NFB-05. A FAMILY-CENTERED NEUROCUTANEOUS SYNDROME CLINIC IN THE AGE OF TARGETED THERAPIES

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On April 10, 2020, the FDA approved selumetinib for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 who have symptomatic, inoperable plexiform neurofibromas. This, combined with the 2016 EXIST-3 data showing the efficacy of adjunctive everolimus in the treatment of tuberous sclerosis associated seizures, have resulted in the re-imagining of the treatment of these neurocutaneous syndromes and subsequently, the multidisciplinary clinics in which they are treated. In early 2021, this reshaping resulted in the launch of a unique, family-centered clinic at Yale New Haven Children's Hospital serving children and young adults up to 30 years of age in the management of NF1, NF2, tuberous sclerosis and schwannomatosis. Here we present the clinical reasoning and benefit of a multidisciplinary, family-centered clinic that manages to combine on-site, real-time access to neuro-oncology, neurology, psychology, dermatology, orthopedics, genetics, and ophthalmology. We will describe how the collaboration of these specialists is essential for providing high-quality, easy-access care to patients and families with the above noted syndromes – particularly with the advent of effective, readily available targeted therapies that carry their own side effects requiring further subspecialty consultation. Furthermore, we will describe previous and ongoing challenges to the creation of such a clinic and offer solutions based on our experience.

NFB-06. LASER INTERSTITIAL THERMAL THERAPY AS A RADIATION-SPARING APPROACH FOR CHILDREN WITH CANCER PREDISPOSITION

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BACKGROUND: Li-Fraumeni (LFS) syndrome confers a predisposition for the formation of a broad range of tumors. Estimates of post-radiation secondary malignancy in the context of LFS cohorts range from 20-50%. Therefore, alternative therapeutic strategies are prioritized. Laser interstitial thermal therapy (LITT) is a minimally invasive technique utilizing thermal ablation for tumor control that is not associated with any ionizing radiation or known mutagenic effect. We describe the case of a child with LFS previously treated for CPC who developed a secondary low-grade glial neoplasm of the brain treated safely with MR-guided LITT as part of a radiation-sparing therapeutic approach. METHODS: Retrospective chart review identified a patient with recurrent CPC associated with LFS who was treated with LITT for a secondary low-grade glial tumor. A descriptive report is provided, including a review of clinical and radiologic outcomes of the procedure. RESULTS: A 4-year-old male with left parietal WHO Grade III CPC associated with a TP53 germline mutation met inclusion criteria. The patient underwent neoadjuvant platinum-based chemotherapy before near-total resection, followed by immunotherapy with 131I-8H9 and 30 fractions of 54Gy total proton therapy. He remained without evidence of disease for two years prior to developing a slow-growing mass adjacent to the left frontal horn. This lesion demonstrated radiographic progression on neuroimaging and was deemed to be a poor candidate for surgical removal. Stereotactic biopsy revealed a low-grade glial neoplasm staining positive for GFAP and Olig2. MR-guided LITT was concurrently performed for ablative therapy of the lesion without complication. Greater than 8-month follow-up has revealed no subsequent disease. CONCLUSIONS: Alternatives to ionizing radiation for brain tumors should be explored for patients with cancer predisposition, such as LFS. Long-term follow up will be needed to ensure local disease control and avoidance of treatment-related neoplasms.

NFB-07. MENINGIOMATOSIS IN AN ADOLESCENT WITH TRAF-7 MUTATION RELATED SYNDROME

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BACKGROUND: Meningiomas are rare primary brain tumors in the pediatric population, associated with multiple genetic mutations. Recent description of mutations in the TRAF7gene, a pro-apoptotic E3 ubiquitin ligase, have been found in up to one quarter of non NF-2 tumors. TRAF is downregulated in human keratinocytes after inhibition of the PI3K/AKT/mTOR signaling. Germ-line mutations in this gene are associated with facial, cardiac malformations, variable intellectual deficiency, and musculoskeletal abnormalities. OBJECTIVE: We report a case of meningiomatosis in an adolescent with TRAF 7 mutation. CASE PRESENTATION: A 17 yo female with complex medical history that includes syndactyly of the left foot, small hands and digits, congenital heart disease, overgrowth of the right lower extremity with lipomatous subcutaneous tumors, connective tissue disorder variant mutation of unknown significance in the gene Col11A2, conductive hearing loss developed meningiomas of both optic nerves requiring decompression and unroofing on two separate occasions, with associated blindness. MRI brain showed bilateral optic nerve sheath enhancement, dysplasia of the corpus callosum, mild hemimegalencephaly, inter-hemispheric fissure 1.5 cm meningioma, bilateral enhancement of internal auditory canals as well as trigeminal and glossopharyngeal nerve, consistent with menigiomatosis. Pathology showed a grade I meningioma with a TRAF7 p.G536S detected by performing a 500 genomic panel (UCSF500). She was started on Everolimus and Bevacizumab. CONCLUSION: Recurrent multiple meningiomas represent a treatment challenge for neuro-oncologists. The evolving understanding of the genetics of these tumors has improved our understanding of their pathogenesis as well as treatment. TRAF 7 mutations are associated with non-NF-2 meningiomas, and distinct phenotypic features. Germ-line testing should be considered in patients with associated malformations, as targeted therapy may improve patient outcomes.

NFB-08. TRAM-01: A PHASE 2 STUDY OF TRAMETINIB FOR PEDIATRIC PATIENTS WITH NEUROFIBROMATOSIS TYPE 1 AND PLEXIFORM NEUROFIBROMAS

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BACKGROUND: Plexiform neurofibromas (PN) are found in up to 50% of patients with neurofibromatosis type 1 (NF1). Trametinib has been used widely to treat PN but limited data has been reported on its efficacy within a clinical trial. METHODS: This ongoing multicenter phase II trial includes patients with pediatric low-grade glioma and PN. The primary objective for PN was to evaluate the overall response rate based on RECIST 1.1 criteria after daily oral trametinib administration for eighteen 28-day cycles. The volumes of PN were centrally quantified using a new semi-automatic 3D segmentation method. RESULTS: As of January 1, 2022, 45 patients with PN were enrolled in the study. Twenty-eight completed treatment and were available for analysis. For these patients, the median age was 11.4 years (range 0.7-19.8) including 16 males (57.1%). The majority did not receive prior systemic therapies (71.4%). The median volume of PN at baseline was 49.5 cm3 (range 2.6 to 469). Among the 28 patients, 25 (89.3%) completed 18 cycles as planned. One patient discontinued due to adverse reaction, one patient refused to continue treatment and one patient discontinued treatment based on physician decision. Median duration of treatment was 15.9 months (range 4.6 to 16.8). Median duration of follow-up was 29.7 months (range 17.7 to 38.1). A total of 32 PN were available for volumetric analysis. Using RECIST evaluation, the overall response rate was 24.1%. Volumetric assessment demonstrated an overall response rate of 60.7% and 62.5% of PN showed a decrease of more than 20% in volume. Median decrease in volume was -30% (range -93.5 to 14.3). Twenty-seven patients (93.1%) had durable response without progression (lasting ≥1 year). CONCLUSION: We report outcome and volumetric quantification of PN treated with trametinib within a large clinical trial. Based on the current results, trametinib appears effective and offers durable response.

NFB-09. TREATMENT OF CARDIAC FIBROMA IN A *PTCH1*-MUTATED GORLIN SYNDROME WITH MEDULLOBLASTOMA

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A 2,5-year-old girl presented vomiting episodes associated with severe motor delay, macrocephaly, and distal hypotonia. Brain MRI showed

hydrocephalus and a non-metastatic lesion in the posterior fossa. A preoperative ECG showed isodifasic T waves in leads V4R and V1, follow-up was recommended. Histology after gross total resection was consistent with Desmoplastic/Nodular Medulloblastoma. At chest X-rays a bifid rib was noted, leading to the diagnosis of Gorlin syndrome (GS; c.3306 + 1G>T in *PTCH1*). During chemotherapy, ventricular tachycardia (VT) occurred, requiring synchronized electrical cardioversion. An echocardiogram revealed an echogenic mass of the left ventricle free wall, but normal coronaries and ventricular function. Cardiac MRI (CMR) confirmed a 21x40x38mm mass, with eccentric development and intense homogeneous enhancement, indicative of cardiac fibroma (CF). A computed tomography excluded local calcifications. Therapy with amiodarone and beta-blocker was initiated. TREATMENT STRATEGY: priority to chemotherapy *vs* cardiac surgery; full-dose chemotherapy, preferring drugs with minor cardiotoxicity; administration in ICU under continuous vital parameters and ECG-monitoring. Other three VTs occurred during treatment or anesthesia, resolved after electrical cardioversion (unsuccessful attempts with i.v. adenosine and amiodarone). Lacking specific guidelines concerning CF in GS, a wait-and-see approach was preferred with close tumor follow-up and regular cardiological assessment (ECG, stress-test, Holter monitoring, CMR). No further arrhythmias were recorded in a 10-year-long follow-up and CMR confirmed CF stability. Medulloblastoma has never recurred. *PTCH1* variants are rarely associated with medulloblastoma (<2%). Only 3–5% of GS present CF, responsible for arrhythmias in 32%. Being non-regressing, total surgical resection is usually performed (without recurrence), with a 27-year-long median survival. When surgery risk/benefit ratio is not favorable or the patient is paucisymptomatic, the treatment plan remains unclear; probably, a conservative approach under a strict cardiological follow-up can be reasonable. In young children with syndromic medulloblastoma, a routine echocardiogram should be performed to rule out CF.

NFB-12. EFFECT OF TRAMETINIB ON LEG LENGTH DISCREPANCY IN A CHILD WITH NF1 RELATED PLEXIFORM NEUROFIBROMA

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INTRODUCTION: Plexiform neurofibroma(PN) is a challenging benign tumor. Recently, MEK inhibitors (MEKi) showed encouraging tumor response. We report the observed effect of Trametinib on leg length discrepancy (LLD) in a child with NF1. CASE DESCRIPTION: A 4 year old girl with sporadic NF1, developed progressive bilateral L1-L5 paraspinal PN extending to the left thigh resulting in hypertrophy of left leg and associated with LLD. At 33 months of age, length difference of 2.8 cm between both femurs was described on scanogram with a projected LLD of at 6.1- 6.2 cm LLD at bone maturity using the multiplier method, a common method of predicting LLD. At 36 months of age, treatment with Trametinib was initiated for her large PN. Ten months into therapy, parents reported impression of decrease swelling of her left thigh enlargement. MRI evaluation showed stable measurement of PN using the RECIST criteria. Repeat measurement on scanogram at 46 months of age disclosed a stable difference of 2.8 cm between both femurs, with a LLD projected at 5.2-5.3 cm at maturity by multiplier method. Bone age at study entry and at 11 months into therapy (Greulich-Pyle) was reported normal for chronologic age. DISCUSSION/CONCLUSION: LLD has not been commonly described in association with NF1 related PN. Given the PN involved mainly the left thigh in our patient, it is reasonable to suggest common underlying mechanism for the PN and faster growth of her left femur. Although with limited time point's measurements, the early observation of stabilization of the LLD, 10 months into Trametinib therapy suggesting a final discrepancy in femurs length less than initially predicted, is encouraging. Further evaluation at completion of treatment and on follow-up are needed. Larger case series will be useful to explore this unexpected and possible clinical effect of MEKi in NF1 children.

NFB-13. RHABDOID TUMOR PREDISPOSITION SYNDROME (RTPS) – FINDING EVIDENCE BY SYSTEMATIC ANALYSES

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BACKGROUND: Individuals with rhabdoid tumor predisposition syndrome (RTPS1 – *SMARCB1*, RTPS2 – *SMARCA4*) have a propensity to develop malignant rhabdoid tumors (MRT). Affected patients typically present < age 12 months with synchronous tumors (SYN) exhibiting an unusually aggressive clinical behavior. Due to the rarity of RTPS, standards for management are evolving. METHODS: Clinical, genetic, and treatment data of 90 patients with RTPS from 16 countries were analyzed (2004 – 2020). Therapy followed the EU-RHAB recommendations. Tumors and matching blood samples were investigated for *SMARCB1* and/or *SMARCA4* mutations using FISH, MLPA and sequencing. DNA-methylation subgroups were determined using DNA methylation arrays. RESULTS: The median age at diagnosis of 52 girls and 38 boys was 5.5 months (0 – 203). 55.5% (50/90) of patients