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Management of Pediatric Low-Grade Glioma

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Abstract

Purpose of review: Pediatric low-grade gliomas have been treated with similar therapies for the last 30 years. Recent biological insights have allowed a new generation of targeted therapies to be developed for these diverse tumors. At the same time, technological advances may redefine the late toxicities associated with radiation therapy. Understanding recent developments in pediatric low-grade glioma therapy is essential to the management of these common pediatric tumors.

Recent findings: It is now well understood that aberrations of the MAPK pathway are key to oncogenesis in low-grade gliomas. This understanding, along with the development of available targeted agents, have heralded a new era of understanding and treatment for these patients. Promising, sustained responses are now being seen in early phase trials among patients with multiply recurrent/progressive disease. Also, newer and highly conformal radiation approaches such as proton beam radiotherapy maintain efficacy of radiation but limit radiation-associated toxicities.

Summary: Novel therapies offer the potential for tumor control with greatly reduced toxicities. However, late effects of these therapies are just now being explored. Improved radiation approaches and targeted agents have the potential to redefine traditional therapy for pediatric low-grade glioma.

Keywords

pediatric low-grade glioma; BRAF; targeted therapy; radiation therapy

Introduction

Recent technical and scientific advances offer novel therapies to children with inoperable or progressive pediatric low-grade glioma (pLGG). Newer radiation techniques, such as proton beam radiation, offer the potential to limit radiation doses delivered to healthy tissue in order

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Conflicts of Interest

to reduce radiation-associated morbidities. Advances in our understanding of the biology of low-grade gliomas have similarly identified the critical role of activation of the mitogen-activated protein (MAP) kinase pathway, paving the way for clinical trials targeting this pathway with promising early results. These advances have expanded our therapeutic options for pLGG and may herald a new era in their treatment.

Epidemiology

Low-grade gliomas are the most common central nervous system (CNS) tumor among children, accounting for approximately one-third of pediatric brain tumors.(1, 2) These tumors include a heterogeneous group of histologies classified by the World Health Organization (WHO) as grades I or II.(3) Prognosis for these tumors is generally excellent, with 10-year overall survival (OS) between 85–96%.(4–6) However, survivors of pediatric glioma often suffer functional, neurologic and endocrine complications from their disease or treatment.(7) As a result, current treatment regimens are designed to maintain this excellent overall survival while reducing late effects.

Treatment for pLGG

The mainstay of therapy for progressive or symptomatic pLGG is complete surgical resection whenever feasible. Completely resected tumors often require no further therapy, and even subtotal resection may induce tumor quiescence for prolonged periods.(8) However, pLGG that cannot be resected or progress after resection often require additional therapy.

Historically, radiation therapy has been used in the up-front and salvage settings for the treatment of pLGG, with a phase II study of 54 Gy delivered to the tumor with a 10 mm margin resulting in 5-year progression-free survival (PFS) and OS of 87% and 96%, respectively.(9) However, traditional photon radiotherapy is associated with troubling side effects including cognitive decline, endocrine deficiencies, secondary malignancies, vascular damage and growth abnormalities. (9–11) Thus, radiotherapy is generally reserved for a subset of pLGG patients who are older and for whom less toxic treatments such as surgery, chemotherapy and targeted agents, have been exhausted.

In the 1980s, chemotherapy was introduced for young children with progressive or incompletely resected pLGG as a means to delay or obviate the need for radiation therapy. This is especially important in children with neurofibromatosis type-1 (NF-1) who are at increased risk of pLGG, typically within the optic pathway. They are also at an increased risk of developing a secondary malignancy due to their germline mutation. Chemotherapy regimens in newly-diagnosed pLGG achieve 3-year PFS between 50–80% depending on the regimen (see Table 1). The most commonly used chemotherapy regimens for pLGGs are carboplatin and vincristine, a combination of thioguanine, procarbazine, CCNU and vincristine (TPCV) or vinblastine alone. Although carboplatin and vincristine may offer slightly inferior PFS compared to TPCV (not statistically significant)(12), the combination avoids the risks of secondary malignancy and infertility posed by the TPCV regimen.

Recent Advances in Radiation Therapy

Sophisticated radiotherapy techniques have been used to harness the efficacy of radiation therapy while mitigating its toxicities. Progress in imaging technology, including high-resolution computed tomography and magnetic resonance imaging and improvements in patient immobilization have allowed tumor targeting with smaller margins and more conformal radiation plans. In addition to sophisticated conformal radiation approaches, newer radiation modalities have allowed sparing of normal brain regions. Proton beam radiotherapy is such a modality that limits the volume of normal brain that is exposed to low and intermediate doses of radiation compared to photon radiotherapy. In a retrospective series of 32 patients treated with proton beam radiotherapy for low-grade glioma with a median follow-up time of 7.6 years, 8-year PFS and OS were 82.8% and 100%, respectively. (13) Although generally well tolerated, significant decline in neurocognitive outcomes were seen in young children (less than 7 years old) and patients whose left temporal lobe/hippocampus received significant doses. Higher doses to the hypothalamus or pituitary were associated with endocrinopathies, and two cases of moya moyo disease were documented as well.

Another highly conformal radiation approach, stereotactic radiation, has been studied in a prospective trial at Dana-Farber Cancer Institute. Relatively small (less than 5 cm) tumors were treated upfront or as salvage with a mean radiation dose of 52.2 Gy in 1.8 Gy fractions. At five years, PFS and OS were 82.5% and 97.8%, respectively, and no marginal failures were observed. The authors concluded that stereotactic radiotherapy provides excellent local control for children with small, localized pLGG. Also, limiting the treatment margins helps limit radiation-related toxicities without compromising local control.(14)

Taken together, highly conformal radiation approaches appear to be safe and effective methods to achieve local control but are still best reserved for the salvage setting. There does not appear to be clear benefit in the immediate post-operative setting. When radiation therapy is employed for pLGG, doses of 52–54 Gy are effective, and planning set-up margin can safely be limited to 1 cm or less to protect adjacent normal tissues.

The Genomic Landscape of pLGG

The last decade has generated unparalleled insights into the underlying biology of pLGG. Long recognized to exhibit clinical heterogeneity, recent landmark genomic profiling efforts(15–17), have confirmed pLGGs to be distinct from low-grade gliomas that occur in adults, and to collectively represent a group characterized by distinct driver alterations. pLGGs most frequently have somatic driver genetic alterations that result in activation of the MAPK pathway.(15–18) Similar MAPK activation can be seen as a result of syndromes genetically predisposed to pLGG, including NF1(19) and tuberous sclerosis.(20) MAPK activation resulting in downstream activation of the mtor pathway is predominant in pLGG and offers a useful target for therapy.(21, 22) The majority of tumors exhibit only a single identifiable driver alteration. As a result, pLGGs are most commonly defined by single structural variants or rearrangements that result in the expression of a fusion protein.

Rearrangements afflicting the genes *BRAF* and *KIAA1549* are the most frequent somatic driver alterations across all pLGGs, and are enriched within pilocytic astrocytomas.(15–17, 23, 24) *KIAA1549-BRAF* rearrangements result in expression of a fusion protein consisting of the N'-terminal of the KIAA1549 protein and the truncated C'-terminal of BRAF, which contains the BRAF kinase. The N' terminal negative regulatory domain of BRAF is not retained in the KIAA1549-BRAF fusion, which results in constitutive activation of the BRAF kinase with downstream activation of MAPK signaling. *BRAF* rearrangements involving other fusion partners including *RNF130*(16), *CLCN6*(16), *GNAI1*(16), *GIT2*(25), *FXR1*(15) and *MKRNI*(16) have also been observed less frequently. A smaller cohort of pLGGs harbor activating *BRAF V600E* mutations(15, 16, 18) and are enriched in gangliogliomas(15, 17) and pleomorphic xanthoastrocytomas(26), frequently associated with loss of *CDKN2A*(27).

The expanding number of pLGGs subjected to genomic profiling has allowed further association of recurrent driver alterations with specific pLGG subtypes. Diffuse astrocytomas have been shown to be enriched with *BRAF* mutations or rearrangements involving the *MYB* (and the related *MYBL1*) family of transcription factors(15, 17, 28, 29). These *MYB* rearrangements result in C' terminal truncation of *MYB/MYBL1*, with resultant loss of its negative regulatory domain and aberrant expression of the truncated protein product. *MYB-QKI* fusion proteins have been shown to define angiocentric gliomas(17), which have also recently been reported to present as brainstem tumors(30, 31). *MYB* rearrangements involving other fusion partners including *PCDHGA1* and *MAML2* have also been described(15, 17, 32); however, their clinical associations remain to be defined. *FGFR1* mutations and rearrangements involving *FGFR1* (including duplications of the *FGFR1* kinase) occur more commonly in dysembryoplastic neuro-epithelial tumors(16, 32, 33), which can also be associated with germline *FGFR1* alterations(33). While pilocytic astrocytomas are largely defined by BRAF alterations, a subset harbor *FGFR1* and *NTRK2* rearrangements(16). Finally, while IDH1 mutations are much more commonly associated with adult low-grade gliomas, they are also infrequently observed in young children(34). The clinical significance and natural history of pediatric IDH1 mutant low-grade gliomas remains to be defined.

Targeted Treatments for Pediatric LGG

Numerous agents that target the MAPK pathway, such as MEK or BRAF inhibitors (see Figure 1) are currently being tested in pLGGs. The drug that has been studied most extensively to date is selumetinib (AZD6244), a selective and potent orally-available, non-ATP competitive small-molecule inhibitor of MEK-1/2. Promising preclinical data(35), led to the phase I Pediatric Brain Tumor Consortium (PBTC) trial of selumetinib in children with recurrent and refractory pLGG (NCT01089101). The recommended phase 2 dose (RP2D) determined among 38 eligible children was 25 mg/m²/dose twice daily (36). Five of 25 patients treated at the RP2D had a centrally-reviewed partial response (PR) and 37% completed all 26 cycles of protocol therapy with at least stable disease. The dose limiting toxicities (DLT) included rash, increased amylase/lipase and mucositis(36).

These results led to the ongoing PBTC phase II trial (NCT01089101) evaluating selumetinib in recurrent/refractory pLGG among 6 strata. The stratification was based upon tumor histology, location, NF1 status, and specific BRAF aberration. Preliminary data revealed response rates of 36–40% in children with NF1 associated pLGG as well as non-NF1 pilocytic astrocytomas harboring a BRAF aberration(37). The most commonly reported toxicities were grade 1/2 CPK elevation, diarrhea, hypoalbuminemia, elevated AST and rash. The Children's Oncology Group (COG) is planning two phase 3 upfront randomized clinical trials comparing selumetinib to standard chemotherapy (carboplatin and vincristine) among patients with NF1- and non-NF1 associated pLGG (personal communication, COG CNS Committee, 2018).

Trametinib is another oral MEK-1/2 inhibitor already approved by the FDA for the treatment of BRAF-mutant melanoma(38). A phase 1/2 pediatric trial (NCT02124772) enrolled 23 patients with refractory/recurrent pLGG. PRs were observed in 3 patients by local investigators and confirmed in 1 patient by independent review (39). The most common adverse events were diarrhea, rash and paronychia.

Binimetinib (MEK-162), a small molecule allosteric inhibitor of MEK-1/2(40) has completed phase 1 testing trial (NCT02285439) in children with recurrent, refractory or progressive pLGG and other Ras/Raf pathway activated malignancies. Seventeen children with pLGG were enrolled and treated at doses between 16 to 32 mg/m²/dose twice daily. An MTD was not established. Four pLGG patients achieved a PR, and 12/17 completed at least 36 weeks of therapy with a median decrease of 29% in 2-dimensional tumor measurements(41). The most common toxicities were asymptomatic elevated CPK, rash, dry skin and lymphopenia. A phase II study is currently ongoing.

Cobimetinib, another oral MEK inhibitor, is FDA-approved in combination with vemurafenib for the treatment of unresectable or metastatic BRAFV600- mutated melanoma and is also undergoing phase 1 testing in recurrent pediatric solid tumors (NCT02639546).

Direct targeting of BRAF using vemurafenib or dabrafenib is another promising approach being studied in pLGG. Dabrafenib and vemurafenib are both orally-bioavailable, potent and selective inhibitors of BRAF kinases that harbor V600 mutations, binding to the ATP-binding domain of mutant BRAF. Both dabrafenib and vemurafenib are FDA-approved in the treatment of BRAF^{V600E/K}-mutated melanoma. Case reports describing dramatic responses to dabrafenib in infants and children with recurrent LGG that harbor BRAF^{V600E} mutations(42, 43) led to an ongoing multi-institutional phase I/IIa trial (NCT01677741) of dabrafenib in children with recurrent BRAF^{V600} mutated solid tumors. Thirty-two children with pLGG have been enrolled. The RP2D was 4.5 mg/kg/day for children >12 years and 5.25 mg/kg/day for children ≤12 years. Independent central radiologic review revealed 13 PR and 1 complete resection (CR)(44) for an overall RR of 44%, with a 1-year PFS and OS of 74% and 44%, respectively. (45). The disease-specific phase 2 component of the study is ongoing. Similarly, early reports of promising vemurafenib activity in children with recurrent BRAF^{V600E} mutant pLGG treated (46, 47) led to the ongoing Pacific Neuro-Oncology Consortium (PNOC) phase I trial of vemurafenib in children with recurrent or refractory gliomas containing the BRAF^{V600E} mutation (NCT01748149).

MAPK-targeting combination therapies are also being explored. Kondyli et al reported that among 6 patients with refractory V600E-mutated pLGG treated with a combination of trametinib and dabrafenib, 4 patients experienced PR, 1 SD and 1 progressive disease (PD) (48). A phase 2 industry-sponsored trial evaluating this combination is currently underway in children with both high and low-grade glioma with BRAF^{V600} mutations (NCT02684058).

Therapies targeting the mtor pathway, such as everolimus, are also currently being evaluated. An ongoing PNOC phase 2 study evaluates everolimus in children with recurrent/progressive pLGG (NCT01734512).

Unfortunately, as with most novel agents, there is a learning curve to our understanding. BRAF and MEK inhibitors harbor unique toxicity profiles that include rashes, cardiac dysfunction, ocular toxicity, CPK elevation and skin infections (36, 49). Prevention and management of these side effects have improved over time and with practitioners' experience. In addition, we now understand the importance of tailoring therapy for pLGGs based on a thorough understanding of the distinct mechanisms of action specific to different BRAF alterations. A pediatric phase II trial of sorafenib, a multi-kinase inhibitor (targeting BRAF, VEGFR, PDGFR, and c-kit) in children with recurrent LGG was halted because of unexpected progression in 9 of 11 patients., including 3 with KIAA1549-BRAF fusion and NF1. Studies have confirmed that this effect is a result of paradoxical ERK activation(50) also reported in NF1loss. Thus, first-generation BRAF inhibitors such as vemurafenib and dabrafenib which target the monomeric forms of BRAF should not be used for tumors with BRAF fusion which function as dimers. This is an important consideration since pilocytic astrocytomas, the most common pLGG, commonly harbor the KIAA1549-BRAF fusion. Fortunately, second-generation BRAF inhibitors such as TAK580, bypass this paradoxical activation and can target both monomeric and dimeric forms of the BRAF oncoprotein, (51). A phase I/II study of TAK580 in children with recurrent/refractory gliomas is currently underway by PNOC.

Conclusion

Early results of novel radiation techniques and MAPK-targeting strategies in pLGG have been quite promising. Novel agents targeting BRAF aberrations have demonstrated high response rates, good PFS and overall manageable toxicity in patients with recurrent disease. However, numerous questions regarding these targeted therapies remain unanswered, such as the appropriate duration of therapy, durability of response once therapy has ceased, late toxicities with chronic administration and the use of these agents as up-front therapy or in combination with other agents. Carefully developed prospective clinical trials will better answer these and other important questions.

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Key Points:

- Therapies that target the activated Ras/Raf/MEK pathway in pLGG offer a novel mechanism of tumor control with well-tolerated toxicities.
- Questions remain regarding how best to incorporate targeted chemotherapy in the management of pLGG.
- Advanced radiation therapy techniques, such as proton therapy, deliver radiation doses more precisely than prior methods and may offer reduced toxicity for children with pLGG when other treatment options are exhausted.

Figure 1 (original):

A simplified diagram of the MAP kinase pathway

Table 1 (original):

Results of chemotherapy trials in newly diagnosed pediatric low-grade glioma. NF1: neurofibromatosis type 1; PFS: progression-free survival; OPHG: optic pathway-hypothalamic glioma; nm: not mentioned.

Author	Year of Publication	Chemotherapy	N(total)	N(NF1)	Tumor location	PFS
Aquino(52)	1999	carboplatin (560mg/m ² every 4 weeks)	12	4	12 OPHG	3yr 83%
Kadota(53)	1999	cyclophosphamide (1.2g/m ² every 3weeks)	15	5	9 OPHG	3mo 64%
Packer(54)	1988	vincristine (1.5mg), actinomycin D (12microg) every 12 weeks	24	nm	nm	3yr 79%
Ater(55)	2016	carboplatin, vincristine	264	127	181 OPHG, 14 thalamus NF1;	3yr: 80% (NF1), 52% (non-NF1);
Ater(12)	2012	TPCV	137	0	67 OPHG, 14 thalamus	3yr 62%,
Laithier(56)	2003	BBS SFOP: procarbazine, carboplatin, etoposide, cisplatin, vincristine, cyclophosphamide	84	23	85 OPHG	3yr 52%
Lassaletta(57)	2016	vinblastine (6mg/m ² weekly)	54	13	30 OPHG, 11 brainstem (nonNF1)	3yr 92% (NF1); 56% (nonNF1)
Massimino(58)	2010	cisplatin (30 mg/m ² /day) and etoposide (150 mg/m ² /day) for 3 days every month	31	<=8	29 OPHG	3yr 78%
Gnekow(59)	2017	VCR/carbo/etoposide	248	0	157 OPHG	3yr 57%
Genkow(59)	2017	carboplatin, vincristine	249	0	158 OPHG	3yr 58%