Infantile Fibrosarcoma With NTRK3–ETV6 Fusion Successfully Treated With the Tropomyosin-Related Kinase Inhibitor LOXO-101

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INTRODUCTION

Infantile fibrosarcoma (IFS) is a rare myofibroblastic/fibroblastic tumor, often arising in the extremities, that most commonly affects patients in the first 2 years of life.[1] Despite similarities with adult-type fibrosarcoma, pediatric IFS has a more favorable clinical course and is nearly always characterized by a t(12;15)(p13;q25) translocation.[2–4] This translocation fuses the ETS variant gene 6 (ETV6) in chromosome 12 with the neurotrophin 3 receptor gene (NTRK3) kinase domain, resulting in activation of multiple signaling cascades including the ras protein (RAS) and phosphatidylinositol 3-kinase–protein kinase B (PI3K–AKT) pathways.[5] Although surgery and chemotherapy can be very effective in treating this disease, a small number of patients develop chemorefractory disease and ultimately die from local or distant complications of their disease.[3,4]

LOXO-101 is an ATP-competitive oral inhibitor of the tropomyosin-related kinase (TRK) family of receptor kinases (TRKA, B, and C), with low nanomolar 50% inhibitory concentrations against all three isoforms, and 1,000-fold or greater selectivity relative to other kinases. Previous work has demonstrated the preclinical activity of LOXO-101 in a cell line model, which harbors an ETV6–NTRK3 fusion.[6]

In this case study, we report the first pediatric patient with IFS and an ETV6–NTRK3 fusion treated with a selective TRK inhibitor, LOXO-101.

MATERIALS AND METHODS

A multicenter pediatric phase I dose-escalation study in patients with advanced solid or primary central nervous system tumors was initiated in December 2015 (ClinicalTrials.gov Identifier: NCT02637687) to evaluate the safety and tolerability of LOXO-101. Eligibility criteria included the age of 1–21 years regardless of the presence of a known TRK alteration, as well as those patients aged 1 month of age or greater with a known NTRK fusion and a diagnosis of IFS or congenital mesoblastic nephroma. An oral liquid formulation of LOXO-101 was developed for patients unable to swallow capsules. Simcyp® Pediatric Simulation modeling (CERTARA, Princeton, NJ) was utilized to establish a pharmacokinetic approach for dosing that takes into account patient age, ontogeny of the clearance pathways that eliminate LOXO-101, and body surface area. The pediatric dose selected for the initial cohort was predicted to equal the exposure achieved in adult patients taking a dose of 100 mg twice a day, the recommended Phase 2 adult dose. Cycles are measured in 28-day increments with continuous dosing. Response assessments by appropriate imaging modalities are scheduled every 8 weeks. Patients continue on therapy until evidence of disease progression or intolerable toxicity.

RESULTS

An otherwise healthy female was born with a large, vascular, right-sided neck mass extending to the face that was initially diagnosed and treated as a rapidly involuting congenital hemangioma. At 6 months of age, the mass grew rapidly and surgical resection was recommended. The patient presented with a large, rapidly growing neck mass. MRI demonstrated a heterogeneous mass with areas of enhancement consistent with fibrous and myxoid components. There was no evidence of local recurrence, metastasis, or involvement of surrounding structures. Pathology revealed a low-grade fibrosarcoma with scattered prominent mitotic figures. The patient was noted to have a large mass in the right-sided neck extending to the face that was initially diagnosed and treated as a rapidly involuting congenital hemangioma. At 6 months of age, the mass grew rapidly and surgical resection was recommended.

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excision/debulking revealed the diagnosis of IFS confirmed by an ETV6 translocation by FISH. Within the first 7 days postoperatively, the tumor rapidly progressed, encroaching the oral cavity. Chemotherapy with vincristine, actinomycin-D, and cyclophosphamide was initiated but the patient experienced disease progression during cycle 1. A new chemotherapy regimen composed of ifosfamide and doxorubicin (ID) was started concurrently with debulking surgery and a tracheostomy was performed for oropharyngeal obstruction. Two additional courses of ID and four courses of ifosfamide and etoposide had minimal impact on the tumor. The tumor progressed to involve the base of the skull, mastoids, and cervical vasculature. Gross surgical resection was performed in October 2015 by a team of multidisciplinary surgeons but clear surgical margins could not be achieved.

Five weeks following surgical resection, magnetic resonance imaging (MRI) of the brain and neck showed a 20 mm × 19 mm × 18 mm hyperenhancing mass involving the skull base of the middle cranial fossa, just anterior and inferior to the inner ear structures (Figs. 1A and 1B). Further chemotherapy was determined to be futile due to lack of response to all standard regimens. Repeat surgical resection was deemed not possible. Therapeutic radiotherapy was possible, but based on the age of the patient and location of the disease, it was expected to produce devastating long-term sequelae.

In December 2015, at the age of 16 months, the patient enrolled in the Phase 1 pediatric study of the oral, selective TRK inhibitor LOXO-101. The parents noted improved engagement and playfulness throughout Cycle 1. At the end of cycle 1 (day 28), an MRI of the brain and neck showed a significant interval reduction in the size and enhancement of the mass by more than 90% from baseline (Figs. 1C and 1D). Repeat scans at the end of Cycle 2 confirmed the size reduction and showed continued decrease in enhancement, confirming partial response (Figs. 1E and 1F). During the preparation of this manuscript, the patient remained under observation in Cycle 5 of dosing with a confirmed partial response by RECIST.[7] During the first two cycles, the patient experienced fever and PCR-confirmed influenza A (considered not related) but no adverse events related to LOXO-101.

DISCUSSION

We report a pediatric patient with refractory IFS with a confirmed ETV6–NTRK3 fusion that responded to LOXO-101, a highly selective pan-TRK inhibitor currently in clinical development. Cancers with chromosomal translocation that result in fusion kinases have historically demonstrated oncogene addiction behavior and dramatic responses to relevant drug inhibitors.[8,9] Fusion kinases involving Abelson murine leukemia viral oncogene homolog 1 (ABL), anaplastic lymphoma kinase (ALK), and ROS proto-oncogene 1 (ROS1) have identified populations that benefit from targeted drugs that are approved by U.S. Food and Drug Administration. The development of these inhibitors for other fusions and specifically for pediatric patients has likely lagged behind adult development because of the limited availability of comprehensive genomic profiling of rare pediatric tumors and the generally favorable outcomes of pediatric cancer patients with conventional modalities such as surgery and cytotoxic chemotherapy.

Fig. 1. Magnetic resonance imaging (MRI) of baseline disease assessment of the (A) neck and (B) oral cavity, with areas of interest highlighted with red arrows. Magnetic resonance imaging demonstrating >90% reduction in tumor masses of the (C) neck and (D) oral cavity following completion of the first month of therapy. Confirmation of the tumor response and decreased enhancement demonstrated by MRI of the (E) neck and (F) oral cavity following the second month of therapy.

Since 1998, IFS,[10] cellular subtype congenital mesoblastic nephroma,[11] and secretary breast cancer[12] have all been shown to harbor the ETV6–NTRK3 fusion. Since the mainstream adoption of next-generation sequencing tools, a growing body of literature has supported the hypothesis that NTRK fusions cause tumorigenesis through the constitutive activation of downstream growth and proliferative pathways.[6,13] NTRK fusions have been recently reported in a variety of pediatric oncologic diseases such as diffuse intrinsic pontine glioma and nonbrainstem high-grade gliomas,[14] pediatric papillary thyroid cancer,[15] spitzoid melanoma,[16] Ph-like acute lymphoblastic leukemia,[17] undifferentiated sarcoma,[18] soft tissue schwannoma,[6] and spindle cell sarcomas.[19]
While the majority of patients with IFS have an ETV6–NTRK3 fusion and are responsive to surgery and/or chemotherapy, a small number of patients are unusually difficult to treat.[4] Wong and colleagues have recently described a case of an ETV6–NTRK3 fusion negative and chemotherapy-refractive IFS found to harbor a lamin a/c–neurotrophic tyrosine kinase receptor type I (LMNA–NTRK1) gene fusion.[20] These two cases serve as helpful reminders that genomic profiling can aid in the morphologic diagnosis of selected pediatric sarcomas, and that actionable, therapeutically useful information may emerge from a molecular diagnosis. As Hong and colleagues have previously shown, a TRK-targeted therapy such as LOXO-101 seems to have efficacy without regard to histologic diagnosis or fusion construct partners.[21]

The radiologic tumor regression and clinical response seen in this patient with an ETV6–NTRK3 fusion positive IFS provide further clinical validation not only of this molecular target in oncology but also for NTRK fusions as drivers of clinical disease. This case report supports the clinical development of selective TRK inhibitors such as LOXO-101 in pediatric patients with an NTRK fusion. This case report underscores the potential promise of targeted therapies in pediatric populations when compelling oncogenic drivers can be identified and potent investigational inhibitors are available. Their role in the neoadjuvant, adjuvant, and metastatic settings as well as safety in inhibiting TRK in infants deserves further clinical investigation.

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