Clinical and Translational Oncology
https://doi.org/10.1007/s12094-023-03175-9

BRIEF RESEARCH ARTICLE

Therapeutic strategies and clinical evolution of patients with infantile fibrosarcoma: a unique paediatric case series

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Received: 16 February 2023 / Accepted: 26 March 2023

Abstract

Background Infantile fibrosarcoma is the most frequent soft tissue sarcoma in newborns or children under one year of age. This tumour often implies high local aggressiveness and surgical morbidity. The large majority of these patients carry the ETV6–NTRK3 oncogenic fusion. Hence, the TRK inhibitor larotrectinib emerged as an efficacious and safe alternative to chemotherapy for NTRK fusion-positive and metastatic or unresectable tumours. However, real-world evidence is still required for updating soft-tissue sarcoma practice guidelines.

Objective To report our experience with the use of larotrectinib in pediatric patients.

Methods Our case series shows the clinical evolution of 8 patients with infantile fibrosarcoma under different treatments. All patients enrolled in this study received informed consent for any treatment.

Results Three patients received larotrectinib in first line. No surgery was needed with larotrectinib, which led to the rapid and safe remission of tumours, even in unusual anatomical locations. No significant adverse effects were observed with larotrectinib.

Conclusion Our case series supports that larotrectinib may be a therapeutic option for newborn and infant patients with infantile fibrosarcoma, especially in uncommon locations.

Keywords Infantile fibrosarcoma · *ETV6–NTRK3* translocation · Molecular profiling · Tumour-agnostic therapy · Tyrosine receptor kinase inhibitor · Larotrectinib

Introduction

Infantile fibrosarcoma (IFS) is a rare tumour, but it is the most frequent soft-tissue sarcoma in newborns or children under 1 year of age. IFS usually originates in the upper and lower limbs and it presents rapid initial growth, though it rarely metastasizes (1–13% of the cases) [1]. Despite favourable overall survival (80–100%) of these patients [2], IFS implies local aggressiveness and a heavy therapeutic burden. First-line treatment of IFS is surgical resection, which may be preceded by chemotherapy with ifosfamide, vincristine, and actinomycin D (IVA regimen or VA regimen if

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Published online: 25 April 2023

alkylating agents and anthracyclines are avoided) in those cases where, due to the size or location of the tumour, the surgery can be mutilating or cause major anatomic and functional damage [2]. Local recurrence may take place after conservative surgery in 17–43% of the cases [2].

The new and revolutionary tumour-agnostic therapies are based on specific genomic signatures instead of the tumour histology or location. Two novel therapies, larotrectinib and entrectinib, are tyrosine receptor kinase (TRK) inhibitors for treating solid tumours with neurotrophic TRK (*NTRK*) gene fusion that are metastatic or unresectable or in the absence of satisfactory therapeutic alternatives. Up to 90.1% of patients with IFS harbour the *NTRK* gene fusion, mainly the specific *ETV6–NTRK3* oncogenic fusion due to the translocation between chromosomes 12 and 15 [3], so TRK inhibitors emerged as a promising strategy for IFS treatment. However, entrectinib is not indicated for patients younger than 12 years [4].

Basket clinical trials have already demonstrated the pan-tumour efficacy of larotrectinib with a favourable safety profile in patients as young as 1 month of age [4, 5]. In 2018, the U.S. Food and Drug Administration (FDA) granted accelerated approval for the aforementioned indication [6]. In Europe, larotrectinib was the first tumour-agnostic approved drug under conditional marketing authorization due to the rarity of *NTRK* fusion-positive tumours [7]. Hence, further comprehensive clinical data outside a trial may be useful to confirm the positive benefit–risk balance and establish solid guideline recommendations for its use in infants. The first case series illustrates different therapeutic approaches to IFS tumours with diverse anatomical locations, including the successful use of larotrectinib that resulted in complete tumour remission.

Methods and results

A total of 8 neonatal and infant patients from University Hospital La Paz, Madrid, Spain were diagnosed with IFS between 2009 and 2022. The follow-up period indicated in Table 1 is based on the date of diagnosis and the approval of this manuscript draft by all coauthors (December 2022). The median age at diagnosis was 42 days [interquartile range (IQR) = 89.5 days]. The most frequent tumour location was the trunk in three (37.5%) patients followed by the axillary, cervical and cervicothoracic junction regions in another three (37.5%) patients. Two (25.0%) patients had locally advanced IFS. None presented metastasis. The presence of *ETV6–NTRK3* gene fusion could be confirmed in four (50.0%) out of six cases in which fluorescence in situ hybridization (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR) examination could be performed (Table 1).

The therapeutic approach to IFS consisted of exclusive surgery in three (37.5%) patients and surgery plus adjuvant chemotherapy in one (12.5%) *ETV6–NTRK3* fusion-positive patient. From 2019, larotrectinib (Vitrakvi, Bayer AG, Germany) was available and given to three (37.5%) fusion-positive patients, either on a compassionate-use or expanded-access basis (Table 1).

The 2-year overall survival rate for all patients was 83.3% (standard error (SE) = 15.2%) and the median follow-up time was 4.44 years (IQR = 8.05 years). A total of six (75.0%) patients were alive and remained disease-free during the follow-up period. The first two (25.0%) patients who had received exclusive oral targeted therapy (larotrectinib) presented complete remission within 3–5 months after the start of the treatment, which was maintained for more than a year without any relevant adverse events. Another newborn was recently diagnosed with a fusion-positive IFS tumour and presented with tumour remission after 6 months of treatment with larotrectinib without any signs of toxicity. We report two (25.0%) deaths. The first patient did not receive any oncologic treatments as he passed away within the first 48 h of life. The second one died at day 67 post-diagnosis, after being treated with surgery and adjuvant chemotherapy. In both cases, the tumours were located in the cervicothoracic and cervical region, respectively (Table 1).

Discussion and conclusions

The results presented herein show the rapid decrease in tumour size and achievement of tumour remission with larotrectinib in three infants with IFS tumours located in trunk and extremities without the need of surgery. Moreover, no safety issues were reported during the follow-up period. The observed clinical benefits of larotrectinib add to the ever-increasing evidence supporting the inclusion of neoadjuvant targeted therapy in routine cancer care and decision-making for IFS tumours carrying the *ETV6–NTRK3* translocation up to pathological complete remission or until conservative surgery is possible [1, 8, 9].

Outdated treatment algorithms for IFS need to be urgently addressed. Clinical guidelines developed by the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) do not contain a specific section for treatments with tumour-agnostic indications, and they do not specifically define their preferential application versus chemotherapy as neoadjuvants for advanced *NTRK*-rearranged soft-tissue sarcomas [10, 11]. The European paediatric Soft-tissue sarcoma Study Group (EpSSG) and the International Soft-Tissue Sarcoma Consortium (INSTRuCT) highlight the use of either conventional chemotherapy or TRK inhibitors in patients with advanced localized disease, as well as the use of TRK inhibitors in

Table 1 Differential characteristics of the study population

Patient	Sex	Year of diagnosis	Age at diagnosis	Tumour location	Tumour description at diagnosis	Assessment of translocation[a]	Treatment	Margin status[b]	Evolution	Follow-up since diagnosis (years)
1	Female	2009	1 d old	Upper limb-trunk: left axillary region	Locally advanced	n.d	Surgery: tumour dissection and *en bloc* resection	R0	Disease-free	13
2	Male	2010	1 d old	Trunk: lumbar region, on giant melanocytic nevus	Localized	n.d	Surgery: complete resection of the nevus and primary closure	R0	Disease-free	13
3	Male	2016	24 GW	H&N-trunk: left cervicothoracic region	Locally advanced	RT-PCR: negative	None		Deceased (within the first 48 h of life)	–
4	Male	2016	3 mo old	H&N: High cervical region (C2–C4)	Localized	RT-PCR: positive	Surgery: C2–C4 right decompressive hemilaminectomy and macroscopic incomplete resection; and adjuvant chemotherapy: IVA	R2	Deceased (67 d after diagnosis)	–
5	Female	2017	9 mo old	Trunk: right pectoral region	Localized	FISH: negative	Surgery: tumour resection	R1	Disease-free	6
6	Female	2019	1 d old	Trunk: abdominal retroperitoneal region	Locally advanced	FISH: positive	Oral larotrectinib 25 mg every 12 h for 1 y. No surgery	R0	Disease-free	3
7	Male	2020	3 mo old	Lower limb: left quadriceps region	Localized	FISH: positive	Oral larotrectinib 25 mg every 12 h for 10 mo. No surgery	R0	Disease-free	2
8	Female	2022	At birth	Lower limb	Localized	FISH: positive	Oral larotrectinib 22 mg every 12 h for 6 mo. No surgery	R0	Disease-free	2

d days, *ETV6* ETS variant gene 6, *FISH* fluorescence in situ hybridisation, *GW* gestation weeks, *H&N* head and neck, *IVA* ifosfamide, vincristine, and actinomycin D, *mo* months, *n.d.* not determined, *NTRK3* neurotrophic tyrosine receptor kinase type 3, *RT-PCR* reverse transcriptase polymerase chain reaction

[a]*ETV6–NTRK3* gene fusion upon t(12;15)(p13.2;q25.3) translocation

[b]R0, no residual tumour; R1, microscopic residual tumour; R2, macroscopic residual tumour

patients with metastatic disease or to avoid mutilating surgery when response to chemotherapy is insufficient [12, 13].

Unlike conventional cytotoxic chemotherapy, TRK inhibitors do not enhance the proliferation of resistant clones, but some acquired resistance mutations have been identified in TRK fusion-positive tumours upon sustained use of these agents. Although the actual frequency of resistance is still unknown, caution must be taken while balancing the achievement of therapeutic goals and the undesired occurrence of these alterations [14].

Limited access to medicine for paediatric patients also creates therapeutic gaps in IFS. Neonates have unique patient characteristics given the immaturity of their organ systems that challenge their safe enrolment in clinical studies and hence the rigorous evaluation of neonatal therapies. In this regard, the ongoing ON-TRK observational study was designed to document any long-term effects of larotrectinib on the growth and development of this paediatric subpopulation [15], but the long-term feasibility of this treatment has already been suggested given the low-grade side effects observed in the corresponding trials [16]. Finally, the galenic development of larotrectinib oral solution also offers an advantage over any other routes of administration and formulations otherwise not suitable for infants.

The limitations of this study include those associated with its retrospective nature. In addition, the small sample size was due to the restricted access of patients to larotrectinib in Spain through compassionate-use programmes or clinical trial enrolment, as it may be the case in other countries and otherwise adds value to the collected patient data. We could also show that larotrectinib monotherapy could be an option for newborn and infant patients with uncommon IFS locations.

The discovery of *NTRK* gene fusion as an actionable molecular target has paved a new way in cancer precision medicine for the youngest and hence the most vulnerable patients with IFS while preventing or minimizing the associated surgical morbidity and chemotherapy side effects. Our findings represent a call for action to prioritize the early molecular profiling of IFS tumours and subsequent use of TRK inhibitors in patients carrying *NRTK*-gene fusion.

Acknowledgements The authors would like to thank the parents of the patients for allowing us to present their clinical data. The authors would also like to thank CRIS Cancer Foundation (https://criscancer.org/en/) for its continuous research support and Bayer Spain for financing medical writing assistance, which was provided by Neus Cantariño (Trialance SCCL, Spain).

Author contributions MDCS and APM contributed to the acquisition, analysis and interpretation of data for the work and wrote the first draft of the manuscript. RJC, PRA, DPLS, ASU, JJP-K, JCLG, JMGC, and EJOC contributed to the acquisition, analysis and interpretation of data for the work. All authors contributed to the manuscript revision, and read and approved the submitted version.

Funding Medical writing services were funded by Bayer Spain.

Data availability statement Data are available at demand.

Declarations

Conflict of interest The authors have nothing else to declare.

Informed consent Patients enrolled in this study received informed consent for any treatment.

Ethical approval Ethical approval of the study was not obtained because we have IC from the patiens.

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