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Midline Low-Grade Gliomas of Early Childhood: Focus on Targeted Therapies

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Abstract

Purpose: Midline low-grade gliomas (mLGGs) of early childhood have a poorer prognosis compared with tumors of other localizations and in older patients. LGGs are associated with aberrant activation of RAS-RAF-MEK pathway, and pharmacological inhibition of the pathway has therapeutic promise. The aim of this study was clinical and molecular characterization of infantile mLGGs, with emphasis on the efficacy of targeted kinase inhibition.

Patients and methods: This study enrolled 40 patients with mLGG age <3 years. The majority of the patients (30/40) received first-line chemotherapy (CT) as per International Society of Paediatric Oncology LGG 2004 guidelines. In all patients, molecular genetic investigation of tumor tissue by polymerase chain reaction and RNA sequencing was performed. The median follow-up was 3.5 years.

Results: First-line CT failed in 24 of 30 recipients. The identified molecular profiles included *KIAA1549::BRAF* fusions in 26 patients, *BRAF* V600E in six patients, *FGFR1::TACC1* fusions in two patients, and rare fusion transcripts in four patients. At disease progression, targeted therapy (TT) was initiated in 27 patients (22 patients received trametinib) on the basis of molecular findings. TT was administered for a median of 16 months, with partial response achieved in 12 of 26 (46%) patients in which response was evaluated. Severe adverse events were detected only on trametinib monotherapy: acute damage of GI or urinary mucosa complicated by hemorrhage and development of transfusion-dependent anemia in four patients and grade 3 skin toxicity in three patients.

Conclusion: mLGGs of early childhood are often aggressive tumors, resistant to CT, and frequently require alternative treatment. The majority of patients harbor druggable molecular targets and respond to molecular TT.