Abstracts

NFB-07. USE OF PEGYLATED INTERFERON ALPHA-2B IN PEDIATRIC PATIENTS AFFECTED BY UNRESECTABLE PLEXIFORM NEUROFIBROMATOSIS: MONOCENTRIC EXPERIENCE
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BACKGROUND: Neurofibromatosis type 1 (NF1) is autosomal dominant neurogenic disorder characterized by progressive cutaneous, neurologic, skeletal, and neoplastic manifestations. Plexiform neurofibromas (PN) are one of the different types of neurofibromas that occur in these patients. Complete surgical resection is not possible due to tumor infiltrative behavior. We evaluated pegylated interferon-α-2b (PI) in patients with unresectable progressive or symptomatic PN. METHODS: Pediatric patients (1–21 years old) affected by unresectable PN, followed at Bambino Gesù Hospital, were treated with PI. We administered PI as a weekly subcutaneous injection at a beginning dose of 1.0 mcg/kg/wk, increased to 3.0 mcg/kg/wk if well tolerated. Paracetamol (15mg/kg) was given 30 minutes prior the dose of PI and then every 4–6 hours as needed. Patients were evaluated with Magnetic Resonance Imaging every 12 months. RESULTS: Fifteen patients (11 female, 4 males) of median age 12 years completed 12 cycles (range: 2 to 12 cycles). Most common adverse events were diarrhea, hematochezia, and fatigue, with one grade 3 neutropenia (30%) and increased liver transaminases level (20%) in two patients. None of them required dose reduction. RESULTS: Six patients showed clinical response. 1/15 patient had a radiological response at MRI, 1/15 experienced progression disease and 8/15 showed a stable disease at MRI evaluation. CONCLUSIONS: Our study demonstrated that Pegylated interferon treatment could be a suitable alternative treatment in terms of stabilization of the tumor size due to its antitumor activity although clinical response does not correlate with radiographic changes.

NFB-08. PHASE II STUDY OF AXITINIB IN PATIENTS WITH NF1-ASSOCIATED PROGRESSIVE VESTIBULAR SCHWANNOMAS
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INTRODUCTION: Vascular endothelial growth factor receptor (VEGFR), platelet derived growth factor receptor (PDGFR), and c-KIT represent clinically and/or preclinically validated molecular targets in vestibular schwannomas. With ongoing randomized trials, these targets are observed at the late-phase-label, twosided design study (ClinicalTrials.gov identifier NCT02129647) to estimate the response rate to axitinib, an oral multi-receptor tyrosine kinase inhibitor targeting PDGF, VEGF and c-KIT, in neurofibromatosis type 2 (NF2) patients with progressive vestibular schwannomas (VS). METHODS: NF2 patients older than 5 years with at least one volumetrically measurable, progressive VS were immediately entering the observation and treatment arms (median age 9 years, range: 5–17 years). RESULTS: Twelve eligible patients (ages: 14–56 years) were enrolled on this study. Seven of twelve patients completed 12 cycles (range: 2 to 12 cycles). The most common adverse events were diarrhea, hematochezia, and fatigue, with one grade 3 neutropenia (30%) and increased liver transaminases level (20%) in two patients. None of them required dose reduction. The primary endpoint was to estimate the objective volumetric response rates to axitinib. Axitinib was given continuously in 28-day cycles for up to 12 cycles. Response was assessed every 3 months with MRI using 3D volumetric tumor analysis and audiograms. Volume response and progression were defined as ≥20% decrease in VS volume, respectively. RESULTS: Twelve eligible patients (ages: 14–56 years) were enrolled on this study. Seven of twelve patients completed 12 cycles (range: 2 to 12 cycles). We observed two imaging and three hearing responses. Best volumetric response was -53.9% after nine months on axitinib. All patients experienced drug-related toxicities, the most common adverse events were diarrhea, hematochezia, and skin toxicity, not exceeding grade 2 and hypertension, not exceeding grade 3. CONCLUSIONS: While axitinib has modest anti-tumor activity in NF2 patients, it is more toxic and appears to be less effective compared to drug-related toxicities, the most common adverse events were diarrhea, hematochezia, and fatigue. Based on these findings, further clinical development of axitinib for this indication does not appear warranted.

NFB-09. ENROLLMENT AND CLINICAL CHARACTERISTICS OF NEWLY DIAGNOSED, NF1-ASSOCIATED VESTIBULAR SCHWANNOMA: PRELIMINARY RESULTS FROM AN INTERNATIONAL MULTI-CENTER NATURAL HISTORY STUDY
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INTRODUCTION: Because treatment and clinical management decisions for children with NF1-OPG remain challenging, we sought to establish evidence-based guidelines. We prospectively enrolled children with newly-diagnosed NF1-OPGs, and gathered standardized clinical neuro-oncology and ophthalmology assessments. METHODS: Only children for unresectable progressive or newly-diagnosed OPGs, confirmed by central review, were eligible. Indications for obtaining the initial MRI, as well as factors associated with the decision to treat with chemotherapy or observe without treatment, were obtained. Quantitative visual acuity (VA), other ophthalmologic and imaging were captured at standard time points. Goal enrollment is 250 subjects. RESULTS: One-hundred thirty-three children (52% female) from 20 institutions met inclusion criteria, and were included in this preliminary analysis. Eighty-six percent of subjects were able to perform quantitative VA testing at enrollment. The most common reasons for the diagnostic MRI included screening related to NF1 diagnosis (36.8%), ophthalmologic concerns (29.1%), and non-ophthalmologic concerns (24.8%), such as headache. To date, twenty subjects have initiated treatment with chemotherapy, twelve (9%) at the time of the initial OPG diagnosis. Median age at OPG diagnosis was 3.1 years. Age and sex distribution were similar in subjects immediately entering the observation and treatment arms (median age 3.5 years, respectively). CONCLUSION: Most children with NF1-OPGs will require initial OPG treatment. Importantly, a large proportion of children are able to complete quantitative VA testing at enrollment. Once enrollment is complete, these data will help to establish evidence-based guidelines for clinical management of NF1-OPGs.

NFB-11. WHITE MATTER DIFFERENCES IN CHILDREN WITH NF1 COMPARED TO CONTROLS
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INTRODUCTION: Neurofibromatosis type 1 (NF1) is a genetic condition in which children develop learning challenges and glioma. White matter tracts (WMT) are implicated in these cognitive functions, while oligodendroglial precursor cells are implicated in both gliomagenesis and white-matter development. Specific WMTr have not been well characterized in NF1. METHODS: Twenty NF1 patients aged 1.4–17.6 years (M = 9.5 years, 24 male) and 20 age-and-sex-matched controls underwent dMRI at 3T (25 acquisitions, b=1000 s/mm²). Automated segmentation of WMTr extracted fractional anisotropy (FA) and mean diffusivity (MD) of 18 major WMTr. Covariance analysis examined the effect of group (NF1/controls) on FA/MD after controlling for intracranial volume. Regression analyses for WMTr that demonstrated that PI could be a suitable treatment for unresectable PN in children with NF1-OPGs remain challenging, we sought to establish evidence-based guidelines. We prospectively enrolled children with newly-diagnosed NF1-OPGs, and gathered standardized clinical neuro-oncology and ophthalmology assessments. METHODS: Only children for unresectable progressive or newly-diagnosed OPGs, confirmed by central review, were eligible. Indications for obtaining the initial MRI, as well as factors associated with the decision to treat with chemotherapy or observe without treatment, were obtained. Quantitative visual acuity (VA), other ophthalmologic and imaging were captured at standard time points. Goal enrollment is 250 subjects. RESULTS: One-hundred thirty-three children (52% female) from 20 institutions met inclusion criteria, and were included in this preliminary analysis. Eighty-six percent of subjects were able to perform quantitative VA testing at enrollment. The most common reasons for the diagnostic MRI included screening related to NF1 diagnosis (36.8%), ophthalmologic concerns (29.1%), and non-ophthalmologic concerns (24.8%), such as headache. To date, twenty subjects have initiated treatment with chemotherapy, twelve (9%) at the time of the initial OPG diagnosis. Median age at OPG diagnosis was 3.1 years. Age and sex distribution were similar in subjects immediately entering the observation and treatment arms (median age 3.5 years, respectively). CONCLUSION: Most children with NF1-OPGs will require initial OPG treatment. Importantly, a large proportion of children are able to complete quantitative VA testing at enrollment. Once enrollment is complete, these data will help to establish evidence-based guidelines for clinical management of NF1-OPGs.
ence between children with NF1 and controls were greater at younger than older ages. CONCLUSION: Microstructural differences were observed in WMTs in children with NF1 compared to controls. These differences were not explained by variations in intratumoral volume and therefore may provide early markers of disease progression in younger children with NF1 compared to controls. These findings have implications for understanding neurocognitive deficits and gloomagemens observed in children with NF1.

NFB-12. TRAMETINIB THERAPY FOR PEDIATRIC PATIENTS WITH REFRACTORY LOW GRADE GLIOMA OR EXTENSIVE SYMPOMATIC PLEXIFORM NEUROFIBROMA
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OBJECTIVE: Refractory symptomatic plexiform neurofibromas (PNF) and inoperable refractory low grade gliomas (LGG) pose a clinical challenge that may be life threatening. Phase 1 and 2 clinical trials of MEK inhibitor with selumetinib in inoperable PNF and LGG have demonstrated promising results. We report our experience of using trametinib for treatment of children on a compassionate basis with extensive PN or LGG refractory disease with selumetinib, as this is available in Canada. METHODS: We have treated children with trametinib on a compassionate basis in our province since 2017. Review of the clinical data regarding this therapy has been IRB approved. RESULTS: Two young patients were treated for indication of life threatening extensive PNF and have had tumor shrinkage and improved quality of life. Treatment has been complicated by paronychia, eczema exacerbation, chondrodermatitis nodularis helicis, RSV and influenza B infection and CTCAE grade 2 pneumonia. In spite of the side effects these two patients remain on treatment due to clear benefit from therapy including: improved hearing and speech, hearing and dysphagia, difficulty eating and reduced pain. We will present the data of additional patients treated with trametinib. CONCLUSION: Trametinib is an effective therapy for life threatening PNF by changing the natural history of tumor growth in young children. Further data is required in terms of tolerance, efficacy and durability of response in such patients in the setting of clinical trials.

NFB-13. TRAMETINIB FOR PLEXIFORM NEUROFIBROMA AND RECURRENT LOW-GRADE GLIOMA
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BACKGROUND: Based on early clinical efficacy data, Seattle Children’s established a standard clinical practice for MEK inhibitor therapy for children with plexiform neurofibroma (PN) or recurrent low-grade glioma (LGG). METHODS: Data were collected using an IRB-approved retrospective chart review. Trametinib was prescribed off-label at 0.025 mg/kg (LGG) and inoperable refractory low grade gliomas (LGG). RESULTS: Two patients were treated for indication of life threatening extensive PNF and have had tumor shrinkage and improved quality of life. Treatment has been complicated by paronychia, eczema exacerbation, chondrodermatitis nodularis helicis, RSV and influenza B infection and CTCAE grade 2 pneumonia. In spite of the side effects these two patients remain on treatment due to clear benefit from therapy including: improved hearing and speech, hearing and dysphagia, difficulty eating and reduced pain. We will present the data of additional patients treated with trametinib. CONCLUSION: Trametinib is an effective therapy for life threatening PNF by changing the natural history of tumor growth in young children. Further data is required in terms of tolerance, efficacy and durability of response in such patients in the setting of clinical trials.

NFB-14. PSYCHOSOCIAL OUTCOMES IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1 AND PLEXIFORM NEUROFIBROMAS
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OBJECTIVE: This case series seeks to examine neurocognitive outcomes, social-emotional functioning, and family burden in young children diagnosed with Neurofibromatosis, type 1 (NF1) with early growing plexiform neurofibromas (PNFs). BACKGROUND: Neurofibromatosis, type 1 (NF1) is a common predisposing chronic disease arising in early childhood, with a broad neurocognitive and social-emotional profile. METHODS: Participants with NF1 and PNFs (n=2) aged 6-7 years completed comprehensive neuropsychological evaluations and parents completed measures of quality of life, social-emotional functioning, family adaptability, and family cohesion. RESULTS: Outcomes suggest broad neurocognitive dysfunction (e.g., executive functioning deficits, attention problems, visual-motor delays, and poor motor coordination), social-emotional challenges (e.g., symptoms of anxiety and depression, and poor social skills), and familial distress. CONCLUSIONS: Findings indicate the value of early and frequent monitoring of children with PNFs in medical systems and multidisciplinary teams, and the importance of early intervention for both children and families.

NFB-15. MITOROPATHIES AND SUBEPENDYMAL GIANT CELL ASTROCYTOMAS: PREDICTIVE VALUE OF GERMINAL TSC1/2 MUTATIONS SCREENING IN FAMILIAL CASES
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mTOR controls several important aspects of cell function particularly in the nervous system. Its hyperactivation has been involved in tuberous sclerosis complex (TSC) and other mTORopathies as well as drug-resistant epilepsy. Mutations in TSC1 and TSC2 genes cause loss of normal inhibitory function of the mTORC1 complex, leading to overgrowth and disruption of neurodevelopment and neoplasms, including SEGAs, TSC1 gene mutations showed through this report, the predictive value of germinal TSC1/2 mutations screening in familial cases.