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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