Childs Nerv Syst. 2024 Jun 15. doi: 10.1007/s00381-024-06486-6. Online ahead of print.

Molecular-targeted therapy for childhood low-grade glial and glioneuronal tumors

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PMID: 38877124 DOI: 10.1007/s00381-024-06486-6

Abstract

Since the discovery of the association between BRAF mutations and fusions in the development of childhood low-grade gliomas and the subsequent recognition that most childhood low-grade glial and glioneuronal tumors have aberrant signaling through the RAS/RAF/MAP kinase pathway, there has been a dramatic change in how these tumors are conceptualized. Many of the fusions and mutations present in these tumors are associated with molecular targets, which have agents in development or already in clinical use. Various agents, including MEK inhibitors, BRAF inhibitors, MTOR inhibitors and, in small subsets of patients NTRK inhibitors, have been used successfully to treat children with recurrent disease, after failure of conventional approaches such as surgery or chemotherapy. The relative benefits of chemotherapy as compared to molecular-targeted therapy for children with newly diagnosed gliomas and neuroglial tumors are under study. Already the combination of an MEK inhibitor and a BRAF inhibitor has been shown superior to conventional chemotherapy (carboplatin and vincristine) in newly diagnosed children with BRAF-V600E mutated low-grade gliomas and neuroglial tumors. However, the long-term effects of such molecular-targeted treatment are unknown. The potential use of molecular-targeted therapy in early treatment has made it mandatory that the molecular make-up of the majority of low-grade glial and glioneuronal tumors is known before initiation of therapy. The primary exception to this rule is in children with neurofibromatosis type 1 who, by definition, have NF1 loss; however, even in this population, gliomas arising in late childhood and adolescence or those not responding to conventional treatment may be candidates for biopsy, especially before entry on molecular-targeted therapy trials.

Keywords: BRAF fusion; BRAF mutation; MEK inhibitor; MTOR inhibitor; Molecular-targeted therapy; VEGF inhibitor.