LGG-29. USE OF BEVACIZUMAB IN PEDIATRIC LOW-GRADE GLIOMA: TEN-YEAR EXPERIENCE IN A SINGLE CENTER

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PURPOSE: Pediatric low-grade gliomas (PLGG) have excellent overall survival but frequently need non-surgical therapy at diagnosis or after progression at unresectable sites such as the optic pathway. Chemotherapy side effects have led to the need for better-tolerated regimens with a sustained response. Bevacizumab, a humanized anti-VEGF monoclonal antibody has been used in monotherapy and/or in combination for these entities. Here we present our experience with its use in PLGG. METHODS: A retrospective, observational, single-institution study between 2008-2018 was performed, reporting the short-term outcomes of safety and efficacy of bevacizumab in progressive PLGG. RESULTS: Twenty-six patients with a median age at diagnosis of 3.32 years old [0.12-14.7] and the median age at the treatment of 8.11 years old [0.41-16.82] were included in the study. Nineteen had optic pathway gliomas and chiasmatic-hypothalamic gliomas (73.1%), 9 of them (47.4%) associated with neurofibromatosis type 1 (NF1). Fourteen non-NF1 tumors were molecularly studied, disclosing BRAF-KIAA1549 fusion transcript in 9 and BRAF V600E mutation in 2. Bevacizumab was administered in combination with other agent(s) in 16 of the 35 treatment courses. Responses were assessed at 3, 6, 12 months, and at the end of treatment. Progression-free survival at 12 months was 94%, and no severe adverse events were observed. CONCLUSIONS: In our series, Bevacizumab in PLGG showed short-term clinical efficacy with a favorable toxicity profile. Larger and long-term prospective studies may determine whether the response is conditioned upon different clinical or molecular features.

LGG-31. PEDIATRIC LOW-GRADE GLIOMAS WITH FGFR1 MUTATIONS AND SPONTANEOUS HEMORRHAGE: CASE SERIES

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Pediatric low-grade gliomas (pLGG) are the most common pediatric CNS neoplasms. Thanks to the advent of molecular tumor diagnostics, we have begun exploring the clinical relevance of FGFR1 (c.1632C>A; p.N546K) mutations in the pLGG population. However, the risk of spontaneous hemorrhage in pLGG patients harboring FGFR1 mutations is even less understood. We present four pLGG cases with FGFR1 mutation and hemorrhagic episodes. Patient 1 presented with an intraventricular hemorrhage and leptomeningeal disease. Pathology was consistent with suprasellar pilocytic astrocytoma, FGFR1, and PTPN11 mutations. Initial therapy consisted of Carboplatin/Vinblastine per ADVL0515. The patient has had several recurrences, and treatment regimens have included ACNS0223, Everolimus, and A9952 regimen A. Patient 2 was diagnosed with an optic pathway glioma, and pathology confirmed FGFR1, MEK2, PTPN11, and NF1 splice site mutations. The patient also has a history of Noonan's Syndrome and has undergone several chemotherapy regimens, including A9952 Regimen A, COG MATCH with Erdafitinib, and Avastin. The best tumor response was seen while on Avastin. The patient has presented with two episodes of intratumoral hemorrhage, both after treatment with Avastin. Patient 3 presented with a sudden brain stem hemorrhage and underwent a biopsy and debulking. The pathology was consistent with a pilocytic astrocytoma with an FGFR1 mutation confirmed by Next-generation sequencing (NGS). Treatment regimens for this patient include A9952 Regimen A and Vinblastine. Patient 4 presented with acute headache and vomiting and was found to have a hemorrhagic suprasellar mass. The patient underwent tumor debulking, and pathology was consistent with low-grade glioma. NGS revealed FGFR1 and KRAS mutations. The patient received therapy as per A9952 Regimen A. Greater surveillance of this molecular and clinical finding is warranted to uncover the association between FGFR1 mutations and hemorrhage in patients with low-grade gliomas.

LGG-32. INTEGRATED BIOLOGIC, RADIOLOGIC AND CLINICAL ANALYSIS OF PEDIATRIC LOW-GRADE GLIOMAS DURING AND AFTER TARGETED THERAPY TREATMENT

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BACKGROUND: Pediatric low grade gliomas (pLGGs) are the most common central nervous system tumor in children, characterized by driver alterations in the RAS and MAPK pathways. Genomic advances have facilitated use of molecular targeted therapies, however their long-term impact on tumor behavior remains critically unanswered. METHODS: We performed an IRB-approved, retrospective chart and imaging review of pLGGs treated with off-label targeted therapy at Dana-Farber/Boston Children's Cancer and Blood Disorders Center from 2010 to 2020. Volumetric analysis was performed for BRAFV600E and BRAF fusion/duplication driven pLGG subsets. RESULTS: Fifty-five patients were identified (dabrafenib n = 15, everolimus n = 26, trametinib n = 11, and vemurafenib n = 3). Targeted agent was used as first or second-line therapy for 58% (32/55). Median duration of targeted therapy was 0.79 years (0.01 – 4.87), and overall median follow-up was 2.50 years (0.01 – 7.39). The 1-year, 3-year, and 5-year EFS from targeted therapy initiation were 62.1%, 38.2%, and 31.8%, respectively. Mean volumetric change for BRAFV600E mutated pLGG on BRAF inhibitors was -54.11%, and median time to best volumetric response was 8.28 months (n = 12). Median time to largest volume post-treatment was 2.86 months. Mean volumetric change for BRAF fusion/duplication pLGG on MEK inhibitors was +7.34% with median time to best volumetric response of 6.71 months (n = 7). Median time to largest volume post-treatment was 2.38 months. CONCLUSIONS: Our integrated clinical and volumetric data suggest the majority of patients receiving BRAF inhibitors or trametinib achieve reduction in tumor volume while on therapy and that tumor stability can be achieved following targeted therapy cessation. Moreover, volumetric analysis shows promise as a tool to assess targeted therapeutic response in pLGGs.

LGG-33. A 40-YEAR COHORT STUDY OF EVOLVING HYPOTHALAMIC DYSFUNCTION IN 90 INFANTS AND YOUNG CHILDREN (<3Y) WITH OPTIC PATHWAY GLIOMAS

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BACKGROUND: Despite high survival, paediatric optic pathway hypothalamic gliomas are associated with significant morbidity and late mortality. Those youngest at presentation have the worst outcomes. METHODS: We aimed to assess presenting disease, tumour location and treatment factors implicated in the evolution of neuroendocrine, metabolic and neuro-behavioural morbidity in children diagnosed before their 3rd birthday and followed over four decades (1981- 2020). RESULTS: Ninety infants/young children followed-up for 9.5 years (range 0.5-25.0) were included in the study. Fifty-two (57.8%) patients experienced endo-metabolic dysfunction (EMD), the large majority (46) had hypothalamic involvement (H+) and lower endocrine event free survival (EEFS) rates. Median time to first endocrine event was 3.4 years, with EEFS declining up to 13.6 years after diagnosis. EMD was greatly increased by a diencephalic syndrome presentation (85.2% vs 46%, p=0.001), H+ (OR 6.1 95% CI 1.7 – 21.7, p 0.005), radiotherapy (OR 16.2, 95% CI 1.7 – 158.6, p=0.017) and surgery (OR 4.8 95% CI 1.3- 17.2, p=0.015), all associated with anterior pituitary disorders. Obesity occurred in 25% of cases and clustered with the endocrinopathies. Posterior pituitary disorders were recorded in 15 subjects (16.7%), only after surgery and/or as a consequence of hydrocephalus in those with suprasellar tumours and hypothalamic disease. Neurobehavioural deficits occurred in over half (52) of the cohort and were associated with H+ (OR 2.5 95% C.I. 1.1 – 5.9, p=0.043) and radiotherapy (OR 23.1 C.I. 2.9 – 182, p=0.003). CONCLUSIONS: Very young children with OPHG carry a high risk of endo-metabolic and neuro-behavioural comorbidities which deserve better understanding and timely/parallel support from diagnosis to improve outcomes. These evolve in a complex hierarchical pattern overtime whose aetiology appears predominantly determined by injury from the hypothalamic tumour location alongside adjuvant treatment strategies.

LGG-34. NEPHROLOGICAL IMPACT OF BRAF INHIBITORS IN A PEDIATRIC POPULATION OF CENTRAL NERVOUS SYSTEM TUMORS: A SINGLE INSTITUTION EXPERIENCE

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BRAF inhibitors (iBRAF) are under investigations in ongoing clinical trials for pediatric brain tumor treatment. Preliminary data regarding the pediatric population report pyrexia, hematological, dermatological, cardiac, and ophthalmic toxicities among the most common adverse events. Acute kidney injury (AKI), mainly due to tubular interstitial injury, has been reported in the adult population. With our study we want to contribute to a more comprehensive knowledge of the short- and long-term nephrological adverse effects of iBRAF in a pediatric population. We collected and reviewed clinical and laboratory data of all patients treated with iBRAF for pediatric central nervous system tumors at our Institution and available for publication. AKI was monitored through serial creatinine measurements, kidney function with estimated glomerular filtration rate (eGFR) and kidney injury with creatinuria/proteinuria ratio. Tubular injury was evaluated with fractional excretion of sodium, potassium and magnesium and with glycosuria. Moreover, urine was examined to detect presence and morphology of erythrocytes. Eight patients were identified, 3 females; median age at treatment start was 9 years (range 2,75 – 18,75). Six patients with BRAFV600E–mutated pediatric Low-Grade Glioma were treated with Vemurafenib, 1 patient with BRAFV600E-mutated pediatric High-Grade Glioma was treated with Vemurafenib and 1 patient with BRAFV600E-mutated Langerhans Cell Histiocytoses was treated with Dabrafenib. Seven patients were considered for analysis. After a median follow up of 3,83 years (range 2,25 – 6,58) no AKI was reported and all patients but two retained normal eGFR at last follow up. No tubular and glomerular injury laboratory findings were detected, and erythrocytes in the urine resulted always below the upper limit of normality. CONCLUSIONS: iBRAF were not associated with AKI and tubular injury. Nevertheless, some data, namely significative decrease of eGFR in two out of seven patients, warrants further investigations.

LGG-35. DYSLIPIDEMIA IN CHILDREN TREATED WITH BRAF INHIBITORS FOR BRAIN TUMOR, A NEW SIDE EFFECT? A SINGLE CENTER RETROSPECTIVE STUDY

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The targeted therapies for brain tumors are innovative and promising oncological treatments and as a result their use has expanded widely. BRAF inhibitors (BRAFi) in recent years have played a central role in disease control of unresectable BRAF-mutated pediatric low-grade gliomas (LGG). Understanding the side effects of these drugs is crucial for clinical practice. The aim of the study was to investigate retrospectively the acute and long-term effects of vemurafenib on lipid metabolism in children treated for an LGG. Children (n=6) treated with vemurafenib at the mean age of 8.41±6.1 exhibited early alterations in plasma lipid profile as demonstrated after 1 month (n=4) by high plasma levels of Low-Density Lipoprotein (LDL 139.5±51.5,mg/dL), Total Cholesterol (TC 221.5±42.1,mg/dL) and Triglycerides (TG 107.8±44.4,mg/dL). Despite dietary recommendations, dyslipidemia persisted 3 months later (LDL 148.8±40.2,mg/dL; TC 238±36.5,mg/dL; TG 115±45.6,mg/dL; n=4) and at long distance follow-up (38±23,months) after treatment with vemurafenib: LDL 139.2±49.1,mg/dL; TC 216.5±38.4,mg/dL; TG 129.7±83.4 mg/dL. This potential side effect suddenly resolved itself in the only patient in which a change of therapy was made (to the combination of dabrafenib and trametinib). BMI was compatible with overweight/obesity at baseline (mean BMI-SDS 0.9±1.8) in 2 patient and normal in 4 patients: during follow-up BMI remained stable in 5 patients and increased in 1 patient. Our findings highlight that Vemurafenib could be associated with an increased risk of dyslipidemia independently of weight. This risk should be anticipated by the identification of high-risk patients and managed by close monitoring of metabolic parameters during routinely follow-up. The association of dabrafenib with trametinib seem not be associated to dyslipidemia, yet more data are needed to explore the hypothesis about the possible role to reduce the risk of dyslipidemia.

LGG-36. ANALYSIS OF BRAF-RELATED MUTATIONS IN PEDIATRIC LOW-GRADE GLIOMA

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BACKGROUND: Most pediatric low-grade gliomas (pLGGs) are driven by a single genetic event resulting in up-regulation of the RAS/MAPK pathway. BRAF-related mutations are the most freauent molecular alteration in the pathway. To explore BRAF-related mutations in pediatric low-grade glioma is helpful for clinical practice. METHODS: In this study, patients with low-grade glioma aged ≤18 years in Guangdong Sanjiu Brain Hospital were enrolled. All patients accepted the tests of BRAF-related mutations with tumor tissue by next-generation sequencing (NGS). Results: A total of 26 patients diagnosed low-grade glioma and underwent NGS detection were included in this study. The male to female ratio was 6:7, and the median age was 9.5 years. 8 patients had tumors located in the cerebral hemisphere, 6 in the third or fourth ventricle, 5 in the cerebellum, 4 in the optic pathway, and 3 in the brain stem. A total of 14 patients took BRAF-related mutations, such as BRAF-KIAA1549 fusion, BRAF p.V600E mutation and other fusion. BRAF-KIAA1549 fusion was detected in 7 patients with pilocytic astrocytoma or pilomyxoid astrocytoma. BRAF p.V600E mutation was detected in 6 patients, two of whom were pleomorphic xanthoastrocytoma. A rare genetic fusion, BCAS1-BRAF fusion, was detected in 1 patient who had brain stem ganglioglioma. Among the 26 patients, 2 patients without BRAF-related mutations had typical multiple cafe-au-lait macules and were diagnosed as NF1-pLGG. These patients were treated with surgery, radiation, chemotherapy and targeted therapy. Only 2 patients received targeted therapy by Trametinib, Vimofinib and Everolimus after progression of the tumor. However, due to the severity of the disease, they eventually died. CONCLUSIONS: More than half of pLGG patients have BRAF-related mutations, which have the opportunity for targeted therapy. However, the optimal timing of targeted therapy still needs further exploration.

LGG-37. LONG-TERM OUTCOME, VISUAL MORBIDITY AND PROGNOSTIC FACTORS IN INFANTS AND YOUNG CHILDREN WITH OPTIC PATHWAY GLIOMA FROM THE GREAT ORMOND STREET HOSPITAL (GOSH) LGG - COHORT

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INTRODUCTION: The treatment aim of childhood optic pathway glioma (OPG) is visual preservation. However, long-term outcomes and prognostic factors implicated remain largely unknown. METHODS: We undertook a retrospective study of infants and young children (IYC) ≤3 years with OPG and logMAR visual acuity (VA) at baseline/follow-up. We derived Overall- (OS), Progression-free (PFS), Radiotherapy-free (RTFS) and Visual event-free survival (vEFS) curves and analysed prognostic factors for visual deterioration and WHO defined blindness (>1.3 logMAR both eyes). RESULTS: Of 81 IYC-OPG (147 evaluable eyes) baseline vision was below 5%ile for age in 33 (41%) and 27 (33%) in one or both eyes respectively, within normal range in 21 (26%). After observation (11), chemotherapy (66) or RT (4), radiological progression occurred in 47 (58%), multiple times in 34.6% (range 2 - 8) and 10yr-PFS was 39.8%. Twenty had RT after 4.2 years from diagnosis (10yr-RTFS 72.4%) and 12% died (10yr-OS 89%). After 8.9 years VA was better/stable/ worse in 36%/32%/32% of subjects, with median time to visual event of 1.7 years (range 0.16 - 12) and 10yr-vEFS 41.3%. Final VA was reduced (>0.2 logMAR) in 23 (28.4%) and 43 (53.1%) in only one or both eyes respectively. Amongst those with unilateral impairment 13/23 affected eyes had no useful vision (light/no light perception). Amongst those with bilateral impairment best eye VA was > 1.0 log MAR in 22/43 (LP/NLP in 10). Infants < 1 year had significantly inferior 10-yrPFS (5.6%), post-chiasmatic involvement was associated with visual deterioration (HR 2.91, 95%CI=1.1- 7.7), and baseline bilateral abnormal for age vision predicted WHO blindness at follow-up (OR 17.9, 95%CI=3.2 – 101.1). CONCLUSIONS: Many IYC-OPG suffer multiple progressions with significant long-term visual morbidity. Predictive factors such as age, tumor location and baseline age-adjusted vision allow patients' selection for early sight rehabilitation and consideration for experimental strategies preventing visual loss.

LGG-38. DOSE-DEPENDENT SEIZURE CONTROL FOR AN NF1 PATIENT TREATED VIA MEK-INHIBITION FOR OPTIC PATHWAY GLIOMA

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BACKGROUND: Low-grade gliomas (LGG) are the most common solid tumor of childhood and can result in neurologic complications, including seizures, focal neurologic deficits, and learning difficulties. Molecularly tar-