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LETTER TO THE EDITOR

Cabozantinib in children with recurrent diffuse gliomas

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To the Editor:

Molecularly-targeted therapy can improve clinical outcomes in various malignancies, including otherwise lethal infantile hemispheric gliomas.[1,2] Here, we describe two pediatric patients with rare glial tumors responding to cabozantinib—a small-molecule inhibitor of tyrosine kinases MET, VEGFR2, RET, and KIT[3,4] approved as anti-angiogenic agent in adult advanced carcinomas.[4] Despite the good blood–brain barrier penetrance,[5] cabozantinib is only moderately efficacious in adult progressive glioblastoma, with 14.5%–17.6% overall response rate[6] and poorer responses associated with a history of anti-angiogenic treatment.[7] Although molecularly guided use of cabozantinib substantively prolonged progression-free survival in adult patients with *MET*-amplified glioma ($n = 3$),[8] ADVL1211 trial demonstrated the lack of efficacy for cabozantinib in pediatric primary brain tumors regardless of putative molecular targets.[9] To date, none of the molecular-guided trials or case reports have explored the use of cabozantinib in pediatric brain tumors.

Case #1: A 4-year-old male presented with paroxysmal headaches, sleep disturbances, and visual hallucinations. The patient underwent partial resection of a tumor in the left parieto-occipital brain region, which histologically disclosed dysembryoplastic neuroepithelial morphology. Four years later, the symptoms resumed, and magnetic resonance imaging (MRI) revealed tumor growth (Figure 1A), and gross total resection was performed. Histological examination revealed a moderately cellular neoplasm different from the primary tumor, with focal oligodendroglioma-like patterns embedded in fibrillar stroma lacking endothelial proliferation. The Ki-67 proliferation index reached 10% (primarily <2%). The diagnosis was updated to "diffuse pediatric-type glioma of uncertain grade" (Figure 1B). Molecular-genetic testing revealed a *GTF2I::MET* fusion transcript originating from chr7 chromothripsis, *ATRX* p.R1803H and p.Q119* mutations, and 1p/19q co-deletion (Figure 1C). The *GTF2I::MET* gene fusion was retrospectively identified in the primary tumor material. The deoxyribonucleic acid (DNA) methylation profile was most consistent with a rare "glioneuronal tumor with *ATRX* alteration, kinase fusion, and anaplastic features" (GTAKA) entity recognized in 2023, yet unlisted in the World Health Organization (WHO) Classification of Central Nervous System Tumors.[10,11]

The patient underwent local radiation therapy to a total dose of 59.4 Gy on the tumor bed. Sixteen months post irradiation, the patient developed a second local recurrence. The *GTF2I::MET* fusion in the tumor suggested cabozantinib sensitivity. The drug was administered orally (40 mg/m^2/day). MRI performed 6 weeks into the treatment revealed complete regression of the tumor.

The treatment-related adverse events included gastrointestinal toxicity (decreased appetite, diarrhea, intestinal bleeding episodes; grade 3), musculoskeletal toxicity (arthralgia, right elbow joint synovitis; grade 2), and cutaneous toxicity (acneiform dermatitis, hair discoloration; grade 1), necessitating a 4-day break and subsequent two-fold reduction of the dose 3 months into the treatment, which fully resolved the toxicity without compromising the clinical benefit. Presently, the complete response on cabozantinib has been maintained for 8 months.

Case #2: A 3-month-old female presented with nystagmus, convergent strabismus, and torticollis. MRI revealed an extensive diffuse tumor of the cerebellum compressing the brainstem, with two nodal components identified in the right cerebellar hemisphere and along the posterior surface of the brainstem (Figure 2A). The patient underwent partial resection. Morphological examination revealed unusual tumor with mixed features of high- and low-grade astrocytoma: a biphasic growth pattern of vascularized neoplastic tissue with distinct areas identified as low- and high-grade glioma components. The Ki-67 proliferation index varied from ≤1% to 2% for low-grade component to ≤40% for high-grade component (Figure 2B). Molecular tests revealed no genomic imbalances or clinically relevant fusion transcripts. The DNA methylation profile matched none of the established methylation signatures. The only identified molecular variant of putative significance was *KIT* p.P627L mapped to the catalytic domain of KIT protein (Figure 2C). The pathogenetic relevance of the substitution was supported immunohistochemically, with phosphoERK1/2 positivity indicating RAS–RAF–MEK–ERK signaling pathway activation (Figure 2B). Of glial/glioneuronal neoplasms, a single case of dysembryoplastic neuroepithelial tumor with a driver point-mutation in *KIT* oncogene has been published[12]; at that, approximately 4% of adult high-grade gliomas harbor *KIT* amplifications albeit not single-nucleotide variants.[13,14]

MRI performed 3 weeks post surgery revealed significant progression. Over the next 3 months, the patient received chemotherapy according to BabyPOG protocol[15]; still, progression was noted. Upon exhaustion of efficacious options, the identified *KIT* p.P627L mutation provided rationale for targeted therapy with a KIT tyrosine kinase inhibitor.

Cabozantinib was commenced orally (at 40 mg/m^2/day), and afforded disease stabilization within 6 weeks. Ten months into the protocol, significant reduction of the contrast-positive nodular structures was documented: from 7.5 to 3 cm^3 in the right cerebellar hemisphere and from 3.8 to 0.75 cm^3 along the posterior surface of the brainstem. The patient is stable, 15 months on cabozantinib.

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