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ORIGINAL PAPER

Therapy with selumetinib in children with neurofibromatosis type 1 in Poland – clinical experience of the first year of the national program

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ABSTRACT

Introduction: Plexiform neurofibroma (PN) is one of the predominant symptoms of neurofibromatosis type 1 (NF1), being responsible for significant morbidity. Medical care of children with NF1 in Poland is supervised by pediatric oncologists. Since 2020 the coordinating medical care (CKOM) pilot program has been held in Poland, consisting of/covering 6 pediatric oncology centers (Bydgoszcz, Gdansk, Olsztyn, Cracow and 2 centers in Warsaw). Since 2024 the treatment for NF1-related PNs with selumetinib (MEK inhibitor) in pediatric patients has been reimbursed due to the national therapeutic program (B.155) provided by the National Health Fund and offered in up to now in 15 pediatric oncology departments, including CKOMs. The aim of this study was to analyze the effectiveness of the national therapeutic program in the first fourteen months of its activity.
Material and methods: A total of 79 pediatric patients were included in the national program from January 2024 to the end of February 2025. We analyzed demographics, tumor location and size. The preliminary data also included adverse effects and the effectiveness of therapy. Patients were assessed before the inclusion into the program and periodically in 4-month periods of treatment.
Results: Overall, partial regression was observed in 35.3% patients already after 8 months of therapy with selumetinib, including 17.6% of them who met the criteria of confirmed partial response; one patient experienced

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progression of the lesion. The most frequently reported adverse effects included the acne-like rash; only one patient required permanent dose reduction of selumetinib.

Conclusions: The findings of our study align with those of the SPRINT study; no additional safety concerns emerged.

KEY WORD:

children, neurofibromatosis type 1, plexiform neurofibroma, selumetinib.

INTRODUCTION

Neurofibromatosis type 1 (NF1) is a rare genetic disease with a birth incidence of up to 1 : 3000 [1–3]. Plexiform neurofibroma (PN), histologically benign tumor of the peripheral nerve sheath, is one of the most common NF1-dependent tumors with a prevalence of up to 50–60% of patients [1–6]. The diagnosis of PN is often made in early childhood. Plexiform neurofibroma may occur in every part of the body, with a prevalence of the head, neck and extremities[4, 5]. Plexiform neurofibroma can cause a variety of morbidities including disfigurement, pain and other symptoms related to the tumor location, such as vision and hearing impairment or motor and airways dysfunction. It constitutes an increased risk of transformation into malignant peripheral nerve sheath tumors and is responsible for mortality risk in patients with NF1 [1, 3–5]. Patients with NF1 are at increased risk of other neoplasia as well [1–3].

Until the second decade of the XXI century, surgery was a standard treatment for PN, however the radical resection of tumor mass is usually not feasible, due to the risk of severe local complications, mostly neurological, and unfavorable location. In up to 50% of patients the high rate of recurrence is the clinically important issue after the debulking surgery only [3]. In June 2021 an innovative selumetinib therapy was approved by the European Medicines Agency for pediatric patients aged over 3 years with inoperable, symptomatic PNs, which has become the breakthrough option in PN therapy [7]. Since January 2024 selumetinib has been available and fully reimbursed in Poland for NF1 children affected by PNs and fulfilling the National Health Fund (NHF) reimbursement inclusion criteria. The objective of our study was the analysis of one-year program in terms of safety and efficacy of selumetinib.

MATERIAL AND METHODS

STUDY DESIGN

The prospective multi-center analysis was performed on a cohort of patients with NF1-related PNs included in the NHF therapeutic program B.155 in Poland.

PATIENTS

From January, 1st, 2024 to February, 28th, 2025, a total number of 79 patients were included into the B.155 therapeutic program. All NF1 patients affected by inoperable and clinically significant PNs, fulfilling B.155 program inclusion criteria (Table 1) were treated in 15 pediatric oncology departments in Poland.

ANALYZED FACTORS

We analyzed patients' demographics, PN location and size (assessed in volumetric magnetic resonance imaging (MRI)) as well as adverse effects of the treatment.

TUMOR RESPONSE EVALUATION AND RESPONSE CRITERIA

Children with NF1-related, inoperable PNs received selumetinib orally twice daily. Imaging analysis (volumetric MRI), laboratory tests and observer-reported outcome measures were performed every 4 cycles of therapy (1 course = 4 cycles, 1 cycle = 28 days). Partial response (PR) was defined as a decrease in tumor volume ≥ 20% from baseline, whereas confirmed partial response (CPR) was proved by meeting the above criterion on at least 2 consecutive MRI periodic scans. Stable disease (SD) was considered as tumor volume changes between –20% and +20% from baseline. Progressive disease (PD) was defined as an increase of the tumor volume ≥ 20% from the baseline (confirmed progressive disease – proved by meeting the PD criterion on at least 2 consecutive MRI periodic scans).

Presented criteria are similar to the Response Evaluation Criteria In Solid Tumors (RECIST), however the PR in RECIST is defined as a decrease of the sum of dimensions ≥ 30% whereas in the B.155 program as a decrease in tumor volume ≥ 20% from baseline [8].

ADVERSE EFFECT ASSESSMENT

Clinical examination, laboratory tests, cardiological and ophthalmological examinations were performed at baseline and on a regular basis at every therapy checkpoint in accordance with the B.155 program requirements. Adverse effects were graded according to the common terminology criteria for adverse events (CTCAE) scale v. 5.0 [9].

RESULTS

DEMOGRAPHICS

We analyzed prospectively 79 patients qualified for selumetinib treatment in the B.155 program by the end of February 2025. 65% of them were male (51/79) and

TABLE 1. Eligibility criteria to the B.155 Polish national therapeutic program

1) Age: ≥ 3 and ≤ 18 years of age.
2) Body surface area ≥ 0.55 m^2.
3) Ability to swallow whole capsules without destroying their shell or spilling the contents.
4) Clinically or molecularly confirmed diagnosis of neurofibromatosis type 1 (NF1) according to the latest criteria of the conference consensus NIH-88.
5) Symptomatic, i.e. causing significant clinical symptoms requiring medical intervention or causing a threat to health or life, inoperable plexiform neurofibroma of at least 3 cm in one dimension which cannot be completely removed surgically without the risk of significant complications due to the location or direct proximity of crucial anatomical structures, invasiveness or rich vascularity, causing a surgical risk of the procedure.
   A patient who has undergone a plexiform neurofibroma (PN) resection may qualify for the treatment provided that the PN has not been completely removed and its volumetric magnetic resonance imaging assessment is possible.
6) Performance status:
   a) adults and children aged at least 16 years of age, at least 70% on the Karnofsky scale,
   b) children under 16 years of age, at least 70% on the Lansky scale.
7) Adequate organ function determined on the basis of laboratory blood test results in accordance with the current summary of product characteristics.
8) Absence of significant co-existing conditions and diseases constituting a contraindication to therapy identified by the Coordination Team or the attending physician, based on the current summary of product characteristics.
9) Absence of ongoing anticancer therapy regardless of the cause, in particular: radiotherapy, chemotherapy, hormonal therapy, anticancer immunotherapy or biological therapy.
10) Absence of transformation of PN into malignant peripheral nerve sheath tumor; in PN with radiological or clinical signs of excitation (atypical PN) based on biopsy and histopathological examination.
11) Absence of pathological changes in an ophthalmological examination suggesting retinal pigment epithelial detachment or central serous retinopathy with reduced visual acuity and glaucoma (excluding visual disturbances related to complications of the development of typical for NF1 optic nerve gliomas or orbital PNs).
12) At least:
   a) 4 weeks since any pharmacological treatment for PN and disappearance all acute adverse effects,
   b) 6 weeks since radiotherapy,
   c) 4 weeks since surgical procedure.
13) No contraindications to the use of selumetinib.
14) Exclusion of pregnancy and breastfeeding.

The qualification criteria must be met cumulatively.

35% female (28/79). The patients were aged 3–18 years with the median age of 12 at the treatment beginning. One patient, included in the program at the age of 17, was excluded from the study due to turning 18 by the first release of the drug. Most patients were treated in the Pediatric Oncology departments of Medical Universities in Bydgoszcz (25/79), Warsaw (16/79) and Lodz (7/79).

Overall, 26 patients (33%) were included in the program due to pain caused by the PN, while 69 due to deformation of their body (87%), including 16 (20%) who experienced both pain and deformation. Additionally, one patient was included into the program due to life-threating tumor located near the trachea.

LOCATION OF THE PN

According to location of the target PN, patients were divided into five groups: head and neck, chest, abdomen, limb and others. The most common location was head and neck (51.9%; 41/79) followed by chest (25.3%, 20/79) and abdomen and limb (17 patients each; 21.5%). Other locations included lumbosacral spine. In 15 patients (19.0%) we found clinically significant PNs located in more than one anatomical region – e.g. enormous tumor spreading from the head and neck to the chest.

EFFICACY OF TREATMENT

Until the end of February 2025, 59 patients completed the first course (4 cycles) of selumetinib therapy. Partial regression occurred in 30.5% (18/59) and stabilization of the PN's volume was observed in 69.5% (41/59) of them. None of the patients presented with the progression of the target lesion.

The evaluation of the tumor volume after eight cycles (2 courses) of therapy with selumetinib was possible in 34 patients among the group of 79 included in the B.155 program. Partial regression was observed in 35.3% (12/34) and SD in 61.8% (21/34) of them. One patient (2.9%) had to be excluded from the program due to the progression of the lesion. After second evaluation, 17.6% (6/34) of patients met the criteria of confirmed partial response.

ADVERSE EFFECTS

The most common adverse effect of selumetinib treatment in the study group was acne-like rash which occurred in 49.4% of cases (39/79), including CTCAE grade 1 in 39.2%; grade 2 in 8.9%; and grade 3 in 1.3%. Paronychia occurred in 31.6% of patients (25/79), including CTCAE grade 1 in 22.8%; 2 in 6.3%; and 3 in

2.5%. Less common adverse effects were hair loss (24.1%; 19/79) and change of hair color (17.7%; 14/79). The most common laboratory effect was kinase creatinine elevation, which was observed in 30.4% of cases (24/79), including CTCAE grade 1 in 24.1%; grade 2 in 6.3%; none of the patients experienced grade 3 and above. Five patients (6.3%) required temporary reduction of the drug dose due to the adverse effects, one of them (1/79, 1.3%) permanently.

DISCUSSION

Selumetinib is an innovative medicine which brings new hope for patients with NF1-related PNs. In patients undergoing this targeted treatment, tumor size reduction was observed, which resulted in restoration of mobility and overall quality of life, reduction of pain and a positive impact on the patients' mental health.

The main finding of our study is that selumetinib administered in patients with inoperable, NF1-related PNs is effective and is responsible for the stabilization or even reduction of the tumor volume. Although this treatment is causing numerous side effects, it is generally well tolerated by patients.

Even though preliminary, the overall efficacy of treatment with selumetinib after 8 cycles, proved by volumetric MRI, indicates that 17.6% of patients met the criteria of confirmed partial response, while in 61.8%, lesions were stable. In comparison, in Phase 2, Stratum 1 SPRINT clinical trial (NCT01362803), 50% of patients experienced CPR after 8 cycles of treatment [6, 10].Our findings indicate that comparable results are expected in the future when more patients get included in the national program. Observations across both 1 and 2 Phase, Stratum 1 SPRINT clinical trial show that median time to initial response was 8 cycles (varying 4–40 cycles), with median time to best response being 8 cycles (varying 4–94 cycles) [6]. The time to best response in the group studied by us is to be defined as the national program in Poland continues – in phase 2, Stratum 1 SPRINT clinical trial best results were observed after 16 cycles [10].

Although adverse effects were quite common in the assessed group of patients, most of them were the results of selumetinib's dermatotoxicity and could be managed with symptomatic treatment. In individual cases a dose reduction was required due to the severity of side effects, in one case out of 79 (1.3%) the reduction was permanent. In general, treatment with selumetinib was well tolerated. What is more, additional positive effects of the therapy (e.g. disappearance of café au lait macules) were observed; these are to be studied further.

A limitation of this study is a relatively short period of therapy (median follow-up was 4 months), with only 43% of patients that could be evaluated after 8 cycles of treatment. Further data collection is necessary to fully analyze the effectiveness of the treatment, especially durability of confirmed partial response, as well as its side effects and how they evolve in time.

CONCLUSIONS

Presented results align with those reported in the SPRINT study. No additional safety issues were observed during our program with selumetinib which is a key observation that should be considered when introducing a new therapeutic agent into real-world use.

DISCLOSURES

1. Institutional review board statement: The study was performed within National Health Service therapeutic program. The study was approved by local Bioethical Committee of Collegium Medicum in Bydgoszcz (decision KB 381/2024).
2. Assistance with the article: None.
3. Financial support and sponsorship: The study was conducted with the support of scholarship program financed by Saving Kids with Cancer Foundation.
4. Conflicts of interest: JnS, AM, AJG, MK, KG, EB, WB, AMM, JW – lecture fees and conference participation from AstraZeneca; KB, JWT – conference participation from AstraZeneca.

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