Evaluation and Treatment of Inoperable Plexiform Neurofibroma in Neurofibromatosis Type-1 Patients

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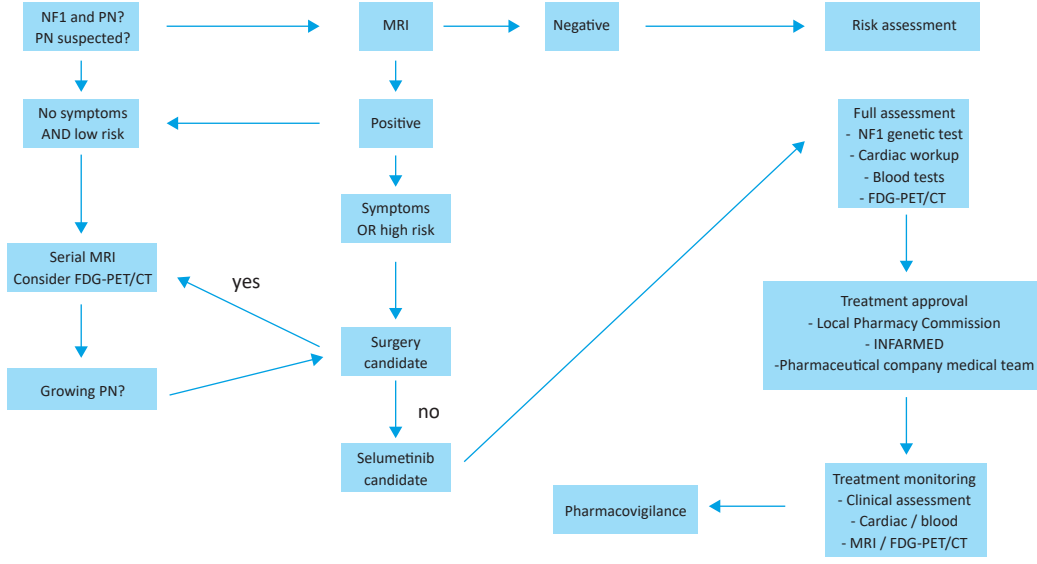
Neurofibromatosis type 1 (NF1) is a tumor predisposition autosomal dominant disorder with an estimated incidence of 1:3,000 individuals.[1] Plexiform neurofibromas (PN), which occur in up to 50% of neurofibromatosis type 1 patients[2], are benign nerve sheath tumors consisting of well-differentiated Schwann cells that tend to grow along the length of the nerve.[3] The lifetime risk of plexiform neurofibromas progression to a malignant peripheral nerve sheath tumor is around 10%.[4]

The transition from plexiform neurofibromas to a malignant peripheral nerve sheath tumor (MPNST) correlates with intermediate histological atypical features, specific molecular markers, such as the heterozygous or homozygous loss of the *CDKN2A/B* loci[5] and increased metabolism in fluorodeoxyglucose positron emission tomography (FDG-PET/CT) studies.[6] Selumetinib (AZD6244, ARRY-142886), an investigational mitogen-activated protein kinase kinase (MEK) 1/2 inhibitor, is a new treatment option for inoperable symptomatic plexiform neurofibromas.[7,8]

Two trials assessed selumetinib efficacy in the treatment of neurofibromatosis type 1 children with inoperable plexiform neurofibromas. A phase I trial reported a partial response rate of 71% (there was tumor volume reduction equal or superior to 20% from baseline in 17 of 24 treated patients).[7] A subsequent phase II trial evaluated the response in 50 children and the results were similar with a partial response in 72% of patients,[8] but selumetinib's long-term side effects and optimal treatment duration are still unknown.



FDG-PET/CT - fludeoxyglucose positron emission tomography; INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde; MPNST - malignant peripheral nerve sheath tumor; MRI - magnetic resonance imaging; NF1 - neurofibromatosis type 1; PN - plexiform neurofibroma.

Figure 1. Proposed algorithm for the assessment, treatment, and follow-up of pediatric patients with suspected or confirmed plexiform neurofibromas.

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We are currently following 31 pediatric patients (age < 21 years) with inoperable plexiform neurofibromas at our institution. Our initial workup includes magnetic resonance imaging (MRI) of target plexiform neurofibromas, FDG-PET/CT, electrocardiogram, echocardiogram, complete blood count, renal and hepatic tests, creatine phosphokinase, and genetic confirmatory testing after geneticist consultation (full assessment period varies between two and four months, pending on previous molecular genetic testing for neurofibromatosis type 1 gene status). The inclusion criteria for selumetinib treatment are inoperable plexiform neurofibromas associated with significant morbidity, baseline MRI, confirmed neurofibromatosis type 1 gene mutation by molecular testing, malignant peripheral nerve sheath tumor exclusion after PET-FDG/CT, normal laboratory results, and cardiac function. If the patient fulfills all of the inclusion criteria, further multi-institutional review and approval follows from local pharmacy commission, Autoridade Nacional do Medicamento e Produtos de Saúde (INFARMED), and the pharmaceutical company medical team (Fig. 1).

Since April 2018, 18 patients started selumetinib treatment. Five patients are under evaluation. Eight patients did not meet all of the inclusion criteria: five had asymptomatic plexiform neurofibromas, one patient refused treatment, one patient had a malignant peripheral nerve sheath tumor and died shortly after diagnosis, and one patient was ineligible for treatment due to low-performance status and died after plexiform neurofibromas related complications.

Among the 17 patients currently under treatment, the median treatment period is five months (0-12 months). Pain resolution/improvement occurred in nine patients out of 11 patients, deformity improvement in seven out of 15 patients, gait improvement in four out of six patients, urinary incontinence resolution/improvement in three of three patients, speech articulation improvement in one out of one patient. Among the 11 out of 18 MRI-reassessed patients, seven out of 11 patients had a plexiform neurofibromas size reduction and the remaining four had a stable disease.

Major toxicities occurred in 14 out of 18 patients: asymptomatic creatine phosphokinase increase in two, asymptomatic left ventricular ejection fraction reduction (≥ 10% drop from baseline) in four, acneiform rash in four, mouth ulcers in one, genital ulcers in one, and paronychia in two patients. Treatment suspension occurred in one patient due to side effects and suspected malignant transformation. Dose reduction was necessary in one patient due to persistent paronychia.

Our results reproduce the positive outcomes found in previous phase I and phase II studies and explain the gradual paradigm shift in favor of early pharmacological treatment. The uncertainties regarding long-term side effects and optimal duration of treatment are two important issues that remain unanswered. Early referral to specialized centers could prevent increased morbidity related to delayed treatment and further plexiform neurofibromas growth.

Keywords: Adolescent; Child; Neurofibroma, Plexiform/diagnostic imaging; Neurofibromatosis 1/diagnostic imaging; Neurofibroma, Plexiform/drug therapy; Neurofibromatosis 1/drug therapy; Selumetinib

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Provenance and peer review

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Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

References

1. Uusitalo E, Leppävirta J, Koffert A, Suominen S, Vahtera J, Vahlberg T, et al. Incidence and mortality of neurofibromatosis: A total population study in Finland. J Invest Dermatol 2015;135:904-6. doi: 10.1038/jid.2014.465.

2. Mautner VF, Asuagbor FA, Dombi E, Fünsterer C, Kluwe L, Wenzel R, et al. Assessment of benign tumor burden by whole-body MRI in patients with neurofibromatosis 1. Neuro Oncol. 2008;10:593-8. doi: 10.1215/15228517-2008-011.

3. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. WHO classification of tumours of the central nervous system. 4th ed. Geneva: World Health Organization; 2016.

4. Evans DG, Baser ME, McGaughran J, Sharif S, Howard E, Moran A. Malignant peripheral nerve sheath tumors in neurofibromatosis 1. J Med Genet 2002;39:311-4. doi: 10.1136/jmg.39.5.311.

5. Carrió M, Gel B, Terribas E, Zucchiatti AC, Moliné T, Rosas I, et al. Analysis of intratumor heterogeneity in neurofibromatosis

type 1 plexiform neurofibromas and neurofibromas with atypical features: Correlating histological and genomic findings. Hum Mutat 2018;39:1112-5. doi: 10.1002/humu.23552.
6. Ferner RE, Huson SM, Thomas N, Moss C, Willshaw H, Evans DG, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet 2007;44:81-8. doi: 10.1136/jmg.2006.045906.
7. Dombi E, Baldwin A, Marcus LJ, Fisher MJ, Weiss B, Kim A, et al. Activity of selumetinib in neurofibromatosis type 1 – related plexiform neurofibromas. N Engl J Med 2016;375:2550-60. doi: 10.1056/NEJMoa1605943.
8. Gross AM, Wolters P, Baldwin A, Dombi E, Fisher MJ, Weiss BD, et al. SPRINT: Phase II study of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886) in children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN). J Clin Oncol 2018;36:10503. doi: 10.1200/JCO.2018.36.15_suppl.10503.