Lorlatinib for the Treatment of ALK Fusion–Positive Infant-Type Hemispheric Glioma: A Case Report

Alyssa M. Greenwell, DO[1]; Scott Baughan, BS[2]; Deniz Altinok, MD[3]; Neena I. Marupudi, MD[4]; William Kupsky, MD[5]; Chandan Kumar-Sinha, PhD[6]; and Hamza S. Gorsi, MD, MPH[7]

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Introduction

The 2021 WHO classification of CNS tumors identified infant-type hemispheric glioma as a distinct entity. These neoplasms typically occur within the cerebral hemispheres. Histologically, they resemble high-grade glioma (HGG) in older children and adults; however, they have a high prevalence of fusion events of receptor tyrosine kinase (*RTK*) genes such as *ALK*, *NTRK1/2/3*, *MET*, or *ROS1*.[1-4] These specific somatic alterations in the *RTK* genes have been found to play an important role in tumorigenesis[5,6] in these patients and are a possible target for treatment.

We present the case of an infant with *ALK* fusion–positive infant-type hemispheric glioma (also called infant high-grade glioma) treated with a molecularly targeted agent lorlatinib after disease progression. Lorlatinib is an US Food and Drug Administration–approved, potent third-generation inhibitor of anaplastic lymphoma kinase (*ALK*) and has the broadest coverage in its class. Specifically designed for CNS penetration, lorlatinib can easily cross the blood-brain barrier and achieve the adequate CNS concentration.[7]

Case Description

A previously healthy 3-month-old, African American female presented to an outside hospital with acute onset vomiting, right-sided facial droop, and focal seizures. Computed tomography scan of the head demonstrated a large right frontal intraparenchymal hemorrhage and mass causing effacement of the right lateral ventricle. Magnetic resonance imaging (MRI) of the brain was performed to better characterize the mass, which revealed a large 5.8 × 5.4 × 4.2 cm (transverse, AP, and craniocaudal) hemorrhagic lesion with lobulated margins in the right frontal lobe.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor in Chief of this journal if needed.

The mass was noted to have a variegated signal that was predominantly hypointense on T2 and a mixed signal with areas of hyperintense signals along the periphery on T1 images, marked diffusion restriction, and increased susceptibility (Fig 1A).

The patient underwent neurosurgical intervention with emergent right frontal craniotomy and gross total resection (Fig 1B). The histopathologic assessment showed tumor cells with large nuclei and sparse cytoplasm arranged in a perivascular, pseudorosette pattern with immunoreactivity to GFAP staining, consistent with the diagnosis of WHO grade IV epithelioid glioblastoma (Fig 2). The molecular analysis of the tumor was performed using next-generation sequencing (PEDS-MI-oncoseq clinical sequencing protocol[8]), which showed *ZNF397-ALK* fusion. This is an in-frame fusion of the N-terminus of *ZNF397* at exon 3 to the C-terminus of *ALK* after exon 20. There was no evidence of CNS metastasis on a complete MRI of the spine or cerebrospinal fluid analysis from a lumbar puncture. Because of the young age of the patient, she was treated with a radiation sparing regimen consisting of carboplatin 8 mg/kg once a day × 2 days and etoposide 3 mg/kg once a day × 3 days for six cycles.[9] She tolerated the chemotherapy well and had no evidence of disease recurrence at the completion of chemotherapy (Fig 1C).

However, 8 months after completion of therapy, she had a localized relapse identified on the surveillance MRI brain (Fig 1D) and underwent repeat right frontal craniotomy and gross total resection of the recurrent brain tumor (Fig 1E). Repeat molecular analysis (PEDS-MI-oncoseq clinical sequencing protocol) confirmed the presence of the same *ZNF 397-ALK* fusion. In addition, copy number gain of chr1q was identified. After surgical resection of the recurrent tumor, she was started on lorlatinib (a third-generation, CNS-penetrant *ALK* inhibitor). The initial dose was 95 mg/m^2/d once a day, on the basis of a published report from the phase I neuroblastoma study, clinical trial information ClinicalTrials.gov identifier: NCT03107988.[10] While on treatment, surveillance MRIs of the brain were performed every 3 months, which continued to show no evidence of disease recurrence (Fig 1F).

Author affiliations and support information (if applicable) appear at the end of this article.

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