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