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Research Article

Clinical and Molecular Characteristics, Management and Outcome of Infantile Fibrosarcoma: A Retrospective 18-Year Single-Institution Review

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ABSTRACT

Infantile fibrosarcoma (IFS) is the most common non-rhabdomyosarcoma soft-tissue sarcoma in children under 1 year of age, with local aggressiveness, but a high cure rate with conservative treatment. We report our experience with 15 patients with histological diagnosis of IFS treated at our Institution from January-2003 to December-2020. The median age was 6.72 months (range: 0-36); 66% were males. The extremities were the most common tumor site (66.7%). The tumor size was > 5 cm in 10 patients. Only one patient had metastatic disease (lung). Molecular studies were performed in 14 patients and were positive in ten: nine *ETV6/NTRK3* and one *RAF1*. Initial non-mutilating surgery was performed in six patients. A delayed surgery could be performed in 4/8 patients after neoadjuvant chemotherapy with Vincristine - Actinomycin-D, and in one patient a watch-and-wait strategy was adopted. With a median follow-up of 58.67 months, all patients are alive except for the patient with metastatic disease. The 5-year overall and event-free survival were 93.5% and 86.5% respectively. Although IFS is locally aggressive, it has a high rate of overall survival due to its good response to chemotherapy and non-mutilating surgery even with involved margins. Advances in molecular genetics have improved diagnosis and refined classification.

Introduction

Infantile fibrosarcoma (IFS) is the most common non-rhabdomyosarcoma soft-tissue sarcoma (STS) in children under 1 year of age accounting for 24.5% of all STS in this age group [1]. IFS may be present at birth or develop during the first five years of life, mainly in infants or children younger than 2 years of age. Around 80% of the cases are diagnosed in the first year of life [1-3]. The tumor is usually located in the extremities and less frequently in the trunk [4, 5]. It is characterized by a low rate of metastasis, high probability of long-term survival, and good response to chemotherapy [2, 4, 5].

In almost all the cases IFS is associated with the t(12;15)(p13;q25) chromosomal translocation, similar to mesoblastic nephroma [4-7]. The *ETV6-NTRK3* fusion transcript or genetic rearrangement is detected by reverse transcriptase - polymerase chain reaction (RT-PCR) or fluorescence in situ hybridization (FISH), and its presence is the gold standard for diagnosis.

Conservative surgery is the treatment of choice, but in unresectable tumors, neoadjuvant chemotherapy without anthracyclines or alkylating agents has been used [4]. New target therapies have shown to be highly effective [8-11]. This study aims to describe our experience with IFS over a period of 18 years analysing clinical and molecular features, response to treatment and outcome.

Materials and Methods

A descriptive retrospective study was conducted evaluating 15 patients with a histological diagnosis of IFS admitted at Hospital de Pediatría J.P.

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Garrahan, Buenos Aires, Argentina, between January 2003 and December 2020, treated according to the EpSSG NRSTS 2005 protocol. Doses were adjusted according to age and weight.
Toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Molecular studies were performed with PCR to identify the presence of the *ETV6-NTRK3* transcript fusion and FISH to detect the *ETV6* gene rearrangement. RNAseq was performed in one case where there was doubt and it was reviewed by an international pathologist. The status of resection margins was classified according to the Intergroup Rhabdomyosarcoma Staging system (IRS). In all patients, except trunk location, ultrasound (US) and/or magnetic resonance imaging (MRI) and thorax computerized tomography (CT) was performed. In patients with measurable disease, response to chemotherapy was evaluated after three cycles of chemotherapy by assessment of radiologically identified tumor volume reduction.

Statistical Analysis

Using the Kaplan-Meier method, overall survival (OS) was estimated from the date of diagnosis to the last follow-up visit or death. Event-free survival (EFS) was calculated from the time of diagnosis to the first event (disease progression, relapse, or death). Survival curves were analysed using the Kaplan-Meier method with the GraphPad Prism 5 programme.

Results

Clinical characteristics of our 15 patients are shown in (Table 1). The male-to-female ratio was 2:1. Symptoms were present at birth in seven patients; however, none of the patients had a prenatal diagnosis. Median age at diagnosis was 6.72 months (range: 0-36), 93.3% of the patients were younger than 12 months. Ten patients were neonates (infants less than 28 days of life). Only one patient was older than two years old at diagnosis.

Median delay in time to diagnosis was 103 days (range:5-283). The most frequent tumor sites were the limbs in 10 patients (66.7%), followed by trunk in 2 patients (13.3%), head and neck in 2 patients (13.3%), intestine, which is an unusual site, in 1 patient (6.7%). Tumor diameter was >5cm in 10 patients. None of the patients had lymph-node involvement and only one presented with metastasis (lung). Due to the characteristics of the lesion observed on US or MRI, the main differential diagnosis was vascular malformations or hemangioma in six patients (Figures 1 & 2). In all cases a histological diagnosis was performed, which was confirmed by positive molecular studies (PCR and/or FISH) in 9 of 14 patients (Table 1) (Figure 3). One patient with *ETV6-NTRK3* fusion negative, showed recurrent fusion involving *RAF1* gene.

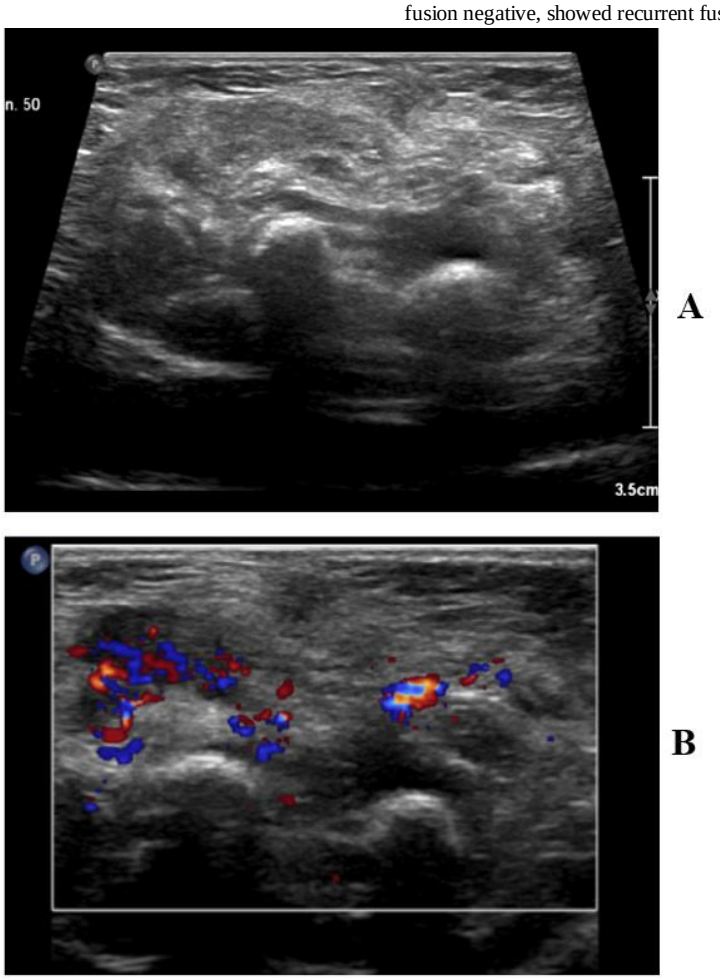

Figure 1: A) & B) The sonographic appearance of IFS is often that of a more or less homogeneous hyperechoic mass with a high growth potential that is liable to compress adjacent structures. Doppler US may confirm the vascularization of the whole tumor together with peripheral circulation.

Table 1: Clinical, Pathologic, Molecular Features, Management and Outcome IFS.

Patient	Sex	Age (months)	Symptoms	Site	Size	Mtts	PCR *ETV6-NTRK3*	FISH *ETV6*	Initial surgery	IRS post 1st Sx	Chemo	2nd surgery	IRS post 2nd Sx	Event	Status	OS (months)
1	M	8.29	Gastrointestinal bleeding	Intestinal	<5cm	no	Positive	Positive	Complete resection	I	No	Yes	I	No	CR	25.44
2	F	1.48	Tumor	Limb	>5cm	no	Negative*	Negative	Biopsy	III	Yes	No	-	PD	SD	34
3	F	0.66	Tumor / Bleeding	Limb	>5cm	no	Positive	Positive	Biopsy	III	Yes	Yes	II	No	SD	33.31
4	F	3.45	Shortness of breath	Trunk	>5cm	no	Positive	Positive	Biopsy	III	Yes	Yes	I	No	CR	65.8
5	M	2.04	Tumor	Limb	>5cm	no	Positive	Positive	Partial resection	III	Yes	No	-	No	CR	15.97
6	M	0.95	Tumor	Limb	>5cm	no	Negative	Negative	Complete resection	II	No	No	-	No	CR	71.93
7	M	8.22	Tumor	Limb	<5cm	no	Positive	Positive	Complete resection	II	No	No	-	No	CR	37.84
8	M	3.98	Tumor / Bleeding	Limb	>5cm	no	Positive	Positive	Partial resection	II	Yes	Yes	I	No	CR	87.9
9	M	9.70	Tumor	H&N	<5cm	no	Negative	N/A	Biopsy	III	No	No	-	No	CR	108.23
10	M	11.31	Tumor	Limb	>5cm	lung	Positive	Positive	Biopsy	III**	Yes	No	-	Death	Death	11.12
11	M	2.27	Tumor	Limb	>5cm	no	Positive	Positive	Biopsy	III	Yes	Yes	I	No	CR	57.83
12	F	2.60	Tumor	Trunk	>5cm	no	Negative	N/A	Complete resection	II	No	No	-	No	CR	197.41
13	M	8.26	Tumor	H&N	<5cm	no	N/A	N/A	Partial resection	III	No	No		No	CR	31.54
14	M	1.45	Tumor	Limb	>5cm	no	N/A	Positive	Biopsy	III	Yes	No		No	CR	110.72
15	F	36.41	Tumor	Limb	<5cm	no	N/A	Negative	Complete resection	I	No	No	-	No	CR	1.12

H&N: Head and Neck; PD: Progressive Disease; CR: Complete Remission; Mtts: Metastasis; SD: Stable Disease; OS: Overall Survival; N/A: Not Available Sx: Surgery.

*Recurrent fusion involving *RAF1*; **metastatic.

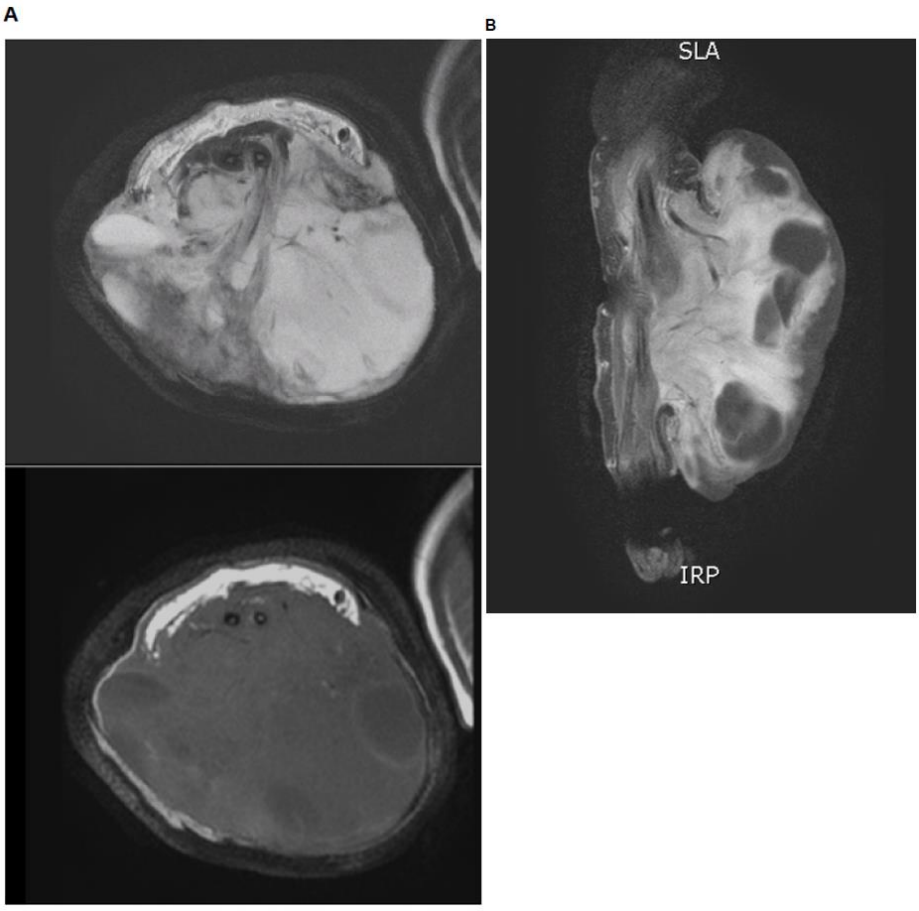

Figure 2: A) & B) Magnetic resonance imaging of the arm: The tumor observed on magnetic resonance imaging is isointense to muscle on T1-weighted and hyperintense on T2-weighted sequences. With internal fibrous septa. The internal sings are heterogeneous (A). An intensive heterogeneous enhancement after contrast enhanced. Osseous erosion is observed in the exam (B).

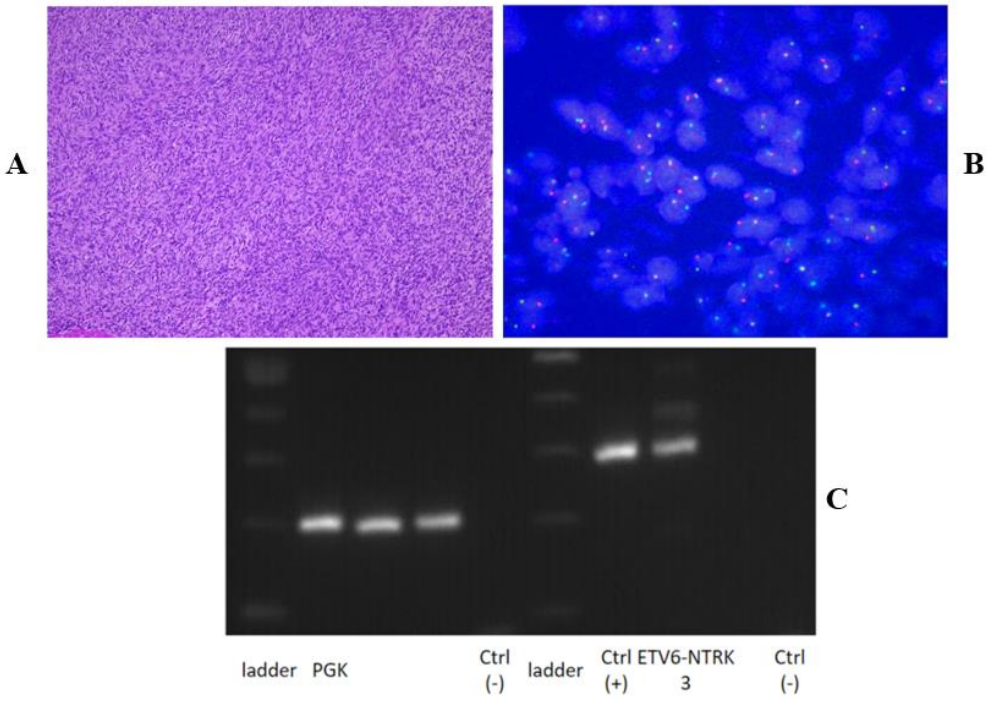

Figure 3: A) H&E 10X: Highly cellular neoplasm composed of sheets, bundles and fascicles of spindle cells with inflammatory cells. 8H&E 10X); **B)** FISH: Rearrangement 12p13 (LSI ETV6 Break Apart); **C)** RT-PCR: *EVT6-NTRK3* fusion gene.

Initial surgery was performed in six patients, three were classified as IRS I and three as IRS II. In all cases, surgery was conservative without significant functional or cosmetic defects. Five patients required no further treatment. The remaining patient needed a second surgery to achieve tumor-free margins as the location (intestine) was difficult to follow-up. None of the patients had relapses. Eight patients received chemotherapy using the Vincristine - Actinomycin-D (VA) regimen according to the EpSSGnonRMS 2005 protocol, four patients received VA regimen as neoadjuvant therapy to facilitate subsequent tumor resection. Of the remaining four patients, two patients achieved complete remission (CR) with only chemotherapy, one patient had progressive disease (PD) after 4.5 months of VA chemotherapy and the other died of disease 11.1 months after diagnosis.

In all four patients who received neoadjuvant chemotherapy, subsequent surgery was feasible. Three of them achieved CR, while the remaining patient had a residual tumor and remained in follow-up with stable disease (SD) 33.3 months after diagnosis. None of the patients received chemotherapy after surgery. In one patient a watch-and-wait approach was adopted. This patient is alive in CR 108.2 months after diagnosis. In two patients cyclophosphamide was added (VAC regimen) after failure to respond to the VA scheme. Initially, one patient presented SD (the only patient with metastasis of the series) and died after 11.1 months due to PD. The other had PD after the first line (VA) and the second line (VAC), requiring a third-line treatment, consisting of ifosfamide-doxorubicin (ID) due to PD and unresectable tumor. Response rate to first-line chemotherapy (CR/PR) was 75%, while 25% of the patients had SD or PD (Table 2).

Table 2: Statistical analysis.

	n=15 (%)	**5 years EFS**	**P (EFS)**	**5 years OS**	**p (OS)**
Primary tumor size					
<5cm	5 (33.3%)	99%	0.3582	99%	0.5271
>5cm	10 (66.7%)	80%		98.5%	
Site					
Limbs	10 (66.7%)	78%	0.5546	89.5%	0.7575
Axial	4 (26.7%)	99.5%		99%	
Other	1 (6.6%)	-		-	
IRS group			0.5546		0.7575
I	2 (13.3%)	-		-	
II	4 (26.7%)	99%		99.5%	
III	9 (60%)	75%		89.5%	
Best surgery at any time			0.2324		0.5134
R0	5 (33.3%)	98.5%		99%	
R1	4 (26.7%)	98.5%		99.5%	
R2 / Biopsy	6 (40%)	67%		83.5%	
Response to CHT	*n= 8*	0.009			0.0113
CR	3 (20%)	99%		99%	
PR	3 (20%)	99%		99%	
SD	1 (6.6%)	0%		0%	
PD	1 (6.6%)	0%		99%	
No CHT	7 (46.7%)	99%		99%	

CHT: Chemotherapy, CR: Complete Remission; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; EFS: Event Free survival OS: Overall Survival.

After a median follow-up of 58.67 months (range:1-197m) all patients, except for the patient with metastatic disease, were alive. At the time of this analysis, two patients had SD and were in radiological follow-up 33.3 and 34 months after diagnosis. Five-year OS and EFS were 93.5% and 86.5%, respectively. Considering patients according to tumor size, primary site, and IRS no statistically significant differences in survival were found (Table 2).

Discussion

The clinical and demographic characteristics of the patients in our series were similar to those of previously reported series, showing a male preponderance (2:1 ratio) and tumor occurring at a very young age with a median age at diagnosis of 6.72 months (range: 0-36 months). Symptom onset was present in neonates (<28 days) in ten patients, 7/10 at birth [1-3]. The most common sign was a painless tumor. Remarkably, in spite of having large, vascularized masses at birth in half the cases, none of the patients in our series had a prenatal diagnosis.

Although rare, patients with a prenatal diagnosis of IFS have been reported [12-17]. These cases were detected on routine US in the third trimester in asymptomatic pregnancies or on US performed due to maternal abdominal distension, and reduced or absent fetal movements [12, 13, 15]. Prenatal US findings should be followed by MRI studies [14].

In our series, median delay in time to diagnosis was 103 days (range: 5-283 days). Tumor location was similar to other reports, mostly in the soft tissues of the limbs, followed by trunk and head and neck [4, 5, 18]. One patient had intestinal IFS, an unusual site [19]. IFS is an intermediate-risk tumor that is locally aggressive but associated with a low incidence of metastasis (<10%) [2, 4, 5]. Only one of our patients had lung

metastasis and none of them had lymph-node involvement. The imaging findings of IFS are non-specific. Benign vascular lesions, such as hemangiomas and vascular malformations, which are more common in this age group, may be distinguished from IFS in which the latter is fed by irregular-caliber arteries in a disorganized branching pattern [14, 20]. A vascular tumor was initially suspected in six patients of our series.

Although non-specific, the most common finding on MRI in IFS is a heterogeneously contrast-enhancing mass which is iso-hyperintense to the skeletal muscle on T1- weighted and hyperintense on T2-weighted images, with hemorrhage in some cases, and less frequent low intensity foci representing fibrous tissue [14, 20]. Histologically, IFS is similar to adult fibrosarcoma. It is a highly cellular lesion consisting of interlacing bundles of cells with oval or spindle-shaped nuclei arranged in a herringbone pattern with an nonspecific immunophenotype [21]. The tumor has the characteristic t(12;15)(p13;q25) chromosomal translocation resulting in fusion of the *ETV6* (*TEL*) gene on chromosome 12 with the neurotrophin-3 receptor *NTRK3* (TrkC) gene on chromosome 15, activating multiple signaling cascades including the *RAS* and *PI3K-AKT* (phosphatidylinositol 3-kinase–protein kinase B) pathways [4-7, 21]. The *ETV6-NTRK3* fusion transcript or gene rearrangement may be detected by RT-PCR and/or FISH, and its presence is the gold standard for diagnosis. In the European series, screening was positive in 87.2%, 74%, and 69.2% (9/13) of the patients studied. In our study, molecular studies confirmed the diagnosis in 9 out of 14 patients [4, 5, 18].

This fusion is also observed in cellular mesoblastic nephroma, myeloid leukemia, secretory breast carcinoma, and mammary-type secretory carcinoma of the skin and salivary gland [5]. Recently, a few tumors with histology features overlapping those of IFS which are negative for the *ETV6-NTRK3* fusion, were identified and called IFS-like sarcomas, including *EML4-NTRK3* variant fusions, a new *TFG-MET* fusion (retaining the *MET* kinase domain) and rearrangements of the *RAF1*, *BRAF*, and *NTRK1/2* genes, (such as the unusual *LMNA-NTRK1*, intragenic *BRAF* deletions associated with tandem duplication in exon 2) [11, 22-25]. These lesions mainly occur within the first two years of life with a predilection for the intra-abdominal and axial location. The clinical course of IFS-like sarcomas is less predictable, with some cases showing aggressive behaviour and even the development of metastasis [22]. In our series, one patient with refractory disease and *ETV6-NTRK3* fusion negative, showed recurrent fusion involving *RAF1* gene detected by RNAseq.

Conservative surgery is the treatment of choice for IFS. Initial tumor surgery should be performed if complete and non-mutilating resection is deemed feasible without the need of posterior adjuvant chemotherapy in IRS groups I-II, although close monitoring is warranted [2, 4, 5]. In our series, initial complete conservative resection was possible in 6 of 15 patients without the need of further treatment. None of the patients had tumor relapse. The use of anthracycline and alkylating agent-free neoadjuvant chemotherapy is indicated in unresectable tumors to reduce tumor size and facilitate delayed conservative resection. The international guidelines recommend the VA regimen due to its high efficacy, lack of long-term toxicity, and response rate of 68-71% (Table 2) [4, 5, 26]. Eight patients received chemotherapy, 4/8 received neoadjuvant therapy and subsequent surgery was feasible; three of them achieved CR, and one of them is being closely monitored with stable residual disease (Table 1).

Hematological toxicity was the most common chemotherapy-related complication, observed in 75% of the patients (n=6), consisting of anemia in 6/6, neutropenia in 3/6, and thrombocytopenia in 2/6. Two patients developed grade 2-3 hepatic veno occlusive disease (VOD). None of the patients died due to chemotherapy-related toxicity.

Alkylating agents (cyclophosphamide or ifosfamide) or anthracyclines may be used in patients with an inadequate response to the VA regimen [4]. In two patients of our series, cyclophosphamide was added (VAC regimen) due to failure to respond to the VA regimen (PD and SD, respectively). One of these patients required third-line treatment consisting of ifosfamide and doxorubicin according to the EpSSG nonRMS 2005 protocol due to PD with unresectable tumor.

Optimal duration of preoperative chemotherapy is not defined in the European guidelines and remains to be clarified. However, it is suggested to be used until surgery is performed [5]. Currently, TRK inhibitors (TRKI) offer a novel treatment that is well tolerated and often highly effective in infants with TRK fusion-positive IFS. Patients with metastatic or refractory disease are candidates for the treatment, mainly in the setting of clinical trials. Outside clinical trials, additional information is needed to resolve the lack of consensus on the use of conventional first-line chemotherapy versus TRKI in patients with localized disease [10, 18, 26, 27].

Larotrectinib is a highly selective small-molecule TRKI available in oral solution, which facilitates its use in young children [8-10]. All eight patients with NTRK gene fusion-positive IFS, treated in a phase I portion of the larotrectinib pediatric trial, responded to treatment: six patients with a partial response and two patients with a CR [28]. Also, in the Phase I/II larotrectinib trials, 28 pediatric patients with TRK fusion-positive IFS had an overall response rate (ORR) of 96% [26, 29]. Larotrectinib was granted accelerated approval based on the results of this clinical trial [9].

Although acute and intermediate-term toxicity related to the use of larotrectinib is generally mild and treatment discontinuation or dose reduction are rarely necessary, little is known about the long-term effects, especially when the drug is administered for prolonged periods of time in infants or young children, since normal TRK proteins are important for early brain development [9, 10, 18, 27, 28]. Therefore, it would be advisable to include neurophysiological and neuropsychological studies in the long-term follow-up of these patients [8, 9, 30]. Additional studies are needed to determine optimal treatment duration and the risk of recurrence after discontinuation [8, 28, 30]. Crizotinib is an oral tyrosine kinase inhibitor (TKI) with proven *in vitro* activity against the *ETV6–NTRK3* transcript fusion. Crizotinib was successfully used in a child with treatment-refractory metastatic IFS harboring an unusual *LMNA-NTRK1* fusion [11]. Considering the advances in molecular biology and novel target therapies [9, 10, 11, 18, 26-28], extensive and mutilating surgery as well as radiotherapy should only be performed after the failure of rescue therapy [4].

On the other hand, a watch-and-wait approach should only be considered in carefully selected patients (younger than 3 months old with

unresectable tumors, who are not at risk of functional deficits or potentially life-threatening disease in case of PD). These patients should be monitored closely during weeks or months with the aim to delay surgery and/or reduce the risk of chemotherapy to which they are more vulnerable because of their young age [4, 5]. In case of PD, neoadjuvant chemotherapy with the VA regimen should be started [5]. Sait *et al*. described a case of spontaneous remission in a 5-month-old patient with molecularly confirmed IFS, who achieved remission without treatment; and Miura *et al*. reported a patient who went into spontaneous regression after partial resection, who presented *ETV6-NTRK3* fusion positive in the initial biopsy at 3 months old, and in a second specimen of partial resection at 1 year old but was fusion negative in the sample from remnant tumor harvested at 4 years old [31, 32]. These genetic changes accompanied by histological changes could suggest that the IFS either disappeared completely due to apoptosis or showed mature transformation to hemangiomatous tissue during the course of the regression [32]. In spite of the anecdotal accounts of spontaneous remission in this type of tumor, the authors recommend weighing the risks against the benefits of surgery and chemotherapy versus a watch-and-wait strategy [31]. In one patient of our series, who was 9 months old at diagnosis, a watch-and-wait approach was adopted, even when it was localized in a risk area (head and neck), but the surgery would be extremely mutilating. The patient was in CR with a follow-up of 9 years. After a median follow-up of 58.67 months, 93.3% of our patients were alive with a 5-year OS and EFS of 93.5% and 86.5%, respectively, with a high probability of long-term survival (90% at 5 years) similar to other series [2, 4, 5]. Our study is limited by its small sample size for any meaningful statistical analysis.

Conclusion

Our study confirms that IFS is associated with an excellent prognosis, with a 5-year survival greater than 90%, achieved with conservative treatment, even in patients with residual disease, with low toxicity. Although refractory cases are scarce, novel target therapies provide a new horizon. Given the advances in the knowledge of molecular biology, it would be important to broaden the range of treatment options for spindle-cell tumors in addition to IFS with *ETV6-NTRK3* fusion. TRK inhibitors offer a novel, well tolerated and often highly effective treatment for patients with IFS and other TRK fusion-positive tumors.

Abbreviation

CR: Complete Remission
CT: Computerized Tomography
EFS: Event-Free survival
FISH: Fluorescence In Situ Hybridization
ID: Ifosfamide-Doxorubicin
IFS: Infantile Fibrosarcoma
IRS: Intergroup Rhabdomyosarcoma Staging
MRI: Magnetic Resonance Imaging
OS: Overall Survival
ORR: Overall Response Rate
PD: Progressive Disease
PR: Partial Response
RT-PCR: Reverse Transcriptase-PCR
SD: Stable Disease
US: Ultrasonography
VA: Vincristine-Actinomycin-D
VAC: Vincristine-Actinomycin-D-Cyclophosphamide
VOD: Hepatic Venoocclusive Disease

REFERENCES

1. Sultan I, Casanova M, Al-Jumaily U, Meazza C, Rodriguez-Galindo C et al. (2010) Soft tissue sarcomas in the first year of life. *Eur J Cancer* 46: 2449-2456. [Crossref]
2. Parida L, Fernandez-Pineda I, Uffman JK, Davidoff AM, Krasin MJ et al. (2013) Clinical management of infantile fibrosarcoma: a retrospective single-institution review. *Pediatr Surg Int* 29: 703-708. [Crossref]
3. Moreno F (2012) Registro Oncopediátrico Hospitalario Argentino: incidencia 2000-2009 supervivencia 2000-2007 tendencia de mortalidad 1997-2010. 1a ed. Buenos Aires: Instituto Nacional del Cáncer.
4. Orbach D, Rey A, Cecchetto G, Oberlin O, Casanova M et al. (2010) Infantile fibrosarcoma: management based on the European experience. *J Clin Oncol* 28: 318-323. [Crossref]
5. Orbach D, Brennan B, De Paoli A, Gallego S, Mudry P et al. (2016) Conservative strategy in infantile fibrosarcoma is possible: The European paediatric Soft tissue sarcoma Study Group experience. *Eur J Cancer* 57: 1-9. [Crossref]
6. Loh ML, Ahn P, Perez-Atayde AR, Gebhardt MC, Shamberger RC et al. (2002) Treatment of infantile fibrosarcoma with chemotherapy and surgery: results from the Dana-Farber Cancer Institute and Children's Hospital, Boston. *J Pediatr Hematol Oncol* 24: 722-726. [Crossref]
7. Lannon CL, Sorensen PHB (2005) ETV6-NTRK3: a chimeric protein tyrosine kinase with transformation activity in multiple cell lineages. *Semin Cancer Biol* 15: 215-223. [Crossref]
8. Caldwell KJ, De La Cuesta E, Morin C, Pappo A, Helmig S (2020) A newborn with a large NTRK fusion positive infantile fibrosarcoma successfully treated with larotrectinib. *Pediatr Blood Cancer* 67: e28330. [Crossref]
9. Bielack SS, Cox MC, Nathrath M, Apel K, Blattmann C et al. (2019) Rapid, complete and sustained tumour response to the TRK inhibitor larotrectinib in an infant with recurrent, chemotherapy-refractory infantile fibrosarcoma carrying the characteristic ETV6-NTRK3 gene fusion. *Ann Oncol* 30: viii31-viii35. [Crossref]
10. Orbach D, Sparber-Sauer M, Laetsch TW, Minard-Colin V, Bielack SS et al. (2020) Spotlight on the treatment of infantile fibrosarcoma in the era of neurotrophic tropomyosin receptor kinase inhibitors: International consensus and remaining controversies. *Eur J Cancer* 137: 183-192. [Crossref]
11. Bender J, Anderson B, Bloom DA, Rabah R, McDougall R et al. (2019) Refractory and metastatic infantile fibrosarcoma harboring *LMNA-NTRK1* fusion shows complete and durable response to crizotinib. *Cold Spring Harb Mol Case Stud* 5: a003376. [Crossref]
12. Scheier M, Ramoni A, Alge A, Brezinka C, Reiter G et al. (2008) Congenital fibrosarcoma as cause for fetal anemia: prenatal diagnosis and in utero treatment. *Fetal Diagn Ther* 24: 434-436. [Crossref]
13. Dumont C, Monforte M, Flandrin A, Couture A, Tichit R et al. (2011) Prenatal management of congenital infantile fibrosarcoma: unexpected outcome. *Ultrasound Obstet Gynecol* 37: 733-735. [Crossref]

14. Ozcan, UA, Karaarslan, E, Damlacik, A, Erzen C (2010) Diagnosis of congenital fibrosarcoma facilitated by pre- and postnatal MRI. *Eur J Radiol Extra* 74: e65-e68.
15. Huang SY, Wang CW, Wang CJ, Chao A, Chao AS (2005) Combined prenatal ultrasound and magnetic resonance imaging in an extensive congenital fibrosarcoma: a case report and review of the literature. *Fetal Diagn Ther* 20: 266-271. [Crossref]
16. Mukai M, Sameshima H, Kodama Y, Yamashita R, Kanek M et al. (2012) Congenital infantile fibrosarcoma in a very low-birth-weight infant. *J Pediatr Surg* 47: e1-e4. [Crossref]
17. Suzuki T, Murakoshi T, Tanaka K, Ogasawara A, Torii Y (2015) Sonographic features of congenital infantile fibrosarcoma that appeared as a sacrococcygeal teratoma during pregnancy. *J Obstet Gynaecol Res* 41: 1282-1286. [Crossref]
18. Sparber-Sauer M, Vokuhl C, Seitz G, Stegmaier S, Hallmen E et al. (2020) The impact of local control in the treatment of children with advanced infantile and adult-type fibrosarcoma: Experience of the cooperative weichteilsarkom studiengruppe (CWS). *J Pediatr Surg* 55: 1740-1747. [Crossref]
19. Mathey MD, Marti JL, Zaratiegui MJ, Giusepucci C, Rose A (2020) [Infantile intestinal fibrosarcoma. Case report with digestive bleeding in an infant]. *Arch Argent Pediatr* 118: e549-e553. [Crossref]
20. Ainsworth KE, Chavhan GB, Gupta AA, Hopyan S, Taylor G (2014) Congenital infantile fibrosarcoma: review of imaging features. *Pediatr Radiol* 44: 1124-1129. [Crossref]
21. Fletcher CDM, Unni KK, Mertens F (2002) editors Pathology and Genetics of Tumours of Soft Tissue and Bone. World Health Organization Classification of Tumours. Lyon: IARC Press.
22. Suurmeijer AJH, Kao YC, Antonescu CR (2019) New advances in the molecular classification of pediatric mesenchymal tumors. *Genes Chromosomes Cancer* 58: 100-110. [Crossref]
23. Kallen ME, Hornick JL (2021) The 2020 WHO Classification: What's New in Soft Tissue Tumor Pathology? *Am J Surg Pathol* 45: e1-e23. [Crossref]
24. Flucke U, van Noesel MM, Wijnen M, Zhang L, Chen CL et al. (2017) TFG-MET fusion in an infantile spindle cell sarcoma with neural features. *Genes Chromosomes Cancer* 56: 663-667. [Crossref]
25. Suurmeijer AJH, Dickson BC, Swanson D, Zhang L, Sung YS et al. (2018) A novel group of spindle cell tumors defined by S100 and CD34 co-expression shows recurrent fusions involving RAF1, BRAF, and NTRK1/2 genes. *Genes Chromosomes Cancer* 57: 611-621. [Crossref]
26. Perreault S, Chami R, Deyell RJ, El Demellawy D, Ellezam B et al. (2021) Canadian Consensus for Biomarker Testing and Treatment of TRK Fusion Cancer in Pediatric Patients. *Curr Oncol* 28: 346-366. [Crossref]
27. Shulman DS, DuBois SG (2020) The Evolving Diagnostic and Treatment Landscape of NTRK-Fusion-Driven Pediatric Cancers. *Paediatr Drugs* 22: 189-197. [Crossref]
28. Laetsch TW, DuBois SG, Mascarenhas L, Turpin B, Federman N et al. (2018) Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. *Lancet Oncol* 19: 705-714. [Crossref]
29. Hong DS, DuBois SG, Kummar S, Farago AF, Albert CM et al. (2020) Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol* 21: 531-540. [Crossref]
30. Vedi A, Holland K, Cross J, Muthusamy B, Behjati S et al. (2020) An infant with ETV6-NTRK3 fusion-positive congenital infantile fibrosarcoma and delayed response to conventional chemotherapy avoiding the need for TRK inhibition. *Pediatr Blood Cancer* 67: e28628. [Crossref]
31. Sait SF, Danzer E, Ramirez D, LaQuaglia MP, Paul M (2018) Spontaneous Regression in a Patient With Infantile Fibrosarcoma. *J Pediatr Hematol Oncol* 40: e253-e255. [Crossref]
32. Miura K, Han G, Sano M, Tsutsui Y (2002) Regression of congenital fibrosarcoma to hemangiomatous remnant with histological and genetic findings. *Pathol Int* 52: 612-618. [Crossref]