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