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The experience of successful treatment of *ETV6-NTRK3*-positive infant glioblastoma with entrectinib

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In recently published articles, the superior outcome of infant patients with high-grade gliomas (HGGs) when compared with older children was demonstrated. Receptor tyrosine kinase (RTK) gene fusions highlight the distinct biology of infant HGGs and could provide the rationale for utilization of targeted therapy.[1,2] Here, we describe a case of *ETV6-NTRK3*-positive infant HGG successfully treated with the TRK/ROS1/ALK inhibitor entrectinib. To date, reports of fusion-targeting therapy in these patients remain sparse.[1,3–5]

Our female patient was diagnosed at 4 months of age, presenting initially with increasing head circumference, vomiting, nystagmus, right-sided hemiparesis, and regression of motor skills. An MRI revealed a large (9 × 5.6 × 9.3 cm), heterogenous tumor with solid, cystic, and hemorrhagic components in the left cerebral hemisphere with accompanying hydrocephalus (Figure 1A). No metastasis was noted.

Due to the high risk of intraoperative bleeding, a biopsy was not performed, and chemotherapy with carboplatin and etoposide and subsequent cyclophosphamide and vincristine was initiated. An MRI was performed after 2 cycles of chemotherapy and showed a 32% reduction of the tumor, at which time a biopsy was safely obtained, followed by neuropathological and molecular analysis. Based on morphology and immunophenotype, this tumor was classified as a high-grade glioma. Molecular testing of tumor RNA revealed the expression of the *ETV6-NTRK3* fusion transcript, where exon 5 of *ETV6* gene was fused in-frame to exon 15 of *NTRK3* gene (COSF571) (Figure 1H). The finding was confirmed by reverse-transcription PCR with Sanger sequencing of the amplicon. The integrative diagnosis was stated as infant (receptor tyrosine kinase driven) glioblastoma.

After the biopsy, the patient received 2 additional cycles of chemotherapy with the same regimen. Repeat neuroimaging revealed disease stabilization, although due to worsening seizure activity, a surgical resection was performed and resulted in near-total tumor resection with residual tumor 1.4 cm^3 (Figure 1B). The tissue samples from both surgeries had identical pathological features such as cellular and nuclear polymorphism, high mitotic activity, and focal microvascular proliferation, in some areas post-treatment changes were noted as well. These findings were matched with diagnosis of glioblastoma.

Because of clinical deterioration (appearance of seizures), presence of residual tumor mass and potential benefit from targeted therapy, entrectinib 100 mg per day orally was administrated as second-line treatment. Entrectinib was obtained from Roche via compassionate use. The neuroimaging performed after 3 months of targeted treatment showed complete response (Figure 1C). Transient neutropenia was the only adverse event requiring a brief (3 day) treatment interruption.

To date, the patient remains stable on entrectinib without evidence of recurrence after 8 months of treatment. The treatment has been exceedingly well tolerated with minimal adverse effects. To our knowledge, sufficient clinical data to suggest a specific duration of therapy have not yet been published. However, because the experience of targeted treatment for malignant gliomas suggests that treatment discontinuation leads to rapid disease progression,[6] we would consider treatment continuation until disease progression or significant toxicity.

Patients with infant HGG harboring NTRK fusions have better outcome comparing to older patients.[1,2] There are no clinical trials, that provide direct comparison of the effectiveness of chemotherapy and targeted therapy. Moreover, rapid disease progression during chemotherapy has been reported.[1,3] Stucklin et al. showed a 5-year overall survival of 42.9% in young patients with hemispheric NTRK-fused gliomas, whereas Torre et al. described progression and recurrence in both reported cases of infantile NTRK-fused gliomas.[2,7]

The first reported case of successful treatment of a patient with *ETV6-NTRK3*-positive HGG with larotrectinib

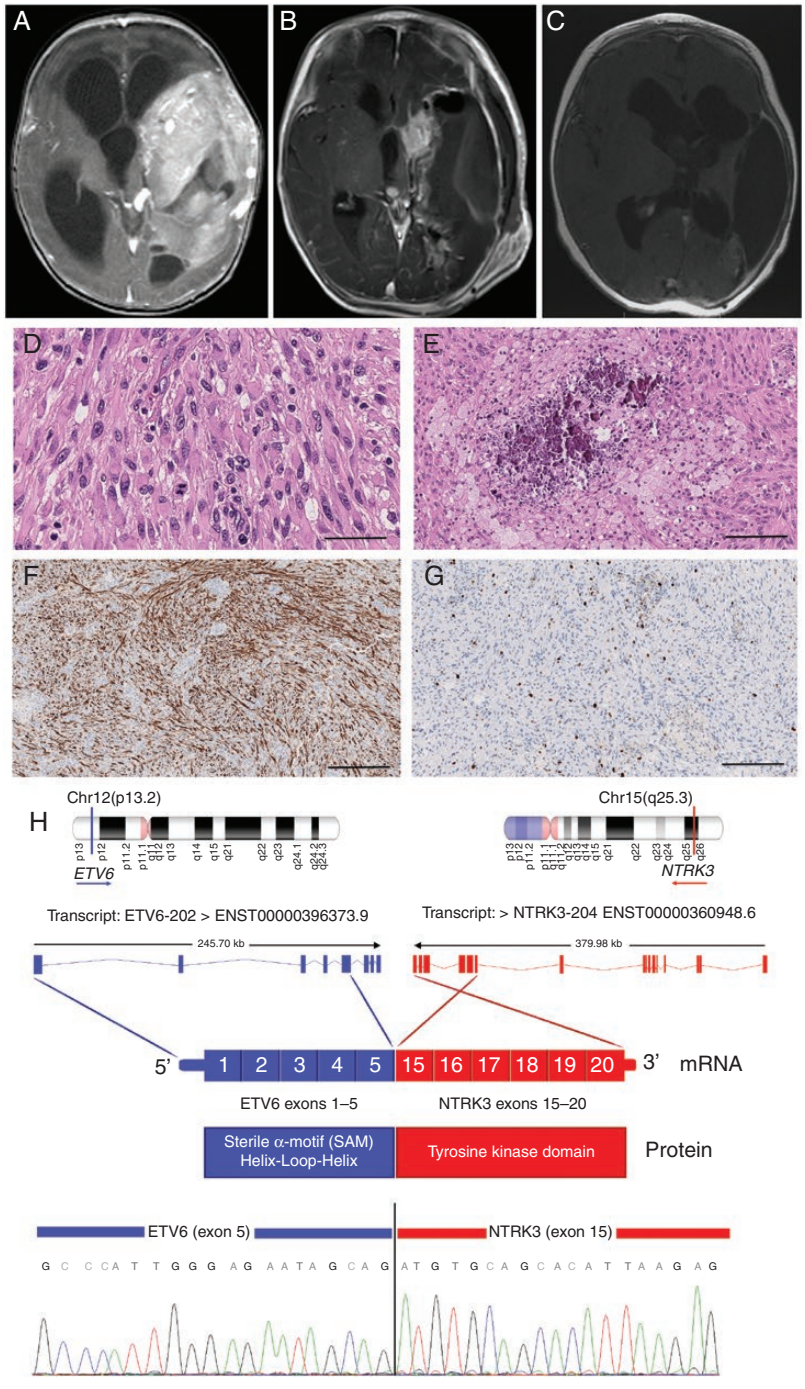

Figure 1. (A) Initial axial T1-weighted contrast brain MR images demonstrating large tumor with contrast enhancement. (B) T1-weighted axial contrast brain MR images performed after second operation. (C) Axial T1-weighted contrast brain MR images after 3 months of entrectinib therapy showing complete tumor regression. (D) Plump neoplastic cells with abundant cytoplasm and moderate nuclear polymorphism. Some mitotic figures are seen. ×400, H&E, x400, scale bar = 40 μm. E. Post-treatment changes are presented as claster of xhanthoma cells with central calcification, H&E, ×200, scale bar = 20 μm. (F) Immunostaining reveals tumor tissue positivity for GFAP expression. GFAP, ×100, scale bar = 10 μm. (G) Increased proliferative activity according Ki67 to 15%. Ki67, ×200, scale bar = 20 μm. (H) Schematic representation of the *ETV6-NTRK3* gene fusion and chimeric protein structure. Sequence analysis of the *ETV6-NTRK3* fusion transcript demonstrates exons 1 to 5 of *ETV6* are fused to exons 15 to 20 of *NTRK3* preserving the tyrosine kinase domain. In Sanger sequence chromatogram the black vertical line indicates the fusion breakpoint. ENST00000396373.9 and ENST00000360948.6 transcripts were used as reference sequences for *ETV6* and *NTRK3* genes respectively, genome build GRCh38.p13.

Table 1. Review of Patients With Infant Glioma, Who Received Targeted Therapy

Parameter/References	Ziegler et al.[3]	Clarke et al.[1] Case 1	Clarke et al.[1] Case 2	Alharbi et al.[4]	Torre et al.[7]	Torre et al.[7]	Torre et al.[7]	Desai et al.[5]	Our Case
Sex	Female	Female	No data	Female	No data	No data	No data	No data	Female
Age at diagnosis	5 months	36 weeks of gestation	11 months	18 months	Pediatric patient	Pediatric patient	Infantile patient	No data	4 months
Tumor location	Right lateral ventricle	Frontal lobe	pons	Frontal lobe	No data	No data	No data	No data	Left cerebral hemisphere
Pathology	High-grade glioma	Glioblastoma (WHO grade IV)	Low-grade neuroepithelial neoplasm	Glioblastoma (WHO grade IV)	No data	No data	No data	Unspecified	Glioblastoma (who grade iv)
Surgery	1) GTR 2) partial resection in progression 3) subtotal resection	1) Biopsy 2) Subtotal resection	1) GTR 2) GTR in progression	GTR	No data	No data	No data	No data	1) Biopsy 2) Subtotal resection
Prior CT	Vincristine, cisplatin, cyclophosphamide, etoposide, carboplatin, ifosfamide	Methotrexate, vincristine, etoposide, cyclophosphamide, thiotepa	Vincristine and carboplatin	No	No data	No data	No data	No data	Carboplatin, etoposide, cyclophosphamide, vincristine
Prior RT	54 Gy to the tumor bed	No	No	No	No data	No data	No data	No data	No
NTRK rearrangement	*ETV6:NTRK3* fusion	*ETV6:NTRK3* fusion	*ETV6:NTRK3* fusion	*ETV6:NTRK3* fusion	Unspecified	Unspecified	Unspecified	*ETV6:NTRK3* fusion	*ETV6:NTRK3* fusion
Inhibitor	Larotrectinib	1) Crizotinib for 9 months 2) larotrectinib 3 months	Larotrectinib	Larotrectinib	Larotrectinib	Larotrectinib	Larotrectinib	Entrectinib	Entrectinib
Response to treatment	MRI at 5 months confirmed the response, with resolution of enhancement in the tumor bed and almost all metastatic lesions	1) 56% reduction in the size of the remaining solid component of the tumor compared to the postsurgery MRI scan 2) further reduction in size reaching 73%	No evidence of recurrence after 12 months of treatment	MRI after 8 weeks of therapy showed marked tumor regression	Decrease in tumor burden	Stable disease	Treatment was terminated due to elevated liver function tests	Complete response	Complete response
Side effects	No	No data	No data	No	No data	No data	Elevated liver function tests	No data	Transient neutropenia

GTR, gross total resection; WHO, World Health Organization.

was published in 2018 in a 3-year-old girl with progressive HGG after irradiation and chemotherapy.[3] Among 12 children with *ETV6-NTRK3*-positive infant HGGs described by Clarke et al., only 2 patients received targeted therapy with larotrectinib and both with significant clinical benefit.[1] One case has also been reported of upfront usage of NTRK inhibition by larotrectinib for a patient with infantile glioblastoma harboring *ETV6-NTRK3* fusion.[4] The phase 1/2 STARTRK-NG trial (NCT02650401) of entrectinib demonstrated encouraging results in patients with NTRK fusion-positive CNS tumors (n = 8), including one patient with *ETV6-NTRK3*-positive high-grade glioma.[5]

There are several cases of successful targeting *ETV6-NTRK3*-positive infant high-grade glioma, with only one patient receiving entrectinib. Among the reported cases treatment was effective and well-tolerated. The summary of published cases of infant glioma with targeted therapy is given in Table 1. These early data suggest that both available NTRK inhibitors (laroctrectinib and entrectinib) could be an effective treatment for patients with *ETV6-NTRK3*-positive infant HGG.

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Conflict of interest statement. The authors have no conflicts to declare.

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