 primary MB patient samples (Data source: "R2 https://hgserver1.amc.nl"). In addition, Navitoclax and Clofarabine have been tested in cells obtained from MB patient-derived-xenografts, which confirmed their specific efficacy in MYC^{high} versus MYC^{low} MB. In summary, our approach has identified promising new drugs that significantly reduce cell viability in MYC^{high} compared to MYC^{low} MB cell models. Our findings point to novel therapeutic vulnerabilities for MB that need to be further validated *in vitro* and *in vivo*.

MBRS-51. MUTATIONS IN BRPF1 FOUND IN SHH MEDULLOBLASTOMA PREVENT INTERACTION WITH TP53 AND LEADS TO RADIORESISTANCE IN VITRO

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Medulloblastoma (MB) is one of the most common pediatric tumors in children. Among them, SHH subgroups of MB (MB_{SHH}) is characterized by constitutive activation of SHH pathway. Somatic mutations in *BRPF1*, a chromatin modifier, is found in more than 5% of MB_{SHH} and accounts for almost 20% of adult MB_{SHH} but its potential role in MB_{SHH} pathophysiology is still unknown. In this study, we first examined the function of Brpf1 on pro-tumorigenic features of MB_{SHH} and evaluated molecular pathways regulated by Brpf1 using Brpf1floxed::Atoh1-*Cre* conditional knockout mice, in which *Brpf1* is conditionally deleted in cerebellar granule neuron progenitors (GNPs). While RNA-seq analysis on GNPs from *Brpf1* WT and KO mice showed significant differences in the pathways related with cell cycle and cell death, deletion of *Brpf1* did not cause acceleration of tumorigenesis in the *Ptch1* heterozygous tumor-prone BACKGROUND: Co-immunoprecipitation followed by mass spectrometry analysis identified interaction partners of BRPF1 including MOZ, MORF and ING5, known partners of BRPF1. Gene ontology analysis also depicted pathways important for cell cycle progression, cell death and response to DNA damage. Consistent with these observations, TP53 was identified as a novel co-factor of BRPF1. Of note, some of MB_{SHH}-relevant *BRPF1* mutations prevented interaction with TP53. According to the previous finding that cytosolic TP53 is required for apoptotic cell death, GNPs expressing the *BRPF1*-R600X mutant gene exhibited the resistance to irradiation-induced cell death. In conclusion, our data revealed that BRPF1 mutants found in MB_{SHH} could prevent the complex formation with TP53, leading to enhanced resistance to cell apoptosis.

MBRS-53. CONTROL OF MEDULLOBLASTOMA VASCULATURE BY A REGULATOR OF NEUROGENESIS

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Medulloblastomas are characterized by poor neuronal lineage specification. Expression of the RE1 Silencing Transcription Factor (*REST*), a regulator of neurogenesis, is aberrantly elevated in human sonic hedgehog (SHH) medulloblastomas. Using a novel transgenic mouse (*RESTTG*) model, we demonstrated that REST is a driver of medulloblastoma genesis and promotes tumor progression in mice with loss of an allele of *Ptch1* (*Ptch+/–)*. Tumor formation in *Ptch+/–/RESTTG* mice occurred with 100% penetrance and a latency of 10–90 days in contrast to *Ptch+/–* mice, which developed tumors at a frequency of 15–20% at 6–9 months of age. Histopathological analyses showed leptomeningeal dissemination of tumors in *Ptch+/–/RESTTG* mice, in addition to a significant increase in tumor vasculature compared to tumors in *Ptch+/–* mice. These findings were recapitulated in xenografted tumors of isogenic low and high-REST medulloblastomas in mice. Proteome profiler human angiogenesis array analyses revealed a REST-dependent increase in vascular endothelial growth factor (VEGF) and placental growth factor (PLGF). Surprisingly, REST elevation also caused co-localization of tumor cells with tumor vasculature, specifically endothelial cells, and was associated with upregulated expression of a number of pro-angiogenic genes, including receptor VEGFR1 and the positive regulator of endothelial differentiation, E26 transformation specific-1 (*ETS1*), in tumor cells. In addition, expression of several anti-angiogenic molecules was downregulated. Knockdown of *ETS1* reversed the above findings. Thus, our data demonstrate that REST elevation not only blocks neurogenesis in medulloblastoma cells, but also modulates the tumor microenvironment by mechanisms that likely involve vascular mimicry.

MBRS-54. POOR SURVIVAL IN REPLICATION REPAIR DEFICIENT HYPERMUTANT MEDULLOBLASTOMA AND CNS EMBRYONAL TUMORS: A REPORT FROM THE INTERNATIONAL RRD CONSORTIUM

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BACKGROUND: Mutations in mismatch repair (MMR) and DNA-polymerase (POL) genes lead to DNA replication repair deficiency (RRD), resulting in a growing group of previously under-recognized childhood brain tumors. Medulloblastoma and embryonal tumors are rarely reported in RRD. Their biological and clinical significance is unknown. METHODS: We analyzed the clinical and genomic data of embryonal tumors registered in the International RRD Consortium. RESULTS: Twenty-six tumors were centrally reviewed to confirm medulloblastoma (n=18), embryonal-tumor, NOS (n=5), and three glioblastoma (excluded). Embryonal tumors were observed at a young age (median: 7-years, IQR: 5;11), and all but one exhibited clinical cues (café-au-lait macules/ family history) of germline RRD. Medulloblastomas with RRD exhibited high-risk features, including anaplastic histology (50%), and SHH-subgroup with TP53-mutation (50%). Importantly, 68% harbored POLE/POLD1 mutations, resulting in median tumor mutation burden of 164 mut/mb. POL-mutated tumors were significantly ultra-hypermutated (>100 mut/mb) than tumors with MMR-deficiency alone (p=0.015). Synchronous and metachronous tumors were observed in 40%. However 90% of the deaths were related to the diagnosis of embryonal CNS tumor. Median survival for the entire cohort was 17-months (95% CI: 10 to 23). Predicted 3-year survival was 37% for medulloblastoma, with no survivors among other embryonal tumors. CONCLUSIONS: This is the largest cohort of replication repair deficient medulloblastoma reported till date. The tumors are hypermutated, harbor somatic mutations in TP53 and/or POLE/POLD1, and have very poor survival with current chemo-irradiation based approaches. These biologically unique tumors expand the spectrum of high-risk TP53-mutant SHH-medulloblastoma, and need novel strategies for treatment.

MBRS-56. RE-EVALUATION OF LEPTOMENINGEAL METASTASIS IN MEDULLOBLASTOMA WITH MAGNETIC RESONANCE IMAGING, RELATED SYMPTOMS AND CEREBROSPINAL FLUID METABOLOMIC PROFILES

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BACKGROUND: Diagnosis of leptomeningeal metastasis (LM) in medulloblastoma is made by positive findings in either MRI or CSF cytology. We studied if CSF metabolomics profile can differentiate the discordant results between MRI and CSF cytology and reflect the sampling time related to treatment. MATERIALS AND METHODS: We prospectively collected 83 CSF samples from 45 medulloblastoma patients. A total of 6,527 low-mass ions (LMIs) were detected using liquid chromatography tandem mass spectrometry (LC-MS/MS). Discriminative low-mass ions (LMIs) between four different MRI and cytology results groups were evaluated and representative LMIs were identified. RESULTS: CSF cytology and MRI finding were both positive for LM in 8 samples and both negative for 47 samples. Tests were cytology (-) and MRI (+) in 20 samples, whereas cytology (+) and MRI (-) status were in the remaining 8 samples. The diagnostic accuracy by area under the curve (AUC) was 0.722 for cytology and 0.888 for MRI each. Based on the exclusiveness of LMI between groups, we verified 27 discriminative LMIs in MRI (+)/ cytology (+), 9 LMIs in MRI (+)/ cytology (-), and 12 LMIs in MRI (-) and cytology (+) group, separately. Metabolic pathways involved in MRI (+)/ cytology (+) group were linoleic acid, phenylalanine, TCA cycle, retinol, arginine-ornithine, nicotinate-nicotinamide, etc. Low-mass-ion discriminant equation (LOME), which could differentiate both different MRI and cytology results and the sampling time or presence of LM-related symptoms was found. CONCLUSION: Non-targeted MSanalysis CSF metabolite in medulloblastomas revealed significantly different profiles, and these results suggest LMI profiles might have a higher sensitivity for LM diagnosis than either MRI or cytology.

MBRS-57. IDENTIFICATION OF *MYC*-DEPENDENT THERAPEUTIC VULNERABILITIES FOR TARGETING GROUP 3 MEDULLOBLASTOMA

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Group 3 medulloblastoma (MB_{Group3}) is a highly aggressive tumour characterised by *MYC* amplification and elevated expression (17% of MB_{Group3}). *MYC* amplification in MB_{Group3} confers a dismal prognosis using standard therapies, and there is an urgent unmet need for novel therapeutic approaches. The identification and targeting of *MYC's* biological dependencies thus represents a promising strategy to treat *MYC*-MB_{Group3} tumours. Three independent isogenic *MYC*-regulable MB_{Group3} human cell-based models, in which elevated *MYC* expression can be directly down-regulated by doxycycline-inducible shRNAs, were developed and used initially to establish *MYC*-dependent growth of each model. Our novel models were then used to investigate *MYC*-dependent drug sensitivity, by characterising responses to a panel of candidate cancer therapeutics and small molecule inhibitors, including a high-throughput compound screen of >500 established/clinically-relevant small molecule inhibitors. This approach identified several specific, consistently observed, druggable *MYC*-dependencies (e.g. cell cycle regulators, DNA-damage response controllers, mitotic control machinery) with potential for the development of treatments against *MYC*-MB_{Group3} tumours. *PLK1*, *CHK1* and *AURK* were identified as prime candidate targets with consistent *MYC*-dependent response profiles. Subsequent validation of each candidate, by genetic and pharmacological target inhibition, confirmed their *MYC*-dependent effects, associated with downregulation of *MYC* and established target-dependent pharmacodynamic biomarkers/pathways. Results were consistent across all of our MB_{Group3} models. In summary, our novel models reveal druggable *MYC*-associated dependencies as a feature of MB_{Group3}. Our findings support the development of *PLK1*, *CHK1* and *AURK* inhibition as therapeutic approaches against *MYC*-dependent MB_{Group3}. Future work is now essential to validate our findings *in vivo*, to support the design of future clinical trials.

MBRS-59. SINGLE-CELL WHOLE-GENOME SEQUENCING DISSECTS INTRA-TUMOURAL GENOMIC HETEROGENEITY AND CLONAL EVOLUTION IN CHILDHOOD MEDULLOBLASTOMA

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Medulloblastomas harbor clinically-significant intra-tumoral heterogeneity for key biomarkers (e.g. *MYC/MYCN*, β-catenin). Recent studies have characterized transcriptional heterogeneity at the single-cell level, however the underlying genomic copy number and mutational architecture remains to be resolved. We therefore sought to establish the intra-tumoural genomic heterogeneity of medulloblastoma at single-cell resolution. Copy number patterns were dissected by whole-genome sequencing in 1024 single cells isolated from multiple distinct tumour regions within 16 snap-frozen medulloblastomas, representing the major molecular subgroups (WNT, SHH, Group3, Group4) and genotypes (i.e. *MYC* amplification, *TP53* mutation). Common copy number driver and subclonal events were identified, providing clear evidence of copy number evolution in medulloblastoma development. Moreover, subclonal whole-arm and focal copy number alterations covering important genomic loci (e.g. on chr10 of SHH patients) were detected in single tumour cells, yet undetectable at the bulk-tumor level. Spatial copy number heterogeneity was also common, with differences between clonal and subclonal events detected in distinct regions of individual tumours. Mutational analysis of the cells allowed dissection of spatial and clonal heterogeneity patterns for key medulloblastoma mutations (e.g. CTNNB1, TP53, SMARCA4, PTCH1) within our cohort. Integrated copy number and mutational analysis is underway to establish their inter-relationships and relative contributions to clonal evolution during tumourigenesis. In summary, single-cell analysis has enabled the resolution of common mutational and copy number drivers, alongside sub-clonal events and distinct patterns of clonal and spatial evolution, in medulloblastoma development. We anticipate these findings will provide a critical foundation for future improved biomarker selection, and the development of targeted therapies.

MBRS-60. THE ACTIONABLE GENOMIC LANDSCAPE OF RELAPSED MEDULLOBLASTOMA IS DEFINED BY MAINTENANCE AND ACQUISITION OF DRIVER EVENTS

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Medulloblastoma relapse (rMB) occurs in 30–40% of patients and is almost universally fatal. Understanding the genomic landscape of rMB, and its relationship to disease characteristics at diagnosis, will be essential to underpin the development of improved therapeutic strategies, delivered at both diagnosis and relapse. Utilising NGS and Illumina DNA methylation arrays, we interrogated the molecular landscape of >100 rMBs, alongside matched diagnostic samples (n>80), encompassing molecular subgroup, novel subtypes, copy number (CNV) and mutational variants. Molecular subgroup and novel subtypes were stable over disease-course. The majority of genomic aberrations were also maintained (total arm-level CNVs at relapse, 60% maintained/40% acquired; deleterious/driver mutations, 75% maintained/25% acquired). Importantly, however, the landscape of alterations differed markedly at relapse, through both selective maintenance and acquisition of specific gene and pathway aberrations. For instance, we observed significant enrichment of subgroup-specific events at relapse, including focal *CDK6/CDK14* amplifications (4/26 (15%) of MB_{Group4}) and *CDKN2A/CDKN2B* deletions (3/48 (6%) of MB_{SHH}). In contrast, mutations in DNA damage response pathways were commonly enriched across all molecular subgroups, most significantly in MB_{SHH} (~40% of rMB_{SHH}; *TP53*, 9/36 (25%); *ATM*, 5/36 (14%)). Driver events in rMB are characterised by both selective maintenance and acquisition across disease-course, and together combine to define its actionable genetic landscape. Evaluation of their clinical and biological significance will be essential to establish their potential (i) as biomarkers to direct disease management and (ii) as a basis for therapeutic strategies targeted against medulloblastoma relapse.

MBRS-61. MOLECULAR SUB-GROUPING OF PEDIATRIC MEDULLOBLASTOMA: CORRELATION WITH CLINICAL AND HISTOLOGICAL FEATURES, A SINGLE INSTITUTIONAL STUDY

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INTRODUCTION: Molecular subgroups of pediatric medulloblastomas are distinctive in infantile and non-infantile age-groups. METHODS: Real-time quantitative PCR based GEP of customized 12 protein-coding genes was performed on 206 FFPE childhood medulloblastoma samples. FISH for *MYC* amplification, monosomy 6 and sequencing for *CTNNB1* exon 3 mutation were done in relevant cases. H&E and reticulin-stained slides were used for histological subtyping. p53-protein immunoreactivity pattern was noted. RESULTS: Infantile (n=33) comprised 57.6% SHH-activated (desmoplastic: 73.7%; MBEN: 15.8% and classic: 10.5%), 21.2% group 3 (large cell/anaplastic [LCA]: 28.6% and none were desmoplastic) and 12% group 4. 40% of group 3 patients died of disease and 21% of the SHH-activated (all desmoplastic) had subsequent local recurrence. Non-infantile (n=173) comprised 19.4% WNT-activated, 12.9% SHH-activated (15% classic, 30% desmoplastic, 10% paucinodular), 19.4% group 3 (63.3% classic & 26.7% LCA), 48.4% group 4 (73.3% classic, 5.3% desmoplastic, 10.7% paucinodular & 1.4% LCA), and non-WNT/non-SHH (NWNS), NOS (n=14,9%) and unclassified (n=4,2.6%). None of WNT-activated were desmoplastic/LCA histology. Non-infantile WNT-activated and group 3 MBs showed 90% monosomy 6 & *CTNNB1* mutation, and 16.7% *MYC*-amplification respectively. 17.4% (13% spinal, 4.4% local) WNT-activated, 31% (12.5% local, 18.5% distant [spinal: 12.5%, intracranial:6%]) SHH-activated, 27% (18% both spinal and local, 9% spinal) group 3 and 31.5% (7.4% local, 5.5% intracranial, 11.2% spinal, 7.4% both spinal and local) group 4 showed metastases during follow up. CONCLUSIONS: SHH-activated and group 3 are the common infantile subgroups but group 4 is not non-existent in infantile age. No desmoplastic (including paucinodular) histological subtype is of WNT- activated and group 3.

MBRS-62. CURAXIN CBL0137 INHIBITS THE VIABILITY OF CANCEROUS CELLS IN PRE-CLINIC MODELS OF MYC-AMPLIFIED MEDULLOBLASTOMA

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Medulloblastoma is a malignant brain tumour that mostly occurs in children, and MYC-amplified medulloblastoma is characterized by pronounced invasiveness and dismal prognosis. There is no effective treatment for Medulloblastoma and its precise pathological mechanism remains obscure. Previous studies indicated that the altered epigenetic machinery manifested in the neoplastic transformation of MYC-amplified MB has become increasingly evident. It is hypothesized that epigenetic genes dependencies associated with small molecule inhibitors that have been approved or are in advanced development may help identify the potential therapeutic targets. By integrating mRNA expression profiles and the corresponding clinicpathologic information of patients suffering from medulloblastoma, and analysing prior CRISPR screening results, we demonstrated that SSRP1 is a negative prognostic factor that functions to stimulate the viability of MB cells. SSRP1 is a subunit of the FACT complex, an important histone chaperone required for transcriptional regulation, DNA replication and damage repair. Its biological effect on tumour proliferation was assessed by using RNA interference and administering CBL0137, a small molecular inhibitor of FACT. Gene expression analysis also demonstrated that CBL0137 selectively downregulated the expression of MYC and NEUROD1. Furthermore, the administration of CBL0137 suppressed tumour growth in mouse xenograft models. This pharmacological method to selectively target MYC transcription was demonstrated in our study, and therefore can be applied as a promising treatment strategy for MYC-amplified medulloblastoma. In Conclusion, we identified an attractive strategy of selectively downregulating MYC transcription by applying inhibitor CBL0137, thereby revealing the potential clinical utility of CBL0137 to improve the prognosis of MYC-amplified medulloblastoma patients.

MBRS-63. THE ROLE OF THE SWI/SNF COMPLEX SUBUNIT SMARCD3 IN MEDULLOBLASTOMA

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Medulloblastoma is the most common malignant brain tumor in children, with the Group 3 (G3) having the worst prognosis of the subgroups (WNT, SHH, and Group 4). We aimed to determine the underlying differences between G3 and the other subgroups, with an emphasis on genes that control the epigenome for developing effective treatments for patients with this disease. To this end, we found that G3 has elevated expression of the SWI/SNF subcomponent, SMARCD3 ($P<0.001$), which serves to guide the SWI/SNF complex to different genomic regions through interactions with various transcription factors. However, little is known about function of SMARCD3 in cancer, particularly in medulloblastoma. Clinically, elevated SMARCD3 mRNA resulted in a poorer prognosis in medulloblastoma patients ($P<0.0001$), which was further validated in 63 patient tumors by immunohistochemical staining for SMARCD3. Interestingly, tumors that had metastasized often had elevated expression of SMARCD3, in all subgroups of medulloblastomas ($P<0.0001$) and G3 only ($P<0.01$) based on analyzing multiple published databases. An orthotopic mouse model further supported that SMARCD3 is highly expressed in metastatic tumors compared to primary tumors. Importantly, CRISPR-CAS9-mediated SMARCD3 deletion decreased cell migration in medulloblastoma cell lines. Mechanistically, SMARCD3 deletion led to decreased H3K27me3, suggesting that SMARCD3 may cooperate with PRC2 in regulation of gene expression. Together, our results indicate that SMARCD3 plays a significant role in the development of metastatic dissemination in medulloblastoma, especially in the G3 subgroup. Thus, targeting the SMARCD3-containing SWI/SNF Complex may effectively prevent tumor dissemination and improve clinical outcomes in children with medulloblastoma.

MBRS-64. STUDY OF ARGININE METHYL TRANSFERASES IN MEDULLOBLASTOMA

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Medulloblastoma is the most common malignant pediatric cancer and a leading cause of childhood cancer-related mortality. There is dire need for new therapies. Molecular sub-classification of medulloblastomas has identified chromatin modifiers as potential drivers of tumorigenesis. Expression of the *RE1* Silencing Transcription Factor (REST), a hub for assembly of repressive chromatin remodelers and a known regulator of neurogenesis, is elevated in a subset of human sonic hedgehog (SHH) subgroup medulloblastomas, and is associated with poor prognosis. Using a novel transgenic mouse model, we showed REST to be a driver of medulloblastoma development. Surprisingly, our studies also revealed a role for REST in promoting proliferation of granule cell progenitors (GCPs), the cells of origin of SHH-driven medulloblastoma, and a concomitant loss of telomeres and increased genomic instability. We performed a gain of function screen using a library of chromatin modifiers to understand the mechanism by which proliferative potential was maintained, despite the loss of telomeres. This screen identified the Protein Arginine Methyltransferase 6 (*PRMT6*) as a high confidence hit. PRMT6 upregulation caused a reduction in CDKN2A, an important regulator of replicative senescence. Evasion of senescence is frequently implicated in tumor progression. Using a chemical screen, we also identified a novel, selective, reversible and competitive inhibitor of PRMT6. The consequence of genetic and pharmacological inhibition of PRMT6 on cell proliferation and senescence will be reported. Thus, our studies are the first to demonstrate a role for arginine methyl transferase family of chromatin modifiers in medulloblastoma genesis.

MBRS-65. FBXW7 ACTS A TUMOR SUPPRESSOR IN MYC-DRIVEN MEDULLOBLASTOMA BY CONTROLLING A FEED-FORWARD REGULATORY LOOP OF PLK1 AND MYC

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Group 3 medulloblastoma (MB) is often accompanied by MYC amplification and has a higher rate of metastatic disease. So, it is critical to have more effective therapies for high MYC expressing sub-groups. Here we report that FBXW7, a substrate recognition component of the SKP1-CUL1-Fbox (SCF) E3 ligase, interacts with and targets c-MYC for polyubiquitination and proteasomal degradation. FBXW7 shows lower expression level in MYC-driven MB compared with other MB subgroups suggesting activity as a tumor suppressor. Genomic deletion or mutation of *Fbxw7* has frequently been identified in many human cancers but not in MB. We demonstrate that overexpression of *Fbxw7* in MB cells induces apoptosis and suppresses proliferation *in vitro* and *in vivo*. Both phospho-deficient (T205A) and phosphomimetic aspartic acid (T205D) mutants deactivate its tumor suppressor function suggesting a conformational change of its protein structure. Mechanistically, PLK1 kinase specifically phosphorylates FBXW7 and promotes its auto-polyubiquitination and proteasomal degradation, counteracting FBXW7-mediated degradation of oncogene substrates, including c-MYC and PLK1. Chip-Seq results show stabilized c-MYC in turn directly activates PLK1 and FBXW7 transcription, constituting a feedforward regulatory loop. Co-immunoprecipitation demonstrates that FBXW7 directly binds to PLK1 and c-MYC, facilitating their protein degradation by promoting the ubiquitination of both proteins. Furthermore, we show that FBXW7 protein can be stabilized by various kinase inhibitors, proposing a mechanism of kinase-targeted agents to treat MYC-driven MB. These results collectively demonstrate how kinase inhibition stabilizes the tumor suppressor FBXW7 in MYC-driven MB, thus revealing an important function of FBXW7 in suppressing MB progression.

MBRS-66. COST-EFFECTIVE METHOD TO INCORPORATE MOLECULAR CLASSIFICATION OF MEDULLOBLASTOMA INTO A LATIN-AMERICAN CLINICAL TRIAL

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BACKGROUND: It is now widely accepted that medulloblastoma actually comprises four distinct molecular subgroups, requiring specific treatment strategies. Implementing routine subgrouping in a time and cost effective manner is a major challenge in Latin America, particularly the development of molecular informed clinical trials. Herein we describe the feasibility of reliable and rapid molecular stratification using a qPCR method integrated with immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH – c-myc, monosomy 6) from heterogeneously fixed, low-quality FFPE samples across Latin America. RESULTS: Fifty-four FFPE samples were classified according to histologic and molecular criteria. Classic medulloblastoma was found in 53.7%, desmoplastic/extensive nodularity in 24.1%, NOS in 16,7% and anaplastic in 5,6%. IHC

markers classified patients in three groups (WNT, SHH and non-WNT/non-SHH) in 98% of cases. PCR-based method confirmed results from IHC in 81,5%. Additionally, we were able to detect WNT activation in 2 patients, previously classified as SHH. For both cases, the presence of monosomy 6 further confirmed WNT subgroup. Integration of these three techniques resulted in the following frequencies: WNT (13.0%), SHH (38.9%), group 3 (9.3%), group 4 (20.3%) and non-WNT/non-SHH (18.5%). From 40 patients with clinical information available, 3-year overall survival (n=40) for low, intermediate and high-risk groups were 100%, 60% and 20%, respectively ($p<0.05$), based only in molecular criteria, which confirmed the prognostic importance of this method. CONCLUSIONS: At an estimated cost of $220 per patient, we are able to implement central molecular diagnosis for the incorporation into a prospective clinical trial protocol in Latin America.

MBRS-67. ROLE OF CYCLIN DEPENDENT KINASE-9 IN *MYC*-ENHANCED MEDULLOBLASTOMA

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Myc is highly expressed in group 3 medulloblastoma (Myc-MB) and influences cell growth, proliferation and oncogenesis by directly promoting the activity of RNA polymerases (RNA Pol). Myc driven RNA Pol II activity is mediated by Positive Transcription Elongation Factor b (pTEFb). pTEFb's catalytic core consists of cyclin dependent kinase-9 (CDK9) and Cyclin T, that phosphorylate and release RNA Pol II into active elongation. CDK9 is over expressed in group 3 MB suggesting that MB may be vulnerable to inhibition of CDK9 (CDK9i). The exact mechanism is not completely known in MB. Genetic depletion of CDK9 suppressed Myc-MB cell clonogenicity *in vitro* and tumor growth *in vivo*. CDK9i by two clinically relevant inhibitors, Atuveciclib and AZD4573, suppressed clonogenicity and cell self-renewal of Myc-MB cell lines. CDK9i in Myc-MB cell lines downregulated Myc and RNA Pol II phosphorylation at Ser2 and Ser5, and, upregulated P21. Further, mice with orthotopic xenografts treated with CDK9 inhibitors survived significantly longer than control mice. RNA-Seq-based gene set enrichment analysis showed that CDK9i decreased c-Myc driven transcriptomic programs and enhanced differentiation networks. ChIP-Seq for Pol2 and Myc, demonstrated that the Myc-driven aberrant transcriptional input can be reversed via CDK9i. These findings highlight the role of CDK9 in Myc-driven pathogenesis and that its inhibition is critical to the treatment of Myc-MB.

MBRS-68. SINGLE NUCLEUS RNA-SEQUENCING DECIPHERS INTRATUMORAL HETEROGENEITY IN MEDULLOBLASTOMA WITH EXTENSIVE NODULARITY (MBEN)

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Medulloblastoma (MB) with extensive nodularity (MBEN) represent a rare subtype of cerebellar tumors of infancy which comprise two histologically distinct components, nodular reticulin-free zones and internodular reticulin-rich regions. We applied single nucleus RNA-sequencing (snRNA-seq) using the 10X Genomics and the SMARTseq V2 protocols, bulk RNA-sequencing, DNA-methylation profiling and DNA-panel sequencing to ten histologically confirmed MBEN specimens. All tumors were classified as sonic hedgehog (SHH) MB based on DNA methylation. Somatic mutations within the SHH-pathway were detected in seven samples (3x *SUFU, 2x PTCH1, 2x SMO*) by DNA panel sequencing. The combined snRNAseq approach resulted in data on ~30.000 single cells. Several non-malignant cell types were identified, e.g. endothelial cells, astrocytes, and microglia. Amongst malignant cell populations SHH-pathway activation and mitotic activity differed revealing actively cycling embryonic stem (ES) cell-like and more differentiated neuronal-like cell types. In addition, distinct histological components of these tumours were subjected to bulk RNA sequencing following microdissection. This approach was repeated for DNA methylation profiling in an independent paraffin embedded MBEN cohort. However, these analyses did not reveal significant transcriptomic differences or differential methylation patterns between the two histological components. In summary, snRNA-seq identified a strongly proliferating, ES-like subset of cells in MBEN, which might represent the driving cell population in these malignancies, while direct analyses of nodular and inter-nodular regions did not reveal any significant differences. These findings suggest that both components originate from the same cell of origin but represent different cellular developmental stages.

MBRS-69. METABOLITE PROFILING OF SHH MEDULLOBLASTOMA IDENTIFIES A SUBSET OF CHILDHOOD TUMOURS ENRICHED FOR HIGH-RISK MOLECULAR BIOMARKERS AND CLINICAL FEATURES

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SHH medulloblastoma patients have a variable prognosis. Infants (<3–5 years at diagnosis) are associated with a good prognosis, while disease-course in childhood is associated with specific prognostic biomarkers (*MYCN* amplification, *TP53* mutation, LCA histology; all high-risk). There is an unmet need to identify prognostic subgroups of SHH tumours rapidly in the clinical setting, to aid in real-time risk stratification and disease management. Metabolite profiling is a powerful technique for characterising tumours. High resolution magic angle spinning NMR spectroscopy (HR-MAS) can be performed on frozen tissue samples and provides high quality metabolite information. We therefore assessed whether metabolite profiles could identify subsets of SHH tumours with prognostic potential. Metabolite concentrations of 22 SHH tumours were acquired by HR-MAS and analysed using unsupervised hierarchical clustering. Methylation profiling assigned the infant and childhood SHH subtypes, and clinical and molecular features were compared between clusters. Two clusters were observed. A significantly higher concentration of lipids was observed in Cluster 1 (t-test, $p=0.012$). Cluster 1 consisted entirely of childhood-SHH whilst Cluster 2 included both childhood-SHH and infant-SHH subtypes. Cluster 1 was enriched for high-risk markers - LCA histology (3/7 v. 0/5), *MYCN* amplification (2/7 v. 0/5), *TP53* mutations (3/7 v. 1/5) and metastatic disease - whilst having a lower proportion of *TERT* mutations (0/7 v. 2/5) than Cluster 2. These pilot results suggest that (i) it is possible to identify childhood-SHH patients linked to high-risk clinical and molecular biomarkers using metabolite profiles and (ii) these may be detected non-invasively *in vivo* using magnetic-resonance spectroscopy.

MBRS-70. FUNCTIONAL DEPENDENCY BETWEEN REST AND DNMT1 IN MEDULLOBLASTOMA

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Medulloblastomas exhibit poor neuronal lineage specification. Expression of RE1 Silencing Transcription Factor (*REST*), a repressor of neurogenesis, is aberrantly elevated in human sonic hedgehog (SHH) medulloblastomas. Constitutive REST expression in mice (*RESTTG*) drives medulloblastoma genesis and promotes tumor progression in the context of *Ptch1* haploinsufficiency (*Ptch+/–),* implicating it as a driver of tumorigenesis. Tumor formation in *Ptch+/–/RESTTG* mice showed significantly decreased latency and increased penetrance compared to that in *Ptch+/–* mice. Since REST silences gene expression by chromatin remodeling, we sought to identify cooperating epigenetic events that contributed to its oncogenic

activity. To this end, we performed a loss of function screen employing a bar-coded library of short hairpin RNAs against epigenes, to identify candidates whose loss could create a proliferative vulnerability in the context of REST-elevation. This screen identified DNA methyltransferase 1 (DNMT1) as a high-priority epigenetic modifier. DNMT1 and the Ubiquitin like with PHD and Ring finger domain 1 (UHRF1) proteins are essential for methylation of hemi-methylated DNA at the replication fork during S-phase. Their expression is downregulated during neuronal differentiation. In human SHH-medulloblastoma tumors, *REST* and *UHRF1* expression are positively correlated with higher levels of both genes noted specifically in the SHH-beta subtype, and is associated with poor prognosis. The requirement for DNMT1/UHRF1 in the context of REST elevation, was established by RNA-Seq and Reduced Representation Bisulfite Sequencing (RRBS), which revealed hypermethylation and downregulated expression of REST-target genes needed for neurogenesis. Thus, DNMT1/UHRF1 is a functional and potential therapeutic vulnerability in REST-elevated SHH medulloblastomas.

MBRS-71. ATAXIA TELANGIECTASIA AND RAD3-RELATED PROTEIN ATTENUATES DNA DAMAGE AND IS A THERAPEUTIC TARGET IN MYC-DRIVEN MEDULLOBLASTOMA

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Group 3 medulloblastoma tumors (Myc-MB), and particularly the 3γ subtype, have the worst prognosis and show a 5-year overall survival of less than 40%. Group 3 tumors are often accompanied by *Myc* amplification and have a higher rate of metastatic disease and relapse. Unfortunately, therapeutic strategies to target *Myc*have remained elusive. Further, the relapse of the MB has been linked to DNA replication stress. Ataxia telangiectasia and Rad3-related protein (ATR) senses persistent DNA damage, which arises due to replication stress, and activates damage checkpoints, thereby leading to increased cell survival. ATR is highly expressed in MB and is thought to contribute to undisturbed DNA replication to protect genomic integrity. Yet, the exact underlying mechanisms involving ATR are still unclear in MB. Inhibition of ATR (ATRi) using the ATR inhibitor, AZD6738, suppressed clonogenicity and cell self-renewal in Myc-MB. ATRi in Myc-MB cell lines downregulated Chk1 and upregulated P21. ATRi also induced cell cycle arrest and increased apoptosis in Myc-MB cell lines. Further, mice with orthotopic xenografts treated with ATR inhibitor survived significantly longer than control mice. High-throughput drug screening showed ATRi to be synergistic with chemotherapeutic agents including gemcitabine, cisplatin and topotecan. The treatment of Myc-MB cells with ATR inhibitor in combination with gemcitabine and with radiation increased in expression of DNA damage markers. These findings emphasize the role of ATR in alleviating DNA replication stress and that its inhibition is critical to the treatment of Myc-MB.

MBRS-72. MIR-212 FUNCTIONS AS A TUMOR SUPPRESSOR GENE IN GROUP 3 MEDULLOBLASTOMA VIA TARGETING NUCLEAR FACTOR I/B (NFIB)

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Medulloblastoma (MB), the most frequent malignant pediatric brain tumor is divided into four primary subgroups, i.e. wingless-type (WNT), sonic hedgehog (SHH), group 3, and group 4. Haploinsufficiency of chromosome 17p13.3 and c-myc amplification distinguish high-risk group 3 tumors and are associated with rapid recurrence and early mortality. We sought to identify the role of miR-212, which resides on chromosome 17p13.3, in the pathophysiology of group 3 medulloblastoma. RNA expression analyses revealed dramatically reduced levels of miR-212 in group 3 tumors and cell lines mainly through epigenetic silencing via histone modification (deacetylation). Restoring *in vitro* expression reduced tumor cell proliferation with decreased p-AKT and p-ERK levels, colony formation, migration and invasion in group 3 MB. Interestingly, a shift in differential c-myc phosphorylation (from serine-62 to threonine-58) was noted, resulting in reduced total c-myc levels, concurrent with elevated cellular apoptosis. In turn, pro-apoptotic binding partners of c-myc, i.e. Bin-1 and $P19^{ARF}$, were upregulated in these cells. A dual luciferase assay confirmed direct targeting of miR-212 to NFIB, a nuclear transcription factor implicated in metastasis and recurrence. Concurrently, increased expression of NFIB was confirmed in group 3 MB tumors with poor survival in high NFIB-expressing patients. Transient NFIB silencing *in vitro* reduced tumor cell proliferation, migration and invasion, and medullosphere formation along with a reduction in stem cell markers (Nanog, Oct4, Sox2, CD133) and the multi-drug resistance maker, ABCG2. Taken together, these results substantiate the tumor suppressive role of miR-212 in group 3 medulloblastomas and provide a potential new therapeutic target, NFIB.

MBRS-73. AN EXPLORATORY ANALYSIS LOOKING AT THE ASSOCIATION OF GERMLINE CODING MUTATIONS WITH IMPAIRED DEVELOPMENT AND ADAPTIVE BEHAVIOR FUNCTION IN PEDIATRIC MEDULLOBLASTOMA PATIENTS TREATED ON HEAD START 4

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Children with brain tumors often carry germline mutations known to contribute to tumorigenesis and treatment response; however, little is known about how these mutations impact developmental and behavioral outcomes. As the molecular mechanisms governing cancerous and normal tissues expand, we hypothesize that specific germline variants may impact baseline neurocognitive function and/or treatment-induced toxicities. In this pilot study, ten children on the Head Start 4 (HS4) clinical trial diagnosed with medulloblastoma were assessed for baseline adaptive functioning using the Adaptive Behavior Assessment System Third Edition (ABAS-III) and germline whole-exome sequencing was performed. After filtering for high impact variants, Welch's T-tests were used to identify mutations associated with lower ABAS-III General Adaptive Composite (GAC) scores, reflecting developmental and adaptive behavior delays compared with peers their age. We found twenty genes with alterations associated with lower scores with p-values less than 0.05. Genes found to be significant included *LAMC1* (p=0.04) and *KRTAP1-1* (p=0.045), which encode members of the laminin and keratin family respectively and are involved in extracellular matrix adhesion. Mutations in *PITX1*, a known suppressor of *RAS*, were also associated with lower ABAS-III GAC scores (p=0.007). We hypothesize that additional analyses of HS4 patients will reveal alterations in cell-to-cell communication and signal transduction pathways, common molecular perturbations in tumors that would likely impact central nervous system function. Validation studies are essential to improve our understanding of the functional impact of germline variants on both tumor and regular tissue biology, allowing for novel strategies to circumvent these delays.

PRECLINICAL MODELS/EXPERIMENTAL THERAPY/ DRUG DISCOVERY

MODL-01. SAFETY IN CONCOMITANT USE OF MEK AND BRAF INHIBITORS WITH BEVACIZUMAB

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BACKGROUND: MEK and BRAF inhibitors are increasingly common treatments for pediatric nervous system tumors. While effective in blocking Ras/Raf/MEK/ERK pathway activation driving tumor progression, the side effect profile differs from traditional cytotoxic chemotherapies. Little data exists on overlapping toxicities with other targeted agents like bevacizumab despite their potential combined therapeutic benefit. METHODS: A retrospective review of patients treated with MEK +/- BRAF inhibitors and bevacizumab from 2015–2019 was conducted. Data collected included demographics, tumor type, neurofibromatosis status, treatment duration, reason for concurrent treatment, and toxicities. RESULTS: Fifteen patients aged 3–24 years old (median age 14 years) were identified. Diagnoses included five high-grade gliomas, four low-grade gliomas, four benign nerve sheath tumors, and one ependymoma. Nearly half (46.7%) were positive for neurofibromatosis type 1. Three patients were treated with a BRAF + MEK inhibitor and twelve were treated with a MEK inhibitor combined with bevacizumab. Duration of treatment ranged from 16–420 days (median 119 days). Reasons for concomitant therapy included progressive disease with neurologic decline (46.7%), painful benign nerve sheath tumors (26.7%), and visual loss with optic pathway gliomas (26.7%). Toxicities while on concurrent therapy included one episode of grade 1 left ventricular dysfunction, one grade 1 bleeding episode, and one grade 2 wound complication. There were no episodes of hypertension, thrombosis, GI perforations, or cytopenias. CONCLUSIONS: Our preliminary experience suggests bevacizumab in combination with MEK and BRAF inhibitors can be used

safely across a variety of pediatric nervous tumors. Larger studies are needed to confirm these findings.

MODL-02. TARGETING REPLICATION STRESS IN PEDIATRIC BRAIN TUMORS

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Pediatric brain tumors harboring amplifications or high overexpression of *MYC-/MYCN* are often associated with poor outcome. High *MYC(N)* expression in these tumors leads to increased transcription, which can be in conflict with DNA replication and subsequently can cause replication stress, R-loops and DNA damage. We hypothesize that high *MYC(N)* expression makes them vulnerable to DNA damage response inhibitors (DDRi) and even more vulnerable to combinations of DDRi and chemotherapeutics. To test this hypothesis we performed *in vitro* drug experiments using Group 3 medulloblastoma (MB) and ETMR cell lines. IC50-values were evaluated of topoisomerase inhibitor Irinotecan (SN-38) and Pamiparib (BGB-290), a brain-penetrant PARP-inhibitor, in monotherapy. All cell lines were sensitive for SN-38 and showed IC50-values in the low nM-range but PARP-inhibitors were ineffective. However, a significant decrease in IC50 can be observed when SN-38 and Pamiparib are used in combination. For *in vivo* treatments, we injected NSG mice with luciferase labelled patient-derived xenograft- (PDX-) cells of various models (MB Group 3, MB SHH, ETMR, RELA EPN), monitored tumor growth via IVIS and randomized the mice into four groups (vehicle, BGB-290, Irinotecan and Irinotecan+Pamiparib) when a predefined threshold of tumor growth was reached. Mice were treated with Irinotecan (or vehicle) once per day i.p. and Pamiparib (or vehicle) twice per day per oral gavage. Treatment with Pamiparib did not show any survival benefit, but mice treated with Irinotecan or the combination showed a clear survival benefit. Treatments are ongoing and more results will be presented at the conference.

MODL-03. ADAPTING PALBOCICLIB FOR MEDULLOBLASTOMA THERAPY BY IMPROVING DRUG DELIVERY AND ADDRESSING RESISTANCE

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CDK4/6 inhibition may be a promising therapy for medulloblastoma. All medulloblastoma subgroups show D-cyclin/CDK4/RB pathway activity, suggesting broad potential for efficacy. To address drug delivery and systemic toxicity limitations, we developed a nanoparticle formulation of CDK 4/6 inhibitor, palbociclib, in poly (2-oxazoline) micelles (POx-palbo). POx-palbo showed reduced systemic toxicity in transgenic mice engineered to develop medulloblastoma, allowing for higher dosing. Pharmacodynamic studies showed POx-palbo suppressed RB phosphorylation acutely and after 24hrs, the effect diminished. This inhibition produced a longer lasting suppression of SHH pathway activity, demonstrated by Gli-luc reporter tumor mice. Importantly, POx-palbo therapy, administered daily, reduced tumor growth and improved the survival of mice with medulloblastoma. While POx-palbo was clearly effective as a single agent, all mice treated with POx-palbo eventually developed progressive disease, as resistant populations of tumors cells emerged. To understand the mechanisms of resistance, we compared tumors early and late in the course of therapy. We found that after 5 days of treatment, palbociclib altered cell cycle progression to produce an extended period of S-phase and that the fractions of cell expressing the stem cell marker Olig2 were markedly increased. Based on these data, we propose that tumors respond to the initial suppressive effect of palbociclib by increasing the pool of Olig2+ stem cells, that these cells show discernably different cell cycle kinetics and are resistant to CDK4/6 inhibition. Combining POx-palbo with additional therapies that target Olig2+ stem cells, by disrupting their prolonged S-phase, or by disrupting Olig2 function, may lead to newly effective medulloblastoma treatment.

MODL-04. MODELING CNS HGNET-BCOR PATHOGENESIS USING NEURAL STEM CELLS

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Central nervous system high-grade neuroepithelial tumor with BCL6-corepressor alteration (CNS HGNET-BCOR) is a recently identified entity characterized by internal tandem duplication (ITD) of BCOR, a core component of polycomb repressive complex (PRC) 1.1. BCOR-ITD exclusively occurs within an essential binding domain, suggesting aberrant epigenetic activities as a possible mechanism of gliomagenesis; however, the effect of this alteration on the transcriptome and DNA methylation are poorly understood. We have generated new CNS HGNET-BCOR models by lentiviral transduction of the BCOR-ITD into human and murine neural stem cells. In the human model, qRT-PCR and subsequent RNA-seq identified a transient derepression of PRC2-target genes comparing to an isogenic model with overexpression of wildtype-BCOR. A similar effect was found in clinical specimens from previous studies. In the murine-cell model, we confirmed increased clonogenicity in soft-agar assays, and tumors developed in mice flanks. Global DNA methylation levels evaluated by ELISA were significantly lower than those of parent cells, and 177 genes were differentially expressed on RNA-seq analysis comparing to BCOR-overexpressing control cells, including upregulation of known oncogenes. These results suggest that BCOR-ITD and associated alterations in the function of PRC1.1 affect methylation patterns in neural stem cells, driving transcriptional changes and oncogenic transformation into CNS HGNET-BCOR. More detailed analyses, including methylation arrays comparisons with clinical samples and in-silico drug sensitivity testing, are being performed.

MODL-06. PRECLINICAL EFFICACY OF THE IMIPRIDONE ONC-206 AGAINST MEDULLOBLASTOMA

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Treatment for medulloblastoma (MB) is typically ineffective for MYC amplified or metastatic SHH, Group 3 and 4 subgroups. Promising preclinical and clinical results have been obtained in brain cancers treated with ONC-201, a selective antagonist of DRD2, a G-protein coupled receptor that regulates prosurvival pathways. Herein, we report the activity of ONC-201 and ONC-206, which has increased non-competitive antagonism of DRD2, against MB. We treated three different MB cell types representative of SHH- and Group 3-like cells, with varied levels of DRD2 expression, and consistently observed increased cell death in a dose-dependent manner at lower doses of ONC-206 compared to ONC-201. We also evaluated ClpP as an additional drug target in MB. ClpP is a mitochondrial protease that has been shown to directly bind and be activated by ONC 201, and is highly expressed at the protein level across pediatric MB, malignant glioma and ATRT, but not normal brain. We observed that similar to ONC-201, ONC-206 treatment of MB cells induces the restoration of mitochondrial membrane potential to the non-proliferative state, degradation of the mitochondrial substrate SDHB, reduction in survivin and elevation in ATF4 (integrated stress response). Importantly, ONC-206 treatment induced significant cell death of patient-derived SHH, WNT, and Group 3 tumors ex vivo and Group 4 cells in vitro, while having no observable toxicity in normal brain. Efficacy studies of ONC-206 against MB in vivo will be reported in preparation for a planned Phase I study of ONC-206 in children with malignant brain tumors.

MODL-08. OPTIMIZATION OF A NOVEL LOCAL DELIVERY SYSTEM FOR THE TREATMENTS OF SUPRATENTORIAL EPENDYMOMA

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Ependymomas are the third most common paediatric brain tumour, incurable in up to 40% of cases. Until recently, ependymomas were regarded as a single disease group with all patients receiving combinations of maximal surgical resection and radiotherapy. Use of chemotherapy has been limited by the resistant nature of the tumour and poor access to tumours behind the blood brain barrier (BBB). It is now known that ependymoma comprises up to nine different molecular subgroups. One subgroup is characterized by a novel fusion protein, C11orf95-RELA, which acts as a potent driver of oncogenesis resulting in a poor prognosis. Here, we present the optimization of a novel drug delivery system that uses biodegradable hydrogels to deliver drugs with potent anti-ependymoma properties into post-resection cavity of supratentorial ependymoma. Our previous high-throughput *in-vivo* drug screens identified candidate ependymoma therapies with poor BBB penetrance properties. Using *in-vitro* delivery assays, we have confirmed and monitored the release of these compounds from the hydrogel. Additionally, we have implemented this delivery system in our preclinical mouse hospital in which mice receive standard-of-care surgery and radiotherapy. The efficacy of hydrogel-based delivery of these compounds is now being tested preclinically, in combination with radiotherapy. Treatment for ependymoma patients have not changed in the last 30 years and therefore an effective chemotherapy could add a great survival benefit to in the clinic.

MODL-09. FEASIBILITY OF ACUTE SLICE CULTURE-SINGLE CELL SEQUENCING DRUG SCREENING AS A TOOL TO SELECT THERAPY FOR CHILDREN WITH RELAPSED BRAIN TUMORS

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Children with relapsed brain tumors are less responsive to treatment. These children often receive therapies without having any robust predictive method of potential benefit. Acute slice culturing(ASC) is a methodology permitting freshly operated tumor to undergo a culturing process preserving the tumor's micro-environment. With the current study, we investigated the feasibility of obtaining therapeutically meaningful data in a timely manner (3–5 days), performing direct drug testing and single cell sequencing using ASC. Previously, we have combined *ex vivo* slices of intact, patient-derived Glioblastoma tissue with single-cell RNA-seq for small-scale drug screening and assessment of patient and cell type-specific drug responses. We generated slices from preclinical mouse glioma models and surgical specimens from adult Glioblastoma patients, as well as from children with relapsed Ependymomas, Medulloblastomas, and Gliomas. We demonstrated that these acute slices preserved both the tumor heterogeneity and tumor microenvironment observed in single-cell RNA-seq of cells directly isolated from tumor tissue. Testing drug responses, we then treated tissue slices from the Glioblastoma mouse models and different patients with multiple drugs and combinations. This technique allowed us to identify drug-induced transcriptional responses in specific subpopulations of tumor cells, patient-specific drug sensitivities, and drug effects conserved in both mouse and human tumors. Preliminary data suggests that we can apply this procedure within 5–7 days and provide real-time drug screening/single cell sequencing ASC results to Recurrent/ Progressive pediatric Low-Grade Gliomas, High Grade Gliomas, Ependymomas and Medulloblastomas.

MODL-11. COMPARISON OF HUMAN & MURINE PA/PXA CHARACTERISTICS

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Pediatric low-grade gliomas (pLGGs) are the most common brain tumors in children. Despite recent advances in the molecular characterization of this heterogeneous set of tumors, the separation of specific tumor types is still not fully established. Pilocytic astrocytoma (PA; WHO grade I) and pleomorphic xanthoastrocytoma (PXA; WHO grade II) are two pLGG types that can be difficult to distinguish based on histology alone. Even though their clinical course is different, they are often grouped as 'pLGG' in clinical trials (and therefore treated similarly). Based on a cohort of 89 human pediatric tumor samples, we show that PAs and PXAs have clearly distinct methylation and transcriptome profiles. The difference in gene expression is mainly caused by cell cycle- and development-associated genes, suggesting a key difference in the regulatory circuits involved in tumor growth. In addition to BRAF V600E, we found *NTRK* fusions and a previously unknown *EGFR:BRAF* fusion as mutually exclusive driving events in PXAs. Both tumor types show marked signs of immune cell infiltration, but with significant qualitative differences, which might represent therapeutic vulnerabilities. To pave the way for further research on PA and PXA, we developed corresponding mouse models using the virus-based RCAS system, which allows introduction of an oncogenic driver into immunocompetent mice for molecular and preclinical research. The murine tumors do not only histologically resemble their human counterparts but also show a similar growth behavior. Expression analysis revealed that the murine PXAs have a stronger gene signature of proliferation and immune cell infiltration compared to PAs.

MODL-12. DEVELOPMENT OF A NOVEL IMMUNOCOMPETENT MOUSE MODEL FOR DIFFUSE INTRINSIC PONTINE GLIOMA

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Diffuse intrinsic pontine glioma (DIPG) is a devastating brain tumor affecting young children. Immunotherapies hold promise however the lack of immunocompetent models recreating a faithful tumor microenvironment (TME) remains a challenge for development of targeted immunotherapeutics. We propose to generate an immunocompetent DIPG mouse model through induced overexpression of interleukin 13 receptor alpha 2 (IL13Rα2), a tumor-associated antigen overexpressed by glioma cells. A model with an intact TME permits comprehensive preclinical assessment of IL13Rα2-targeted immunotherapeutics. Our novel model uses the retroviral avian leucosis and sarcoma virus (RCAS) for *in vivo* gene delivery leading to IL13Rα2 expression in proliferating progenitor cells. Transfected cells expressing IL13Rα2 and PDGFB, a ligand for platelet derived growth factor receptor, alongside induced p53 loss via the Cre-Lox system are injected in the fourth ventricle in postnatal pups. We validated the expression of PDGFB and IL13Rα2 transgenes *in vitro* and *in vivo* and will characterize the TME through evaluation of the peripheral and tumor immunologic compartments using immunohistochemistry and flow cytometry. We confirmed expression of transgenes via flow cytometry and western blotting. Comparison of survival dynamics in mice inoculated with PDGFB alone with PDGFB+IL13Rα2 demonstrated that co-expression of IL13Rα2 did not significantly affect mice survival compared to the PDGFB model. At time of application, we initiated experiments to characterize the TME. Preliminary data demonstrate establishment of tumors within and adjacent to the brainstem and expression of target transgenes. Preclinical findings in a model recapitulating the TME may provide better insight into outcomes upon translation to clinical application.

MODL-13. GENETICALLY ENGINEERED PIG MODEL OF RHABDOID TUMOR PREDISPOSITION SYNDROME-1

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Atypical teratoid/rhabdoid tumor (AT/RT) is the most common malignant CNS tumor of children below 6 months of age. The majority of AT/RT demonstrate genomic alterations in the *SMARCB1* gene. There are two major hurdles in the development of safe and effective treatments for AT/RT: first, the mouse models do not fully recapitulate the disease seen in patients and their predictivity of clinical efficacy is still unproven. Second, due to a small patient population, the ability to recruit enough patients for clinical trials is challenging. Genetic studies have demonstrated that germline deletion of *SMARCB1* exons 4 and 5 predisposes to AT/RT at an early age. Comparison of human, swine, and mouse *SMARCB1* genes show similarities in gene and protein structure, with 100% amino acid identity between swine and human SMARCB1 isoforms. Thus, we hypothesized that germline deletion of exons 4 and 5 will predispose heterozygote swine to AT/RT development. *SMARCB1*$^{+/-}$ founder pigs are obtained using a CRISPR/Cas9 mediated gene-editing of conventional crossbred swine embryos, followed by embryo transfer into female swine surrogates. They are evaluated for clinical criteria used to diagnose AT/RT and by MRI at 6, 12, and 24 months of age, followed by histopathology and molecular analysis of the tumors as they are detected. Generating a large animal model of AT/RT would represent a breakthrough in the field from a genomic, pathophysiologic, preclinical and therapeutic perspective.

MODL-14. SMALL MOLECULE TARGETING OF ONCOGENIC FGF2-FGFR SIGNALING IN BRAIN TUMORS

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FGF2, the ligand of FGF receptors (FGFRs), is expressed in the developing and adult brain. FGF2-FGFR1 signaling causes the induction and maintenance of cancer stem cells through ERK-dependent up-regulation of ZEB1 and Olig2 in glioblastoma. In SHH medulloblastoma, Olig2 triggers tumor initiation

from GCPs, maintains quiescent stem-like cells during the disease and contributes to tumor outgrowth at recurrence. We found that FGF2-FGFR signaling causes increased growth and tissue invasion through the FGFR adaptor protein FRS2 in SHH and group-3 medulloblastoma [1]. Thus, targeting of FGFR-FRS2 signaling could abrogate brain tumor growth and spread by repressing tumor-promoting functions that are induced by microenvironmental FGF2. Using virtual screening combined with functional validation, we identified protein-protein interaction inhibitors (F2i) that bind FRS2 and abrogate FGFR signaling to the MAP-ERK pathway. Consistent with the requirement of FRS2 for pro-invasive signaling downstream of FGFR1 in medulloblastoma, F2i also efficiently block FGF2-induced migration and invasion in medulloblastoma-derived cells. Selected F2i display excellent binding kinetics with a similar Kd as the natural ligand domain of FGFR and cause steric alterations in the targeted protein domain. On-target activity was confirmed by thermal proteome profiling. Neither *in silico* screening nor empirical testing revealed significant off-target activity of the compounds. No toxicity of F2i was observed in cell-based models with confirmed functional activity on invasion and MAPK activation. Thus, we identified novel, low molecular weight pharmacological protein-protein interaction inhibitors with an excellent potential to specifically block FGFR functions relevant for brain tumor progression. 1. Santhana Kumar et al., *CellReports* **23**, 3798–3812.e8 (2018).

MODL-15. THE COMBINATION TREATMENT OF PARP INHIBITOR AND TMZ, OR DAG WILL BE PROMISING TREATMENT IN SF8628

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Diffuse midline glioma, H3 K27M-mutant (DMG) is a newly defined entity. The prognosis of DMG is poor. Because surgical resection is often incomplete for DMG, radiotherapy and chemotherapy are important. Temozolomide (TMZ) is an alkylating agent that adds a methyl group to DNA (O6-guanine, N7-guanine, and N3-adenine). TMZ-induced cytotoxicity is mainly derived from O6-methylguanine, which is repaired by O6-methylguanine DNA methyltransferase (MGMT). It has been reported that most of DMG lacked MGMT promoter hypermethylation, which is thought to contribute to less effectiveness of TMZ to DMG. The purpose of the study is to explore the way to inhibit the proliferation of DMG. A DMG cell line, SF8628, was used for the experiments. SF8628 had the expression of MGMT and was revealed to be resistant to TMZ. Because N7-methylguanine and N3-methyladenine are repaired via base excision repair, poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor combined with TMZ was considered to be effective to suppress the proliferation of SF8628. As expected, PARP inhibitor enhanced TMZ-induced cytotoxicity in SF8628. Dianhydrogalactiol (DAG) is a bifunctional DNA-targeting agent forming N7-alkylguanine and inter-strand DNA crosslinks. DAG reduced the clonogenicity of SF8628. Moreover, inhibition of homologous recombination enhanced the DAG-induced cytotoxicity in SF8629. The combination treatment of PARP inhibitor and TMZ, or DAG were revealed to be promising treatments in SF8628.

MODL-16. ABEMACICLIB, A SELECTIVE CDK4/6 INHIBITOR, RESTRICTS GROWTH OF PEDIATRIC GLIAL-LINEAGE TUMORS IN VITRO AND IN VIVO

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BACKGROUND: Glial-lineage tumors constitute a heterogeneous group of neoplasms, comprising gliomas, oligodendrogliomas, and ependymomas, which account for 40%–50% of all pediatric central nervous system tumors. Advances in modern neuro-oncological therapeutics are aimed at improving neoadjuvant chemotherapy and deferring radiotherapy because radiation exposure may cause long-term side effects on the developing brain in young children. Despite aggressive treatment, more than half the high-grade gliomas (pHGGs) and one-third of ependymomas exhibit recurrence within 2 years of initial treatment. METHODS: By using integrated bioinformatics and through experimental validation, we found that at least one gene among CCND1, CDK4, and CDK6 was overexpressed in pHGGs and ependymomas. RESULTS: The use of abemaciclib, a highly selective CDK4/6 inhibitor, effectively inhibited cell proliferation and reduced the expression of cell cycle–related and DNA repair–related gene expression, which was determined through RNA-seq analysis. The efficiency of abemaciclib was validated in vitro in pHGGs and ependymoma cells and in vivo by using subcutaneously implanted ependymoma cells from patient-derived xenograft (PDX) in mouse models. Abemaciclib demonstrated the suppression of RB phosphorylation, downstream target genes of E2F, G2M checkpoint, and DNA repair, resulting in tumor suppression. CONCLUSION: Abemaciclib showed encouraging results in preclinical pediatric glial-lineage tumors models and represented a potential therapeutic strategy for treating challenging tumors in children.

MODL-17. SHP2 INHIBITORS SHOW ACTIVITY AGAINST NF1-DEFICIENT GLIOMAS AND ENHANCE MAPK PATHWAY INHIBITION IN BRAF-V600E MUTANT GLIOMAS

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INTRODUCTION: Activation of the RAS-MAPK signaling cascade is common in pediatric gliomas. Based on the role of SHP2 in RAS pathway signaling, we hypothesized that NF1-deficient pediatric glioma models would respond to SHP2 inhibitor monotherapy whereas BRAF-V600E gliomas would not. However, we postulated that the latter would exhibit increased sensitivity to a BRAF inhibitor (BRAFi) in combination with SHP2i. Here we demonstrate that the SHP2 inhibitors SHP099 and RMC-4550 (SHP2i) show significant single-agent activity in vitro against NF1-deficient glioma cells and that the combination of RMC-4550 with BRAFi shows increased activity in BRAF-V600E glioma cells relative to the single-agents. METHODS: Using a panel of NF1 mutant/deficient and BRAF-V600E mutant glioma cell lines we examined effects on cell viability and protein expression levels of total and phosphorylated MEK, ERK, and AKT. RESULTS: LN229 and U87 NF1-deficient glioma cells are sensitive to SHP2i alone but not A375 cells (melanoma, BRAF-V600E). Additionally, we show that in multiple BRAF-V600E glioma cell lines BRAFi sensitivity increases when combined with a SHP2i. Immunoblots show decreased expression of pERK and pMEK in LN229 cells following SHP2i exposure, while A375 cells maintain MAPK pathway signaling. A sustained decrease in the expression of pERK after 24 hours was observed in BRAF-V600E glioma cells with BRAFi in combination with SHP2i, consistent with relief of feedback inhibition. In vivo studies using orthotopic xenograft models are underway. CONCLUSION: SHP2i shows preclinical activity in vitro against NF1-deficient pediatric glioma cell lines as a single-agent and against BRAF-V600E gliomas in combination with BRAFi.

MODL-19. DIPG HARBOUR ALTERATIONS TARGETABLE BY MEK INHIBITORS, WITH ACQUIRED RESISTANCE MECHANISMS OVERCOME BY COMBINATORIAL UP- OR DOWN-STREAM INHIBITION

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The survival of children with DIPG remains dismal, with new treatments desperately needed. In the era of precision medicine, targeted therapies represent an exciting treatment opportunity, yet resistance can rapidly emerge, playing an important role in treatment failure. In a prospective biopsy-stratified clinical trial (BIOMEDE), we combined detailed molecular profiling (methylation BeadArray, exome, RNAseq, phospho-proteomics) linked to drug screening in newly-established patient-derived models of DIPG *in vitro* and *in vivo*. We identified a high degree of *in vitro* sensitivity to the MEK inhibitor trametinib (GI50 16-50nM) in samples which harboured genetic alterations targeting the MAPK pathway, including the non-canonical *BRAF*_G469V mutation, and those affecting *PIK3R1*. Treatment of PDX models and the patient with trametinib at relapse, however, failed to elicit a significant response. We generated trametinib-resistant clones (62-188-fold, GI50 2.4–5.2μM) in the *BRAF*_G469V model through continuous drug exposure, and identified acquired mutations in *MEK1/2* (*MEK1*_K57N, *MEK1*_I141S and *MEK2*_I115N) with sustained pathway up-regulation. These cells showed the hallmarks of mesenchymal transition, with overexpression of key proteins involved in invasion/migration, such as collagen-family proteins, integrins, MMPs and AHNAK2, amongst others. Resistant clones were conversely sensitive to the upstream receptor tyrosine kinase inhibitor dasatinib (GI50 36-93nM), and combinations of trametinib with dasatinib and the downstream ERK inhibitor ulixertinib showed synergistic effects *in vitro*. These data highlight the MAPK pathway as a therapeutic target in DIPG, and show the importance of parallel resistance modelling and rational combinatorial treatments likely to be required for meaningful clinical translation.

MODL-20. A BIOBANK OF ~100 PATIENT-DERIVED MODELS REPRESENTING BIOLOGICAL HETEROGENEITY AND DISTINCT THERAPEUTIC DEPENDENCIES IN PAEDIATRIC HIGH GRADE GLIOMA AND DIPG

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Paediatric high-grade glioma comprise multiple biological and clinical subgroups, the majority of which urgently require novel therapies. Patient-derived models represent useful tools for mechanistic and preclinical investigations based upon their retention of key genetic/epigenetic features and their amenability to high-throughput approaches. We have collected ~100 i*n vitro* models representing multiple subtypes (H3.3/H3.2/H3.1K27M, H3.3G34R/V, BRAF, MYCN_amp, NTRK_fusion, hypermutator, others) established under 2D (laminin) and/or 3D (neurosphere) conditions, credentialed by phenotypic (growth, invasion/migration) and molecular (methylation array, DNA sequencing, RNAseq) comparison to the original tumour sample. These were derived from patients at our local hospitals (n=29), as part of national co-clinical trials (n=19), from international collaborating centres (n=11), or shared directly by research groups worldwide (n=45). These have variously been subjected to pharmacological (approved/experimental drug libraries) and/or genetic screening (whole-genome CRISPR) to identify specific biological dependencies. Many have been established as orthotopic xenografts i*n vivo* (PDX), with detailed pathological and radiological correlations with the clinical disease, and with tumorigenic latencies ranging from 48–435 days. This resource has allowed us to identify genotype-specific synthetic lethalities and responses to targeted inhibitors, including olaparib (PARP) with *ATRX*, nutlin-3 (MDM2) with *PPM1D*, AZD1775 (WEE1) with *TP53*, and CYC065 (CDK9) with *MYCN*-amplification. Combinatorial screening highlighted synergies in *ACVR1*-mutant DIPG between novel ALK2 inhibitors and ONC201 (DRD2). Rapid screening allows for feedback of drug sensitivities to treating clinicians at relapse, whilst mechanistic underpinning of these interactions and use of the models to identify specific mediators of resistance will allow for rational future trial design.

MODL-21. INTEGRATIVE APPROACHES IN FUNCTIONAL GENOMICS TO IDENTIFY GENETIC DEPENDENCIES IN PEDIATRIC BRAIN CANCER

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The precise decoding of human genomes facilitated by the advancements in next-generation sequencing has led to a better understanding of genetic underpinnings of pediatric brain cancers. Indeed, it is now evident that tumours of the same type harbour distinct driving mutations and molecular aberrations that can result in different prognosis and treatment outcomes. The profounder insight into the the identity, amount and types of molecular aberrations has paved the way for the advent of targeted therapies in precision medicine. Nevertheless, less than 10% of pediatric cancer patients harbour actionable mutations. Strictly limited therapeutic options that are firstly available for brain cancers and secondly acceptable for children's development further impede the breakthrough in the survival rate in pediatric brain cancers. This underscores a desperate need to delve beyond genomic sequencing to identify biomarker coupled therapies that not only featured with treatment efficacy in the central nervous system but also acceptable side effects for children. The Hudson-Monash Paediatric Precision Medicine (HMPPM) Program focuses on utilising genetic profiles of patients' tumour models to identify new therapeutic targets and repurpose existing ones using high-throughput functional genomics screens (2220 drugs and CRISPR screen of 300 oncogenic genes). Using a large compendium of over sixty patient derived paediatric brain cancer models, we provide proof-of-concept data that shows an integrative pipeline for functional genomics with multi-omics datasets to perform genotype-phenotype correlations and, therefore, identify genetic dependencies. Herein, using several examples in ATRT, DIPG and HGG, we show how functional interrogations can better define molecular subclassification of tumours and identify unique vulnerabilities.

MODL-22. DEVELOPING A REAL-TIME PERSONALIZED DRUG TESTING PLATFORM FOR PEDIATRIC CNS CANCERS

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INTRODUCTION: The relatively small size of biopsied CNS tumors has presented a historical challenge for real-time drug screens. Moreover, in vivo assessment of drug response does not often benefit patients with aggressive gliomas given the relatively long time (>8 months) of tumor engraftment in the classic mouse PDX models. Here, we aimed to develop an innovative real-time in vivo and in vitro drug screening platform capable of analyzing a minimal number (<1E6) of cells obtained at biopsy. METHODS: Existing primary cells were used to test 6 different culture platforms. The top platform was selected and used to expand tumor cells obtained of DMG biopsy. Tumor cells were validated using the minION sequencing platform. Single and combination drug (n=7) screens were performed. Effective drugs were further evaluated in zebrafish PDX and non-tumor bearing models to assess efficacy and toxicity, respectively. RESULTS: A total of 8 biopsies were obtained. Successful cell expansion was achieved in 6/8 (75%) and a limited drug screen in 3/6 (50%) of cases. Single and combination drug (n=7) assays identified responder and non-responders to candidate drugs. Systemic toxicity of effective drugs was tested in non-tumor bearing zebrafish. Tumor cells were engrafted in zebrafish providing the opportunity for an in vivo screen. The entire process was completed within 21 days on average. CONCLUSIONS: A novel platform was developed for rapid in vitro and in vivo drug screens of tumor cells obtained at biopsy. This platform will provide the opportunity to establish personalized therapy for heterogeneous cancers including DMGs.

MODL-23. DNA METHYLATION AND COPY NUMBER VARIATION PROFILE FOR CHARACTERIZATION OF PEDIATRIC BRAIN TUMOR PRIMARY CELL LINES

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BACKGROUND: In vitro models of pediatric brain tumors (pBT) are instrumental for both understanding the oncogenic molecular mechanisms and identifying/testing new therapeutic strategies. DNA methylation (DM) is a stable epigenetic modification recently used to classify tumors. We aim to apply DM and Copy Number Variation (CNV) profiling to characterize pBT primary cell lines and tumors. METHODS: We included 36 pBT tissues from different histology (13 LGG, 9 DIPG, 9 HGG, 3 MB, and 2 Ependymomas), paired to their derived primary cultures. Cultures were established in two-dimensional (2D) or three-dimensional (3D) condition, as stem-cell or in serum-supplemented medium. For 9 cultures, both early (P2-P3) and long-term passages (>P4) were considered. Samples were analyzed for DM and CNV profiles using Illumina EPIC arrays and data compared with those of the brain tumor classifier. RESULTS: At early passages all cells retained the same DM and genetic patterns of original tumors, with no differences related to 2D/3D methods or presence of serum in media. Primary cell lines analyzed at > P4 and cultured in serum diverged from the primary tumor. CONCLUSIONS: DM profiles and CNV are useful tools to detect the recapitulation of pBT-derived primary cell-lines from the original tumor. Whatever subgroups tested, results suggest that in vitro models should be passaged as little as possible to retain the epigenetic and genetic alterations of the tumors and thus to be considered relevant for basic and translational biology. Ongoing experiments are aimed to determine how stable DM and CNV are in other conditions/tumor subgroups.

MODL-24. AN ORGANOTYPIC CHUNK CULTURE TECHNIQUE TO STUDY DISEASE MECHANISM AND DEVELOP TARGETED THERAPEUTICS FOR PEDIATRIC ADAMANTINOMATOUS CRANIOPHARYNGIOMA

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BACKGROUND: Advances in the treatment of Adamantinomatous Craniopharyngioma (ACP) face challenges with translation to clinical study due to the absence of robust culture models of the disease. We developed a technique for culturing human ACP tissue in an organotypic chunk culture format that retains the tumor microenvironment for a duration sufficient to evaluate potential targeted therapeutics. METHODS: Intraoperatively

collected tumor tissue from pediatric ACP was cut into volumes of approximately 3 mm^3 and rested over a semi-permeable insert placed in the wells of a 6-well plate. Specimens were cultured in (1) Control media, media containing (2) Tocilizumab, (3) Trametinib, and (4) combination of Tocilizumab and Trametinib, for 24 and 96 hours. Specimens were harvested for paraffin embedding, protein and gene expression assays. Supernatants were collected to assay secreted components. Paraffin embedded specimens were sectioned and stained for H&E, Pan-CK, Beta-Catenin, cleaved Caspase-3, Ki-67, and Phospho-ERK. RESULTS: H&E staining revealed characteristic histologic features of ACP with epithelial cells with palisading nuclei, wet keratin and ghost cells. Tumor sections were markedly positive for epithelial cell markers, Pan-CK and Beta-Catenin. Ki-67 and cleaved Caspase-3 were restricted to a small fraction of cells, indicating low index of proliferation and apoptosis under the culture conditions. The response to drug treatments shall be determined using gene expression assays and evaluation of the secreted components. CONCLUSION: The organotypic chunk culture technique appears to maintain the viability and integrity of ACP tumors for several days and may serve as an appropriate model for pre-clinical studies to develop targeted therapeutics for pediatric ACP.

MODL-25. REPLICATION REPAIR DEFICIENT MOUSE MODELS PROVIDE INSIGHT ON HYPERMUTANT BRAIN TUMOURS, MECHANISMS OF IMMUNE EVASION, AND COMBINATORIAL IMMUNOTHERAPY

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Replication repair deficiency (RRD) is the leading cause of hypermutant brain tumours in children. RRD is caused by defects in one of four mismatch repair (MMR) genes and mutations in *POLE* or *POLD1*. Such tumours are resistant to common therapeutic agents and animal models are needed to study RRD in vivo and test novel therapies like immune checkpoint inhibitors (ICIs). To model RRD brain tumours specifically, we engineered a *Pole* mutant mouse model harbouring the S459F mutation (*PoleS459F*). We combined *PoleS459F* mice with conditional *Msh2* knockout (*Msh2LoxP*) and *Nestin-cre* mice. All *Nestin-cre+Msh2LoxP/LoxPPoleS459F/+* mice rapidly succumbed to posterior fossa brain tumours between 8.6 and 12.4 weeks. Importantly, tumours exhibited hallmark "ultrahypermutation" (~350 mutations/Mb) and the corresponding signatures characteristic of human combined MMR and *POLE*-proofreading glioblastoma. Interestingly, *Nestin-cre+Msh2LoxP/LoxPPoleS459F/S459F* mice failed to establish normal cerebella, suggesting such mutational loads may not support normal brain development. Furthermore, *OLIG2-cre+Msh2LoxP/LoxPPoleS459F/+* mice failed to develop tumors. Tumors transplanted into syngeneic vs immunocompromised animals egrafted well orthotopically in the mouse hindbrain but significantly less efficiently when engrafted subcutaneously. Furthermore, immunocompromised and subcutaneous tumors revealed striking differences in mutational burden and clonal architecture, suggestive of nonautonomous immunoediting. Finally, anti-PD1 was sufficient to treat subcutaneously engrafted tumors in immunocompetent animals. This first mouse model of immunocompetent, hypermutant brain tumors can be used to uncover unique characteristics of RRD tumour evolution and allow for immune based therapeutic preclinical testing. Experiments to assess combinational ICIs and other therapeutic interventions in orthotopically transplanted tumors will also be presented.

MODL-26. CHILDREN'S BRAIN TUMOR NETWORK: ACCELERATING RESEARCH THROUGH COLLABORATION AND OPEN-SCIENCE

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The Children's Brain Tumor Network (formerly known as Children's Brain Tumor Consortium- CBTTC) is a global organization pioneering a model of open-science medical research to improve treatment and discover cures. Started in 2011, our objective was to utilize a regulatory, agreement, and governance architecture to remove existing research barriers that slowed down the pace of research and collaboration. Our network now includes 17 institutions working together to empower research. As of December 2019, over 3,600 subjects have been enrolled resulting in collection of over 45,000 specimens. Clinical data collection is longitudinal and includes medical history, diagnosis, treatment, pathology slides and reports, radiology imaging and reports, and outcome data. The tissue is collected flash-frozen, in freezing media, and fresh for the generation of pre-clinical models including cell lines. Blood is collected from the subject, with blood or saliva collected from the parents for germline comparison. Additionally, the Children's Brain Tumor Network- Pediatric Brain Tumor Atlas has generated 952 WGS and RNAseq, 221 proteomics, with annotated clinical data. All of this data, both generated raw and processed data, has been made available broadly to the scientific community via cloud-based platforms, including the Gabriella Miller Kids First Data Resource Portal, Cavatica, and PedCbioportal. As of January 2020, we have 45 approved biospecimen requests and 80 genomic/molecular data requests. In summary, the Children's Brain Tumor Network's goal is to accelerate the pace of discovery by providing resources and expanding the network of scientists working towards a cure.

MODL-27. MEK INHIBITION WITH TRAMETINIB SLOWS PROGRESSION OF MEDULLOBLASTOMA AND ATYPICAL TERATOID RHABDOID TUMOR IN ORTHOTOPIC XENOGRAFT MURINE MODEL

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BACKGROUND: Combination of surgery, chemotherapy, autologous transplantation, irradiation constitutes treatment of CNS embryonal-cell tumors (Medulloblastoma-MBL, atypical teratoid rhabdoid tumor-AT/RT). Targeted agents to improve survival and decrease side effects are necessary. We hypothesize that inhibiting MAPK pathway in MBL and AT/RT may be beneficial. METHODS: IHC(pERK) was performed on clinical tumors. *Trametinib*(MEK inhibitor) was tested on MBL(UW228, D283, DAOY); AT/RT(CHLA06, BT12) cell-lines. Luminescent cell-viability assay was done(72 hrs) and with crystal violet assay(10 days). Orthotopic, xenografts of MBL and AT/RT were made in *NOD-Scid gamma* mice. Mice were given *Trametinib* daily by gavage for 6 weeks(0.6mg/kg b.w). Western blot was performed on protein from cell lines and tumor xenografts incubated with *Trametinib*. H&E staining was done on murine tumors. RESULTS: AT/RT(48%) and MBL(57%); Anaplastic(50%), Desmoplastic(40%), Classic(38%); Group 4(66%), Group 3(20%), SHH(55%), WNT(0%) showed presence of pERK(clinical samples). In-vitro, *Trametinib* completely abrogated the phosphorylation of ERK at 125nM in AT/RT and 50nM in MBL. The IC50 after 10 days exposure was 10nM for AT/RT and 35nM for MBL. *Trametinib* treated mice showed delay in tumor growth and significant survival advantage in both AT/RT (p=0.00336) and MBL (p=0.0069). Murine tumors showed decreased proliferation (H&E). CONCLUSION: *Trametinib* decreased cell proliferation, increased survival in our murine model in both MBL and AT/RT. Pre-clinical results indicate benefits in subgroups of AT/RT and MBL with active MAPK pathway.

MODL-28. IMMUNE PRIMING WITH INTERFERON-Γ COMBINED WITH EPIGENETIC MODULATION IN PEDIATRIC BRAIN TUMORS

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Systemic interferon-γ (IFNγ) has been shown to induce major histocompatibility complex class I (MHC-I) and T cell infiltration in solid tumors in adult patients, demonstrating a potential strategy to abrogate tumor-intrinsic mechanisms of immune escape. Pediatric brain tumors (PBT) may be particularly sensitive to this approach but have a paucity of immunogenic tumor antigens for presentation on MHC-I. Decitabine and other DNA methyltransferase (DNMT) inhibitors promote expression of oncofetal antigens and endogenous immune responses through epigenetic alterations. We tested the convergence of these immune priming mechanisms using a novel combination of IFNγ and decitabine across a spectrum of PBT. Primary human cell lines (Med-411FH, PBT-05FH, GBM-511FH, CCHMC-GBM-1, CCHMC-GBM-4, ATRT-310FH) and murine transgenic models were treated with IFNγ alone or in combination with decitabine and evaluated expression of cell surface MHC-I and PD-L1, interferon response genes (ISGs), and oncofetal antigens. PBT showed exquisite sensitivity to IFNγ, increasing expression of MHC-1/PD-L1 along with ISGs (*TAP1, MX1, IRF1*). Decitabine enhanced IFNγ-induced gene expression of oncofetal antigens NY-ESO-1 and MAGE-A1. In a medulloblastoma flank tumor model, MHC-I was increased by 40-fold following intraperitoneal IFNγ treatment (p=0.01), with a 3-fold increase in PD-L1 (p=0.005) compared to untreated controls. Effect on CD8+ T cell killing and validation in humanized models is ongoing. Immune priming of PBT with IFNγ is feasible and results in more substantial MHC-I upregulation compared to hypomethylating agents alone. These results provide a strong rationale for priming prior to checkpoint inhibition as a compelling therapeutic strategy in immunologically-quiescent PBT.

MODL-29. EVALUATING TUMOR-IMMUNE INTERACTIONS IN MOUSE MODELS OF DIFFUSE INTRINSIC PONTINE GLIOMA

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BACKGROUND: While adult gliomas show some level of immune cell infiltration, diffuse intrinsic pontine glioma (DIPG) is characterized as having an "immune cold" state. We have developed new immunocompetent mouse models of DIPG. These models faithfully recapitulate the pathological hallmarks of DIPG and provides a unique platform to investigate immune modulatory therapies and potential therapeutic benefits of check point inhibitor combination therapies. METHODS: To evaluate the effects of CDK4/6 inhibition (CDK4/6i) on cell proliferation and immune interactions we performed a series of in vitro and in vivo studies using DIPG mouse models. In vitro assays included dose response curves, transcriptional profiling, and MHC1 expression. In vivo preclinical studies treated mouse models with CDK4/6i with or without immune check-point inhibitors (ICI). We also examined other candidate immune modulatory therapies in vitro. RESULTS: CDK4/6i (Abemeciclib) reduced proliferation of DIPG cells derived from mouse models, and displayed a modest increase in immune activation by MHC1 expression and transcriptome. Pilot in vivo preclinical studies did not show any significant changes in DIPG proliferation or immune changes with CDK4/6i treatment, ICI treatment, or the combination of CDK4/6i + ICI. In vitro testing of other immune-modulatory drugs identified additional candidates that can be tested in vivo. CONCLUSION: CDK4/6i displayed in vitro action, but lacked efficacy in DIPG mouse models in vivo. Further use of spontaneous DIPG mouse models will provide a rapid preclinical platform to evaluate in vivo tumor-immune interactions, drug efficacy, and mechanisms of resistance.

MODL-30. DISSECTING THE ROLE OF MULTI-CILIOGENESIS NETWORK IN CHOROID PLEXUS TUMOR

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The choroid plexus (CP) in brain ventricles consists of a fibro-vascular core encapsulated by epithelial cells that possess clusters of primary cilia on cell surface. CP tumors are rare primary brain neoplasms that most commonly occur in young children. Compared to the benign CP papilloma, choroid plexus carcinoma (CPC) is poorly understood and highly lethal with few treatments available. Molecular, cytogenetics and genomics studies uncovered complex alterations in CPC including frequent chromosomal loss and recurrent focal aberrations, whereas abnormal NOTCH signaling is observed in many CP tumors. We showed that activation of both NOTCH and Sonic Hedgehog (SHH) signaling in mice drives the formation of aggressive CP tumor. Molecular and histology analyses demonstrated that these murine CP tumors closely resemble their human counterparts, which also display aberrant SHH and NOTCH signaling, suggesting they may represent potential therapeutic avenues. Indeed, treatment with vismodegib, an FDA-approved SHH pathway inhibitor, suppresses CP tumor growth. Unlike multi-ciliated CP epithelial cells, tumor cells in these animal models are characterized by a solitary primary cilium. Though key genes of the multi-ciliogenesis circuit driven by Geminin coiled-coil domain-containing protein 1 (GEMC1) are expressed in CP epithelium, GEMC1-dependent transcriptional program is suppressed in NOTCH-driven CP tumors. Importantly, CPCs in humans consist of tumor cells with a solitary primary cilium and exhibit profound defects multi-ciliogenesis program. Together, these results indicate that a solitary primary cilium is crucial for CPC development, whereas multi-ciliogenesis circuit possesses tumor suppressive functions and may represent a novel therapeutic target in CPC.

MODL-31. RADIATION-DERIVED TREATMENT-RESISTANT PDX AND CELL CULTURE MODELS RECAPITULATE THE CHARACTERISTICS OF MATCHED PRIMARY/RECURRENT PEDIATRIC HIGH-GRADE GLIOMA

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BACKGROUND: Pediatric high-grade glioma (pHGG) is the most common cause of childhood cancer death. Recurrence after therapy is a major challenge, since recurrent pHGG proliferates aggressively and resists therapy. We developed and validated preclinical models of matched primary and recurrent tumors, providing a method to study recurrence and potential therapies. METHODS: We irradiated H3K27M thalamic pHGG cells (BT245) (8 Gy/week,2Gy fractions x3 weeks) and propagated the surviving cells (BT245R). We developed a murine recurrence model by orthotopically implanting BT245 cells, irradiating the resultant tumors (4 Gy/day x2d) and propagating irradiated (BT245RM) or control (BT245CM) tumor cells at endpoint. We performed phenotypic analyses, RNA-Seq, and drug testing. RESULTS: BT245R cells were more stemlike than BT245, with an 8-fold greater rate of neurosphere formation (p<0.03). Geneset enrichment analysis showed similar molecular changes in BT245RM cells and primary/recurrent H3K27M pHGG patient sample pair, including relaxation of the G2/M cell cycle checkpoint (Hallmark_G2M_Checkpoint: BT245RM NES=-5.95, FDR=0.0; patient NES=-5.86, FDR=0.0), downregulation of MYC targets (Hallmark_MYC_Targets_V1: BT245RM NES=-7.43, FDR=0.0; patient NES=-5.86, FDR=0.0), and decreased differentiation (Go_Regulation_of_Stem_Cell_Differentiation: BT245RM NES=-3.35, FDR=0.0; patient NES=-3.15, FDR=0.0). Enrichment of the protein_kinase_C_signaling in BT245RM (NES=2.18,FDR=0.03) suggested response to MAPK pathway inhibition. BT245R cells were twice as sensitive as BT245 cells to the MEK inhibitor trametinib (p<0.05). CONCLUSIONS: Our neurosphere and murine orthotopic patient-derived xenograft models recapitulate gene expression changes of matched primary/recurrent pHGG. RNA-Seq analysis validated the model against patient samples and identified trametinib as potentially effective in recurrent pHGG.

NEUROFIBROMATOSIS

NFB-01. FUNCTIONAL CHARACTERIZATION OF ATRX LOSS IN NF1-ASSOCIATED GLIOMA AND MPNST

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To identify the biologic relevance of ATRX loss in NF1-associated gliomagenesis, we studied the effects of *Atrx* loss using four previously characterized $Nf1^{+/-}Trp53^{+/-}$ murine glioma lines. Lines 130G#3 and 158D#8 (corresponding to grade IV and III gliomas, respectively) displayed preserved ATRX protein expression compared to NIH-3T3 cells. We studied the effects of *Atrx* knockdown in these two lines in the presence and absence of the TERT inhibitor, BIRBR1532. Using a telomere-specific FISH assay, we identified increased signal intensity after *Atrx* knockdown, only in the presence of the TERT inhibitor. These features are reminiscent of ALT, although there were no significant alterations in cell growth. Next, we studied the effect of *ATRX* loss in MPNST lines ST88-14, NF90-8, STS-26T. These cell lines all expressed ATRX and DAXX. However, STS-26T contained a TERT promoter mutation and ST88-14 had a known SNP in the *TERT* promoter, while NF90-8 had no alterations. ATRX siRNA knockdown showed no significant effects in cell proliferation or apoptosis. However, *ATRX* knockdown resulted in rare ultra-bright foci, indicative of ALT. Next, we studied the *in vitro* effect of the ATR inhibitor VE-821 in MPNST cell lines. Only NF90-8 (lacking *TERT* alterations) demonstrated a decrease in growth after ATRX knockdown and VE-821 treatment. However, ATRX

knockdown alone did not affect sensitivity to carboplatin. Our findings further support a role for ATRX loss with subsequent ALT activation in a biologic subset of NF1-associated malignancies, thereby opening an opportunity for therapeutic targeting of these aggressive tumors using specific classes of drugs.

NFB-02. TREATMENT OF PAIN AND TUMOR GROWTH IN NF2

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BACKGROUND: Neurofibromatosis Type 2 (NF2) is an autosomal dominant disorder characterized by multiple nervous system tumors. Chronic pain affects the majority of patients with NF2 and is the primary factor that contributes to decreased quality of life. There are limited therapies that effectively reduce pain in NF2, but intravenous (IV) bevacizumab has been reported to provide significant relief to patients suffering from debilitating pain. CASE STUDY: James is a 24-year-old who initially presented with manifestations of NF2 at age 10, and by 15 years old had developed daily pain affecting his neck, back, and lower extremity. He has multiple CNS schwannomas, meningiomas, neurofibromas, and meets clinical NF2 criteria. While genetic testing did not reveal a mutation in his gDNA, low level skipping of exon 4 via RNA supports (likely mosaic) NF2. James's pain was poorly controlled with multiple oral medications, including opioids. James started IV bevacizumab at age 16 that improved his pain. He was critically dependent on bevacizumab for pain control and required continuous IV pain medication when bevacizumab was held for a surgical procedure. Following five years of bevacizumab he developed worsening toxicities including hypertension, proteinuria, and elevated hemoglobin. James transitioned to therapy with trametinib, a MEK inhibitor, and was able to wean off bevacizumab six months later. Treatment of NF2 related pain with trametinib instead of bevacizumab has improved his QOL with decreased medical visits, improved pain management, and decreased side effects. FUTURE IMPLICATIONS: Treatment of NF2 tumor related pain can be managed with MEK inhibitors.

NFB-03. TRAMETINIB FOR ORBITAL PLEXIFORM NEUROFIBROMAS IN YOUNG CHILDREN WITH NF1

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Plexiform neurofibromas (PN) in NF1 are diagnosed in early childhood and may grow rapidly during this period. In 10% of patients they involve the orbital-periorbital area and may cause visual problems including glaucoma and visual loss from amblyopia (deprivational, strabismic, or refractive), optic nerve compression or keratopathy. Ptosis, proptosis and facial disfigurement lead to social problems and decreased self-esteem. Complete surgical removal is usually impossible and there is a tendency for regrowth after debulking. Recently inhibitors of the RAS/MAPK pathway have been investigated for their activity in PN. We describe 5 young children with NF1 and PN of the orbital area treated with the MEK inhibitor trametinib followed clinically and by volumetric MRI. Treatment was initiated at mean age 26.8 months (SD ±12.8) and continued for median 25 months (range 17– 48). Reasons for initiating treatment were visual compromise and progressive tumor growth. Doses were as recommended. One child reported decreased orbital pain after one week and another, with involvement of the masseters, had increased ability to chew food. Toxicities were mostly to skin and nails grades 1–2 as expected. Additionally, 60% had debulking surgery of preseptal eyelid tumor in first year of medical treatment. Volumetric MRI measurements showed reduction of 8–26% at 1 year from baseline with a maximal reduction of 45% in two patients at 22 & 45 months. No change in visual function was recorded following treatment initiation. In conclusion, trametinib may decrease tumor size in young children with orbital PN and may prevent progressive disfigurement.

NFB-04. EXAMINING DIFFUSION, ARTERIAL SPIN-LABELED PERFUSION, AND VOLUMETRIC CHANGES IN THE NEUROFIBROMATOSIS TYPE 1 BRAIN USING AN ATLAS-BASED, MULTI-PARAMETRIC APPROACH

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BACKGROUND: Neurofibromatosis Type 1 (NF1) is a multisystem disorder with wide ranging clinical implications. Patients may present with macrocephaly, stroke, and cognitive deficits, all of which may impede normal neural development. We applied atlas-based, multi-parametric MRI analysis of regional brain to evaluate diffusion, arterial spin-labeled (ASL) perfusion, and volumetric changes in children with NF1. METHODS: Children evaluated for NF1 from 2009 to 2018 at Stanford University (n=78) were retrospectively reviewed and compared to healthy controls (n=100). All patients underwent diffusion-weighted (DWI) magnetic resonance imaging at 3T, and children with brain tumors were excluded. Using atlas-based DWI analyses, we assessed volume, median apparent diffusion coefficient (ADC), and cerebral blood flow in the cerebral cortex, thalamus, caudate, putamen, globus pallidus, hippocampus, amygdala, nucleus accumbens, brain stem, and cerebral white matter. We also measured volume of the lateral ventricles. Multivariate analysis of covariance was used to test for differences between controls and NF1 patients, controlling for gender and age at time of imaging. RESULTS: Comparing NF1 to controls, we detected increased volume and decreased ASL cerebral blood flow in white matter and all subcortical and cortical structures except for brainstem volume. Median ADC was also increased in the thalamus, pallidum, hippocampus, and brainstem. CONCLUSIONS: Using a multi-parametric approach, we demonstrate quantitative measures of microstructural and physiologic changes of the NF1 brain. Atlas-based, quantitative MRI brain signatures may serve as biomarkers of neural development and further provide insight into associated cognitive dysfunction or risks for vasculopathy-related strokes in children with NF1.

NFB-05. AN UNUSUAL PRESENTATION OF RECURRENT LANGERHANS CELL HISTIOCYTOSIS OF THE CRANIOFACIAL BONES IN A PATIENT WITH NEUROFIBROMATOSIS TYPE I

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Neurofibromatosis type 1 (NF1), predisposes patients to benign and malignant tumors due to lack of suppression of the mitogen activated protein kinase (*MAPK*) signaling pathway. Langerhans cell histiocytosis (LCH) manifests in numerous ways, from localized lesions to multisystem organ involvement secondary to a constitutively active *MAPK* signaling cascade often driven by *BRAF* mutations. While both LCH and NF1 are characterized by overactive *MAPK* signaling, there are few reports of the two diseases occurring simultaneously. We report a novel case of a patient with underlying NF1 and recurrent LCH without a *BRAFV600E* mutation. She initially presented at 2 years of age with an aggressive appearing mass of the left temporal bone found on surveillance imaging. Pathology was consistent with Langerhans histiocytosis and she was treated with the LCH-III protocol for patients with high-risk LCH due to the location of her lesion. Five years after completion of therapy, MRI demonstrated development of a calvarial mass consistent with relapsed LCH in a new risk site. Lesional curettage was performed and pathology confirmed recurrence of LCH with juvenile xanthogranulomatous features. *BRAF* testing of blood and the lesion were negative for any *BRAF* alterations. Further genomic evaluation of the tumor is in progress at this time to evaluate for other known mutations associated with LCH. The patient is currently receiving monthly cytarabine treatment which she has tolerated to date. Our patient represents a unique presentation of recurrent LCH in a patient with NF1 and further molecular evaluation may help identify other drivers of LCH activation.

NFB-06. TREATMENT CHALLENGES IN PEDIATRIC GLIOBLASTOMA MULTIFORME WITH CONCURRENT SOMATIC AND GERMLINE NF1 MUTATIONS WITH GERMLINE MISMATCH REPAIR MUTATIONS: TWO UNIQUE CASES

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INTRODUCTION: We report the first known cases of pediatric glioblastoma (GBM) with prior clinical NF1 diagnoses, one with concurrent germline Lynch syndrome (LS) and NF1, and the other with somatic NF1 mutation and germline constitutional mismatch repair deficiency (CMMRD). METHODS: Two pediatric GBM cases with prior NF1 clinical diagnoses based on neurocutaneous criteria were reviewed. Next generation sequencing and immunohistochemical staining were used for somatic and germline *NF1* and MMR gene mutation detection, and for MMR protein expression, respectively. RESULTS: Sixteen year old male with prior NF1 clinical diagnosis had resection of right frontal GBM revealing somatic mutations of POLE and PMS2, but not NF1. His father had confirmed LS with MSH2 mutation and no neurocutaneous stigmata. Patient's germline testing revealed both pathogenic MSH2 plus NF1 mutations confirming LS and NF1. Treatment consisted of chemoradiation with temozolomide followed by adjuvant temozolomide with stable disease at 8 cycles. Nineteen year old male with former NF1 clinical diagnosis had 2 GBMs, first in left midbrain biopsied revealing somatic PMS2 and NF1 mutations underwent radiation then 7 cycles of temozolomide, then new left frontal GBM underwent re-

section followed by radiation and 5 cycles of pembrolizumab stable at 5th cycle. CONCLUSION: Children with NF1 stigmata and GBM can have concurrent NF1 and LS, or CMMRD with NF1 somatic mutations. Our patients tolerated alkylating agents, despite risk for secondary malignancies as upfront therapy and at recurrence checkpoint inhibitors. Upfront therapy in GBM with mismatch repair syndrome with checkpoint inhibitors should be studied.

NFB-07. USE OF PEGYLATED INTERFERON A- 2B IN PEDIATRIC PATIENTS AFFECTED BY UNRESECTABLE PLEXIFORM NEUROFIBROMAS: MONOCENTRIC EXPERIENCE

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BACKGROUND: Neurofibromatosis type 1 (NF1) is autosomal dominant neurogenetic disorder characterized by progressive cutaneous, neurologic, skeletal, and neoplastic manifestations. Plexiform neurofibromas (PN) are one of the different types of neurofibromas that occur in these patients. Complete surgical resection is difficult due to the tumor infiltrative behavior. We evaluated pegylated interferon- α-2b (PI) in patients with unresectable progressive or symptomatic PN. METHODS: Pediatric patients (1–21 years old) affected by unresectable PN, followed at Bambino Gesù Hospital, were treated with PI. We administered PI as a weekly subcutaneous injection at a beginning dose of 1.0 mcg/kg/wk, increased to 3.0 mcg/kg/wk if well tolerated. Paracetamol (15mg/kg) was given 30 minutes prior the dose of PI and then every 4–6 hours as needed. Patients were evaluated with Magnetic Resonance Imaging (MRI) every 12 months after treatment start in case of stable disease. RESULTS: 10 patients (3 females, 7 males) were enrolled. Median age was 12 years old. The median duration of treatment was 12,6 months. Grade 3 neutropenia (30%) and increased liver transaminases level (20%) were the most common toxicity. 6/10 patients experienced an improvement about pain. 7/10 patients showed clinical response. 1/10 patient had a radiological response at MRI, 1/10 experienced progression disease and 8/10 showed a stable disease at MRI evaluation. CONCLUSIONS: Our study demonstrated that PI could be a suitable treatment for unresectable PN in terms of stabilization of the tumour size due to its antitumor activity although clinical response does not correlate with radiographic changes.

NFB-08. PHASE II STUDY OF AXITINIB IN PATIENTS WITH NEUROFIBROMATOSIS TYPE 2 AND PROGRESSIVE VESTIBULAR SCHWANNOMAS

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INTRODUCTION: Vascular endothelial growth factor receptor (VEGFR), platelet derived growth factor receptor (PDGFR), and c-KIT represent clinically and/or preclinically validated molecular targets in vestibular schwannomas. We conducted a single institution, prospective, open-label, two-stage phase II study (ClinicalTrials.gov identifier NCT02129647) to estimate the response rate to axitinib, an oral multi-receptor tyrosine kinase inhibitor targeting VEGFR, PDGFR and c-KIT, in neurofibromatosis type 2 (NF2) patients with progressive vestibular schwannomas (VS). METHODS: NF2 patients older than 5 years with at least one volumetrically measurable, progressive VS were eligible. The primary endpoint was to estimate the objective volumetric response rates to axitinib. Axitinib was given continuously in 28-day cycles for up to of 12 cycles. Response was assessed every 3 months with MRI using 3-D volumetric tumor analysis and audiograms. Volumetric response and progression were defined as ≥20% decrease or increase in VS volume, respectively. RESULTS: Twelve eligible patients (ages: 14–56 years) were enrolled on this study. Seven of twelve patients completed 12 cycles (range: 2 to 12 cycles). We observed two imaging and three hearing responses. Best volumetric response was -53.9% after nine months on axitinib. All patients experienced drug-related toxicities, the most common adverse events were diarrhea, hematuria and skin toxicity, not exceeding grade 2 and hypertension, not exceeding grade 3. CONCLUSIONS: While axitinib has modest anti-tumor activity in NF2 patients, it is more toxic and appears to be less effective compared to bevacizumab. Based on these findings, further clinical development of axitinib for this indication does not appear warranted.

NFB-09. ENROLLMENT AND CLINICAL CHARACTERISTICS OF NEWLY DIAGNOSED, NEUROFIBROMATOSIS TYPE 1 ASSOCIATED OPTIC PATHWAY GLIOMA (NF1-OPG): PRELIMINARY RESULTS FROM AN INTERNATIONAL MULTI-CENTER NATURAL HISTORY STUDY

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INTRODUCTION: Because treatment and clinical management decisions for children with NF1-OPG remain challenging, we sought to establish evidence-based guidelines. We prospectively enrolled children with newly-diagnosed NF1-OPGs, and gathered standardized clinical neuro-oncology and ophthalmology assessments. METHODS: Only children with NF1 and newly diagnosed OPGs, confirmed by central review, were eligible. Indications for obtaining the initial MRI, as well as factors associated with the decision to treat with chemotherapy or observe without treatment, were obtained. Quantitative visual acuity (VA), other ophthalmic features, and imaging were captured at standard time points. Goal enrollment is 250 subjects. RESULTS: One-hundred thirty-three children (52% female) from 20 institutions met inclusion criteria, and were included in this preliminary analysis. Eighty-six percent of subjects were able to perform quantitative VA testing at enrollment. The most common reasons for the diagnostic MRI included screening related to NF1 diagnosis (36.8%), ophthalmologic concerns (29.3%), and non-ophthalmologic concerns (24.8%), such as headache. To date, twenty subjects have initiated treatment with chemotherapy, twelve (9%) at the time of the initial OPG diagnosis. Median age at OPG diagnosis was 3.1 years. Age and sex distribution were similar in subjects immediately entering the observation and treatment arms (median age 3.0 versus 3.5 years, respectively). CONCLUSION: Most children with NF1-OPGs are observed at time of their initial OPG diagnosis, rather than treated. Importantly, a large proportion of children are able to complete quantitative VA testing at enrollment. Once enrollment is complete, these data will help to establish evidence-based guidelines for clinical management of NF1-OPGs.

NFB-11. WHITE MATTER DIFFERENCES IN CHILDREN WITH NF1 COMPARED TO CONTROLS

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INTRODUCTION: Neurofibromatosis type 1 (NF1) is a genetic condition in which children develop learning challenges and glioma. White matter tracts (WMT) are implicated in these cognitive functions, while oligodendroglial precursor cells are implicated in both gliomagenesis and white-matter development. Specific WMTs have not been well characterized in NF1. METHODS: Twenty NF1 patients aged 1.4–17.6 years (M = 9.5 years, 24 male) and 20 age-and-sex-matched controls underwent dMRI at 3T (25 directions, b=1000 s/mm^2). Automated segmentation of WMTs extracted fractional anisotropy (FA) and mean diffusivity (MD) of 18 major WMTs. Covariance analysis examined the effect of group (NF1/controls) on FA/MD after controlling for intracranial volume. Regression analyses for WMTs determined the interaction of FA/MD with age for NF1 patients compared to controls. Significance was set at $p<0.05$ after correcting for multiple comparisons using false discovery rate. RESULTS: Compared to controls, children with NF1 had significantly decreased FA in 8 and increased MD in 12/18 tracts. Differences held after controlling for intracranial volume. The interaction between group and age accounted for a significant proportion of the variance in FA in 9 and in MD in 16/18 tracts. FA and MD differ-

ences between children with NF1 and controls were greater at younger than older ages. CONCLUSION: Microstructural differences were observed in WMTs in children with NF1 compared to controls. These differences were not explained by intracranial volume and were most pronounced in younger children with NF1 compared to controls. These findings have implications for understanding neurocognitive deficits and gliomagenesis observed in children with NF1.

NFB-12. TRAMETINIB THERAPY FOR PEDIATRIC PATIENTS WITH REFRACTORY LOW GRADE GLIOMA OR EXTENSIVE SYMPTOMATIC PLEXIFORM NEUROFIBROMA

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OBJECTIVE: Refractory symptomatic plexiform neurofibromas (PNF) and inoperable refractory low grade gliomas (LGG) pose a clinical challenge that may be life threatening. Phase 1 and 2 clinical trials of MEK inhibition with selumetinib in inoperable PNF and LGG have demonstrated promising results in pediatrics, however access has been limited to enrollment on clinical trial. Phase 1 clinical trial for trametinib a MEK 1 and 2 inhibitor has been completed, publication is pending. Thus we have treated a series of children on a compassionate basis with extensive PN or LGG refractory disease with trametinib, as this is available in Canada. METHODS: We have treated children with trametinib on a compassionate basis in our province since 2017. Review of the clinical data regarding this therapy has been IRB approved. RESULTS: Two young patients were treated for indication of life threatening extensive PNF and have had tumor shrinkage and improvement of clinical status. Treatment has been complicated by paronychiae, eczema exacerbation, chondrodermatitis nodularis helicis, RSV and influenza B infection and CTCAE grade 2 pneumonia. In spite of the side effects these two patients remain on treatment due to clear benefit from therapy including: improved respiratory compromise, hearing and dysphagia. We will present the data of additional patients treated with trametinib. CONCLUSION: Trametinib is an effective therapy for life threatening PNF by changing the natural history of tumor growth in young children. Further data is required in terms of tolerance, efficacy and durability of response in such patients in the setting of clinical trials.

NFB-13. TRAMETINIB FOR PLEXIFORM NEUROFIBROMA AND RECURRENT LOW-GRADE GLIOMA

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BACKGROUND: Based on early clinical efficacy data, Seattle Children's established a standard clinical practice for MEK inhibitor therapy for children with plexiform neurofibroma (PN) or recurrent low-grade glioma (LGG). METHODS: Data were collected under an IRB-approved retrospective chart review. Trametinib was prescribed off-label at 0.025 mg/kg daily for up to two years. Physical exam and laboratory monitoring were monthly for 3 months, then every 3 months. Retinal examination, ECHO/ECG were every 3 months. Tumor response was evaluated by MRI every 3 months for LGG; imaging for PN was dependent on tumor location. RESULTS: 30 patients received trametinib; 17 LGG, 16 PN (3 both); 22 with Neurofibromatosis, Type-1 (NF1); 16 female/15 male; median age 11 (range 4.1–22.6). Most common tumor location was optic pathway (n=11) and face/neck (n=10). Most common adverse events (AE) were dermatologic and gastrointestinal. Ten had dose interruption/reduction, only one discontinued therapy for AE. Six received dermatology specialty care for AE. With median follow-up of 12 months, only 3 patients had progression, one with NF1. One-year EFS was 100% for PN and 88%+7 for LGG. Driver mutations were identified in 9 of 10 tumors tested (5 BRAF fusion, 1 BRAFV600E, 1 FGFR1+NF1, 1 FGFR1+PTPN11, 1 NF1). Radiology review of response will be presented. CONCLUSIONS: This real-world pediatric cohort supports efficacy and tolerability of MEK inhibitor therapy for short-term control of plexiform neurofibroma and low-grade glioma with and without NF1. Further studies are warranted to evaluate comparative efficacy, combination therapy and duration of therapy.

NFB-14. PSYCHOSOCIAL OUTCOMES IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1 AND PLEXIFORM NEUROFIBROMAS

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OBJECTIVE: This case series seeks to examine neurocognitive outcomes, social-emotional functioning, and family burden in young children diagnosed with Neurofibromatosis, type 1 (NF1) with early growing plexiform neurofibromas (PNFs). BACKGROUND: Neurofibromatosis, type 1 (NF1) is a common predisposing chronic disease arising in early childhood, with an incidence of approximately 1:3000. Though NF1 displays a wide range of phenotypic variability, the primary feature of the disease is peripheral nerve sheath tumors called neurofibromas. Less is well known regarding the broader neurocognitive and social-emotional profile in presentations with more complex tumor growths, namely PNFs, which are present in at least half of the NF1-affected population. METHODS: Participants with NF1 and PNFs (n=2) aged 6-7years completed comprehensive neuropsychological evaluations and parents completed measures of quality of life, social-emotional/behavioral functioning of child, parental stress, family adaptability, and family cohesion. RESULTS: Outcomes suggest broad neurocognitive dysfunction (e.g., executive functioning deficits, attention problems, visual-motor delays, and poor motor coordination), social-emotional challenges (e.g., symptoms of anxiety and depression, and poor social skills), and familial distress. CONCLUSIONS: Findings indicate the value of early and frequent monitoring of children with PNFs in medical systems and multi-disciplinary teams, and the importance of early intervention for both children and families.

NFB-16. MTOROPATHIES AND SUBEPENDYMAL GIANT CELL ASTROCYTOMAS: PREDICTIVE VALUE OF GERMINAL TSC1/2 MUTATIONS SCREENING IN FAMILIAL CASES

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mTOR controls several important aspects of cell function particularly in the nervous system. Its hyperactivation has been involved in tuberous sclerosis complex (TSC) and other mTORopathies as well as drug-resistant epilepsy. Mutations in TSC1 and TSC2 genes cause loss of normal inhibition of mTORC1 complex, leading to cell overgrowth and disruptions in synaptogenesis. Many children and adults with TSC harbour neurologic defects especially subependymal giant cell astrocytomas (SEGAs) in the brain. Here, we have performed mutational analysis followed by a genetic counselling for a Tunisian family from Sfax town harboring epileptic seizures associated to a neurocutaneous disorder. Index cases were referred for renal angiolipomas (RAL) associated to seizures crisis and were diagnosed as having TSC. The first 26-year-old patient complained of epilepsy since the age of 22 with left temporal crisis related to cortical tubers near the Heschl's gyrus. His brother, a 36-year-old man presented more severe epileptic crisis (since 15 years-old), multiples RAL, subependymal nodules, and a rapid evolution of his mTORopathy with tumoral progression of his renal and central nerve lesions: renal cell carcinoma and SEGAs. TSC1 gene mutation screening showed heterozygous two bp deletion at codons 213 and 214 of exon 5. SEGAs are rare, low-grade glioneuronal brain tumors that occur almost exclusively in TSC patients but can lead to nervous complications. We showed through this report, the predictive value of germinal TSC mutations screening in familial cases, because early recognition of the molecular defect may lead to appropriate management of the tumoral progression.

NFB-17. MEK INHIBITOR BINIMETINIB SHOWS CLINICAL ACTIVITY IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1-ASSOCIATED PLEXIFORM NEUROFIBROMAS: A REPORT FROM PNOC AND THE NF CLINICAL TRIALS CONSORTIUM

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BACKGROUND: Plexiform neurofibromas (PNs) can cause significant morbidity. In this phase 2 study, we assessed imaging and functional outcomes to the MEK-inhibitor Binimetinib in pediatric patients with PNs. METHODS: Children (age 1–17 years) with PN that were progressive or causing significant morbidity were eligible. Binimetinib is dosed twice-daily (starting dose of 32mg/m^2) for maximum of 24 four-week courses. Participants with partial response (PR; >20% decrease in PN volume on central MRI review) at cycle 12 may stay on therapy. Participants undergo MRI and functional assessments at baseline and after courses 4, 8, 12, 18 and 24. Functional assessments are based on PN location. RESULTS: Here we present 1-year response data. Twenty participants (55% male) with median age 12 years (range 2–16 years) enrolled; 19 are evaluable for response. Median baseline tumor volume was 326 ml (range, 8-6661 ml). Fourteen participants (74%) met criteria for PR, with 11 achieving PR by course 5. Median maximal PN volume reduction was 25.5% (range, 9–54%). As of August 2020, 14 participants received at least 12 cycles of Binimetinib; 10 remain on therapy. Off study reasons include treatment associated toxicities (n=2), subject withdrawal (n=2), non-compliance (n=2), prolonged treatment delay (n=1), and lack of response (n=3). Thirteen participants underwent dose reduction. Institution-reported related grade 3 toxicities included dry skin, weight gain, muscle weakness, rash, paronychia, cellulitis, diarrhea, gastric hemorrhage and CPK increase. CONCLUSIONS: Binimetinib appears reasonably well-tolerated and shows promising activity in children with NF1-associated PNs. Outcomes on functional improvement will be reported at the meeting.

NFB-18. IMMUNE FUNCTION IN CHILDREN TREATED WITH TRAMETINIB

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BACKGROUND: Trametinib (Tr) has been applied in the treatment of children with various tumor types, often for prolonged periods. Little is known regarding immune function (IF) following prolonged Tr in this age group. OBJECTIVE: Describe laboratory measures of IF in children on Tr. METHOD: Patients receiving Tr had low grade glioma with BRAF anomalies (6), or neurofibromatosis-1 (16) with glioma or plexiform neurofibroma. IF was evaluated using leukocyte/lymphocyte counts, immunoglobulin levels, and antibody titres. RESULTS: 22 patients received Tr. 2 also received Dabrafenib. Median age at Tr initiation of Tr was 7.75 years. As of June 2020, 7 patients have had IFT; results are pending on 15. Median duration of Tr therapy at time of IF was 3.5 years (0.8 – 4). In these 7 patients, median white cell count was 6.9 x 10^9/L (4.1 – 12.6), neutrophils 4.2 x 10^9/L (1.8 – 6.8) and lymphocytes 3.2 x 10^9/L (1.4 – 7). IgG levels, B cells and CD8 cytotoxic T cells were normal across 7/7 patients:medians 9.47 g/L (8.62 – 17), 0.51 x 10^9/L (0.2 – 1.26) and 0.58 x 10^9/L (0.25 – 2.03) respectively. CD3 and CD4 T cells: median 2.08 x 10^9/L (0.67 – 4.62) and 1.34 x 10^9/L (0.35 – 2.31), borderline low in 1 heavily pre-treated patient. An adequate immune response was present in all 4 vaccine antigens tested in 5/5 patients. CONCLUSION: IF appears relatively intact, relevant for immunisation and infection precautions in children on Tr. Data on the complete cohort will be presented.

NURSING/PATIENT CARE

NURS-01. INTRACEREBROVENTRICULAR DRUG ADMINISTRATION FOR TREATMENT OF PEDIATRIC BRAIN TUMORS

Caroline Fitzgerald, and Kathryn Matson; Boston Children's Hospital, Boston, MA, USA

Intrathecal (IT) chemotherapy, given via lumbar puncture (LP) or an intracerebroventricular (ICV) device has become a safe and effective way to deliver chemotherapy into the cerebrospinal fluid (CSF) space. The blood brain barrier makes treating tumors with CSF dissemination difficult with systemic chemotherapy alone. IT chemotherapy is often necessary for tumors which disseminate into the CSF space including embryonal tumors and choroid plexus carcinomas. It is also used for relapsed or recurrent tumors. Giving IT chemotherapy via an ICV device instead of via an LP can be preferable as it requires no deep sedation and allows for more uniform drug distribution. Drugs given IT include methotrexate, cytarabine, hydrocortisone, etoposide, and topotecan. ICV devices can be placed in patients with adequate CSF flow and a flow study can be done if needed to confirm. Accessing the ICV device for administration of chemotherapy is typically done by a physician or nurse practitioner using sterile technique. Our institution has had success using music therapy and child life specialists for assistance with coping during the procedure as patients are awake. The procedure has few complications the most common being infection usually with skin flora. It can also cause nausea and headache. There are few long term risks.

NURS-02. CLINICAL MANAGEMENT OF PATIENTS RECEIVING CAR T CELL THERAPY FOR CNS TUMORS

Susan Holtzclaw, and Corrine Hoeppner; Seattle Children's Hospital, Seattle, WA, USA

Chimeric antigen receptor (CAR) T cells are an innovative new therapy with proven efficacy in some pediatric cancers such as leukemia and lymphoma, but much less experience in solid tumors, especially tumors of the central nervous system (CNS). Seattle Children's has three open Phase 1 CAR T cell studies (BrainChild-01, -02, and -03 targeting HER2, EGFR, and B7-H3, respectively) for recurrent/refractory CNS tumors and DIPG (BrainChild-03 only). As of December 2019, four patients have been treated at Seattle Children's Hospital with CAR T cells infused on a weekly schedule through indwelling catheters into the tumor resection cavity or ventricular system. Given the scrutiny of clinical care needed for Phase 1 studies, we are now able to report detailed clinical information that we have learned during the treatment of these patients. Clinical care includes the judicious use of steroids, the clinical support of patient's symptoms pre- and post-infusion, and the management of peritumoral edema. We will also discuss the psychosocial support needed for families who travel long distances to receive this therapy compounded by the many emotional components of being enrolled on any Phase 1 trial. Case studies and experience from a Nurse Practitioner role will be provided and discussed.

NURS-03. DEVELOPMENT OF A PATIENT-HELD TREATMENT SUMMARY FOR PAEDIATRIC CNS TUMOUR PATIENTS

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BACKGROUND: Following the Scottish Government Cancer Plan 2012–15*(1)* 'End of Treatment' summaries for paediatric oncology patients treated in SE Scotland have been successfully implemented. However, it became evident that the particular needs of patients with CNS tumours were not adequately captured on the standardised documentation. METHODS: In view of these difficulties an alternative document was prepared specifically for this patient cohort by the multi-disciplinary team, including Nurse Specialists, Paediatric Neuro-oncology and Neuro-psychology. This was designed to be a flexible, fluid summary to be used for all such patients regardless of tumour grade or treatment modality and included those undergoing surveillance only. OUTCOMES: The document is primarily completed by the Neuro-Oncology Nurse Specialist alongside the patient and family, usually following initial treatment and is used alongside their holistic needs assessment. The document is circulated to all involved professionals, including Primary Care, and a copy is retained by the patient. This then provides a concise source of information detailing diagnosis and treatment, any specific ongoing sequelae and details of red flag symptoms to alert patients and health professionals to the potential of relapse or other associated significant health problems. These treatment summaries are currently being piloted and have been well received thus far. They will be formally audited in due course with the aim to use nationally throughout Scotland in future.

NURS-04. COMBINATION OF NEURO-ONCOLOGY AND DERMATOLOGY CLINICS IMPROVE THE MANAGEMENT AND KNOWLEDGE OF SKIN-RELATED TOXICITIES WITH MEK AND BRAF TARGETED THERAPY

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BACKGROUND: The recent advancement in treating pediatric low grade glioma has led to upfront use of MEK and BRAF (MAPK) inhibitor therapy. At the Hospital for Sick Children we are the National leaders in treating pediatric oncology diagnosis with MAPK therapies. DESIGN: After treating several patients on MAPK inhibitors with various degrees of skin toxicity, we found we had poor and inconsistent access to dermatology services and as oncology practitioners had limited front-line knowledge about skin management. It was determined that a more formalized expertise and time with dermatology was needed. In 2018, in combination with the derma-

tology team, our new agents and innovative therapy and the nursing team we collaborated to develop a combined oncology and dermatology clinic. This clinic occurs twice a month to give our families and oncology teams better front-line access to dermatology knowledge and care. RESULTS: The dermatology and oncology team have collaborated to provide information sessions for the oncology medical team about current research, skin grading and education. This combined approach has allowed us to ensure that each new family starting MAPK inhibitor therapy undergoes a baseline skin assessment, education on prophylactic skin measures and easier access to dermatology within their oncology clinic. We are also developing guidelines to consistently treat common skin related toxicities. CONCLUSION: The early involvement of the dermatology clinic and increase knowledge with the nursing and medical team has allowed our families to gain confidence in managing skin related complication and reducing the need to hold targeted therapies as a result of dermatological toxicity.

NURS-06. NURSING PROFESSIONALS AND THEIR AID IN RESEARCH BIOBANKING

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Nursing teams play an integral role in the care of patients with brain tumors; however nurses do not often see themselves as essential contributors to translational research. Recent development of nurse-researcher relationships and involvement of the multidisciplinary team have led to successful biobanking strategies. Though there are challenges associated with fostering these relationships, their vital role has significantly enhanced participant recruitment and sample collection at one large urban Children's Hospital. Researchers at the institution have established a biobank to collect samples from pediatric brain tumor patients at diagnosis, during therapy, and post mortem using conventional methods. However, a collaborative environment between nursing and research teams greatly enhanced the growth of the biobank. We have increased patient recruitment by more than 50% in the past four years and supported different types of specimen collection. Our success entails: 1) development of nurse-researcher relationships, 2) an efficient consent process, 3) streamlined sample collection, and 4) appreciation of the vital role of the nursing team in clinical data collection pertinent to molecular analysis. Additionally, the support of nursing is valuable during post mortem consents and provides emotional support to the family to fulfil their wish to donate. Nurses play a major role in coordination of the post-mortem donation process, and assist in the formation of partnerships within the community to promote this opportunity to families. As biobanking continues to be an important part of bench research, all institutions should recognize and support the vital role that nurses can have in enhancing this endeavor.

NURS-07. STAFF EDUCATION THROUGH NURSING AND PHARMACY COLLABORATION

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Even within the focused field of pediatric oncology, there are healthcare providers who lack education regarding the specialized population of children with brain tumors. In order to improve staff knowledge of pediatric neuro-oncology, nursing and pharmacy developed a collaborative Lunch and Learn program to provide additional education. An eight week brain tumor curriculum was developed, and informal sessions grouped by diagnosis were held over lunch between the neuro-oncology nursing team (nurse practitioners and nurse coordinator) and a clinical pharmacy resident. A nurse practitioner provided academic literature and the pharmacy resident did further research and developed an outline for discussion. During these sessions, nursing was able to contribute academic knowledge and clinical experience, while pharmacy presented an overview of each tumor and provided education about medications. After each session, the pharmacy resident presented the information from the Lunch and Learn to all staff oncology pharmacists, which then increased their working knowledge of neuro-oncology as a whole, helping them feel better able to manage this population within their scope of practice. Because this innovative collaboration was so successful in heightening knowledge and awareness of the care and management of pediatric neuro-oncology patients for all those involved, the team now has future plans to utilize a similar model to provide neuro-oncology education to clinic and inpatient RNs.

NURS-08. A CASE REPORT OF RARE AND PROFOUND ANTEROGRADE AMNESIA IN A PAEDIATRIC SURVIVOR OF A BIFOCAL NON GERMINOMATOUS GERM CELL TUMOUR AND DIABETES INSIPIDUS

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We present the case of a 12yo female who presented to the emergency department with increasing agitation, confusion, fluctuating GCS, hydrocephalus, and deranged electrolytes. MRI revealed tumour in pineal region and filling the third ventricle. Biopsy and tumour markers confirmed the diagnosis of bifocal Non Germinomatous Germ Cell Tumour (NGGCT). The diagnosis was complicated with the secondary diagnoses of diabetes insipidus and profound permanent anterograde amnesia. Whilst DI is common in NGGT in pineal region, anterograde amnesia is a very rare condition in paediatrics. Thus there is paucity of literature available to the clinicians to know how much improvement to expect or how to target rehabilitation whilst undergoing curative therapy, chemotherapy and craniospinal irradiation; however the importance of a consistent and coordinated nursing and allied health team approach with structure and errorless learning must be initiated from the beginning if independence is to be achieved.

NURS-09. INTRODUCTION OF A WELLNESS PROGRAM FOR PEDIATRIC NEURO-ONCOLOGY PROVIDERS

Kaaren Waters[1], Helene Morgan[2], Kasey Rangan[1], Kim Bira[1], Tom Davidson[1,3], Nathan Robison[1,3], and Ashley Margol[1,3]; [1]Cancer and Blood Disease Institute and Division of Hematology-Oncology, Children's Hospital Los Angeles, Los Angeles, CA, USA, [2]Office of Academic Affairs, Children's Hospital Los Angeles, Los Angeles, CA, USA, [3]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

INTRODUCTION: Pediatric oncology providers have unique and rewarding careers. The medical and psychosocial complexity of caring for pediatric oncology patients and their family units is simultaneously inspiring and challenging. In addition, the complex demands of the healthcare system can lead to chronic stress, burnout, and disruption to the healthcare professional's individual well-being. Time constraints, lack of resources, and limited access to wellness interventions serve as barriers for providers to address adaptive coping within themselves. Identifying gaps to achieving wellness and implementing interventions may lead to improved equanimity for pediatric oncology providers in their personal lives as well as their medical practice. METHODS: An interdisciplinary team of nurse practitioners and physicians in a large pediatric neuro-oncology program at an academic institution completed anonymized wellness self-assessments regarding the areas of emotional, environmental, intellectual, occupational, physical, social, spiritual, coping, and professional role wellness. The results were analyzed and barriers to provider health and well-being were identified. Tailored and regularly scheduled wellness interventions were implemented for the study participants addressing the identified wellness barriers. Participants will each complete post-intervention wellness self-assessments to evaluate the effectiveness of the program. CONCLUSION: The introduction of a provider wellness program exemplifies a feasible approach to identify barriers and evaluate efficacy of wellness interventions in achieving multi-factorial provider wellness. Secondary aims include dissemination of findings, with the intention of cultivating improvement in provider quality of life throughout the healthcare profession, and the ultimate goal of improving care to patients and families.

NURS-10. IMPROVEMENTS IN A BEHAVIORAL TRAINING AND PHARMACOLOGICAL ANXIOLYSIS ALGORITHM FOR INCREASED COMPLIANCE IN PEDIATRIC PATIENTS IN PREPARATION FOR RADIATION THERAPY: A RETROSPECTIVE ANALYSIS

Judy Tran[1], Jennifer Holt[1], Danielle Crump[2], Anita Shea[2], Lin Whetzel[3], Andrea Lattimore[1], Rebecca Carson[4], and Roberta Anderson[2]; [1]Sibley Memorial Hospital, Washington, DC, USA, [2]Johns Hopkins Medical Institute, Baltimore, MD, USA, [3]Childrens National Hospital System, Washington, DC, USA, [4]Cincinnati Children's Hospital, Cincinnati, OH, USA

BACKGROUND: In the pediatric population, the probability of compliance with radiation involves multifactorial elements. Younger pediatric patients often require anesthesia to ensure accurate delivery of radiotherapy. The purpose of this analysis was to refine our algorithm in pediatric patients to better identify children who would benefit from behavioral training and/or anxiolysis intervention with the goal of minimizing anesthesia use. METHOD: Retrospective data was collected from electronic medical records from 150 pediatric oncology patients <18 years old, treated with photon and proton radiation at our center from August 2016 to December 2019. We identified potential socio-developmental treatment factors thought to impact behavioral compliance and categorized risk factors based on an algorithm to determine risk for noncompliance with radiotherapy. RESULTS: Six categories demonstrated statistical significance ($p<0.05$) in their influence on behavioral compliance during radiotherapy: age category (specifically age <7: Odds ratio [OR] 3.0, 95% Confidence Interval [CI] 1.0, 9.1), need for sedation with prior imaging studies ($p<0.001$), parental premonition of requiring anesthesia for successful treatment ($p<0.001$), duration of treatment, primary language ($p<0.001$), and use of total body irradiation (OR 3.1, 95% CI 1.1, 9.3). CONCLUSION: Identification of pre-radiation risk factors allowed for better recognition of patients at risk for treatment non-compliance and for requiring daily sedation. Future studies should focus on implementing the algorithm prospectively in an effort to identify

and direct early intervention with behavioral training and/or anxiolytics to minimize the need for sedation.

NURS-11. MARIJUANA, HEMP, AND THE CHILD WITH CANCER: PATIENT, PARENT, AND CLINICIAN EDUCATION

Molly Hemenway; Univ of Colorado, Children's Hospital Colorado, Aurora, CO, USA

Many pediatric oncology patients report medical marijuana (MMJ) and hemp-based CBD use. Eleven states and Washington, DC have legalized marijuana for recreational use for adults greater than 21. Medical marijuana is legalized in 33 states. Additionally, due to the bipartisan Farm Bill passed in December of 2018, hemp is federally legal. Marijuana has medical legalization in 23 countries worldwide. Clinical trials in adults have examined MMJ for cancer-related symptoms. New research is emerging on MMJ in anticancer therapy, MMJ receptors on tumor cells, and the potential role for MMJ as an immunomodulator. Few pediatric oncology studies have evaluated MMJ. We describe the initial findings of a prospective observational study of MMJ on the quality of life (QOL) in pediatric brain tumor patients. Specific aims included (1) MMJ's association with symptoms (nausea, anxiety, pain, fatigue, and cognitive problems) and (2) MMJ's impact on family dynamics. The legality of hemp plus the increasing use of MMJ raises concerns with pharmacological interactions with CBD and the medications routinely administered to children with cancer. Nurses are the frontline for discussions with patients about MMJ and must be aware of the emerging field of MMJ in pediatric cancer. Additionally, nurses can influence patient care protocols and processes for alternative therapy administration enabling an open dialogue between providers, parents, and patients regarding treatments, symptoms, adverse effects, and drug interactions. Education about how to have conversations about important facets to cover and consider is crucial to patient safety and increased quality of life.

NURS-12. MAKING SURVIVORS HEALTHIER: A MULTIDISCIPLINARY APPROACH TO HYPOTHALAMIC OBESITY

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BACKGROUND: Pediatric survivors of hypothalamic/suprasellar tumors have significant morbidities that greatly impact their quality of life. Management of hypothalamic obesity has traditionally fallen between multiple subspecialties without a timely and comprehensive approach. METHODS: A multidisciplinary group of key players from neuro-oncology, endocrinology, nutrition, neurosurgery, and bariatric surgery were identified. Through this collaboration, a clinical algorithm for early identification of and intervention for hypothalamic obesity was developed. The goal of the quality improvement process is to increase the number of encounters with a registered dietitian (RD) with earlier and more consistent referrals to a specialized, multidisciplinary weight management program [Lifestyle Medicine; (LM)] for counseling and pharmacologic interventions. Indications for referral to LM were BMI >95th percentile, crossing >2 BMI percentiles on growth curve and/or hyperphagia symptoms. A retrospective review of pediatric patients who have suprasellar/ hypothalamic tumors was also conducted. Data collected included demographics, tumor type, BMI, RD visit, and LM clinic referral/visit. RESULTS: Fifty patients were identified for analysis six months following clinical algorithm institution. Thirty-three (66%) patients had craniopharyngioma, 15 (30%) had low-grade gliomas, and two (4%) had germ cell tumors. Thirty-three (66%) patients were noted to be obese (defined as BMI >95th percentile) at review. The median BMI of the entire cohort was 93rd (range, 1st-137th) percentile. Thirty-four (68%) patients had been seen by an RD. Twenty-seven (82%) of the obese patients had been referred to LM. CONCLUSIONS: The development and implementation of the process for hypothalamic obesity prevention and intervention will be discussed.

OTHER (NOT FITTING ANY OTHER CATEGORY)

OTHR-02. MULTIMODALITY TREATMENT FOR CHILDREN WITH CENTRAL NERVOUS SYSTEM (CNS) TUMOR IN OUR INSTITUTE

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BACKGROUND: The brain tumor has a highest mortality rate among childhood malignant tumors. Development of peripheral blood stem cell transplant combined chemotherapy and radiation therapy improved the survival rate of patients with pediatric brain tumor drastically late years. Because of its complicated treatment plan, neurosurgeons cannot readily manage these aggressive therapies which require minute whole body control including prevention of lethal infection due to bone marrow suppression. Even if such treatment is effective and patient survives, the aftereffects may reduce patient's QOL. PURPOSE: We report outcomes of the patients with CNS tumor after multimodality treatment. In addition, we introduce the activity contents by the in-hospital children brain tumor multi-disciplinary medical treatment team organized in March 2016. METHODS: We retrospectively reviewed 29 patients (under 15 years old) diagnosed as CNS tumors with total of 43 tumor surgeries between January 2001 and December 2019. RESULTS: The histopathological diagnoses were 7 germ cell tumor, 7 astrocytic tumor, 4 ependymal tumor, 4 medulloblastoma, 2 craniopharyngioma, 2 AT/RT and 3 others. The mean age at first surgery was 7.4 y.o. (range: 0.3–14.8). Both chemotherapy and radiation therapy were performed in 22 cases out of 29. There were 15 survivors (11 ambulant, 3 W/C, 1 bedridden), 12 deaths, 2 lost follow-ups. Mean follow-up period was 66 months (range: 1–206). CONCLUSION: To improve outcomes, we hold on a regular basis of team meeting, discuss treatment plan, and share information. Recently, we also care issues of the patients, such as fertility and palliative medicine.

OTHR-07. CHRONIC ENCEPHALOPATHY DUE TO METHOTREXATE NEUROTOXICITY AS A RARE COMPLICATION IN A CHILD WITH LEUKEMIA: A CASE REPORT

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Methotrexate (MTX) is an essential component of chemotherapy for childhood acute lymphoblastic leukemia (ALL). Both intravenous (IV) and most commonly intrathecal (IT) routes of MTX have been complicated in acute, subacute, and chronic neurotoxicity syndromes. A 9-year-old girl had been diagnosed with standard risk ALL since 2011 with first chemotherapy protocol was Indonesian protocol standard risk ALL 2006 and remission in 2012. On July 2015, patient was diagnosed as relapse ALL and underwent Indonesian protocol high risk ALL 2013. The last chemotherapy protocol of patient was Indonesian protocol high risk ALL 2013 maintenance phase 89th weeks with total dosage of MTX was 336 mg (IT), 6000 mg/m2 (IV), and 2500 mg/m^2 orally. Her presenting symptom was progressive decrease of consciousness since 3 months before hospital admission. First brain computed tomography (CT-Scan) and magnetic resonance imaging (MRI) revealed brain atrophy. One month later she had abnormality in behavior and functional ability with second brain CT-Scan revealed brain atrophy and lacunar infarct in left pons. This case can be in accordance with chronic encephalopathy due to MTX. It is important to recognize early complications taking the form of subclinical or symptomatic CNS damage (e.g. headache, dizziness, tremor, ataxia, aphasia, dysarthria, emotional instabilities, seizures, hemiparesis, encephalopathy) that can occur in the course of chemotherapy especially MTX. Determination of the cause of encephalopathy is associated with considerable difficulty despite the use of various diagnostic methods and also treatment of MTX neurotoxicity is mainly supportive and recovery is usually complete. Keywords: imaging, methotrexate, neurotoxicity, leukemia

OTHR-09. CENTRAL DIABETES INSIPIDUS: A RARE UNREPORTED SIDE EFFECT OF TEMOZOLOMIDE IN PEDIATRICS

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Temozolomide is a chemotherapeutic agent commonly used in the treatment of central nervous system tumors. While there are case reports of temozolomide associated central diabetes insipidus (CDI) in adults, this has not been reported in children. We describe the first case of temozolomide associated CDI in a pediatric patient. The patient was a previously healthy 12yr old male diagnosed with anaplastic astroblastoma. He underwent gross total resection of the lesion and was subsequently treated with focal radiation therapy and concurrent temozolomide. On day 21 of therapy he developed thrombocytopenia, severe polyuria and polydipsia. Temozolomide was held and he underwent a preliminary evaluation for CDI. Initial laboratory findings were concerning for CDI, and he was admitted for further work-up and to assess the need for desmopressin. Additional laboratory tests demonstrated normal anterior pituitary function and his serum sodium normalized

when allowed to drink to thirst, mitigating the need for desmopressin. Temozolomide was not restarted and the symptoms of polyuria and polydipsia resolved and did not recur. Upon review, the tumor did not involve the pituitary or hypothalamus. Additionally, these areas were not involved in the irradiation field. CDI is a rare but clinically significant side effect of temozolomide, reported in adults. Given this is the first report of CDI secondary to temozolomide in a pediatric patient, we speculate that this is likely under-recognized in children. Prompt recognition and treatment is necessary to prevent severe sequelae of hypernatremia.

OTHR-12. ANEURYSMAL BONE CYST RESEMBLING A POSTERIOR FOSSA TUMOR

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We presented the case of a 6-year-old boy who was seen in the emergency room because of signs of intracranial hypertension and left cerebellar syndrome. The CT scan revealed a heterogeneous lesion within the left hemisphere displacing the fourth ventricle and eroding the occipital bone. The MRI showed the same heterogeneous lesion majorly cystic, involving the bone and displacing the left cerebellar hemisphere. A minor hydrocephalus was evident in both studies. A suboccipital craniectomy was done and a cystic epidural tumor remodeling and eroding the bone was noted. The histopathological diagnosis corresponded to an aneurysmal bone cyst. Aneurysmal bone cyst is a rare benign tumor accounting for 3–6 % of tumors of the cranial base. We discuss the unusual location of the lesion.

OTHR-14. DIENCEPHALIC SYNDROME SECONDARY TO PITUITARY STALK THICKENING

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BACKGROUND: Diencephalic syndrome (DS) is a rare condition associated with neoplastic lesions of the sellar-suprasellar region, whose pathophysiological mechanisms are still unclear. DS occurs in <10% of hypothalamic gliomas and has also been described in suprasellar germinomas, craniopharyngiomas, epidermoid cysts, rarely with non-suprasellar lesions such as brainstem gliomas. DS has not been associated with isolated pituitary stalk thickening. Isolated pituitary stalk thickening (IPST) presents a diagnostic challenge, ranging from benign (craniopharyngioma) to malignant lesions (germinoma, metastasis, histiocytoses of the Langerhans group). The coexistence of diabetes insipidus (DI) with anterior pituitary dysfunction and IPST implies more risk to harbor neoplasia. CASE REPORT: A 6-year old girl presented with DI and inadequate weight gain (despite regular caloric intake) and preservation of linear growth. Neurological examination showed no abnormalities. However, physical examination revealed a malnourished patient (both weight-for-age value and body-mass-index below the third percentile). Blood tests and negative IgA anti-endomysial antibodies excluded malabsorption as a cause of her malnutrition; endocrine work-up excluded thyroid dysfunction, growth hormone deficiency, and adrenal insufficiency. Magnetic resonance imaging (MRI) showed thickening of the pituitary stalk with a transverse diameter of 7 mm. The patient underwent a biopsy through a supraorbital eyebrow approach. Histopathological examination revealed lymphocytic hypophysitis, with tissue markers all negative for germinoma. The girl is currently under follow up with serial MRI every three months. CONCLUSION: DS should be considered as a differential diagnosis in any child with failure to thrive, and imaging studies should be performed even if there are no additional neurological symptoms.

OTHR-16. CONCURRENT USE OF APREPITANT AND IFOSFAMIDE IN PEDIATRIC CANCER PATIENTS

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BACKGROUND: Aprepitant, a selective neurokinin-1 receptor antagonist, is commonly used for prevention of chemotherapy-induced nausea and vomiting. Its use with ifosfamide is controversial due to the putative risk of potentiating neurotoxicity via inhibition of cytochrome P450 3A4 (CYP3A4). The current literature examining this interaction is inconclusive, and little data exists in pediatrics. We seek to describe a single-institution experience with concurrent aprepitant and ifosfamide administration. METHODS: A retrospective review of patients treated with ifosfamide and aprepitant from 2009–2018 was conducted. Data collected included demographics, tumor type, number of days of concurrent therapy, dosing, and documented of neurotoxicity. RESULTS: Twenty patients aged 7–21 years (median 17 years) were identified. Diagnoses included thirteen sarcomas and seven CNS tumors (6 germ cell tumors; 1 intracranial sarcoma). Five patients received high dose ifosfamide (>2,000mg/m^2/day). The number of concurrent ifosfamide and aprepitant doses ranged from 2–18 (median, 8.5). Only one patient (5%) developed ifosfamide-induced neurotoxicity: a 7-year-old female with a nongerminomatous germ cell tumor who presented with seizures and somnolence. She received methylene blue and returned to her neurologic baseline. She completed her ifosfamide course without incident. She was the only patient to require weight-based aprepitant dosing and to receive the liquid formulation. CONCLUSIONS: Aprepitant should be used with caution when administered concurrently with ifosfamide due to the risk of neurotoxicity. However, the incidence of neurotoxicity in this retrospective pediatric cohort was low. This interaction may be more significant in younger patients due to age-related differences in hepatic metabolism, but further study is required.

PATHOLOGY AND MOLECULAR DIAGNOSIS

PATH-01. MOLECULAR PROFILING OF PAEDIATRIC CENTRAL NERVOUS SYSTEM TUMOURS IN AUSTRALASIA – AN UPDATE ON THE AIM BRAIN AND MNP2.0 PROJECTS

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The Access to Innovative Molecular Profiling for Paediatric Brain Cancers (AIM BRAIN) project is a trial testing the feasibility of clinical implementation of diagnostic methylation and molecular profiling for central nervous system (CNS) tumours in Australia and New Zealand. AIM BRAIN builds on an existing study, MNP2.0, and allows cross-validation of results derived from identical samples in separate laboratories in Melbourne, Australia, and DKFZ, Heidelberg, Germany. Parallel methylation profiling (Illumina 850K EPIC array) from co-enrolled cases has revealed excellent concordance between laboratories with 50/51 cases (98%) yielding identical classification using the DKFZ Molecular Neuropathology 2.0 Classifier v11b4. 77/91 (85%) of AIM BRAIN cases classified concordantly by methylation array when compared to their diagnostic histopathology. Of these 77 cases, 16 had classifications below a threshold of 0.90, however still classified correctly. In 14 discordant cases either the histopathology was not well defined, not represented on the classifier, or a very low classification score was obtained. Molecular profiling through MNP2.0 identified 49/167 (29.3%) tumours with gene fusions including BRAF-KIAA1549 (n=29), *RELA-C1lorf95* (n=5) and 15 rare or novel fusions. BRAF-KIAA1549 was almost exclusively associated with pilocytic astrocytoma (28/29) and RELA-*C1lorf95* with ependymoma. Six pathogenic germline mutations were identified in *TP53* (n=2), *BRCA1*, *NF1*, *LZTR1* and *ATM*. The incidence of germline predisposition was low (4%) and sex biased towards females (5F:1M), ($p<0.08$). Our findings confirm methylation profiling as a robust platform for classifying CNS tumours with potential to reveal new CNS tumour entities when combined with molecular profiling.

PATH-03. HIGH-GRADE NEUROEPITHELIAL TUMOR SHOWING BCOR IMMUNOPOSITIVITY WITHOUT EXON 15 INTERNAL TANDEM DUPLICATIONS IN A FIVE-YEAR-OLD BOY: A CASE REPORT

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Recent DNA methylation profiling clarified several rare entities of pediatric CNS tumors from institutionally-diagnosed primitive neuroectodermal tumors (PNETs). One of which is CNS high-grade neuroepithelial tumor with *BCOR* alteration (CNS HGNET-*BCOR*), and it carries in-frame internal tandem duplications (ITD) of the *BCL6 corepressor (BCOR)* in exon 15. In the report, we describe a case of immunohistologically-diagnosed CNS HGNET-*BCOR*, which lacks exon 15 ITD of *BCOR*. A five-year-old boy visited a local hospital complaining uncontrolled vomiting for two months,

and magnetic resonance imaging (MRI) showed a large well-circumscribed mass in his left cerebellum with ventricular dilatation. He referred to our hospital, and an additional MRI revealed diffuse and weak enhancement of gadolinium and low ADC values in mass. Immediately, he underwent total removal of the tumor and ventricular drainage, and his consciousness recovered soon after surgery. The tumor presented high BCOR expression by IHC, but target PCR did not identify exon 15 ITD of *BCOR*. As the previously-reported clinical and imaging features of CNS HGNET-*BCOR* resembled our case, we clinically diagnosed it as a similar phenotype of CNS HGNET-*BCOR* without exon 15 ITD. He received 60 Gy of extended-local irradiation with concomitant temozolomide and discharged without any neurological deficits. Since *BCOR* alterations, including ITD, gene fusions, and mutations, play an oncogenic role in several cancers, the present case might harbor another gene aberration of *BCOR*.

PATH-04. AN ENHANCED AI-DRIVEN PLATFORM FOR PRECISION MOLECULAR BRAIN TUMOR DIANOSTICS

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Tumors of the CNS represent one of the most complex groups of human cancer, with a vast number of different entities occurring across a spectrum of ages and anatomic locations. This heterogeneity makes accurate diagnosis challenging, with the current gold standard relying on multiple subjective elements. We recently proposed a classification algorithm based on tumor DNA methylation profiling as an objective way to assign samples to over 80 distinct molecular classes. Here we present a substantial update to our machine learning-based algorithm, with more than 170 molecular classes now being represented amongst the 5,915 samples in our reference cohort. These new classes include further subclassification of known groups such as medulloblastoma and ependymoma, as well as multiple new molecular entities described here for the first time. A further improvement is the introduction of a more rationally layered output, making use of 'families' of closely-related molecular classes to improve the compatibility with the current WHO classification of CNS tumors. This approach is designed to increase the clinical relevance of the primary output, while also retaining the full information content from the random forest-driven classification. Benchmarking our new algorithm by cross-validation and on an independent validation cohort indicates a retention of the excellent accuracy of diagnosis (error-rate < 4%), with a significant improvement in the proportion of confidently classifiable tumors compared with our previous tool. We believe that this approach, freely accessible through an online web portal, has the potential to enhance diagnostic precision and thereby support clinical care for brain tumor patients.

PATH-05. A CASE OF PILOCYTIC ASTROCYTOMA HARBORING THE FGFR1 GENE MUTATION WITH A PREDOMINANT OLIGODENDROGLIOMA-LIKE COMPONENT

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Pilocytic astrocytomas rarely present with oligodendroglioma-like morphological features, which gives rise to a diagnostic challenge. In this report we present a case of pilocytic astrocytoma harboring the FGFR1 mutation, accompanied with a predominant oligodendroglioma-like component, thus initially diagnosed as oligodendroglioma. A 14-year-old female presented with syncope and simple partial seizure involving her right upper limb. Contrast-enhanced MRI revealed an enhancing lesion with substantial cystic portion and perifocal edema in the left parietal lobe. Open surgery was performed and a gross total resection of the tumor was achieved. On initial histopathological diagnosis, tumor cells with monotonous round nuclei and perinuclear halo predominated with branching capillaries, which were strongly suggestive for oligodendroglioma. Immunohistochemically, IDH1 R132H was negative, and Ki-67 index was around 5%. The patient was thus initially diagnosed as oligodendroglioma, WHO grade II, based on the 2007 WHO classification criteria. However, histopathological re-review revealed a minor astrocytic component with Rosenthal fibers and rare eosinophilic granular bodies, thus the diagnosis was changed as pilocytic astrocytoma. FGFR1 K654E mutation was confirmed by Sanger sequencing. Although she postoperatively developed mild sensory disturbance in her right hands, finger agnosia, and left-right disorientation, her symptoms had gradually improved, and she was discharged on day 17 with a Karnofsky performance status (KPS) of 90 and no cognitive decline. Without any adjuvant therapies, she has remained recurrence-free for 85 months. While the diagnosis of pilocytic astrocytoma with predominant oligodendroglioma-like component can be challenging, analysis of IDH1 and FGFR1 mutations can be beneficial in certain cases.

PATH-06. IMAGE-BASED MACHINE LEARNING CLASSIFIER FOR PEDIATRIC POSTERIOR FOSSA TUMOR HISTOPATHOLOGY

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BACKGROUND: Pediatric posterior fossa (PF) tumors can include astrocytomas, ependymomas, and medulloblastomas, all of which demonstrate unique histopathology. Whole slide image analyses can be time consuming and difficult. Therefore, we used machine learning to create a screenshot-based histopathology image classifier that can distinguish between types of pediatric PF tumors. METHODS: We took 179 histopathology slides from Stanford University, dated from 2008–2019: 87 astrocytomas, 42 ependymomas, and 50 medulloblastomas, per pathology report. Each slide was viewed under a microscope at 20x. Then, a screenshot was taken of the region of interest representative of principal slide pathology, confirmed by a trained neuropathologist. These screenshots were used to train Resnet-18 models pre-trained on the ImageNet dataset and modified to predict three classes. Various models with different hyperparameters were trained using a random hyperparameter search method. Trained models were evaluated using 5-fold cross-validation, assigning 20% of the dataset for validation with each evaluation. Qualitative analysis of model performance was assessed by creating Class Activation Map (CAM) representations of image predictions. RESULTS: The top performing Resnet-18 model achieved a cross-validation F1 of 0.967 on categorizing screenshots of tumor pathology into three types. Qualitative analysis using CAMs indicated the model was able to identify salient distinguishing features of each tumor type. CONCLUSIONS: We present a PF lesion classifier capable of distinguishing between astrocytomas, ependymomas, and medulloblastomas based on a histopathology screenshot. Given its ease of use, this tool has potential as an educational tool in an academic setting.

PATH-07. QUALITY ASSURANCE IN CEREBROSPINAL FLUID CYTOLOGY ASSESSMENT FOR MEDULLOBLASTOMA STAGING LEADS TO POTENTIAL IMPROVED RISK-GROUP ASSESSMENT IN THE PROSPECTIVE MULTICENTER HIT-2000 TRIAL

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BACKGROUND: Cerebrospinal fluid (CSF) dissemination of medulloblastoma (M1 stage) is a high-risk prognostic factor. However, because diagnostic criteria for M1 staging are missing we specified process-related and cytomorphological parameters influencing the predictive value of the CSF status. PATIENTS AND METHODS: CSF samples and cytology reports from 405 medulloblastoma patients of the prospective multicenter trial HIT-2000 were reviewed and related to 5-year progression free survival (5y-PFS). RESULTS: Tumor cells were detected in 237/1073 CSF cytospins. M1-patients and M2/3 patients with radiologically detected metastases showed a worse 5y-PFS than M0 patients (54% and 52% vs. 76%; p=0.01 and p<0.001). Lumbar sampling was more sensitive than ventricular sam-

pling. M0 diagnosed specimens containing >50% lytic cells and/or less than 10 nucleated cells showed a decreased 5y-PFS (61%). Further investigation of cytological parameters revealed a poor outcome for cases harboring > 3 tumor cell clusters and individual tumor cells (5y-PFS 33%) vs. cases with ≥ 2 individual tumor cells but no clusters (5y-PFS 61%). In bi-variable Cox-regression, ≥ 2 vs. 0 or 1 tumor cells were associated with a Hazard Ratio (HR) of 0.52 (95%-Confidence Interval (CI): 0.12, 2.30; p=0.39), whereas > 3 vs. no tumor cell clusters were associated with a HR of 8.94 (95%-CI: 1.66, 48.22; p=0.01). CONCLUSIONS: CSF staging in medulloblastoma should comprise lumbar specimens with <50% lytic cells and a minimum of 10 nucleated cells. The predictive value of CSF cytology in M1 cases may predominantly depend on tumor cell clusters. The latter finding needs to be confirmed in prospective trials.

PATH-08. THE IMPORTANCE OF RE-DIAGNOSIS OF TUMORS PREVIOUSLY CLASSIFIED AS CENTRAL NERVOUS SYSTEM PRIMITIVE NEUROECTODERMAL TUMORS

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BACKGROUND: The recent molecular analyses have revealed that central nervous system primitive neuroectodermal tumors (CNS PNETs) those having clusters of small round tumor cells are genetically different tumors. However, the concepts of CNS PNET are complicated, and it is difficult to diagnose them appropriately in clinical field. To overcome this difficulty, we reviewed previous studies associated with CNS PNETs, and carried out several approaches, those are relatively easy access to use in clinics, for our 8 samples of embryonal brain tumors diagnosed CNS PNETs in our institution, initially. METHODS: We used in combination with immunohistochemistry (IHC), Sanger sequence, Pyrosequence, polymerase chain reaction (PCR), real time PCR and copy number analysis referring recent reports. RESULTS: In terms of the diagnosis three out of 8 cases were changed based on the results in this study from previous diagnoses. CONCLUSION: In this review, it seemed that either the histopathological evaluation or molecular analyses would be not enough to make accurate diagnosis of CNS embryonal brain tumors, and it is essential to combine both of them including recent comprehensive analysis methods.

PATH-09. SJMB12 CLINICAL TRIAL: DISCREPANCY BETWEEN LOCAL AND CENTRAL PATHOLOGY IN ASSESSING ANAPLASTIC MEDULLOBLASTOMA – REPORT FROM A SINGLE SITE EXPERIENCE

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INTRODUCTION: SJMB12 is a phase 2 clinical trial led by the St. Jude Children's Research Hospital (St. Jude) that enrolls patients with medulloblastoma based on their biological subgroup. The large cell/anaplastic (LCA) histologic variant has been identified as an important independent risk factor associated with poor outcome. However, the histologic criteria for LCA is subjective, making the distinction between anaplastic and non-anaplastic medulloblastoma difficult in some cases. METHODS: Pathological central review was performed at St. Jude. For all patients enrolled in the study to date, concordance was assessed between the initial and central review diagnosis and histologic variant calls made at the Royal Children's Hospital Melbourne (RCH) and at St. Jude, respectively. RESULTS: Since the SJMB12 clinical trial opened locally in 2014, 34 patients were enrolled, and 31 were eligible for this retrospective study. A total of 12 (39%) cases with discordance were identified. The most frequent disagreement was between the designation of LCA (10 cases, 32%). In five cases the tumour was not designated as LCA variant locally. In five cases the initial designation of LCA was refuted centrally. Overall, this led to a change of treatment stratum for four patients (13%). CONCLUSION: A high discordance rate exists between neuropathologists in the designation of LCA variant. Differences in interpretation of the subjective histologic criteria and inconsistencies in the material submitted for central review contributed to the discordance. Incorporation of more objective histologic criteria and implementation of unbiased diagnostic tools may improve the generalisability of future risk stratification.

PATH-10. PROGNOSTIC RELEVANT IMMUNOPHENOTYPES OF PEDIATRIC HIGH-GRADE NON-BRAINSTEM GLIOMAS

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Pediatric diffuse astrocytomas comprise a wide range of malignancies with variable prognosis. The 4th grading system used now not always correctly characterizes the biological behavior of these tumors. We collected 24 pediatric supratentorial non-brainstem high grade glioma cases. Patient age ranged from 1 to 18 years old (median 11y). Main tumor locations were as follows: parietal lobe 8 cases; temporal lobe, 10 cases; frontal lobe, 3 cases; occipital lobe 3 cases. Eight of them were totally removed. All patients were treated with standard CT and RT. The main objective was to assess the prognostic impact of histopathological and molecular criteria on progression-free(PFS) and overall survival (OS) of high grade gliomas. The following criteria were analyzed: IDH1 R132H, BRAF V600E expression, ALT-phenotype, CDKN2A deletion, 1p/19q co-deletion, glial and neuronal markers expression. **RESULTS:** IDHR132H mutation was identified in 3 cases. 4 cases carried BRAFV600E mutation with CDKN2A deletion and displayed PXA phenotype. 5 cases showed undifferentiated glial morphology and ALT–phenotype. Also there was a group of tumors without any of the above mentioned genetic changes. Interestingly 3 of them were post radiation tumors. Statistical analysis showed that low OS correlated with ALT-phenotype(p-0.015), absence of neuronal markers expression and absence of molecular changes (p-0.03). Mutation of IDH1R132H was a favorable prognostic factor as in the adult population. PFS was affected only by the presence of neuronal expression (p-0.015). Employing immunohistochemical analysis with surrogate molecular markers in complex with FISH can provide additional prognostic information in case of pediatric high grade gliomas.

PATH-11. PROSPECTIVE (EPI-)GENETIC CLASSIFICATION OF > 1,000 PEDIATRIC CNS TUMORS—THE MNP 2.0 STUDY

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The large variety of CNS tumor entities affecting children and adolescents, some of which are exceedingly rare, results in very diverging patient outcomes and renders accurate diagnosis challenging. To assess the diagnostic utility of routine DNA methylation-based CNS tumor classification and gene panel sequencing, the *Molecular Neuropathology 2.0* study prospectively integrated these (epi-)genetic analyses with reference neuropathological diagnostics as an international trial for newly-diagnosed pediatric patients. In a four-year period, 1,215 patients with sufficient tissue were enrolled from 65 centers, receiving a reference neuropathological diagnosis according to the WHO classification in >97%. Using 10 FFPE sections as input, DNA methylation analysis was successfully performed in 95% of cases, of which 78% with sufficient tumor cell content were assigned to a distinct epigenetic tumor class. The remaining 22% did not match any of 82 represented classes, indicating novel rare tumor entities. Targeted gene panel sequencing of >130 genes performed for 96% of patients with matched blood samples detected diagnostically, prognostically, or therapeutically relevant somatic alterations in 48%. Germline DNA sequencing data indicated potential predisposition syndromes in ~10% of patients. Discrepant results by neuropathological and epigenetic classification (29%) were enriched in histological high-grade gliomas and implicated clinical relevance in 5% of all cases. Clinical follow-up suggests improved survival for some patients with high-grade glioma histology and lower-grade molecular profiles. Routine (epi-)genetic profiling at the time of primary diagnosis adds a valuable layer of information to neuropathological diagnostics and will improve clinical management of CNS tumors.

PATH-13. PLEOMORPHIC XANTHOASTROCYTOMA INTEGRATED GENOMIC CHARACTERIZATION - WHAT HAVE WE LEARNED?

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Pleomorphic xanthoastrocytoma (PXA) is a rare astrocytoma occurring predominantly in children and young adults. It is characterized histologically by large pleomorphic, spindled and lipidized cells with frequent eosinophilic granular bodies and pericellular reticulin deposition. *BRAF* p.V600E mutation and *CKDN2A/B* deletion are the most common genetic alterations. We report the integrated genomic characterization of a cohort of 67 patients (37 F, 30 M; median age 20.3 years (interquartile 13.4–32.9) with histologically defined PXA (52, 78%) or anaplastic PXA (A-PXA) (15, 22%), using genome-wide cytogenetic (ThermoFisher Oncoscan, n=67), methylation profiling (Illumina EPIC array, n=43), and targeted next generation sequencing (n=32). *BRAF* p.V600E mutation (n=51, 76.1%) and *CDKN2A/B* deletion (n=63; 94%) were the most frequent alterations. Of 16 *BRAF* p.V600E negative cases, 7 showed an alternative *BRAF* activating mutation (n=2), *NF1* (n=3) mutation or *ATG7-RAF1* fusion (n=2). Targeted *TERT* analysis found promoter mutations in 3 (of 58) cases, but TERT amplification was absent. Supervised and unsupervised methylation profiling against a comprehensive reference cohort demonstrated consensus grouping with the PXA class in 36 of 43 cases; while the minority grouped with a ganglioglioma class (n=3), with reactive brain or had no resolvable subgroup (n=4). Follow-up was available in 61 patients (91.0%) (median 63 months). Overall survival was significantly different between PXA and A-PXA (5-year:80.4% vs. 55.1%; p=0.001), but not progression-free survival (5-year:61.7% vs. 39.8%; p=0.128). Our data confirm the high frequency of MAP-K abnormalities and *CDKN2A/B* deletion in PXA. WHO grade remains a strong predictor of patient overall survival.

PATH-14. GENETIC SUSCEPTIBILITY AND OUTCOMES OF PEDIATRIC, ADOLESCENT AND YOUNG ADULT IDH-MUTANT ASTROCYTOMAS

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INTRODUCTION: Previously thought to be rare, recent case series have shown that *IDH* mutations in young patients are more common than previously described. In this study, we analyzed *IDH*-mutant tumors to determine clinical significance of these mutations in children, adolescents and young adults. METHODS: Through this multi-institution study (10 institutions), we collected 64 IDH1/2-mutant infiltrating astrocytoma specimens from 58 patients aged 4–26 (M:F, 0.4:0.6). Specimens included 46 low-grade (LGG) and 18 high-grade (HGG) astrocytomas. Tumor sequencing data (n=45), germline sequencing data (n=37) and outcome data (n=40) was analyzed. RESULTS: Similar to adults, most sequenced tumors had a co-mutation in the *TP53* gene, while *ATRX* mutations were less common and primarily seen in HGGs. Approximately 60% (n=21) of patients with germline data available had a mutation in a cancer predisposition gene. Mismatch repair (MMR) mutations were most common (n=12; MSH6 n=9), followed by *TP53*mutations (n=7). All patients with MMR gene mutations had HGGs and poor progression free (PFS=10% at 2 years, mean TTP=9 months) and overall (OS <30% at 2 years) survival. Despite an OS of 90% at 5 years, many LGG patients had tumor progression/recurrence requiring additional treatment (PFS= 80% at 2 yrs, 40% at 5 yrs, mean TTP=3.5 years). Four LGG tumors (2 with *TP53+ATRX*loss, 2 with *TP53* loss+1p19q co-deletion) underwent malignant transformation. CONCLUSION: *IDH*-mutant tumors in pediatric patients are strongly associated with cancer predisposition and increased risk for progression/recurrence or malignant transformation. Routine screening for *IDH1/2* mutations in children with grade 2–4 astrocytomas could greatly impact patient management.

PATH-15. PROTEOMIC SIGNATURES PREDICT GRADE IN PEDIATRIC AND YOUNG ADULT INFILTRATIVE ASTROCYTOMAS

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BACKGROUND: Infiltrative astrocytomas in children and young adults pose a treatment challenge due to the difficulty of achieving gross total resection and tumor resistance to irradiation and chemotherapy. Histopathologic grade is an essential part of determining prognosis and treatment, but it is subjective and provides limited understanding of the molecular mechanisms underlying tumor development and progression. METHODS: We performed liquid chromatography/mass spectrometry (LC/MS-MS) on 28 FFPE samples of primary infiltrative astrocytomas (10 grade II, 8 grade III and 10 grade IV – WHO classification) from Nationwide Children's Hospital (NCH). Initial unsupervised clustering was performed. Lasso regression yielded a protein signature separating low- and high-grade tumors which was validated using a similar cohort of pediatric and young adult infiltrative astrocytomas from the Proteomic Data Commons (PDC) (n=28) of the National Cancer Institute. RESULTS: Unsupervised clustering of NCH samples essentially recapitulated grade and lasso regression yielded a 10-protein signature that distinguished grade II from grade III/IV tumors. This 10-protein signature when applied to the PDC validation dataset, accurately predicted grade for 89.3% of the tumors (p=0.00014). CONCLUSIONS: We identified a quantitative protein signature that can reliably distinguish between low- and high-grade infiltrative astrocytomas from FFPE tissue. Further validation will enable the development an objective prognostic proteomic clinical test that complements and may outperform current histopathological strategies. Additionally, proteomic profiling of tumors will clarify the molecular mechanisms contributing to treatment resistance and tumor progression and help identify novel treatment targets. Independent functional validation and characterization of proteins is ongoing.

PATH-16. CORRELATION OF PATHOLOGICAL AND RADIOGRAPHICAL DIAGNOSES FOR CHILDREN WITH BRAIN TUMORS AT TWO MAJOR HOSPITAL IN KENYA

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BACKGROUND: Central nervous system (CNS) tumors are the leading solid tumors in the childhood population but vastly underreported in the African population. There's limited data on childhood brain tumors as well as the histopathological distribution in Kenya. Our study aimed at assessing the spectrum as well as the level of correlation with imaging in diagnosis of brain tumors within two major hospital settings. DESIGN: This was a cross-sectional retrospective descriptive study conducted at the two major hospitals in Kenya: Kenyatta National Hospital (KNH) and Moi Teaching and Referral Hospital (MTRH). Children who underwent treatment for brain tumors between 2015 and 2017 and whose tissue biopsies were available at the laboratory archives were included. RESULTS: 87 cases were available for review, and the majority of the affected population were of ages 5–9 years. The most affected site was infratentorial compartment (48.3%) with gliomas and medulloblastoma being equally distributed. Majority of the gliomas were low grade (69%) with pilocytic astrocytoma being the most common subtype (42.9%). The overall sensitivity for the diagnosis of brain tumors through radiology was 69.4%. The level of correlation of histopathological to radiological diagnosis was statistically insignificant with P and kappa values of 0.814 and -0.024 respectively. CONCLUSION: Gliomas and medulloblastomas were the commonest tumors at both centers. Histopathological diagnoses have a high concordance of agreement among various morphologists. The level of correlation between histopathological and radiological diagnosis was high. Next steps include standardizing clinical, radiological and pathological details within Kenya.

PATH-17. INTRAGENIC COPY NUMBER BREAKPOINT ANALYSIS OF METHYLATION DATA FROM CNS TUMOURS IDENTIFIES NOVEL SUBGROUP-SPECIFIC CANDIDATE FUSION GENE ENRICHMENTS

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Methylation array-based molecular profiling has redefined the classification of brain tumours and now forms an important part of their integrated

diagnosis, providing both subgroup assignment and genome wide DNA copy number profiles. These latter data can be used to identify intragenic breakpoints which are frequently associated with structural variations resulting in therapeutically targetable oncogenic fusion genes. To systematically assess the landscape of these alterations, we combined publicly available methylation datasets resulting in a total of 5660 CNS tumours, around half paediatric, and including >1000 high grade glioma and DIPG. These were analysed by standard methodology (MNP, conumee), and intragenic breakpoint enrichment was compared within methylation subgroups, superfamilies, and tumours with no high-scoring classification. Benchmarking included sequence-verified cases such as infant hemispheric gliomas (IHG) with *ALK*(15%) and *ROS1*(7%) fusions, and pathognomic alterations associated with specific entities such as RELA-EPN, MYB-LGG and HGNET-MN1. We identified previously unreported enrichments of well-recognised fusion targets such as *NTRK2*in GBM_MID and *NTRK3*in DMG_K27 (both 5%), *MET*in A_IDH / A_IDH_HG (3–5%), and *FGFR1/3*in GBM_G34 (8–9%). Novel recurrent kinase gene candidates to be verified and explored further include *IGF1R*in 2–12% cases spanning glioma subgroups, and *TIE1*in poorly classified tumours. This latter 'NOS' group were also enriched in various transcription factor targets of breakpoints, including *TCF4*and *PLAGL2*. Despite limitations due to sample quality, resolution or balanced translocations, breakpoint analysis of methylation copy number profiles provides simple screening for structural rearrangements which may directly influence targeted therapy in paediatric CNS tumours.

PATH-18. HIGH-GRADE NEUROEPITHELIAL TUMOR (HGNET) IN A PEDIATRIC CASE-SERIES

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The central nervous system (CNS) high-grade neuroepithelial tumor is a recently described molecular entity. We report 2 new CNS HGNET cases sharing common clinical presentation and pathologic features. In summary, CNS HGNET represents a rare tumor occurring in young patients with dismal prognosis. We think it is important to report these cases to spread the experience and raise the knowledge of the medical community.

PATH-19. MOLECULAR CLASSIFICATION BASED ON THE DNA METHYLATION PROFILE OF CENTRAL NERVOUS SYSTEM (CNS) TUMORS IN CHILDREN: TWO-YEARS EXPERIENCE AT THE BAMBINO GESÙ HOSPITAL

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INTRODUCTION: Pediatric brain tumors (PBT) represent the second most common pediatric cancer, with the highest mortality rate among childhood malignancies. Improvement of PBT diagnostic accuracy is fundamental to optimize treatment strategy. OBJECTIVES: We aimed to explore the impact of DNA methylation arrays implementation in PBT clinical practice. METHODS: 214 PBT were analyzed by Illumina 850KEPICmethylation array. Low score and discordant cases were collegially reviewed. RESULTS: Calibrated score was 0.8 or higher in 159 cases (74.3%), with pathological diagnosis confirmation in 132 cases and molecular subgroup definition in 47 of them, including cases of medulloblastoma, CNS neuroblastoma FOXR2, HGNET MN1; methylation profiling amended diagnosis in 10 cases, e.g. HGNET BCOR and anaplastic PXA, was non-contributory in 4 and misleading in 12 cases, including glioneural tumors and tumors arising in syndromic contexts. Calibrated score ranged between 0.8 and 0.3 in 37 cases (17.3%) and was below 0,3 (no match) in 18 cases (8.4%). Calibrated score below 0,8 was more frequently assigned to low grade gliomas and low grade glioneural tumors ($p < 0.0006$). Challenging/very rare cases, e.g. intracranial AFH with EWSR1:CREM fusion and nonRELA supratentorial ependymomas, were assigned to "no match subgroup"; in syndromic patients the score tended to be lower ($p=0.07$); no correlation between score and age < 3-years was found ($p=0.1$). CONCLUSION: Methylation profiling refine on diagnostic accuracy in PBT classification. Improvements are needed in classifying low grade glioma/glioneuronal tumors and challenging/very rare PBT. In syndromic cases, there is a high rate of misleading profiles and/or low scores.

PATH-20. METHYLATION ARRAY PROFILING OF PEDIATRIC BRAIN TUMORS; SINGLE CENTRE EXPERIENCE

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BACKGROUND: Significant heterogeneity of pediatric brain tumors poses major challenge on diagnostics. Therefore, we aimed to evaluate feasibility of methylation array in the diagnostic process. METHODS: Methylation array (Infinium MethylationEPIC, Illumina) was performed on DNA extracted from fresh frozen tissue from prospective newly diagnosed and selected retrospective patients. Results from Heidelberg classifier (www.molecularneuropathology.org) were compared to the histological diagnosis and further genetic testing was performed to establish integrated morphological/molecular diagnosis. RESULTS: Within years 2018–2019, we performed methylation array profiling of 102 samples consisting mainly of ependymoma, medulloblastoma high-grade and low-grade glioma. High calibrated score (>0.9) was achieved in 62 patients (61%). In 46 cases (74%) with score >0.9, the histological diagnosis matched the methylation class (MC). In the remaining cases (16) that were classified by histopathology mainly as ependymomas, the methylation profiles were classified as novel molecular entities (HGNET_BCOR, HGNET_MN1, etc.) or different tumor type. In 40 cases (39%) with the score <0.9, six were found to have high normal tissue content. Nine cases had no match in the classifier and 25 were assigned MC with score 0.3 to 0.89. In 20 out of 34 cases with low score, the molecular diagnosis could be confirmed based on copy number variants inferred from the methylation array or using additional testing for gene fusions and mutations. CONCLUSIONS: Our experience on the first 100+ cases demonstrated that methylation array could be integral part of diagnostic process in order to establish integrated morphological and molecular diagnosis of pediatric brain tumors.

PATH-21. TELOMERE LENGTH ANALYSIS OF CNS TUMORS IN THE PEDIATRIC BRAIN TUMOR ATLAS

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Subsets of pediatric cancers, including high grade glioma (pHGG), have high rates of uniquely long telomeres, associated with ATRX gene mutations and alternative lengthening of telomeres (ALT). Ultimately, these cancers may benefit from a therapy stratification approach. In order to identify and further characterize pediatric brain tumors with telomere lengthening (TL), we determined the intratelomeric content *in silico* from paired WGS of 918 tumors from CBTTC Pediatric Brain Tumor Atlas (PBTA). The results were highly concordant with experimental assays to determine ALT in a subset of 45 pHGG tumors from the set. Overall, 13% of the PBTA cohort had telomere lengthening. We confirmed the highest rate of TL (37%) in the pHGG cohort (37/100 tumors; 30/82 patients). There was no statistical difference in age, gender or survival in subset analysis. As expected, the patient pHGG tumors with telomere lengthening were enriched for ATRX mutations (60%, q= 1.76e-3). However, 6 tumors without ATRX mutation also had normal protein expression, suggesting a different mechanism of inactivation or TL. The pHGG tumors with telomere lengthening had increased mutational burden (q=8.98e-3) and included all known pHGG cases (n=6) in the cohort with replication repair deficiencies. Of interest, the second highest rate of telomere lengthening was 9 subjects (24%) in the craniopharyngioma cohort. None of the craniopharyngioma tumors had ATRX mutations or low ATRX expression, and 55% of those with TL had CTNNB1 mutations. Finally, lower rates of telomere lengthening were found in medulloblastoma (10%), ependymoma (10%), low grade astrocytoma (8%) and ganglioglioma (7/47, 15%).

PATH-22. COMPARISON OF SUPERVISED CLASSIFICATION METHODS FOR CENTRAL NERVOUS SYSTEM TUMORS BASED ON DNA-METHYLATION

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Classification of brain tumors using methylation profiling is an important diagnostic advance, reducing subjectivity and improving interpretability of clinical outcome data. Despite the recognized value of methylation profiling

in the clinical laboratory, the performance characteristics of different supervised classification models has not been directly compared. We developed 3 methods using methylation profiles to classify CNS tumors: an exact bootstrap k-nearest neighbor (kNN), a multi-layer perceptron neural net (NN), and a random forest classifier (RF). We trained these methods on the publicly available CNS tumor reference cohort (GSE90496) with 2,801 profiles and 91 classes. We evaluated the performance of these methods by leave-out-25% cross-validation. The relative performance of these methods were evaluated in terms of accuracy, precision, and recall for class or class family. The kNN, RF, and NN classifier had an estimate error rate of 10.74%, 4.01%, and 1.89%, respectively for class prediction and an error rate for family prediction of 5.97%, 0.90%, and 0.6%, respectively. At perfect recall for class assignment, the RF and kNN had a precision of 0.96 and 0.89 while the NN reached 0.98. For family assignment, the precision for the three classifiers was almost 1.0 with recall of nearly 0.8. At the recall rate of 1.0, the precision dropped to 0.94, 0.991 and 0.994 for kNN, RF, and NN, respectively. Overall, the NN showed improved performance metrics compared to the kNN and RF in CNS tumor classification for both class and class family assignment.

PATH-23. ADULT SPINAL CORD ASTROBLASTOMA WITH EWSR1-BEND2 FUSION

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The most recurrent fusion of CNS high-grade neuroepithelial tumor with MN1alteration(HGNET-MN1) is *MN1- BEN Domain Containing 2*(BEND2) fusion. Recently, there was a report of a 3-month-old boy with spinal astroblastoma, classified as CNS HGNET-MN1 by DKFZ methylation classification but positive for EWSR1-BEND2 fusion(Yamasaki, 2019). Here, we report a 36-year old man with a spinal cord astroblastoma with EWSR1 alternation. The patient presented with back pain, gait disorder and dysesthesia in lower extremities and trunk was referred to our hospital. MRI showed intramedullary tumor in Th3-5 level, displaying low-intensity on T1 weighted image, high-intensity on T2 weighted image, and homogeneous gadolinium enhancement. Partial removal was performed with the laminectomy. The tumor extended to extramedullary and its boundary was unclear. Histological examinations showed the epithelium-like tumor cells with eosinophilic cytoplasm with high cellularity palisade, intracellar fibrosis, and mitosis. Immunohistochemical staining showed positive for Olig2, GFAP, EMA, SSTR2, S-100, but negative for p53, PgRAE1/AE3. The tumor was diagnosed as astroblastoma, and was classified as HGNET-MN1 by the DKFZ methylation classifier. However, the MN1 alternation was not detected by fluorescence in situ hybridization, instead EWSR1 and BEND2 alternations which suggested EWSR1-BEND2 fusion were detected. After radiation therapy of 54Gy/30fr with bevacizumab and temozolomide, the residual tumor reduced the size and his symptoms improved. This case provides evidence that *EWSR1-BEND2* fusion is recurrent in HGNET-MN1 and, as previously reported, suggests the importance of BEND2 in this entity. These two cases suggested that it may be the BEND2 alteration that biologically defines the HGNET-MN1 subclass rather than MN1.

PATH-24. MOLECULAR CLASSIFICATION OF HIGH RISK INFANT EMBRYONAL BRAIN TUMORS ENROLLED IN THE ACNS0334 TRIAL: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

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Young children with embryonal brain tumors including medulloblastoma (MB), supratentorial primitive neuro-ectodermal tumor, or pineoblastoma have historically been considered high-risk patients with poor outcomes despite the use of intensive radiation-sparing treatment. In the ACNS0334 phase III trial, 91 consented children <36 months old with the above diagnoses were randomized to intensive induction chemotherapy with or without methotrexate followed by consolidation with stem cell rescue. Here we present the results of a centralized integrated molecular analysis including global methylation profiling (65/91), and whole exome sequencing of tumor (46/91) and germline (35/91) DNA. Unsupervised clustering analyses of methylation profiles using multiple orthogonal methods against a reference dataset of 1200 pediatric brain tumors, revealed known and new molecular entities. For tumors diagnosed as MB on central pathology review, 7.3% (3/41) had a non-MB molecular diagnosis (2 embryonal tumor with multiple rosettes/ETMR, 1 group MYC pineoblastoma), with the remainder as MB Group SHH (11/41), Group3 (25/41), and Group4 (2/41). Among histologic non-MBs, 3/24 (12.5%) were molecular entities not intended for trial inclusion (1 each for ATRT, pleomorphic xanthoastrocytoma, and high-grade glioma). ETMR, historically considered a rare entity, was molecularly identified in a significant proportion (14/65; 21.5%) of samples. Among MB-SHH, we detected deleterious PTCH1 mutations in 6/9 tumors but none among 5 germline samples tested; a germline SUFU frameshift mutation with tumor LOH was also observed in MB-SHH. Correlation of these and other molecular features to the parallel clinical analysis will yield important markers of risk stratification and predictors of treatment response.

PATH-25. GENOME-WIDE METHYLATION ANALYSIS CAN SEGREGATE RADIATION-INDUCED GLIOBLASTOMA FROM LATE RECURRENCE OF MEDULLOBLATOMAS

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It could be difficult to diagnose recurrent medulloblastoma with conventional diagnostic tools because other lesions mimic relapse of the tumor from both a morphological and radiological standpoint, particularly when it happens late. We report two medulloblastoma cases, both of which seemed to develop late-recurrence more than 5 years from the initial surgery. Genome-wide methylation analysis revealed that one of the recurrent tumors was in fact a radiation-induced glioblastoma. The first patient was a 6-year-old female patient who developed a posterior fossa tumor. The pathological diagnosis was medulloblastoma with focal desmoplasia. She was in complete remission for 9 years after the treatment but developed an intradural lesion in her thoracic spine. The lesion was biopsied and pathologically confirmed as recurrence of the tumor. The second patient was a female patient who developed non-metastatic medulloblastoma at the age of 10. She suffered local recurrence 5 years after the diagnosis. Biopsy was performed, and the pathological diagnosis was relapse of the tumor. We performed unsupervised hierarchical clustering of the methylation data from our cases and reference data. In contrast to consistency of methylation profiling and copy number abnormalities between primary and recurrent tumors of case 1, the analysis revealed that the recurrent tumor of case 2 was distinct from medulloblastomas and clustered with "IDH-wild type glioblastomas", which suggested that the recurrent tumor was radiation-induced glioblastoma. This report highlights the clinical utility of molecular genetic/epigenetic approach to confirm diagnosis of brain tumor recurrence.

PATH-26. RNA SEQUENCING OF FORMALIN-FIXED PARAFFIN-EMBEDDED SPECIMENS IN DIAGNOSTIC ROUTINE IDENTIFIES CLINICALLY RELEVANT GENE FUSIONS

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Pediatric brain tumor entities harbor a variety of gene fusions. Whilst other molecular parameters like somatic mutations and copy number alterations have become pivotal for brain tumor diagnostics, gene fusions are only less well covered by routinely applied methylation arrays or targeted next-generation sequencing of DNA. In a routine diagnostic setting we established and optimized a workflow for investigation of gene fusions in formalin-fixed paraffin-embedded (FFPE) tumor tissues by using RNA sequencing. Assessing different tools for calling fusions from raw data, we found relevant fusions in 66 out of 101 (65%) analyzed cases in a prospective cohort collected over 26 months. In 43 (43%) cases the fusions were of decisive diagnostic relevance and in 40 (40%) cases the fusion genes rendered a druggable target. Besides the relevance of pathognomonic fusions for diagnostics, especially the detection of druggable gene fusions yields direct benefit to the patients. This approach allows for an unbiased search for fusion events in the tested samples. Besides rare variants of established fusions which were not detected by prior targeted analyses, we identified previously unreported fusion events. Exemplified on KIAA1549:BRAF fusion, we in addition provide an overview of the detection accuracy of different methods, including breakpoint detection in DNA methylation array data and fusion gene detection in DNA panel sequencing data. Our data show that RNA sequencing has great diagnostic as well as therapeutic value by clinically detecting relevant alterations.

PATH-27. MUTATION DETECTION USING PLASMA CELL-FREE DNA IN CHILDREN WITH CENTRAL NERVOUS SYSTEM TUMORS

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BACKGROUND: The role of plasma cell-free DNA (cfDNA) as a cancer biomarker for tracking treatment response and detecting early relapse has been well described for solid tumors outside the central nervous system (CNS). However, the presence of a blood-brain barrier complicates the application of plasma cfDNA analysis for patients with CNS malignancies. METHODS: cfDNA was extracted from plasma of pediatric patients with CNS tumors utilizing a QIAmp® MinElute® kit and quantitated with Qubit 2.0 Fluorometer. Extensive genomic testing, including targeted DNA and RNA solid tumor panels, exome and transcriptome sequencing, as well as copy number array, was performed on matched tumor samples as part of the Texas KidsCanSeq study. An Archer® Reveal ctDNA28 NGS kit was then used for assaying the sensitivity of detecting tumor-specific mutations in the plasma of these patients. RESULTS: A median of 10.7ng cfDNA/mL plasma (Interquartile range: 6.4 – 15.3) was extracted from 78 patients at time of study enrollment. Longitudinal samples from 24 patients exhibited a median yield of 7.7ng cfDNA/mL plasma (IQR: 5.9 – 9.1). An initial cohort of 6 patients was identified with 7 somatic variants covered by the Archer® Reveal kit. Four of seven mutations identified in matched tumor specimens were detected in patient plasma at variant allele frequencies ranging from 0.2–1%. CONCLUSIONS: While challenging, detection of cfDNA in the plasma of pediatric patients with CNS tumors is possible and is being explored in a larger patient cohort along with pilot studies investigating cerebrospinal fluid as an additional source for tumor-specific cfDNA.

PATH-28. MOLECULAR DIAGNOSIS FOR CENTRAL DIAGNOSIS OF BRAIN TUMORS FROM 2016 TO 2019— A REPORT FROM THE JAPAN CHILDREN'S CANCER GROUP (JCCG)

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INTRODUCTION: Since 2016, the Japan Children's Cancer Group (JCCG) has established a nationwide network that prospectively provides pathological review and molecular analysis. METHODS: Patients who were diagnosed with brain tumors between ages 0 and 29 were eligible. The central office at National Center for Child Health and Development served as a hub for the hospitals involved and institutions conducting pathological and molecular analysis, and managed the patients' clinical information and tumor samples. Histopathology of all cases were centrally reviewed. Routine non-NGS based analyses were conducted based on histological diagnosis and included pyrosequencing for glioma-associated hot spot mutations and PFA/PFB classification for ependymoma, RT-PCR for *RELA* fusion and *BRAF* fusion, and nanostring for subgrouping medulloblastoma. In selected cases, methylation analysis, RNA sequencing and exon sequencing of 93 genes were performed in selected cases. RESULTS: In total, 985 cases were registered to this study in four years. Frozen samples were collected from approximately 80% of cases. The number increased from 152 in 2016 to 326 in 2019. They includes glioma (n=268), medulloblastoma (n=161), ependymoma (n=103), germ cell tumor (n=93), ATRT (n=29) and others. In 55 % of the glioma cases, at least one abnormality was detected by the routine analysis. The detailed analysis for atypical cases identified targetable alternations. DISCUSSION: This nationwide central diagnostic system has now been well established. Current issues and future prospective of the system will be discussed.

PATH-29. HIGH FREQUENCY OF CLINICALLY-RELEVANT TUMOR VARIANTS DETECTED BY MOLECULAR TESTING OF HIGH-RISK PEDIATRIC CNS TUMORS – PRELIMINARY FINDINGS FROM THE TEXAS KIDSCANSEQ STUDY

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BACKGROUND: DNA and RNA-based tumor sequencing tests have the potential to guide the clinical management of children with CNS tumors. However, data describing the utility of these tests are limited. METHODS: Children with high-risk or recurrent CNS tumors are included in the diverse cohort of patients enrolling in the KidsCanSeq study from six Texas sites. DNA and RNA from FFPE tumor is subjected to targeted sequencing using a 124-gene mutation panel and an 81-gene fusion panel. Tumor capture transcriptome sequencing, exome sequencing, and copy number array (as well as germline panel and exome testing) are also performed. Tumor variants are classified using AMP/ASCO/CAP consensus guidelines. RESULTS: A total of 74 children with high-risk/recurrent CNS tumors enrolled as of 1/28/20. Targeted tumor DNA and RNA panel testing was completed for 57 patients with varied diagnoses. At least one tumor variant with strong or potential clinical significance was identified in 43 of 57 (75%) tumors, with therapeutic significance in 20 of 57 (35%) tumors. The 38 therapeutically-relevant variants most frequently affected MAPK signaling (BRAF x9, EGFR x3, FGFR2, FGFR3, KRAS, NF1, NTRK2) and the AKT/mTOR pathway (PIK3CA x3, PTEN x2, mTOR, TSC1, PIK3R1). Most had not been detected by prior targeted diagnostic testing (27/38, 71%). CONCLUSION: Integrated DNA and RNA-based panel testing identified variants with potential to impact clinical decision-making in a majority of children with high-risk/recurrent CNS tumors. The comparative yield of panel testing vs. exome/transcriptome/array will be evaluated in the KidsCanSeq study cohort.

PATH-30. EXOSOMES AS A SOURCE OF PLASMA CTDNA TO IDENTIFY POINT MUTATIONS IN PEDIATRIC GLIOMA PATIENTS

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Surgery consists in the mainstay of treatment in most gliomas, but in many cases, a resection is not feasible. Liquid biopsy is an ideal tool providing a minimally invasive method through plasma or CSF sampling to assess cell-free tumor DNA (ctDNA). Here we explore the feasibility of detecting DNA in plasma exosomes (exoDNA) extracted from glioma patients and further investigate its use in identifying molecular alterations. Exosomes were isolated from 2ml of plasma from 24 patients (13 LGG, 8 HGG, 3 DIPG) and fully characterized by nanoparticle tracking analysis and transmission electron microscopy. DNA was extracted from 13 samples (exoDNA) so far. Five patients had confirmed point mutations in the primary tumor (3BRAFV600E; 1FGFR1N546K; 1H3.3), additionally, 3 samples were collected from clinically diagnosed DIPG patients to inquire H3K27M mutations. DNA was extracted successfully from all exosome samples; a pre-amplification step was needed and direct sequencing was carried out for BRAFV600E. FGFR1N546K and H3K27M mutations were sought in patients with positive tumors. Wildtype BRAF fragment was identified in 12/13samples (1 patient failed sequencing). However, none of the five tumor positive patients nor the DIPG patients had mutations detected at the exo-DNA level. There is growing evidence that CSF may be the ideal source of ctDNA in brain tumor patients, therefore although we could not detect mutations in plasma DNA we are currently analyzing CSF exoDNA and cell-free DNA to evaluate if this proves a successful strategy and weather exoDNA is more representative of the tumor content.

PATH-31. THE IMPACT OF MOLECULAR PROFILING OF PEDIATRIC CNS TUMORS ON TUMOR DIAGNOSIS AND MANAGEMENT - A SINGLE CENTER EXPERIENCE

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BACKGROUND: Next generation sequencing (NGS) plays a role in neuro-oncology research and in clinical diagnosis and management. Here, we describe how NGS for pediatric CNS tumors impacted clinical diagnosis and therapy at a single institution. METHODS: NGS was performed using the UCSF 500 Gene Panel (targeted sequencing platform covering about 500 cancer associated genes). Patients were selected for NGS based on tumor pathology /need to identify therapeutic targets. We collected data on patient demographics, tumor histology/pathway alterations/therapeutic targets/therapy and used descriptive statistics for data analysis. RESULTS: Between January 2016 and July 2019, about one-third of patients with CNS tumors seen at our institution (N=29) were interrogated. NGS revealed pathway alterations in 20/29 patients. Treatment recommendations/modifications based on pathway alterations/therapeutic targets impacted the therapy of 18 patients. Patient groups: Medulloblastoma (N=6), alterations in WNT, SHH, and TP53 pathways (Vismodegib recommended for SHH pathway alteration but not used). **High-grade glioma** (N=4), alterations (with treatment changes) included, NF1(Trametinib, Everolimus); MSH2/MLH1(Nivolumab); CDKN2A/CDKN2B/CDKN2C(Abemaciclib); EGFR (Osimertinib, Afatinib); H3K27M (Panobinostat/ONC201); BRAFV600 (Dabrafenib, Trametinib); **ATRT** (N=1) SMARCB1; Low Grade Glioma (N=10), BRAFV600(Vemurafenib) /BRAFKIAA1549 fusion (Trametinib)/PIK3CA; **DIPG** (N=5), H3K27M/BCOR/ P53/ACVR/PIK3CA (LY3023414, Everolimus)/PDGFR(Dasatinib); Ependymoma (N=3), PFA/PFB/RELA Fusion. Seven patients were treated with targeted therapy + conventional therapy. In 8 patients targeted therapy remains an option but not yet needed. CONCLUSIONS: NGS of pediatric brain tumors is widely available and contributes to the diagnosis/therapy of pediatric CNS tumors. Optimal chemotherapy/targeted therapy combinations are areas of study.

NEUROPSYCHOLOGY/QUALITY OF LIFE

QOL-01. LONGITUDINAL COMPARISON OF NEUROCOGNITIVE TRAJECTORIES IN PEDIATRIC MEDULLOBLASTOMA PATIENTS TREATED WITH PROTON VERSUS PHOTON RADIOTHERAPY

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PURPOSE: By reducing dose to normal brain tissue, proton radiotherapy (PRT) may lessen neurocognitive risk traditionally associated with photon radiotherapy (XRT). We examined change in neurocognitive scores over time in pediatric medulloblastoma patients treated with PRT versus XRT. METHODS: Neurocognitive scores from 79 patients (37 PRT, 42 XRT) were examined. Patients were treated between 2007–2018 on the same treatment protocols that differed only by craniospinal modality (PRT versus XRT). Change in scores over time since diagnosis were compared between groups. RESULTS: Groups were similar on most demographic/clinical variables: sex (67.1% male), age at diagnosis (mean 8.6 years), CSI dose (median 23.4 Gy), length of follow-up (mean 4.3 years), and parental education (mean 14.3 years). Boost dose (p<0.001) and margin (p=0.001) differed between groups. Adjusting for covariates, the PRT group exhibited superior outcomes in global IQ, perceptual reasoning, and working memory versus the XRT group (all p<0.05). The XRT group exhibited significant decline in global IQ, working memory, and processing speed (all p<0.05). The PRT group exhibited stable scores in all domains except processing speed (p=0.003). Posterior fossa syndrome imparted risk independent of modality. CONCLUSION: This is the first study comparing neurocognitive trajectories between pediatric patients treated for medulloblastoma with PRT versus XRT on comparable, contemporary protocols. PRT was associated with more favorable neurocognitive outcomes in most domains compared to XRT, although processing speed emerged as vulnerable in both groups. This is the strongest evidence to date of an intellectual sparing advantage with PRT in the treatment of pediatric medulloblastoma.

QOL-02. PERCEPTIONS OF LATE EFFECTS CARE NEEDS AMONG SURVIVORS OF PEDIATRIC BRAIN TUMOURS

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OBJECTIVES: Pediatric brain tumour survivors are at risk of long-term consequences of therapy. Comprehensive late effects care may mitigate these risks, but the best care model is unclear. We sought to describe the care experience and quality of life (QOL) of pediatric brain tumour survivors at the McMaster Children's Hospital joint adult/pediatric Neuro-Oncology clinic. METHODS: Cross-sectional survey data were collected. Care needs were assessed with the Cancer Care Experience Questionnaire (CCEQ), Cancer Worry Scale (CWS), and Self-Management Skills Scale (SMSS). Quality of life was measured utilizing the PedsQL Brain Tumor Module. Data were analyzed descriptively. RESULTS: Thirty-two childhood brain tumor survivors and/or their parents participated. Their malignancies included embryonal tumors (medulloblastoma/ATRT) (62%), ependymoma (22%), and germ cell tumours (16%). Among 77%, therapy included chemotherapy, surgery and radiation. Most respondents reported high quality cancer care, although some could not recall discussions of late effects risks and health promotion. Mean cancer worry scores were low (71.8 (± 28.4)). Survivors reported limited self-management skills (58.5 (±18.2)), with support required in clinic visits, arranging medical appointments, filling prescriptions and tasks of daily living. Overall median QOL scores were in the 'good' range (parental report 72.3 (±17.7), survivor 68.2 (±16.6)). CONCLUSION: In comparison to other childhood cancer survivor cohorts, this group of long-term brain tumour survivors appear to have similar QOL, fewer cancer worries, and increased need for aid with self-management. Given this, along with the positive care experience reported, this clinic model of care appears to meet the needs of this population.

QOL-04. INFLUENCE OF FAMILY, SCHOOL, AND HOSPITAL SYSTEMS IN SUPPORTING SURVIVORS OF PEDIATRIC BRAIN TUMORS WITH NEUROCOGNITIVE LATE EFFECTS

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OBJECTIVE: Pediatric brain tumor survivors (PBTS) are at risk for developing neurocognitive late effects that may interfere with academic and adaptive functioning. To mitigate the potential impact, some PBTS may implement strategies independently, while others may rely on system-level support from family, school, or hospital systems. Given the limited knowledge on survivor and family perspectives of these supports, we conducted a mixed-methods study involving PBTS and their caregivers to examine the

influence of family, educational, and hospital supports, and identify areas of unmet need. PARTICIPANTS AND METHODS: PBTS (N=56,M_{age}=18.12,range=10–25) completed questionnaires on academic accommodations. Medical chart reviews provided diagnosis and treatment information. A subset of families, who did not significantly differ from the larger sample on demographics, completed qualitative interviews (N=25). Three coders identified themes separately for parents and survivors and reached consensus (kappa's > .78) using thematic content analysis. RESULTS: Families emphasized the role of family support, including providing individualized help, setting up a structured learning environment, and suggesting metacognitive strategies. Parents also emphasized how they have adjusted their expectations. At school, 53% reported an individualized education plan. Formal accommodations (e.g., modified coursework, small group instruction, extra time) were helpful, yet some noted barriers, including embarrassment and lack of follow-through. Survivors emphasized the value of informal accommodations. Families described unmet needs related to connecting with other survivors, navigating community and educational resources, and transitioning to adulthood. CONCLUSIONS: PBTS seem to rely on systems-level supports to mitigate neurocognitive effects. Future work should strengthen communication between systems and adult transition services.

QOL-05. TUMOR LOCATION IS LESS LIKELY INFLUENCE ON COGNITIVE DYSFUNCTION IN CHILDREN

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INTRODUCTION: Though several factors are known to influence on long-term cognitive function in children with brain tumor, the impact of tumor localization to specific cognitive function was not well known. Here we investigated the influence of local brain resection by surgery on postoperative cognitive outcome in school-aged children. METHODS: Participants were seven pediatric patients who underwent craniotomy for tumor resection in our hospital (mean age, 13.9 years). Their diagnosis were WHO grade 1 or 2 glioma (n=6) and hemangioma (n=1). Tumor were mainly located in following regions; frontal, n=2; parietal, n=2; temporal, n=3 (These lesions included hippocampus or were located very close to it). Temporal assessments for cognitive function of several functional domains were performed according to tumor location until post-op 1 year. Based on MRI, we estimated cognitive dysfunctions and compared them to observational symptoms. RESULTS: Preoperative cognitive function was normal in all patients. Cognitive dysfunctions estimated from resected area were as follows (cumulative total number); memory or working memory disorder, n=4; visuospatial cognitive disorder, n=3; disorder of processing speed, n=2; facial or topographical agnosia, n=2; Gerstman syndrome, n=1. Just after surgery, cognitive function was declined in two functional domains of two patients, which were only 16.7% of estimated deficit from resected region. They recovered completely until 3 months postoperatively, and returned to school without any deficits. CONCLUSIONS: In pediatric lower-grade tumor, focal cognitive symptom was unlikely to be induced by local resection.

QOL-06. QUALITY OF LIFE IN MEDULLOBLASTOMA SURVIVORS IN WESTERN MEXICO

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BACKGROUND: Treatment of children with medulloblastoma (MB) can lead survivors to lidiate with long term sequelae and affect their quality of life (QoL). This study evaluates QoL in long term MB survivors. DESIGN/METHODS: Clinical files of MB survivors from 1997 to 2016 were retrospectively analyzed. QoL was defined by Schipper Criteria in a five dimensional evaluation: clinical data, physic effects of treatment, academic develop, functional state and self welfare report. RESULTS: Clinical data: Twenty eight survivors were identified, mean age at review was 18 years, median follow up was 106 months. Functional state: Last visit Karfnosky/lansky were 90 to 80% in 25% of patients. Physic effects of treatment: Cerebellar Mutism or ataxia were present in 25% of cases. Two patients required external dispositives. Audiometry detected an auditive tonal decrease in 25% of cases. An endocrine disfunction was present in 46% of cases, 32% required hormone replacement and 28% having short size. Renal damage without dialysis was detected in 7% and 10% had a transient tubulopaty. One case had bilateral amaurosis and 14% uses glasses. Three patients had a life partner. One female has offspring and two males had azoospermia. Academic development: While 90% attends to school, 35.7% complained of learning difficulties and 18% needed special education. Self welfare report: Difficulties in social environment were described in 21% and 14% still feeling sick during years. CONCLUSIONS: Survivors of MB had adverse physical effects, followed by academic development, functional state and self welfare report and all this has a negative impact in their QoL.

QOL-07. CORTICAL VOLUME AND THICKNESS IN ADULT SURVIVORS OF CHILDHOOD POSTERIOR FOSSA TUMORS

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PURPOSE: A brain tumor treatment including cranial radiotherapy has previously been associated with long-term neurocognitive sequelae. Since underlying neurological mechanisms remain inconclusive, we investigated cortical features in childhood posterior fossa tumor survivors. METHODS: T1-weighted MRI (MPRAGE, resolution=.98x.98x1.2mm) was acquired to investigate the cortical structure in adult survivors of childhood infratentorial tumors (n=19, 15males) (16.4–34.8 years old, >2years after treatment). These scans were compared to age- and gender- matched controls. Supratentorial cortical volume and thickness were investigated using voxel-based morphometry (VBM) and surface-based morphometry (SBM), respectively. We compared patients and controls, irradiated (n=13) versus non-irradiated patients, and investigated the age at radiotherapy (peak level: p<.001). RESULTS: Lower GM volumes were encountered in multiple brain areas of patients compared to controls, with the largest clusters in the right and left occipital fusiform gyri. Irradiated patients showed lower GM volumes then non-irradiated patients in the superior and middle frontal gyri, the right supramarginal gyrus and precuneus. Age at radiotherapy was associated with GM volume in the inferior frontal gyrus. SBM yielded larger cortical thickness in patients in the left precuneus, inferior temporal and fusiform gyrus. The opposite effect was only marginally significant, in the left temporal lingual gyrus. Age at radiotherapy was not associated with cortical thickness, but radiotherapy was associated with lower thickness of the left pars opercularis. CONCLUSION: Widespread differences in cortical volumes and thickness were observed in posterior fossa tumor survivors. Both radiotherapy and age at radiotherapy could be suggested as risk factors for long-term cortical development.

QOL-09. WHOLE-BRAIN WHITE MATTER NETWORK CONNECTIVITY IS DISRUPTED BY PEDIATRIC BRAIN TUMOR TREATMENT

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INTRODUCTION: Treatments for pediatric brain tumors (PBT) are neurotoxic and lead to long-term deficits that are driven by the perturbation of underlying white matter (WM). It is unclear if and how treatment may impair WM connectivity across the entire brain. METHODS: Magnetic resonance images from 41 PBT survivors (mean age: 13.19 years, 53% M) and 41 typically developing (TD) children (mean age: 13.32 years, 51% M) were analyzed. Image reconstruction, segmentation, and node parcellation were completed in FreeSurfer. DTI maps and probabilistic streamline generation were completed in MRtrix3. Connectivity matrices were based on the number of streamlines connecting two nodes and the mean DTI (FA) index across streamlines. We used graph theoretical analyses to define structural differences between groups, and random forest (RF) analyses to identify hubs that reliably classify PBT and TD children. RESULTS: For survivors treated with radiation, betweeness centrality was greater in the left insular ($p < 0.000$) but smaller in the right pallidum ($p < 0.05$). For survivors treated without radiation (surgery-only), betweeness centrality was smaller in the right interparietal sulcus ($p < 0.05$). RF analyses showed that differences in WM connectivity from the right pallidum to other parts of the brain reliably classified PBT survivors from TD children (classification accuracy = 77%). CONCLUSIONS: The left insular, right pallidum, and right inter-parietal sulcus are structurally perturbed hubs in PBT survivors. WM connectivity from the right pallidum is vulnerable to the long-term effects of treatment for PBT.

QOL-11. COMPARISON OF TREATMENT BURDEN RATING SCALES ON NEUROCOGNITIVE OUTCOMES IN A MIXED SAMPLE OF PEDIATRIC BRAIN TUMOR SURVIVORS

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BACKGROUND: Predicting neurocognitive outcomes in pediatric brain tumor (PBT) patients is challenging. Rarity of PBT makes inclusion of detailed risk factors (e.g., treatment modality, intensity, individual complications) difficult when sample sizes are small. The Neurological Predictor Scale (NPS) summarizes complications and treatment factors associated

with neurocognitive risks and has modest validation. Recently, the Pediatric Neuro-Oncology Rating of Treatment Intensity (PNORTI) was developed to evaluate the impact of treatment intensity on psychosocial outcomes but has not been compared to neurocognitive outcomes. This study compared the NPS and PNORTI in terms of relationship to neurocognitive outcomes known to be at risk in PBT survivors. METHODS: 88 PBT survivors' neuropsychological outcomes were retrospectively analyzed in relation to the NPS and PNORTI. Variables of interest included IQ, working memory, and processing speed. RESULTS: NPS associated with lower IQ (rs=-.476, p=.001), lower working memory (rs=-.323, p=.010), and lower processing speed (rs=-.389, p=.007) in patients diagnosed at a younger age, but only processing speed for children diagnosed after age 7 years (rs=-.262, p=.036). PNORTI was not correlated with neurocognitive variables for either group. CONCLUSION: NPS has value in predicting neurocognitive outcomes, though much more in a younger age at diagnosis group compared to older patients. The PNORTI did not demonstrate predictive value for these neurocognitive domains in our sample. Given the potential clinical and research value of a summary rating of treatment burden relating to long-term outcome, future research should include relationship to psychosocial outcomes and quality of life.

QOL-12. CLINICAL SIGNIFICANCE OF RADIATION-INDUCED CEREBROVASULAR DISEASE IN CHILDHOOD BRAIN TUMOR SURVIVORS

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BACKGROUND: Childhood brain tumor survivors have a high risk of early cerebrovascular disease, but currently its clinical significance is unknown. METHODS: In a nation-wide study, we investigated 68 childhood brain tumor survivors treated with radiotherapy by using magnetic resonance imaging (MRI) and neuropsychological examination after median follow-up time of 20.6 years (range 5.0 – 33.1 years) since radiotherapy. Associations between imaging markers of cerebrovascular disease, white matter hyperintensities and the results of neuropsychological examination were investigated. RESULTS: Majority (65 %) of the survivors was diagnosed with cerebrovascular disease at median age of 27.1 years (range16.2 – 43.8 years). The presence of imaging markers of cerebrovascular disease or white matter hyperintensities was associated with poorer performance in verbal (VIQ) and performance (PIQ) intelligent quotient, working and semantic memory, executive functions, visuospatial ability, and immediate and general auditive memory ($P < 0.05$). Survivors with microbleeds performed worse in PIQ, processing speed, executive functions, and visuospatial ability ($P < 0.05$). Lacunar infarcts were associated with difficulties in visuospatial ability ($P < 0.05$). Survivors with white matter hyperintensities in MRI had higher impairment of working and semantic memory, visuospatial ability, and general auditive memory ($P < 0.05$). Cerebrovascular and small-vessel disease burden associated with poorer neurocognitive performance. CONCLUSION: The imaging markers of cerebrovascular disease and white matter hyperintensities were related to poorer cognitive performance in radiation-treated long-term survivors of childhood brain tumor. Longitudinal studies are urgently needed to investigate how cerebrovascular disease and related cognitive impairment progress in the survivors.

QOL-13. NEUROCOGNITIVE OUTCOMES ACCORDING TO RISK-ADAPTED TREATMENT REGIMENS FOR CHILDREN OLDER THAN 4 WITH MEDULLOBLASTOMA AND POSTERIOR FOSSA EPENDYMOMA – RESULTS OF THE HIT2000 TRIAL

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OBJECTIVES: Reduced neuropsychological outcomes are a major concern in pediatric patients with malignant brain tumors. We aimed to estimate decline in cognitive function according to treatment regimens. METHODS: Cross-sectional analysis of cognitive functions tested with the Neuropsychological Basic Diagnostic tool (NBD) in 279 patients >4 years at diagnosis (median: 8.66; range: 4.01–18.98) with medulloblastoma (n=110, 23.7–25.0Gy CSI; n=131, >30Gy CSI) or posterior fossa ependymoma (n=38 local radiotherapy) who participated in the HIT-2000 trial. Multivariable regression analysis was conducted to adjust for postoperative cerebellar mutism syndrome, preoperative hydrocephalus, postoperative shunt placement, the interval between diagnosis and assessment, sex and age. RESULTS: Mean time from diagnosis to assessment was 5.1 years. Increasing CSI-dose was significantly associated with a deterioration in performance of most subtests, particularly in areas of fluid intelligence (mean z-values per test for no CSI/23.4Gy/>30Gy respectively: matrix reasoning:-0.40/-0.52/-0.98, p<.001), short-term memory (number recall: -0.07/-0.58/-0.64, p=.002), visuo-spatial skills (visual-motor integration:-0.49/-0.68/-1.12, p<.001) and fine motor skills (dominant-hand:-1.09/-1.80/-2.12, p=.008; non-dominant-hand:-1.47/-2.59/-2.82, p=.003; bimanual coordination:-1.33/-2.68/-2.76, p=.001). These differences were retained after adjustment for confounding variables. Within medulloblastoma patients treated with >30Gy CSI, selective attention, but no other function was reduced in patients treated with pre-radiotherapy chemotherapy including intraventricular MTX (selective attention (with chemotherapy/without chemotherapy mean z-values: -0.66/0.00, p=.006)). Patients with SHH-activated medulloblastoma did significantly better than WNT or Group3/Group4 medulloblastoma patients in fluid intelligence and fine motor skills. CONCLUSION: CSI dose among other highly relevant factors had significant effects on neuropsychological outcome. Pre-radiotherapy intraventricular MTX had only minor effects. Patients with SHH-activated medulloblastomas showed a more favorable outcome when compared to patients in the other subgroups.

QOL-14. A BIOPSYCHOSOCIAL APPROACH TO BRAIN INJURY REHABILITATION FOLLOWING TREATMENT FOR PAEDIATRIC BRAIN TUMOURS: CAN PHARMACOTHERAPY AID NEUROPSYCHOLOGICAL OUTCOME?

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Long term survival following paediatric brain tumours has vastly improved in recent decades. Consequently there is a drive towards improved quality of survivorship. Brain tumours, surgical resection and adjuvant therapies represent mechanisms for brain injury and can therefore negatively impact a child's neuropsychological trajectory; affecting cognition, behaviour, emotional and adaptive functioning and educational/occupational outcomes. A biopsychosocial approach to rehabilitation should target each of these domains through supported remediation, environmental modification and psychoeducation for young people and the key systems around them (e.g. families, education). There is a growing evidence base for the role of concordant psychopharmacologies to improve neuropsychological outcome. Since 2015 children treated at RHSC Edinburgh for brain tumours have been offered pharmacotherapy alongside usual rehabilitation approaches if they demonstrate significant difficulties with Attention, Processing Speed and/or Executive Function on formal neuropsychological assessment. Patients are referred to a Consultant Psychiatrist or Paediatrician (as per local protocol) for medication selection, titration and monitoring. A short case series (N=14) is presented outlining brain tumour pathologies, treatment modalities, neuropsychological profile and rationale for recommending pharmacotherapy. Approximately 50% of patients took up the offer. The treatment/s offered and self or parents reported outcomes is summarised. Pharmacotherapy was broadly effective; "*it's been like night and day*", although for one case (N=1) the side effects outweighed any benefit; "*she became even more emotional*". Findings indicate that pharmacotherapy should be considered alongside conventional neurorehabilitation techniques for CYP with specific cognitive difficulties following treatment for paediatric brain tumours.

QOL-15. NEURAL NETWORK INTEGRITY FOR FACIAL AFFECT RECOGNITION IN SURVIVORS OF MEDULLOBLASTOMA

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BACKGROUND: Medulloblastoma survivors are at risk for social deficits, yet underlying mechanisms are poorly understood. METHODS: Facial affect recognition was assessed in 50 medulloblastoma survivors treated with craniospinal radiation (median[range] 21.4[12.5–30.9] years old, 11.0[5.7–22.6] years since diagnosis) and 56 non-cancer age-, sex-, and race-matched controls. Brain activation and connectivity in core regions/nodes of the face perception network (fusiform gyri, occipital gyri, superior temporal sulcus) were examined using structural and functional neuroimaging. Structural networks were constructed from diffusion tensor imaging (DTI) data and individual node strength and efficiency were assessed. Functional MRI (fMRI) was conducted using a 1-back facial affect recognition task with assessment of regional differences in task-related cerebral blood flow (BOLD). Standardized neurocognitive testing was completed with 24 hours of brain imaging. RESULTS: Medulloblastoma survivors performed worse on a behavioral measure of facial affect recognition (P=0.003) compared to matched controls. During the facial affect recognition task, controls demonstrated greater BOLD activation of the left and right fusiform gyri and the left and right middle occipital gyri compared to survivors ($P's$<0.05, corrected for multiple comparisons). DTI indicated weaker core node strength in survivors in the right lateral occipital gyri (P=0.02) and efficiency was lower in the left (P=0.01) and right (P=0.03) occipital gyri compared to controls. CONCLUSIONS: Medulloblastoma survivors have deficits in facial affect recognition and reduced activation and efficiency in brain regions comprising the face perception network compared to matched controls. Interventions targeting this specific skill and neural network may improve social functioning in survivors.

QOL-17. BIOLOGICAL CORRELATES OF QUALITY OF SURVIVAL AND NEUROCOGNITIVE OUTCOMES IN MEDULLOBLASTOMA; A META-ANALYSIS OF THE SIOP-UKCCSG-PNET3 AND HIT-SIOP-PNET4 TRIALS

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Relationships between biological factors (genetic, tumour molecular subgroup) and neurocognitive/Quality of Survival (QoS) outcomes in medulloblastoma survivors are emerging, based on studies of limited retrospective cohorts. Integrated investigations of the medulloblastoma late-effects pathway (considering biological, clinical and treatment factors), using larger clinically-controlled cohorts, are now essential to determine their independent significance and potential for clinical application. In a combined cohort of SIOP-UKCCSG-PNET3 and HIT-SIOP-PNET4 patients (n=150), molecular subgroup (MB_{WNT}, MB_{SHH}, MB_{Grp3}, MB_{Grp4}) was assessed against QoS measures [health status: HUI3; emotional and behavioural difficulties: SDQ; Health-related Quality of Life (HrQoL): PedsQL]. Additionally, in DNA remaining from HIT-SIOP-PNET4 (n=74), 39 candidate SNPs (involved in metabolism, DNA maintenance/repair, neural growth/repair and oxidative stress/inflammation) were genotyped by multiplexed MALDI-TOF MassArray and assessed against Wechsler Intelligence Scale (WISC) scores. Molecular subgroup was significantly associated with HrQoL and health status in univariate analyses; MB_{Grp4} predicted significantly worse outcomes than MB_{SHH} and MB_{Grp3} ($p<0.05$), but not in multivariate analyses taking into consideration other significant and reported QoS predictors (e.g. treatment, gender, age). In contrast, 6 SNPs were significantly associated with ≥1 WISC domain; 4/6 showed associations across domains. 3 SNPs were independently prognostic in multivariate analyses, and further significant associations were apparent at the gene (*BDNF, APOE*) and pathway (folate) level. This cross-discipline, international study encompassing two medulloblastoma trials has identified relationships between molecular subgroup, genotype and survivorship outcomes. These findings now require assessment in larger series, to inform our understanding of medulloblastoma survivorship outcomes and impact future disease management strategies.

QOL-18. A LONGITUDINAL STUDY OF NEUROCOGNITION IN CHILDREN TREATED FOR A BRAIN TUMOR

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It is well known that neurocognition in children treated for a brain tumor can be affected. However, studies on the trajectory of these neurocognitive problems are scarce. In the present study we investigated the evolution of neurocognition between timepoints of diagnosis, 2, 4 and 6 years later. A total of 53 children diagnosed with a brain tumor were recruited in this study, of which all completed a comprehensive neuropsychological test battery at three successive timepoints and 30 at 4 timepoints. The first assessment was conducted as soon as possible after diagnosis and before initiation of chemo- and/or radiotherapy. Mean age at diagnosis was 8.06 years. The most common diagnoses were pilocytic astrocytoma (n=28) and medulloblastoma (n=10). 24.5% and 18.9% of these patient groups received focal or craniospinal irradiation, respectively. A repeated measures analysis with cranial irradiation (no, focal, craniospinal) as between-subjects factor demonstrated a significant interaction effect between time and type of irradiation for overall intelligence (p=0.02) for children with three assessments. The same interaction effect was found for overall intelligence and processing speed for children with four assessments (p=.005 and p=.002, respectively). The group who received craniospinal irradiation demonstrated the most pronounced decline. Interestingly, no main time effect or interaction effect was found for general memory functioning. Our results demonstrate that not all neurocognitive functions in children treated for a brain tumor decline after treatment. Overall IQ and processing speed are the most vulnerable outcomes in our cohort, especially for the children treated with craniospinal irradiation.

QOL-19. PARENT-REPORTED COGNITIVE PROBLEMS AND DIRECT ASSESSMENT OF COGNITION IN CHILDREN TREATED FOR A BRAIN TUMOR

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The Pediatric Perceived Cognitive Function (PedsPCF) item bank is a short parent and self-reported cognitive screening questionnaire developed in the context of pediatric oncology. The PedsPCF demonstrated satisfactory psychometric properties and the scores of the PedsPCF are found to be associated with clinical outcomes. Today little research is available to evaluate whether the PedsPCF is correlated with direct assessments of neurocognitive domains. The aim of the current study is to investigate whether important cognitive domains, such as different aspects of intelligence, memory, visuomotor integration can predict the PedsPCF score. We obtained 100 PedsPCF filled in by parents from children treated for a brain tumor. All these children completed a comprehensive neuropsychological battery. Mean age at diagnosis was 7.47 years and mean age at completion of PedsPCF and testing 13.84. The most common diagnoses were pilocytic astrocytoma (n=43) and medulloblastoma (n=14). A linear regression model with verbal comprehension, perceptual reasoning, processing speed, visuomotor integration as predictors for overall PedsPCF score was significant (p.005), but the overall model fit was limited (adjusted R^2: 14%). Visuomotor integration and processing speed were significant predictors (beta = 0.56 and -0.29). Our results are in line with the overall finding that the correlation between questionnaires assessing quality of survival and direct assessments of cognition are low. For clinical practice these results are important as the PedsPCF can't be used to replace direct cognitive assessments or vice versa.

QOL-20. IMPACT OF RADIATION DOSE AND VOLUME ON MEMORY FUNCTIONING IN CHILDREN WITH MEDULLOBLASTOMA: A REPORT FROM CHILDREN'S ONCOLOGY GROUP (COG) ACNS0331

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BACKGROUND/OBJECTIVES: We examined longitudinal verbal and visual memory functioning in children treated for medulloblastoma on COG protocol ACNS0331. METHODS: Children with medulloblastoma participated in neuropsychological testing at three timepoints over a 6-year period. Children aged 3–7 years were randomized to receive craniospinal irradi-

ation (CSI) of either 23.4Gy (standard dose; SDCSI) or 18Gy (lower dose; LDCSI). Children aged 8+ received SDCSI. All children were also randomized to receive either a reduced radiation boost to the involved field (IFRT) or a standard boost to the whole posterior fossa (PFRT). Memory functioning was evaluated an average of 0.67(T1), 2.95(T2), and 4.90(T3) years post-diagnosis. RESULTS: Of 464 eligible patients enrolled on ACNS0331, 354 (76%; 65.3% male, 83.1% white) completed some neuropsychological testing. Mean age at diagnosis was 9.1 years (range=3–19). Verbal and visual short-term memory and learning were broadly within the average range for the overall sample at all three timepoints. However, a large percentage of children exhibited scores ≥1SD below the mean on tasks of verbal learning both immediately (43.4%) and after a delay (40.7%) at T3. In addition, 58.6% of children randomized to SDCSI exhibited impairment in verbal learning after a delay compared to 34.8% of children randomized to LDSCI, and 35.0% of those aged ≥8 at diagnosis receiving SDCSI. CONCLUSIONS: Younger children receiving SDCSI have particularly high rates of memory impairment five years after diagnosis of medulloblastoma. Limiting CSI dose and/or volume in young children treated for this diagnosis may improve outcomes for memory functioning.

QOL-21. DEVELOPMENT AND UTILISATION OF A NEURO-ONCOLOGY REHABILITATION TEAM: 2018–2019 UPDATE

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INTRODUCTION: A multi-disciplinary Neuro-Oncology Rehabilitation Team (NORT) was established at our institution in 2014. We reviewed NORT inputs, processes and outputs in 2018 to 2019 compared to our previously presented data from 2015, soon after service inception. METHODS: Retrospective analysis of patients who received NORT input June 2018 - May 2019 compared to 2015 data. Descriptive analysis of changes to NORT operational processes and structure. Complexity of rehabilitation needs was measured using the Rehabilitation Complexity Scale-Extended V13 (RCS). RESULTS: 54 children received NORT input in 2018–2019 (10 children in 2015) with total of 129 outputs. NORT input was highest in children with high grade glioma (median reviews: 3; median RCS: 5) and ependymoma (median reviews: 3; median RCS: 5). Pilocytic astrocytoma formed the largest tumour group (n = 11; median reviews: 2; median RCS: 7). 11% patients were referred to neurologist (9% already known); 17% referred to community services (44% already known); 31% referred to neuropsychology. In 2015, outputs were predominantly referral to occupational therapy and physiotherapy. 6 patients (11% of 54) were discharged in 2018–2019 (40% of 10 patients in 2015). 4 patients died. Between 2015 and 2019, developments included: clarifying referral and discharge pathways, use of screening measures, neuropsychology integration, therapy-led drop-in clinics, use of RCS-E. DISCUSSION: There has been a clear increase in utilisation and scope of work of NORT over last 4 years. The strength of this team is multidisciplinary working and expertise. Further developments planned: multidisciplinary rehabilitation interventions and NORT outcome tools.

QOL-22. MACHINE-LEARNING INFERENCE MAY PREDICT QUALITY OF LIFE SUBGROUPS OF ADAMANTINOMATOUS CRANIOPHARYNGIOMA

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BACKGROUND: Due to disease and/or treatment-related injury, such as hypothalamic, visual, and endocrine damage, quality of life (QoL) scores after childhood-onset Adamantinomatous Craniopharyngioma (ACP) are among the lowest of all pediatric brain tumors. Decision-making regarding management would be aided by more complete understanding of a patients likely QoL trajectory following intervention. METHODS We retrospectively analyzed caregiver and patient-reported QoL-instruments from the first 50 patients (ages 1–17 years at diagnosis) enrolled in the international Advancing Treatment for Pediatric Craniopharyngioma (ATPC) consortium. Surveys included 205 pediatric-relevant questions and were completed at diagnosis, and 1- and 12-months following diagnosis. Using Multiple Correspondence Analysis (MCA), these categorical QoL surveys were interrogated to identify time-dependent patient subgroups. Additionally, custom deep learning classifiers were developed using Google's TensorFlow framework. RESULTS By representing QoL data in the reduced dimensionality of MCA-space, we identified QoL subgroups that either improved or declined over time. We assessed differential trends in QoL responses to identify variables that were subgroup specific (Kolmogorov-Smirnov p-value < 0.1; n=20). Additionally, our optimized deep learning classifier achieved a mean 5-fold cross-validation area under precision-recall curve score > 0.99 when classifying QoL subgroups at 12 month follow-up, using only baseline data. CONCLUSIONS: This work demonstrates the existence of time-dependent QoL-based ACP subgroups that can be inferred at time-of-diagnosis via machine learning analyses of baseline survey responses. The ability to predict an ACP patient's QoL trajectory affords caregivers valuable information that can be leveraged to maximize that patient's psychosocial state and therefore improve overall therapy.

QOL-23. ASSESSING THE IMPACT OF METHYLPHENIDATE ON LATE COGNITIVE EFFECTS IN PAEDIATRIC BRAIN TUMOUR SURVIVORS: A SERVICE-BASED EVALUATION

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OBJECTIVE: One of the most disabling side effects of treatment in survivors of brain tumours is the resultant reduction in level of processing speed and attention. This study aimed to evaluate intellectual and psychological benefit of short-acting methylphenidate to survivors of brain tumour. METHODS: Paediatric BT patients attending a UK specialist treatment centre received assessment of cognitive performance. All patients identified with attentional difficulties were screened for contraindications to methylphenidate. Participants (N=23), mean age 11.09 years, completed a 6-month trial of methylphenidate. Measures of attention (Test of Everyday Attention for Children 2; SNAP-IV), side-effects (Stimulant Side-Effects Rating Scale), Health-Related Quality of Life (PEDS-QL), and experience of methylphenidate questionnaire (purpose-developed semi-structured questionnaire) were administered prior to medication and after six months. RESULTS: Participants showed improvement in selective attention ($t(18)$=-5.4, p=<.001, d=.93) and processing speed ($t(16)$=-3.0, p=.01) at follow up. Family ratings of attention were significant ($t(17)$=14.46, p<.001, d=-1.19). Change in subjective measures of Health-Related Quality of Life (HRQoL) was also statistically significant as reported by children ($t(16)$=3.91, p=.001, d=-.99), and on a parental-report measure of child HRQoL ($t(15)$=-8.19, p<.001, d=-1.09). HRQoL measures show improvement to physical, academic, and emotional domains as reported by participants. CONCLUSIONS: Paediatric BT survivors showed benefit from provision of methylphenidate in terms of reduced attentional and processing deficit, and in terms of emotional wellbeing. Treatment was well tolerated. Continued follow-up of the current participants in a longitudinal study aims to evidence longer-term benefit to participants.

QOL-24. DIFFERENTIAL IMPACT OF TUMOR LOCATION, LOCAL AND CRANIOSPINAL IRRADIATION ON NEUROPSYCHOLOGICAL LONG-TERM OUTCOME IN CHILDREN WITH MEDULLOBLASTOMA, EPENDYMOMA AND SUPRATENTORIAL PNET: A LONGITUDINAL MULTICENTER OUTCOME ASSESSMENT OF CHILDREN FROM THE HIT-2000 AND HIT-REZ TRIALS

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Neurocognitive deficits are frequent in childhood brain tumor survivors and affect mental intelligence, psychomotor and executive abilities. The differential impact of factors such as disease (location, histology) or treatment (local *(LI) vs.* craniospinal irradiation (CSI)) on these parameters is not fully understood. Between 2007–2011 and 2013–2017 300 testings were performed on-site by one neuropsychologist. Of these, 274 tests from n=208 children with medulloblastoma (MB), ependymoma (EP) and supratentorial embryonal tumors (SET) <4 years at diagnosis are currently included into the analysis. Applied tests included the Bayley II, WUEP-KD, K-ABC, tapping speed (TS), CPT_Hits/CPT_DT, and, as a new score, CPT_Power which integrates the latter. Treatment consisted of surgery and chemotherapy ± LI/CSI. All children receiving CSI and MB children with LI showed substantial deficits in general intelligence scores. In contrast, children with MB or SET without CSI/LI and those with EP receiving LI performed surprisingly well after 2 and 5 years follow-up. Motor function (TS) was reduced in all children except those with SET without irradiation. Of note, mental processing speed (as measured in CPT_Power) was not essentially reduced in MB and EP patients, indicating that mental processing is less affected than motor speed (TS) in children with infratentorial tumors. In conclusion, our data show that besides the established detrimental effects of CSI on general intelligence, infratentorial tumor location is a main risk factor for motor dysfunction irrespective of irradiation. Appropriate sensitive testing tools are warranted to assess cognitive function without the interfering influence of motor dysfunction.

QOL-25. MICROSTRUCTURAL BRAIN CHANGES ASSOCIATED WITH NEUROCOGNITIVE AND FUNCTIONAL OUTCOMES OF INTRACRANIAL GERM CELL TUMUOR SURVIVORS – A DIFFUSIONAL KURTOSIS IMAGING STUDY

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BACKGROUND: Childhood intracranial germ cell tumour (iGCT) survivors are prone to radiotherapy-related neurotoxicity which can lead to neurocognitive dysfunction. Diffusion kurtosis imaging (DKI) is a MRI technique that quantifies microstructural changes in the grey and white matter of the brain. This study aims to investigate the associations between MR-DKI metrics, the cognitive and functional outcomes of childhood iGCT survivors. METHOD: 20 childhood iGCT survivors who had received cranial radiotherapy were recruited. DKI parameters were determined for iGCT survivors and 18 control subjects. Neurocognitive assessment using the Hong Kong Wechsler Intelligence Scales for Children (HKWISC)/ Wechsler Adult Intelligence Scale – Revised (WAIS-R) and functional assessment using the Lansky/ Karnofsky performance scales were performed for GCT survivors. RESULTS: There were significant negative correlation between the IQ scores and the mean diffusivity (MD) in multiple white matter regions of iGCT survivors including: anterior limb of internal capsule, superior fronto-occipital fasciculus, anterior corona radiata, uncinate fasciculus, cingulum and hippocampus. Mean kurtosis (MK) values of the superior fronto-occipital fasciculus were positively correlated with IQ scores. For grey matter, the MD of the olfactory, insula, caudate, heschl gyrus, parahippocampal gyrus, hippocampus, anterior cingulum, frontal inferior operculum, middle and superior temporal gyrus, middle and superior frontal orbital gyri, cuneus and precentral gyrus were negatively correlated with IQ scores. Most of the microstructural changes with associated functional impairment were white matter regions. CONCLUSION: Our study identified vulnerable brain regions with significant white and grey matter microstructural changes that were associated with impaired cognitive function or deficits in physical functioning.

QOL-26. I'VE GOT FRIENDS NOW: PAEDIATRIC PATIENTS' EXPERIENCES OF METHYLPHENIDATE TREATMENT FOR NEUROCOGNITIVE LATE-EFFECTS ASSOCIATED WITH BRAIN TUMOUR

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BACKGROUND: Whilst rates of survival following paediatric brain tumour have increased, quality of survival continues to present a significant challenge to children and their families. The neurocognitive impact of cranial radiotherapy (CRT) in childhood upon future intellectual development is well established. Both CRT and chemotherapy are associated with medium-term slowed speed of cognitive processing, attention, and memory impairment, and with longer-term failure to achieve pre-morbid intellectual potential and low Health-Related Quality of Life (HRQoL).Methylphenidate is a psychostimulant drug shown to be effective in alleviating some of the neurocognitive symptoms of cancer treatment, however the subjective experience of paediatric participants is not reported. AIM: The current study aimed to explore the subjective experience of HRQoL in paediatric neuro-oncology patients currently receiving methylphenidate. METHODS: A retrospective audit was conducted on 12 paediatric neuro-oncology patients in receipt of methylphenidate. Both standardised and novel measures were used to assess aspects of HRQoL, specifically; social life, perceived independence, mood, confidence, school life, self-esteem, interpersonal relationships and fatigue levels. Data collected were analysed using Thematic Analysis. RESULTS: Five key themes were identified; physical, emotional, social, academic and neuropsychological impact. CONCLUSION: The current findings evidence the perception of patients that methylphenidate supported them to regain previously lost functionality. Methylphenidate has the potential to increase HRQoL in this population and to provide children with the opportunity to regain a sense of normality in their lives.

QOL-27. SWALLOWING ASSESSMENT IN PEDIATRIC PATIENTS WITH BRAIN TUMOR

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BACKGROUND: Neurosurgical intervention is the initial modality of treatment for the vast majority of pediatric brain tumors. However, studies on the swallowing process in pediatric patients with brain tumors are scarce, especially comparing changes that can be identified before and after surgery. In clinical practice, it is possible to observe that these patients may present modifications in the swallowing phases both before and after surgery. Therefore, we conducted a longitudinal study with a cohort of 20 patients ranging in age from 0 to 17 years, in order to characterize the swallowing disorders. RESULTS: 30% of the patients presented some change in orofacial motricity in the organs related to initiation, coordination, and maintenance of swallowing at the time of hospital admission, and 65% of the patients exhibited these changes after surgery. Due to worsening in swallowing after surgery, 40% of the patients required modification of the consistence of oral diet or required the use of an alternative route of feeding. CONCLUSIONS: There is a high prevalence of swallowing disorders in pediatric patients with brain tumors, mainly regarding the proper functioning of organs related to initiation, coordination, and maintenance of swallowing even before the surgical intervention, and these changes increase after surgery - especially in patients with posterior fossa tumors. The role of the speech/language pathologist is of paramount importance, given their role in the assessment and adequacy of the feeding route, identifying patients at risk of pulmonary aspirations, minimizing swallowing complications, and also facilitating communication with patients and their families.

QOL-28. NEUROCOGNITIVE PROFILE OF PEDIATRIC MEDULLOBLASTOMA PATIENTS PRIOR TO RADIATION THERAPY

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Neurocognitive late effects are unfortunately common following treatment for pediatric medulloblastoma. While radiation therapy is an essen-

tial component of treatment for most pediatric medulloblastoma patients, it is associated with neurocognitive compromise. Effects include deficits in cognitive speed and performance efficiency, aspects of attention, as well as working memory. Yet long after treatment it is difficult to tease apart relative contributions of other risk factors to neurocognitive functioning beyond radiation. We examined neurocognitive functioning in a sample of pediatric medulloblastoma patients prior to radiation therapy, including investigation of neurocognitive risk factors such as hydrocephalus, presence of posterior fossa syndrome, and duration of neurological symptoms prior to diagnosis. Results indicated that the sample functioned in the average range in terms of overall IQ (n=34, X̄=103). Patients also functioned in the normal range in terms of language-based ability (X̄=106), nonverbal ability (X̄=104), and working memory (X̄=103). However, the sample performed statistically significantly lower than the general population in terms of cognitive speed and efficiency (z=-2.026, p=.043). The sample was also rated by parents as exhibiting more attention problems relative to the general population (z=1.988, p=.047). There was no specific association with hydrocephalus, duration of symptoms, or history of posterior fossa syndrome. Results suggest weaknesses in attention and processing speed may exist in some pediatric medulloblastoma patients prior to radiation therapy secondary to tumor and related complications. Implications for future research are presented, along with difficulties inherent to "baseline" assessment with pediatric brain tumor survivors.

QOL-31. USE OF PATIENT-REPORTED OUTCOMES TO IDENTIFY YOUTH AT RISK FOR IMPAIRED OVERALL HEALTH

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Pediatric brain tumor survivors often experience persistent and clinically significant late-effects following treatment. Critical to understanding morbidity is utilization of patient-reported outcomes (PROs). The current study evaluated PROs of individuals previously diagnosed with a pediatric brain tumor and identified risk factors for less optimal overall health. Participants included 127 youth 10.59±4.81 (M±SD) years old at survey completion and 4.45±3.82 years from diagnosis of a brain tumor (34.6% Pilocytic Astrocytoma, 9.4% Medulloblastoma, 9.4% Ependymoma, 7.9% Craniopharyngioma, 38.6% Other). Outcomes were assessed via Patient-Reported Outcomes Measurement Information System (PROMIS) parent-proxy measures. Overall health was assessed via PROMIS Global Health (i.e., a measure of general, physical, mental, and social health). Univariate and logistic regression analyses examined potential demographic, medical, and psychosocial factors (e.g., age, race, diagnosis, treatment) related to poor global health. Initial descriptive analyses suggested that most youth experienced anxiety symptoms (T-score M±SD=50.71±11.54), depressive symptoms (47.96±10.34), cognitive functioning (46.52±9.10), and fatigue (55.14±10.62) similar to their peers. However, 31.0% of youth experienced impaired global health (T-score<40). After adjusting for other potential covariates, the final model suggested that youth with significant anxiety (OR=6.20, CI=1.56–24.65), youth with significant fatigue (OR=3.96, CI=1.26–12.41), and youth who did not undergo a gross total resection (OR=0.25, CI=0.07–0.96) were at risk for impaired global health. Identifying those at-risk for impaired health is essential to reducing survivor morbidity and optimizing overall quality of life following treatment. Current data suggest potentially modifiable factors that may improve long-term outcomes for survivors of pediatric brain tumors.

QOL-32. THE PROMOTE STUDY: HEALTH-RELATED QUALITY OF LIFE COMMUNICATION NEEDS OF CHILDREN, ADOLESCENTS, AND THEIR FAMILIES ATTENDING OUTPATIENT CONSULTATIONS AFTER TREATMENT FOR A BRAIN TUMOUR

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BACKGROUND: Childhood brain tumours and their treatment can reduce health-related quality of life (HRQoL) and cause anxiety and depression, withdrawal, and social isolation. Improved communication within outpatient consultations may allow early identification and treatment of these issues. We explored family communication needs in survivors of childhood brain tumours receiving six-monthly follow-up outpatient review within the English NHS. METHODS: Semi-structured interviews were conducted with 18 families whose child aged 8–17 years had finished treatment for a brain tumour within the preceding five years. Thematic analysis used the Framework Method. RESULTS: Adjusting to change and finding a "new normal" was the overarching theme to emerge. HRQoL issues included fatigue, coping with physical changes, challenges at school, isolation, and adjusting to changes in abilities. Survivors described a need for greater knowledge about and more support with changes in cognitive functioning. Parents spoke about the impact on the wider family and their changed role in supporting the child's HRQoL. Communication barriers included short-term memory loss, shyness, and the need to suppress or regulate emotions evoked by these issues. Communication needs included more information regarding recovery and rehabilitation and/or help managing anxiety or emotional health. CONCLUSION: The above communication needs and barriers should be addressed. Having a digital record to document and monitor this information systematically could improve service planning and provide patients and their families with the resources to reach their full potential and experience a better HRQoL.

QOL-33. THE PROMOTE STUDY: DEVELOPMENT AND TESTING OF KLIK-UK, AN ONLINE PLATFORM, TO ENHANCE OUTPATIENT COMMUNICATION ABOUT HEALTH-RELATED QUALITY OF LIFE (HRQOL) AT THREE UK CHILDREN'S BRAIN TUMOUR TREATMENT CENTRES (CBTTCS)

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BACKGROUND: The HRQoL of survivors of childhood brain tumour is significantly reduced into adulthood but is not systematically assessed. In the UK, referral for appropriate support is often reactive rather than proactive. We developed KLIK, the online Dutch platform, for use to enable the systematic assessment of HRQoL in the UK NHS using patient-reported outcomes measures (PROMs) which could be fed back to clinicians during outpatient review appointments. METHODS: PARTICIPANTS: Children aged 5–17.9 years, receiving outpatient care >6 monthly for a brain tumour diagnosed within preceding 5 years and their parents and clinicians. SETTING: Three UK CBTTCs – UHS, Southampton; GOSH, London; and QMC, Nottingham. PROCEDURE: KLIK-UK was developed throughout the study and barriers and opportunities for its use logged. A. Development phase: relevant PROMs were identified through systematic literature review[1] and families' views regarding choice of PROMs, communication needs within consultations, and KLIK-UK were obtained by interview. B: Feasibility phase: KLIK-UK was tested in outpatient review appointments followed by interviews with the family and clinician. RESULTS: 57 families and 10 clinicians participated. The PedsQL-Core module was preferred by families. Communication needs and barriers were identified. All clinicians reported that they could see the potential value of using KLIK-UK but views differed as to whether they could use it within their current timetable. Analysis of interviews from the feasibility phase will be reported. CONCLUSION: KLIK-UK is ready for use in the UK but will need to be adapted according to local resources, needs, and preferences. [1]Bull et al. 2019 https://doi.org/10.1093/nop/npz064

QOL-34. CAREER FAIR AND RESOURCE EXPO: ADVOCATING FOR THE LONG TERM SUCCESS OF BRAIN TUMOR SURVIVORS

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Pediatric cancer survivors have increased unemployment and lower educational attainment rates. This is most significant in brain tumor survivors who show five-fold relative odds increase in unemployment over other pediatric cancer survivors. The long-term effects of brain tumor treatment potentiate the difficulty with work and school reintegration seen in the broader Adolescent and Young Adult (AYA) population. To address this, our team designed an annual job fair for AYA Neuro-Oncology survivors. Vendors were invited representing disability advocacy groups, legal services, scholarship organizations, and employers with strong disability services, several who offered on-site interviews. Additionally, brain tumor survivors served as inspirational speakers for the event. Between thirty to forty survivors have attended each event. Pre- and post-surveys, as well as 3- and 6- month follow up was obtained. Universally, the day was engaging and motivating, both for survivors and staff, and stimulated conversation for pursuing career or aca-

demic success within families and the care team. While all the patients took applications, none of the patients completed the on-site interviews, finding them overwhelming. Even at the 3- and 6-month follow-ups following the first event, the survivors continued to be at varying levels of application completion; no one who was previously unemployed attained new employment. This improved after pre-event meetings were held with survivors to participate in resume building and interview preparation. Currently, two survivors obtained employment and are still employed at 1 year and five survivors were able to advocate for their disabilities services in college with help of a non-profit legal assistant.

QOL-36. USE OF CANNABINOIDS IN THE PEDIATRIC CENTRAL NERVOUS SYSTEM TUMOR POPULATION

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BACKGROUND: Cannabinoids, including cannabidiol (CBD) and tetrahydrocannabinol (THC), are a class of compounds found in marijuana. Numerous studies in adults have examined cannabinoid use in management of cancer-related symptoms such as nausea, anorexia, and pain. Less is known about the use in the pediatric oncology population. METHODS: A prospective observational study has been ongoing since 2016 at Children's Hospital Colorado to evaluate cannabinoids' impact using PedsQL™ modules on quality of life of pediatric patients with central nervous system (CNS) tumors who are 2–18 years old. Laboratory assessments of T-cell activity and pharmacokinetics of CBD, THC and associated metabolites are in process. Diaries with exploratory information on cannabinoid use patterns are being collected. RESULTS: Thirty-three patients (14:19; male:female) have been enrolled with a median age of 6.4 years (range, 2.9–17.7 years). The most common tumor type in enrolled patients is embryonal tumors (13/33; 39%). Nine (27%) patients have low-grade glial/glioneuronal tumors, and eight (24%) had high-grade/diffuse midline gliomas. The remaining patients had ependymoma or craniopharyngioma. The median time on cannabinoids is 9 months. Most (n=20) patients have used oral products with CBD and THC. One patient continues on cannabinoid therapy in follow up. Preliminary immune function analyses identified impaired neutrophil superoxide anion production and chemotaxis in patients taking cannabinoids at early time points on therapy. CONCLUSIONS: Families of children with various CNS tumors are pursuing cannabinoid therapy for both antitumor and supportive care purposes. Analysis of the impact of cannabinoids on patients' quality of life is ongoing.

QOL-37. USE OF COMPUTERIZED NEUROPSYCHOLOGICAL MEASURES TO ASSESS COGNITIVE MORBIDITY IN CHILDREN UNDERGOING ACTIVE RADIATION THERAPY

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Cognitive late effects of brain tumors and related treatments are well-established; however, limited information regarding changes in cognition during radiation therapy (RT) is available. Recent advances in computerized neuropsychological assessments for monitoring of acute and late treatment effects have been developed, though the feasibility of using these tools in a population undergoing active RT has limited empirical evidence. This study investigated performance of pediatric patients with brain tumors actively undergoing RT on the NIH Toolbox (N = 10; M age = 11.29 ± 3.35 years; 86% Caucasian; 86% female). Given significant individual variability, one-sample proportion tests were calculated to assess whether the proportion of patients with performances >1 standard deviation below the mean significantly differed from normative expectations. Of the 12 participants that were enrolled in the study, 10 completed the NIH Toolbox during active RT. Compared to normative expectations, a greater proportion of participants undergoing active RT exhibited deficits on measures of processing speed, working memory, and response inhibition (p=<.01). Differences between participants and normative expectations were not seen on measures of visual memory and vocabulary (p=>.05). Seventy-seven percent of recruited participants completed computerized assessment during active RT, suggesting reasonable feasibility within the small cohort recruited. Consistent with the literature regarding late effects of RT, performance on computerized measures of cognitive functioning mediated by processing speed and aspects of executive functioning were lower for patients undergoing active RT. Further investigation will focus on clarifying the trajectory of deficits across treatment course and comparing computerized measures to traditional neuropsychological measures.

QOL-38. USE OF COMPUTERIZED NEUROPSYCHOLOGICAL MEASURES TO ASSESS COGNITIVE MORBIDITY IN SURVIVORS OF CHILDHOOD BRAIN TUMORS

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Treatment of central nervous system (CNS) tumors in pediatric populations is associated with significant cognitive morbidity. Documentation of neuropsychological deficits is vital to treatment and educational planning. We investigated the feasibility and utility of a computerized neuropsychological measure (NIH Toolbox Cognitive Battery) in differentiating individuals who received tumor treatment from healthy controls. Participants included pediatric CNS tumor survivors (N = 85; Mean Age = 13.47; SD = 4.76) at least 1-year post-completion of treatment and healthy sibling controls (N = 20; Mean Age = 10.2; SD = 3.21) who completed the NIH Toolbox. Ninety-eight percent of the participants enrolled completed the computerized tasks. The overall logistical regression model, with NIH Toolbox tests as predictors, was statistically significant [$\chi 2$ (7, N = 105) = 26.176; p < .001] and improved correct group classification from 81% to 82.9%. Picture Sequencing (β = -0.059; Wald = 6.942; p = .008) and Flanker (β = -0.083; Wald = 7.473; p = .006) were both statistically significant and negatively predictive of membership in the treatment group. For each 1 unit increase in standard score on measures of working memory and inhibition, odds of membership in the treatment group decreased by 6.2% and 8.7%, respectively. Consistent with the literature, worse performance on computerized measures of cognitive functioning mediated by executive functioning was correlated with a history of brain tumor treatment. Further investigation will focus on comparing computerized neuropsychological tools to traditional comprehensive neuropsychological evaluations and clarifying the trajectory of these deficits across recovery.

QOL-40. THE IMPACT OF TASK COMPLEXITY ON INFORMATION PROCESSING SPEED AND NEURAL COMMUNICATION IN PAEDIATRIC BRAIN TUMOUR SURVIVORS

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Paediatric brain tumour survivors (PBTS) experience slower information processing speed (IPS) that contributes to difficulty performing tasks of minimal (MC) and greater complexity (GC), and is related to aberrant neural communication. It is still unknown whether deficient IPS exists during *increasing* complexity. We aim to determine if PBTS experience deficient IPS and neural communication relative to typically developing children (TDC) during an increasingly complex visual-motor reaction time (RT) task. During magnetoencephalography recording, participants (n=58, 12.69 ±3.24 years) pressed a button with their left or right thumb after an arrow pointing in the corresponding direction appeared on a screen. During two MC conditions, the arrow pointed in a single direction. During a GC condition, the arrow alternated direction randomly. Mean RT >3SD and signal artifacts were removed prior to analyses. The phase lag index (PLI) estimated neural communication between 90 cortical sources. Linear regression and Network Based Statistics assessed group differences in mean RT and the PLI. PBTS demonstrated increased RT relative to TDC during the GC condition (p=0.04, M_{PBTS}=354.00s, M_{TDC}=326.00s). Group differences in mean RT during MC conditions and the PLI during all conditions were not detected (p>0.05). These results suggest PBTS experience slower IPS during GC. Reduced IPS is thought to contribute to difficulty recruiting cognitive resources needed to perform more complex tasks. Subtle deficits in neural communication may underlie slower IPS. The weighted PLI is superior to the PLI when estimating small differences in neural communication. We will now use the weighted PLI to assess task-related neural communication.

QOL-41. CARDIAC DYSFUNCTION IN MEDULLOBLASTOMA SURVIVORS TREATED WITH PHOTON IRRADIATION

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BACKGROUND: Medulloblastoma is an aggressive central nervous system (CNS) tumor that occurs mostly in the pediatric population. Treat-

ment includes surgical resection, craniospinal radiation (CSI) and chemotherapy. Children who receive standard photon radiation (RT) are at risk for cardiac toxicities. Potential late effects include coronary artery disease, left ventricular scarring and dysfunction, valvular damage and atherosclerosis. Current survivorship guidelines recommend routine ECHO surveillance for these patients but this comes at significant health care costs over a lifetime. We describe the experience of cardiac dysfunction in medulloblastoma survivors in a multi-institution study. METHODS: A retrospective chart review of medulloblastoma patients treated between 1980 and 2010 with radiation at Lurie Children's Hospital and Dana-Farber/ Boston Children's Hospital who had an echocardiogram done following completion of therapy. RESULTS: 168 patients were treated for medulloblastoma during the study time. Of whom, 80 patients had echocardiogram follow up and 76 received photon irradiation. The latter were included in the study. The mean age at CSI was 8.6 years (range 2.9- 20), and mean number of years post RT at echocardiogram 7.4 years (range 2–16). Mean ejection fraction (EF) was 60.03% and shortening fraction (SF) 33.8%. Four patients (5%) had abnormal results, all of which had EF<50%. CONCLUSION: Patients who received craniospinal irradiation for medulloblastoma therapy have relatively normal echocardiograms post treatment. Although RT may result in cardiac risks, echocardiograms may not be the most cost effective or efficacious mode to evaluate the risk in these survivors long term.

QOL-43. ENDOCRINE AND METABOLIC CHANGES IN CHILDREN TREATED FOR MEDULLOBLASTOMA

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We examined 63 patients (40 males/23 females) after complex treatment of medulloblastoma. Patients had a median age (range) of 11.3 (5.5 ÷ 17.9) years. The median time after the end of treatment was 3.7 (1.5 ÷ 11.6) years. Endocrine disorders were detected with the following frequency: growth hormone deficiency - 98.41% (62 of 63 patients), thyroid hormone deficiency – 69.8% (44/63), adrenal hormone deficiency - 17.4% (11/63). Three cases (4.7%) of premature sexual development were also detected. Lipids levels, beta-cell function and insulin resistance (IR) during 2-h oral glucose tolerance test were evaluated. A mono frequent bioelectrical impedanciometer was used to measure body composition. Overweight (SDS BMI> 1) was observed only in 16 patients (3 girls and 13 boys), obesity (SDS BMI> 2) in 1 boy. Dyslipidemia was found in 34 patients (54%). All patients underwent oral glucose tolerance test. Insulin resistance (ISI Matsuda <2.5 and/or HOMA-IR> 3.2) was detected in 7 patients (11/1%), impaired glucose tolerance (120 min glucose ≥7.8 mmol / l) was observed in 2 patients with IR and in 2 patients without IR. At the same time, IR and impaired glucose tolerance were encountered in only 5 children with overweight and no one with obesity. All patients with impaired glucose tolerance had normal values of fasting glucose (4.3 ÷ 5.04 mmol / l) and HbA1c (4.8 ÷ 5.8%). A bioelectrical impedanciometer was used to measure body composition in 49 cases, the percentage of adipose tissue was increased in 14 patients (28%) with normal BMI.

QOL-44. ASSESSMENT OF NEUROCOGNITIVE FUNCTION AND MRI PARAMETERS IN LONG-TERM SURVIVORS WITH POSTERIOR FOSSA TUMORS: A COMPARISON BETWEEN MEDULLOBLASTOMAS TREATED BY REDUCED-DOSE CRANIOSPINAL IRRADIATION AND OTHER TUMORS

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BACKGROUND: Children with medulloblastoma cannot avoid chemoradiotherapy including craniospinal radiation, although prognosis of medulloblastoma has improved and previous studies have reported a significant risk of intellectual disturbance by these treatments. We retrospectively analysed neurocognitive functions, clinical MRI parameters of patients with posterior fossa tumors, especially medulloblastomas. MATERIALS AND METHODS: Twenty-two patients (12 medulloblastomas, 5 ependymomas, 5 astrocytomas) treated in our institution were enrolled in this study. Mean age was 7.8 years and 6.5 years, percentage of hydrocephalus at onset was 66.7% and 60%, respectively in medulloblastoma group and in other tumor group (ependymoma and astrocytoma). Postoperative chemoradiotherapy including reduced-dose craniospinal irradiation (18Gy) was done for medulloblastoma group and local radiation or operation only was done for other group. Version 3 or 4 of Wechsler Intelligent Scale for Children (WISC) was used by neurocognitive function analysis. Ventricular size, white matter volume and other parameters were also was estimated based on MRI. Follow-up duration was 6–17 years (mean: 10.5 years). RESULTS: Evaluations of neurocognitive functions based on WISC pointed out lower performance IQ than verbal IQ in long term survivor of both group, especially working memory (P=0.05). Both hydrocephalus and cranial nerve complications was influenced lower scores of WISC, but age at onset did not influence WISC scores. Comparison between both group showed there was no significant difference about cognitive function and white matter volume. SUMMARY: Chemoradiotherapy including reduced-dose craniospinal irradiation and for medulloblastomas did not have significant risk increasing neurocognitive disfunction. But long-term follow-up and assessment of health-related quality of life are further needed.

QOL-46. LATE EFFECTS CARE FOR CHILDHOOD BRAIN TUMOUR SURVIVORS: A QUALITY IMPROVEMENT PROJECT

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BACKGROUND: Childhood and adolescent brain tumor survivors are at risk for considerable late morbidity and mortality from their disease and the treatment they receive. Surgery, chemotherapy, radiation therapy and tumor location all have the potential to impact the physical, psychological, functional and social health of these survivors. Comprehensive late effects care may mitigate these risks, but the necessary elements of this care model is unclear. We describe a quality-improvement initiative to improve the long-term follow-up (LTFU) care provided to brain tumour survivors at the McMaster Children's Hospital. METHODS: An anonymous needs assessment circulated to health providers was used to evaluate the LTFU practices. Utilizing this feedback as well as the LTFU guidelines from the Children's Oncology Group a care plan was made for these survivors. RESULTS: 17 of 33 (52%) health care staff responded to the survey, this included 70% physicians or nurse practitioners, and 30% nurses and allied health staff. Improvements suggested included consistent inclusion of additional care providers (i.e. social work, dietitians, endocrinology) reported by 76%, as well as a need for improved patient education and surveillance for late effects of therapy. CONCLUSION: Treatment summaries with surveillance care plans and LTFU resources were created for all survivors of childhood brain tumours at risk of treatment-related complications. Late effects counselling with distribution of these materials is ongoing as part of this quality improvement initiative. To provide comprehensive management, a neuro-oncology specific late effects programs with multi-disciplinary support is essential for the care of brain tumour survivors.

QOL-48. INTERDISCIPLINARY SPIRITUAL CARE TRAINING IN PEDIATRIC NEURO-ONCOLOGY

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INTRODUCTION: Pediatric neuro-oncology requires attention to not only cancer biology and therapeutics, but also to the suffering of the patient. In addressing patient suffering, consensus guidelines direct attention to the spiritual distress and resources of patients and families. A lack of training has been a key barrier to integrating this aspect of health into patient care. METHODS: A neuro-oncologist and a chaplain participated in a train the trainer for the Interprofessional Spiritual Care Education Curriculum (ISPEC) through the George Washington University's Institute for Spirituality and Health. After the train the trainer, the online curriculum was offered to interdepartmental team members, combined with in-person discussion groups, which met weekly for six sessions. A survey was given before and after the training, and Likert scores were analyzed using the Wilcoxon rank-sum non-parametric test. OUTCOMES: 17 interdisciplinary members participated in the training. These members included neuro-oncologists, neuro-surgeons, rehabilitation physicians, nurse practitioners, nurses, physical therapists, music therapists, a child life specialist, a school liaison, and a patient experience specialist. The training resulted in multiple improvements, including increased ability to identify spiritual issues (p=.0278) and increased ability to respond to these issues (p=.0056). CONCLUSION: ISPEC addressed a key barrier to providing generalist spiritual care to patients with pediatric brain tumors. Diverse disciplines were repre-

sented during the training. With implementation of interdisciplinary spiritual care, outcomes that may be measured in the future include improved quality of life, patient satisfaction, and the resilience of both patients and team members.

QOL-49. THE IMPACT OF OTOTOXICITY AND VISUAL IMPAIRMENT ON EDUCATION IN CHILDREN TREATED FOR CNS TUMOURS

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INTRODUCTION: Children treated for CNS tumours experience a very high burden of adverse effects. Platinum-based chemotherapy and cranial radiotherapy can cause ototoxicity, which may be particularly problematic in patients who have impaired vision and cognition as a result of their tumour and associated treatment. This study assessed the prevalence of impaired hearing and vision and how this may impact upon education. METHODS: 53 patients diagnosed with solid tumours in Edinburgh, UK between August 2013–2018 were included in the study. Patients were split into three groups according to treatment received: Group 1 – cisplatin-based chemotherapy and cranial radiotherapy; Group 2 - platinum-based chemotherapy, no cranial radiotherapy; Group 3 – benign brain tumours treated with surgery only. Data was collected retrospectively from patient notes. RESULTS: Overall 69.5% of those treated with platinum-based chemotherapy experienced ototoxicity as assessed by Brock grading and 5.9% of patients had reduced visual acuity. Patients in Group 1 had the highest prevalence of both. 44.4% of patients in Group 1 needed increased educational support following treatment, either with extra support in the classroom or being unable to continue in mainstream school. 12.5% of Group 2 patients required such support and 31.3% in Group 3. CONCLUSIONS: Children with CNS tumours frequently require support for future education but those treated with both platinum-based chemotherapy and cranial radiotherapy are at particular risk, which may be compounded by co-existent ototoxicity and visual impairment. It is essential to provide appropriate support for this patient cohort in order to maximise their educational potential.

QOL-51. LISTENING BEFORE WE SPEAK: A PATIENT-CENTERED APPROACH TO DEVELOPING RESOURCES FOR PEDIATRIC BRAIN TUMOR SURVIVORS AND THEIR FAMILIES

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In the United States, more than 28,000 children and teenagers live with the diagnosis of a primary brain tumor (Porter, McCarthy, Freels, Kim, & Davis, 2010). In 2017, an estimated 4,820 new cases of childhood primary brain and other central nervous system tumors were expected to be diagnosed in children ages 0 – 19 in the United States (Central Brain Tumor Registry of the United States, 2017). Survivors suffer from lifelong side effects caused by their illness or by various treatments. Commonly identified late effects of treatment include a decline in intellectual functioning and processing speed, performance IQ deficits, memory deficits, psychological difficulties, deficits in adaptive functioning (daily life skills), and an overall decrease in health-related quality of life (Castellino, Ullrich, Whelen, & Lange, 2014). To address the ongoing challenges these survivors and their families face, the Pediatric Brain Tumor Foundation (PBTF) met extensively with working groups comprised of survivors and caregivers to develop the outline for a comprehensive Survivorship Resource Guidebook. In 2019, the PBTF published the guidebook which categorizes survivor and caregiver needs into three primary areas: physical and mental health, quality of life, and working the system. Expert authors included survivors and caregivers themselves in addition to medical and mental health professionals. Key outcomes discovered during the creation and production of this resource highlight how caregivers, survivors and professionals can collaborate to provide needed information and practical help to one segment of the pediatric cancer population who experience profound morbidities as a result of their diagnosis and treatment.

QOL-53. GENOME ASSOCIATIONS WITH NEUROCOGNITIVE OUTCOMES, CEREBRAL MICROBLEEDS (CMBS), AND BRAIN VOLUME AND WHITE MATTER (WM) CHANGES IN PEDIATRIC BRAIN TUMOR SURVIVORS

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OBJECTIVE: To identify genetic predictors of neurocognition, CMBs, brain volume, and WM changes in pediatric brain tumor survivors. METHODS: Patients were selected from an existing cohort (RadART) if they had: 1) at least one neurocognitive evaluation using computer-based CogState; 2) available DNA; 3) standard imaging. Candidate gene or genome-wide genotyping was performed on all patients. CMBs were identified using a semi-automated algorithm developed in MATLAB. Volume of T2/FLAIR WM signal abnormality was measured using a semi-automated method based on a convolutional neural network. Brain volume and cortical thickness were measured using FreeSurfer volumetric analysis. Logistic and linear regression were done to compare phenotypes with candidate genotypes. Genome-wide efficient mixed-model analysis was done to compare neurocognition and CMBs. Gene set analysis was done using https://fuma.ctglab.nl/. RESULTS: APOE4 was a candidate variant associated with non-lobar, larger volume CMBs ($p<0.05$). At the GWAS-level (n=225), specific genes trended with visual memory, psychomotor function, and CMB count ($p<5x10^{-8}$). Using gene set analyses, there were gene set trends seen with CMB count and psychomotor function. Small sample size and low mutant allele frequency limited reliability of these findings. Preliminary volumetric analysis show reduced volume within the right parietal, medial occipital and inferior temporal lobes with increased cortical thickness in the left occipital and medial parietal lobe in patients carrying the ApoE4 allele. WM signal assessments are ongoing. CONCLUSION: Genetic markers may be associated with neurocognition, CMBs, brain volume and WM changes in pediatric brain tumor survivors; however, larger cohorts are needed to confirm specific gene relevance.

QOL-54. HEIGHT, WEIGHT AND CARDIOVASCULAR EFFECTS OF STIMULANTS ON CHILDREN WITH BRAIN TUMOR

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INTRODUCTION: Children with brain tumors may develop inattention, slow processing, and hypersomnia. Stimulant medications improve these problems but their effect on growth, heart rate, and blood pressure are inadequately explored. METHODS: We retrospectively studied children with brain tumors treated at our institution that had data available for one-year pre and two year post stimulant treatment. Tumor location, gender, radiation treatment (RT), age at RT, drug type, and hormone therapy were variables of interest. RESULTS: We identified 65 children (35 males) that fulfilled eligibility criteria. Focal RT was utilized in 58; 11 additionally received whole brain RT. Thirty were treated for hypersomnia and inattention, 8 for hypersomnia alone, and rest for inattention. Modafinil was the first drug in 18 (27.7%) and methylphenidate in the others. Forty-seven (72.3%), 40 (61.5%) and 49 (75.4%) were on thyroxine, cortisone and growth hormone respectively. There was no difference in pre and post stimulant BMI, heart rate, and blood pressure. There was also no difference between modafinil and methylphenidate groups. Rate of increase in height slowed on stimulants ($p=0.0096$). Thyroxine treatment correlated with increase in BMI after stimulants ($p=0.0434$). Younger age ($p=0.0003$) and higher BMI ($p=0.0063$) pre stimulants correlated with increased heart rate on stimulants, while higher age at RT (0.0159) correlated with elevated systolic BP on stimulants. No association of studied variables was found with height and diastolic BP. CONCLUSION: Stimulants are well tolerated by children with brain tumors that are appropriately managed for endocrine deficiencies but may reduce the trajectory of height attainment.

QOL-55. INTEGRATED MULTI-SCALE MODEL FOR PEDIATRIC BRAIN TUMOR SURVIVAL PREDICTION

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Brain tumors are the most common solid tumors affecting children, and its prognosis has been a great challenge for physicians and researchers. With the advances in high-throughput sequencing technology and digital pathology, more quantitative data is now becoming available and more information may potentially be discovered in whole slide images (WSIs) and molecular tumor characteristics to determine survival and treatment. Imaging and genomic data, though very different in nature, both may contain different aspects of disease characteristics that are important for survival prediction. Hence our work aims to build a framework to integrate two data modules, whole-slide histopathology image data, and RNA sequencing data, for a unified model to improve pediatric brain tumor survival outcome prediction. The imaging data and genomic data are both of high dimensions and on different scales. We use two independent

modules, each of which consists of a deep neural network, to extract lower dimensional features from imaging and genomic data respectively. We concatenate the extracted features and use a third neural network to train a Cox regression model using the merged feature as input. Each module is first pre-trained with TCGA adult brain tumor data, and subsequently fine-tuned with pediatric brain tumor data. The entire pipeline is tested on the holdout pediatric brain tumor dataset. Preliminary results suggest that the integrated framework achieves improved prediction performance than using each single data module alone. The concordance index (C-index) of integrated model is 0.68, compared to 0.62 with imaging data only, and 0.66 with genomic data only.

QOL-56. THE RELAPSED AND OR PROGRESSED BRAIN TUMOURS IN CHILDREN: RHC, GLASGOW EXPERIENCE

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INTRODUCTION: The outcome for children with relapsed or progressed brain tumours is poor. The aim of this project was to identify total number of children who have relapsed or progressed with Brain tumour and to determine the types of tumours, treatment offered and assess outcome. METHODS: This is a retrospective study of all patients treated for relapsed or progressed brain tumours between 2007 and 2017 at the Royal Hospital for children. Patients were identified using the unit database. Clinical data included demographics, histologic diagnosis, treatment characteristics and outcome which was obtained from electronic records. RESULTS: 46 children were included (22M:24F). The median age of diagnosis was 5 years. There were 16 histological subtypes of brain tumours: pilocytic astrocytoma (n=12, 26%), optic pathway glioma (n=4,7%), medulloblastoma (n=8, 17%), ependymoma (n=4, 9%), high grade glioma (n=3, 7%, DIPG (n=2, 4%) and others 13(32.2%). 28(61%) had relapsed at a median time of 18 months. Tumour progression occurred in 18(31%) at a median time of 21.5 months. Post-relapse or progression therapy included surgery (14, 30%), chemotherapy (17, 40%) and radiotherapy (5, 10.9%). 50% of the patients remain alive with 17(37%) being stable and 6(13%) with progression of disease. 50% had died of disease progression. CONCLUSIONS: The relapse and or progression was seen 61% of patients. The commonest tumours in this cohort were pilocytic astrocytoma and medulloblastoma. Chemotherapy was the most used regimen followed by surgery and radiotherapy. Primary dissemination at the time of diagnosis was associated with poor prognosis.

QOL-57. SOUTHERN CALIFORNIA KAISER PERMANENTE PEDIATRIC NEURO-ONCOLOGY PROGRAM DEVELOPMENT

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KEY MESSAGE: Standardization of care for subspecialty patients require centralization and support across multi-disciplinary groups within the Kaiser Permanente medical group, which is a large health maintenance organization (HMO) in the United States. BACKGROUND: Prior to the development of a Pediatric Neuro-Oncology program, Southern California Kaiser Permanente pediatric neuro-oncology patients were routinely referred to respective regional academic centers for consultation. The process was not standard across the region, resulting in additional costs and differences in treatment recommendations, potentially affecting outcomes. METHODS: A Pediatric Neuro-Oncology program was established, July 2017, based at the Kaiser Permanente Los Angeles Medical Center (LAMC), consisting of pediatric neuro-oncology, pediatric neurosurgery, pediatric neuro-radiology, pediatric radiation oncology, and pediatric neuro-oncology case management. RESULTS: A Pediatric Neuro-Oncology tumor board was established to meet on a bi-monthly basis. Pediatric neuro-oncology patients across the Southern California now have their magnetic resonance imaging (MRI) reviewed by the same pediatric neuro radiologists. Neuropathology is standardized and sent to Children's Hospital Los Angeles and reviewed at the molecular neuropathology tumor board attended by the pediatric neuro-oncologist. Cases discussions regarding the patients include the regional pediatric neurosurgeons, the pediatric radiation oncologists, and the pediatric neuro-oncologist, and treatment plans are recommended and recorded by the case manager. CONCLUSIONS: Centralization of care has allowed for more consistent and standard care across the Southern California Region, but requires support from multi-disciplinary groups.

QOL-58. ASSESSING FATIGUE EXPERIENCED BY PEDIATRIC PATIENTS WITH INTRACRANIAL NEOPLASMS

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BACKGROUND: Indiana University possessed one of the earliest clinical proton facilities in the United States. The purpose of this study was to assess fatigue and nausea/vomiting in children with central nervous system (CNS) tumors undergoing radiation therapy as part of their treatment regimen, and to understand what factors influence fatigue. DESIGN: The study was approved by the institutional review board at Indiana University and consent and/or assent from eligible participants was obtained prior to enrollment. The validated Fatigue Scale is scored on a 5-point Likert scale. Surveys were completed 1) prior to radiation therapy, 2) week three of radiation therapy, and 3) week six of radiation therapy. A score of 41 or higher for the Fatigue Scale-Parent (< 7 years), 12 or higher for the Fatigue Scale-Child (8–12 years), and 17 or higher for the Fatigue Scale-Adolescent (13–18 years), indicates significant cancer-related fatigue. RESULTS: The study aimed to recruit a total of 50 patients during the eligible period; however, data on 31 individual participants were available for analysis. 25 patients underwent proton radiation therapy, while 6 patients underwent conventional photon therapy. The mean age of children was 8.8 years. Of the 31 patients, 22 recorded scores indicating significant cancer-related fatigue at some point during radiation therapy. CONCLUSIONS: Cancer related fatigue continues to be a challenge, with limited understanding of factors that might predict clinically relevant fatigue This work demonstrates the feasibility of conducting symptom research for children undergoing radiation therapy; further research is needed to characterize predictors of fatigue.

QOL-59. CEREBELLAR MUTISM SYNDROME AND THE SURGICAL RISK FACTORS: A PROSPECTIVE MULTICENTRE STUDY OF 500 PATIENTS UNDERGOING TUMOUR SURGERY IN THE POSTERIOR FOSSA

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OBJECTIVE: Cerebellar mutism syndrome (CMS) is a severe neurological complication of tumour surgery in the posterior fossa in childhood. The incidence is reported between 8 and 39%, where CMS sets in within days of surgery and resolves within months, yet long-term sequelae are seen in most patients. This prospective cohort study investigates the course of CMS and the surgical cause of the syndrome. POPULATION AND METHODS: We included 500 children with a tumour in the posterior fossa with planned surgery or open biopsy. Enrolment was conducted between 2014 and 2020 in 26 centres in ten European countries. Speech, neurological symptoms and surgical procedure were registered in predefined standardized forms pre-operatively and at three post-operative follow-ups within one year. PRELIMINARY RESULTS: A total of 426 children underwent primary surgery and were eligible for analyses. CMS occurred in 56 patients (13.1%) one day (median; IQR: 0–2 days) after surgery and resolved within 38 days (median; IQR: 4–52 days). Another 58 patients (13.6%) had less severe speech impairment. Mutism was associated with lower age (OR: 0.91 [95%CI: 0.85;0.98, p=0.014]), medulloblastoma (OR: 2.5 [95%CI: 1.4;4.7, p=0.0036]) and ATRT (OR: 12.9 [95%CI: 3.4;51.9, p=0.00018]) and tumour location in the fourth ventricle (OR: 4.0 [95%CI: 2.3;7.2, p<0.0001]). Preliminary multivariate analyses revealed no significant association between mutism and surgical access. CONCLUSION: CMS is a common complication predominantly seen in younger children after tumour surgery for a medulloblastoma or ATRT in the fourth ventricle. The incidence is not related to the surgical access in this study population.

CRANIOPHARYNGIOMA AND RARE TUMORS

RARE-01. MANAGEMENT AND OUTCOMES OF PAEDIATRIC CRANIOPHARYNGIOMA: A 15-YEAR EXPERIENCE IN SINGAPORE

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BACKGROUND: Craniopharyngiomas are rare embryonic malformations of the sellar region with high survival rates but high morbidity due to long-term sequelae caused by the location of the tumour. We summarise our institution's experience on the management and outcomes of paediatric craniopharyngiomas in Singapore. METHODS: This was a retrospective review of all paediatric patients (18 years and below) with histologically diagnosed craniopharyngioma managed by the National University Hospital, Singapore from January 2002 to June 2017. Data on clinical presentation, imaging, treatments, and outcomes were extracted from the electronic medical records using a standardized data collection form. Data analysis was conducted using RStudio (Version 1.2.5033). Institutional ethics approval was obtained for the study. RESULTS: We identified 12 cases of paediatric craniopharyngiomas. The majority of cases were male (8, 66.7%) and the median age at presentation was 6.0 (IQR 3.8 – 9.5). Initial surgical management was tumour excision (11, 91.7%) or insertion of a reservoir into the cyst cavity (1, 8.3%). All cases had diabetes insipidus, 10 (83.3%) had endocrine dysfunction, and 8 (66.7%) had visual impairment on long term follow up. 7 (58.3%) cases had recurrence, and 3 (25.0%) had demised. Cox-regression showed that females (HR=33.9, p=0.049), and Chinese race (HR=13.3, p=0.034) were at higher risk for recurrence, but age at diagnosis and residual tumor on post-operative MRI was not significant. CONCLUSION: The management of craniopharyngioma is complex as it is complicated by high recurrence rates and significant long-term morbidity. Further research on treatment strategies focusing on maintaining quality of life is important.

RARE-02.RE-IRRADIATION FOR RECURRENT CRANIOPHARYNGIOMA

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PURPOSE: Patients with recurrent craniopharyngioma after radiotherapy (RT) have few treatment options. At our institution, re-irradiation has been offered to selected individuals with recurrent craniopharyngioma not suitable for further surgery, intracystic therapy or targeted agents. METHODS: A retrospective study was performed of patients with craniopharyngioma treated with two courses of fractionated RT. First RT (RT1) prescriptions ranged from 50–54 Gy in 25–30 fractions; re-irradiation (RT2) prescriptions were 54 Gy in 30 fractions with full, in-field overlap of dose. The maximum dose to organs-at-risk (brainstem, optic structures) were maintained at or below the prescription dose. There was no cumulative dose limit to any structure. RESULTS: We identified four patients. Median RT1-to-RT2 interval was 5.8 years (range, 4.7–20.4). Cumulative maximum doses to optic chiasma and nerves were >100 Gy in all four patients. With a median follow-up of 33 months after RT2, three patients had disease control and are alive at 9, 23 and 42 months from RT2; one patient developed progressive disease and died 33 months after RT2. In three evaluable patients, vision remained stable or improved after RT2; the remaining one patient had no light perception prior to re-irradiation. Two patients had neuropsychological testing before and after RT2; neurocognitive domains were generally stable in one patient but working memory declined in the second patient. CONCLUSIONS: Despite exceeding usual tolerances for optic chiasm and nerves, visual outcomes were stable in all living patients. Re-irradiation should be discussed as a treatment option for patients with recurrent craniopharyngioma but without other therapeutic options.

RARE-03. AGGRESSIVE RESECTION FOR PEDIATRIC CRANIOPHARYNGIOMAS VIA ENDOSCOPIC ENDONASAL APPROACH

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OBJECTIVE: In recent years, the endoscopic endonasal approach (EEA) has been increasingly used for pediatric craniopharyngiomas. We here present our experience and the outcomes of the EEA resection of pediatric craniopharyngiomas. MATERIALS AND METHODS: Between April 2014 and December 2019, 16 cases of pediatric craniopharyngiomas were operated at the Osaka city university (OCU) hospital. Eight patients were diagnosed with primary craniopharyngiomas while 8 had a recurrent tumor. There were 5 males and 11 females, with a mean age of 10.7 years (3–17 years). EEA was selected in all patients and a case of large mutilobulated tumor was resected by combination of microscopic transcranial approach. RESULTS: Gross total resection was achieved in 14 patients and near total resection in other 2. Post-op CSF leak occurred in 3 patients, which was treated with re-exploration. Pituitary stalk was preserved intraoperatively in 4 cases, and 15 patients developed diabetes insipidus and anterior hormonal replacement therapy was required in 15 patients at last follow-up. Visual improvement was noted in 4 patients while vision remained unchanged in the rest. Neuropsychological function status was preserved in all patients, and there was no new-onset obesity postoperatively. The mean follow-up duration was 35.1 months (2 – 69 months) and 4 of 8 recurrent cases had re-recurrence during this period, however there was no recurrent in 8 primary cases. CONCLUSIONS: EEA should be the surgical modality of choice for treating pediatric craniopharyngiomas. It results in better visual and cognitive outcomes with a significantly increased extent of resection.

RARE-04. INTELLECTUAL DEVELOPMENT IN CHILDREN WITH PEDIATRIC CRANIOPHARYNGIOMA AFTER TUMOR REMOVAL

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INTRODUCTION: Intellectual assessment in children with craniopharyngioma after tumor removal is still unknown. We assessed intellectual development in children who underwent microsurgical resection in our institute over the last twelve years. MATERIALS AND METHODS: Ten children among 41 patients with craniopharyngioma treated and followed at Kagoshima University Hospital between 2007 and 2019 were reviewed. We also assessed intellectual development in 10 years or younger children with craniopharyngioma one year after tumor removal. Intelligence was assessed using the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV). RESULTS: Ten children underwent microsurgical tumor removal. The mean age at surgery was 5.8 (range 1–10) years. Transcranial approach was performed in 8 children, transsphenoidal approach in two children. The mean follow up period was 110 months. Gamma knife surgery (GKS) was performed in 6 children less than 6 months after first surgery. Regional recurrences occurred in 5 children, and additional GKS was performed in four children, second microsurgical removal in one child. Severe obesity with a transient electrolyte imbalance occurred in one child. Eight children with GH deficiency underwent GH replacement therapy. Eight children were assessed working memory index (WMI), processing speed index (PSI), Perceptual reasoning index (PRI), and verbal comprehension index (VCI) using WISC 4. Each mean value of WMI, PSI, and PRI was lower than VCI, except for 2 children with normal full scale intelligence quotient. CONCLUSION: WMI, PSI and PRI in children with intellectual disabilities were lower tendency than VCI after surgical removal of craniopharyngiomas in the present study.

RARE-06. OPTIMIZATION OF PROTON RADIATION THERAPY FOR GIANT CRANIOPHARYNGIOMAS

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Craniopharyngiomas are benign intracranial tumors located in the sellar and suprasellar region. Their size and extent of invasion into surrounding structures vary considerably. While the majority of craniopharyngiomas on presentation are between 1–3 cm without hypothalamic invasion, a significant proportion of patients present with 'giant' craniopharyngiomas of >4cm in dimension with large cystic extension through the 3rd ventricle. These tumors pose a challenge both for surgical resection as well as for radiation therapy. Proton beam therapy (PBT) has become the preferred standard of care after subtotal resection of pediatric craniopharyngiomas. In the setting of giant craniopharyngioma, the use of proton therapy allows a reduction of dose to surrounding normal brain, but changes in cyst volume can result in either under-coverage of tumor or excess dose to surrounding brain, an effect further magnified by the sharp gradients associated with proton dose distributions. In this case report we describe the proton treatment planning and intra-treatment monitoring of two patients with giant craniopharyngiomas with largest pre-operative of dimension 6cm, and 9cm, respectively, and 6cm and 5.5cm, respectively, pre-radiation. Both patients had drains inserted to Ommaya reservoirs. We performed surveillance imaging during RT utilizing spiral computer tomography (CT) on a weekly basis and reconstructed the treatment dose on the surveillance CTs to ensure target coverage and normal tissue sparing. We compared the dosimetry in

these cases for PBT versus intensity-modulated radiation therapy, characterized the cyst evolution during treatment in 3 dimensions, and define an optimized protocol for treatment planning and intra-treatment monitoring.

RARE-07. THE LANDSCAPE OF GENOMIC ALTERATIONS IN ADAMANTINOMATOUS CRANIOPHARYNGIOMAS

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INTRODUCTION: Adamantinomatous craniopharyngiomas (ACPs) are characterized by activating mutations in the *CTNNB1* gene. Here we perform a comprehensive genomic analysis of 23 ACPs to define the landscape of genomic alterations in this disease. METHODS: We performed whole-genome sequencing of 24 ACPs and their matched normal tissues. We used Mutect 2.0 to detect mutations and indels in these samples and MutSig2CV to identify significant mutations. Copy numbers were called using the GATK4 pipeline and GISTIC 2.0 was applied to identify significant alterations. Finally, SvABA was applied to identify genome-wide structural variants and rearrangements. RESULTS: 18/24 (75%) of the sequenced ACPs harbored activating mutations in exon 3 of CTNNB1 gene with an average variant allele fraction (VAF) of 0.4±0.1. These mutations have previously been shown to activate the WNT signaling pathway in these tumors. No other significantly recurrent mutations were detected in our samples. The ACPs were quiet with regard to copy number alterations and no recurrent amplifications or deletions were detected. 528 structural variations and rearrangements were detected in total in all 24 samples with an average of 22 variants per sample. Gene-Set Enrichment Analysis (GSEA) of the RNAseq data revealed upregulation of WNT/B-catenin (FDR q-value <0.25) in the CTNNB1 mutant samples compared to CTNNB1 WT samples. CONCLUSION: Our study identified previously described activating CTNNB1 mutations in the majority of ACPs. In addition, we identified several rearrangements and structural variations in these tumors that could play an important role in the pathogenesis of the disease.

RARE-08. CYST FLUID CYTOKINES MAY PROMOTE EPITHELIAL-TO-MESENCHYMAL TRANSITION IN PEDIATRIC ADAMANTINOMATOUS CRANIOPHARYNGIOMA

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BACKGROUND: Despite poor clinical outcomes, no targeted therapies have been established for the treatment of Adamantinomatous Craniopharyngioma (ACP). The only known genetic aberration is a mutation in *CTNNB1* that results in the nuclear accumulation of beta-catenin. Nuclear beta-catenin is an established inducer of Epithelial-to-Mesenchymal Transition (EMT). ACP cyst fluid is enriched with pro-inflammatory and SASP cytokines, many of which are also directly implicated in EMT. We sought to investigate the role of EMT in ACP pathology. METHODS: Normal human epithelial cells were cultured and treated with ACP cyst fluid (10%) for 1, 2, 4 and 8 days. Cell morphology was monitored by live cell brightfield microscopy. The expression of EMT associated genes, ZEB1, ZEB2, SNAI-1, SLUG, TWIST, E-Cadherin, Beta-Catenin and Vimentin was determined by RT-qPCR. RESULTS: ACP cyst fluid treated epithelial cells were markedly transformed into long, spindle-shaped cells. ACP cyst fluid treatment resulted in the progressive up-regulation of ZEB2 over 8 days (**RQ=12.0; P<0.01**), the progressive up-regulation of SNAI-1 over 4 days (**RQ=5.1; P<0.05**) and up-regulation of Vimentin (**RQ=2.2; p<0.01**), identified only on Day 8. CONCLUSION: ACP cyst fluid can induce EMT-like changes in normal human epithelial cells. In conjunction with the frequency of beta-catenin mutation in ACP, it is possible that EMT plays a crucial role in the pathology of ACP. Understanding ACP pathology in the context of the EMT paradigm may aid the development of new targeted therapeutics.

RARE-09. PRESERVATION OF ENDOCRINE FUNCTION AFTER OMMAYA RESERVOIR INSERTION IN CHILDREN WITH CYSTIC CRANIOPHARYNGIOMA

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INTRODUCTION: Children with craniopharyngiomas (CP) can be subjected to significant morbidities caused by radical surgery and/or radiation with severe long-term consequences. Ommaya reservoir Insertion (ORI) into cystic CP represents a minimally invasive procedure that aims to preserve endocrine, hypothalamic and neurocognitive function. The purpose of this study was to determine the relevance of upfront ORI (+/- intracystic treatment) for preservation of endocrine function. METHODS: A retrospective chart review of children with CP treated at the Hospital for Sick Children between 01/01/2000 and 15/01/2020 was undertaken. Endocrine function was reviewed at the time of initial ORI or surgical resection and throughout the course of follow-up. Event free survival (EFS) was defined as the time to additional surgical resection or irradiation. RESULTS: Fifty-five patients with sufficient endocrine follow-up data were included. The median age of diagnosis was 8.3 years (range 2.1–18.0 years), 31 were males. ORI was performed as upfront treatment in 30 patients, gross total or partial resection in 24 patients and radiation in 1 patient, respectively. Endocrine function remained stable after ORI with a median EFS of 19.2 (0 – 105.3) months while the majority of patients who underwent surgical resection had documented worsened endocrine function postoperatively (median of 0; range 0 – 29.4 months) (p< 0.001). The event most commonly related to secondary endocrine deterioration was initial or delayed surgical resection. CONCLUSIONS: Endocrine function was preserved in patients with upfront ORI (+/- intracystic treatment). Further studies will elucidate the implications of ORI with respect to ophthalmological, vascular and neurocognitive long-term outcome.

RARE-10. ADAMANTINOMATOUS CRANIOPHARYNGIOMA RESIDES OUTSIDE THE BLOOD BRAIN BARRIER

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BACKGROUND: Adamantinomatous craniopharyngioma (ACP) is a devastating skull-base tumor believed to derive from epithelial remnants of the primordial craniopharyngeal duct (Rathke's pouch), which gives rise to the anterior pituitary gland. Genetically engineered mouse models of ACP demonstrate that perturbation of the fetal anterior pituitary can generate tumors analogous to ACP. Clinical and preclinical data indicate that IL-6 blockade may contribute to ACP tumor control, with the most common agent being the humanized monoclonal antibody, tocilizumab. This agent demonstrated poor blood-brain barrier (BBB) penetration in primates. We present findings from two children enrolled on a phase 0 clinical trial (NCT03970226) of a single dose of preoperative intravenous tocilizumab prior to resection of newly diagnosed ACP. METHODS: Blood samples were obtained at multiple timepoints. Serum was isolated via ficoll separation. Tumor tissue and cyst fluid were obtained 4–6 hours following the single IV dose of tocilizumab. Tissue was snap-frozen. Tumor was homogenized in RIPA buffer. Free tocilizumab in serum, cyst fluid, and tumor tissue was measured using enzyme-linked immunosorbent assay (ELISA) against a standard curve. RESULTS: Both patients in this trial demonstrated clinically relevant levels of tocilizumab (≥ 4µg/mL) in serum, cyst fluid, and tumor tissue, compared to undetectable levels in control samples. CONCLUSION: ACP resides outside BBB protection. In addition to demonstrating the feasibility of systemic delivery of tocilizumab, these findings indicate that other large molecules, including those known to have poor BBB penetration, may be systemically delivered as part of an antitumor regimen in the treatment of ACP.

RARE-11. QUANTITATIVE MR IMAGING FEATURES ASSOCIATED WITH UNIQUE TRANSCRIPTIONAL CHARACTERISTICS IN PEDIATRIC ADAMANTINOMATOUS CRANIOPHARYNGIOMA: A POTENTIAL GUIDE FOR THERAPY

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METHODS: Through the Advancing Treatment for Pediatric Craniopharyngioma (ATPC) consortium we accumulated preoperative MRIs and tumor RNA for 50 unique ACP patients. MRIs were assessed quantitatively for 28 different features and analyzed using Multiple Factor Analysis (MFA) and optimal clustering was determined via maximization of Bayesian Information Criterion (BIC). Following bulk RNAseq, differential expression and pathway enrichment were performed using standard methodologies (i.e., DESeq2 and GSEA). RESULTS: MRI features were well represented in the first 3 dimensions of MFA (variance explained=67.32%); specifically tumor/cyst size, ventricular size, and cyst fluid diffusivity. Using this three-way axis, we identified 3 patient subgroups. Transcriptional differences between these subgroups indicated one group was enriched for DNA damage response and MYC related pathways, one group enriched for SHH, and one group enriched for WNT/β-catenin and EMT-related pathways. CONCLUSION: This preliminary work suggests that there may be unique gene expression variants within ACP, which may be identified preoperatively using easily quantifiable MRI parameters. These radiogenomic signatures could provide prognostic information and/or guidance in the selection of antitumor therapies for children with ACP.

RARE-12. VASCULOPATHY IN PEDIATRIC CRANIOPHARYNGIOMA PATIENTS TREATED WITH SURGERY AND RADIOTHERAPY

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PURPOSE: As much as 40% of pediatric brain tumor patients will experience varied levels of Vasculopathy (VS), however few predictive factors have been described. Here we describe the type and timing of VS and explore the relationship between treatment modality and the timing, location, and distribution of VS. METHODS: 94 pediatric Craniopharyngioma patients underwent surgery and proton radiotherapy. Pre- and post-treatment imaging, cumulative physical and biological proton dose maps, clinical characteristics, and measures of dyslipidemia were evaluated. MR and MRAs were evaluated for pre- and post-radiotherapy VS (type, workup, location, and severity). VS events were segmented and described according to their normal brain region, and vascular territory. RESULTS: 47 patients were found to have 154 confirmed VS of varying severity with a median time to event of 3.41 years 95% CI 3.08–3.88. 22% (N=21) of patients had ≥1 pre-existing instances of VS and 26.6% (N=25) had a dyslipidemia at diagnosis. Forty-six (48.9%) patients had evidence of VS post-RT with 9.5% (N=9) being clinically significant. Aspirin was recommended in 10.6% (N=10) patients. Only 4 (4.2%) patients required revascularization. Clinical characteristics were not predictive of VS. An increased frequency of VS were observed along the operative corridor and high-dose radiotherapy field. CONCLUSIONS: VS often precedes radiotherapy necessitating appropriate baseline imaging. Surgery type and extent are interrelated to the risk for radiotherapy-induced VS. While the spatial radiotherapy dose distribution approximated most vascular injury events, it was not all-inclusive. Spatial modeling of biological and physical dose may offer insights into therapy related vascular injury.

RARE-13. INFLAMMATORY MYOFIBROBLASTIC TUMOR MIMICKING DESMOPLASTIC INFANTILE GANGLIOGLIOMA (DIG) OF THE TEMPORAL LOBE

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Inflammatory myofibroblastic tumor (IMT) is a mesenchymal neoplasm composed of fascicles of myofibroblastic spindle cells in a background of prominent inflammatory infiltrate. It is categorized as 'intermediate, rarely metastasizing' in the World Health Organization classification of tumors of soft tissue and bone. We present a novel case of concurrent brain and lung tumor with diagnosis of TFG-ROS1-rearranged IMT in a 14 year old female patient, in which targeted next-generation sequencing became a powerful tool for detection of genomic alterations in both lung and brain tumors. At age 9, the patient's lung mass was incidentally found and investigated for various infectious diseases with negative result. At age 14, she presented with seizure and was noted to have a stable size lung mass and a left temporal lobe tumor. The left temporal lobe tumor showed a desmoplastic spindle cell neoplasm involving the meninges and cerebral cortex and Desmoplastic Infantile Ganglioglioma (DIG) was considered one of differentials. Subsequently, her right lung mass was resected and showed a similar spindle cell neoplasm with a background of dense fibrosis and chronic inflammation, consistent with Inflammatory Myofibroblastic Tumor. Molecular microdissection revealed that both tumors shares TFG-ROS1 fusion which is associated with (t(3;6) (q12;q22)), thus it is strongly suggestive that two tumors arose from the same origin. No predisposition syndrome was identified.

RARE-14. DEVELOPMENT OF ANAPLASTIC ASTROCYTOMA AS A THIRD MALIGNANCY IN A PEDIATRIC PATIENT WITH CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY (CMMRD): A CASE REPORT AND EVALUATION OF TUMOR GENOMICS IDENTIFYING BIALLELIC *MSH6* MUTATIONS

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Congenital mismatch repair deficiency (CMMRD) is a pediatric cancer predisposition syndrome secondary to biallelic mutations in mismatch repair genes including *MLH1, MSH2, MSH6*, and *PMS2*. Due to the resulting lack of repair mechanisms, these patients develop a high intracellular mutational burden and have a high risk of development of multiple malignancies at a young age. Similar to patients with Lynch Syndrome (monoallelic mutations in MMR genes), these patients are at risk for development of central nervous system (CNS) tumors including high grade gliomas. Forty-eight percent of patients with CMMRD are diagnosed with a CNS malignancy. In this interesting case, a patient developed three metachronous malignancies prior to the age of 13, including Burkitt lymphoma, T-Cell lymphoma and anaplastic astrocytoma. Genomic analysis revealed a high mutational burden in his initial tumors, with multiple oncogenic mutations, as well as a previously unreported germline compound heterozygous *MSH6* E744fs*12 and R248fs*8 alteration. He received a gross total resection of the tumor which in previous studies has been shown to have the highest impact on survival. Surgery was followed by radiation and ongoing treatment with an immune checkpoint inhibitor with stable disease at 6 months. The purpose of this case report is to describe the interesting presentation of CMMRD and discuss the previously unreported biallelic *MSH6* mutations.

RARE-15. EARLY PSEUDOPROGRESSION POST-RADIATION IN PAEDIATRIC HIGH-GRADE GLIOMA PATIENTS WITH CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY: TWO CASE REPORTS FROM A SINGLE CENTRE

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BACKGROUND: Constitutional Mismatch Repair Deficiency (CMMRD) is a cancer predisposition syndrome caused by biallelic mutations in the mismatch repair pathway, and high-grade glioma (HGG) constitute the most prevalent brain tumours. Pseudoprogression alludes to radiological changes that mimic tumour progression, but are in fact due to other causes such as therapy related inflammation. It can occur as early as three months post treatment. To our knowledge, its characteristics in CMMRD patients has not been reported. METHODS: We retrospectively identified seven patients with CMMRD and history of HGG at The Royal Children's Hospital, Melbourne from 2005 to 2019. Our objective was to review the characteristics of pseudoprogression in this cohort. RESULTS: Out of the seven patients, two with constitutional loss of PMS2 demonstrated evidence of pseudoprogression. Patient 1 presented at 16 years old with a cerebellar anaplastic astrocytoma. She developed clinical and radiological progression within two weeks of starting radiotherapy, persisting up to four months after completion. However, six months post radiation she improved without intervention and the tumour remains stable five years post therapy. Patient 2 presented at 17 years old with a midbrain anaplastic astrocytoma, and showed signs of progression four weeks after completion of radiotherapy. She was then treated with Bevacizumab, an anti-VEGFA antibody with remarkable response. She subsequently received Nivolumab, a checkpoint inhibitor with ongoing stable disease for four

months. CONCLUSION: Our findings showed that pseudoprogression can occur early in the treatment course in CMMRD patients. Identification of this entity is important for appropriate clinical management.

RARE-16. SEVEN CASES OF RETINOBLASTOMA WITH CNS INVOLVEMENTS

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Treatment strategy for trilateral retinoblastoma (TRb: very rare RB with brain tumor) or retinoblastoma with central nervous system (CNS) involvement is not established yet. We retrospectively reviewed our seven cases of these rare almost fatal tumors. Their ages at diagnosis are 0y3m-1y10m (median 1y3m) (Male 4, Female 3). Only one had RB family history. Their affected eyes were bilateral 3, unilateral 3 and no 1. Their CNS involvements were suprasellar tumor 4, pineal tumor 1 and cerebrospinal fluid (CSF) cytology positive 2. Three of the suprasellar tumor patients had spinal metastasis. Four of the seven patients were TRb and one were genetically classified suprasellar retinoblastoma. All of them were treated with chemotherapy and four received high-dose chemotherapy. Three brain tumors of four TRb almost disappeared with chemotherapy. Two of them also received radiotherapy but relapsed. Although one radiation-free long-term TRb survivor developed secondary osteosarcoma, he got remission again and live 5 more years. One CSF positive Rb patient with chiasm invasion died of disease 11 months later. The other patient had no chiasm invasion nor CSF involvement at diagnosis, but his CSF cytology turned to positive after his second cycle of chemotherapy. He got remission with radiotherapy and high-dose chemotherapy, and alive without disease for 4 years. 2-year RFS and 2-year OS of all patients were 40% and 60%. Although our TRb patients responded to chemotherapy, it was difficult to avoid radiotherapy except one. Data accumulation is necessary for better treatment of these cancer-predisposed patients.

RARE-17. SURVIVAL BENEFIT FOR INDIVIDUALS WITH CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY SYNDROME AND BRAIN TUMORS WHO UNDERGO SURVEILLANCE PROTOCOL. A REPORT FROM THE INTERNATIONAL REPLICATION REPAIR CONSORTIUM

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BACKGROUND: Constitutional mismatch repair deficiency syndrome (CMMRD) is a severe cancer predisposition syndrome resulting in early onset central nervous system (CNS) and other cancers. International guidelines for surveillance exist but no study has systematically evaluated the efficacy of this protocol. METHODS: We surveyed all confirmed CMMRD patients in the International Replication Repair Deficiency Consortium. A surveillance protocol consisting of frequent biochemical, endoscopic and imaging (CNS and total body MRI) studies were employed. Survival analyses and efficacy of each method were assessed. RESULTS: Surveillance data were collected from 105 CMMRD individuals from 41 countries. Of the 193 malignant tumors, CNS malignancies were the most common (44%). The surveillance protocol uncovered 49 asymptomatic tumors including 16 glioblastomas and medulloblastomas. Five-year overall survival was 89% for tumors discovered by surveillance, and 61% for symptomatic tumors (p<0.004). Similarly, 5-year survival was 82+/-11% and 24+/-6% for surveillance and non-surveillance of brain tumors (p=0.005). Yearly total body and q6 month brain MRI detected asymptomatic cancers in all but 3 symptomatic CNS gliomas. These were tumors uncovered when time between scans was >6 months as per protocol. Finally, of the low grade tumors identified asymptomatically, 5 were low grade gliomas. All of the low grade gliomas, which were not resected transformed to high grade tumors at a median of 1.6 ± 0.9 years. CONCLUSION: These data support a survival benefit in CMMRD patients undergoing a surveillance protocol. Adherence to protocol and resection of lower grade lesions may improve survival for patients with CNS tumors.

RARE-18. GENETIC EVALUATION IN PATIENTS WITH CHOROID PLEXUS TUMORS

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INTRODUCTION: Choroid plexus tumors (CPT) are rare intraventricular neoplasms of epithelial origin. They usually occur in the 2nd year of life, corresponding to 0.4–0.6% of intracranial tumors in this age group. They are sub classified, according to WHO 2016, in choroid plexus carcinoma (CPC), atypical choroid plexus papilloma (ACPP) and choroid plexus papilloma (CPP). Li-Fraumeni syndrome (LFS) is present in 50% of patients with CPC. In Brazil, the *TP53* p.R337H mutation affects 0.3% of the population in the South/Southeast. OBJECTIVE: Evaluate the incidence of genetic mutations in patients with choroid plexus tumors and therefore the importance of genetic evaluation. PATIENTS AND METHODS: Between 1992–2019, 38 patients were diagnosed with CPT in our institution, 23 with CPC. From 2012, 21 patients were referred for genetic evaluation, 16 of which had CPC (2 had previously CPP). Positive family history for neoplasms was present in 87.5%; 37.5% compatible with LFS, 50% of them with mutations. All the patients with positive, but unspecific, family history of neoplasms, had pathogenic mutation. The molecular investigation of the *TP53* gene in patients with CPC was performed and positive in 56.2%: R337H (5 patients), R110C, R158H, H179R, R196* (1 patient each). Of those with R337H, p53 protein immunohistochemistry resulted in 90–100% positivity. One of the patients with CPP that evolved to CCP had the H179R mutation. Clinical course was similar among them, and with those without mutations. CONCLUSION: These results confirm the need for genetic evaluation in patients with choroid plexus tumors for adequate therapeutic management and long-term follow-up.

RARE-19. PEDIATRIC HIGH GRADE GLIOMA WITH DNA REPAIR PATHWAY ABERRATIONS, CLINICAL CHARACTERISTICS AND OUTCOME

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DNA mismatch repair machinery is an integral part of the human genome and its defect has been involved in tumorigenesis and treatment resistance. Heterozygous monoallelic germline loss of function in MLH-1, MSH-2, MSH-6 or PMS-2 is involved in Lynch syndrome, whereas biallelic mutations cause constitutional mismatch repair deficiency (CMMRD) which is associated with hematologic malignancies and glioblastoma. We report here the clinical characterization and molecular analyses of 7 patients who presented with gliomas and MMR machinery aberrations. Two patients had a clinical diagnosis of NF-1 with dermatologic stigmata, of whom one patient has CMMRD and the other has Lynch syndrome. Two patients had a known family history of Lynch syndrome upon their diagnosis of glioma. Three patients with high-grade glioma and negative family history, 2 had germline mutations in MMR genes, and one had numerous mutations including MMR genes with microsatellite instability. Patients were initially treated with chemotherapy and radiation for high-grade gliomas (HGG); 5/7 had progression. Median time to progression was 12 months (range: 5–52), and median time from progression to death was 7 months (range: 2–25). One patient had low-grade glioma initially but progressed to HGG and is currently on therapy. Another patient treated with temozolomide and radiation is currently receiving maintenance therapy without any disease recurrence. Although the literature data on brain tumors with MMR deficiency is limited, these consistently show that MMRD-associated gliomas are treatment-resistant and have a dismal outcome. Collaborative efforts are needed to better understand this subgroup of pediatric HGG and to define optimal treatment strategy.

RARE-20. MALIGNANT PERIPHERAL NERVE SHEATH TUMOR OF A CRANIAL NERVE IN AN INFANT WITH NEUROCUTANEOUS MELANOSIS

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At one month of age, a female presented with a giant congenital nevus along lower back and thighs and hydrocephalus. A ventriculoperitoneal shunt was placed. An MRI was done at six months, initially reported as normal. At eleven months of age, five months after original MRI, patient presented with dysconjugate gaze and lethargy. MRI showed new 3.8 x 3.7 x 3.4 cm right cerebellopontine angle mass extending into Meckel's cave and foramen ovale along with leptomeningeal disease extending from the mass along the entire length of the spinal cord. Retrospective review of prior MRI revealed subtle leptomeningeal enhancement concerning for neurocutaneous melanosis (NCM). Given the leptomeningeal disease, family elected for open biopsy and debulking of lesion instead of aggressive resection. Histologically, the mass showed hypercellular spindle cell neoplasm with mitotic activity and necrosis mixed with remnants of normal cranial nerve. GFAP was negative, excluding a glioma. HMB-45, MITF, panmelanoma, and Melan-A were negative, excluding melanoma. A negative myogenin stain ruled out ectomesenchymoma. S-100 protein and SOX-10 positivity with variable loss of staining for trimethylation of histone H3 K27 were indicative of malignant peripheral nerve sheath tumor (MPNST). Given the course of the mass, trigeminal nerve MPNST was presumed. Given the poor prognosis of intracranial MPNST and NCM, family elected to forgo treatment and was discharged with hospice. She died 25 days after surgery. Cranial nerve MPNST is rare. MPNST in patients with NCM has not previously been reported to our knowledge.

RARE-21. CANCER SPECTRUM IN GERMLINE SUFU MUTATION CARRIERS: A COLLABORATIVE PROJECT OF THE SIOPE HOST GENOME WORKING GROUP

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BACKGROUND: Little is known about cancer risk associated with pathogenic germline *SUFU* variants. METHODS: Data of all previously published and 25 still unpublished patients with a pathogenic germline *SUFU* mutation were compiled. RESULTS: 124 patients in 67 families were identified, most of them ascertained after the occurrence of a medulloblastoma (MB) or as part of Gorlin syndrome cohorts. Overall, 30 patients were healthy carriers and 94 patients developed a total of 129 tumors (up to 4 tumors/patient): 68 MBs, always as first tumor (median age at diagnosis: 1.5yr [0.1–5]), 22 patients with at least 1 basal cell carcinoma (BCC) (median 10/patient) (median age at first BCC: 43yr, [17–52]), 15 meningiomas (median age 43yr, [13–72]), 7 ovarian stromal/fibrous tumors (median age 12yr [5–34]), and 17 other tumors including 5 sarcomas (median age: 50yr [7–79]). Median age at last follow-up was 30yr. Nineteen patients died, including 11 from MB. Second malignancies were diagnosed

in 21 patients including 13 in MB survivors. Mutations were inherited in 58/66 (88%) of cases in which inheritance could be tested and de novo in 8. In 6/67 families (9%), >2 children were diagnosed with a MB. CONCLUSION: In this large cohort of germline *SUFU* mutation carriers, MB in infants is the most frequent tumor but the spectrum also includes typical Gorlin syndrome tumors (BCC, meningiomas, and ovarian stromal/fibrous tumors) either as first tumors or as second malignancies. This broad tumor spectrum and the high risk of second malignancies justify the implementation of specific cancer surveillance programs.

RARE-22. GERMLINE PATHOGENIC VARIANT C.1552G>A;P.E518K IN DGCR8 CONFERS SUSCEPTIBILITY FOR SCHWANNOMATOSIS AND THYROID TUMORS

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Germline mutations in *DICER1* cause a pleiotropic susceptibility syndrome characterized by the development of pediatric or early-onset tumors including pleuropulmonary blastoma, Wilms tumors, pineoblastomas, multinodular goiter (MNG) and thyroid cancers. Somatic mutations in the other two microprocessors *DROSHA* and *DGCR8* have been found in Wilms Tumors and pineoblastomas. We present here two families with peripheral schwannomatosis and thyroid tumors carrying a germline variant c.1552G>A;p.E518K in *DGCR8*. Family one had six affected members with early-onset MNG and five of them developed schwannomatosis. All five members were heterozygous for the variant. One of the carriers had also been diagnosed with a choroid plexus papilloma at 7 years old. The common second event in all tumors tested was the loss of chromosome 22 at the somatic level. In family two, a 35-year-old male was diagnosed with a peripheral schwannoma at the age of 12. Since then, he has developed seven extra peripheral schwannomas (one of which was an ancient schwannoma) and papillary thyroid cancer. *DGCR8* lies on chromosome 22q, adjacent to the three schwannoma genes: *LZTR1*, *SMARCB1* and *NF2*. The variant, c.1552G>A;p.E518K localizes to the first RNA-binding domain of *DGCR8* and structural modelling predicts that it abolishes proper binding of RNA. It is also a hotspot somatic mutation in Wilms tumors. Using miRNA profiling, we show that this variant disrupts global microRNA production and *DGCR8* mutated tumors show a specific miRNA profile different from *DGCR8* wild type tumors. These findings reinforce *DGCR8* as a novel susceptibility gene for schwannomatosis and thyroid tumors.

RARE-23. NOVEL NF1 MUTATIONS IN TWO OCCURRENCES OF GLIOBLASTOMA MULTIFORM IN A PATIENT WITH CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY SYNDROME

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Constitutional mismatch repair deficiency (CMMRD) syndrome is a rare cancer predisposition syndrome in children. Its main associated tumor types include brain and CNS tumors, hematologic malignancies, intestinal polyps and colorectal tumors, and other malignancies. Tumor genesis within this population is highly complex and poorly understood. We describe a case of a patient with two occurrences of glioblastoma multiforme (GBM), each with unique NF1 mutations. The patient is a female with CMMRD who was first diagnosed with GBM of the right frontal lobe in 2015. She subsequently underwent gross total resection, radiation to the field and concomitant and maintenance therapy with Temozolomide and Everolimus, due to high suspicion for NF-1. Genetic studies didn't show NF-1, instead revealing a diagnosis of CMMRD. Molecular testing of the GBM showed a high mutational burden and an NF1 mutation. Later, screening revealed stage IV colon cancer, for which she underwent subtotal colectomy, partial liver resection and chemotherapy. Molecular testing from the colon cancer found a hypermutant malignancy without mutations in NF1. Surveillance imaging detected a mass at the original site of her GBM, for which she had a resection. Notably, the genetic profile of the second tumor substantially different from the original tumor and the colon cancer sample, but had new mutations in NF-1. These findings highlight the significant variability in the genetic profiles of tumors in the context of CMMRD. It is also worth considering that NF1 is one of the first in a cascade of mutations leading to GBM in these patients.

RARE-24. LARGE CONGENITAL MELANOCYTIC NEVI AND NEUROCUTANEOUS MELANOCYTOSIS: A RETROSPECTIVE CASE SERIES

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Neurocutaneous melanocytosis (NCM) is a rare disease characterized by excessive proliferation and deposition of melanocytes in the leptomeninges and brain parenchyma, occurring in children with large congenital melanocytic nevi (LCMN). Manifestations of NCM range from asymptomatic CNS melanin deposition to cranial neuropathies, seizures, and hydrocephalus. Patients with NCM are at risk for malignant melanoma. We conducted a retrospective, single-institution study of patients with LCMN evaluated at Memorial Sloan Kettering Cancer Center from June 2000 to January 2020. Of 55 patients studied, 15 had no radiographic NCM, and 40 had radiographic NCM at initial evaluation. MRI findings included: focal melanocytosis (33), diffuse leptomeningeal disease (4), solid melanoma (3). Malformations were identified in 13, including arachnoid cyst (4), congenital hydrocephalus (4), Dandy-Walker malformation (3), and tethered cord (1). Twenty-one patients completed imaging once and were followed clinically. Seventeen with serial imaging (10 with focal melanocytosis, 7 with normal MRI) remained stable over a median 24-month follow up (range: 1–124). Six had suspected radiographic progression of NCM without melanoma. Malignant melanoma developed in 11 patients, 5 with focal melanocytosis on initial imaging. Median time from focal melanocytosis identification to melanoma diagnosis was 80 months (range: 18–200). Median age at melanoma diagnosis was 9.9 years (range: 1.1–25.3). Median survival from melanoma diagnosis was 9.1 months (range: 1–60.4). Focal NCM on neuroaxis imaging does not predict time to transformation to malignant melanoma. Serial imaging is not indicated in absence of disease-modifying treatment. Clinical follow up of at-risk individuals is essential in early identification of complications.

RARE-25. RETINAL ASTROCYTOMA MTOR INHIBITOR THERAPY IN TUBEROUS SCLEROSIS MOSAICISM

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INTRODUCTION: Everolimus is an inhibitor of mTORC1 (mammalian target of rapamycin complex 1), it is Health Canada and FDA approved for SEGA and renal angiomyolipoma in the setting of tuberous sclerosis complex (TSC). There is little data available in regards to this treatment of TSC associated retinal astrocytoma (RA). Although the behaviour of RA is often indolent or slowly progressive, aggressive behaviour with retinal detachment and neovascular glaucoma requiring enucleation has been reported in several patients. Definite TSC diagnosis is established when either two major features or one major and two minor features are present. Probable TSC diagnosis is established when one major plus one minor feature is present. METHODS: We report a child with probable TSC mosaicism, with negative serum NGS for TSC but RA and retinal achromic patch on the left. A left retinal peripapillary astrocytoma around optic nerve and very close to fovea was noted. There was concern that if it grew or there were to be any leakage it would cause visual impairment. This lead to therapy with everolimus 4.5 mg/m2/d aiming for level between 5 and 10 mcg/L. RESULTS: This boy has had a gradual reduction of the RA over the last 29 months, with healthy retina in the region no longer occupied by the lesion and preserved vision. He has tolerated therapy well with occasional mouth ulcers. CONCLUSION: mTORC1 inhibition is effective therapy to preserve vision in the setting of retinal astrocytoma and tuberous sclerosis mosaicism.

RARE-26. RETROSPECTIVE ANALYSIS OF PEDIATRIC CHOROID PLEXUS TUMORS

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BACKGROUND: Choroid plexus tumors (CPT) include choroid plexus papilloma (CPP), atypical choroid plexus papilloma (aCPP), and choroid plexus carcinoma (CPC). Because of their rarity, limited data are available on the current status of treatment and outcomes for pediatric CPTs. METHOD: We retrospectively reviewed clinical information on patients with CPT patients aged between 0 and 30 years at diagnosis and were treated in 8 institutions in Japan. RESULTS: Of forty-two cases initially diagnosed as CPT, 18 cases were reviewed by central pathologists. As a result, the diagnosis of CPC or aCPP in five cases were changed to other tumors including AT/RT and astroblastoma. The remaining 37 cases were subjected to analysis. Median age at diagnosis was two years (0 to 25) and the mean follow-up period was seven years. All 26 patients with CPP (n=20) or aCPP (n=6) underwent gross-total resection without adjuvant therapy. Of them 24 patients are alive without recurrence. Four patients of patients with CPC (n=11) died of cancer. Five patients including three patients experienced local relapse, achieved complete remission after resection of tumor plus chemoradiotherapy. All three patients with dissemination of CPC at diagnosis or relapse died of the disease. At least three patients were diagnosed with Li-Fraumeni syndrome: one died of medulloblastoma and one patient developed osteosarcoma. CONCLUSION: Compared with the excellent prognosis of CPP, the survival rates for CPC, especially disseminated CPC are unsatisfactory. Our results also underline the importance of considering genetic testing of TP53 for patients with CPC.

RARE-27. DOUBLE MUTATIONS: DIFFERENT GERMLINE AND TUMOR MUTATIONS LEAD TO POOR OUTCOMES

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BACKGROUND: As genetic testing for both germline and tumor mutations has increased in completeness, complexity, and availability, more mutations and their impact on patient outcomes have been identified. METHODS: A retrospective review of pediatric patients who have identified germline mutations and a different tumor mutation was conducted. Data collected included demographics, tumor type, germline mutation status, tumor mutation status, relapse status, and patient outcome. RESULTS: Six patients aged 8–13 years old (median age 10 years) were identified for analysis. Four patients had pilocytic astrocytoma and two had pilomyxoid astrocytoma. One of the patients with pilocytic astrocytoma also had MPNST diagnosed very early at age 9. The combination of germline/tumor mutations is as follows: Neurofibromatosis Type I (NF1)/BRAF v600e, NF1, CHEK2/MYB-QKI, NF1, Klinefelter, ATM, MUTYH, GPC3/BRAF-KIAA fusion, NF1/BRAF-KIAA (2 patients), and Marfan's/BRAF-KIAA. The number of relapses per patient following initial diagnosis range from 3–7 with an average of 3.3. Four of the patients are alive and on therapy, which two are deceased. The two deceased patients both had NF1/BRAF-KIAA fusions and pilocytic astrocytomas. CONCLUSIONS: Patients with differing and compounded germline and tumor molecular genetic mutations have worse outcomes. These patients have more relapses and death when compared to those patients with one mutation, either germline or tumor. Broad molecular testing and germline testing for mutations is crucial in determining patient risk for poor outcomes.

RARE-29. PRIMARY CENTRAL NERVOUS SYSTEM NON-HODGKIN LYMPHOMA IN AN 11-YEAR-OLD BOY: A CASE REPORT

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BACKGROUND: Primary central nervous system lymphoma (PCNSL) are very rare in children. CLINICAL CASE: An 11-year-old male presented with a 2 months history with myoclonic movements in the upper right limb, and a sudden frontal headache, gait disturbance due to right hemiparesis and an ipsilateral convulsive episode. Upon admission he had critical condition, with hypertensive skull syndrome, Glasgow of 12, Karnofsky 40%, right hemiparesis, swallowing disorder, facial paralysis, and loss of photo motor reflex and unilateral amaurosis. A CT and MRI showed a huge tumor mass in the left tempo-parietal region, infiltrating the white matter and shifting the midline. A Tumor biopsy was done, and reported diffuse small cell non-Hodgkin lymphoma of high-grade, Burkitt type. Systemic lymphoma workup was negative. He received six cycles of chemotherapy based on high dose methotrexate, rituximab and triple intrathecal.After the second cycle an ophthalmologic evaluation was done, and found infiltration to the right retina, for which 6 cycles of intra vitreous chemotherapy with methotrexate were applied, he showed an excellent response, and recovered all his neurological functions except that right hemianopia persist. Control MRI showed partial response at 2nd cycle and complete response after the 4th cycle. No Radiation was performed. CONCLUSION: This report highlights the fact that pediatric PCNSL may be effectively treated by a combination of HDMTX and rituximab-based chemoimmunotherapy without irradiation. Lack of awareness of this rare entity may lead to extense resections of brain, and potential permanent secuelae that were avoided in this illustrative case.

RARE-30. A RARE CASE OF PRIMARY EWING'S SARCOMA OF THE CERVICAL SPINE

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Ewing sarcoma family of tumors predominantly affect the pediatric population in the long bones of the extremities or the pelvis, and only 8% of cases arise within the spine. Primary Ewing's sarcoma of the cervical spine is extremely rare and less than 30 cases have been reported in the literature thus far. Here we present a case of primary Ewing's sarcoma of the cervical spine in a 28-year-old female who presented with a three-month history of neck pain and right arm radiculopathy. MRI revealed a homogeneously contrast enhancing, eccentric mass with dural tail at C2-C7. After undergoing a hemilaminectomy, histopathology confirmed extraosseous Ewing's sarcoma with CD99 positivity. A comprehensive systemic and neuraxis work-up ruled out overt metastasis. We extrapolated data from children's cooperative group studies and IESS-II clinical trial to formulate a three phase treatment protocol as described below. To date, patient is in remission with no evidence of any residual disease in the cervical spine. In conclusion, although Primary Ewing's sarcoma of the cervical spine is extremely rare it should be considered a differential diagnosis in patients with neck pain and a spinal mass under the age of thirty. Less than 25% of EFT's present with overt metastasis and almost all have subclinical metastatic disease at the time of diagnosis, therefore, a comprehensive evaluation and systemic chemotherapy is recommended. We recommend a multidisciplinary approach of surgical decompression to preserve neurological functions, followed by compressed chemotherapy regimens, reevaluation for local treatment, and adjuvant chemotherapy.

RARE-31. RECURRENT CHOROID PLEXUS CARCINOMA IN THE SETTING OF LI-FRAUMENI SYNDROME: REPORT OF TWO CHILDREN MANAGED WITH INTENSIVE RE-INDUCTION AND MARROW-ABLATIVE CONSOLIDATION CHEMOTHERAPY WITHOUT IRRADIATION FOLLOWED BY MOLECULARLY-TARGETED BIOLOGICAL THERAPY

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BACKGROUND: The optimal management for children with recurrent choroid plexus carcinoma (CPC), is not established. We report two children with germline TP53 mutations, whose CPC relapses were managed with marrow-ablative chemotherapy and oral biologically-targeted therapies. PA-

TIENTS: Patient A: A 17 months old male presented with non-metastatic bilateral CPC. A de novo mosaic germline TP53 mutation was identified. After near-total resections, 16 months of standard chemotherapy were administered; 18 months later, localized tumor growth developed, again near-totally resected. Two cycles of re-induction chemotherapy were administered followed by three cycles of thiotepa/carboplatin with autologous hematopoietic cell rescue (AuHCR) and subsequently 21 months of sirolimus and thalidomide, continuing without residual or recurrent disease. Patient B: A 30 months old male presented with left lateral ventricular non-metastatic CPC. A de novo TP53 germline mutation was identified. Following subtotal resection, craniospinal irradiation with boost was administered followed by eight cycles of standard chemotherapy; 18 months later, localized recurrence developed; gross total resection was followed by 15 months of standard dose chemotherapies; four months thereafter, a second local recurrence developed, again gross totally resected. He then received one cycle of high-dose cyclophosphamide followed by three cycles of thiotepa/carboplatin with AuHCR. Subsequently he received sirolimus and thalidomide for 12 months, complicated by progressive pancytopenia. A small localized CPC recurrence was noted, gross totally resected, concomitant with myelodysplastic syndrome; he underwent an allogeneic matched unrelated donor marrow transplantation. CONCLUSIONS: Marrow-ablative chemotherapy with post-transplant targeted biological therapy may afford durable survival for select children with recurrent CPC.

RARE-32. PEDIATRIC METASTATIC SKULL BASE CHORDOMA WITH TP53 MUTATION – A CASE REPORT AND REVIEW OF THE LITERATURE

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Chordoma is an uncommon bone tumor arising from notochordal remnant, which accounts for 1–4% of all bone malignancies. It commonly occurs along the cranial-spinal axis, and skull base is one of most frequent sites, representing 35–49% of all chordoma cases. Surgical resection is widely accepted as the first choice of treatment. There are only limited number of reports about pediatric chordoma cases, and its biological behavior including genetic backgrounds were largely unknown. Here, we present a 5 year-old girl with a large aggressive skull base chordoma of 6 cm in maximum diameter, which eventually had multiple systemic metastasis. We initially tried chemotherapy based on the protocol for the osteosarcoma, but in vain. Because the tumor was highly vascularized on angiography, after embolization of the feeding arteries and bilateral internal maxillary arteries, endoscopic endonasal surgery was performed. The tumor was sufficiently removed, achieving effective mass reduction, and the residual tumors involving the lower cranial nerves and craniocervial junction were additionally treated with Gamma Knife radiosurgery. However, one month later, it showed systemic metastasis to bilateral cervical lymph nodes and lung. We tried chemotherapy with nivolmab and imatinib for this patient, whereas they showed the partial effect. The genetic analysis revealed somatic TP53 c.569C>T, (p.P190L) mutation in chordoma specimen. In the past literature, we found only one study of the adult chordoma cases, in which majority of the patients had somatic TP53 mutation (p.P72R). Further investigation with large number of the cases is essential to clarify the molecular biology of pediatric chordomas.

RARE-33. GIANT CELL TUMOR OF THE SKULL BASE WITH A HISTORY OF A SUCCESSFUL RESPONSE TO DENOSUMAB AND LATER DEVELOPING A SECOND TUMOR

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BACKGROUND: Giant cell tumor of bone(GCTB) is a rare neoplasm with unpredictable behavior, possible malignant transformations, and/or lung metastases. Surgery is usually the treatment of choice. In unresectable or metastatic cases, treatment with denosumab is a new treatment option. CASE PRESENTATION: A 14-years-old female presented with cachexia, dysphagia, diplopia, discoordination, strabismus, and multiple cranial nerve palsies in 10.2015. MRI revealed intra-extracranial mass arising from C2 vertebrae, compressing the medulla oblongata and the left cerebellar hemisphere, invading to the sphenoid bone and nasopharynges. Biopsy showed a GCTB. Surgical resection was done, which was incomplete because of tumor location (cranial nerve and vertebral artery involvement). Then local radiation therapy was performed 50.4Gy. During RT patient's condition declined and MRI showed disease progression. Treatment with denosumab 120mg q4w was initiated in 03.2016, which yielded successful results. Disease was under control for three years until 03.2019. Then she returned with clinical symptoms of diplopia and severe headache. MRI showed local tumor progression. Repeated biopsy revealed undifferentiated pleomorphic sarcoma, which could be either a malignant transformation of GCTB or a new tumor. The patient later underwent two cycles of chemotherapy with Ifosfamide/Doxorubicin. MRI after 2nd cycle showed marked tumor progression. The patient didn't receive any further treatment because of cachexia and died due to disease progression in 12.2019. CONCLUSION: To our knowledge, this is the youngest patient ever reported with a skull base tumor with such a clinical development, successful and long-time remission with denosumab and with such a chemotherapy-resistant malignant transformation or second cancer.

RARE-34. UK CHILDREN'S CANCER AND LEUKAEMIA GROUP (CCLG): GUIDELINES FOR THE MANAGEMENT OF MENINGIOMA IN CHILDREN, TEENAGERS AND YOUNG ADULTS

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Primary tumours of the meninges are rare accounting for only 0.4–4.6% of all paediatric tumours of the central nervous system. Due to the rarity of these tumours in children, and the consequent absence of collaborative prospective trials, there is no clear consensus on how the unique characteristics of paediatric meningiomas impact clinical status, management approach, and survival. Much of the evidence and treatment recommendations for paediatric meningiomas are extrapolated from adult data. Translating and adapting adult treatment recommendations into paediatric practice can be challenging and might inadvertently lead to inappropriate management. In 2009 Traunecker *et al.* published guidelines for the management of intracranial meningioma in children and young people on behalf of UK Children's Cancer and Leukaemia Group (CCLG). Ten years later we have developed the updated guidelines following a comprehensive appraisal of the literature. Complete surgical resection is the treatment of choice for symptomatic meningiomas, while radiotherapy remains the only available adjuvant therapy and may be necessary for those tumours that cannot be completely removed. However, significant advances have been made in the identification of the genetic and molecular alterations of meningioma, which has not only a potential value in development of therapeutic agents but in surveillance of childhood meningioma survivors. This guideline builds upon the CCLG 2009 guideline. We summarise recommendations for the diagnosis, treatment, surveillance and long-term follow up of children and adolescents with meningioma.

RARE-35. PINEOBLASTOMA IN CHILDREN SIX YEARS OF AGE OR LESS: FINAL REPORT OF THE HEAD START I, II AND III EXPERIENCE

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BACKGROUND: We report the outcomes of patients with pineoblastoma enrolled on the Head Start I-III trials. METHODS: Twenty-three children were enrolled between 1991–2009. Treatment included maximal surgical resection followed by five cycles of intensive-chemotherapy and consolidation with marrow-ablative chemotherapy and autologous hematopoietic cell rescue (HDCx/AuHCR). Irradiation following consolidation was reserved for children over six years of age or those with residual tumor at the end of induction. RESULTS: The median age was 3.12 years (range:0.44–5.72). Three patients withdrew from the protocols and two patients experienced chemotherapy-related mortality. Eight patients experienced progressive disease (PD) during induction chemotherapy. Ten patients received HDCx/AuHCR; eight experienced PD post-consolidation. Seven patients received craniospinal irradiation (CSI) with a median dose of 20.7 Gy (range:18–36 Gy) with boost(s) (median dose 27 Gy, range:18–36 Gy); three received CSI as adjuvant therapy (2 post-HDCx/AuHCR) and four upon progression/recurrence. The 5-year progression-free survival (PFS) and overall survival

(OS) were 9.7% (95%,CI:2.6–36.0%) and 13% (95%,CI:4.5–37.5%), respectively. Three patients survived beyond five years. Nineteen patients relapsed in the following sites: local site (n=4), distal site (n=6), local and distal sites (n=9). Favorable OS prognostic factors were CSI (hazard ratio (HR)=0.30 (0.11–0.86), p=0.025), and HDCx/AuHCR (HR=0.40 (0.16–0.99), p=0.047). CONCLUSION: CSI and HDCx/AuHCR were statistically associated with improved survival. The overall poor outcomes and high PD rate during later induction cycles and following consolidation chemotherapy warrants consideration of fewer induction cycles before consolidation and the intensification of consolidation with multiple cycles of marrow-ablative chemotherapy.

RARE-36. DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMORS: A REVIEW OF CLINICAL AND MOLECULAR CHARACTERISTICS, AND OUTCOME IN A PEDIATRIC POPULATION AT A SINGLE CENTER

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BACKGROUND: Neuronal and mixed neuro-glial tumors of the central nervous system (CNS) are relatively rare. Dysembryoplastic neuroepithelial tumor (DNET) is a benign, rare, slow-growing tumor, but in many cases is associated with intractable epilepsy. OBJECTIVE: To report the experience with DNET at a single free-standing children's institution. METHODS: A retrospective chart review of 24 patients with confirmed DNET between 2001 and 2019 was performed. Data was collected on clinical characteristics, tumor location, surgical management, histopathological and molecular findings, and outcomes. RESULTS: Mean age at diagnosis was 10 years (range 2 to 19 years), with female predominance (54.2%). Most common presenting symptoms were seizures (79.2%) and headaches (12.5%). Location of the tumor was temporal (29.2%), frontal (25.0%), parietal (16.7%), cerebellar (12.5%) and occipital (4.2%). A gross total resection was achieved in half the cases. Recurrence occurred in 4 patients (16.7%), all of whom had subtotal resections. The average follow up since diagnosis was 4.6 years (range 0.3 to 14 years). Nineteen patients presented with seizures, of which 63.2% were seizure free after surgery. The samples with molecular genetic testing (microarrays or FISH), were all normal except one patient positive for BRAF V600E mutation. CONCLUSIONS: This is the first and largest review of pediatric DNETs in the last 10 years. Despite majority of patients having a favorable outcome after surgery, a subset of patients remains symptomatic. As molecular mechanisms in DNET remain unknown, future aim is to describe the molecular characteristics of our DNET population, and correlate with outcomes.

RARE-37. NOONAN SYNDROME AND GLIONEURONAL TUMORS: A CENTRAL NERVOUS SYSTEM CANCER PREDISPOSITION ASSOCIATION?

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BACKGROUND: Noonan syndrome (NS) is associated with germline Ras signaling pathway mutations, RAS overactivation and increased tumorigenesis risk. Rosette-forming glioneuronal tumors (RFGT) are rare indolent tumors. We report the molecular profiling of two patients with NS and RFGT. PATIENT 1: A 22-year-old male with NS was diagnosed with RFGT after partial tumor resection followed by focal irradiation. He was enrolled on a comprehensive genomic profiling study involving paired tumor-normal whole exome sequencing and RNA sequencing of the disease-involved tissue, revealing a germline *PTPN11* alteration (p.Gly60Ala) consistent with NS, and a somatic deletion (p.Ile442_Thr454del) in *PIK3R1* and a somatic variant (p.Lys656Glu) in *FGFR1* with concomitant increased expression of *PIK3R1* and *FGFR1* by RNA-sequencing. The patient remains without tumor progression now nine months since irradiation. PATIENT 2: A 19-year-old male with persistent headaches, underwent a brain MRI demonstrated multiple abnormal signals in the pineal region and midbrain. He had a stereotactic biopsy revealing RFGT. He was enrolled on the genomic study revealing a germline *PTPN11* alteration (p.Asn308Asp) resulting in a new diagnosis of NS. Several family members were subsequently identified with clinical features of NS, including his mother and two siblings, enabling appropriate counseling. Two somatic variants were found in *trans* in *PIK3R1* (p.Thr454_Phe456del and p.Glu451_Asn453delinsAsp), and a somatic variant (p.Val695Met) in *FGFR1*, with resultant overexpression of *PIK3R1*. The patient is monitored with surveillance imaging. CONCLUSION: We report the molecular profiling of two patients with NS and RFGT; strongly suggesting their connection to RASopathies through the overactivation of the MAPK and PI3K/AKT/mTOR signaling pathways.

RARE-38. CLINICAL PRESENTATION OF MGA-NUTM1 FUSION TRANSCRIPT SARCOMA

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BACKGROUND: MGA-NUTM1 fusion gene tumor are recently described as new subtype of NUTM1-rearranged tumors. Regarding its rarity, standard treatment has not been reported. Here we described clinical presentation, radiologic finding, immunohistological profile, and treatment of a boy with MGA-NUTM1 fusion gene tumor. CASE REPORT: A 13-year-old boy with 2-month history of progressive right hemiparesis and headache. Magnetic resonance imaging (MRI) revealed 7.8 x10.6 x 8.0 cm well defined heterogeneous enhancing mass at left fronto-parietal lobe. CT chest and abdomen, bone scan, MRI spine, and CSF studies were unremarkable. He underwent craniotomy with total tumor removal. Pathology demonstrated high grade spindle cell sarcoma. The immunohistological profile was positive for BCOR, NUT1, and TEL1, but negative for CD34, STAT6, desmin, SMA, actin sarcomeric, EMA, PR, S100, SOX10, BCL 6, and SABT2. The INI-1 showed nuclear expression and Ki-67 was positive in 50% of tumor nuclei. Molecular test for MGA-NUTM1 fusion transcript was positive, while SYT-SSX1, SYT-SSX2, and SYT-SSX4 fusion transcripts were negative. Four months after operation, MRI showed newly-seen two small enhancing foci at lateral and inferior aspects of the surgical cavity. He underwent re-surgery. Then focal radiation (54Gy and boost up to 60Gy at recurrent area) to the resection cavity was decided. Post-radiation chemotherapy including ifosfamide 3 g/m^2 and etoposide 150 mg/m^2 on Day 1–2, and carboplatin 500 mg/m^2 on Day 3, every 21–28 days was started. He has completed the first course of chemotherapy without any complication. CONCLUSION: MGA-NUTM1 fusion CNS sarcoma is rare. Treatment may require surgery, radiation and chemotherapy.

RARE-39. MOLECULARLY CONFIRMED ATYPICAL CHOROID PLEXUS PAPILLOMA WITH INTRACRANIAL DISSEMINATION

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INTRODUCTION: Among choroid plexus tumors (CPTs), metastasis occurs more frequently as pathological grading increases. There could be an underestimation of pathological diagnosis if disseminated CPTs are diagnosed with lower grade tumors such as choroid plexus papilloma (CPP) or atypical choroid plexus papilloma (aCPP). Thus, molecular diagnosis using genome-wide DNA methylation profiling may be useful to clarify malignant potential among thetumor entity. Here, we report about a case of aCPP with intracranial dissemination that was molecularly diagnosed by methylation profiling. CASE DESCRIPTION: A 2-year-old girl presented with a history of vomiting. Brain magnetic resonance imaging showed a large tumor mass in the right lateral ventricle and diffuse enhancement surrounding her brainstem, which suggested dissemination. Gross total resection of the mass was performed. Intraoperative findings revealed multiple spot metastatic lesions on the inner wall of lateral ventricle. The pathological diagnosis was aCPP owing to the presence of a glandular structure with a papillary pattern suggesting a neoplasm of epithelial origin, increased cellularity, several necrotic areas, and an intermediate number of mitoses. The CPT-SIOP-2000 treatment protocol was followed without radiation therapy, and the disseminated lesion was disappeared during the chemotherapy. Methylation data of the current case was entered into a recently

published classifier, and the tumor was classified as methylation class "plexus tumor, subclass pediatric A" with high confidence (calibrated score 0.96), which includes cases diagnosed as CPP and aCPPs. CONCLUSION: Our case indicates the clinical significance of molecular confirmation of diagnosis among CPTs, particularly lower grade tumors with dissemination.

RARE-40. CASE REPORT: LONG-TERM SURVIVOR OF A RARE, PEDIATRIC PRIMARY HISTIOCYTIC SARCOMA (HS) OF THE CENTRAL NERVOUS SYSTEM (CNS) FOLLOWING COMPLETE RESECTION, CHEMOTHERAPY AND ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (ALLO-HCT)

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We report an unusual case of a patient with primary CNS-HS a very rare neoplasm of histiocytic lineage with usually poor prognosis. An 8 year old boy presented with a one month history of headaches, nausea and vomiting. Physical examination revealed nystagmus and dysmetria. Brain MRI revealed a localized 2.4 cm posterior fossa (cerebellar) mass with restricted diffusion. The patient underwent a gross total resection of the mass. Initial post-operative lumbar puncture was positive for rare malignant cells. Pathology showed a focally necrotic neoplasm, composed of nests and cords of large relatively uniform cells with abundant eosinophilic cytoplasm, moderately pleomorphic nuclei and numerous mitotic figures, consistent with CNS-HS with juvenile xanthogranuloma phenotype, as supported by positive IHC expression of CD163, CD68, CD14, fascin, and Factor XIIIa, while negative for CD1a, Lymphoid and Myeloid markers, and BRAFv600e mutation. He was treated with two cycles of clofarabine and cytarabine and triple intrathecal (IT) chemotherapy. He developed generalized seizures and MRI showed demyelination consistent with IT methotrexate toxicity; MTX was then discontinued. He was then given two additional cycles of cladribine and weekly intrathecal therapy prior to consolidation with an Allo-HCT using a 10/10 HLA allelic-matched unrelated donor. His conditioning regimen included total body irradiation and cyclophosphamide. He did well post-transplant with peripheral blood chimerism at 1 year showing > 95% donor cells. He remains disease-free with an excellent quality of life since August 2016. We report one of the few known survivors of this unusual and highly malignant entity.

RARE-41. SECOND MALIGNANCIES FOLLOWING TREATMENT FOR PRIMARY CENTRAL NERVOUS SYSTEM TUMORS IN PEDIATRIC PATIENTS: A SINGLE-INSTITUTIONAL RETROSPECTIVE REVIEW

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Second malignant neoplasms following treatment for primary central nervous system (CNS) tumors in children are rare occurrences but may often have dire consequences, particularly, if thought to be induced by prior therapies. The authors retrospectively reviewed pediatric patients with primary CNS malignancies from the University of Wisconsin over the last 25 years (1994 – 2019) with any secondary malignant neoplasm and determined seven patients met criteria. Treatment modalities were reviewed with all patients receiving surgery, chemotherapy, and radiotherapy for treatment of their first malignancy. The second neoplasms found included 4 high-grade gliomas, 1 meningioma, 1 thyroid carcinoma, and 1 myelodysplastic syndrome. The median latency time between diagnoses was 9 years (range 4 -17 years). The outcomes varied according to histopathology of the second neoplasm with the high-grade glioma patients all deceased from progressive disease. The high-grade gliomas were thought to have been induced by prior radiation in most cases. The remaining patients are still alive, at the time of this writing, and in follow up after treatment for their second neoplasm. Thus, long-term follow up is essential for children treated for a primary CNS tumor given the variety of second neoplasms that could arise with differential consequences. In addition to our single institutional outcomes, we will also present an updated review of the literature of pediatric patients with primary CNS tumors and second malignancies.

RARE-42. PRIMARY INTRACRANIAL SARCOMA WITH *DICER1*-MUTATION - TREATMENT RESULTS OF A NEW MOLECULAR ENTITY

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OBJECTIVE: An unexpectedly high incidence of sarcomas of the Central Nervous System (SCNS) was recently observed in Peru. We describe clinical and biological characteristics of the disease. METHODS: Seventy pediatric patients with primary SCNS diagnosed between January 2005 and June 2018 were analyzed. DNA methylation profiling and gene panel sequencing was available from 28 and 27 tumors, respectively. RESULTS: Median age was 6 years (range 2–17.5), 66/70 patients had supratentorial tumors, 56 patients intratumoral hemorrhage at diagnosis. Three patients fulfilled clinical criteria of NF1; 35 had café-au-lait spots and/or freckling. DNA-methylation profiling classified 28/28 as "intracranial spindle cell sarcoma with rhabdomyosarcoma-like features and *DICER1* mutations". *DICER1* mutations were found in 26/27, *TP53* mutations in 22/27, and *RAS*-pathway gene mutations (*NF1, KRAS, NRAS*) in 19/27 tumors, all of which were somatic (germline control available in n=19 cases). Survival was analyzed in 57 patients with non-metastatic disease who received adjuvant therapy. Two patients had metastatic disease, eleven did not receive or abandoned treatment. Two-year OS was 66.3% (95%-CI: 54–81%), 2-year PFS 51% (38–67%). PFS was highest in patients treated with postoperative ICE chemotherapy followed by radiotherapy and ICE (2y-EFS 79% [59–100%], n=18) and worse after upfront radiotherapy followed by ICE (40% [19–85%]; n=10) or VAC (50% [28–88%], n=12) and radiotherapy only (21% [6–71%], n=11; p=0.008). CONCLUSION: Primary SCNS with *DICER1* mutation have an aggressive clinical course. A combination of chemotherapy and radiotherapy seems beneficial. A link to a cancer predisposition syndrome could not be established so far.

RARE-43. FAVORABLE OUTCOME OF A YOUNG GIRL WITH RECURRENT METASTATIC PINEOBLASTOMA ASSOCIATED WITH A DICER1 MUTATION

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Pineoblastomas have been thought to portend a poor prognosis, especially in younger children or those with metastases. Long term survivors after relapse, especially for those with metastatic disease are rare. We report a young girl with a DICER1 mutation who survived recurrent metastatic pineoblastoma. She was initially diagnosed at the age of 3 with a localized pineoblastoma, underwent gross total surgical resection, and received high dose chemotherapy with autologous stem cell transplant per COG ACNS0334 without radiation therapy. 16 months after completion of treatment, she relapsed at primary site with widespread spinal metastasis. She then received cranial spinal radiation of 3600Gy with proton beam, with boost to primary to 5580Gy, followed by chemotherapy with Temozolomide, Irinotecan and Avastin per COG ACNS0821. She is now 3 years and 3 months from completion of treatment, is doing well clinically with stable imaging findings. No particular alteration was identified from the tumor molecular testing of her initial pineoblastoma. Of note, she was diagnosed with pleuropulmonary blastoma soon after her initial diagnosis of pineoblastoma, and was found to have a DICER1 mutation (c.2062C>T; pR688*) thought to be a nonsense mutation. While radiation therapy following recurrence is known to improve the outcome, more recent studies suggest that tumors lacking the molecular features of high grade glioma also has a positive impact on prognosis. In addition, we speculate that DICER1

mutations might increase sensitivity of cancer cells to some chemotherapy through modulating gene expression and /or interfering with DNA repair mechanisms, therefore, affecting treatment outcome.

RARE-44. CLINICAL CHARACTERIZATION AND OUTCOME; OUR EXPERIENCE OF CHORDOMAS IN PEDIATRIC AND YOUNG ADULTS

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Pediatric chordomas are exceedingly rare and there are limited data to guide treatment decisions. We report a retrospective analysis of 19 patients with chordomas who received treatment at our institution from 2001–2020. Of the 19 patients, 15 had clival (79%), 3 cervical and 1 sacral chordoma. There were 9 males (47%). Median age at diagnosis of 10.6 years. Eight patients had gross total (42%) and 11 (58%) had sub-total resection. As front line therapy 15 patients (79%) underwent surgery followed by radiation (1 photon and 14 proton), 3 patients (16%) received surgery and chemotherapy (anaplastic histology) and 1 patient received only surgery. For patients treated with radiation therapy the average prescribed dose was 70 Gy (range: 52–74). Post-surgery and radiation, 14 of 15 patients remained in remission. Five (26%) patients had progressive disease (PD) with median time to progression of 13 months of whom 3 died of disease at median of 18 months. Treatment of PD consisted of chemotherapy and radiation for 3, re-resection with radiation for 1 and chemotherapy alone for 1 patient. The patients with metastatic and anaplastic disease mean survival is 21 month versus 45 for the rest of the cohort. In summary, post-operative adjuvant radiation provided an overall good outcome in majority of patients. Patients with anaplastic pathology and metastasis at diagnosis had worse outcome. Those who relapsed, subsequent treatment was palliative at best with short survival. Molecular analysis is warranted in future for better disease stratification.

RARE-45. SARCOMAS INVOLVING THE CENTRAL NERVOUS SYSTEM AT INITIAL PRESENTATION IN CHILDREN AND YOUNG ADULTS: A CASE SERIES

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Sarcomas of bone, soft tissue, or neural origin may occasionally invade the central nervous system (CNS), causing diagnostic and therapeutic challenges. We aim to investigate the clinical features of sarcomas involving the CNS at initial presentation. During 2015/01–2019/12, nine consecutive patients (4 Males and 5 Females) younger than 30 years of age treated at a University Healthcare System in Northern Taiwan were included. The median age was 8.7 years (range, 2–24 years); diagnoses were Ewing Sarcoma with *EWSR1* rearrangements (*n*=4), *CIC-NUTM1* Sarcoma (*n*=1), Osteosarcoma (*n*=2), Malignant Peripheral Nerve Sheath Tumor (MPNST; *n*=1), and extramedullary myeloid sarcoma (*n*=1). The tumors originated from the skull (*n*=1), dura (*n*=1), vertebra (*n*=4), spinal canal (*n*=1), or extra-CNS sites (*n*=2). Four patients had metastases (1 Ewing sarcoma, 2 osteosarcoma, and 1 extramedullary myeloid sarcoma). The main symptom at diagnosis was facial/eye pain (*n*=2), back pain (*n*=3), arm weakness (*n*=1), or gait disturbance (*n*=3). Upfront neurosurgical decompression (*n*=7) or urgent radiotherapy (*n*=1) was performed in most patients. At a median follow-up duration of 20.1 months, the overall survival rate was 70%. All patients with Ewing sarcoma (*n*=4) and *CIC-NUTM1* sarcoma (*n*=1) achieved Complete Response after surgery, interval-compressed chemotherapy, radiotherapy, and adjuvant chemotherapy. Patients with stage IV osteosarcoma (*n*=2) had Partial Response; the patients with MPNST and extraskeletal myeloid sarcoma died of Progressive Disease at 18 and 3 months after diagnosis, respectively. We conclude that timely decompression, early diagnosis, and histology-driven multimodality treatment are effective strategies in managing sarcomas involving the CNS.

RARE-46. A THIRTEEN YEAR PATIENT JOURNEY OF INFANT GIANT CLIVAL CHORDOMA: CASE REPORT AND LITERATURE REVIEW

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In 2006 we reported the youngest case of a large clival chordoma, a 15-week old baby, the second case to present without skull base involvement and the fourth case of chordoma in a patient with tuberous sclerosis. This unusually rare case (surgically un-resect able) underwent endoscopic skull-base diagnostic biopsy and a novel chemotherapy regime that aimed to control his disease[i]. Initial tumour control was achieved with chemotherapy (Ifosfamide, doxorubicin with dexrazonane, intrathecal hydrocortisone, methotrexate, cytarabine). Carboplatin and etoposide were later given for a further year. Following this, Sirolimus and imatinib were used for another twelve months due to primary tumour regrowth and three new skull-vault lesions. Sirolimus alone was continued for an additional year, but stopped due to optic neuritis. Imatinib was given until further progression two years later, leading to a change to everolimus. Surgery for the ventral foramen magnum was performed a year later. The patient received further surgery and radiotherapy for tumour recurrence. Sadly the tumour metastasised and he succumbed at age 13. Chordomas are aggressive and recur frequently. Complete primary resection followed by radiotherapy/proton beam therapy offers the best chance of cure but is not an option in infants with giant lesions, as in our case. We inform on alternative targeted treatment strategies and review the literature on these rare lesions. [i] Kambogiorgas D, St George EJ, Chapman S, English M, Solanki G: Infantile Clivus chordoma without clivus involvement: Case report and review of the literature, Childs Nerv System (2006) 22:1369–1374

RARE-47. DIFFUSE LEPTOMENINGEAL DISSEMINATED GLIONEURONAL TUMOR: CASE-SERIES

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Diffuse leptomeningeal disseminated glioneuronal tumor (DL-GNT) is a rare brain tumor that presents as a plaque-like subarachnoid tumor, commonly involving the basal cisterns and interhemispheric fissure of children but lacking intraparenchymal tumor. Here we report two cases focusing on clinicopathologic features. In all patients, radiography revealed characteristic leptomeningeal thickening and enhancement with minor superficial parenchymal lesions. The broadcast of the knowledge about this type of disease is important to increase awareness on this subject.

RARE-48. CHARACTERISTICS AND OUTCOME OF DIFFUSE LEPTOMENINGEAL GLIONEURONAL TUMOR (DLGNT): A SINGLE INSTITUTION EXPERIENCE

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Diffuse leptomeningeal glioneuronal tumors (DLGNT) are rare with an unknown etiology and unestablished incidence. Most frequently reported genetic alteration is *KIAA1549-BRAF* fusion. We present four DLGNT cases diagnosed between 2005–2018. Patient 1 is a female who presented with a 2-year history of back pain subsequently diagnosed with pilocytic astrocytoma. Re-imaging 3 months post-resection revealed a low grade glioneuronal tumor with BRAF duplication. Patient 2 is a female who presented with recurrent vomiting, dizziness, and hydrocephalus. The patient underwent biopsy which was consistent with oligodendrogliomatosis; no genetic analysis was done. Patient 3 is a male who presented with worsening headaches and intermittent vomiting. Approximately 5 months after resection, imaging showed leptomeningeal disease and further testing revealed *KIAA1549-BRAF* fusion and 1p deletion. Patient 4 is a male who presented with hydrocephalus. Imaging showed disseminated leptomeningeal enhancement without a dominant mass lesion; biopsy and clinical history confirmed the diagnosis. All four patients received chemotherapy, Patients 1 and 3 underwent radiation therapy, and Patient 3 received a MEK-inhibitor to which he had a great response. However, the patient was non-compliant and had PD which continued despite re-starting therapy. Patients 1, 2, and 3 have died of progressive disease; survival was Patient 1, 276 days, Patient 2, approximately 7 years and 8 months, and Patient 3, 2 years and 11 months. Patient 4 remains alive with disease 4.5 years from diagnosis. There is much to be learned about this rare, poorly understood disease but hope for improvement through therapeutic targeting of the MAPK pathway.

RARE-49. CHOROID PLEXUS ADENOMA WITHOUT ASSOCIATED HYDROCEPHALUS PRESENTING AS PRECOCIOUS PUBERTY

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Precocious puberty (PP) is a rare presentation of intracranial pathology unrelated to the pituitary. PP in this setting is considered a paraneoplastic phenomenon, achieved through synthesis of sex-hormones by the tumor itself or via alterations in the release of gonadotrophins from the pituitary. The latter has been described with masses adjacent to the pituitary or with those which cause hydrocephalus. We describe a case of a choroid plexus papilloma (CPP) without hydrocephalus presenting as precocious puberty.

An 18 month-old female presented with 4-months of weight loss, bilateral galactorrhea and constipation. Her weight decreased from the 15th to below the 1st percentile. CBC, celiac and thyroid studies were normal. Prolactin was at the upper limit of normal (25.8;ref 3.3–26.3). Breast ultrasound demonstrated symmetric breast tissue development. She was referred to pediatric gastroenterology for constipation and failure to thrive. Caloric supplementation, bowel regimen and barium enema were recommended. One week later, she was admitted with dehydration, painful constipation and further weight loss in the setting of an acute febrile illness. MRI revealed a normal pituitary and an intraventricular mass without hydrocephalus. She underwent gross total resection of the mass, later determined to be a choroid plexus papilloma. The patient's galactorrhea resolved abruptly following resection. Because of her galactorrhea, our patient underwent neuroimaging revealing an incidental mass without associated hydrocephalus. To our knowledge, precocious puberty and hyperprolactinemia have not been described in neoplasms distant from the pituitary. Thus, these lesions should be recognized as a potential etiology of precocious puberty and hyperprolactinemia.

RARE-50. TREATMENT RESPONSE OF CNS HIGH-GRADE NEUROEPITHELIAL TUMORS WITH MN1 ALTERATION

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BACKGROUND: CNS high-grade neuroepithelial tumor with MN1 alteration (CNS HGNET-MN1) are a rare entity recently described as a high-grade tumor containing a mixture of solid and pseudopapillary patterns with MN1 rearrangement. METHODS: CNS HGNET-MN1 patients were identified using genome wide methylation arrays across 5 institutions (the Hospital JP Garrahan, Hospital for Sick Children, the University Hospital Motol, Royal Children`s Hospital and Christchurch Hospital) and was correlated with treatment and outcome. Central imaging review with radiological features analysis was performed. RESULTS: We identified 9 patients harboring CNS HGNET-MN1 tumors through application of the Heidelberg brain tumor classifier. Seven tumors were T supratentorial and two in the spinal cord. Median age was 5 (range 3.6–14.6). All patients had surgery (6 GTR and 3 STR) as initial management followed by radiotherapy (focal 5/CSI 1) and systemic chemotherapy in 2 patients. Four of the 9 patients relapsed by 3 years post diagnosis, with 2 local and 2 metastatic failures despite complete surgical resections and radiotherapy. Three patients died due to tumor relapse after 24 months despite upfront radiotherapy. Seven of 9 patients had an initial diagnosis of ependymoma. CONCLUSION: Treatment of CNS HGNET-MN1 remains a major challenge with multiple failures, despite aggressive surgical resections and upfront involved field radiotherapy. Further multicenter, international prospective studies are required to determine the optimal treatment strategy for this group of tumors.

RARE-51. MOLECULAR INSIGHTS INTO MALIGNANT PROGRESSION OF CHOROID PLEXUS PAPILLOMA (CPP)

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Malignant transformation of CPP is rare and the mechanisms remain elusive. We report a case of progression of papilloma into carcinoma where we performed molecular sequencing of both samples. A boy was found to have a brain mass soon after birth. The gross total resection (GTR) was diagnostic of CPP. Six years later he developed a recurrent mass that demonstrated progression to a choroid plexus carcinoma (CPC). The patient received chemotherapy according to a "HeadStartII" protocol. He is 2.5 years off therapy and disease-free. A sequencing study consisting of 1700 genes and tumor transcriptome was done. The analysis of both samples revealed a germline variant of TP53(R248W) with LOH and an allele frequency of 39% in the germline sample, suggesting a mosaicism. Analysis of both samples identified extensive aneuploidy and similar pattern of gains in chromosomes 7/8/12/20/21/X. Copy number aberrations newly acquired in the carcinoma included copy gain of chromosomes 5q/12/15q/20, and copy loss of chromosomes 5q/13/22. The papilloma was found to harbor 3 somatic mutations with 4% to 21% allelic fractions, all lost in the carcinoma. These mutations were of unknown significance and with too low allelic fractions to be responsible for the transformation. More pertinently, chromosomal aneuploidy was significant with additional losses in the carcinoma. This resulted in the losses of two critical tumor suppressor genes, RB and BRCA2, playing a possible role in the observed transformation. The "HeadStart" experience suggested that the prognosis of TP53 mutant CPC may be improved in the absence of radiation therapy.

RARE-52. *RB1* GENE DELETIONS ARE THE NOVEL MECHANISM OF CHOROID PLEXUS TUMORS (CPT) ONCOGENESIS

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BACKGROUND: CPTs are known to be rare *TP53*-dependent neoplasms, while major molecular alterations underlying tumor progression, especially in *TP53*-wild type cases, are still unclear. METHODS: 18 primary CPT, including 16 choroid plexus carcinomas (CPC) and two atypical choroid plexus papillomas (CPP), were evaluated for copy number status of 87 major oncogenes and tumor suppressor genes by nCounter Cancer CNV assay by Nanostring and *TP53* and *RB1* by MLPA. Germline *TP53* nucleotide substitutions were analyzed by Sanger sequencing. RESULTS: Pathogenic germline *TP53* variants were present in 4 cases confirming Li-Fraumeni syndrome (LFS). Two patients have somatic *TP53* substitutions. Only one patient with LFS harbored somatic *TP53* deletion. In 7 patients, heterozygous deletions of *RB1* involving from 3 exons to the whole coding sequence detected by MLPA were discovered. All these findings were validated by nCounter CNV assay. Additionally, four patients have *WT1* deletions, two patients – *BRCA2*, and in 1 case - *NF1*, concomitant with *RB1* deletions in 3 cases. Interestingly, in one patient who faced a progression of CPP to CPC germline, *RB1* deletion was detected, and in both subsequent tumors, the length of the deleted region progressively increased. Notably, that *RB1* deletions are mostly mutually exclusive to *TP53* substitutions. 3 of 4 patients with *RB1* deletions having follow-up period >1 year faced with tumor-related adverse events. CONCLUSIONS: Somatic or uncommon germline *RB1* heterozygous deletions have been unraveled as a novel mechanism of aggressive CPT and could be implemented in prognosis definition schemes.

RARE-53. PINEAL PARENCHYMAL TUMOR OF INTERMEDIATE DIFFERENTIATION (PPTID) AND DICER1 SYNDROME: A CASE REPORT

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BACKGROUND: DICER1 syndrome is a rare inherited tumor predisposition syndrome linked to an increased risk of several malignancies. Affected individuals most commonly develop pleuropulmonary blastoma (PPB) and ovarian sex cord-stromal tumors. Brain tumors in these patients are rare, however; the increased frequency of pineoblastoma in this population has been established. Traditionally, pineal parenchymal tumors of intermediate differentiation (PPTIDs) have not been associated with DICER1 syndrome, with research suggesting alternative mutations driving tumorigenesis. These tumors are pathologically and clinically diverse, with long-term surveillance based on therapeutic interventions. Here we describe a case of a germline DICER1 mutation in a patient with a PPTID, suggesting that this mutation is not limited to pineoblastoma as previously reported. CASE: We describe a 19 year-old female with a WHO grade III PPTID treated with multimodal therapy including surgery, craniospinal irradiation (CSI) and chemotherapy. She was noted to have a thyroid mass at diagnosis and was subsequently diagnosed with a benign thyroid nodule, followed most recently by a cataract with pathology concerning for medulloepithelioma of the ciliary body. Due to the known association between medulloepithelioma and DICER1 syndrome, targeted germline sequencing was obtained and confirmed a pathogenic heterozygous mutation. CONCLUSION: To our knowledge this

is the first report of a PPTID in a patient with DICER1 syndrome. This association highlights the clinical implications of molecular evaluation in pediatric brain tumors, for both immediate therapeutic decisions and long-term surveillance.

RARE-54. MOLECULAR ANALYSIS OF ROSETTE-FORMING GLIONEURONAL TUMOR AT MIDBRAIN; REPORT OF TWO CASES

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Rosette-forming glioneuronal tumor (RGNT) is a tumor that primarily arises at posterior fossa. We experienced two rare cases of RGNT located at midbrain and investigated their molecular features. Case 1 is a 23-year-old female, and Case 2 is an 18-year-old male. Both cases were surgically removed by the occipital transtentorial approach. Histological analysis demonstrated a biphasic pattern of neurocytic and glial components. The former consisted of neurocytic rosettes and perivascular pseudorosettes, and the latter was GFAP positive, corresponding to the diagnosis of RGNT. Both cases have an excellent clinical course without receiving chemotherapy or radiation therapy. Small residual tumors of both cases shrunk and maintained for 27 and 12 months, respectively. Case 1 underwent DNA methylation array and a subsequent DNA methylation-based classifier, indicating that the case matched RGNT with a 0.99 calibrated score. Also, we identified FGFR1 K656 mutation. Pyrosequence analysis of other genes such as IDH1 R132, IDH2 R172, BRAF T599, BRAF V600, H3F3A K27, H3F3A G34, HIST1H3B K27, TERT C228, FGFR1 N546 had no mutations. RT-PCR of KIAA1549-BRAF fusion was not detected. DNA methylation status of Case 2 is under investigation. Pyorosequence analysis identified TERT C228 mutation but did not identify other mutations such as FGFR1 N546 and K656. Midbrain RGNT corresponds to the histological and molecular features of RGNT. RGNT needs to be differentially diagnosed in the case of a midbrain tumor.

RARE-55. CHALLENGES AND SPECIFIC STRATEGIES FOR CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY SYNDROME IN LOW RESOURCE SETTINGS. ON BEHALF OF THE INTERNATIONAL RRD CONSORTIUM IN LOW RESOURCE SETTINGS PANEL

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Germline biallelic mutations in one of the mismatch repair genes (MSH2/MSH6/MLH1/PMS2 results in constitutional mismatch repair deficiency (CMMRD), a condition associated with multiple tumors arising from multiple organs during childhood, and these individuals rarely reach adulthood. The paucity of information with respect to these conditions leads to mismanagement and may be a factor in the high mortality of patients with CMMRD. Two international consortia, the European CARE4CMMRD, and the international replication repair deficiency (RRD) consortium, are addressing the many challenges associated with this condition. To address specific issues surrounding the management of CMMRD in low and middle income countries (LMIC), a multidisciplinary taskforce of 11 specialists from nine countries was formed. Preliminary conclusions are: 1) Immunohistochemistry for CMMRD should be considered for all patients with suggestive clinical features. In countries where CMMRD is common, malignant gliomas, colon cancers and T cell lymphomas should be stained routinely as the prevalence of CMMRD in these tumors can exceed 40%. 2) Temozolomide should not be used in the management of malignant glioma. By contrast, preclinical studies have suggested increased sensitivity to nitrosoureas. For the management of CMMRD related lymphoma and leukemia, mercaptopurines should not be avoided or discontinued as a part of the standard of care before more data are collected. 3) Management with checkpoint inhibitors should be limited to centers with intensive care units and expertise in complex supportive care to manage side effects of immune therapy. 4) Surveillance protocols have demonstrated long term survival benefits and should be implemented in LMIC.

RARE-56. PERITONEAL SEEDING OF A DIFFUSE LEPTOMENINGEAL GLIONEURONAL TUMOR IN A CHILD

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Diffuse leptomeningeal glioneuronal tumors (DLGNT) are rare neoplasms of the central nervous system and have been included in the 2016 update of the WHO classification. This is the first description of a DLGNT disseminating to the peritoneal cavity via a ventriculoperitoneal shunt (VPS) in a child. We describe an 11-year old girl who received a VPS for a Dandy-Walker malformation at the age of seven, and was diagnosed with a spinal pilocytic astrocytoma with leptomeningeal metastases six months later. She received chemotherapy (SIOP-LGG protocol) with partial response, and had progressive disease eight months after therapy cessation. Following a novel biopsy, the diagnosis was revised to a DLGNT, with a KIAA1549-BRAF fusion and loss of 1p. She received vinblastine, but was clinically progressive and craniospinal radiotherapy was initiated. 13 months later, she suddenly presented with ascites. The inferior vena cava was compressed due to the ascites, and an abdominal drain was placed, with massive fluid release. Abdominal MRI indicated an omental cake and peritoneal contrast enhancement. Bone metastases were suspected in the iliac and femoral bones. Anatomopathological examination of the ascites showed an atypical cell population, with irregular, hyperchromatic and enlarged nuclei resembling the primary tumor. The cells were positive for synaptophysin, MAP2 and weakly positive for S100. Pan-NTRK staining was negative. The diagnosis of a metastatic localization of the DLGNT was made, due to seeding of tumoral cells via the VPS. Treatment with a MEK-inhibitor was initiated, but was stopped due to progressive disease and she died 3 weeks later.

RARE-57. PEDIATRIC CHORDOMA: WHOLE EXOME SEQUENCING OF 11 PEDIATRIC CHORDOMA SAMPLES

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Chordoma is a rare tumor and while *SMARCB1* alterations have been observed in poorly differentiated chordomas, conventional chordomas are not well understood. We interrogated nuclear and mitochondrial genomes of 11 chordoma samples from 7 children. Frozen tumor tissue DNA was extracted and whole exome libraries generated using Agilent SureSelect Human All Exon V6 kit plus mtDNA genome capture kit. Libraries were sequenced using Illumina Nextseq 500. MuTect2, VarDict and LUBA variant callers were used with allele frequency cutoff 2%. Potential germline variants were filtered bioinformatically. In total, 656±74 high-confidence somatic variants, including 368±43 nonsynonymous variants per sample were detected. Of 2,607 combined unique nonsynonymous variants, 95% were missense. Remaining high impact variants were frameshift (37%), stop gain (39%), splice acceptor/donor (22%), start and stop loss (2%). Of the unique nonsynonymous variants, 137 fall within Cosmic Cancer Census Genes, including high impact variants in *SETD2, MLLT4*. No previously reported *TBXT*, *CDKN2A*, *PI3K*, *LYST* mutations identified. Tumor Mutation Burden/Megabase was 10±1. The mitochondrial analysis revealed heteroplasmic m.11727C>T *MT-ND4* missense variants in three tumors resected at different time points from the same patient, and another heteroplasmic m.1023C>T rRNA mutation from the primary and recurrent tumors of another patient. Intriguingly, two Children's Brain Tumor Tissue Consortium patients with chordoma had identical heteroplasmic m.10971G>A *MT-ND4* nonsense mutations. Pediatric chordomas appear to lack somatic nuclear mutations. Observing recurrent mitochondrial mutations across multiple tumors from the same and/or different patients is striking, suggesting they may be implicated in tumorigenesis and be potential diagnostic markers.

RARE-58. CONGENITAL METASTATIC CHORDOMA OF THE CLIVUS

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Chordomas are rare midline axial skeletal neoplasms that typically present in adults. They are infrequent in childhood with typical localization in the spheno-occipital skull base. They are derived from remnants of the embryonic notochord. We present the case of 4 months old girl, who was born with „blueberry muffin" syndrome and was first negatively diagnosed for neuroblastoma and leukemia (two negative skin biopsies were performed) was admitted with axial laxity. In imaging testes there was a tumor of the scull base, metastases in the lungs and kidneys (that were not seen at previous assessments) and a small lesion in the heart. The third biopsy of skin lesion was performed and pathological examination revealed a neoplasm composed of cords, clusters, and chains of multivacuolated cells embedded within a myxoid matrix and separated by fibrous septa. No atypical and dedifferentiated features were present. Mitotic activity was not observed. Neoplastic cells showed the typical cytoplasmic immunostaining for EMA, S100 and cytokeratin AE1/AE3, strong nuclear brachyury expression, and retention of nuclear INI-1 expression. The diagnosis of chordoma was established. Neoplastic tissue and blood samples were obtained for molecular analysis using next generation sequencing, including germline mutations assessment (are ongoing). Chemotherapy as for soft tissue sarcomas was undertaken. Currently a patient is on treatment with improvement of neurological status.

RARE-59. CARDIAC REMODELING IN PATIENTS WITH CHILDHOOD-ONSET CRANIOPHARYNGIOMA – RESULTS OF HIT-ENDO AND KRANIOPHARYNGEOM 2000/2007

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BACKGROUND: Hypothalamic obesity caused by childhood–onset craniopharyngioma results in long–term cardiovascular morbidity. Knowledge about clinical markers and risk factors is rare. PATIENTS AND METHODS: A cross–sectional study on transthoracic echocardiographic parameters was performed to determine the associations with clinical and anthropometric parameters in 36 patients with childhood-onset adamantinomatous craniopharyngioma. RESULTS: Body mass index (BMI) correlated with the thickness of interventricular septum in diastole (IVSd) ($r=0.604$, $p<0.001$) and left ventricular diastolic posterior wall in diastole (LVPWd) ($r=0.460$, $p=0.011$). Due to wide range of disease duration, 17 pediatric and 19 adult patients were analyzed separately. In the adult subgroup (age at study ≥18 years), BMI correlated with IVSd ($r=0.707$, $p=0.003$), LVPWd ($r=0.592$, $p=0.020$) and left ventricular internal diameter in diastole (LVIDd) ($r=0.571$, $p=0.026$). In the pediatric subgroup (age at study <18 years), no correlation between cardiac parameters and BMI was observed. Only LVIDd correlated with disease duration ($r=0.645$, $p<0.001$). All cardiac functions were within the normal range, indicating no association with severe functional impairments. CONCLUSIONS: Cardiac remodeling in patients with childhood-onset craniopharyngioma correlates with the degree of hypothalamic obesity and disease duration. However, echocardiography has limited sensitivity in craniopharyngioma patients with obesity, so cardiac magnetic resonance imaging (MRI) should be considered as an alternative diagnostic approach for patients with craniopharyngioma and hypothalamic obesity.

RARE-60. PREGNANCIES AFTER CHILDHOOD CRANIOPHARYNGIOMA – RESULTS OF KRANIOPHARYNGEOM 2000/2007

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BACKGROUND: Data on female fertility, pregnancy, and outcome of offspring after childhood-onset craniopharyngioma (CP) are rare. STUDY DESIGN: Observational study on pregnancy rate and offspring outcome in female CP patients recruited in KRANIOPHARYNGEOM 2000/2007. RESULTS: A total of 451 CP patients (223 female) have been recruited, and 269 (133 female) were postpubertal at study. Six of 133 female CP patients (4.5%) with median age of 14.9 years at CP diagnosis had 9 pregnancies, giving birth to 10 newborns. Three patients achieved complete surgical resections. No patient underwent postoperative irradiation. Five natural pregnancies occurred in 3 CP patients without pituitary deficiencies. Four pregnancies in 3 CP patients with hypopituitarism were achieved under assisted reproductive techniques (ART) (median 4.5 cycles, range: 3–6 cycles). Median maternal age at pregnancy was 30 years (range: 22–41 years). Six babies (60%) were delivered by caesarean section. Median gestational age at delivery was 38 weeks (range: 34–43 weeks); median birth weight was 2,920 g (range: 2,270– 3,520 g), the rate of preterm delivery was 33%. Enlargements of CP cysts occurred in 2 women during pregnancy. Other complications during pregnancy, delivery, and postnatal period were not observed. CONCLUSIONS: Pregnancies after CP are rare and were only achieved after ART in patients with hypopituitarism. Close monitoring by an experienced reproductive physician is necessary. Due to a potentially increased risk for cystic enlargement, clinical, ophthalmological, and MRI monitoring are recommended in patients at risk. Perinatal complications, birth defects, and morbidity of mothers and offspring were not observed.

RARE-61. BODY COMPOSITION AND NUCHAL SKINFOLD THICKNESS IN PEDIATRIC BRAIN TUMOR PATIENTS

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BACKGROUND: Obesity, cardiovascular disease (CVD), and relapse/progression have major impact on prognosis in pediatric brain tumor (BT) patients. Cranial MRI is part of routine follow-up. METHODS: In a cross-sectional study, we analyzed nuchal skinfold thickness (NST) on MRI performed for BT follow-up monitoring as a novel parameter for body composition (BC) and CVD in 177 BT patients (40 WHO grade 1–2 BT; 31 grade 3–4 BT; 106 craniopharyngioma (CP)), and 53 healthy controls (HC). Associations of NST with body mass index (BMI), waist-to-height ratio (WHtR), caliper-measured skinfold thickness (cSFT), and blood pressure (BP) were analysed in BT and HC. RESULTS: CP patients showed higher BMI, WHtR, NST and cSFT when compared with BT and HC, whereas these differences were not detectable between BT and HC. However, WHO grade 1–2 BT patients were observed with higher BMI, waist circumference and triceps cSFT when compared to WHO grade 3–4 BT patients. NST showed high correlations with BMI, WHtR, and cSFT. NST, BMI and WHtR had predictive value for CVD in terms of increased BP, and in multivariate analysis, only BMI was selected for the final model resulting in an odds ratio of 1.25 (1.14–1.379). In CP patients with hypothalamic involvement/lesion or gross-total resection, rate and degree of obesity were increased. CONCLUSIONS: As monitoring of MRI and BC play an important role in follow-up after BT, NST could serve as a novel useful parameter for assessment of BC and CVD risk in BT patients.

RARE-62. VISUAL FUNCTION IN CHILDREN WITH CRANIOPHARYNGIOMA AT DIAGNOSIS: A SYSTEMATIC REVIEW

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Childhood craniopharyngioma is a rare and slow growing brain tumour, often located in the sellar and suprasellar region. It commonly manifests with visual impairment, increased intracranial pressure and hypothalamic and/or pituitary deficiencies. Visual impairment in childhood adversely affects a child's daily functioning and quality of life. We systematically reviewed the literature to provide an extensive overview of the visual function in children with craniopharyngioma at diagnosis in order to estimate the diversity, magnitude and relevance of the problem of visual impairment. Of the 543 potentially relevant articles, 84 studies met our inclusion criteria. Visual impairment at diagnosis was reported in 1041 of 2071 children (50.3%), decreased visual acuity was reported in 546 of 1321 children (41.3%) and visual field defects were reported in 426 of 1111 children (38.3%). Other ophthalmological findings described were fundoscopic (32.5%) and orthoptic abnormalities (12.5%). Variations in ophthalmological testing methods and ophthalmological definitions precluded a meta-analysis. The results of this review confirm the importance of ophthalmological examination in children with craniopharyngioma at diagnosis in order to detect visual impairment and provide adequate support. Future studies should

focus on long-term visual follow-up of childhood craniopharyngioma in response to different treatment strategies to provide insight in risks and ways to prevent further loss of vision.

RARE-63. CYST WALL OF ADAMANTINOMATOUS CRANIOPHARYNGIOMA CONTAINS TUMOR CELLS THAT COULD LEAD TO RECURRENCE AFTER SURGERY

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BACKGROUND: Adamantinomatous craniopharyngioma (ACP) is the primary subtype of craniopharyngioma in children, frequently with mutations in exon 3 of the *CTNNB1* gene. Most ACP consists of both a solid tumor and one or more cysts. Despite surgical resection of the solid tumor followed by radiation, recurrence involving the cystic component is common, suggesting that the cyst wall contains tumor cells. We present here conclusive molecular pathology evidence of the presence of tumor cells in the cyst wall similar to those in the solid tumor. METHODS: We used standard H&E staining and immunohistochemistry (IHC) to compare the histopathology characteristics between the matched cyst wall and solid tumor of 11 cases of ACP as well as their *CTNNB1* expression and exon 3 mutation. RESULTS: Samples of the cyst wall and solid tumor were collected separately during the operation of 11 cases of ACP through careful dissection. The cyst wall showed the nested cell clusters and peripheral palisading epithelium which are identical to those in the solid tumor. The cyst wall and solid tumor both showed Ki67 and nuclear β-catenin expression by IHC. There is no difference in the transcription level of *CTNNB1* between the cyst wall and the solid tumor, both being significantly higher than that in normal brain tissue. Exon 3 mutations of the *CTNNB1* gene of the cyst wall and the solid tumor are identical in each case. CONCLUSION: Follow-up of clinical cases suggests that tumor cells in residual cyst wall may be the cause of recurrence after surgery.

RADIATION ONCOLOGY

RONC-01. PROTON BEAM THERAPY IN THE MULTIDISCIPLINARY THERAPY FOR PEDIATRIC BRAIN AND SPINAL TUMOR AT KOBE CHILDREN'S HOSPITAL WITH KOBE PROTON CENTER

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It could be remarked that Radiotherapy (RT) has the important role for the multidisciplinary therapy to Malignant Pediatric Central Nervous System tumor. And recently among RT, Proton Beam Therapy (PBT) is expected to be effective and decrease serious late effects after RT in malignant pediatric tumor. PBT could be controlled precisely the dose and depth and spare the normal structures outside the target. Thus, PBT becomes applicable for pediatric solid tumor to insurance in April, 2016 in Japan. We have worked in closer cooperation with Hyogo Prefectural Ion Beam Medical Center and started PBT from April 2015. And from December 2017, our PBT has transferred to adjacent new medical center (Kobe Proton Center) which has the only institute that equipped the exclusive gantry for children in our country. The treated cases are 28 boys and 35 girls (age average 8.2 years oid). They are 15 Germ cell tumor, 14 Ependymoma, 13 Medulloblastoma, 4 Chordoma, 4 Atypical teratoid/rhabdoid tumor, 2 Craniopharyngioma and others. We have simulated the applications of not only broad beam but also scanned beam to limit the dose distribution and prepare for the cranio-spinal irradiation. All cases underwent magnetic resonance imaging to evaluate the results at out clinic and also the complications are assessed after treatments. The effect of PBT in this series is similar to our experience of traditional RT. There are a few controllable complications such as conventional RT. Farther more follow up is necessary to evaluate the advantage of PBT which could reduce delayed complications of RT.

RONC-02. MEASURING THE EFFECT OF CLINICALLY-RELEVANT RADIOTHERAPY PROTOCOLS ON THE JUVENILE MOUSE BRAIN

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Treatment for medulloblastoma involves craniospinal irradiation which is associated with devastating late effects. Clinical trials that simply reduce radiotherapy dosage have resulted in inferior survival rates, whereas new chemo/radiotherapy combinations that improve survival have been identified using preclinical models. However, the potential late effects of novel treatments are currently understudied and the assessment of radiation-induced late effects in mice remains challenging. Here, we aimed to measure the effect of multifractionated radiotherapy on the juvenile mouse brain as a baseline measure for future studies. NOD/Rag1-/- mice received either 8Gy whole-brain radiotherapy (WBRT) using an X-RAD SmART preclinical platform, 18Gy fractionated WBRT (9x2Gy doses), single, or multiple sham treatments beginning at postnatal day (P)16. Mice were aged to adulthood (>P63), then high resolution anatomical brain scans were obtained on a Bruker 9.4T MRI to measure the effects of WBRT on whole brain and specific regional area volumes. A single 8Gy dose (n=10) markedly reduced brain volume by 8.5% compared to single-sham controls (n=11, $p<0.0001$), whereas fractionated 18Gy treatment (n=7) did not cause significant differences in brain volume compared to multi-sham controls (n=4, $p>0.99$). Current analyses are focused on measuring treatment effects on specific areas of the brain, as well as other anatomical differences using a range of MRI techniques. These results will serve as a valuable tool to measure potential treatment-associated effects caused by novel chemo/radiotherapy combinations on the developing brain. This will enable future studies to assess the potential safety of novel treatment to inform clinical decision making.

RONC-03. NEUROCOGNITIVE CHANGES AFTER RADIATION FOR PEDIATRIC BRAIN TUMOURS: WHICH BRAIN SUBSTRUCTURES ARE MOST IMPORTANT?

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INTRODUCTION: The contribution of different intracranial structures on neurocognitive decline after radiation therapy (RT) in children is unclear. METHODS: This was a retrospective study of children with brain tumours treated from 2005 to 2017. Patients with longitudinal neurocognitive assessments and photon dosimetric data (if RT given) were included. Full scale intelligence quotient (FSIQ) was the primary endpoint; sub-indices of neurocognition were modelled separately (perceptual reasoning [PRI], processing speed [PSI], verbal comprehension [VCI] and working memory [WMI]). Multivariable linear mixed effects models were used to model endpoints, with age at diagnosis & dose to different brain regions as fixed effects and patient-specific random intercepts. RESULTS: Sixty-nine patients were included; ten patients did not receive any RT (i.e. low-grade glioma). Median neurocognitive follow-up was 3.2 years. Right hippocampus mean dose was a strong predictor of declines in FSIQ ($p < .001$), VCI ($p = 0.002$) and PRI ($p = 0.049$). Dose to 50% of the supratentorial brain (D50) was the strongest predictor for WMI ($p < .001$) and PSI ($p < .001$). Each gray increase in mean right hippocampus dose resulted in a decrease of 0.038 FSIQ points/year. After adjusting for dose to brain substructures, younger age & presence of a ventriculoperitoneal shunt were also associated with decreased FSIQ. CONCLUSIONS: Mean dose to the right hippocampus was associated with declines in FSIQ, VCI and PRI, while supratentorial brain D50 was associated with WMI and PSI. Efforts should be made to reduce unnecessary dose to these brain structures.

RONC-04. RE-IRRADIATION AFTER TREATMENT OF MEDULLOBLASTOMA; RELAPSED CASES AND SECOND CANCER CASES

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PURPOSE: Late complications such as brainstem necrosis are great concern of re-irradiation for brain tumor. Proton beam therapy can reduce radiation dose of organs at risk such as brainstem, so is expected to reduce late complications. PATIENTS AND METHODS: Patients with medulloblastoma treated with re-irradiation from January 2015 to February 2019 at the Kobe Children's Hospital and the Kobe Proton Center were reviewed. There were three cases of relapsed medulloblastoma and three cases of second cancer (glioblastomas). RESULTS: In relapsed cases, all three cases treated with 12 Gy in 8 fractions cranio-spinal irradiation followed by gamma knife radiosurgery (one) or 28.8 Gy (RBE) in 16 fractions of proton beam therapy (two). Follow-up periods were 8 to 19 months (median

12 months) and all three cases survived without relapse. In second cancer cases, all three cases were treated with 40.05 Gy per 15 fractions of radiation therapy (2 cases were treated with photon and one case with proton). However, all cases relapsed and two cases died of disease. CONCLUSION: Twelve Gy in 8 fractions cranio-spinal irradiation followed by 28.8 Gy (RBE) in 16 fractions of proton beam therapy is thought to be useful for the relapsed case. Re-irradiation for second cancer was disappointing and further study is warranted.

RONC-05. PRESERVING VISION IN OPTIC PATHWAY GLIOMA AMONG PATIENTS WITHOUT NEUROFIBROMATOSIS TYPE 1

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PURPOSE: Sporadic optic pathway/hypothalamic gliomas (OP/HGs) represent a unique entity within pediatric low-grade glioma. Despite favorable survival, the location makes treatment difficult and local progression debilitating. We conducted longitudinal assessment of visual acuity (VA) among patients treated in the modern era with chemotherapy (CT) or early radiotherapy (RT). METHODS: Clinical characteristics were abstracted for patients treated over a 15-year period (2000–2015) at a single institution. Comprehensive ophthalmologic data taken at three to six-month intervals was examined with age-appropriate VA metrics converted to LogMAR scale. Kaplan-Meir "blindness-free survival" (BFS) curves were calculated as time to bilateral functional blindness (i.e. LogMAR ≥ 0.8 in both eyes), stratified by treatment and compared using log-rank test. RESULTS: Thirty-six patients with median follow-up of 7.6 years (range: 2–17) were identified. Median age at diagnosis was 2.5 years (IQR: <1–5). Early RT was administered as initial therapy (n=6) or first-line salvage (n=5) in a total of eleven patients (31%) at a mean age of 12 years (range: 6–17). Twenty-five patients (69%) were maintained primarily on CT with a mean age at initiation of 2.4 years (range <1–8). Of these, five patients received RT after ≥2 systemic therapy regimens. In terms of visual preservation, five/eight-year BFS rates were 84%/59% and 100%/100%, for CT and early RT, respectively (p=0.046). CONCLUSIONS: In a contemporary cohort, early RT, defined as initial or 1st line salvage therapy for OP/HGs manifested in superior VA. Children undergoing CT are at highest risk of functional blindness following five years of treatment.

RONC-06. VOLUMETRIC-MODULATED ARC WHOLE-BRAIN RADIOTHERAPY FOR THE PREVENTION OF PERMANENT ALOPECIA IN PEDIATRIC PATIENTS

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Permanent alopecia is a grave late complication of multi-drug chemotherapy (CTx) plus cranial irradiation, reducing both patient self-esteem and quality of life in pediatric patients. We started to use craniospinal irradiation (CSI) using the volumetric-modulated arc whole-brain radiotherapy (VMAT-WBRT) in order to prevent permanent alopecia. We treated 5 pediatric patients with CSI using VMAT-WBRT, and report the initial clinical outcome. Five consecutive patients (4–11 years old) who received CSI using VMAT-WBRT from June 2015 to November 2018 were included into this study. One patient with embryonic carcinoma received radiotherapy (RT) with concurrent CTx; four patients with medulloblastoma (two patients with standard risk, and two patients with high risk) received RT followed by CTx. The prescribed doses of CSI were 23.4–35.2 Gy in 13–22 fractions, respectively. Optimization for VMAT-WBRT was performed to reduce doses to the hair follicles with keeping the dose coverage to the planning target volume. Although all patients experienced temporary alopecia, their hair fully recovered over the whole scalp within 8 months after finishing RT. One patient had disease progression after 6 months after completing CTx; this patient who was diagnosed as Group 3 subtype had diffuse meningeal dissemination confirmed with contrast enhanced spinal MRI before RT. The other four patients had no evidence of recurrence. Although CSI with VMAT-WBRT might be one of considerable options, more cases are needed to verify the efficacy to prevent permanent alopecia for pediatric patients who receive multi-drug CTx and cranial irradiation.

RONC-08. SURVIVAL IMPACT OF POSTOPERATIVE RADIOTHERAPY TIMING IN PEDIATRIC AND YOUNG ADULT EPENDYMOMA

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INTRODUCTION: Postoperative radiotherapy is commonly given for WHO Grade 2–3 intracranial ependymoma. Clinicians generally aim to begin radiotherapy ≤5 weeks following surgery, but the optimal timing remains uncertain. METHODS: The National Cancer Database was queried for patients (age ≤39 years) with localized WHO Grade 2–3 intracranial ependymoma treated with surgery and postoperative radiotherapy. Multivariable logistic regression was used to identify factors associated with delayed postoperative radiotherapy, defined as starting >8 weeks after surgery. Overall survival (OS) curves were plotted based on radiotherapy timing (≤5 weeks, 5–8 weeks, and >8 weeks after surgery) and compared by log-rank test. Multivariate analysis (MVA) was used to identify factors associated with OS. RESULTS: In the final analytic set of 1,043 patients, age ≥21 years (OR 2.07, 95% CI 1.56–2.74) and WHO Grade 2 tumors (OR 1.41, 95% CI 1.08–1.85) were significantly associated with delayed time to adjuvant radiotherapy. No difference in 3-year OS was observed in patients who initiated radiotherapy ≤5 weeks, 5–8 weeks, and >8 weeks after surgery (89.8% vs. 89.1% vs. 88.4%; p= 0.796). On MVA, anaplastic histology (HR 2.414, 95% CI 1.784–3.268, p<0.001) and subtotal resection (HR 2.398, 95% CI 1.519–3.788, p<0.001) were significantly associated with reduced OS. Timing of radiotherapy, total radiotherapy dose, age, insurance status, and other factors were not significant. CONCLUSION: Delayed postoperative radiotherapy was not associated with inferior survival in patients with intracranial ependymoma, suggesting delayed radiotherapy initiation may be considered in patients requiring longer postoperative recovery or referral to an appropriate radiotherapy center.

RONC-09. PSEUDOPROGRESSION AFTER PROTON THERAPY OF PEDIATRIC SPINAL PILOCYTIC ASTROCYTOMA AND MYXOPAPILLARY EPENDYMOMA

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BACKGROUND: Pseudoprogression after proton therapy of CNS tumors is a challenging clinical situation. The rate of pseudoprogression after proton therapy of pediatric spinal tumors is unknown. METHODS: Records of pediatric patients with spinal pilocytic astrocytoma (sPA; n = 9) or myxopapillary ependymoma (MPE; n = 6) with gross disease treated with proton therapy with at least 6 months of follow up from completion of proton therapy were retrospectively reviewed for demographics, treatment characteristics, and occurrence of pseudoprogression. Pseudoprogression was defined as a post-radiation increase in tumor size with subsequent decrease in size without additional tumor-directed therapy. RESULTS: The median age at radiation for sPA patients was 10.1y (range, 7.0 – 16.2y) and 12.7y (range, 7.9 – 14.4y) for MPE patients. The median prescribed dose was 45 GyRBE (range, 39.6 – 50.4 GyRBE) for sPA patients and 50.4 GyRBE (range, 45 – 54 GyRBE) for MPE patients. One sPA patient received concurrent vincristine. Median follow up after proton therapy was 44 months (range, 9 – 99 months). Six of nine sPA patients (67%) had pseudoprogression occurring at a median of 81 days (range, 34 – 136 days) after proton therapy; no MPE patients developed pseudoprogression (0%; p < 0.03). Two sPA patients with pseudoprogression were symptomatic and improved with medical therapy. CONCLUSION: Preliminary analysis suggests that pseudoprogression occurs frequently within 6 months after proton therapy for sPA and infrequently after proton therapy for MPE.

RONC-12. TREATMENT AGE AND NEUROCOGNITIVE OUTCOMES FOLLOWING PROTON BEAM RADIOTHERAPY FOR PEDIATRIC LOW GRADE GLIOMA

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INTRODUCTION: Younger age at radiotherapy increases cognitive risk for patients with pediatric low grade glioma (LGG). We examined the impact of age at treatment on cognitive trajectories in LGG patients treated with proton radiotherapy (PRT) compared to patients treated without radiotherapy (surgery only; SO). METHODS: We examined cognitive

scores of 48 LGG patients on a prospective, longitudinal study. General linear mixed models evaluated change in cognitive scores over time. RESULTS: The sample included 16 patients treated with PRT and 32 with SO (median follow-up=3.1 years, range 0.9–6.1). Median age of PRT patients was 8.2 years at diagnosis (range 1.0–14.4) and 9.4 years at PRT (range 4.2–16.7). 13 PRT patients also received surgery: 53.8% biopsy, 30.8% subtotal resection, 15.4% gross total resection. Tumor sites included: 31.2% hypothalamic/suprasellar, 25.0% optic pathway, 18.8% temporal, 25.0% other. Median age of SO patients was 8.2 years at diagnosis (range 2.9–18.6). Surgical outcomes were: 75.0% gross total resection, 21.9% biopsy/other. There were no group differences in diagnosis age, tumor volume, or shunt history (all $p>0.05$). Both PRT and SO groups displayed stable cognitive functioning over time (all $p>0.1$). Slopes (i.e., change in scores over time) did not differ between groups (all $p>0.1$). Age at treatment was not associated with slope or performance at last follow-up in either group (all $p>0.05$). CONCLUSIONS: We observed stable cognitive functioning, independent of age at treatment, following PRT for LGG. Outcomes were similar to patients receiving surgery only. Further examination in a larger sample is warranted.

RONC-13. RADIATION INDUCED BRAIN STEM GLIOMA AFTER RADIATION THERAPY FOR MIXED GERM CELL TUMOR

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We report a case of radiation-induced glioma in the pons after radiation therapy for germ cell tumor. A 17-year-old man was diagnosed as HCG and AFP secreting germ cell tumor at the age of 9. The tumor was located in the suprasellar region, which filled up most part of the third ventricle. Five courses of chemotherapy with cisplatin, etoposide, and cyclophosphamide, and whole ventricle plus local radiation therapy (total 51.2 Gy / 32Fr) were performed. After the treatment, most part of the tumor was regressed, and only small enhanced lesion remained. Six years after the treatment, he started to be ataxic, and worsened. An MRI revealed an enhanced lesion in the pons. Lesion biopsy was performed via the right cerebellar peduncle. Histopathological diagnosis confirmed the lesion was high grade glioma. He underwent extended local radiation therapy (50.4 Gy / 28 Fr) and administered temozolomide. Later, bevacizumab was added, and 3 months after treatment started, the size of the tumor was reduced and his symptoms were improving. There is no established treatment for radiation induced glioma. However, additional radiation therapy, temozolomide and bevacizumab appears to be useful to reduce tumor size and resolve the symptoms, even if it is transient.

RONC-15. OUTCOMES OF BRAIN AND SKULL-BASE TUMOURS IN ADOLESCENTS AND YOUNG ADULTS TREATED WITH PENCIL BEAM SCANNING PROTON THERAPY

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BACKGROUND: The use of highly conformal proton therapy in adolescents and young adults (AYAs) for management of brain/skull-base tumours is becoming increasingly common. This study aims to assess the long-term clinical outcomes, prognostic factors and employment status of AYAs (15–39 years) treated with pencil-beam-scanning proton-therapy (PT). METHODS: Between 1997–2018, 176 AYAs were treated with PT at the Paul Scherrer Institute. Median age was 30 years (range, 15–39) and the male/female ratio was 0.8. RESULTS: After a median follow-up of 66 months (range, 12–236), 24 (13.6%) local failures and 1 (0.6%) distant failure were observed between 6 and 152 months after PT. The most common histologies treated were chordomas/chondrosarcomas (61.4%), followed by meningiomas (14.2%) and gliomas (15.3%). The 6-year local-control (LC), distant-progression-free survival and overall-survival (OS) rate was 83.2%, 97.4% and 90.2% respectively. On univariate analysis, age ≥24 years was a negative prognostic factor for LC. Recurrent disease, infratentorial tumours and low-grade-glioma histology were poor prognostic factors for both LC and OS. The 6-year ≥G3 PT-related late toxicity-free survival was 88.5%. The moderate-high grade late toxicity crude rates were 37.8% G2, 12.2% G3, 0.6% G4 and 0.6% G5. No secondary malignancies were observed. The unemployment rate was 7.3% at PT, rising to 25.3% at survivorship. High-grade(≥G3) toxicity rate in the unemployed vs employed group was 21% vs 8.5%. CONCLUSION: PT is an effective treatment for AYAs with brain/skull-base tumours with good tumour control and acceptable long-term toxicity. Despite having satisfactory clinical outcomes, around 1 in 4 AYAs surviving brain/skull base tumours are unemployed.

RONC-16. PROTON BEAM THERAPY FOR PATIENTS WITH INTRACRANIAL EPENDYMOMA UNDER 3 YEARS OLD: INITIAL CLINICAL OUTCOMES

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BACKGROUND: Proton beam therapy (PBT) provides dosimetric benefits in sparing normal tissue when treating pediatric patients with brain tumors. We report the preliminary clinical outcomes of surgery and adjuvant PBT for patients under 3 years old diagnosed as intracranial ependymoma at our institute. METHODS: This is a retrospective review of the medical records for 3 children with ependymoma in the fourth ventricle, diagnosed between March 2013 and September 2019. PBT was performed after tumor resection in all the patients. RESULTS: Gross total resection was achieved in 2 males and 1 female patients with fourth ventricle WHO grade II to III ependymoma at 15, 18, and 37 months old. All the patients received adjuvant PBT (54.0 GyE/30 fractions) to the postoperative tumor bed under general anesthesia or sedation. PBT was acutely well tolerated, with mostly mild alopecia and skin reactions at the irradiated sites. At a median follow-up of 54 months (4–59 months) after irradiation, all the patients are alive without recurrence. No serious late adverse events were observed in any of the patients. CONCLUSION: The number of patients in this study remains small for drawing any definite conclusion, however our preliminary results are still encouraging. Further studies of a large number of pediatric patients with long term follow-up are needed to more fully assess tumor control and late adverse events.

RONC-17. STEREOTACTIC RADIOSURGERY FOR SPINE METASTASES IN PEDIATRIC MALIGNANCIES

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BACKGROUND: Spine stereotactic radiosurgery (SSRS) is a non-invasive technique that delivers ablative radiotherapy for optimal control of bony disease. While SSRS is known to provide excellent local control (LC) and minimal toxicity in adults, the role of SSRS in pediatrics is less clear. PURPOSE: To evaluate SSRS in pediatric patients with spinal metastases. METHODS: A retrospective review of patients (<18 yrs) treated with SSRS at MDACC was performed after IRB approval. Descriptive statistics were utilized for analysis. RESULTS: From 2011–2019, 12 metastatic osseous sites (3 cervical, 4 thoracic, 5 lumbar-sacral) in 9 patients were treated. Median follow-up was 9 months (range 2–41). Six males (67%) and 3 females (33%) all KPS ≥70, received radiation to ≤3 contiguous vertebral bodies. Median age was 16 yrs (range 8–18). No patients required sedation. Histologies included 7 osteosarcomas, one rhabdomyosarcoma and one Ewing's sarcoma. Metastatic epidural spinal cord compression scores ranged from 0 (6), 1b (3) and 3 (3). No sites had surgery prior to SSRS and one site received prior conventional radiation. SSRS doses included 24 Gy in 1 fraction (7), 24–27 Gy in 3 fractions (4) and 50 Gy in 5 fractions (1). Six-month LC was 83% with one local failure following 27 Gy. OS at 6 and 12 mo were 55% and 23%. There was no grade ≥3 acute toxicity, no radiation myelopathy or vertebral compression fractures. CONCLUSION: In this initial report, SSRS represents a promising modality that is well tolerated and provides excellent LC. However, further follow-up is warranted in the pediatric setting.

RONC-18. ANALYSIS OF BRAIN TUMOR INDUCED BY IRRADIATION IN CHILDHOOD - A SINGLE INSTITUTIONAL ANALYSIS

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BACKGROUND: Radiation-induced brain tumors are rare tumors that appear during long-term follow-up after radiation therapy. Children are at greater risk for radiation -induced brain tumors than adults. The clinical characteristics of radiation-induced brain tumor treated at our hospital

were retrospectively examined. PATIENTS AND METHODS: Clinical characteristics of seven radiation-induced brain tumors that developed in 6 patients irradiated in their childhood at our hospital were analyzed. The background disease, age at irradiation, irradiation dose, period from irradiation to onset, pathological diagnosis, and treatment for radiation-induced brain tumor were examined. RESULTS: Background diseases for irradiation were leukemia in 3 patients, germinoma in 2, medulloblastoma in 1, and the average cranial irradiation dose was 23.2 Gy. The patients tended to be young at irradiation (2–17 yeays; median:4 years old). The time between irradiation and the onset of radiation-induced brain tumors ranged from 9.5 to 39.1 years (median:28 years). Radiation-induced brain tumors comprised 6 meningioma (grade I:5, grade II:1) and 1 high-grade gliomas. All patients underwent surgical removal of the radiation-induced brain tumors and 2 received additional irradiation. During a median of 5.3 years of follow-up after the diagnosis of radiation-induced brain tumors, 2 underwent second surgery, while the remaining 4 have no recurrence. DISCUSSION: In most cases, radiation-induced brain tumors occur for a long time after irradiation in childhood. Monitoring of radiation-induced brain tumors as well as primary tumor recurrence was considered important.

RONC-19. TWO CASES OF RE-IRRADIATION FOR LATE RECURRENT OR RADIATION-INDUCED TUMOR AFTER RADIATION THERAPY FOR PEDIATRIC BRAIN TUMORS

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BACKGROUND: As the outcome of pediatric brain tumors improves, late recurrence and radiation-induced tumor cases are more likely to occur, and the number of cases requiring re-irradiation is expected to increase. Here we report two cases performed intracranial re-irradiation after radiotherapy for pediatric brain tumors. CASE 1: 21-year-old male. He was diagnosed with craniopharyngioma at eight years old and underwent a tumor resection. At 10 years old, the local recurrence of suprasellar region was treated with 50.4 Gy/28 fr of stereotactic radiotherapy (SRT). After that, other recurrent lesions appeared in the left cerebellopontine angle, and he received surgery three times. The tumor was gross totally resected and re-irradiation with 40 Gy/20 fr of SRT was performed. We have found no recurrence or late effects during the one year follow-up. CASE 2: 15-year-old female. At three years old, she received 18 Gy/10 fr of craniospinal irradiation and 36 Gy/20 fr of boost to the posterior fossa as postoperative irradiation for anaplastic ependymoma and cured. However, a anaplastic meningioma appeared on the left side of the skull base at the age of 15, and 50 Gy/25 fr of postoperative intensity-modulated radiation therapy was performed. Two years later, another meningioma developed in the right cerebellar tent, and 54 Gy/27 fr of SRT was performed. Thirty-three months after re-irradiation, MRI showed a slight increase of the lesion, but no late toxicities are observed. CONCLUSION: The follow-up periods are short, however intracranial re-irradiation after radiotherapy for pediatric brain tumors were feasible and effective.

RONC-20. RECURRENT HIGH-GRADE ASTROBLASTOMA TREATED WITH STEREOTACTIC RADIOTHERAPY

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INTRODUCTION: Astroblastoma is a rare, mostly supratentorial glial tumor, occurring predominantly in children and young adults. However, treatment strategies have not yet been established for this rare disease. CASE PRESENTATION: A 6-year-old male presented with headache and nausea. CT and MR imaging revealed a left frontal mass lesion with slight edema and macrocalcifications. Gross tumor resection was performed. Histological examination found neoplastic cells with astroblastic characteristics, and a striking perivascular array of pseudorosettes. The final diagnosis was high-grade astroblastoma. MR imaging 13 months after surgery suggested local recurrence and enlargement was found 3 months later. Stereotactic radiotherapy (SRT) was performed. MR imaging after SRT showed enhanced cyst formation around the tumor bed, suggesting tumor recurrence. However, ^{11}C-methionine PET revealed radiation necrosis. The last follow-up MR imaging 15 months after SRT showed no further recurrence. CONCLUSION: Astroblastoma is rare, so no optimal management is known. SRT may be effective to treat recurrent astroblastomas. ^{11}C-methionine PET/CT is useful for the differentiation from radiation necrosis.

RONC-21. IDENTIFICATION OF EPIGENETIC DRUGS AS RADIOSENSITIZERS IN PEDIATRIC HIGH-GRADE GLIOMAS

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Pediatric high-grade gliomas (pHGG) are malignant brain tumors with a high mortality rate. Radiotherapy (RT) is one of the cornerstones of current pHGG treatment, while the efficacy of chemotherapeutics remains inferior. The use of chemotherapeutics that specifically sensitize tumor cells to irradiation are poorly understood, but may help to increase the effect of RT in pHGG treatment. Since recent studies revealed pHGG to be epigenetically dysregulated, we tested 148 epigenetic drugs on eight primary pHGG models in the presence and absence of RT, to assess their radiosensitizing potential. Based on synergy scores, we found 22 compounds that resulted in enhanced cytotoxicity in the presence of RT. The effect of these compounds on pHGG was further investigated by tracking spheroid growth microscopically for 30 days, identifying four molecules that stopped spheroid-expansion solely in combination with RT ($p=<0.001$, multilevel regression). Parallel cell-viability assays reported identical results. Furthermore, tumor migration in 3D matrigel growth assays, using non-toxic doses of the four identified compounds, revealed that two compounds (the selective HDAC-inhibitors; chidamide and entinostat) stop the infiltrative growth characteristics of pHGG cells, exclusively in combination with RT. RNA-Seq data showed that entinostat and chidamide inhibit DNA-repair pathways like the Fanconi anemia cascade and homologous recombination. Since we anticipate that entinostat- or chidamide-induced radiosensitization can be enhanced by blocking kinase-driven escape mechanisms, we are currently conducting a kinome-wide CRISPR/Cas9 knockout screen in three primary pHGG models to develop combinational therapies. These results highlight entinostat and chidamide as potential radiosensitizers in pHGG treatment.

RONC-22. SECOND TUMORS IN PEDIATRIC PATIENTS TREATED WITH PROTON THERAPY TO THE CENTRAL NERVOUS SYSTEM

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BACKGROUND: Previous institutional data suggests the 10-year cumulative incidence of second tumors is 3% in children treated with photon radiation for central nervous system (CNS) malignancy, with 90% of these tumors occurring in areas receiving ≤36 Gy. Comparative figures for children treated with proton therapy (PT) does not exist. METHODS: 1056 consecutive pediatric patients with a median follow-up of 5.0 years were treated between 2006–2019 with double-scattered PT to a site within the craniospinal axis. 230 patients were ≤3 years old and 14 had neurofibromatosis. A second tumor was defined as any solid neoplasm with histologic features different from the original tumor that had arisen within the irradiated volume. RESULTS: Five patients developed second tumors resulting in a 5- and 10-year cumulative incidence of 0.2% (95% CI: 0–1.2%) and 1.6% (95% CI: 0.6%-3.9%), respectively. Of those who developed second tumors, median age at radiation was 4.3 years old (range, 2.1 to 5.1 years old) and diagnoses consisted of medulloblastoma (n=2), ependymoma (n=2), and craniopharyngioma (n=1). The second tumors included high grade gliomas (n=3) and high grade sarcoma (n=1) that occurred in regions receiving at least 54 Gy. One patient with neurofibromatosis developed both a low-grade glioma and choroidal melanoma in craniospinal irradiation regions receiving 36 Gy. Four of five patients with second tumors are alive. CONCLUSION: The reduction in moderate-to-low dose radiation exposure from proton therapy may be associated with a decreased incidence of second tumors in children treated for CNS neoplasms. More follow-up is needed to confirm these findings.

RONC-23. NOVEL APPROACH TO REDUCE ACUTE ESOPHAGEAL TOXICITY IN CRANIO-SPINAL IRRADIATION USING INTENSITY MODULATED PROTON THERAPY

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INTRODUCTION: We present our experience of a novel approach using intensity modulated proton therapy(IMPT) for cranio-spinal irradiation(CSI) leading to reduced acute esophageal toxicity and reduced treatment interruptions. MATERIAL AND METHODS: Seven children younger than 12 years old treated consecutively with CSI using IMPT were included in this study. Three among 7 children received concurrent chemotherapy(CCT). En-

tire vertebral body(VB) was part of target volume in all patients. The IMPT plan was generated using 3 fields with single field optimisation technique. Last 5 patients were treated using dose gradient(DG) (98-93%) deliberately created in anterior most 3-5mm of VB. Initial 2 patients were treated with intention of covering entire VB with 98% isodose. Monte Carlo algorithm was used for dose calculations and optimisation, and robustness assessed for 3mm setup and 3.5% range uncertainty. RESULTS: The CSI dose ranged from 21.6GyE to 35GyE. In patients without DG, maximum and mean dose to esophagus(36.67GyE vs. 25.45GyE, 31.53GyE vs. 20.41GyE), midline mucosa(28.95GyE vs. 25.31GyE, 21.8GyE vs. 14.61GyE) and bowel bag(32.9GyE vs. 24.27GyE, 3.59GyE vs. 3.21GyE) were higher compared to patients with DG. Both patients where DG was not created, developed grade 2 esophageal toxicities requiring supportive care and treatment interruptions(4 and 2days). All 5 patients with DG did not develop significant esophageal toxicity and had no interruptions. CONCLUSION: Creating a dose gradient over anterior VB using IMPT reduces dose to esophagus and midline mucosa leading to lower acute esophageal toxicity which potentially avoids treatment interruptions during CSI.

RONC-24. PROTON THERAPY FOR PEDIATRIC EPENDYMOMA: MATURE OUTCOMES FROM THE UNIVERSITY OF FLORIDA AND MASSACHUSETTS GENERAL HOSPITAL

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OBJECTIVE: Report long-term efficacy and toxicity of proton therapy for pediatric ependymoma. MATERIALS AND METHODS: Between 2000–2017, 318 children with nonmetastatic grade II/III intracranial ependymoma received proton therapy at Massachusetts General Hospital and the University of Florida. Median age was 3.5 years (range, 0.7–21.3 years); 56% were male. Most (69%) tumors were in the posterior fossa and classified as WHO grade III (64%). Eighty-four percent had a gross total or near total tumor resection before radiotherapy and 30% received chemotherapy. Median radiation dose was 55.8 CGE (range, 50.4–59.4 CGE). RESULTS: Median follow-up was 6 years (range, 0.6–19.2 years). Seven-year local control, progression-free survival, and overall survival rates were 77.1% (95% CI 71.7–81.7%), 64.4% (95% CI 58.6–69.8%), and 82% (76.9–86.2%), respectively. Subtotal resection was associated with inferior local control (60% vs 80%; p<0.01), progression-free survival (49% vs 67%; p<0.01), and overall survival (69% vs 84%; p<0.05). Male gender was associated with inferior progression-free (59% vs 71%; p<0.01) and overall survival (77% vs 89%; p<0.05). Twenty patients (6.2%) require hearing aids; of these, 12/20 received cisplatin. Grade 3+ brainstem toxicity rate was 1.6% and more common in patients who received >54 CGE. The rate of second malignancy was 0.9%. CONCLUSION: Proton therapy offers commensurate disease control to modern photon therapy without unexpected toxicity. The high rate of long-term survival justifies efforts to reduce radiation exposure in this young population with brain tumors. Independent of modality, this large series confirms extent of resection as the most important modifiable factor for survival.

RONC-25. A CASE OF PEDIATRIC PONTINE GLIOMA TREATED WITH GAMMA KNIFE SURGERY

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BACKGROUND: Pediatric brainstem gliomas rarely occur and are a heterogeneous group of diseases, which increases the difficulty of treatment strategy. Here, we present a case of pediatric pontine glioma treated with Gamma Knife surgery (GKS) after open biopsy. CASE DESCRIPTION: An 11-year-old boy presented with diplopia due to the left MLF syndrome. MRI showed a well-circumscribed, protruding tumor with partial gadolinium enhancement in the dorsal pons. An open biopsy was performed via the suprafacial triangle following midline suboccipital approach. Histological examinations revealed high cellularity and mild atypia. Immunohistochemistry demonstrated positive stain for GFAP and Olig2 antibodies, and negative for p53 protein. The Ki67-labeling index was 6.8%. Pyrosequence analysis indicated IDH1/2 wild type (wt), BRAF V600 wt, H3F3A K27 wt, FGFR1 wt, and TERT wt. The final diagnosis was pediatric diffuse astrocytoma, WHO grade II, pons. GKS was performed one month after the biopsy. After transient worsening of the symptom, it disappeared gradually. The tumor is stable for three years with mild shrinkage of the size. DISCUSSION: Gross total resection (GTR) of pediatric low-grade, brainstem gliomas may result in a good prognosis. However, unlike pilocytic astrocytoma, diffuse astrocytoma is not easy to perform GTR without any complications. There are some reports regarding GKS for brainstem gliomas, which prove an increase in progression free survival rate. No marked tumor regression is achieved in our case, but tumor growth is well-controlled so far. CONCLUSION: GKS after biopsy can be a useful treatment option for pediatric low-grade brainstem gliomas.

RONC-26. A CASE OF RADIATION NECROSIS OF THE CEREBELLUM 16 YEARS AFTER CHEMORADIOTHERAPY FOR MEDULLOBLASTOMA

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BACKGROUND: If new lesions are observed during follow-up of the malignant tumor after treatment, it is difficult to distinguish whether the tumor is a recurrent lesion, secondary cancer, or radiation necrosis of the brain. We have encountered a patient with symptomatic radiation necrosis of the cerebellum 16 years after treatment of medulloblastoma. CASE PRESENTATION: A 24-year-old man who had received a tumor resection and chemoradiotherapy for cerebellar medulloblastoma at the age of 8 presented with dizziness. For the past 16 years, there was no recurrence of the tumor. He subsequently underwent MRI scan, and T1-Gd image showed enhanced lesion in the right cerebellar peduncle. Cerebrospinal fluid cytology analysis was negative for tumor. We suspected tumor reccurence or secondary cancer, and performed lesion biopsy. The result of the pathological examination was radiation necrosis of the cerebellum. DISCUSSION: The interval of radiation necrosis of the brain and radiotherapy can vary from months to more than 10 years. So, whenever a new lesion is identified, radiation brain necrosis must be envisioned. According to guidelines in Japan, there is no absolute examination for discriminating tumor recurrence from radiation brain necrosis and diagnosis by biopsy may be required. CONCLUSION: We experienced a case of symptomatic radiation necrosis of the cerebellum 16 years after treatment. In patients showing new lesion after long periods of time, the possibility of radiation necrosis to be considered.

RONC-27. PROTON THERAPY REDUCES DOSE TO CRITICAL CENTRAL NERVOUS SYSTEM STRUCTURES IN MEDULLOBLASTOMA: A DOSIMETRIC ANALYSIS OF CHILDREN'S ONCOLOGY GROUP (COG) ACNS0331

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BACKGROUND: Recently published data demonstrated proton therapy (PRT) significantly reduced cognitive decline relative to photons for pediatric medulloblastoma. These findings imply that reductions in dose to critical CNS structures during the boost phase may account for better outcomes over time. Here, we examine differences in dosimetric data for medulloblastoma patients treated on ACNS0331 with photon (Intensity Modulated Radiation Therapy, 3D-Conformal Radiation Therapy) vs PRT to identify potential structures responsible for cognitive benefit. METHODS: COG ACNS0331 was a randomized trial examining the impact of reduced craniospinal irradiation (CSI) dose (standard vs low dose, in patients aged 3–7) and volume (whole posterior fossa vs involved field) in pediatric medulloblastoma patients. We identified 136 patients (IMRT=95, 3DCRT=28, Proton=13) enrolled on ACNS0331 with complete radiation and imaging data and re-contoured 10 critical brain structures to calculate dose. RESULTS: Proton therapy significantly reduced the dose to critical structures. For example, temporal lobe mean dose and V30 were 30Gy/38% (PRT), 40Gy/89% (IMRT), 41Gy/84% (3DCRT)), hippocampi mean dose were 51 Gy (IMRT), 52 Gy (3DCRT), and 44Gy (PRT) and cochlear mean dose were 43 Gy (IMRT), 49 Gy (3DCRT), and 31Gy (PRT). Dose to several other critical structures were also significantly reduced including the whole brain, supratentorium, cerebellum, and pituitary. CONCLUSIONS: Proton therapy greatly reduces dose to critical CNS structures when compared to IMRT or 3DCRT. Further studies are needed to correlate dose reductions in these structures with improved cognitive outcomes.

RONC-31. ADVANCED ECHOCARDIOGRAPHY WITH MYOCARDIAL-STRAIN-ANALYSIS DESCRIBES SUBCLINICAL CARDIAC DYSFUNCTION AFTER CRANIOSPINAL IRRADIATION (CSI) IN PEDIATRIC AND YOUNG ADULT PATIENTS WITH CENTRAL NERVOUS SYSTEM (CNS) TUMORS

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CSI is part of the treatment of CNS tumors and is associated with cardiovascular disease; data in pediatric/young-adult patients are limited. Myocardial-strain-analysis can reveal subclinical dysfunction. Retrospective,

single-center study in CNS tumor patients managed with CSI from 1986–2018. Clinical details, and echocardiography including myocardial-strain-analysis were collected at T1=first echocardiogram after CSI, and T2=most recent echocardiogram. Data are mean±standard deviation. Echocardiograms were available in 44 patients (36%female, 14±8.0years) at T1 and 39 patients (38%female, 21.0±11.3years) at T2. Standard echocardiography was normal for all subjects. At T1, global longitudinal peak systolic strain (GLS) was -16.3%±3.7% in CSI vs. -21.6%±3.5% in controls ($p<0.0001$); global radial peak systolic strain (GRS) was 21.5%±10.1% in CSI vs. 26.5%±7.4% in controls, and global circumferential peak systolic strain (GCS) was -19.5%±6.0% in CSI vs. -21.4%±3.4% in controls ($p<0.05$, both comparisons). At T2, GLS was -15.8%±5.2% in CSI vs. -21.9±3.5% in controls ($p<0.0001$); GRS was 22.6%±10.4% in CSI vs. 27.1±8.2% in controls ($p<0.05$); GCS was -20.5%±6.9% in CSI vs. -21.8±3.5% in controls ($p=0.10$). For 17 patients with myocardial-strain-analysis available for both time points: difference in GLS was 0.06±7.2% ($p>0.95$); GRS was 5.5±9.5% ($p<0.05$); GCS was -3.4±4.9% ($p<0.05$). Subclinical dysfunction is present at first echocardiogram after CSI. Myocardial impairment may recover with time, however further analysis is needed to identify risk factors and trends. These results argue for inclusion of baseline cardiovascular assessment and longitudinal follow-up in CNS tumor patients post CSI.

RONC-32. LOCAL CONTROL FOLLOWING PROTON THERAPY FOR PEDIATRIC CHORDOMA

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BACKGROUND: Due to the location and high dose required for disease control, pediatric chordomas are theoretically well-suited for treatment with proton therapy, but their low incidence limits the clinical outcome data available in the literature. METHODS AND MATERIALS: Between 2008 and 2019, 29 patients with a median age of 14.8 years (range, 3.8–21.8) received proton therapy for non-metastatic chordoma at a single institution. Twenty-four tumors arose in the clivus/cervical spine region and 5 in the lumbosacral spine. Twenty-six tumors demonstrated well-differentiated histology and 3 were dedifferentiated or not otherwise specified (NOS). Approximately half of the tumors underwent specialized testing: 14 were brachyury-positive and 10 retained INI-1. Seventeen patients had gross disease at the time of radiation. The median radiation dose was 73.8 GyRBE. RESULTS: With a median follow-up of 4.3 years (range, 1.0–10.7), the 5-year estimates of local control, progression-free survival, and overall survival rates were 85%, 82%, and 86%, respectively. Excluding 3 patients with dedifferentiated/NOS chordoma, the 5-year local control, progression-free survival, and overall survival rates were 92%, 92%, and 91%, respectively. Serious toxicities included 3 patients with hardware failure or related infection requiring revision surgery, 2 patients with hormone deficiency, and 2 patients with Eustachian tube dysfunction causing chronic otitis media. CONCLUSION: In pediatric patients with chordoma, proton therapy is associated with a low risk of serious toxicity and high efficacy, particularly in well-differentiated tumors. Complete resection may be unnecessary for local control and destabilizing operations requiring instrumentation may result in additional complications following therapy.

NEUROSURGERY

SURG-02. INITIAL MANAGEMENT OF HYDROCEPHALUS IN THE PEDIATRIC AND YOUNG-ADULT PATIENTS WITH BRAIN TUMORS; THE EFFICACY OF LONG-TERM INDWELLING EXTERNAL VENTRICULAR DRAINAGE

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BACKGROUND: Pediatric and Young-Adult (AYA) brain tumors often present with hydrocephalus. As temporary cerebrospinal fluid (CSF) diversion procedure, we perform long-term indwelling external ventricular drainage (EVD) in the case of the management of CSF diversion more than two weeks presumably. The aim of this study is to investigate the initial management for hydrocephalus in pediatric /AYA patients with brain tumor, especially about long-term EVD. MATERIALS AND METHODS: The patients less than 30 years of age diagnosed with brain tumor between 2005 and 2019 were retrospectively analyzed. Procedures of long-term EVD were similar to that of ventriculoperitoneal shunt (VPS) operation. Using flow-control VPS system, peritoneal catheter passed out of the body at the anterior chest, and distal end of the catheter was connected to standard EVD system. RESULTS: In total of 345 patients with brain tumor, 109 had hydrocephalus at presentation. Among them, 25 patients (23%) underwent long-term EVD. The main reasons for selecting long-term EVD were to avoid intraperitoneal dissemination (n=13), and to maintain longer period of CSF diversion for the treatment of tumor (n=12). The median of long-term EVD was 38 days (range: 12 – 222 days). Although one case suffered from drainage tube occlusion at 59 days, there were no other complications such as infection or accidental evulsion. Eventually, 3 cases required permanent VPS for persistent hydrocephalus. CONCLUSION: Long-term EVD is safe and effective option for CSF diversion. This procedure should be taken into consideration if patients have a risk of dissemination and may elude permanent VPS.

SURG-03. IMMERSIVE VIRTUAL REALITY APPLICATIONS IN NEUROSURGICAL ONCOLOGY

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Tridimensional (3D) rendering of volumetric neuroimaging is increasingly been used to assist surgical management of brain tumors. New technologies allowing immersive virtual reality (VR) visualization of obtained models offer the opportunity to appreciate neuroanatomical details and spatial relationship between the tumor and normal neuroanatomical structures to a level never seen before. We present our preliminary experience with the Surgical Theatre, a commercially available 3D VR system, in 60 consecutive neurosurgical oncology cases. 3D models were developed from volumetric CT scans and MR standard and advanced sequences. The system allows the loading of 6 different layers at the same time, with the possibility to modulate opacity and threshold in real time. Use of the 3D VR was used during preoperative planning allowing a better definition of surgical strategy. A tailored craniotomy and brain dissection can be simulated in advanced and precisely performed in the OR, connecting the system to intraoperative neuronavigation. Smaller blood vessels are generally not included in the 3D rendering, however, real-time intraoperative threshold modulation of the 3D model assisted in their identification improving surgical confidence and safety during the procedure. VR was also used offline, both before and after surgery, in the setting of case discussion within the neurosurgical team and during MDT discussion. Finally, 3D VR was used during informed consent, improving communication with families and young patients. 3D VR allows to tailor surgical strategies to the single patient, contributing to procedural safety and efficacy and to the global improvement of neurosurgical oncology care.

SURG-04. THE APPLICATION OF EN BLOC RESECTION IN THE OPERATION OF PEDIATRIC POSTERIOR FOSSA TUMOR

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OBJECTIVE: To explore the efficacy and safety of en bloc resection therapy on posterior fossa tumor in children. METHODS: A retrospective analysis was conducted on the clinical data of 94 patients with posterior fossa tumor admitted to Department of Pediatric Neurosurgery, Xinhua Hospital Affiliated to Shanghai Jiaotong University School Of Medicine from January 2018 to December 2019. Among them, 35 cases were treated with traditional resection (control group) and 59 cases with en bloc resection (observation group). We counted the amount of blood loss and the time during tumor resection, We compare the symptoms and signs between the two groups and determine a extent of tumor resection based on microscopic observation and preoperative and postoperative imaging comparison. RESULT: The total tumor resection rate of the observation group (88.1%, 52 / 59) was significantly higher than that of the control group (62.85%, 22 / 35, $P < 0.05$). The average bleeding volume of 90.8ml in the observation group was significantly smaller than that of the control group (113.3ml, $P < 0.05$), and the average operation time of 38.6min in the observation group was shorter than that of the control group (57.4min, $P < 0.05$) only for tumor resection procedure. CONCLUSION: En bloc resection technique can effectively accelerate the resection time, reduce intraoperative bleeding and improve the total resection rate of tumors in children's posterior cranial fossa.

SURG-05. AN AWAKE SURGERY FOR A CHILD SUFFERING FROM EPILEPSY DUE TO DYSEMBRYPLASTIC NEUROEPITHELIAL TUMOR LOCATED IN THE LEFT PARIETAL LOBE

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BACKGROUND: An awake surgery is a useful measure to remove tumors located close to eloquent areas of the brain to reduce surgical complications and maximize the resection. However, it has some disadvantages compared to surgeries under general anesthesia. Generally speaking, applying it to a child under 15 years-old (y/o) is hesitating because of anxiety, poor tolerance, failure to cooperate in tasks and so forth. Here, we present a case of a 13y/o girl who underwent an awake surgery due to dysembryplastic neuroepithelial tumor (DNT) located in the left parietal lobe. CASE PRESENTATION: She consulted our hospital for epileptic seizures. MRI showed a multilocular mass lesion in the left parietal lobe. The tumor was located in or close to eloquent areas. The epilepsy was refractory even with multiple antiepileptic drugs (AEDs). A Wada examination revealed that her speech area is on the left hemisphere. The operations were performed in two stages. Prior to the operations, we had several thought-out simulations in the operating room and ICU with her, her parents, and our staff including nurses and lab technicians. The first operation was to perform tumor biopsy and place intracranial electrodes. The histological diagnosis was DNT. Video electroencephalogram showed that the epileptogenic lesion was around the tumor. The second operation resulted in total tumor resection and reduction of paroxysmal epileptic spikes without major complications. She is seizure free for more than three years with two AEDs. CONCLUSION: Careful preparations may enable an awake surgery even for a child under 15y/o.

SURG-06. AWAKE CRANIOTOMY FOR BRAIN TUMOR IN PEDIATRIC PATIENTS

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BACKGROUND: The challenge of surgery in neurooncology is to achieve the maximum extent of resection while preserving eloquent functions. Intraoperative cortical mapping during resection of a brain tumor allows direct stimulation in eloquent areas with a reduction in postoperative deficits. This procedure has been performed in adults and children down to the age of 11 years. There are only two cases reported on the literature of an 8-year-old and 9-year-old child submitted to an awake craniotomy for brain tumor resection. Pediatric patients are prone to more risks than adults because they become easily agitated after pain sensation. Extensive preparation for the procedure is essential for pediatric patients in order to avoid a lack of cooperation. CASE PRESENTATION: Two patients, with 9-year-old presented with seizures due to a tumor in the left temporoparietal region. In order to identify language and motor–controlling areas during resection, we proposed an awake craniotomy. Because of their ages, they were prepared by a multidisciplinary team. The children's cooperation during the mapping procedure and tumor resection were exceptional. Postoperative cranial MRI confirmed partial resection of the lesion, whose remnant was located in the left motor area. No seizures occurred during the postoperative period, and both were discharged without a neurological disability on the fifth day after the surgery. Histology revealed a dysembryoplastic neuroepithelial tumor (WHO grade I). CONCLUSION: Brain mapping during resection of a tumor in an awake pediatric patient is feasible and can be safely performed even in patients under 11-year-old.

SURG-07. CEREBELLAR PEDUNCLE TUMORS IN PEDIATRIC NEUROSURGERY: FEW CITATIONS FOR BEING RARE OR FOR LACK OF AWARENESS

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We present a case-series of 6 pediatric patients, with a follow-up for a minimum of 1 year, with a diagnostic, therapeutic and prognostic description. This type of disease was first mentioned by Professor Tomita in 1986, in a case-series with 4 patients, with few citations in literature, no other case series cited at the literatures. and in our oncology center of excellence it is an entity that draws attention for diverging from intrinsic tumors of the cerebellum, fourth ventricle and trunk. In this way, we created an algorithm approaching these patients and would like to present this associated to honouring the esteemed professor in neurosurgery.

SURG-08. SUPRASELLAR DERMOID CYST IN A PEDIATRIC PATIENT

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BACKGROUND: Intracranial dermoid cysts (DC) are rare congenital non-neoplastic lesions that account for 0.04 – 0.6% of all intracranial tumors. They are formed by a fibrous capsule composed of epidermal and dermal derivatives (hair follicles, sebaceous and sweat glands), enclosing a viscous fluid. Intradural DC often arise in the midline and are more common in infratentorial locations. CASE REPORT: A 14-year-old male patient presented with headache, partial motor seizures and behavioral changes. Neurological examination and endocrine workup revealed no abnormalities. Brain magnetic resonance imaging showed a lesion that was 4.4cm x 2.2cm x 4.4cm in size, located at supraselar region, and extended superiorly to the left lateral ventricle and anterolaterally to the left orbitofrontal lobe, associated with hyperintense fat droplets in the right lateral ventricle. We performed a left transventricular microsurgical approach. The tumor capsule was coagulated and opened and a subtotal resection with peacemeal removal of the the lesion was obtained: it had gelatinous consistency, composed of droplets of fat and hair and keratinized scamous epihelium content. A total removal of the DC capsule was not possible due to its firm adherence to optic chiasm and to hypothalamus. Histological examination revealed dermoid cyst. CONCLUSION: Surgery is the only effective treatment, and its goal should be the radical resection of the lesion to avoid recurrence. Whenever radical resection is not possible, because of the adhesions of the cyst capsule to surrounding tissues, a subtotal resection with piecemeal removal may be a satisfactory option in such cases to avoid high morbidity.

SURG-09. REACTIVATION OF *HERPES SIMPLEX* VIRUS AFTER NEUROLOGIC SURGERY

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BACKGROUND: Herpes simplex virus encephalitis (HSVE) is a rare complication after neurosurgery, and its clinical picture mimics features of other most frequent infectious complications of bacterial origin. Probable triggering factors are manipulation and surgical stress, since most cases occur due to reactivation rather than primary infection. The main symptoms include fever and altered consciousness. DNA identification of HSV by PCR has accuracy. Even with adequate treatment, HSVE is associated with a mortality of 30%, and potential neurologic sequelae such as cognitive and motor. CASE REPORT: An 18-year-old male patient presented with loss of vision due to cystic craniopharyngioma. We inserted an Omaya catheter and drained the cyst. On the third day, he presented with fever, seizures, and decreased consciousness. Magnetic resonance imaging (MRI) showed high signal intensity on T2-weighted and FLAIR images in the left frontal and temporal lobe, cingulate gyrus, and corpus callosum, with mass effect. He was submitted to decompressive craniectomy and empirical antibiotic therapy. CSF and blood cultures were negative. Due to inexpressive clinical improvement after 48 hours, CSF was collected for polymerase chain reaction (PCR), and we performed a brain biopsy and started intravenous acyclovir. Histology and PCR confirmed HSVE type 1 and 2. He received antiviral for two weeks and was discharged after CSF PCR negative. CONCLUSION: Clinical suspicion, CSF PCR, and imaging are of paramount importance for early diagnosis of HSVE, which should be considered in the differential diagnosis of recent postoperative neurologic surgery in cases of unexplained postoperative fever with altered consciousness.

SURG-10. SPECTROSCOPIC MEASUREMENT OF 5-ALA-INDUCED INTRACELLULAR PROTOPORPHYRIN IX IN PEDIATRIC BRAIN TUMORS

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OBJECTIVE: 5-ALA guided resection of glioma in adults enables better delineation between tumor and normal brain, allowing improved resection and improved patients' outcome. Recently, several reports were published regarding 5-ALA for resection of pediatric brain tumors. The aim of the study was to determine the intracellular fluorescence of PPIX in pediatric brain tumors by hyperspectral imaging and to compare it with visually observed intraoperative fluorescence. METHODS: 5-ALA was administered orally four hours prior to surgery. During tumor resection the surgeon assessed the fluorescence signal to be strong, weak or absent. Subsequently, fluorescence intensity of samples was measured via spectroscopy. In addition, clinical data, imaging and laboratory data were analyzed. RESULTS: Eleven children (1–16 years) were operated. Tumor entities included: three medulloblastomas, two pilocytic astrocytomas (PA), two anaplastic ependymomas and one diffuse astrocytoma, anaplastic astrocytoma, pilomyxoid astrocytoma and anaplastic pleomorphic xanthoastrocytoma. Strong fluorescence was visible in all anaplastic tumors and one PA; one PA demonstrated weak fluorescence. Visible fluorescence was strongly associated with intracellular fluorescence intensity and PPIX concen-

tration (P<0.05). Within all tumors with visible fluorescence the intracellular PPIX concentration was greater than 4 μg/ml. Except for moderate and transient elevation of liver enzymes, no 5-ALA related adverse events were reported. CONCLUSION: We demonstrate a strong association between intraoperative observations and spectrometric measurements of PPIX fluorescence in tumor tissue. As in former studies, fluorescence signal was more commonly observed in malignant glial tumors. Further prospective controlled trials should be conducted to investigate the feasibility of 5-ALA guided resection of pediatric brain tumors.

SURG-12. PAEDIATRIC BRAIN TUMOUR SURGERY: HOW CAN WE REPORT OUR SURGICAL OUTCOMES AND OPERATIVE MORBIDITY?

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OBJECTIVE: Our objective was to quantify resection outcomes and operative morbidity in paediatric brain tumour surgery using existing scales, assessing their applicability. METHODS: We investigated morbidity using the Clavien-Dindo (CD) scale and the Drake classification. All paediatric patients receiving a biopsy or craniotomy for an intracranial tumour in a single tertiary paediatric neurosurgery centre between January 2008 and December 2018 were studied. Complications up to day 30 post op were graded. RESULTS: There were 459 operations: 92 biopsies and 367 craniotomies comprising 166 infratentorial and 292 supratentorial tumours. Median age was 9 years (56% male). The surgical goal was achieved or exceeded in 94% of cases. Thirty-day mortality was 1.31% with all deaths related to disease and none to surgical complications. The overall CD score was 1 in 10.9% of cases, 2 in 18.9%, 3A in 1.7%, 3B in 11.8%, and 4 in 1.1%. There was no operative morbidity in 54% of cases. Using the Drake classification, meningitis was seen in 3.92% of cases, seizures in 3.92%, neurological deficit (that persisted at 30 days) in 8.5%, CSF leak in 5.01%, wound infection in 1.96%, haemorrhage 1.75 %, shunt infection in 1.53%, shunt block in 0.65%, medical complications in 2.4%, and others in 3.05%. CONCLUSIONS: This is the largest series presenting morbidity from paediatric brain tumour surgery, and the first to validate the CD scale. Our morbidity on the Drake scale was comparable with other series. There is a need to develop improved tools to quantify morbidity in this high-risk specialty.

SURG-14. ENDOSCOPIC SURGERY FOR PEDIATRIC INTRAVENTRICULAR TUMOR WITHOUT HYDROCEPHALUS: INDICATION, SURGICAL TECHNIQUE, AVOIDANCE OF COMPLICATION, AND ITS PROSPECT

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INTRODUCTION: Neuroendoscopic surgery is useful for intraventricular tumors accompanied by ventriculomegaly. However, it is often challenging for cases with small ventricles. Our institution is actively performing surgeries for pediatric intraventricular tumors without frank ventriculomegaly. METH ODS: Seven cases of intraventricular tumors without ventriculomegaly (5 cases of subependymal giant cell astrocytoma (SEGA) and 2 cases of germ cell tumors (GCTs)) were analyzed. The age ranged between 3 and 14 years (median 5 years). The sizes of SEGA were between 10-27mm, and all the tumors showed an enlargement around the foramen of Monro, which was the indication for surgery. Biopsy and third ventriculostomy were performed for GCTs. For resection, after making a small craniotomy of 2 x 3 cm, ellipse-cone-like sheath with a diameter of 12mm or 17mm was inserted through it to the lateral ventricle, which enabled a wide surgical view. Under a rigid endoscope of 4mm diameter, 2 types of surgical instruments were employed, making the microsurgical procedure like under a microscope, with a wider view, possible. For the cases of tumor resection, septostomy and placement of a drain in the ventricle were performed at the end of surgery. RESULTS: The lesions were safely approached in all the cases. For resection, endoscopic microsurgery was possible, and tumor was totally removed in all the cases. No postoperative complication was observed in any of them. CONCLUSIONS: Our experience shows that tumor resection can be safely achieved with the aid of endoscope even for cases without ventriculomegaly.

SURG-15. THE SURGERY OF THALAMIC LESIONS IN PEDIATRIC BRAIN TUMORS

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BACKGROUND: Pediatric brain tumors are occurred in the center of central nervous system. Since mid-line glioma has defined in the new classification, thalamus has attracted attention as a site that requires surgical intervention. However, the surgery for thalamus is a challenging procedure for neurosurgeons. In this study, we studied our surgical cases of patients suffering from pediatric brain tumors in thalamus and/or thalamic regions to evaluate the safety of surgeries and the consideration of appropriate surgical approaches. METHODS: We reviewed neuroradiological images, medical record, and, surgical videos for the assessment of surgical fields in patients under the age of 15 who had surgical treatments at our institution. RESULTS: We had six cases that could be analyzed. The lesions in the posterior parts of the thalamus had been operated by the occipital transtentorial approach. The lesions in the superior parts of thalamus were treated with transcortical transventricle approach. It was possible to achieve sufficient removal of tumors and have good surgical view. The monitoring of motor function and visual function was used in all cases. After removal, we could have a nice view of the important structures around thalamus. CONCLUSIONS: The surgeries for thalamus and thalamic regions were safety with enough considerations for neurological examinations and radiological imaging. The intra operative monitoring for motor and visual function should be used.

SURG-16. SURGICAL TECHNIQUES TO AVOID COMPLICATIONS DURING REPEAT RESECTIONS FOR PEDIATRIC BRAIN TUMORS

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Complications due to repeat resection for recurrent pediatric brain tumors remain unclear. The present study focused on surgical techniques to avoid surgical morbidities during repeat resections for pediatric brain tumors. This study included 57 consecutive repeat resections for 28 pediatric patients under the age of 15 with recurrent brain tumors. Resections were performed 2–14 times for each patient by the senior author (TK). Reviewed factors were wound-related complications, bleeding/ischemic complications, and Eastern Cooperative Oncology Group performance status (PS) before and after surgery. No patients presented any complications to decrease PS, postoperatively. No wound-related complications were worthy of special mention. Surgical techniques to prevent wound-related complications are as follows: 1) shaving the hair around the previous skin incision just before the surgery; 2) washing and disinfecting around the skin incision using chlorhexidine soap and an alcohol swab, followed by Povidone-Iodine solution; 3) after craniotomy, removing all granulation tissues, residual titanium plates, and screws; 4) brushing all surgical fields and a bone flap before opening the dura mater using Povidone-Iodine solution followed by normal saline; 5) maintaining a bone flap in normal saline with antibiotics; 6) changing all the surgical instrument and gloves; 8) closing the dura mater completely to prevent CSF leakage, and 8) using postoperative antibiotics for six days. Meticulous dissecting postsurgical adhesion of brain and dura mater, arteries and nerves; usage of neuronavigation system and neuromonitoring to understand the anatomy radiologically and functionally; applying papaverine hydrochloride for spastic arteries, are important to avoid complications during the intracranial procedure.

SURG-17. CLINICAL CHARACTERISTICS AND OUTCOMES OF EPILEPSY-RELATED BRAIN TUMOR IN CHILDREN

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OBJECTIVE: Epilepsy is one of the earliest symptoms in pediatric brain tumor. Gross total resection (GTR) of the tumor does not necessarily achieve seizure free, therefore it is controversial whether surrounding epileptic foci should be resected at the initial surgery. The aims of this study are to report clinical characteristics and outcome of pediatric epilepsy-related brain tumor (ERBT) and to discuss treatment strategy. METHODS: Subjects were children less than 18 years old who underwent surgery for ERBT. Patients in whom epilepsy had been controlled before surgery were excluded. Data were collected from medical record and retrospectively reviewed. RESULTS: Twenty-one children (8 boys and 13 girls) were analyzed in this study. The mean age at surgery was 6.8 years. Tumor was astrocytic tumor in 10, gangliogioma in 4 and dysembryoplastic neuroepithelial tumor in 3. Intracranial subdural electrodes were placed prior to tumor resection in 5 cases. GTR was achieved in 14 (67%). Seizure free was achieved in 15 (71.4%). GTR was significantly associated with seizure free (p=0.002). CONCLUSION: In most of ERBT, seizure free can be achieved by lesionectomy alone. However, the resection of surrounding epileptic foci is required in some cases. Detailed examinations to detect the epileptic foci should be performed in ERBT, particularly in case of drug-resistant intractable epilepsy.

SURG-19. COMPLETE RESOLUTION OF ADHD AFTER GROSS TOTAL RESECTION OF DYSEMBRYIOPLASTIC NEUROEPITHELIAL TUMOR

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A 3-year-old boy with a history of attention-deficit/hyperactivity disorder (ADHD) presented a single focal tonic seizure. A thorough physical examination revealed no neurological deficit. A contrast enhanced MRI showed an isointense lesion in the anterior part of the cingulate gyrus extending through the left frontal lobe. After initial evaluation, the parents refused surgical treatment and a close follow up was then considered. At the age of five, the ADHD become more evident and the patient was started on methylphenidate. Poor clinical response was seen with the initiation of stimulant. The boy presented a second generalized seizure and the parents agreed surgical management. An interhemispheric approach was then performed and a gross total resection was achieved. The histopathological diagnosis corresponded to a dysembryoplastic neuroepithelial tumor (DNET). Four years after the resection, the patient is seizure free and the ADHD has also resolved without the need of medication. The disappearance of seizures is common after surgical resection of DNET tumors, but this case establishes an association with ADHD.

SURG-20. DIENCEPHALIC SYNDROME IN PEDIATRIC NEUROSURGERY

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This report details the histories of twelve patients with clinical diencephalic syndrome who collectively demonstrate the variability found in the syndrome with respect to: (1) clinical course, (2) site of the tumor, and (3) ease of obtaining radiologic confirmation of the presence of a tumor. Timely diagnosis of diencephalic syndrome is not often the case for patients presenting with failure to thrive (FTT) because of its rarity and lack of specific symptoms. These cases illustrate the importance of cranial imaging and consideration of diencephalic syndrome for children presenting with FTT despite normal or increased caloric intake.

SURG-21. ENDO- AND EXOSCOPIC SURGERY FOR PEDIATRIC NEUROSURGICAL OPERATION

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INTRODUCTION: Recently endo- and exoscopic surgeries have been gradually performed in neurosurgery. To improve the accuracy and safety of our endoscopic procedures, we are currently trialing 4K or 8K systems. Here we report our experience of endo- and exoscopic procedures for pediatric neurosurgery. METHODS: We retrospectively identified 22 patients (15 males, 7 females; mean age, 9.2 years) who underwent surgery for sellar lesions and intraventricular or intraparenchymal lesions with an endo- or exoscopic procedure at our institute between 2010 and 2020. We used a full HD endoscope system (Storz) and an organic electroluminescence (EL) monitor (Sony), and a 4K system (Sony and Olympus). VITOM 3D (Storz) was used as the exoscope. Videoscope (Olympus) was used as a flexible scope for intraventricular tumors. RESULTS: We performed surgical procedures as 11 biopsies, 6 third ventriculostomies, 5 resections, and 3 fenestrations. The full HD system with organic EL monitor presented high color contrast. We could easily distinguish between tumor microstructure and the normal structure with the 4K system comparing to full HD. Moreover, electronic zoom function enabled us to discriminate tumor boundaries without having to move the endoscope closer. As a result, we could delineate the surgical working space. VITOM 3D was simple to sharpen the focus on the wider surgical field, similar to the application of an operating microscope. CONCLUSION: In pediatric neurosurgery, an endo- or exoscope enables clear visual recognition of a boundary between tumor and normal area.

SURG-22. CERVICAL SPINE ANEURYSMAL BONE CYST OF A PEDIATRIC PATIENT

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BACKGROUND: Aneurysmal bone cysts (ABCs) are benign, expanding lesions that represent 15% of all primary spine tumors, and only 2% have been found at the cervical level. There are different therapeutic options; the most successful is complete surgical resection. Although not always possible, due to high blood loss that occurs during the procedure, a combination of surgery with other treatment modalities was used in 40% of the cases reported so far. We describe a pediatric patient that we managed with embolization plus surgery. CASE REPORT: A 5-year-old girl presented with painful torticollis associated with a left posterior cervical mass, without neurological impairment. Magnetic resonance imaging of the cervical spine showed a multiseptated bony lesion with multiple fluid levels, involving the posterior elements of C2, associated with diffuse soft tissue enhancement of the left paravertebral muscles. We proposed a multi-staged treatment with pre-operative arterial embolization followed by the posterior surgical approach. Super selective embolization of the left ascending cervical artery was performed. The right ascending cervical artery also contributed to the tumor blush, but due to its connection to the right vertebral artery and, therefore, associated with a high risk of neurological injury, we prefer not to embolize it. Two days later, we performed a posterior surgical approach, with a gross total resection of the tumor. Histological examination revealed an ABC. CONCLUSION: An aneurysmal bone cyst is a rare cervical spine lesion that demands a multidisciplinary approach due to its locally aggressive behavior and the excessive blood loss related to surgery.

SURG-24. NOVEL MALLEABLE FORCIPES FOR ENDOSCOPIC ASSISTED TECHNIQUE IN PEDIATRIC BRAIN TUMORS

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Recent advances in optical devices and surgical instruments have been applied to neurosurgery. Even with modifications, one of the most serious risks is injury of neuronal and vascular structure caused by operation of surgical instruments in a narrow surgical field. Fixed instruments are not practical for pediatric brain tumor surgeries because the length of the curved or angled tip portion is limited because of the narrow entrance. We developed a novel malleable forceps to resolve the difficulties related to microsurgical procedures. The malleable forceps has two shafts with a sharp cup at the tip. The entire forceps was made of stainless steel, with a silver and nickel alloy inserted between 10 and 40 mm from the tip. In the alloy part, the surgeon can flex the forceps freely using a special cylinder. The special cylinder is useful to prevent from slipping of the cups of tip. The maximum angle that can be bent is 70 degrees vertically. We also developed a monoshaft malleable forceps. We used these flexible forcipes in the case of various pediatric brain tumors including craniopharyngioma. We performed tumor resection by anterior interhemispheric trans-lamina terminalis approach. After procedure of tumor resection using microscope, endoscope inserted around the pituitary stalk. The piece of calcified tumor could be easily removed without any complications. These forcipes can be deformed to an appropriate angle and can be applied to various cases, especially pediatric brain tumors.

SURG-29. A SINGLE CENTRE EXPERIENCE OF USING INTRA-OPERATIVE MRI IN MANAGING PEDIATRIC CRANIAL NEURO-ONCOLOGY CASES

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The University of Malaya Medical Centre, Kuala Lumpur had acquired a intraoperative MRI (iMRI) brain suite via a public private initiative in September 2015. The MRI brain suite has a SIEMENS 1.5T system with NORAS coil system and NORAS head clamps in a two room solution. We would like to retrospectively review the cranial paediatric neuro-oncology cases that had surgery in this facility from September 2015 till December 2019. We would like to discuss our experience with regard to the clear benefits and the challenges in using such technology to aid in the surgery. The challenges include the physical setting up the paediatric case preoperatively, the preparation and performing the intraoperative scan, the interpretation of intraoperative images and making a decision and the utilisation of the new MRI data set to assist in the navigation to locate the residue safely. Also discuss the utility of the intraoperative images in the decision of subsequent adjuvant management. The use of iMRI also has other technical challenges such as ensuring the perimeter around the patient is free of ferromagnetic material, the process of transfer of the patient to the scanner and as a consequence increased duration of the surgery. CONCLUSION: Many elements in the use of iMRI has a learning curve and it improves with exposure and experience. In some areas only a high level of vigilance and SOP (Standard operating procedure) is required to minimize mishaps. Currently, the iMRI gives the best means of determining extent of resection before concluding the surgery.

SOCIAL WORK/PATIENT SUPPORT/PALLIATIVE CARE

SWK-02. WEAVING COMFORT AND SUPPORT FOR CHILDREN WITH BRAIN TUMORS AND THEIR FAMILIES IN AN OUTPATIENT CLINIC

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Parents of children diagnosed with brain tumors report high levels of stress at diagnosis and feelings of "being lost" on transition to outpatient follow-up care (Jackson AC, *et al*, 2007). Ssori is a Japanese form of free-style weaving that encourages people facing life-limiting challenges to discover inner strengths. We report our experience with Saori weaving with brain tumor patients and their families in a pediatric oncology outpatient clinic at a major university medical center. During 2019, we offered weaving sessions twice a week. We had a total of 151 encounters with hematology/oncology patients (age 5–18 years), siblings, or parents. Among these patients there were 20 with primary brain tumor diagnoses. Weaving was offered in the art therapy area of the clinic. After creating a fabric, the weavers had the opportunity to have their work sewn into functional objects, such as pillows, bags, purses, or healing pouches filled with beans that can be heated or cooled for comfort. Brain tumor patients readily engaged in weaving, despite various degrees of neurologic disability including hemiparesis or low vision. In the words of an 8 y/o weaver. "This is so cool. Daddy, can we always come when the weavers are here, so I can weave?" And from a mother: "This is great. She's focused and busy!" Case studies, including a presentation of Legacy work, will be reported. In conclusion, Saori weaving can be an impactful intervention for childhood brain tumor patients and their families in an outpatient clinic setting.

SWK-03. CAREGIVER EXPERIENCES FOR PEDIATRIC BRAIN TUMOR PATIENTS AND THEIR FAMILIES AT A DEDICATED MEDICAL SPECIALTY CAMP

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BACKGROUND: Medical specialty camps have provided children with unique psychosocial experiences; however, dedicated pediatric brain tumor camps are rare in the United States, except in limited locations. This study aimed to glean caregiver perceptions from a dedicated family brain tumor camp, and to learn about the family experience with navigating a neuro-oncology diagnosis. DESIGN: Flying Horse Farms is a non-profit organization located in Mt. Gilead, Ohio and a member of the SeriousFun Children's Network, a global community of camps and programs serving children with serious illnesses and their families, at no cost. The institutional review board at Ohio University approved this project at Flying Horse Farms in September 2017. Consent from caregivers was obtained prior to participation in the study, which provided the opportunity to complete three separate phases: a pre-camp survey, attend a semi-structured interview during the weekend, and complete a post-camp survey. RESULTS: 11 families were present for the weekend, and 10 families consented to participate in all three phases. For 6 families, this was their first experience at Flying Horse Farms. For 9 of the 10 families, the camp met their expectations. Additionally, 9 out of 10 families reported they would be interested in attending a diagnosis specific camp again in the future. CONCLUSIONS: This work demonstrates the feasibility of conducting research at a medical specialty camp without restricting the camp experience. Better understanding of the attendee's attitudes toward camp may enhance the experience and the neuro-oncology journey in the future.

SWK-04. A MOBILE AUGMENTED REALITY APP FOR SURGICAL PREPARATION FOR CHILDREN WITH BRAIN TUMORS

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BACKGROUND: Children with brain tumors experience significant anxiety secondary to diagnosis and interventions such as surgical management. Preoperative anxiety is known to adversely affect operative outcomes and overall quality of life. Programs that utilize "child-friendly" approaches have been shown to ease anxiety, decrease analgesic requirements, shorten hospital stay, and contribute toward better outcomes. Implementation of these programs is limited due to time, cost, and staffing constraints as well as sociodemographic factors (i.e., language barriers). Therefore, an effective and cost-efficient method could be advantageous. We sought to develop a universally available APP that can assist with these goals and address the current barriers. METHODS: In conjunction with a philanthropic resource (Brain Tumor Foundation, New York, NY, USA) a developer was tasked with creating an App for children with brain tumors. The developer integrated published clinical research, multi-specialty input, and patient and family testimonials for possible integration into the tool. RESULTS: A mobile App was developed that is modifiable for patient-specific features (age, language, and ethnicity). Initial evaluations of the prototype by healthcare providers, appropriately aged children, and their parents have demonstrated positive engagement, appeal, and ease of use. CONCLUSIONS: The mobile App provides a rapid, affordable, and modifiable platform for assisting children with brain tumors cope with their diagnosis and intervention options. Validation with measurable outcomes is planned. The App is currently being evaluated for purposes of psycho-social clinical research tool.

SWK-05. EDUCATIONAL APPROACH TO GRIEF MANAGEMENT

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Pediatric neuro-oncology has a high mortality rate compared to other childhood cancers. This project sought to bring Awareness to the Grief and Trauma that families undergo during treatment through end of life. It also sought to create a pool of parent partners to support families receiving palliative care and to mend the healthcare relationship that is severed when a child passes away. The educational series included Grief Workshops for Bereaved Parents using the ATTEND model, a mindfulness-based bereavement model and seminars with traumatic grief experts for providers. This provided a better understanding on how healthcare workers are influential in the "death story" of a child and how this can dictate the family's lifelong grief journey. Grief workshops consisted of 2 English and 1 Spanish speaking cohort each with 10–12 bereaved parents. The curriculum provided psychoeducation with the goal of creating a safe space to validate, clarify, and understand the events that happened in their child's life; support for the parent as they explore emotional awareness; relief of emotional tension; support as the parent expresses their perspective of their new world to others that are in their life; and support as the parent finds meaning in their child's life and untimely death. At the end of each group surveys showed that parents found that the group provided a safe community, a place to say their child's name, a place to share their story, and a need to advocate for future oncology parents who undergo this journey.

SWK-06. ANSWERING 900 VOICES: A NATIONAL NONPROFIT ORGANIZATION RESPONDS TO A NATIONWIDE COMMUNITY HEALTH NEEDS ASSESSMENT THAT ELUCIDATED KEY CHALLENGES FACED BY PEDIATRIC BRAIN TUMOR FAMILIES

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The five-year relative survival rate for childhood primary brain and other central nervous system tumors is nearly 75 percent (Central Brain Tumor Registry of the United States, 2017). Nevertheless, childhood brain tumor survivors often suffer from lifelong side effects caused by their illness or treatments such as surgery, radiation and chemotherapy. To define the nature and extent of problems survivors and their families face, the Pediatric Brain Tumor Foundation (PBTF), the world's largest nonprofit solely dedicated to children and teens with brain tumors, conducted a 2017 national community health needs assessment in collaboration with the Sol Price Center for Social Innovation at the University of Southern California. The assessment found that pediatric brain tumor patients and their families face key challenges in four general areas: 1) interpersonal and emotional support, 2) logistical and financial support, 3) information and medical education gathering, and 4) educational and vocational anxieties. In 2020, the PBTF's response to the 900 assessment participants who represent the thousands living with the effects of this disease includes the launch of a national Peer to Peer Mentoring program to meet the ongoing challenges families face; the disbursement of emergency financial assistance to hundreds of families in the throes of treatment; and the distribution of a resource notebook for newly diagnosed families and a comprehensive guidebook for survivors and their families. The results of the needs assessment suggest additional clear, actionable areas for impact not only by the PBTF but by medical professionals, other nonprofit organizations and governmental agencies.

SWK-07. A MULTINATIONAL SURVEY OF PAEDIATRIC NEURO-ONCOLOGY SERVICES: A EUROPEAN RESEARCH NETWORK (ERN) PAEDCAN PROJECT

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BACKGROUND: Brain tumours are clinically and biologically highly diverse and account for 25% of paediatric neoplasms. They carry the highest mortality and morbidity of tumour groups. Their management presents

significant challenges with performing modern diagnostic assessments, applying multimodal treatment and establishing interdisciplinary cooperation. Outcomes across Europe differ significantly with varying 5year survival reports of 42–79%. This SIOP-Europe PaedCan survey assessed the structures and facilities for individual states and highlight areas for cooperation and support. DESIGN: An online questionnaire was sent to SIOP-Europe Brain Tumour Group members. This had 55 questions assessing pathology, staging, surgery, radiotherapy and paediatric oncology infrastructure. For analysis of the data we divided countries into lower and higher economic status according to GDP (World Bank 2019) with a cut off of $30,100. RESULTS: There were 388 respondents from 44 countries in 181 different institutions. In the lower GDP group we noted decreased access to biological characterisation of tumours and interdisciplinary tumour boards. In this group of nations, patients were less likely to have treatment by a paediatric specialist neurosurgeon, paediatric neuro-oncologist, neuroradiologist, and paediatric radiation oncologist. There was also less availability to perform early MRI (ventilated) and less access to proton beam therapy. This study supports the aim of the ERN to produce a roadmap document with specific standards and publish guidelines for all relevant diagnostic and therapeutic components of care. The ERN also aims to identify a network of institutions to provide patient advice and training to equalise treatment and outcomes for all children across Europe.

SWK-08. DELAYED DIAGNOSIS OF CENTRAL NERVOUS SYSTEM (CNS) TUMORS IN CHILDREN: PERSPECTIVE FROM THE FRONTLINE

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Delayed diagnosis of CNS tumors in children is well documented, partially due to challenges in recognizing rare diagnoses. Our objective was to describe Canadian family physicians' attitudes and confidence in diagnosing and managing pediatric CNS tumors. A standardized questionnaire was administered at a Canadian national family physicians' conference. Items were based on observations from our institutional study of prediagnostic symptomatic interval in pediatric CNS tumors. 449 surveys were completed. 302/443 (68%) physicians practice in cities. 153/447 (34%) report encountering parents that inquire about their children having brain tumors. 261/449 (58%) have not managed a pediatric brain tumor. 153/447 (34%) report they are not confident, 255/447 (57%) somewhat confident and 39/447 (9%) confident in managing a suspected brain tumor in a stable child. 259/447 (58%) would refer directly to a hospital/specialist. The reported median time for suspicion of a brain tumor was 8–14 days for children with vomiting and/or headache and 1 day for children with seizure and/or ataxia. 410/447 (97%) report not knowing any guidelines to help with management. 235/447 (53%) suggested barriers they experience to include 52/235 (22%) wait times for imaging/specialists, 37/235 (16%) geographical location of the child, 27/235 (12%) knowledge, 25/235 (11%) access to imaging/specialist, and 15/235 (6%) patient-related factors or system barriers, and 8/235 (3%) specialist attitudes. 68/235 (29%) identified no barriers in their practice. This study provides insight into family physicians' perceived challenges and barriers in diagnosing and managing new suspected pediatric CNS tumors. Educational effort and overcoming systemic perceived barriers may increase physicians' confidence.

SWK-09. SELF-CARE OUTCOMES AND INTERVENTIONS FOR CHILDREN WHO HAVE HAD A BRAIN TUMOUR: EVIDENCE AND HYPOTHESES. WHAT SHOULD SELF-CARE INTERVENTIONS FOR CHILDREN WITH PAST OR PRESENT BRAIN TUMOUR BE?

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OBJECTIVE: To determine the evidence with regards to self-care outcomes and interventions for children who have been treated for a brain tumour and identify when best to intervene. METHODS: A scoping review of the literature with regards to self-care interventions, outcomes and mechanisms was undertaken. The information from these themes were populated onto a logic model alongside the clinical expertise of the team. The logic model was used to develop hypotheses to inform subsequent research; and identified areas for further patient and public involvement. RESULTS: Of 27 papers found, 13 were deemed relevant. The literature suggested the diagnosis of a brain tumour can have a long-term negative impact on self-care outcomes whilst evidence with regards to interventions to promote self-care is scarce. The child's physical and cognitive functions were identified as hypothesised factors influencing self-care, while health related quality of life and participation in other life domains were secondary consequences of self-care. The team expertise was further used to hypothesise that parent factors (emotions, identity, actions), the child's emotional functions and personal factors as well as peer relationships and norms may influence children's self-care. These factors were not covered in the existing literature. CONCLUSIONS: Subsequent research will investigate the hypotheses developed to further specify factors that self-care interventions for children and young people with a brain tumour should target. This will involve specifying when, how and to whom interventions should be targeted.

SWK-10. TELEHEALTH IN OUTPATIENT PEDIATRIC NEURO-ONCOLOGY CARE

Shannon Raber[1], Carly Hoffman[1], Carol Yarbrough[2], Linda Branagan[2], Neela Penumarthy[3], Jami Manning[1], Alyssa Reddy[2], Anuradha Banerjee[2], Cassie Kline[2], and Sabine Mueller[2,4]; [1]University of California San Francisco - Benioff Children's Hospital, San Francisco, CA, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]University of Washington, Seattle, WA, USA, [4]Zurich Children's Hospital, Zurich, Switzerland

BACKGROUND: Telehealth is an emerging modality that can include patient evaluation, review of test results, and clinical decision-making. Access to care and quality of life are challenges for patients with pediatric brain tumors and their families. Herein we describe the introduction of video visits within our outpatient services led by nurse practitioners and nurse coordinators. METHODS: The pediatric neuro-oncology program at University of California, San Francisco - Benioff Children's Hospital (UCSF) established a robust telehealth practice to improve access to care for children and young adults with brain and spine tumors. Our nursing team identifies appropriate time points to offer video visits in lieu of in-person visits. Families are guided to connect through secure video conferencing. Data was collected retrospectively through electronic medical record schedules, billing records, and UCSF patient satisfaction surveys. RESULTS: Since 2015 we have utilized telehealth for over 400 encounters. The service was limited to patients located in California. Introduction of telehealth resulted in savings of 2300 hours of travel by car, over $22,000 in gas, and over 127,000 miles traveled. Surveys indicate patient satisfaction is equal to or better than in-person experiences. Anecdotally, this service allows for face-to-face contact with patients who have significant barriers to travel. Challenges have included technology platforms, native language, provider and patient acceptance, and billing. CONCLUSION: Overall, telehealth is feasible as a tool to deliver outpatient care in pediatric neuro-oncology. Implementation of video visits in clinical practice increases access to neuro-oncologic care and improves quality of life for patients and families.

SWK-11. ASSESSMENT OF THE INDIRECT COSTS ASSOCIATED WITH PROTON THERAPY TREATMENT FOR ALBERTA PATIENTS REFERRED OUT OF COUNTRY

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BACKGROUND: Proton therapy for benign and malignant tumors has dosimetric and clinical advantages over photon therapy. Patients in Alberta, Canada are referred to the United States for proton treatment. The Alberta Heath Care Insurance Plan (AHCIP) pays for the proton treatment and the cost of flights to and from the United States (direct costs). This study aimed to determine the out-of-pocket expenses incurred by patients or their families (indirect costs). METHODS: Invitation letters linked to an electronic survey were mailed to patients treated with protons between 2008 and 2018. Expenses for flights for other family members, accommodations, transportation, food, passports, insurance, and opportunity costs including lost wages and productivity were measured. RESULTS: Fifty-nine invitation letters were mailed. Seventeen surveys were completed (28.8% response rate). One paper survey was mailed at participant request. Nine respondents were from parent/guardian, 8 from patients. All patients were accompanied to the US by a family member/friend. Considerable variability in costs and reimbursements were reported. Many of the accompanying family/friends had to miss work; only 3 patients themselves reported missed work. Time away from work varied, and varied as to whether it was paid or unpaid time off. CONCLUSIONS: Respondents incurred indirect monetary and opportunity costs which were not covered by AHCIP when traveling out of country for proton therapy. Prospective studies could help provide current data minimizing recall bias. These data may be helpful for administrators in assessing the societal cost of out-of-country referral of patients for proton therapy.

SWK-12. PEDIATRIC NEURO-ONCOLOGY PARENT PERSPECTIVE ON ASPECTS OF SOCIAL AND EMOTIONAL SUPPORT FOR ONLINE APPLICATION

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Addressing family needs for social/emotional support is part of the duty of oncology care teams. This research presents a (2020) scoping review and a (2019) focus group initiated to explore pediatric neuro-oncology parent experience of social/emotional support in conjunction with developing an online peer application to address family needs. Currently, the value of online support is in the forefront of clinical conversation. The focus group queried eight parents whose children were under neuro-oncology treatment in the Northwest USA. Thematic findings include—parents want supportive peers who have (1) a personal and deep understanding of parenting a child with serious illness (they "get it"); (2) particular characteristics and skills that promote and sustain relationships, including—(a) good social skills, (b) ability to engage in "balanced" (cancer/non-cancer) conversations, (c) individual similarities (beliefs, age of children, cancer diagnosis/treatment), (d) logistic commonalities (location, availability), (e) pro-social personal characteristics (i.e. sense of humor, emotional/social flexibility), and an (f) ability to navigate and maintain social/emotional boundaries. Parents also initiated discussion about "the burden of supportive relationships" and supporting families doing "normal" activities without worrying about treatment side effects and contagions. The literature review supports finding (1) above; reveals the paucity of evidence-based supports available to this population; underscores the critical need for practitioners and researchers to develop more evidence-based supports and interventions for families of children experiencing cancer; and supports practitioners' consistently assessing parent and sibling social and emotional needs and then consistently referring or intervening when needs are identified.

TUMOR BIOLOGY (NOT FITTING A SPECIFIC DISEASE CATEGORY)

TBIO-01. SEX DIFFERENCES IN REDOX STATE UNDERLIE GLUTAMINE DEPENDENCY IN MALE GLIOBLASTOMA

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Glioblastoma (GBM) is an aggressive brain tumor in children and adults. It occurs more commonly in males, but female patients survive significantly longer. Understanding the molecular mechanisms that underlie those sex differences could support novel treatment strategies. In this regard, we found that male and female GBM patient samples differ in their metabolite abundance and that males exhibit a significantly higher abundance of amino acid metabolites. We confirmed those findings in a murine model of GBM, which has previously yielded important insights into sexual dimorphism in GBM. Furthermore, we found that male GBM cell cultures are significantly more sensitive to amino acid deprivation, which was almost entirely driven by amino acids involved in the synthesis of the antioxidant glutathione. Glutaminase 1 (GLS1) mediates the conversion from glutamine to glutamate, a crucial component of glutathione. We found that male GBM cells exhibited higher levels of GLS1, suggesting they are more dependent on glutamate. Indeed, we found that male GBM cells are more sensitive to pharmacological GLS1 inhibition with the clinical inhibitor CB-839. This correlated with significantly increased reactive oxygen species (ROS) in males compared to females. We further confirmed sex differences in redox state through pharmacological depletion of glutathione that resulted in a significant increase in ROS and cell death in male GBM. Together, these data indicate that male GBM cells are more dependent on glutamine to regulate ROS levels. This reveals novel sex-specific metabolic targets for GBM and underlines the importance of considering sex in metabolic targeting approaches.

TBIO-02. IMMUNE PROFILING OF RARE EMBRYONAL BRAIN TUMORS REVEAL EVIDENCE OF DYSREGULATED INTERFERON SIGNALLING AS A POTENTIAL DETERMINANT OF IMMUNOLOGICAL HETEROGENEITY

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Embryonal brain tumors (EBTs) remain the most common malignant pediatric brain tumors. Despite recent advances and improved understanding of the molecular biology of EBTs, clinical outcomes remain poor for rare EBTs. Previous large-scale genomic studies of rare EBTs have shed light on distinct genomic, transcriptomic and epigenomic profiles. Interestingly, these studies have revealed prominent tumor heterogeneity that provides opportunity to develop novel treatment strategies to improve patient outcomes. To examine the tumor microenvironment and identify tumor- specific biological dependencies, we performed deconvolution analysis of bulk gene expression (171 RNA-seq, 236 microarrays) and 586 methylation arrays, which revealed significant intra and inter-tumoral heterogeneity and implicated interferon (IFN)-mediated signalling as a determinant of a distinct immunological profile in rare EBTs. To further elucidate the importance of IFN signalling, we performed scRNA-seq on 20 primary samples, which provided evidence of a spectrum of IFN-immunological responses that vary from immunosuppressive to immunologically exhaustive that occur in a host dependent manner. To further validate our findings, we utilised a genetically engineered murine model of Atypical Teratoid Rhabdoid Tumor and primary xenografts in humanised mice to corroborate our in-silico profiles in vivo. Through amalgamation of our in-silico data with our in vivo data, we have identified evidence that dysregulated IFN responses represent a core element of the immunological heterogeneity present within subsets of rare EBTs. An improved understanding of the immune milieu in rare EBTs will provide avenues to develop specific onco-immune targets to address this clinical need.

TBIO-03. THE GIFT FROM A CHILD PROGRAM IS EMPOWERING POST-MORTEM TISSUE DONATION ACROSS THE UNITED STATES

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The Gift from a Child (GFAC) program was inspired by the dream of one child to donate his brain for research, recognizing the need to study tumor tissue collected at diagnosis, recurrence, and at the time of death. Founded by the Swifty Foundation in 2016, GFAC currently is comprised of five "Centers of Excellence" at institutions with expertise in pediatric neuro-oncology. Partnering with the Children's Brain Tumor Network, the program's mandate is twofold: make it possible for families to donate no matter where they live in the United States and make tissue available to scientists globally to empower discovery. In order to overcome barriers that have stifled postmortem collection in the past, GFAC has invested in Tissue Navigators - individuals at each center who coordinate all aspects of donation and communicate with families, medical providers, and laboratory scientists. In 2019 alone, GFAC coordinated 55 autopsy collections from multiple diagnosis. A key metric of the program is also capturing the global sharing and usage of each tissue sample, ensuring that tissue isn't simply "banked" but is actively being actively used to help unravel tumor biology. To date, tissue has been used for genomic and molecular data generation, preclinical model development including cell lines and PDX models, and for novel drug screening. Together with Children's Brain Tumor Network, the Gift from a Child program is helping to ensure the most precious gift that a family can make is used to accelerate the path to cures.

TBIO-05. GENOME-SCALE NUCLEOTIDE-SPECIFIC CHARACTERIZATION OF 5-HYDROXYMETHYLCYTOSINE IN PEDIATRIC CENTRAL NERVOUS SYSTEM TUMORS

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Though aberrant cytosine modifications are prevalent in cancer, nucleotide-specific 5-hydroxymethylcytosine (5hmC) modifications remain understudied, including in pediatric CNS tumors. Brain 5-hydroxymethylation is linked with development and differentiation. We measured genome-scale nucleotide-specific 5hmC in patients with diagnoses of glioma, ependymoma, and embryonal tumors under age 18 (n=36), and in non-tumor pediatric brain tissues (n=3). DNA was processed with tandem oxidative (OxBS) and bisulfite (BS) treatments followed by hybridization to the Illumina Methylation EPIC Array that interrogates over 860,000 CpG sites. We used the OxyBS R package to determine levels of 5hmC and 5mC. Mean 5hmC levels were lower in tumors (gliomas 4.1%, ependymomas 3.9%, and embryonal

tumors 3.4%) compared to nontumor tissues (5.3%). We subset to the CpGs with the 5% highest 5hmC content for downstream analyses (37,173 CpGs). These sites were enriched among regulatory elements, including TFBS (Odds Ratio 1.14 p-value 3.57E-20) and super-enhancers (OR 1.93, p-value 1.14E-126). Linear mixed-effects models adjusted for age, sex, and cell type proportions tested the CpG-specific differences in 5hmC between tumor and nontumor samples, as well as between tumor subtypes. 5hmC levels were depleted across tumors compared with nontumor brain tissues, including at CpG islands. Model-based clustering (RPMM) results indicated that patients with low 5hmC patterns have poorer overall survival and increased risk of recurrence. Our results indicate that 5hmC localizes to sites in the DNA critical to gene regulation and is associated with patient outcomes. This study offers an opportunity to potentially contribute to classification markers for childhood brain tumors.

TBIO-06. BDNF-TRKB SIGNALING REGULATES NEURON-GLIOMA SYNAPTOGENESIS AND PROMOTES TUMOR PROGRESSION

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Pediatric high-grade gliomas (pHGG) are a devastating group of diseases that urgently require novel therapeutic options. We have previously demonstrated that pHGGs hijack mechanisms of brain development and plasticity to their advantage. Here, we investigated the role of microenvironmental BDNF on pediatric gliomas, independent of the NTRK fusion events commonly identified in infant HGG. Genetic deletion or pharmacological blockade of *NTRK2* (TrkB), in patient-derived pediatric glioma increases survival in multiple DIPG and pGBM patient-derived orthotopic xenograft models. Unlike the paracrine BDNF-TrkB signaling observed between subpopulations of adult HGG malignant cells, pediatric glioma express TrkB, but not BDNF ligand. BDNF is secreted by normal brain cells in response to neuronal activity and conditioned medium experiments from cortical slices of mice indicates the brain microenvironment as the chief source of BDNF ligand. Addition of recombinant BDNF protein increases pediatric glioma cell proliferation and activates the canonical downstream MAPK signaling pathway, an effect that is blocked by genetic or pharmacological TrkB inhibition in pHGG. However, the glioma growth-promoting effects of BDNF in vivo cannot be explained by stimulation of MAPK signaling alone. We therefore examined the effects of BDNF signaling on neuron-to-glioma synapse formation, a newly recognized microenvironmental interaction important for pediatric glioma progression. We find that BDNF-TrkB signaling promotes neuron-to-glioma synaptogenesis in neuron-glioma co-culture. We are presently exploring the role for BDNF-TrkB signaling in glioma synaptic plasticity and function. Funding: Abbie's Army Foundation

TBIO-07. SINGLE-CELL TRANSCRIPTOMIC PROFILE REVEALS MACROPHAGE HETEROGENEITY IN SONIC-HEDGEHOG MEDULLOBLASTOMA AND THEIR DISTINCT RESPONSES TO DIFFERENT TREATMENT MODALITIES

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Tumor-associated macrophages (TAMs) are an important component of the tumor microenvironment. Pro-inflammatory macrophages can suppress while anti-inflammatory macrophages can promote tumor growth. Despite their abundance in many tumors, the origins and diversity of TAMs are not well understood, especially in pediatric brain tumors. Using single-cell RNA sequencing in a genetically engineered mouse model (Ptch+/-:p53-/-) of SHH-MB, we identified the dual microglia and monocytic origin of macrophage and their transcriptomic heterogeneity. We demonstrate differential recruitment and function of macrophages under distinct modalities of tumor therapy of molecular targeted hedgehog inhibition versus radiation. We additionally identify a monocytic macrophage population recruited post-radiation that is immune suppressive, suggesting a mechanism for radiation treatment failure. These insights uncover potential strategies for immunomodulation as adjunctive therapy for radiation.

TBIO-08. BASE-RESOLUTION METHYLOMES OF GLIOMAS BEARING HISTONE H3.3 MUTATIONS REVEAL A G34 MUTANT-SPECIFIC SIGNATURE SHARED WITH BONE TUMORS

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BACKGROUND: Two recurrent mutations, K27M and G34R/V, in H3F3A, encoding non-canonical histone H3.3, are reported in pediatric and young adult gliomas, whereas G34W mutation was prevalent in bone tumors. In contrast to K27 mutation, it remains elusive how G34 mutations affect the epigenome. Here we performed whole-genome bisulfite sequencing of four G34R-mutated gliomas and the G34V-mutated glioma cell line KNS-42. Similarly, we analyzed seven and three gliomas harboring K27M and no mutations in H3F3A, respectively. These data were compared with those on bone tumors. RESULTS: G34R-mutated gliomas exhibited lower global methylation levels, similar CpG island (CGI) methylation levels, and compromised hypermethylation of telomere-proximal CGIs compared with those bearing K27M and no mutations. Hypermethylated regions specific to G34R-mutated gliomas were enriched for CGIs, including those of OLIG1, OLIG2, and canonical histone genes in the HIST1 cluster. These CGIs were hypermethylated in osteosarcomas with, but not without, the G34W mutation. In KNS-42 cells, CGIs with G34V-mutated histone H3.3 exhibited higher methylation levels than those with wild-type histone H3.3. This effect was also observed in the G34R-mutated glioma samples. CONCLUSIONS: Gliomas bearing G34R/V mutations display characteristic methylomic alterations, some of which are shared by osteosarcomas with the G34W mutation. Deposition of G34 variants may lead to elevated methylation of otherwise hypomethylated, histone H3.3-bearing CGIs.

TBIO-09. *IN SILICO* ANALYSIS IDENTIFIES A PUTATIVE CELL-OF-ORIGIN FOR *BRAF* FUSION-POSITIVE CEREBELLAR PILOCYTIC ASTROCYTOMA

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Childhood cancers are increasingly recognized as disorders of cellular development. This study sought to identify the cellular and developmental origins of cerebellar pilocytic astrocytoma, the most common brain tumor of childhood. By leveraging publicly available gene expression data from such tumors and controlling for driver mutations, a set of eight known neuro-developmental genes were identified as being upregulated in cerebellar pilocytic astrocytoma. Mapping those genes onto mouse neurodevelopmental atlases identified significant overlap in their expression within the ventricular zone of the cerebellar anlage. Further analysis with a single cell RNA-sequencing atlas of the developing mouse cerebellum defined this overlap as occurring in ventricular zone progenitor cells at the division point between GABA-ergic neuronal and glial lineages, a developmental trajectory which closely mirrors that previously described to occur within pilocytic astrocytoma cells. Furthermore, ventricular zone progenitor cells and their progeny exhibited evidence of MAPK pathway activation, the paradigmatic oncogenic cascade known to be active in cerebellar pilocytic astrocytoma. Gene expression from developing human brain atlases recapitulated the same anatomic localizations and developmental trajectories as those found in mice. Taken together, these data suggest this population of ventricular zone progenitor cells as the cell-of-origin for *BRAF* fusion-positive cerebellar pilocytic astrocytoma.

TBIO-11. DEEP LEARNING-BASED SINGLE-CELL RNA SEQUENCING DIFFERENTIATION IDENTIFIES SIMPLE AND COMPLEX TRANSCRIPTIONAL NETWORKS FOR SUBPOPULATION CLASSIFICATION

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BACKGROUND: Genomic assays capable of cellular resolution (i.e. scRNA-seq) are becoming ubiquitous in biomedical research. Machine learning, and the subtype known as Deep Learning, have broad application within scRNA-seq analytics. However, methods to facilitate the classification of cell populations are lacking. We present the novel computational framework HD Spot, which generates interpretable and robust Deep Learning classifiers that enable unbiased interrogation of linear and non-linear genomic signatures. METHODS: HD Spot is written in python and relies on Google's TensorFlow2 deep learning framework. Four datasets of immune cells were obtained from the publicly available Seurat repository, generated using the 10X chromium platform. Data preprocessing used standard Seurat methodology. HD Spot generated optimized classifiers via a custom platform. Network interpretability was achieved using Shapley values. Ontology analysis was performed using Metascape. RESULTS: HD Spot identified meaningful ontologic signatures across all tested datasets. In the binary case of control versus IFN-B stimulated CD4+ T cells, gene ontologies reflected T_{h0} and T_{h2} T cell populations, congruent with T cell activation. In the 9-class case of PBMCs, HD Spot identified meaningful gene networks characteristic of the ground-truth populations using raw feature counts alone. When feature counts are processed into expression values, HD Spot demonstrates increased specificity of top genes and respective ontologies between subpopulations. CONCLUSION: This work introduces a broadly applicable computational tool for the advanced bioinformatician to decipher complex cellular heterogeneity (e.g., tumors) in an unbiased way. Additionally, HD Spot lowers the barrier for novice bioinformaticists to derive actionable insights from their data.

TBIO-12. THE SPECTRUM OF MITOCHONDRIAL DNA (MTDNA) MUTATIONS IN PEDIATRIC CENTRAL NERVOUS SYSTEM (CNS) TUMORS

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To explore the role of mitochondrial DNA mutations in pediatric CNS tumors, we analyzed 749 tumor-normal paired whole genome sequencing data sets from the Children's Brain Tumor Tissue Consortium (CBTTC). We detected 307 somatic mtDNA mutations in 222 CNS tumors (29.6%). Most frequently observed were missense mutations (38.1%). We also detected 34 loss-of-function mutations. Different pediatric CNS tumor subtypes have distinct mtDNA mutation profiles. For categorical comparisons, we analyzed subtypes with at least 15 samples. The highest number of mtDNA mutations per tumor sample was in meningiomas (0.85), while atypical teratoid rhabdoid tumors (ATRTs) had the lowest number per sample (0.18). High-grade gliomas had a higher number of mtDNA mutations per sample than low-grade gliomas (0.56 vs. 0.31) ($p = 0.0011$), with almost twice as many missense mtDNA mutations per sample (0.22 vs. 0.13) ($p < 0.001$), and higher average heteroplasmy levels (11% vs. 9%). The average heteroplasmy was 10.1%, ranging from 15.6% in medulloblastoma to 6.36% in schwannoma suggesting that these are clonal alterations and not artifacts. Intriguingly, the two chordoma patients in the CBTTC database had an identical heteroplasmic m.10971G>A *MT-ND4* nonsense mutation. Similarly, our patient with recurrent gliofibroma harbored the same somatic *MT-ND4* synonymous variant (m.10700A>G) detected at 53% heteroplasmy in the initial tumor, 79% in the first recurrence, and 97% in the second recurrence. Although the functional consequences of these alterations are not yet understood, our findings suggest that sequencing the mtDNA genome may be used to characterize CNS tumors at diagnosis and monitor disease progression.

TBIO-13. USE OF NEXT GENERATION SEQUENCING TO IDENTIFY MOVE DRIVERS OF CRYPTIC, CLINICALLY AGGRESSIVE BRAIN TUMORS

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INTRODUCTION: Next generation sequencing (NGS) is an emerging technology which allows for in-depth analysis of pediatric brain tumors. NGS has particular use in the context of ambiguous or aggressive neoplasms, where it can be leveraged to discover novel drivers, inform pathologic classification, and direct targeted therapies. OBJECTIVE: The objective of this case series was to utilize NGS technology to illuminate the biology of aggressive brain tumors with ambiguous pathologic features and clinically aggressive behavior. METHODS: FFPE tumor tissue and matched germline DNA were subjected to whole exome sequencing (WES). Data were analyzed according to the GATK pipeline. RESULTS: The first case is a 6-year-old male who presented with innumerable foci of leptomeningeal nodules throughout the neuroaxis. Original pathology was CNS embryonal tumor. WES identified loss of chromosome 1p and 16q with gain of 1q and amplification of *MYC* and *OTX2* loci (cytogenetic aberrations characteristic of group 3 medulloblastoma) and a deleterious mutation in *BCL7B*, a known tumor suppressor gene. The second case is a 2-year-old female who presented with a parietal lobe mass diagnosed as high grade neuroepithelial tumor with *C11orf95* translocation, but no *RELA* fusion. WES revealed loss of small region of chromosome 2p and mutations in *IDH3G, TRAF2,* and *JMJD1C*, suggesting novel targets for further study. CONCLUSIONS: In both cases, NGS studies were able to shed light on the underlying tumor biology and/or refine the pathologic diagnosis. These data underscore the utility of applying NGS technology to study the biology of pediatric brain tumors.

TBIO-14. CHARACTERISATION OF THE ARGININE PATHWAY ENZYMES IN PAEDIATRIC BRAIN TUMOURS TO DETERMINE SUSCEPTIBILITY TO THERAPEUTIC ARGININE DEPLETION

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INTRODUCTION: Extracellular arginine dependency (auxotrophy) is increasingly being recognised in several tumours. This is due to the inability of cancer cells to recycle or synthesise intracellular arginine through the urea cycle pathway compared to normal cells. Whilst adult glioblastoma is known to exhibit this, the expression of the arginine pathway enzymes has not been delineated in paediatric brain tumours. METHODS: We used immunohistochemical methods to stain for arginine pathway enzymes in Paediatric High grade glioma (pHGG), low grade glioma (pLGG) and medulloblastoma (MB) tumour tissue microarrays (TMAs). The antibodies detected protein expression of the metaboliser Arginase (Arg2), recycling enzymes ornithine transcarbamoylase (OTC), Arginosuccinate synthetase (ASS1) and arginosuccinate lyase (ASL) as well as the transporter SLC7A1. RESULTS: Deficiency of OTC, ASS1 and ASL were seen in 92%, 98% and 93% of pHGG samples (n=156) respectively, with deficiency defined as low (<20%) or negative antibody expression. Identical results were seen in pLGG (n=98) - 83%, 97% and 95% were deficient in OTC, ASS1 and ASL. Both pHGG and pLGG highly expressed SLC7A1 and Arg2, demonstrating that they could transport and utilise arginine. In MB (n=82), this auxotrophic signature was again seen in 90% of TMAs with absent or low expression of OTC, ASS1 and ASL and high Arg2 and SLC7A1 expression. CONCLUSIONS: These results show that pHGG, pLGG and MB are arginine auxotrophs. Pegylated arginase (BCT-100) is currently in Phase I/II trials in relapsed pHGG. Our results suggest that therapeutic arginine depletion may also be useful in MB and pLGG.

TBIO-15. MODELING DEVELOPMENTAL GENE EXPRESSION DYNAMICS AT CELLULAR RESOLUTION TO INTERPRET PEDIATRIC BRAIN TUMOR TRANSCRIPTIONAL PROGRAMS

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A central challenge in understanding the biology of pediatric brain tumors is defining the cellular and molecular context where oncogenesis occurs. We hypothesize that spatiotemporally restricted cell types are uniquely susceptible to specific genetic alterations, which alter normal neurodevelopmental programs and ultimately lead to oncogenesis. The resulting tumors retain some transcriptomic features of their lineage of origin. To delineate these origins, we assembled a densely sampled developmental time course of the mouse forebrain and pons, doubling our recently published single-cell atlas. This dataset comprises >100,000 cells at 9 timepoints from E10-P6. However, while single cell transcriptomics reveal rich gene dynamics during cell differentiation, interpretation of individual genes can be challenging due to data sparsity. Leveraging this time-series, we present strategies to model and visualize the expression of a given gene across differentiation of distinct lineages. We demonstrate an interactive web app to interrogate the expression of genes or gene sets during brain development, extract temporally correlated genes, and search active transcription factor regulatory modules. Finally, we profile the expression of core transcriptional programs of several pediatric brain tumor entities during development. Our analyses reveal genes with restricted expression patterns that elucidate tumor etiology. More broadly, these resources harness single cell data to enable exploration of neurodevelopmental gene programs with great relevance to pediatric brain tumor oncogenesis.

TBIO-16. NOTCH1 PATHWAY AS TARGET FOR DRUG INTERVENTION FOR HISTONE 3 G34R MUTATED PHGG

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There have been no significant improvements in the treatments for childhood High-Grade Glioma (pHGG) and Diffuse Intrinsic Pontine Glioblastoma (DIPG), which continue to have a very poor prognosis. These cancers harbor mutations affecting histone 3 (H3) proteins; 80% of DIPGs with histone H3 K27M somatic mutations whilst 30% of pHGGs exhibit H3.3 G34R or G34V mutations. We have generated and validated a histone 3.3 G34R mutant-specific antibody and investigated the downstream effects of H3.3 G34R mutations in pHGG. In order to identify the genes that may be deregulated by G34R mutant histone expression, we have performed chromatin immunoprecipitation (ChIP) assays with our H3.3 G34R and wild type H3 antibodies, using pHGG H3 G34R mutant and wild-type cell lines. Initial analyses of ChIP data have implicated deregulation of cell-signaling pathways including Notch1, Hedgehog, PPAR-1, PLC-beta and Androgen, in H3 G34R mutated pHGG. We are currently determining the effects of altered expression of Notch1 pathway components on tumorigenesis of H3 G34R mutated pHGG, through gene and protein expression and inhibition assays. Specifically we find that the Notch1 pathway component HES1 shows increased expression in G34R mutant cells compared to controls, directing our evaluation of the utility of gamma-secretase inhibitors as potential therapeutics. These analyses may underpin development of novel treatment strategies for H3 mutated pHGG.

TBIO-17. INTEGRATIVE ANALYSES OF BRAFV600E MUTATED GLIOMAS: FROM MOLECULAR BIOLOGY TO RADIOLOGY AND TREATMENTS

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BRAFv600e mutation is encountered mostly in low-grade pediatric gliomas (LGG) and epileptogenic glioneuronal tumors, such as gangliogliomas (GG). Less frequently this mutation is present in high-grade glial (HGG) or glioneuronal tumors. Recent publications were highlighting BRAF mutation and CDKN2A deletion, as independent prognostic factors linked to a worst outcome in LGGs. We studied retrospectively a monocentric cohort of 12 LGGs (9 GG and 3 pilocytic astrocytomas) and 9 HGG (5 "de novo" tumors and 4 with a long past of LGG evolution) with BRAFv600e positivity. The patients were aged from 1 to 47 years. LGGs were under 20 years and only 3 patients with HGGs had less than 18 years. We focused on extended tumors' biology assessment by DNA single-cell analyses, RNAsequencing, NGS, metabolomics, radiology (MRI, PET-scanning and spectroscopy) and correlated them to tumor's data. One LGG had a CDKN2A deletion. Six had a complete surgical resection, 2 had a minimal residue and 4 had chemotherapies after partial surgery and relapsed. All HGGs had a surgical resection followed by chemotherapy and radiotherapy and additional CDKN2A deletion. Two pediatric HGGs relapsed rapidly. Only one benefited positively from targeted therapy. Specific radiological and spectroscopic signs were linked to the BRAF mutation itself and those different groups (LGGs, HGGs and LGGs with long term evolution of HGG), where specific molecular pathways and metabolomic profiles are associated. Currently, we are going further in the correlations to be able to predict in LGG their potential long-term evolution, where MAPK pathway modulations might be involved.

TBIO-18. ESTABLISHING A PIPELINE FOR INDIVIDUALIZED TREATMENT OPTIONS FOR PEDIATRIC BRAIN CANCER

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INTRODUCTION: Despite being able to characterize pediatric brain tumors such as medulloblastoma and high-grade gliomas using detailed molecular analysis tools, this knowledge hasn't been translated to better treatment methods. In this project, we aim to create a biobank of pediatric brain tumors (PBTs), characterize samples using next generation molecular diagnostics and identify patient specific drug-treatment options using high-throughput drug screening (HTDS). METHODS: To establish tumor spheres from biopsies, we mechanically dissociated the tissue and digested it in trypsin. The cells isolated were cultured in serum free DMEM medium. Immunocytochemistry analysis was done to compare the spheres and original tumor. After the second passage, DNA was extracted and subjected to low-pass whole genome nanopore sequencing. HTDS with a library of FDA/EMA-approved anticancer drugs and investigational compounds was also performed. RESULTS: We've established tumor sphere cultures that grew to passage two and onwards from five juvenile pilocytic astrocytomas, two gangliogliomas and two midline gliomas. The spheres expressed markers of stem cells (Nestin), neurons (β3-tubulin) and glial (GFAP), similar to the original tumor. Copy number profiling and methylation-based classification of the spheres showed the same alterations and classification as the biopsy. HTDS revealed significant differences in drug sensitivity including patient-specific vulnerabilities to anticancer drugs. CONCLUSION: We've created a protocol to generate tumor spheres from PBTs. We are also building a biobank comprising high and low grade PBTs. Our tumor spheres maintain the characteristics of the original tumor and can be used for further downstream analysis including drug screening.

TBIO-19. INTEGRATED GENOMIC, PROTEOMIC AND PHOSPHOPROTEOMIC ANALYSIS OF SEVEN TYPES OF PEDIATRIC BRAIN CANCER

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We performed a comprehensive proteogenomic analysis across seven childhood brain tumors for a deeper understanding of their functional biology. Whole genome sequencing, RNAseq, quantitative proteomic profiling and phosphoproteomics were performed on 219 fresh frozen tumor samples representing the histologic diagnoses of: low grade astrocytoma (93), ependymoma (32), high grade astrocytoma (26), medulloblastoma (22), ganglioglioma (18), craniopharyngioma (16) and atypical teratoid rhabdoid tumor (12). Unsupervised clustering analysis based on proteomics data reveals eight clusters with distinct protein profiles and pathway activities. While some clusters coincide with histologic diagnoses, a couple of clusters appear to be a mixture of different diagnoses, including one cluster consisting of "aggressive" tumors characterized by poor survival and high stemness scores. By integrating proteomic data with RNAseq and WGS data, we characterize the impact of mutations (H3K27M, BRAFV600E, BRAF fusion) and CNVs upon the proteome across various diagnoses. Multiomics based kinase-substrate association analysis and co-expression network analysis reveal targetable active kinase networks within these tumors. Proteomic data reveals unique biology associated with H3K27M mutation status in HGG and BRAF aberrations in LGG. Characterization of the tumor microenvironment through deconvolution analyses based on multi-omics data reveals 5 distinct tumor clusters associated with different populations of infiltrating immune cells and the relative activity of the immune system based upon the expression of pro-inflammation or immunosuppressive markers. This study reports the first large-scale deep comprehensive proteogenomic analysis crossing traditional histologic boundaries to uncover foundational pediatric brain tumor biology including functional insight that helps drive translational efforts.

TBIO-21. LNC-TALC PROMOTES O^6-METHYLGUANINE-DNA METHYLTRANSFERASE EXPRESSION VIA REGULATING THE C-MET PATHWAY BY COMPETITIVELY BINDING WITH MIR-20B-3P

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Long noncoding RNAs (lncRNAs) have emerged as new regulatory molecules implicated in diverse biological processes, including therapeutic resistance. However, the mechanisms underlying lncRNA-mediated temozolomide (TMZ) resistance in glioblastoma (GBM) remain largely unknown. To illustrate the role of lncRNA in TMZ resistance, we induce TMZ resistant GBM cells, perform a lncRNA microarray of the parental and TMZ-resistant cells, and find an unreported lncRNA in GBM, lnc-TALC (temozolomide-associated lncRNA in glioblastoma recurrence), correlated with TMZ resistance via competitively binding miR-20b-3p to facilitate c-Met expression. A phosphorylated AKT/FOXO3 axis regulated lnc-TALC expression in TMZ-resistant GBM cells. Furthermore, lnc-TALC increased MGMT expression by mediating the acetylation of H3K9, H3K27 and H3K36 in MGMT promoter regions through the c-Met/Stat3/p300 axis. In clinical patients, lnc-TALC is required for TMZ resistance and GBM recurrence. Our results reveal that lnc-TALC in GBM could serve as a therapeutic target to overcome TMZ resistance, enhancing the clinical benefits of TMZ chemotherapy.

TBIO-24. USING MOLECULAR GUIDED THERAPY IN PEDIATRIC NEURO ONCOLOGY PATIENTS: THE SUCCESS AND BARRIERS

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Remarkable advances have been made in pediatric brain tumor treatments, however many of these children suffer significant side effects from standard chemotherapy-based treatment. Recent advances in precision medicine offer great hope to pediatric patients in terms of improved therapeutic precision, safety, and efficacy. However, there are barriers to implementing precision medicine that are best approached from a multidisciplinary perspective. The goals of the Riley Hospital for Children at Indiana University Health Precision Genomics Neuro Oncology program are to optimize the treatment of children by assessing children's cancers for actionable molecular targets and finding available, affordable therapies that treat those actionable targets. Children are referred to the Riley Precision Genomics Neuro Oncology program at the time of diagnosis or with relapse. Tumor tissue is tested for somatic and germline findings. Riley's Precision Genomics Neuro Oncology program has received 55 patient referrals. Of these 55 patients, 46 (84%) had molecular analysis completed, and the results of 40 (87%) patients indicated actionable tar-

gets. Of the 40 patients with results, 23 (58%) patients went on to receive genomics guided therapy. Limited availability of tissue has accounted for 6 (13%) patients' lack of results. Many guided therapy options are oral medications, which positively impact patient's quality of life. The learner will increase their knowledge of how molecular guided therapy is now innovatively being used to treat children with cancer, and the challenges involved.

TBIO-26. NON-CANONICAL OPEN READING FRAMES ENCODE FUNCTIONAL PROTEINS ESSENTIAL FOR CANCER CELL SURVIVAL

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The brain is the foremost non-gonadal tissue for expression of non-coding RNAs of unclear function. Yet, whether such transcripts are truly non-coding or rather the source of non-canonical protein translation is unknown. Here, we used functional genomic screens to establish the cellular bioactivity of non-canonical proteins located in putative non-coding RNAs or untranslated regions of protein-coding genes. We experimentally interrogated 553 open reading frames (ORFs) identified by ribosome profiling for three major phenotypes: 257 (46%) demonstrated protein translation when ectopically expressed in HEK293T cells, 401 (73%) induced gene expression changes following ectopic expression across 4 cancer cell types, and 57 (10%) induced a viability defect when the endogenous ORF was knocked out using CRISPR/Cas9 in 8 human cancer cell lines. CRISPR tiling and start codon mutagenesis indicated that the biological impact of these non-canonical ORFs required their translation as opposed to RNA-mediated effects. We functionally characterized one of these ORFs, *G029442*—renamed *GREP1* (Glycine-Rich Extracellular Protein-1)—as a cancer-implicated gene with high expression in multiple cancer types, such as gliomas. GREP1 knockout in >200 cancer cell lines reduced cell viability in multiple cancer types, including glioblastoma, in a cell-autonomous manner and produced cell cycle arrest via single-cell RNA sequencing. Analysis of the secretome of GREP1-expressing cells showed increased abundance of the oncogenic cytokine GDF15, and GDF15 supplementation mitigated the growth inhibitory effect of *GREP1* knock-out. Taken together, these experiments suggest that the non-canonical ORFeome is surprisingly rich in biologically active proteins and potential cancer therapeutic targets deserving of further study.

TBIO-27. RASOPATHIES AND BRAIN TUMOROGENESIS: ARE SOS1 MUTATIONS ARE CONCERNED?

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Germ line gain-of-function mutations in several members of the RAS/MAPK pathway, including PTPN11 are associated with signalopathies named Rasopathies and known as Noonan syndrome and closely related conditions. Patients harboring Rasopathies are at increased risk of myeloproliferative diseases and solid tumors, such as neuroblastoma. Mutations of SOS1, the gene encoding a guanine nucleotide exchange factor for Ras, represent the second most frequent genetic defect in Rasopathies. However, SOS1 mutations are rare in human malignancies and patients with germline SOS1 mutations may not be at increased risk of developing cancer. Here, we report a SOS1 variant found to segregate in a Tunisian pedigree with many members affected by brain tumors as well as epileptic disorder. During our genetic counselling for congenital heart diseases, a 9-year-old female born at Sfax from a consanguineous couple and having pulmonic valvular stenosis, has been investigated at the molecular level. Screening of mutations in the entire coding sequence of PTPN11, Braf and SOS1, was conducted using HRM analysis and bidirectional sequencing. Heterozygous single nucleotide substitution of SOS1 gene: c.1655 G>A was confirmed. This mutation affected the PH-REM linker domain with substitution of residue Arg552 to Lys: p.Arg552Lys. This mutation accounts for one-third of all mutations reported in SOS1 during Rasopathies. Although no other molecular exploration was done, family history revealed other affected children by neurodevelopmental and epileptic conditions as well as recurrent brain malignancies in the paternal family. Two aunts developed blindness and then died subsequently to tumor progression.

VIRAL/GENE THERAPY AND OTHER NOVEL THERAPIES

THER-01. AWAKING THE IMMUNE SYSTEM WITH AN IMMUNO-ONCOLYTIC VIRUS AS A THERAPEUTIC STRATEGY FOR DIPGS

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Diffuse intrinsic pontine glioma (DIPG) is an aggressive brain tumour, being the leading cause of paediatric death caused by cancer. Despite all the advances made regarding effective therapies, the survival is dismal. Our lab has engineered the oncolytic virus Delta-24-ACT armed with the costimulatory ligand 41BBL in order to increase the antitumoral effect of the adenovirus. 41BB is a costimulatory receptor which promotes the expansion of activated T cells and the generation and maintenance of CD8 T memory cells. Therefore, we propose the use of Delta-24-ACT as a therapeutic approach for DIPG tumours. We observed that Delta-24-ACT is able to infect and replicate in NP53 and PDGFB-driven, two DIPG murine cell lines. Furthermore, 41BBL is expressed in the membranes of the infected cells and results with immunogenic cell death as shown by the different DAMPs. Injection of Delta-24-ACT in DIPG model was safe, showed no sign of toxicity and led to a significantly increase in the median overall survival, generating anti-glioma memory in long-term survivors. Mechanistic experiments, showed an increase of T cell infiltration (mainly CD8), decrease of proliferating cells and a reduction of the number of vessels in FFPE brain samples in the treated mice. We are currently performing nanostring analyses to assess the changes in the transcriptional immune phenotype of treated versus control mice. In summary, our data suggest that Delta-24-ACT is safe and induces a potent antitumor immune response in DIPG models mainly based in the activation of CD8 lymphocytes recruited by the viral activity.

THER-02. EVALUATION OF THE ONCOLYTIC VIRUS DELTA24-RGD AS AN ANTI-TUMOR AGENT IN PRECLINICAL MODELS OF LOCALIZED AND DISSEMINATED AT/RT

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Current therapies for atypical teratoid/rhabdoid tumors (AT/RTs) are suboptimal, resulting in a 2-year OS below 20% and the development of severe side effects. Therefore, we need to explore alternative therapeutic approaches for this disease. Since the virus Delta24-RGD has already demonstrated its efficacy and safety as a therapeutic agent for brain tumors, including pediatric patients, here we propose to evaluate the anti-tumor effect of Delta24-RGD in AT/RT. In vitro, Delta24-RGD infects and replicates in AT/RT cultures followed by oncolysis, obtaining IC_{50} values below 1 PFU/cell. In vivo, a single local injection of Delta-24-RGD in three infratentorial AT/RT models (BT-12, CHLA-06 and CHLA-266) extended significantly the median OS (50 to 78 days BT-12; 21 to 31 days CHLA-06; 64 to 110 days CHLA-266). Delta-24-RGD also increased the survival of mice bearing supratentorial CHLA-266 tumors (from 93 to 132 days). Next, we evaluated the efficacy of Delta24-RGD in a model mimicking metastatic disease through intraventricular injection of BT-12-luciferase cells. Administration of Delta24-RGD inhibited tumor growth and development of metastases, leading to an increased OS and nearly 70% of long-term survivors. The interaction between Delta24-RGD and the immune system was evaluated in humanized mice models bearing CHLA-06. In this model, Delta24-RGD treatment extended OS (from 23 to 34 days) and we characterized the anti-tumor immune landscape in control and Delta24-RGD treated mice by transcriptional and functional analyses. These results underscore the potential of Delta24-RGD as a promising therapeutic choice for patients affected by AT/RT.

THER-03. IN VITRO EVALUATION OF THE EFFECT OF CANNABIDIOL ON PAEDIATRIC BRAIN TUMOUR CELL LINES USING A PULSED TREATMENT REGIME

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Paediatric brain tumours are the second most common cancer after haematological malignancies. Intermittent dosing regimens are typical for chemo-

therapy drugs in order to avoid excessive damage to organs and avoid the onset of late effects. Cannabidiol (CBD) has been shown to have cytotoxic properties on paediatric brain tumour cell lines. Although CBD is far less toxic and damaging than the classical chemotherapy options which are currently available to children suffering with brain tumours, there are some possible side effects. Given that the half-life of the drug is 24 hours, it was important to establish the nature of the effect of cumulative dosing on top of the remaining drug in the system. The pHGG cell line, SF188 was cultured in different concentrations of CBD with either 1, 2 or 3 doses being given on consecutive days. 24 hours after the last dose the cells were analysed using the resazurin assay. It was observed that the amount of drug required for an EC_{50} to be obtained decreased; 17.6μM (1 dose), 8μM (2 doses), 5μM (3 doses) and that cell survival was reduced to nearly 0% in those cells which received multiple does of CBD at 17.6μM. In order to mimic the intermittent dosing regime, the cells were returned to the incubator for 4 days before the resazurin assay was repeated. The decrease in viability was maintained over the extended culture period meaning that the ability of even the apparent "healthy" cells to proliferate had been permanently affected.

THER-04. IS THERE A ROLE FOR CANNABIDIOL IN THE TREATMENT OF CHILDHOOD BRAIN TUMOURS?

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Brain tumours are the leading cause of cancer related death in children with limited treatment options and high recurrence rates. Recent evidence suggests there may be anti-tumoral properties of cannabinoids, and of cannabidiol (CBD) in particular. We evaluated the effect of CBD on paediatric brain tumour cell lines in 2D and 3D spheroids; pHGG (SF188), ependymoma (BxD-1425EPN) and human astrocytes. At the CBD EC_{50} concentration, astrocytic cell death was insignificant. 3D spheroids decreased in size by approximately 20% when cultured in CBD compared to cells only after 5-day exposure. Cell death increased with time after a single dose of CBD. Western Blot showed an increase in Lc3b expression (autophagy) after 24 hours incubation (early cell death) with CBD in both BxD-1425EPN and SF188 with PARP expression (apoptosis) increased after 5 days incubation (late cell death). Cell cycle analysis showed a decrease of cells in G_1 and no change in G_2 indicating cell cycle arrest. In hypoxia, SF188 and BxD-1425EPN cells showed decreased cell death after 24 hours and 5 days when compared to normoxia and an EC_{50} within acceptable limits could not be achieved. SF188 cells pre-treated with receptor antagonists indicate that CBD was not acting through CB_1, CB_2, GPR18, PPARα or PPARγ receptors but may act as a partial agonist of the TRPV1 and 5-HT_{1A} receptors and a full agonist of the GPR55 receptor (resazurin assay). This provides evidence that CBD is effective at killing paediatric brain tumour cells and does not have a significant effect on normal astrocytes.

THER-05. GENETICALLY STABLE POLIOVIRUS VECTOR CARRYING H3.3K27M ANTIGEN FOR TREATMENT OF DIFFUSE MIDLINE GLIOMA BY INTRAMUSCULAR INJECTION

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BACKGROUND: H3 K27M-mutant diffuse midline glioma (DMG) is invariably lethal. Viruses naturally engage innate immunity, induce antigen presentation, and mediate CD8 T cell priming against foreign antigens. Polioviruses, in particular, are uniquely tropic for dendritic cells (DC) and potently activate DC, inducing Th1-dominant cytokine profiles, CD8 T cell immunity, and enhanced epitope presentation. Thus, poliovirus is ideally suited for vectored delivery of signature tumor neoantigens, e.g. the H3 K27M feature of DMG. However, poliovirus vector design is inherently limited by genetic instability and the underlying neuropathogenicity of poliovirus. METHODS: We created a genetically stable, polio:rhinovirus chimera vector devoid of neuropathogenicity and modified for stable expression of the HLA-A2 restricted H3.3 K27M antigen (RIPO (H3.3)). RESULTS: RIPO(H3.3) infects, activates, and induces H3.3K27M antigen presentation in DCs in vitro. Given intramuscularly in vivo, RIPO(H3.3) recruits and activates DCs with Th1-dominant cytokine profiles, efficiently primes H3.3K27M-specific CD8 T cells, induces antigen-specific CD8 T cell migration to the tumor site, delays tumor growth, and enhances survival in murine tumor models. CONCLUSION: This novel approach leverages the unique ability of polioviruses to activate DCs while simultaneously introducing the H3.3 K27M antigen. In this way, DCs are activated optimally in situ, while being simultaneously infected to express/present tumor antigen. RIPO(H3.3), given by intramuscular injection, will be evaluated in a clinical trial for children with H3 K27M-mutant diffuse midline glioma.

THER-06. THERAPEUTIC EFFICACY OF RRV-MEDIATED PRODRUG ACTIVATOR GENE THERAPY IN CLINICAL TRIALS OF RECURRENT HIGH-GRADE GLIOMA AND IN MURINE ORTHOTOPIC MODELS OF INTRACEREBRAL GLIOMA AND INTRACEREBELLAR MEDULLOBLASTOMA

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Toca 511, a clinical-stage tumor-selective retroviral replicating vector (RRV), encodes optimized yeast cytosine deaminase (CD), which converts the prodrug 5-fluorocytosine (5-FC) to the active drug 5-fluorouracil (5-FU) within infected cancer cells. In preclinical models of intracerebral glioblastoma, 5-FU generated locally by Toca 511 (RRV-CD) prodrug activator gene therapy has also been shown to kill immunosuppressive myeloid cells in the tumor microenvironment, leading to anti-cancer immune activation and long-term survival. Early-phase clinical trials of Toca 511 in recurrent high-grade glioma showed highly promising evidence of therapeutic benefit, leading to a Phase III trial completed in late 2019 (n=400 patients, randomized 1:1 vs. standard chemotherapy), which appeared to show negative results overall. However, additional analysis showed possible efficacy in prespecified subgroups, and further clinical investigation is being pursued. In preclinical studies, we have also evaluated RRV for use in medulloblastoma, the most common malignant tumor of the pediatric nervous system. Both established and primary human medulloblastoma cell lines supported efficient RRV replication in vitro, with spread to >90% of cells by day 10 post-inoculation, and RRV-CD-transduced medulloblastoma cells showed significant dose-dependent reduction of viability upon exposure to 5-FC, compared to controls. In an intracerebellar HDMB03 medulloblastoma model, RRV-CD-treated mice exhibited long-term survival while on sequential cycles of 5-FC prodrug, until prodrug treatment was stopped, after which 25% long-term survival was observed (median survival 110 days) as compared to controls (median survival 28 days, 100% lethality) (p=0.00007). These results support further evaluation of RRV-mediated prodrug activator gene therapy for pediatric brain tumors.

THER-07. INHIBITION OF THE RAS SIGNALING ENHANCES VIRAL ONCOLYSIS IN MALIGNANT GLIOMAS

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Pediatric malignant glioma indicates rapid proliferation, widely infiltrative properties and resistance to various therapies, and carries a very poor prognosis. There are methods of using virus within novel therapies under development against malignant neoplasms, which have been studied for many years already. We examined the treatment with sunitinib or GW5074 to our experimental model of vaccinia virus therapy for malignant glioma, and then evaluated changes in the tumoricidal activity, the viral infectivity, and the impact on the Ras signaling pathway. Glioma cells (U251MG, LN229, LN18, rat C6) infected with vaccinia virus was fatal, in its course of death, apoptosis and autophagy were induced. The activity of Ras signaling in vaccinia-infected cells heightened in the early stage and declined in the late stage Inhibition of the Ras signaling pathway at the early stage of viral infection prevented vaccinia virus replication, while viral oncolysis was not inhibited when the pathway was blocked after sufficient viral spread. Glioma cells infected with vaccinia virus are led to cell death. Vaccinia virus regulates Ras or other survival signaling pathways in the infected cells. It enhances the signaling in the early stage (viral replicative period), however

suppresses in the later stage (virus-releasing stage). Inhibition of the Ras signaling pathway at the early stage of viral infection prevents vaccinia virus from replicating, while viral oncolysis appears to be accelerated when the pathway was blocked after sufficient viral reproduction.

THER-08. SGT53 – A NOVEL P53 NANOMEDICINE INDUCES SIGNIFICANT RESPONSES IN CHILDREN WITH RECURRENT MEDULLOBLASTOMA AND CHOROID PLEXUS CARCINOMA: A REPORT OF TWO CASES

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BACKGROUND: Abnormal p53 function commonly defines high-risk CNS tumors, but functional restoration has eluded investigators. SGT-53 is a targeted nanomedicine encapsulating a plasmid DNA encoding wild-type human p53 with a transferrin receptor-targeting scFv on the nanocomplex surface resulting in efficient delivery across the BBB and robust tumor binding/uptake. Data generated by collaborators demonstrated synergy with irradiation and chemotherapy. REPORT: Two children with recurrent CNS malignancies have been treated with SGT-53, each receiving greater than 50 infusions in combination with irradiation and chemotherapy with no grade 3/4 AEs positively attributed to SGT-53. The first was an 11yo male with recurrent disseminated p53+ SHH medulloblastoma, with bulky intracranial/thoracolumbar disease. He received irradiation followed by biweekly doses of SGT-53 and temozolomide, bevacizumab and irinotecan given one week out of four. This patient exhibited a complete response of all disease on his first follow-up scan 8 weeks after therapy initiation and remained in remission for 8 months. The second patient was a 3yo male with disseminated recurrent choroid plexus carcinoma. He received CSI with SGT-53, followed by SGT-53, temozolomide and irinotecan as described above, again with no related grade 3/4 AEs. He experienced a partial response to all sites of disease and completed therapy after six months, progressing 7.8 months after initiating treatment. CONCLUSIONS: SGT-53 was well tolerated in two heavily-pretreated patients despite aggressive combinatorial strategies. The majority of the AEs experienced were mild and manageable. Each patient had significant responses, suggesting that SGT-53 should be evaluated in a clinical trial for similar patients.

THER-09. ONCOLYTIC ADENOVIRUS, DNX-2401, FOR NAIVE DIFFUSE INTRINSIC PONTINE GLIOMAS: A PHASE I CLINICAL TRIAL

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The objective of this trial is to determine the safety, tolerability, and toxicity of DNX-2401 in newly diagnosed DIPG patients (NCT03178032) followed by radiotherapy. Secondary endpoints are overall survival at 12 months, percentage of responses and induced immune response against tumor. Tumor biopsy was performed through the cerebellar peduncle, followed by intratumoral injection of DNX-2401 (N=12). Three patients were treated with $1x10^{10}$vp and given the lack of toxicity we escalated to $5x10^{10}$vp. The procedure was well tolerated and reduced tumor volume was demonstrated in all patients after combined treatment (virus + radiotherapy). We performed molecular studies (RNAseq and the Oncomine Childhood Research Panel from Thermo Fisher). The immune cell composition of the biopsies pre-virus injection was assessed using multiplexed quantitative immunofluorescence. T cells were hardly detectable in these tumors while macrophages were abundant. Using a multiplexed TCR-sequencing mRNA-based assay to analyze 18 available paired pre- and post-treatment samples from the trial, we detected increased clonal T cell diversity following treatment with the virus. We also measured pre and post treatment neutralizing antibodies and their relationship with survival. Finally, we performed functional studies using 2 cell lines isolated from patients included in this trial to assess the response to the virus (infectivity, viability, T-cell recognition). In summary, the virus has shown safety and efficacy in some patients. The information obtained in this clinical study would aid understanding the response of DIPG patients to viral therapies and, therefore, to better tailor this strategy to improve the survival of these patients.

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