Comment on: "A newborn with a large NTRK fusion positive infantile fibrosarcoma successfully treated with larotrectinib"

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Title Page

Manuscript Title

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Abbreviation	Full-term phrase
IFS	Infantile fibrosarcoma
TRK	Tropomyosin receptor kinase

Main Text

To the Editor:

In the May 2020 issue of Pediatric Blood & Cancer, Dr. Helmig and colleagues describe a case of an infantile fibrosarcoma (IFS) diagnosed at 17 days of life and treated successfully with larotrectinib[1], an oral tropomyosin receptor kinase (TRK) inhibitor targeted against the fusion protein product of the ETV6-NTRK gene rearrangement identified on genetic analysis of the biopsy.

We report a similar case of a lower extremity mass in an ex-36 week male infant that was first noted at birth and thought to be a hemangioma. The mass continued to grow (Figs. 1A and 1B) and presented with acute rupture at 37 days of life (Fig. 1C). Due to extensive bleeding he rapidly deteriorated into hemorrhagic shock requiring aggressive fluid resuscitation with a massive transfusion protocol. Emergent direct puncture embolization using hemostatic slurry was performed by interventional radiology (Fig. 1E) which successfully controlled the bleeding. MRI revealed a large, infiltrative, heterogeneous enhancing mass extending from the foot posteriorly up into the knee measuring 11.4 x 4.8 cm (Fig. 1F), and biopsy revealed a spindle cell sarcoma with a "hemangiopericytomatous pattern", possibly representing IFS. While awaiting molecular confirmation, due to rapid life threatening tumor growth one cycle of vincristine, actinomycin and cyclophosphamide was given (Fig. 1G). Molecular analysis confirmed the presence of an ETV6-NTRK fusion and he was started on oral larotrectinib at standard dosing of 100mg/m^2/dose twice daily. He responded well to larotrectinib with rapid response to therapy within 2 weeks (Fig. 1H), continued response at 4 weeks (Fig. 1I) and 10 weeks (Fig. 1J), and near-total resolution of the mass by 19 weeks (Figs. 1K and 1L). As of this report he is 55 weeks on therapy (14 cycles) with minimal visible disease with post-sclerotherapy scarring and full use of the extremity including normal ambulation.

As the previous authors were concerned that their patient was 19 days old and weighed only 4 kg, they initiated larotrectinib cautiously at a low dose of 1 mg/kg/dose twice daily. Our case demonstrates that we were able to safely administer the full dose in a patient who was 50 days old and weighed only 3.35 kg at the time of initiation of treatment. Furthermore, although our patient presented in critical condition, upon stabilization of his hemorrhage and one cycle of bridging chemotherapy, we were able to successfully initiate targeted therapy. We observed an excellent response to larotrectinib with rapid regression of the lesion, allowing us to spare the limb and preserve function. Helmig et al reported a drop in hemoglobin after one week on larotrectinib, attributed to intra-tumoral hemorrhage. In our patient's case, rupture of the tumor preceded onset of therapy, suggesting that rupture was a natural progression of the disease rather than a drug effect. They reported significant weight gain and growth in head circumference on larotrectinib. Although our patient has remained along the first percentile for weight throughout treatment, we have seen an enlargement of his head and his head circumference has crossed two percentile curves. Further investigation regarding a possible connection to larotrectinib is warranted.

Our case demonstrates the natural history of IFS and the importance of early recognition of these lesions postnatally to prevent severe complications. Taken together, these cases highlight the safety and

efficacy of larotrectinib, even in infants in the first months of life. It is well-tolerated, easy to administer, and allowed for limb preservation in both cases.

Conflict of Interest Statement

Carolyn Fein Levy owns Pfizer stocks. The authors report no conflict of interest concerning the materials or methods used in this study or the results specified in this manuscript.

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References

Caldwell KJ, Cuesta EDL, Morin C, Pappo A, Helmig S. A newborn with a large NTRK fusion positive infantile fibrosarcoma successfully treated with larotrectinib. *Pediatr Blood Cancer* . 2020;67:e28330. https://doi.org/10.1002/pbc.28330

Legend

Figure 1 Photographs of the lesion taken in the first month of life (A), 1 week prior to presentation (B), and in the emergency room (C). US showing dilated vessels with calcifications within the mass (D), filling of the vessels with contrast during embolization (E), and MR imaging (F) at diagnosis. Photographs taken post VAc (G), 2 weeks on Larotrectinib (H), 4 weeks on Larotrectinib (I), and 10 weeks on Larotrectinib (J). MR imaging (K) and photograph (L) taken at 19 weeks.