Targeted therapy with entrectinib in children with NTRK rearranged mesenchymal neoplasms

Maja Pavlović, Domagoj Buljan, Aleksandra Bonevski*

Non-rhabdomyosarcoma soft-tissue sarcoma (“RMS-like” and “non-RMS-like” tumours- NRSTS) of childhood is a highly heterogeneous group of tumours. Within the subgroup of undifferentiated sarcomas (UDS), new entities have been described based on molecular markers found through increasingly available genetic analysis in the new 2020 classification of the World Health Organization (WHO). In recent years, the importance of genetic analysis and the detection of molecular tumour markers has been growing due to the possibility of targeted therapy application and the determination of prognosis or disease course. We will present two patients with soft tissue sarcoma and neurotrophic tyrosine receptor kinase (NTRK) gene rearrangement, focusing on excellent therapeutic response to NTRK inhibitor targeted therapy with good drug tolerance.

Keywords: SOFT TISSUE; SARCOMA; NTRK FUSION; ENTRECTINIB; MOLECULAR TARGETED THERAPY; CHILDREN

SHORT INTRODUCTION

Within the group of non-rhabdomyosarcoma soft-tissue sarcoma (NRSTS) in the previous classifications of the World Health Organization (WHO) based on conventional histological analysis and immunohistochemistry, a group called “Undifferentiated small round cell sarcoma other than Ewing sarcoma” was identified. However, the increasingly available genetic analysis (Next Generation Sequencing - NGS) of tumours within this group reveals new entities based on the molecular markers of tumour cells. Therefore, the 2020 5th edition of the WHO classification introduces new sarcoma entities, among which we highlight the “NTRK-rearranged spindle cell neoplasm” (1). The standard of care for paediatric patients with soft-tissue sarcoma is multimodality therapy consisting of multi-agent chemotherapy plus surgery and/or radiation therapy. The literature emphasizes the favourable therapeutic effect of tyrosine kinase inhibitors in sarcomas with detected NTRK rearrangement (2). Accordingly, in our two patients, we observed an excellent therapeutic response without the development of severe side effects even after long-term drug use. The importance of confirming new sarcoma entities lies in the possibility of targeted therapy and determining the different course and prognosis of the disease.

CASES

A nine-month-old girl initially presented with recurrent chalazion of the right upper eyelid. Conservative multi-month local therapy with antibiotics and corticosteroids did not yield a satisfactory clinical response. At the ages of two and three years, excision of the formation was performed, with the pathological finding corresponding to a chalazion and capillary hemangioma. Systemic therapy with beta-blockers was introduced in addition to local treatment without clinical effect. In the third year of life, radical excision of the formation was performed with reconstruction. Histopathological analysis with molecular analysis established the diagnosis of “NTRK-rearranged spindle cell neoplasm” (LMNA-NTRK fusion) by the new classification of soft tissue tumours of the World Health Organization from 2020 (1). The neoplasm was characterized by increased cellularity and relatively low mitotic activity. Resection margins were positive.

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The possibility of an aggressive clinical course could not be excluded. Oral entrectinib therapy in a standard paediatric dose of 300 mg/m² daily (divided into two doses) was initiated as first-line therapy. The patient has tolerated the medication very well and has been without the clinical or radiological signs of local relapse (magnetic resonance imaging) for more than three years of follow-up. She is currently taking entrectinib.

A 12-year-old boy presented with a solid expansive lesion of the lesser pelvis extending towards the groin and anterior abdominal wall (locoregional disease – Figure 1). Tumour tissue sampling confirmed a malignant peripheral nerve sheath tumour (MPNST). Neoadjuvant systemic chemotherapy according to the EpSSG-NRSTS protocol followed by the radiotherapy (total dose of 66 Grey) accomplished only partial reduction of the tumour mass (Figure 2), prompting next-generation sequencing on formalin-fixed paraffin-embedded tissue blocks (FoundationOne®Heme) that confirmed LMNA-NTRK1 fusion. Oral entrectinib has been initiated in a standard paediatric dose of 300 mg/m² once daily leading to significant tumour shrinkage (Figure 3) that enabled complete surgical resection after only a few months of therapy. No viable tumour cells were found in the material. The adverse effects registered in this case were forearm fracture and increased appetite accompanied by significant weight gain that is diminished after medication dose reduction. He has been receiving this medication for two years. In a follow-up period of another two years (after the drug was discontinued), our patient is still in remission.

DISCUSSION

Non-rhabdomyosarcoma soft-tissue sarcomas (NRSTS) from nonepithelial, extraskeletal tissues comprise 4% of childhood cancers (3). The rarity of each histotype of NRSTS makes the performance of clinical trials on a single tumour type very difficult. Therefore, they are treated as one group according to standard protocols of different groups like the International Society of Pediatric Oncology - Mixed Mesenchymal Tumor (SIOP MMT) group, German Cooperative Weichteilsarkom Study (CWS) Group, the European Paediatric Soft Tissue Sarcoma Study group (EpSSG), the Italian Soft Tissue Sarcoma Committee (AIEOP STSC), and Children’s Oncology Group (COG) (3). Those patients are treated with standard multimodality therapy (i.e., chemotherapy plus surgery and/or radiation therapy). Although tumour size and surgery (postsurgical stage) are the most significant prognostic factors, pathology is essential for risk stratification of NRSTS and evaluating prognosis (4). NRSTS are generally considered moderate or poorly chemo-sensitive tumours (5); therefore, targeted therapy seems valuable in those patients.

Tropomyosin receptor kinase (TRK) is encoded by the neurotrophic tyrosine receptor kinase genes (NTRK) 1, 2, and 3. Fusions of these genes lead to activation of TRK, having tumourigenic potential through hyperactivation of downstream signalling pathways that impact cell cycle proliferation, differentiation, and survival (6). NTRK fusions are detected in many different types of tumours and were first discovered in colon carcinoma in 1982 (7). Regarding sarcomas, the ETV6-NTRK3 fusion was first described in congenital fibrosarcomas in 1998 (8). Regardless of tumour type, NTRK-fused neoplasms can be successfully treated with
NTRK inhibitors with a good tolerance profile. The Food and Drug Administration (FDA) approved the first-generation TRK inhibitors, LOXO-101 (larotrectinib) in 2018 (9) and entrectinib in 2019 (10), for the treatment of tumours with NTRK fusions in both adult and paediatric patients. The European Medicines Agency (EMA) approved larotrectinib in 2019 and entrectinib in 2020. In some cases, additional mutations lead to resistance to therapy (6). Fortunately, the next-generation TRK inhibitors such as LOXO-195 (11) and TPX-0005 (12) are available.

The first-line NTRK inhibitor (entrectinib) given in a paediatric dose of 300 mg/m² once daily orally was generally well tolerated in our two cases (13). In the first case, it was introduced as a first-line therapy with excellent response, no significant adverse events and no development of resistance to the drug despite the long period of therapy (more than three years). In the second case, an unsatisfying response to standard therapy was an indication for the NGS analysis. Fortunately, NTRK gene rearrangement was detected, and entrectinib was introduced, with an excellent response. Goulding et al. first described a paediatric case with NTRK1-rearranged sarcoma receiving neo-adjuvant TRK inhibitor with an excellent response that can be compared to our first case (14). The overall objective response rate (ORR) of the patients with advanced or metastatic NTRK fusion-positive solid tumours (n = 54) treated with entrectinib was 57%, with 7% achieving a complete response and median progression-free survival of 11 months (15). A multicentre, open-label, phase 1/2 study by Laetsch et al. showed a high response rate in 24 paediatric patients with advanced TRK fusion tumours treated with TRK inhibitors with a good tolerance profile comparable with our cases (16). The most common side effects of entrectinib are hepatotoxicity (42%), dizziness (38%), cognitive impairment (27%) and skeletal fractures (23%), mostly grade 1/2 and manageable/reversible with dose modifications (17). Although some adverse events occurred in the second patient, they were manageable, toxicities Grades 2 according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Both patients are still in remission within three and two years of the follow-up, and no late effects have been noticed. Despite these facts, late effects, including late relapse and secondary tumours, are little known so far. Long-term follow-up and more cases are needed to provide us with more information.

In conclusion, implementing the targeted therapy has enabled the avoidance of mutilating surgery and the adverse effects of conventional cytostatic agents in the first case. Excellent control of malignant mesenchymal tumours has been achieved in the second case. The NGS analysis is significant for treating patients and predicting clinical course and outcome. Therefore, the extent of genetic analysis in the future will reveal some other new entities suitable for targeted therapy and with better outcomes for our patients.

**Abbreviations:**

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<tr>
<th>Acronym</th>
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<tr>
<td>RMS</td>
<td>Rhabdomyosarcoma</td>
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<td>NRSTS</td>
<td>“non-RMS-like” soft tissue sarcoma</td>
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<td>UDS</td>
<td>Undifferentiated sarcoma</td>
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<td>WHO</td>
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<td>NTRK</td>
<td>Neurotrophic tyrosine receptor kinase</td>
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<td>NGS</td>
<td>Next Generation Sequencing</td>
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<td>CWS Group</td>
<td>Cooperative Weichteilsarkom Study Group</td>
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<td>STSC</td>
<td>Soft Tissue Sarcoma Committee</td>
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<td>EpSSG</td>
<td>European Paediatric Soft Tissue Sarcoma Study Group</td>
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<td>COG</td>
<td>Children’s Oncology Group</td>
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<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
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<td>FDA</td>
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S A Ž E T A K

Ciljana terapija entrektinibom u djece s mezenhimalnim neoplazmama s NTRK rearanžmanom

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Mekotkivni ne-rabdomiosarkomi djece dobi vrlo su heterogena skupina tumorova. U podskupini nediferenciranih sarkoma, prema nađenim molekularnim biljezama u sklopu sve dostupnije genetske analize, u novoj klasifikaciji Svjetske zdravstvene organizacije iz 2020.g., navedene su nove dijagnoze. Zadnjih godina raste važnost genetske analize i detekcije molekularnih markera tumorova zbog mugućnosti primjene ciljne terapije i boljeg utvrđivanja prognoze odnosno tijeka bolesti. Prikazat ćemo dva pacijenta s mekotkivnim sarkomom i rearanžmanom u nereceptorskom tirozin kinaza (NTRK) genu, s naglaskom na odličan terapijski odgovor na ciljnu terapiju NTRK inhibitorom i dobru toleranciju lijeka.

Ključne riječi: MEKOTKIVNI SARKOM, NTRK FUZIJA, ENTREKTINIB, MOLEKULARNA CILJNA TERAPIJA, DJECA