Cells in both states were treated with different BH3-mimetics. Inhibition of metabolic activity was measured after 72 hours. Target expression was assessed by RT-qPCR and Western blot. On-target activity of BH3-mimetics was determined by immunoprecipitation (IP) of Bcl-xL/BAK. Results: BH3-mimetics with strong binding affinity for Bcl-xL (Navitoclax, A-1131852, A-1155463) showed selectivity for senescent cells in 2/3 models (DKFZ-BT66 and DKFZ-BT314) and acted in nanomolar ranges. IC_{50}s for Navitoclax (C_{max} 6600nM in patients) were 40nM (OIS) vs. 200nM (proliferation) and 170nM (OIS) vs. 3700nM (proliferation) in DKFZ-BT66 and DKFZ-BT314, respectively. Target engagement was evident in the Bcl-xL/BAK-IP, and target expression of Bcl-xL was similar in all models studied. The relative resistance of senescent DKFZ-BT308 despite on-target activity is currently being investigated. Conclusion: Senolytic treatment of PA with BH3-mimetics targeting Bcl-xL is a promising new strategy directly targeting the major senescent part of the tumor in clinically archivable concentrations. However, our data suggests that not all PAs may respond to treatment. The analysis of comparative gene expression analysis and BH3-profiling is ongoing to define predictive biomarkers.

LGG-12. SAFETY AND EFFICACY OF DUAL THERAPY WITH DABRAFENIB AND TRAMETINIB IN AN INFANT WITH BRAF V600E MUTANT INOPERABLE LOW GRADE GLIOMA

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Objective: To describe safety and efficacy of dual targeted therapy with dabrafenib (BRAFi) and trametinib (MEKi) in an infant with inoperable low grade glioma with BRAF V600E mutation. Introduction: Safety and efficacy of dual targeted therapy with BRAFi and MEKi for pediatric low grade glioma (pLGG) is currently being evaluated, however, infants are usually not included in these clinical trials. Case: We report a case of a 2-month-old male infant who presented with involuntary movements and gaze deviation concerning for seizures. MRI brain revealed a tumor involving the medulla, T2/FLAIR dimensions: 2.5 x 2.2 x 2.7 cm and drop metastases to the cauda equina. An EEG ruled out seizure activity. Tumor biopsy was performed revealing Ganglioglioma, WHO grade I. IHC and somatic next generation sequencing revealed BRAF V600E point mutation. Germline testing was negative. Due to tumor progression on traditional chemotherapy, compassionate use of dual targeted therapy with dabrafenib (5.25mg/kg/day divided twice daily) and trametinib (0.032mg/kg daily) was initiated at 4.5 months of age. The patient has tolerated dual therapy for nearly 1 year without significant toxicity with exception of grade I skin rash. In terms of functional outcomes, previously noticed vocal cord paresis has resolved and our patient with global developmental delay continues to make developmental gains, albeit slowly. On recent neuroimaging, pLGG has continued to grow T2/FLAIR dimensions: 3.5 x 3.5 x 3.7 cm, however, combination therapy has halted the rate of growth of this tumor. Conclusion: To our knowledge, our patient is the youngest to receive combination of BRAFi and MEKi. Tumor targeted therapy could be an important treatment option for infants with inoperable pLGG where aggressive surgery and radiation therapy are associated with significant morbidity. Multi-institutional clinical trials that include infants are needed to further comment on safety and efficacy of these agents.

LGG-13. PILOCYTIC ASTROCYTOMAS WITH NOVEL BRAF FUSIONS DEMONSTRATE MAPK PATHWAY ACTIVATION

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Background: Pilocytic astrocytomas (PAs) are the most common pediatric low-grade glioma subtype. Oftentimes, PAs demonstrate somatic genetic alterations, the most common being the *BRAF-KIAA1549* fusion, which results in constitutive activation of the MAPK pathway. Better understanding of the effects of other RAF fusions is necessary to determine the potential utility of MAPK-targeting therapies. Methods: Three patients presented to Children's Hospital Colorado and were ultimately diagnosed with PAs harboring previously unreported gene fusions identified as *FYCO-RAF1*, *CCTTNNBP2-BRAF*, and *SLC44A1-BRAF*. Utilizing immunohistochemistry, we stained novel samples and controls for ERK and pERK (phosphorylated ERK) to assess the activation of the MAPK pathway. PAs with known *BRAF-KIAA1549* fusions (4 samples) and normal brain tissue (5 samples) were used as positive and negative controls, respectively. We additionally performed RNA sequencing to better understand expression changes associated with these fusions, utilizing Metascape and GSEA (Gene Set Enrichment Analysis) for analysis. Results: Immunohistochemistry of negative control samples demonstrated less p-ERK than ERK (ratios of 0.6–0.9, mean 0.8). All samples with novel fusions demonstrated statistically significantly higher p-ERK expression compared to negative controls (ratios of 1.3–1.7, mean 1.4). These experimental samples also all fell within the p-ERK to ERK expression range of the positive control samples, which demonstrated the widest range of expression (ratios of 1.1–4.5, mean 2.2). Our molecular analysis further confirmed these results, with GSEA demonstrating positively upregulated MAPK and ERK pathways in 2 positive controls and 1 novel fusion sample. Metascape analysis emphasized overall similar gene expression between these samples, demonstrating many shared genes and functional pathways. Conclusions: We identified 3 previously unreported RAF fusions in PA that demonstrate activation of the MAPK pathway, although not as extensively as seen in some positive control samples with *BRAF-KIAA1549* fusions. MEK inhibition may be a useful therapeutic strategy in these tumors if targeted therapy is indicated.

LGG-14. PRESENTATION CHARACTERISTICS AND TREATMENT OUTCOMES FOR PEDIATRIC OPTIC PATHWAY GLIOMAS IN QATAR

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Objectives: To review the presentation characteristics and treatment outcomes for pediatric optic pathway gliomas (OPG) in Qatar. Methods: Retrospective review of data for children with OPG from January 2009 to February 2021. Presenting features, diagnostic imaging and indications for treatment were reviewed. Progression free survival (PFS) and overall survival(OS) were computed using standard statistical methods. Medical notes were also reviewed for visual outcomes. Results: Nineteen patients were diagnosed with OPG during the study period. There were 10 (52%) females. Median age was 29 months (range 6–186) months. Eleven (57%) tumors were related to neurofibromatosis Type 1 (NF-1). Nine (47%) of OPG were located in optic nerves, 5 (26%) were chiasmatic/suprasellar, while the remaining 5(26%) involved a combination of structures. Seven(36%) children presented with oculo-visual symptoms. Another 7 were diagnosed on screening imaging for NF-1. Seven(36%) children had debulking surgery/biopsy, while the remaining patients were diagnosed on neuro-imaging alone. Thirteen (68%) patients were treated with chemotherapy and 2 received additional radiotherapy. Indications for non-surgical treatment included visual impairment (46%) and large/progressive tumor (54%). Carboplatin based regimes were used as first line chemotherapy for 76 % of patients. Five (38%) patients required more than one lines of treatment. OS and PFS at 36 months were 100% and 48%. Baseline visual assessment showed 5 children each (26%) had unilateral and bilateral visual impairment, while 9 (48%) had normal vision. Of the 6 children receiving chemotherapy for visual impairment, 2 (33%) showed improvement. Of the 7 children treated for large/progressive tumors, 3 (42%) showed partial response, 2(28%) had progressive disease and 1 had stable disease after the first line therapy. Conclusions: Our results are in-keeping with international data for optic pathway gliomas. Early referral and diagnosis may improve visual outcomes for this group of tumors.

LGG-15. COMPREHENSIVE ANALYSIS OF MYB/MYB1-ALTERED GLIOMAS: A MULTI-INSTITUTIONAL EXPERIENCE OF 33 GLIOMAS

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Background: Pediatric diffuse gliomas harbor recurrent genetic alterations, including those in *MYB* and *MYBL1*. Regardless of histopathologic classification, low-grade diffuse gliomas with *MYB/MYBL1* alterations represent a single disease entity. Additional insight is needed to define optimal therapeutic strategies for these tumors. Methods: We retrospectively reviewed gliomas with *MYB* or *MYB1L* alterations treated or referred for pathologic review at St. Jude Children's Research Hospital (St. Jude). Tumor specimens were centrally reviewed. Molecular characterization and clinical data were collated from St. Jude and referring institutions. Results: Thirty-three patients were identified. Two tumors had *MYBL1* alterations, while 31 had *MYB* alterations. *MYB-QKI* fusion was the most common alteration. Eighteen (55%) were male. The median age at diagnosis was 5 years (range, 0–40 years). Most tumors were in the cerebral cortex (22/33), and the most common presentation was seizures (16/33). Three patients (9%) presented with hydrocephalus and required cerebrospinal fluid diversion. Two patients (6%) presented with metastatic disease. Gross-total resection was achieved in 15 patients (45%).

Of the 7 patients receiving cytotoxic chemotherapy, no substantial response was observed. Of the 6 patients who received RT, one had disease progression. The median follow-up was 5.9 years. The 5-year event-free survival was 88.1%, while the 5-year overall survival was 96.3%. Two patients died, one of unclear cause and one of treatment-related acute myelogenous leukemia. Using log-rank tests, no difference in outcomes was observed based on molecular characteristics, degree of resection, metastatic status, or treatment modality. Conclusions: Although tumors with *MYB* and *MYBL1* alterations present with varying molecular and clinical features, they represent a group of tumors with favorable outcomes. Further characterization is required to identify the subgroup of tumors with a higher propensity for progression.

LGG-16. TO BE PRECISE - KNOW YOUR TARGETS: INSTITUTIONAL EXPERIENCE WITH TUMOR TARGETED THERAPY FOR RECURRENT/PROGRESSIVE PEDIATRIC LOW-GRADE GLIOMA AND PLEXIFORM NEUROFIBROMA

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Introduction: The oncogenic drivers of pediatric CNS tumors are rapidly being identified with the implementation of high throughput genetic screening. Precision medicine approaches to treatment have shown promising results, but data remains limited in the community oncology setting. We aim to describe our institutional experience using targeted therapies for plexiform neurofibroma and recurrent/progressive pediatric low-grade glioma (pLGG). Methods: We performed a retrospective chart review of all patients treated with tumor targeted therapies for recurrent/progressive pLGG and plexiform neurofibroma over the past 5 years. Results: Ten patients treated with tumor targeted therapies were identified. Regimens included combination Dabrafenib and Trametinib (n=3), Trametinib monotherapy (n=2), Selumetinib (n=3), Vemurafenib (n=1), and Larotrectinib (n=1). Median age at therapy initiation was 11.5 years (range 1.1 - 18 years). Tumor molecular status included BRAFV600E mutation (n=4), NF1 mutation (n=2), KIAA1549-BRAF fusion (n=1), NACC-NTRK fusion (n=1), and FGFR1 mutation (n=1). Patients trialed an average of 2 treatment regimens prior to targeted therapy initiation (range 0–5). Mean duration of therapy was 14.5 months (range .5–33 months) with 8 patients remaining on treatment. Based on modified RANO criteria, responses included partial (n=1), stable disease (n=8), and progressive disease (n=1). Progressive disease was noted after 4 months of treatment with Dabrafenib and Trametinib combination therapy, but rate of tumor growth was decreased. Subjective functional improvement was seen in 50% of patients. The most common toxicities included rash (n=5) and pyrexia (n=2). Trametinib was discontinued in one patient due to intra-tumoral hemorrhage of unclear etiology. Conclusion: Treatment of pediatric CNS tumors with targeted agents appears to be feasible and efficacious in the community oncology setting. Multi-institutional clinical trials are currently ongoing for each of these therapies. There remains a need for community oncology institutional data regarding their use.

LGG-17. CLINICAL OUTCOME OF PEDIATRIC LOW GRADE GLIOMA WITH POSITIVE BRAF-FUSION TREATED WITH MEK INHIBITOR

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Background: Low grade glioma (LGG) is the most common central nervous system (CNS) tumor in children. Some are treated with surgery alone, while chemotherapy is given for unresectable tumor with clinical symptoms or progression. Conventional chemotherapy is effective but 30–40% patients may have reactivation of disease requiring re-treatment throughout lifetime. MEK inhibitor for BRAF-fusion positive LGG is a new treatment option for refractory cases. Methods: Retrospective search in territory-wide pediatric oncology registry for children diagnosed with LGG from 2010–2020 in Hong Kong. To identify patients with molecular confirmed BRAF-fusion positive LGG and any treatment with MEK inhibitor. Results: Twelve patients (N=12) were identified with BRAF-fusion positive LGG, male:female was 1:2, age 0.3–15.1yr (median 5.0yr) at presentation. The median follow up duration was 1.8yr. Five patients (42%) had surgical resection only. Seven patients (58%) were given chemotherapy with Carboplatin / Vincristine. Five out of seven (n=7) treated patients (71%) have partial response at their initial treatment. Two patients (29%) had progressive disease during treatment and switched to second-line chemotherapy, vinblastine however without improvement. Three patients required re-treatment as disease reactivation. Total five patients had refractory diseases were treated with MEK inhibitor, Trametinib including one diagnosed NF-1. All of them have adverse skin reaction and raised transaminase with one required dose reduction. They have been taking the MEK inhibitor for 0.1–3.3 yr with sustainable partial response. Conclusion: Pediatric LGG has overall favourable prognosis. Some of them treated with surgery alone while conventional chemotherapy could also achieve satisfactory disease control. For refractory disease with BRAF-fusion positive, MEK inhibitor is a well tolerated treatment option showing sustainable partial response. However, prolonged medication and disturbing skin reaction are still a major concern for this group of patients. On-going clinical trials to compare conventional chemotherapy versus MEK inhibitor could give us more insight about the clinical benefit, patient selection and treatment duration.

MODELS

TMOD-01. A PROGNOSTIC NOMOGRAM MODEL AND ONLINE SOFTWARE FOR PATIENTS WITH NEWLY DIAGNOSED LOWER-GRADE GLIOMAS

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The nomogram represents a statistical model that incorporates multiple risk factors to estimate individualized survival probabilities. In this study, we developed a nomogram which provides an important tool for individulized survival predicition for newly diagnosed low-grade gliomas (LGG). A total number of 582 newly diagnosed LGG patients were included; the median age was 39.93 years and 42% were female. Cox regression analysis showed that younger age at diagnosis, WHO grade II vs. III, the IDHmut-codel vs. the IDHwt, and the IDHmut-non-codel vs. the IDHwt were significantly associated with better prognosis. The adjuvant treatment following surgery showed a trend towards improved survival. Subsequently, the nomogram to estimate 60-, 90-, and 120-month survival probabilities was established. Our data showed that the age at diagnosis was the largest contributor to patient survival, followed by molecular subtype, WHO grade, treatment and gender. The calibration plot showed that the observed and the nomogram predicted OS curves were well-aligned. In addition, we also validated our nomogram for LGG patients who received postsurgical adjuvant therapy through cross-validation and the calibration plot. Finally, we developed a free online tool for this nomogram (softwarewebsite:https://rrlnnomogram.shinyapps.io/LGG_Nom_Asian/). Overall, this model should be a useful tool for counseling patients in clinical practice including treatment decisions, follow-up, and prognosis.

TMOD-02. GEBTO: GENETICALLY ENGINEERED BRAIN TUMOR ORGANOIDS AS A NOVEL PRECLINICAL MODEL

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Background: One of the bottlenecks in basic and translational research on pediatric brain tumors, is the lack of suitable and representative preclinical models to study tumor biology and drug sensitivity. Over the last decades, extensive molecular characterization has uncovered many entities and subgroups with their unique oncodriving events. However, this heterogeneity is currently not reflected in the models available, especially not for *in vitro* models. Objectives: We aim to generate genetically engineered brain tumor organoids (GEBTO) to represent the molecular variety of embryonal brain tumors and ependymomas. Method: Human brain organoids derived from embryonic stem cells are generated to represent the region of tumor origin. To mimic oncodriving events, DNA plasmids are introduced via electroporation in the organoid cells to knockout tumor suppressor genes or overexpress oncogenes. Results: Cerebellar and cerebral forebrain organoids were generated as the tissue of origin for medulloblastoma and supratentorial ependymoma (ST-EPN), respectively. Based on the detection of GFP protein encoded by DNA plasmids, the organoid cells can be manipulated within a wide developmental window, which corresponds with the presence of the proposed cells of origin. Different oncodrivers and combinations thereof are now being tested to see whether they result in ectopic growth in cerebral or cerebellar organoids. When successful, the GEBTOs are histologically and molecularly characterized using (single cell) transcriptomic and epigenomic analyses to see how well they resemble human tumors. Discussion: Although further development is required, GEBTOs provide a novel avenue to model especially rare pediatric brain tumors, for which tissue and therefore patient-derived models are limited. It also allows for in-depth analyses of the potential cells of origin and the contribution of different mutations to tumor biology.