

[Chilids Nerv Syst.](#) 2024 Jul 31. doi: 10.1007/s00381-024-06504-7. Online ahead of print.

Future perspective of targeted treatments in pediatric low-grade glioma (pLGG): the evolution of standard-of-care and challenges of a new era

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PMID: 39085626 DOI: [10.1007/s00381-024-06504-7](https://doi.org/10.1007/s00381-024-06504-7)

Abstract

While surgery, when possible, remains the mainstay of pediatric low-grade glioma (pLGG) management, adjuvant therapy has significantly evolved over time. Radiation therapy was commonly used in the late 1990s for tumors that could not be resected or recurred. This resulted in significant late morbidity in this population and mortality related to secondary malignancies and chronic health conditions. Chemotherapy became the mainstay of adjuvant therapy but children still experienced late morbidity secondary to exposure to multiple lines of treatment over time. Targeted therapies emerged after the identification of frequent genetic alterations in the mitogen activated protein kinase (MAPK) pathway including KIAA1549-BRAF fusions and BRAF-V600 mutations and the near universal upregulation of the MAPK pathway in these tumors. Both BRAF and MEK inhibitors have shown efficacy in the treatment of pLGG and have led to prolonged stability in some cases. Multiple phase III clinical trials are now comparing targeted therapy to standard-of-care chemotherapy regimens setting the stage for targeted therapy to replace chemotherapy as the first-line treatment in some cases. Targeted therapy, however, is not without its challenges. There are clear examples of resistance and mechanisms of resistance have not been fully elucidated. There is also no clear duration for these therapies and rebound growth is a well-known phenomenon especially in BRAF-V600 mutant tumors. Targeted therapies are also fairly recent developments and long-term toxicities and functional outcomes are still being monitored. Very young and adolescent/young adult LGGs also carry molecular features that may not be addressed by inhibition of the MAPK pathway. Adjuvant therapy for pLGG has evolved from radiation for all unresectable or residual tumors to molecularly driven targeted therapies with improved quality of life, late effects, and less off-target toxicities. While there is still much to learn in regard to newer targeted therapies for pLGG, the era of targeted therapies for pediatric LGG is upon us.

Keywords: BRAF inhibitors; Low grade glioma; MAPK inhibitors; MEK inhibitors; Targeted therapy.

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