LOW GRADE GLIOMA

LGG-01. CHILDREN WITH SUPRATENTORIAL MIDLINE PILOCYTIC ASTROCYTOMAS EXHIBIT MULTIPLE PROGRESSIONS AND ACQUISITION OF NEUROLOGIC DEFICITS OVER TIME

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Pilocytic astrocytomas are the most common solid tumor of childhood and can arise anywhere in the central nervous system, including the posterior fossa (pf-PA), supratentorial midline (sm-PA; including optic pathway, hypothalamus, thalamus), and brainstem (bs-PA). Location (sm, bs) has been previously proposed as a prognostic factor for PA, but is difficult to separate from resection status on multivariate analysis. To overcome this limitation, we assembled a large cohort of children (n = 251) with biopsy-proved PA treated at St. Louis Children's Hospital from 2003 – 2021 and analyzed outcomes only in patients with subtotal resection (STR; n = 81). We excluded patients with NF1, as NF1-associated gliomas often display a more indolent clinical course than their counterparts. We identified that children with STR sm-PA had a higher likelihood of multiple progressions compared to children with STR bs-PA and pf-PA. This was associated with worsening neurologic deficits over time, consistent with the sm location as a poor prognostic factor. Furthermore, the only children in our cohort with leptomeningeal dissemination or death harbored sm-PAs. Tumors in this location were also associated with an increased likelihood of non-BRAF-fusion genetic alterations and multiple oncogenic mutations. Overall, these data support location as an independent prognostic factor for PA in cases in which a gross-total resection cannot be achieved. Treating neuro-oncologists may thus wish to consider early intervention rather than watch-and-wait strategies at first progression of STR sm-PA. These patients may also benefit from earlier consideration of molecularly targeted therapy.

LGG-02. CARDIAC TOXICITY IN PATIENTS RECEIVING SINGLE-AGENT MEK INHIBITION

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BACKGROUND: MEK inhibitor therapy is increasingly being utilized for the treatment of pediatric tumors, including low-grade glioma, plexiform neurofibroma and Langerhans cell histiocytosis. These drugs are well-tolerated but do have risk of toxicity, including cardiac toxicity. The purpose of this study is to better characterize MEK inhibitor-induced cardiac toxicity in pediatric patients. METHODS: Retrospective review of all patients who underwent MEK inhibitor mono-therapy for at least 3 months, 2015- 2021, age 25 years or less, at St. Louis Children's hospital and Cardinal Glennon Children's hospital. RESULTS: We evaluated 31 patients, 19 (61%) with brain tumors and 12 (39%) without. Of the thirty-one, fifteen (48%) had NF1, 1 had Tuberous sclerosis. Cardiac toxicity consisted of asymptomatic sinus tachycardia, bradycardia, or decreased ejection fraction (EF). Thirteen patients (42%) experienced an asymptomatic decrease in left-ventricular ejection fraction (EF), Grade I-III. Time on therapy before decreased EF was 5 days to 21 months, median 2.8 months. Decreased EF developed in 5 of 13 patients receiving selumetinib and 8 of 18 receiving trametinib. Of the patients who developed decreased EF, 11 (85%) had brain tumors, 6 (46%) had NF1, and 89% had received prior systemic therapy. Out of the patients who had received no prior systemic therapy (6), 2 (33%) had decreased EF, while 11/25 (44%) of those who had received prior systemic therapy did. Drug was held temporarily for 6 patients, with dose limiting toxicity for 5 patients. Drug was discontinued for 1 patient after EF continued to decline despite dose reduction. Patients showed improvement in EF as early as 2 weeks after holding therapy. CONCLUSIONS: Cardiac toxicity in our patients was limited to asymptomatic reduction in ejection fraction, sinus bradycardia and tachycardia, reinforcing the need for appropriate monitoring via echocardiography. Prior systemic therapy was associated with decreased EF.

LGG-03. PEDIATRIC SPINAL DEFORMITIES CONCOMITANT WITH SPINAL CORD PILOCYTIC ASTROCYTOMA

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INTRODUCTION: Childhood spinal cord tumours may lead to spinal deformity. Rapid scoliosis progression, a left thoracic curve and early onset scoliosis are associated with an increased risk of intraspinal anomalies, therefore magnetic resonance imaging (MRI) should be performed. CASE PRESENTATION: A 1-year-old girl presented with progressive early onset scoliosis. MRI of the spine showed diffuse intramedullary lesion at vertebral level T5 – T11 and abnormal curvature of the thoracic spine to the right – 39-degree Cobb angle, after a few moths – 71-degree. Blood and cerebrospinal fluid examination ruled out a neuroinfection and autoimmune diseases. Histology revealed BRAF V600E-mutant pilocytic astrocytoma (PA) (IDH non-mutant), DNA methylation profiling – PA, MGMT promoter methylation – not detected, SNP-A karyotyping – normal. Treatment with weekly vinblastin was started due to non-operable tumour and progressive scoliosis. Spinal deformity was managed using serial casting with only mild correction of curvature. In the second case report, a 14-year-old boy either presented with progressive scoliosis. Spine x-ray showed abnormal curvature of the thoracic spine to the left - 89-degree Cobb angle and after a few years - 120-degree. MRI of the spine detected intramedullary tumour masses located at vertebral level T3-T5. Surgical resection revealed BRAF V600E-mutant PA (IDH, ATRX, TERT non-mutant), DNA methylation profiling – PA, MGMT promoter status – not methylated, SNP-A karyotyping – non-specific trisomy of chromosome 5. The patient was followed-up by routine spine MRI. However, after 8 months new spinal cord masses appeared. It was decided to correct scoliosis only after the total tumour removal. CONCLUSIONS: Intramedullary spinal tumours are overall rare in the pediatric population. Of these, PA accounts for the majority, however treatment remains challenging. BRAF V600E mutation has relatively high frequency in PA. This mutation identification opens more treatment options such as targeted therapy with BRAF V600E and MEK inhibitors for progressive disease.

LGG-04. CLINICAL AND MOLECULAR CHARACTERIZATION OF METASTATIC PEDIATRIC LOW GRADE GLIOMAS

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BACKGROUND: Despite being the most common central nervous system tumor in children, ≤5% of pediatric low grade gliomas (pLGG) present with metastases. Due to their rarity, there is a paucity of clinical and molecular data in metastatic pLGGs. To address the need, we analyzed a cohort of 22 patients with pLGG followed at Texas Children's Hospital who presented with metastatic disease. RESULTS: The predominant histology was pilocytic astrocytoma (16/22, 73%); average age at diagnosis was 4 years 11 months. The most common sites of primary disease were optic pathway/chiasm (7/22, 32%) and suprasellar (5/22, 23%). Metastatic disease was most commonly noted in the leptomeninges (12/22, 55%). 16/22 patients (73%) were treated with up-front medical therapy following tumor biopsy/resection, the majority with carboplatin-based therapy; the remaining 6 patients received only surgery up-front. Only 2/22 patients (9%) did not progress after their initial treatment with an average follow-up of 42 months. 14 patients (14/22, 64%) had continued disease progression after at least 2 therapeutic interventions; however, only 3 patients (3/22, 14%) eventually received craniospinal radiation. 10 patients (10/22, 45%) received treatment with an agent targeting the mitogen-activated protein kinase (MAPK) pathway. 20/22 patients (91%) were alive at last follow-up (average 72 months). 4/21 patients (19%) harbored a BRAF V600E mutation while 7/20 (35%) had a BRAF::KIAA1549 duplication/fusion. 8/20 patients (40%) were wildtype for both analyzed molecular alterations in BRAF. 8 patients had germline whole exome sequencing performed and all were negative for pathogenic/likely-pathogenic variants related to their clinical phenotype. Methylation analyses are pending on patients with available tumor tissue. CONCLUSION: In our cohort of patients with metastatic pLGG, most tumors progressed despite numerous therapeutic regimens, but the overall survival was >90%. 40% of patients were wild type for the 2 most common MAPK alterations seen in pLGG.

LGG-05. A NINE-MONTH-OLD BOY WITH REGRESSION OF MILESTONES AND SEVERE CONSTIPATION: AN UNUSUAL CASE OF A SPINAL PILOCYTIC ASTROCYTOMA

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Pilocytic astrocytoma (PA), a World Health Organization Grade 1 tumor, is the most common brain tumor in children between 5 and 14 years of age and the second most common in children younger than 5 and older than 14. Although classical to the cerebellum and hypothalamic regions, it can also arise in the spinal cord. A nine-month-old boy with a history of torticollis and plagiocephaly presented with a four-month history of regression of milestones, irritability and severe constipation. He was noted to have flaccid paralysis of the lower extremities and decreased reflexes. Ophthalmologic exam was significant for papilledema and magnetic resonance imaging of the spine were notable for a large infiltrative heterogeneously enhancing lesion extending from T4 to the conus containing several loculated intratumoral cysts with abnormal enhancing margins from T4 to T8. He underwent embolization and complete tumor resection. Post-op MRI was notable for an oval shape non-enhancing soft tissue measuring 8 mm along the medial wall of the left lateral ventricle. Comprehensive tumor molecular profiling on the resected spinal tumor tissue (Caris MI), revealed an NTRK1 fusion, MEF2D-NTRK1, Exon 12. Larotrectinib was initiated at 100mg/m2 per dose oral twice daily to target this specific mutation. Follow up imaging 3 months later showed decrease in the size of intracranial lesions. To date, there is only one other case report demonstrating intracranial metastasis from a spinal PA. Due to the size of his spinal lesion, we believe this was his primary site; however, as described in the literature, there is no definitive way to determine the initiating lesion. The use of comprehensive molecular profiling facilitated the discovery of a targetable oncogenic mutation that changed initial management. To the best of our knowledge there has been only one other case report describing this specific fusion in a pediatric spinal CNS tumor.

LGG-06. SELUMETINIB IN PEDIATRIC PATIENTS WITH NON-NEUROFIBROMATOSIS TYPE 1-ASSOCIATED, NON-OPTIC PATHWAY (OPG) AND NON-PILOCYTIC RECURRENT/PROGRESSIVE LOW-GRADE GLIOMA HARBORING BRAFV600E MUTATION OR BRAF-KIAA1549 FUSION: A MULTICENTER PROSPECTIVE PEDIATRIC BRAIN TUMOR CONSORTIUM (PBTC) PHASE 2 TRIAL

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BACKGROUND: A greater understanding of the Ras-MAP kinase pathway in pediatric low-grade glioma (LGG) paired with the availability of selective inhibitors has enhanced the ability to target this pathway with therapeutic intent. METHODS: The PBTC conducted a multi-institutional phase II study (NCT01089101) evaluating selumetinib (AZD6244, ARRY-142886), a MEK I/II inhibitor, in children with recurrent/progressive LGG assigned to 6 strata and treated at a dose of 25 mg/m2/dose PO BID for up to two years. Here we present stratum 5 which enrolled children without NF1, non-OPG and non-pilocytic LGG harboring either a BRAFV600E mutation or BRAF-KIAA1549 fusion. RESULTS: Twenty-four of 25 children enrolled were eligible; 23 were evaluable for the primary radiologic response endpoint. Enrollment stopped early due to slow accrual and initiation of COG ACNS1931. The most common histologies were ganglioglioma (42%) and astrocytoma NOS (33%). Thirteen tumors (54%) had BRAF-KIAA1549 fusion; 11 (46%) had the BRAFV600E mutation. Five of 23 (22%) evaluable patients achieved a centrally confirmed partial response (PR), 12 (52%) had stable disease and 6 (26%) had progression with a 2-year progression-free survival of 75 + 9%. Four of 11 (36%) patients with a BRAFV600E mutation and 1/12 (8%) with a BRAF-KIAA1549 fusion achieved a PR. The 2-year PFS did not significantly differ between tumors with BRAFV600E mutation (82 + 12%) versus BRAF-KIAA1549 fusion (68 + 13%) (n=24, p=0.548). No patient remains on therapy. The most common attributable toxicities were grade 1/2 ALT/AST elevation, dry skin and leukopenia. Rare grade 3/4 toxicities included elevated CPK, rash, paronychia, fever, weight gain and sinus tachycardia. CONCLUSIONS: Despite lower than planned accrual, selumetinib met the design threshold for success in treating children with recurrent/progressive non-pilocytic, non-OPG LGG without NF1 that harbored the common BRAF aberrations. Ongoing phase 3 prospective studies will better determine the role of this agent in this population.

LGG-07. NOVEL CRISPR/CAS9 INDUCED KIAA1549:BRAF FUSION MODEL FOR PRECLINICAL STUDIES OF PEDIATRIC GLIOMAS

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BACKGROUND: Pediatric Low Grade Gliomas (pLGG) are the most common group of central nervous system (CNS) tumors in children and cause significant morbidities. Pilocytic astrocytoma (PA) is the most frequent pLGG. KIAA1549:BRAF fusion is a well-established oncogenic driver in PA. Oncogene induced senescence (OIS) has prevented establishing PA cultures for in vitro and in vivo studies. Here we look at a novel NIH-3T3 fibroblast model harboring KIAA1549:BRAF fusion gene via CRISPR/Cas9 somatic genome engineering technology.

OBJECTIVES: Establishing that the CRISPR/Cas9 edited NIH-3T3 fibroblast model with the KIAA1549:BRAF fusion is valuable for in vitro and in vivo studies without early OIS. DESIGN/METHOD: CRISPR/Cas9 editing technology was used to establish a KIAA1549:BRAF fusion positive cell model. This cell model was studied in vitro with MEK inhibitor cobimetinib (GDC-0973) and using WST-1 viability assay, clonogenic assay, senescence β-galactosidase staining, and western blot. In vivo murine models with subcutaneous fusion positive NIH-3T3 fibroblast tumors were treated with GDC-0973. Survival studies and tissue studies were subsequently done. RESULTS: A fusion positive NIH-3T3 fibroblast model was successfully established. Increased BRAF cDNA expression and higher levels of p-ERK were observed. In vitro studies showed decreased viability with GDC-0973. Clonogenic assay showed qualitative and quantitative decreases in viable cells. P-ERK target inhibition was established without induction of senescence. In vivo studies demonstrated successful subcutaneous tumor implantation, therapy efficacy, and target inhibition. CONCLUSION: CNS tumors, most commonly pLGG, in children cause significant morbidities. KIAA1549:BRAF fusion is an oncogenic driver in PA. In vitro and in vivo studies are important for pre-clinical models. OIS has prevented establishing adequate fusion positive animal cell models. Here we have demonstrated a successful CRISPR/Cas9 edited fusion positive NIH-3T3 fibroblast model.

LGG-08. MR IMAGING OF PEDIATRIC LOW-GRADE GLIOMAS: PRETHERAPEUTIC DIFFERENTIATION OF *BRAF* V600E MUTATION, *BRAF*-FUSED AND WILD-TYPE TUMORS IN PATIENTS WITHOUT NEUROFIBROMATOSIS-1

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OBJECTIVE: The prognosis and treatment of pediatric low-grade gliomas (pLGGs) is influenced by their molecular subtype. MRI remains the mainstay for initial work-up and surgical planning. We aimed to determine the relationship between imaging patterns and molecular subtypes of pLGGs. METHODS: This is a bi-institutional retrospective study for patients diagnosed from 2004 to 2021 with pathologically confirmed pLGG, molecularly defined as *BRAF* fusion (*KIAA1549-BRAF*), *BRAF* V600E mutation, or wild-type (negative for both *BRAF* V600E mutation and *BRAF* fusion). Two neuroradiologists, blinded, independently reviewed imaging parameters on the initial MRI and discrepancies were solved by consensus. Bivariate analysis was used followed by pairwise comparison of Dwass, Steel, and Critchlow-Fligner methods to compare the 3 molecular subtypes. Agreement between reviewers was assessed using Kappa (k). RESULTS: 70 patients were included: 30 with *BRAF* fusion, 19 with *BRAF* V600E mutation, and 21 wild-type. There was substantial agreement between the two readers for overall imaging variables (k=0.75). *BRAF* fusion tumors compared to V600E and wild-type had larger size (p=0.0022), greater mass effect (p=0.0053), and increased rate of hydrocephalus (p=0.0002). *BRAF* fusion tumors had increased frequency of diffuse enhancement compared with *BRAF* V600E and wild-type (p <0.0001). *BRAF* V600E mutant tumors were more often located in a cerebral hemisphere (p