Pediatric-Type Diffuse Low-Grade Glioma

Subjects: Oncology

Contributor: Sudarshawn Damodharan , Diane Puccetti

Pediatric-type diffuse low-grade glioma (LGG) are the most common pediatric brain tumor, accounting for approximately one-third of all cases. These tumors are designated as WHO grade 1 or 2 and encompass a wide array of histology and varying molecular backgrounds. Many of these tumors are incidentally found on head imaging with intervention needed when adverse symptoms present or when found to have progressive disease. Pediatric diffuse LGGs are primarily heterogenous in nature and can be molecularly classified into distinct subgroups; diffuse astrocytoma MYB- or MYBL1-altered, angiocentric glioma, polymorphous low-grade neuroepithelial tumors, and diffuse LGG MAPK pathway-altered.

pediatrics CNS tumors treatment

1. Diffuse Astrocytoma, MYB- or MYBL1-Altered

This category of pediatric LGG is an infiltrative astroglial neoplasm that is driven by genetic alterations to the MYB or MYBL1 proto-oncogenes [1]. These tumors are typically classified as WHO grade 1. They primarily localize to the cortical and subcortical areas of the brain without further extension [2].

2. Angiocentric Glioma

These gliomas typically aggregate within the perivascular spaces of the CNS and carry a distinct MYB-QKI gene fusion [3][4]. They are primarily given a WHO grade 1 designation and are most commonly located within the cerebral cortex [3][4].

3. Polymorphous Low-Grade Neuroepithelial Tumor

These tumors are indolent cerebral neoplasms carrying a WHO grade 1 distinction [5][6]. Alterations within the MAPK pathway play a role in tumor development with most associated with BRAF mutations or FGFR fusions [5]. The primary location of these tumors are within the cortical and subcortical components of the temporal lobes of the brain [7].

4. Diffuse LGG, MAPK Pathway-Altered

These gliomas occur primarily in children and universally carry an alteration within a gene associated within the MAPK pathway [8]. Typically, they also carry concurrent alterations in FGFR1 or a BRAF fusion [9][10]. They occur

throughout the craniospinal axis with some literature pointing to more common alterations depending on the region of occurrence such as a higher incidence of tumors with BRAF fusions within the cerebellum [10]. There is a high prevalence of these tumors in patients with neurofibromatosis type 1 (NF1) with on-going research focusing on targeted therapies to combat this [11][12].

5. Pilocytic Astrocytoma

Pilocytic astrocytomas are the most common LGG seen in the pediatric population, accounting for approximately 20% of all brain tumors in children and young adults [8][13]. They have a predilection for diseases associated with germline mutations in the MAPK pathway including NF1 and Noonan syndrome [8]. Additional common molecular alterations found include BRAF p.V600E and FGFR1 mutations or fusions [8]. These neoplasms most commonly occur in the cerebellum and are generally slow growing and well circumscribed making them amenable to surgical resection. The majority carry a WHO grade 1 distinction with malignant transformation rarely seen [13].

6. Treatment

The primary treatment for most LGGs includes an upfront biopsy, if not amenable for a safe gross total resection, to establish the diagnosis and to perform molecular analysis which has now become standard of care [8][14]. This is typically followed by as safe of a gross total resection as possible. Depending on the location of the tumor, resection is sometimes not possible and observation with sequential imaging is carried out as the majority of these tumors remain indolent [14].

In cases where patients with LGGs become clinically symptomatic (i.e., abnormal neurologic symptoms and vision changes) but are unable to have a surgical intervention, treatment with either conventional chemotherapy or radiation therapy has been utilized. In the past, radiation therapy had been used for up-front treatment of LGGs or at the time of progression [15]. A prior phase II study was performed that delivered 54 Gy to the tumor and did result in good progression free survival (PFS) and overall survival rates (OS) of 87% and 96% [16]. However, significant side effects were seen including neurocognitive delays and increased risk of secondary malignancies [16]. Because of these risks, radiation is typically not utilized or offered for LGG management under normal circumstances.

Chemotherapy is utilized more commonly for the medical management of LGGs that cannot be surgically removed. The most commonly utilized systemic chemotherapy regimens for LGG in children include carboplatin and vincristine or vinblastine alone [17]. These chemotherapy regimens have led to similar PFS to those who received radiation therapy but with significantly reduced toxicity and side effect profiles in multiple phase II studies performed in children with LGGs [18][19].

Given the increased molecular understanding of pediatric LGGs, more targeted agents have become available primarily targeting the MAPK pathway [8] (**Table 1**). The two most common agents being utilized are MEK and BRAF inhibitors. Selumetinib is a selective small molecule inhibitor of MEK-1/2 which has shown promising results in this setting. Most recently, a phase II trial was conducted for selumetinib for pediatric LGG in patients without

NF1 via the Pediatric Brain Tumor Consortium (PBTC) [20]. This showed either stable to improved disease status in patients with either recurrent or progressive LGGs with further studies on-going [20]. Currently, the Children's Oncology Group (COG) is conducting a phase III randomized clinical trial assessing upfront selumetinib to standard chemotherapy (carboplatin and vincristine) among patients with and without NF1 associated LGGs (NCT04166409). Dabrafenib and vemurafenib are small molecule BRAF kinase inhibitors that have also been utilized in LGGs that harbor BRAF V600E mutations. A phase I trial conducted by the Pacific Neuro-Oncology Consortium (PNOC) looked to assess the utility of vemurafenib in children with recurrent or refractory gliomas harboring the BRAF V600E mutation [21]. The trial showed that approximately half the patients had a positive response to vemurafenib and that the drug was well tolerated [21]. More on-going therapies are looking at MAPK combination therapies with both MEK and BRAF inhibitors with preliminary results from an on-going phase II study showing improved response rates and PFS to the agents individually or to standard chemotherapy (NCT02684058). A phase 2 study evaluating the pan-RAF inhibitor tovorafenib (DAY101) has also shown promising preliminary results for refractory LGGs in children with BRAF alterations (NCT04775485). There is still much to be learned about molecular inhibitors, with long-term toxicities not known, but they do pose a more targeted approach for the medical management of pediatric LGG.

Table 1. Active clinical trials for pediatric LGG utilizing targeted therapies.

Study Title	NCT Number	Targeted Therapeutic Intervention	Country
DAY101 vs. Standard of Care Chemotherapy in Pediatric Patients with Low-Grade Glioma Requiring First-Line Systemic Therapy (LOGGIC/FIREFLY-2)	NCT05566795	Drug: DAY101	USA, Canada, Czechia, Korea, Switzerland
A Study to Evaluate DAY101 in Pediatric and Young Adult Patients with Relapsed or Progressive Low-Grade Glioma and Advance Solid Tumors	NCT04775485	Drug: DAY101	USA
SJ901: Evaluation of Mirdametinib in Children, Adolescents, and Young Adults with Low-Grade Glioma	NCT04923126	Drug: Mirdametinib	USA
A Study of the Drugs Selumetinib Versus Carboplatin/ Vincristine in Patients with Neurofibromatosis and Low-Grade Glioma	NCT03871257	Drug: Selumetinib Sulfate	USA, Canada

Study Title	NCT Number	Targeted Therapeutic Intervention	Country
A Study of the Drugs Selumetinib vs. Carboplatin and Vincristine in Patients with Low-Grade Glioma	NCT04166409	Drug: Selumetinib Sulfate	USA, Canada
A Study to Compare Treatment with the Drug Selumetinib Alone Versus Selumetinib and Vinblastine in Patients with Recurrent or Progressive Low-Grade Glioma	NCT04576117	Drug: Selumetinib Sulfate	USA
Trametinib and Everolimus for Treatment of Pediatric and Young Adult Patients with Recurrent Gliomas	NCT04485559	Drug: Everolimus Drug: Trametinib	USA
A Trial of Dabrafenib, Trametinib and Hydroxychloroquine for Patients with Recurrent LGG or HGG With a BRAF Aberration	NCT04201457	Drug: Dabrafenib Drug: Trametinib	USA
Pediatric Low-Grade Glioma–MEK inhibitor Trial vs Chemotherapy	NCT05180825	Drug: Trametinib	France
BGB-290 and Temozolomide in Treating Isocitrate Dehydrogenase (IDH)1/2-Mutant Grade I-IV Gliomas	NCT03749187	Drug: PARP Inhibitor BGB-290	USA
Pediatric Long-Term Follow-up and Rollover Study	NCT03975829	Drug: Dabrafenib Drug: Trametinib	USA

Clinical trials found on www.clinicaltrials.gov as of 5 June 2023.

1. Wefers, A.K.; Stichel, D.; Schrimpf, D.; Coras, R.; Pages, M.; Tauziede-Espariat, A.; Varlet, P.; Schwarz, D.; Soylemezoglu, F.; Pohl, U.; et al. Isomorphic diffuse glioma is a morphologically and molecularly distinct tumour entity with recurrent gene fusions of MYBL1 or MYB and a benign disease course. Acta Neuropathol. 2020, 139, 193–209.
2. Bale, T.A.; Rosenblum, M.K. The 2021 WHO Classification of Tumors of the Central Nervous System: An update on pediatric low-grade gliomas and glioneuronal tumors. Brain Pathol. 2022,

32, e13060.

3. Bandopadhayay, P.; Ramkissoon, L.A.; Jain, P.; Bergthold, G.; Wala, J.; Zeid, R.; Schumacher, S.E.; Urbanski, L.; O′Rourke, R.; Gibson, W.J.; et al. MYB-QKI rearrangements in angiocentric glioma drive tumorigenicity through a tripartite mechanism. Nat. Genet. 2016, 48, 273–282.
4. Buccoliero, A.M.; Caporalini, C.; Scagnet, M.; Mussa, F.; Giordano, F.; Sardi, I.; Migliastro, I.; Moscardi, S.; Conti, V.; Barba, C.; et al. Angiocentric glioma-associated seizures: The possible role of EATT2, pyruvate carboxylase and glutamine synthetase. Seizure 2021, 86, 152–154.
5. Huse, J.T.; Snuderl, M.; Jones, D.T.; Brathwaite, C.D.; Altman, N.; Lavi, E.; Saffery, R.; Sexton-Oates, A.; Blumcke, I.; Capper, D.; et al. Polymorphous low-grade neuroepithelial tumor of the young (PLNTY): An epileptogenic neoplasm with oligodendroglioma-like components, aberrant CD34 expression, and genetic alterations involving the MAP kinase pathway. Acta Neuropathol. 2017, 133, 417–429.
6. Fei, X.; Zhao, J.; Wei, W.; Wang, W.; Kong, X.; Qian, R.; Niu, C.; Yao, Y. Clinical, Radiological, Pathological Features and Seizure Outcome With Surgical Management of Polymorphous Low-Grade Neuroepithelial Tumor of the Young Associated With Epilepsy. Front. Oncol. 2022, 12, 863373.
7. Kurokawa, M.; Kurokawa, R.; Capizzano, A.A.; Baba, A.; Ota, Y.; Pinarbasi, E.; Johnson, T.; Srinivasan, A.; Moritani, T. Neuroradiological features of the polymorphous low-grade neuroepithelial tumor of the young: Five new cases with a systematic review of the literature. Neuroradiology 2022, 64, 1255–1264.
8. Ryall, S.; Tabori, U.; Hawkins, C. Pediatric low-grade glioma in the era of molecular diagnostics. Acta Neuropathol. Commun. 2020, 8, 30.
9. Khatua, S.; Wang, J.; Rajaram, V. Review of low-grade gliomas in children--evolving molecular era and therapeutic insights. Childs Nerv. Syst. 2015, 31, 643–652.
10. Venneti, S.; Huse, J.T. The evolving molecular genetics of low-grade glioma. Adv. Anat. Pathol. 2015, 22, 94–101.
11. Rodriguez, F.J.; Ligon, A.H.; Horkayne-Szakaly, I.; Rushing, E.J.; Ligon, K.L.; Vena, N.; Garcia, D.I.; Cameron, J.D.; Eberhart, C.G. BRAF duplications and MAPK pathway activation are frequent in gliomas of the optic nerve proper. J. Neuropathol. Exp. Neurol. 2012, 71, 789–794.
12. Kiuru, M.; Busam, K.J. The NF1 gene in tumor syndromes and melanoma. Lab. Investig. 2017, 97, 146–157.
13. Salles, D.; Laviola, G.; Malinverni, A.C.M.; Stavale, J.N. Pilocytic Astrocytoma: A Review of General, Clinical, and Molecular Characteristics. J. Child. Neurol. 2020, 35, 852–858.

14. Hollon, T.; Hervey-Jumper, S.L.; Sagher, O.; Orringer, D.A. Advances in the Surgical Management of Low-Grade Glioma. Semin. Radiat. Oncol. 2015, 25, 181–188.
15. Wang, T.J.C.; Mehta, M.P. Low-Grade Glioma Radiotherapy Treatment and Trials. Neurosurg. Clin. N. Am. 2019, 30, 111–118.
16. Merchant, T.E.; Kun, L.E.; Wu, S.; Xiong, X.; Sanford, R.A.; Boop, F.A. Phase II trial of conformal radiation therapy for pediatric low-grade glioma. J. Clin. Oncol. 2009, 27, 3598–3604.
17. de Blank, P.; Bandopadhayay, P.; Haas-Kogan, D.; Fouladi, M.; Fangusaro, J. Management of pediatric low-grade glioma. Curr. Opin. Pediatr. 2019, 31, 21–27.
18. Ater, J.L.; Zhou, T.; Holmes, E.; Mazewski, C.M.; Booth, T.N.; Freyer, D.R.; Lazarus, K.H.; Packer, R.J.; Prados, M.; Sposto, R.; et al. Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: A report from the Children′s Oncology Group. J. Clin. Oncol. 2012, 30, 2641–2647.
19. Lassaletta, A.; Scheinemann, K.; Zelcer, S.M.; Hukin, J.; Wilson, B.A.; Jabado, N.; Carret, A.S.; Lafay-Cousin, L.; Larouche, V.; Hawkins, C.E.; et al. Phase II Weekly Vinblastine for Chemotherapy-Naive Children With Progressive Low-Grade Glioma: A Canadian Pediatric Brain Tumor Consortium Study. J. Clin. Oncol. 2016, 34, 3537–3543.
20. Fangusaro, J.; Onar-Thomas, A.; Poussaint, T.Y.; Wu, S.; Ligon, A.H.; Lindeman, N.; Campagne, O.; Banerjee, A.; Gururangan, S.; Kilburn, L.B.; et al. A phase II trial of selumetinib in children with recurrent optic pathway and hypothalamic low-grade glioma without NF1: A Pediatric Brain Tumor Consortium study. Neuro Oncol. 2021, 23, 1777–1788.
21. Nicolaides, T.; Nazemi, K.J.; Crawford, J.; Kilburn, L.; Minturn, J.; Gajjar, A.; Gauvain, K.; Leary, S.; Dhall, G.; Aboian, M.; et al. Phase I study of vemurafenib in children with recurrent or progressive BRAF(V600E) mutant brain tumors: Pacific Pediatric Neuro-Oncology Consortium study (PNOC-002). Oncotarget 2020, 11, 1942–1952.