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Pediatric low-grade glioma: State-of-the-art and ongoing challenges

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This paper serves as an overview on Pediatric Low-Grade Glioma (pLGG) and an introduction to a series of manuscripts on specific topics pertaining to pLGG.

Abstract

The most common childhood central nervous system (CNS) tumor is pediatric low-grade glioma (pLGG), representing 30%–40% of all CNS tumors in children. Although there is high associated morbidity, tumor-related mortality is relatively rare. pLGG is now conceptualized as a chronic disease, underscoring the importance of functional outcomes and quality-of-life measures. A wealth of data has emerged about these tumors, including a better understanding of their natural history and their molecular drivers, paving the way for the use of targeted inhibitors. While these treatments have heralded tremendous promise, challenges remain about how to best optimize their use, and the long-term toxicities associated with these inhibitors remain unknown. The International Pediatric Low-Grade Glioma Coalition (iPLGGc) is a global group of physicians and scientists with expertise in pLGG focused on addressing key pLGG issues. Here, the iPLGGc provides an overview of the current state-of-the-art in pLGG, including epidemiology, histology, molecular landscape, treatment paradigms, survival outcomes, functional outcomes, imaging response, and ongoing challenges. This paper also serves as an introduction to 3 other pLGG manuscripts on (1) pLGG preclinical models, (2) consensus framework for conducting early-phase clinical trials in pLGG, and (3) pLGG resistance, rebound, and recurrence.

Key Points

1. Several landmark genomic efforts have confirmed that pediatric low-grade glioma (pLGG) is largely characterized by aberrant activation of MAPK/ERK and mTOR pathway signaling.
2. pLGG is conceptualized as a chronic disease of childhood, underscoring the importance of functional outcomes and quality-of-life measures as endpoints in therapeutic trials for this population.
3. Leveraging a deeper molecular understanding of pLGG has led to the investigation of numerous novel treatment agents targeting the MAPK/ERK and mTOR pathways in recurrent and newly diagnosed children.

Pediatric low-grade glioma (pLGG) is the most common central nervous system (CNS) tumor encountered in childhood.[1,2] Over the last decade, a wealth of information has become available about its natural history, demonstrating that most individuals will survive their disease well into adulthood.[3,4] In fact, pLGG is now commonly accepted as a chronic disease, and therefore, more emphasis has been placed on functional outcomes and minimizing long-term morbidities to maximize quality of life.[5] There has also been a greater understanding about the cell-intrinsic and cell-extrinsic molecular drivers of pLGG, leading to numerous clinical trials prospectively evaluating the efficacy of molecularly targeted therapies.[6–11]

With this greater understanding of the molecular landscape, natural history, and a shift to focus on functional outcomes, the International Pediatric Low-Grade Glioma Coalition (iPLGGc) was established. The iPLGGc represents an international working group of specialists (Neuro-Oncologists, Neurosurgeons, Neuroradiologists, Neurologists, Geneticists, Radiation Oncologists, Neuropathologists, Scientists, Patient Advocates, and others in the field of Neuro-Oncology) who collaborated to develop an international committee, resulting in prior coalition manuscripts.[12,13] In 2020, the coalition formed 4 major working groups to address key issues/challenges in pLGG including (1) preclinical modeling; (2) treatment resistance, rebound, and recurrence; (3) clinical trial conduct considerations; and (4) quality of life and late effects (Figure 1).

The most recent iPLGGc meeting was held in Atlanta, GA, in November 2022, where the topics discussed herein were highlighted. This current review aims to provide an overview and update the state-of-the-art in pLGG, including epidemiology, histology, molecular landscape, treatment paradigms, survival outcomes, functional outcomes, and radiologic imaging. This overview will also highlight the current challenges we face as a pLGG community. Furthermore, this article will also serve as an introduction to 3 additional manuscripts written by iPLGGc working groups highlighting unique aspects of pLGG, including (1) preclinical models, (2) the development of a more universal platform for prospective early-phase clinical trials in pLGG, and (3) pLGG resistance, rebound, and recurrence.

Epidemiology

pLGG comprises 30%–40% of all pediatric CNS tumors, including a heterogeneous group of World Health Organization (WHO) grades 1 and 2 glioma, glioneuronal and neuronal neoplasms.[14] The most common location of pLGG is the cerebellum followed by the cerebral hemispheres, deep midline structures, optic pathway, and brainstem.[15] It is well established that children with the cancer predisposition syndrome neurofibromatosis type 1 (NF1) have an increased risk of developing pLGG, particularly of the optic pathway and brainstem.[16] Individuals with NF1 account for over 70% of the optic pathway/hypothalamic gliomas in children, and it is estimated that 15%–20% of all children with NF1 will develop an optic pathway glioma (OPG) during early childhood.[17,18]

Histology and Molecular Landscape

The 2021 WHO CNS tumor classification now has 1 section on glioma, glioneuronal tumors, and neuronal tumors that include both adult and pediatric tumors. This grouping is made up of the following major categories: (1) adult-type diffuse glioma, (2) pediatric-type diffuse low-grade glioma, (3) pediatric-type diffuse high-grade glioma, (4) circumscribed astrocytic glioma, (5) glioneuronal and neuronal tumors, (6) and ependymal tumors (Table 1). Though included in this section on glioma, glioneuronal tumors, and neuronal tumors, the ependymal tumors will not be a focus of this overview. Pediatric-type diffuse low-grade glioma is divided into 4 distinct entities: (1) diffuse astrocytoma, MYB- or MYB1-altered, (2) angiocentric glioma, (3) polymorphous low-grade neuroepithelial tumor of the young, and (4) diffuse low-grade glioma, MAPK pathway-altered.[19] Tumors that have historically been classified as pLGG now fall under several subcategories within the 2021 WHO glioma, glioneuronal, and neuronal tumor sections, including pediatric-type diffuse low-grade

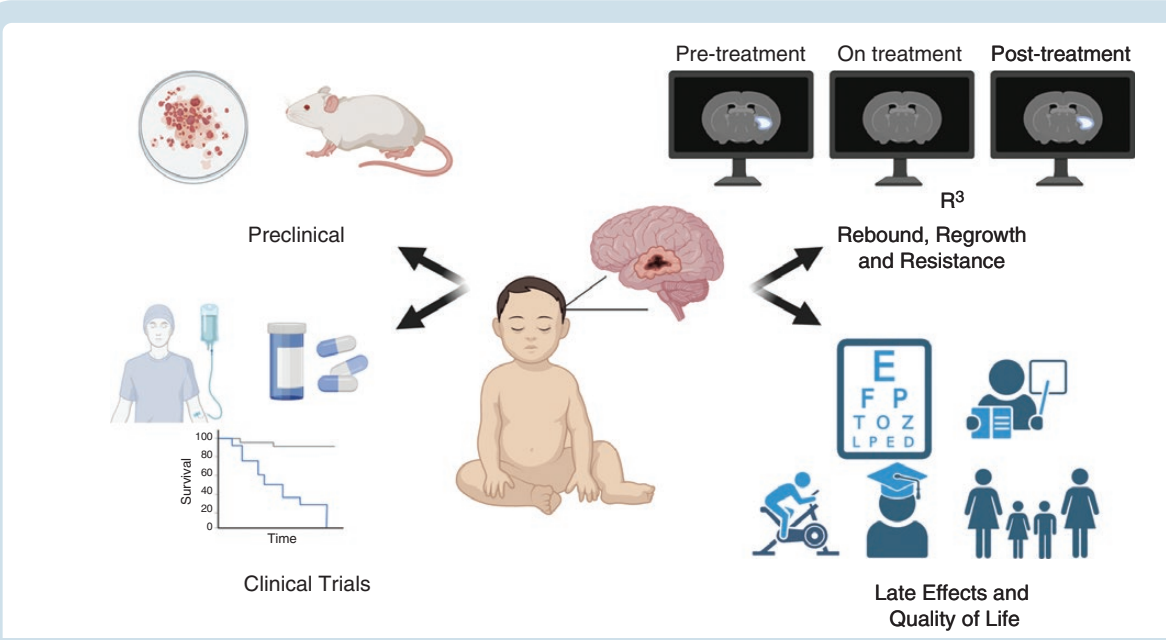

Figure 1: International pediatric low-grade glioma coalition working groups addressing key challenges in pLGG. *Figure was created using Biorender.com

Table 1. 2021 WHO Classification of Gliomas, Glioneuronal Tumors, and Neuronal Tumors*

Adult-type diffuse gliomas	**Glioneuronal and neuronal tumors#**
• Astrocytoma, IDH-mutant	• Ganglioglioma
• Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	• Gangliocytoma
• Glioblastoma, IDH-wildtype	• Desmoplastic infantile ganglioglioma/desmoplastic infantile astrocytoma
Pediatric-type diffuse low-grade gliomas#	• Dysembryoplastic neuroepithelial tumor
• Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	• Diffuse glioneuronal tumor
• Angiocentric glioma	• Myxoid glioneuronal tumor
• Polymorphous low-grade neuroepithelial tumor of the young	• Diffuse leptomeningeal glioneuronal tumor
• Diffuse low-grade glioma, MAPK pathway-altered	• Mutinodular and vacuolating neuronal tumor
	• Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)
Pediatric-type diffuse high-grade gliomas	• Central neurocytoma
• Diffuse midline glioma, H3 K27-altered	• Extraventricular neurocytoma
• Diffuse hemispheric glioma, H3 G34-mutant	• Cerebellar liponeurocytoma
• Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype	**Ependymal tumors**
• Infant-type hemispheric glioma	• Supratentorial ependymoma
	• Supratentorial ependymoma, *ZFTA* fusion-positive
Circumscribed astrocytic gliomas#	• Supratentorial ependymoma, *YAP1* fusion-positive
• Pilocytic astrocytoma	• Posterior fossa ependymoma
• High-grade astrocytoma with piloid features	• Posterior fossa group A (PFA) ependymoma
• Pleomorphic xanthoastrocytoma	• Posterior fossa group b (PFB) ependymoma
• Subependymal giant cell astrocytoma	• Spinal ependymoma
• Chordoid glioma	• Spinal ependymoma, *MYCN*-amplified
• Astroblastoma, *MN1*-altered	• Myxopapillary ependymoma
	• Subependymoma

#Underlined categories represent those which include pediatric low-grade glioma (pLGG).
*Reference: WHO Classification of Tumours Editorial Board. Central Nervous System Tumours. Lyon (France): International Agency for Research on Cancer; 2021. (WHO classification of tumours series, 5th ed.; vol. 6). https://publications.iarc.fr/601.

glioma, circumscribed astrocytic tumors, and glioneuronal and neuronal tumors (Table 1).[19] For example, the most common type of pLGG, the pilocytic astrocytoma, remains a distinct entity, but it is now characterized as a type of circumscribed astrocytic tumor. Another key concept in the 2021 WHO CNS tumor classification is the recommendation to utilize integrated and layered diagnoses including tumor site, a combination of a tissue-based histologic diagnosis and molecular diagnosis, histopathological classification, CNS tumor grade, and molecular information.[19]

Several landmark genomic efforts have systematically mapped somatic driver events across pLGG, confirming it is largely characterized by aberrant activation of MAPK/ERK pathway signaling.[20–25] First, pLGG encompasses subgroups of molecularly defined gliomas that are largely driven by single-driver genetic events.[21,26,27] Second, structural variants in the *BRAF* gene are the most common somatic driver event, found in approximately 70% of all sporadic pLGG.[26,27] These structural variants lead to the expression of a fusion protein that contains the 3′ terminal BRAF kinase, with the uncharacterized protein KIAA1549 representing the most common fusion partner.[25] A smaller subset of pLGG harbor single nucleotide variants in the *BRAF* gene, most frequently the oncogenic $BRAF^{V600E}$ mutation.[23,28] Third, the second most frequent groups of sporadic pLGG are those that harbor fibroblast growth factor receptor (*FGFR*) family gene alterations. While structural variants and fusions involving FGFR3-TACC3 have been described in adult gliomas, pLGG most commonly harbor alterations that impact FGFR1, with FGFR2 rearrangements found in a smaller subset of pLGG.[20] *FGFR1*-altered pLGG harbor either structural variants, the 2 most frequent being FGFR1-TACC1, or a duplication centered on the FGFR1 kinase resulting in an internal kinase duplication or kinase-activating single nucleotide variants, including *FGFR1* N546K and K656E hotspot mutations.[20] While tumors with structural variants involving FGFR1 and FGFR2 follow the single-driver paradigm of pLGG, gliomas harboring single nucleotide variants in FGFR1 do not. These tumors frequently harbor second (and sometimes third) single nucleotide variants that converge on regulators of MAPK/ERK or mTOR signaling, including the *PTPN11*, *PIK3CA*, and *NF1* genes. The role of these additional mutations in gliomagenesis is unclear and is currently being investigated. Fourth, rarer subtypes of pLGG harbor recurrent alterations in genes, including the MYB family of transcription factors or NTRK.[20,22] While *MYBL1* alterations most frequently occur in pLGG with diffuse histological features,

MYB-QKI rearrangements are enriched in angiocentric gliomas.[22] Lastly, genome-wide methylation profiling of thousands of gliomas has revealed tumors diagnosed as pLGG to include multiple rare subgroups of tumors with distinct methylation/copy-number profiles.[24] While methylation profiles have yet to be formally incorporated into the diagnostic criteria in the 2021 WHO Classification for CNS tumors, a multi-omic approach incorporating methylation profiling and assignment to subtype/methylation class can improve diagnostic accuracy in a substantial proportion of individuals with molecular pLGG enrolled in a multi-institute clinical trial spanning 2 continents.[29]

While pLGG harbors fewer somatic driver alterations relative to other cancers, they also harbor significant transcriptional heterogeneity, with cells expressing MAPK programs, cell-cycle programs, and senescence programs.[20,22,30–33] Indeed, senescence programs have been shown to be the most closely associated with cells expressing the highest levels of MAPK programs. These populations of senescent cells may provide clues to the mechanisms underlying pLGG quiescence upon transition to adulthood, and they may also represent potential opportunities to therapeutically target pLGGs using senolytics.[34]

In contrast to most pediatric glioma, adult glioma is commonly characterized by *IDH1/2* mutations, frequently with co-occurring alterations, like *ATRX* alterations, 1p/19q deletion, or *TP53* mutation.[35,36] The 2021 WHO distinguishes between "pediatric type" and "adult type" diffuse gliomas, with *IDH*-mutant gliomas now classified as an "adult type" tumor (Table 1).[19] However, studies have also revealed *IDH*-mutant glioma in children and adolescents, though far less frequently.[21,37] A multi-institutional analysis evaluated the frequency, genomic landscape, and survival outcomes of children with *IDH*-mutant glioma.[37] Among 851 children with glioma who underwent next-generation sequencing, 78 (9.2%) harbored *IDH1/2* mutations. The frequency was similar between low-grade glioma and high-grade glioma. The overall frequency was higher in children ages 10–21 years compared to younger children, revealing a higher occurrence rate among adolescents in this series. Despite excellent short-term overall survival (OS), many disease-associated deaths were reported after 10 years. These initial findings suggest that the clinical behavior and natural history of pediatric and adolescent *IDH1/2*-mutant glioma are similar to adults.[37]

All of these molecular findings have significant implications for the diagnostic workflow of children with pLGG, particularly given the variability in available assays within and across countries. While it is unrealistic (and unnecessary) to expect every institute to have assays for in-house testing, it is imperative that, as a community, we establish mechanisms by which testing is available through central referral centers. At a minimum, assays need to be designed to detect genetic alterations that are relevant to pLGG. An integrated approach that is sufficient to detect structural variants/copy-number alterations, single nucleotide variants, and expressed fusion proteins to help inform histopathological interpretation is essential. In fact, multiple groups have reported methods to integrate such assays into clinical trials and standard practice, including the Children's Oncology Group which has developed the Molecular Characterization Initiative pipeline.[38–40]

Treatments and Outcomes

The mainstay of therapy for many pLGG patients is complete surgical resection when feasible, which can lead to excellent long-term recurrence-free survival.[41–43] This is particularly true for children diagnosed with cerebellar pilocytic astrocytomas. However, many pLGGs arise within structures of the brain that cannot be safely resected without causing substantial morbidity, for example, the optic pathway; midline locations involving the hypothalamus, thalamus, or brainstem; or those intricately associated with motor pathways.[44] Tumors in these locations, in addition to those pLGGs with multiply recurrent or metastatic disease, often require therapy beyond surgery with a few exceptions.

Chemotherapy

Historically, the mainstay of treatment for patients who require systemic therapy after surgery has been chemotherapy. There are several accepted first-line chemotherapies, including combinations of carboplatin and vincristine (CV); combinations of thioguanine, procarbazine, lomustine, and vincristine (TPCV); vinblastine monotherapy; and carboplatin monotherapy.[45–51] The prospective data on carboplatin monotherapy in the upfront setting is somewhat limited; however, available data suggest similar effectiveness relative to other chemotherapy regimens.[49–51] There is also an ongoing randomized, multicenter, phase II trial in chemotherapy-naïve patients testing the efficacy of bevacizumab combined with vinblastine (NCT02840409). The results are still forthcoming.

In previously untreated patients with sporadic pLGG, most chemotherapies have 5-year progression-free survival (PFS) rates ranging from 45% to 55%.[46–50] However, approximately 50% of children will require alternative second-line chemotherapy. Chemotherapies have many associated toxicities, including risks for myelosuppression, peripheral neuropathy, allergic/anaphylactic reaction, constipation, sodium dysregulation, secondary malignancy, and renal and hepatic dysfunction.[46–48] Once a child's tumor recurs following initial systemic therapy, there are several second-line chemotherapies available, including vinblastine monotherapy (if previously not used), monthly carboplatin monotherapy (if not previously used), and a combination of bevacizumab and irinotecan, though second-line therapies are country- and practitioner specific.[52–54] Of note, there are data demonstrating that when vision is deteriorating in a patient with an OPG, bevacizumab seems to be a particularly effective treatment.[55–57]

Once an individual with a pLGG recurs, available data suggest that response rates and PFS to subsequent chemotherapies drop significantly, and these children are also at higher risk of suffering further progressions. One large analysis based on the SIOP-LGG 2004 data evaluating subsequent therapies after recurrence revealed several risk factors for worse outcome/progression, including age less than 1 year, tumor dissemination, or progression within 18

months after the start of chemotherapy. PFS rates declined with subsequent lines of treatment.[58] Since many children will have multiple recurrences throughout childhood with numerous chemotherapy interventions, alternative therapies are needed.

Importantly, chemotherapy should remain the first-line treatment for patients with unresectable and/or progressive pLGG that requires therapy outside of a clinical trial with rare exceptions (as described in the Targeted Therapy section). There is still some controversy, however, about which specific pLGG patients with residual tumor require systemic therapies. There are situations, for example, in which residual tumor post-surgery may be observed alone with surveillance imaging. This is often practitioner dependent, and there are no universally accepted guidelines. Also, as described more in detail in the Functional Outcomes section, patients with NF1-associated pLGG are not always treated because of residual tumor or tumor growth if they are clinically stable.

Targeted Therapies

Leveraging a deeper molecular understanding of pLGG has led to the testing of numerous novel treatment agents targeting the MAPK/ERK and mTOR pathways in children with pLGG. In recurrent and progressive pLGG, several studies have evaluated the safety and preliminary efficacy of targeted therapies. For example, the MEK inhibitor, selumetinib, was evaluated in a phase 1 safety and dose-finding trial led by the Pediatric Brain Tumor Consortium (PBTC).[59] This trial established the recommended phase 2 dose (RP2D) of selumetinib in this population, and it led to a PBTC-sponsored prospective phase 2 study showing imaging response rates of 30%–40% in children with recurrent and progressive pLGG (both with and without NF1).[7,8] Common attributable toxicities were mostly grade 1 and 2, including creatine phosphokinase (CPK) elevation, hypoalbuminemia, rash, anemia, dry skin, fatigue, and diarrhea.[8] Another phase 1 prospective trial in children with *BRAF*^{V600E}-mutant tumors tested the safety and preliminary efficacy of the MEK inhibitor, trametinib, in recurrent pLGG revealing a 15% response rate, and the trial established the RP2D.[6] The most common adverse events were paronychia, diarrhea, and dry skin.[6] This same trial also tested the combination of trametinib with dabrafenib in pediatric *BRAF*^{V600E}-mutant low-grade glioma. There were no dose-limiting toxicities encountered, and the objective response rate was 25% using the combination.[6] Similarly, there is phase 2 data on another MEK inhibitor, MEK162 (binimetinib), in children with progressive or recurrent pLGG.[60] These data showed that among 85 patients enrolled and evaluable for response, 56% had a radiographic response.[60] Although the details of the attributable toxicities were not delineated in the abstract, 22% of patients discontinued therapy due to toxicity, most commonly dermatologic.[60] There is also recent data on the second-generation RAF inhibitor, tovorafenib. FIREFLY-1 (NCT04775485) was a multicenter phase 2 study evaluating the efficacy and safety of tovorafenib monotherapy in patients with BRAF-altered cancers. In children with multiple recurrent pLGG, a 64% overall response rate among 69 children was reported utilizing the adult Radiologic Assessment in Neuro-Oncology (RANO) criteria as the primary measure of response.[11] The most common treatment-related adverse events were hair color changes, increased CPK levels, anemia, fatigue, and maculopapular rash.[11]

There is also early-phase data on first-generation BRAF inhibitors. In a phase 1 study led by the Pacific Pediatric Neuro-Oncology Consortium (PNOC), vemurafenib was tested in children with *BRAF*^{V600E}-mutant gliomas to determine the RP2D and dose-limiting toxicities.[9] The best radiographic responses reported included 1 complete response (CR), 5 partial responses, and 13 stable disease.[9] The most common toxicity reported was maculopapular rash.[9] This led to a phase 2 study evaluating the efficacy of vemurafenib in recurrent *BRAF*^{V600E}-mutant gliomas (NCT01748149). Another study evaluated the safety and preliminary efficacy of dabrafenib in children with recurrent *BRAF*^{V600E}-mutant pLGG.[61] Among all patients enrolled, the overall response rate was 44%.[61] The most common treatment-related adverse events were fatigue, rash, dry skin, pyrexia, and maculopapular rash.[61]

Agents that target the mTOR pathway have also been studied. The Pediatric Oncology Experimental Therapeutics Investigators' Consortium (POETIC) reported the efficacy and pharmacokinetics of the mTOR inhibitor, everolimus, in children with radiographically progressive pLGG.[62] Among 23 evaluable patients, 2 had a partial response, 10 had stable disease, and 11 had clinical or radiographic progression.[62] The most common toxicities were grade 1 and 2, and rare attributable grade 3 and 4 toxicities included elevated liver enzymes, mucositis, and neutropenia.[62] These data along with the early trametinib data have led to a PNOC phase 1 trial evaluating the combination of trametinib and everolimus in patients with recurrent low- and high-grade gliomas (NCT04485559).

For children whose pLGG harbor FGFR alterations, FGFR inhibitors have become of great interest. The NCI-Children's Oncology Group (COG) Pediatric Molecular Analysis for Therapy Choice (MATCH) trial evaluated numerous molecularly targeted therapies in a phase 2 setting based on the genetic alterations in any given patient's tumor (NCT03155620). One arm (APEC1621B) examined the use of the FGFR inhibitor, erdafitinib, in patients with tumors harboring activating alterations of FGFR 1/2/3/4.[63] Preliminary data show that among 11 patients with low-grade glioma or glioneuronal tumors, partial response or stable disease was observed in 54% (6/11).[63] Overall, the drug was well tolerated with common previously reported FGFR inhibitor toxicities observed (eg, hyperphosphatemia and nail changes/infections).[63] However, a recent retrospective analysis in children with recurrent FGFR-altered gliomas treated with FGFR inhibitors revealed slipped capital femoral epiphyses in 3/7 patients and increased linear growth velocity.[64] Future trials are needed to further test the safety and efficacy of FGFR inhibitors in pLGG patients whose tumors harbor FGFR alterations.

For newly diagnosed and previously untreated pLGG, there are multiple ongoing and recently completed prospective trials utilizing targeted therapies. In the Children's Oncology Group (COG) alone, there are 2 prospective randomized trials comparing selumetinib, an MEK inhibitor, to carboplatin/vincristine. One of these trials is for

children with NF1-associated pLGG (NCT03871257) and another is for non-NF1 and non-*BRAF*^{V600E}-mutant pLGG (NCT04166409). There is also a large prospective trial led by the French Group (Strasbourg, France), called PLGG-MEKTRIC, comparing the MEK inhibitor trametinib to weekly vinblastine (NCT05180825). Another study led by Day One Biopharmaceuticals in collaboration with the SIOP LOGGIC consortium (LOGGIC/FIREFLY-2) will compare tovorafenib, an oral brain-penetrant second-generation RAF inhibitor to physician's choice (CV or vinblastine monotherapy) (NCT05566795).

Recently, data were published on a prospective trial for children with previously untreated *BRAF*^{V600E}-mutant pLGG comparing dabrafenib plus trametinib (D +T) to CV.[65] There was a response rate and median PFS of 47% and 20.1 months, respectively, using D +T compared to 11% and 7.4 months in the CV group.[65] Based on these data, in March 2023, the Food and Drug Administration approved D +T for children 1 year of age and older with newly diagnosed *BRAF*^{V600E}-mutant pLGG requiring systemic therapy. Grade 3 or higher adverse events occurred in 47% of the D +T patients versus 94% of those receiving CV.[65] Pediatric neuro-oncologists now consider this treatment to be the standard-of-care therapy for these select patients, though it is still unclear whether monotherapy with a first-generation BRAF inhibitor alone would be just as efficacious. The phase 1/2 study of dabrafenib monotherapy for children with recurrent/refractory BRAF^{V600E}-mutant pLGG showed a 44% response rate.[61] In another phase 1/2 study for children with recurrent/refractory BRAF^{V600E}-mutant pLGG, the response rate for the combination of dabrafenib plus trametinib was 25%.[6] It is difficult to compare these since they were both early-phase trials and the main objective was not response/efficacy nor was a direct comparison intended. Also, there is no prospective trial testing dabrafenib monotherapy in previously untreated BRAF^{V600E}-mutant pLGG that we are aware of. The preliminary phase 1 data does, however, suggest that the overall toxicity was reduced with the combination therapy (D +T) compared to trametinib monotherapy, which may be 1 rationale for the use of the combination regimen.[6]

IDH inhibitors have also been tested given their relevance to the low-grade glioma population. A recent phase 3, double-blinded trial randomly assigned grade 2 *IDH*-mutant glioma patients who had not had previous systemic therapy to receive either vorasidenib (an oral brain-penetrant IDH1/IDH2 inhibitor) or placebo.[66] Patients were required to have measurable non-enhancing disease for eligibility which was defined as 1 or more target lesions measuring greater or equal to 1 cm by 1 cm in the 2 longest dimensions.[66] Among 331 enrolled patients, the PFS was statistically significantly improved in the vorasidenib group, with a median PFS of 27.7 months versus 11.1 months in the placebo group.[66] This was a pivotal trial for adult low-grade *IDH*-mutant glioma; however, although adolescents (12 y/o and older) were eligible, only 1 patient less than 18 years old (y/o) was enrolled who was randomly assigned to placebo.[66] This makes it virtually impossible to draw any conclusions about the use of vorasidenib in younger patients (less than 18 y/o) with *IDH*-mutant grade 2 pLGG. Further testing of this strategy in children and adolescents with *IDH*-mutant low-grade glioma is warranted.

Although targeted therapies have begun to impact some treatment paradigms in pLGG, it should be noted that with the exclusion of Tuberous Sclerosis Complex-associated subependymal giant cell astrocytoma (everolimus) and *BRAF*^{V600E}-mutant pLGG (dabrafenib + trametinib), the role of targeted inhibitors as upfront treatment is yet unclear and currently being evaluated in numerous ongoing prospective clinical trials (NCT03871257, NCT04166409, NCT05566795, NCT05180825).[10,67]

The use of targeted therapies cannot be discussed without commenting on the financial implications of these agents. It is already well described that childhood cancer can negatively impact a family financially due to travel costs, decreased work hours, and the added costs of therapy itself.[68] Although molecularly targeted therapies in some ways have begun to revolutionize cancer therapy, the cost of these agents and the rising overall cost of cancer care often cause significant financial toxicity for patients and their families.[69] In fact, many newer cost-sharing insurance policies have increased out-of-pocket expenses in the United States. This has led to worse financial well-being, quality of life, psychosocial health, and treatment adherence in adult studies.[70] The impact of financial toxicity, however, is country specific and likely distinct in countries with universal healthcare systems.[71] As far as we are aware, the specific impact of targeted therapies on the financial toxicity within the pLGG population has not yet been well explored.

Radiation Therapy

Although radiation therapy (RT) is an effective treatment modality for pLGG, it is associated with substantial risk of late effects, including neurocognitive deficits, endocrine abnormalities, secondary malignancy, and vascular complication; therefore, it is not recommended for the majority of children diagnosed with pLGG.[72–74] However, modern RT techniques may minimize some of these toxicities.[75] There are rare clinical situations when the use of RT must be considered, particularly when the risk of tumor progression and poor survival outcome outweigh RT-related toxicity.[75] RT is also typically avoided in children with NF1, given the high risk of secondary malignancy and neurovascular complications.[76–78]

Imaging and Response Assessment

Although this topic will be touched upon in a subsequent iPLGGc early-phase clinical trials manuscript in this issue, it is important to discuss how to best measure pLGG on neuroimaging and how to best assess tumor response. It has long been recognized that pLGG is distinct from adult LGGs, both biologically and clinically.[5] While the Radiologic Assessment in Neuro-Oncology (RANO) group provided recommendations for assessment in adult LGG, it is known that pLGG is unique and may require separate recommendations.[79,80] This may be due to the underlying biologic differences between adult and pediatric LGGs. In addition, adult LGGs have a higher rate of malignant transformation, whereas this is exceedingly rare in children.[81]

Historically, clinical studies often utilized different measures of radiologic response, making comparisons of therapeutic agents across international studies virtually impossible. This is in addition to the selection biases already present in many small studies because pLGG comprises a heterogeneous group of tumors with varying unique histology and molecular biology. To minimize these challenges and adopt more universal measures of image acquisition and assessment of response, the Radiologic Assessment in Pediatric Neuro-Oncology (RAPNO) group was established.[79] The RAPNO pLGG working group is an international panel of Pediatric and Adult Neuro-oncologists, Clinicians, Neuroradiologists, Radiation Oncologists, and Neurosurgeons, which developed to address the unique challenges in assessing pLGG. The committee's final recommendations included specific imaging response assessments, with additional guidelines for visual functional outcomes in individuals with optic pathway tumors. Although these recommendations need to be validated in prospective clinical trials, they provide a universal framework for assessing pLGG and their response to therapy, which will allow better comparisons across studies.[79] RAPNO recommends that baseline brain MRI (or baseline spine MRI depending upon the primary lesion location), be performed pre-operatively and 24–72 h post-operatively, and that the post-operative scan should be utilized as the new baseline for response to systemic (and RT) therapy assessments. Also, RAPNO states that in those pLGG patients enrolled in a clinical trial, imaging should be obtained every 12 weeks while on therapy. For patients with tumors in the optic pathway/hypothalamic region, it is recommended that specific orbital MRI sequences should be obtained in addition to the brain MRI. RAPNO also provides guidelines on the best way to measure visual acuity (VA) and VA changes in patients with optic pathway tumors. These are based upon those previously reported by the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration.[82] RAPNO specifically recommends utilizing T2/FLAIR images to measure a tumor and in assessing radiographic response, as contrast enhancement in pLGG is an unreliable measure of tumor response or progression. They also provide very specific definitions of responses, including CR, major response, partial response, minor response, stable disease, and progressive disease. There are many other specific details within the published RAPNO recommendations, including how to assess/measure cysts, guidance on advanced imaging techniques, and the specific technical aspects of imaging, including the following: the specific imaging sequence to obtain, slice thickness, gap percentage, and descriptions of in-plane resolution.[79] The iPLLGc strongly recommends that these guidelines be included in future clinical trials for consistency, cross-study comparison, and necessary validation.

Functional Outcomes

With a better understanding of the natural history of pLGG, the pLGG community has come to recognize the importance of prioritizing functional outcomes and maximizing a patient's quality of life.[3] Several studies have shown that there is often a disconnect between responses assessed on standard MRI relative to specific functional outcomes, particularly vision. In a multicenter retrospective study of children with NF1-associated OPG assessing visual outcomes following chemotherapy, there was a poor correlation between radiographic response and VA outcomes.[83] It also should be noted that individuals with NF1-associated pLGG often have an indolent course, and some may not require treatment at all, even in the face of progressive tumor alone, further highlighting the need to assess and integrate functional outcomes.[84–86] This same disconnect in imaging and vision has also been documented in children with non-NF1 OPG.[87] The international academic pLGG community realizes that overall survival and standard MRI imaging response alone are not sufficient to fully monitor response to therapy, emphasizing the incorporation of specific functional endpoints, including vision, motor, and neuropsychological outcomes. Many current clinical trials have incorporated these measures, both as primary and secondary objectives, in prospectively assessing children with pLGG.

The functional outcome that has gained significant traction and has the most validated measures is VA in children with OPG. Both the REiNS International Collaboration and subsequently, the RAPNO pLGG working group have published guidance on assessing VA within pLGG clinical trials providing recommendations on what constitutes VA response, stability, and progression.[79,82] The iPLLGc strongly supports utilizing these recommendations to not only better assess VA universally across international trials, but also to gain a better appreciation for how specific therapies impact VA response. Therefore, visual outcomes are assessed carefully and regularly, rather than solely relying on radiographic response, to monitor whether a treatment is effective in individuals with OPGs and VA dysfunction.[83,87,88] Since we know that the majority of these children will survive well into their adulthood, this important functional outcome (vision) has been prioritized.[3,16,89,90] An ongoing prospective trial through the Children's Oncology Group (COG) randomizes children with previously untreated NF1-associated pLGG to selumetinib versus CV (NCT03871257). In this trial, a co-primary outcome in children with OPG is to evaluate if the efficacy of treatment with selumetinib as measured by VA using Teller Acuity Cards, as recommended by the REiNS committee, is superior to treatment with CV.[82] This is the first prospective trial for children with pLGG, that we are aware of, in which a functional endpoint serves as a primary outcome measure. We anticipate that this trend will continue as further functional assessment measures are better understood, prospectively tested, and validated.

The iPLGGc additionally believes that other functional outcomes, like adaptive behavior in daily living, neurocognitive outcomes, motor outcomes, and quality of life/patient-reported outcomes, are also crucial to assessing the overall outcomes of children with pLGG; however, many of these measures are not yet sufficiently validated to incorporate them into measures of response. Some of these functional outcomes are already incorporated into ongoing prospective trials internationally as secondary and exploratory objectives with the hope of

validating them as future measures of patient outcomes/response to specific therapies.

Challenges

Despite the significant advancements in our understanding of the molecular landscape of pLGG and the use of targeted therapies, there remain many ongoing challenges. Three of the major challenges include preclinical pLGG models, standardization of pLGG early-phase clinical trials, and the phenomena of resistance, rebound, and recurrence in pLGG. These will be more fully addressed in subsequent manuscripts within this issue, but we will briefly discuss each of these below.

Agreeing on the best preclinical models for testing new therapies and deciding what preclinical data is needed to move therapies forward into clinical trials in children remains challenging. As discussed in a dedicated paper on pLGG preclinical models, all currently available models have limitations. While it is desirable to recapitulate every and all aspects of pLGG biology in a given model, this currently is not feasible. The quintessential biological characteristics of pLGG such as replicative, oncogene-induced senescence, and spontaneous proliferation stop render models unsuitable for many applications in laboratory research, requiring new models for long-term and repetitive experiments. The designs and conclusions of preclinical experiments need to consider these limitations, and the implementation of a minimum set of preclinical data points increases the likelihood of clinical translatability.

Another hurdle for the pLGG community is developing effective early-phase clinical trials that are universally consistent and comparable with respect to eligibility, clinical assessments, radiographic evaluation, and response. Until now, many studies have used unique criteria for each of these, making comparison across studies and between agents nearly impossible. The manuscript dedicated to standardizing early-phase pLGG clinical trials will address many of these issues in an effort to propose a universally agreed-upon set of guidelines for these trials moving forward.

In the era of molecularly targeted agents, some tumors exhibit accelerated and rapid growth after discontinuing a targeted agent like a BRAF or MEK inhibitor.[91] This rapid regrowth after discontinuation represents tumor "rebound." In contrast, other pLGGs develop resistance and progress during therapy, while some progress at varying time points after stopping a targeted agent which is defined as recurrence.[8,92,93] Unfortunately, specific temporal definitions of resistance, rebound, and recurrence have not been established, and preclinical data aimed at defining the biology behind these events are also lacking. This will be the focus of another pLGG manuscript within this issue with a goal of not only better defining these phenomena but also addressing how best to evaluate and approach these in the future.

With respect to our current understanding of the pLGG molecular landscape, there are many questions that remain, including why some tumors that look histologically and biologically similar respond differently to the same targeted therapies. These differences could reflect the presence of additional molecular aberrations, alterations in cellular metabolism, the impact of the tumor microenvironment, and patient characteristics. In particular, the impact of the tumor microenvironment may play a larger role than anticipated in both maintaining the tumor as well as response to targeted agents, as gene expression of MAPKi sensitivity signatures (MSS) correlates with tumor immune cell infiltration.[94] Recently, a novel MAPKi sensitivity score was published, predicting the heterogeneous response of pLGGs harboring the same genetic driver to MAPKi driven by immune infiltration.[94] In a possible future application, the MSS could be used in clinical trials to predict the heterogeneous response of pLGGs harboring the same genetic driver to MAPKi and stratify patients into different trials or treatment arms.[94] Other contributing factors include clinical characteristics, such as patient age, tumor location, tumor size, tumor growth rate, and drug metabolism. The hope is that some of these unanswered questions will be further addressed in the preclinical and translational setting leading to a universal better understanding of the relationship among tumor biology, patients' clinical characteristics, and survival outcomes. An example of these differences being addressed in the preclinical setting is demonstrated in a publication characterizing a cohort of over 1000 clinically annotated pLGG.[23] Eighty-four percent of cases harbored a driver alteration in the MAPK pathway, while those without an identifiable alteration also commonly showed upregulation of the MAPK pathway. The authors suggested that pLGG can be further classified based upon alteration type, and that subclassification of clinical and molecular correlates allowed for the stratification of individuals into different risk categories, which potentially could impact future treatment paradigms.[23] Risk stratification historically has not been used universally in deciding upon the best treatment paradigm in children with pLGG.

There are many other challenges that we face in the pLGG community, specifically as we treat more and more children with targeted therapies. For example, the best duration of treatment is unknown. Many pLGG trials have arbitrarily treated children for 2 years, but there is no scientific rationale behind this chosen duration. For many practitioners, 2 years have become an accepted duration of therapy in pLGG. Although biologically, genetically, and clinically distinct from pLGG, there are some data in adult melanoma suggesting treatment with BRAF inhibitors plus/minus MEK inhibitor inhibitors (in *BRAF*^{V600E}-mutant melanoma) can be effectively stopped when a patient has a prolonged CR to therapy.[95] In 1 small study, they identified 13 adult melanoma patients treated with BRAF +/– MEK inhibitors, who stopped therapy after a prolonged CR (median = 34 months) and only observed recurrence in 3/13 (23%) patients. In the 10 patients with sustained CR off therapy, the median follow-up after stopping therapy was 19 months (range 8–36). They also retrospectively measured circulating tumor DNA (ctDNA) in longitudinal plasma samples. ctDNA was eventually detected in 2 of 3 recurrent disease cases, but it was not detectable in 1 patient with an isolated brain recurrence. They suggested that targeted therapy could possibly be stopped in *BRAF*^{V600E}-mutant melanoma tumors with no evidence of disease (by imaging and ctDNA) after prolonged treatment and a durable

CR.[95] Although intriguing, these data are difficult to translate to the pLGG population for several reasons. First, a CR is uncommon in the pediatric population using targeted therapy as seen in numerous early-phase studies.[7,8,10] Therefore, if practitioners awaited a CR in pLGG patients before stopping therapy, they would likely treat indefinitely with possibly no additional benefit and possible increased toxicity. Second, ctDNA as a marker in pLGG has not been well studied or validated.[96] Finally, unlike melanoma, many pLGG tumors frequently remain stable for prolonged periods of time and often become senescent.[97] A recent consensus paper on MEK inhibitor use in children with NF1 also reaffirms that 2 years are an accepted duration of therapy for MEK inhibitors in NF1-associated pLGG based on recent clinical trials.[98] Future clinical trials should investigate the length of needed therapy in pLGG, if feasible.

Another poorly understood practice in the era of targeted therapy is that of retreatment. Preliminary prospective data with the MEK inhibitor selumetinib in children with recurrent pLGG suggest that retreatment is effective at regaining response or stability in individuals who progress after stopping therapy.[99] There are also data in adult melanoma that retreatment may be an effective strategy when using BRAF and MEK inhibitors.[100,101] Other than these examples, there is little evidence to guide practitioners; however, many experts in the pLGG community agree that if a patient responds to a targeted therapy and then progresses after stopping, retreatment with this same agent is a viable treatment option. However, there has not been a universal consensus concerning retreatment.

Another challenge is developing rational combination therapy strategies in an effort to increase the response rate, prolong the duration of response, and overcome previous resistance. Many ongoing trials are testing combination therapies with anti-resistance agents, other targeted therapies, and chemotherapies. The hope is that these prospective trials will answer some of these questions. For example, there is currently a phase 1/2 trial being conducted through the PBTC testing the safety and efficacy of dabrafenib plus trametinib plus hydroxychloroquine (D + T + HCQ) as well as T plus HCQ in children and with BRAF-altered or NF1-associated gliomas who have previously received a RAF and/or MEK inhibitor (NCT04201457). The rationale is based on preclinical data suggesting that HCQ may have antitumor activity by inhibiting treatment-induced autophagy.[102] They tested this hypothesis in vemurafenib-resistant *BRAF*^{V600E}-mutant brain tumors and found that both genetic and pharmacologic autophagy inhibition were able to overcome molecularly distinct resistance mechanisms, inhibited tumor cell growth, and increased cell death.[102]

Not all patient tumors respond to single-agent targeted therapy and others may recur after stopping single-agent therapy. The PNOC group is attempting to improve response rate and duration of response by utilizing a combination of targeted therapies, trametinib (an MEK inhibitor) with everolimus (an mTOR inhibitor) in children with recurrent low- and high-grade gliomas (NCT04485559). The goal is to conduct an initial phase 1 dose escalation study followed by a dose expansion in children with recurrent pLGG at the RP2D. Another trial being conducted through the COG is comparing the use of selumetinib alone (a MEK inhibitor) to the combination of selumetinib with the chemotherapy agent, vinblastine (NCT04576117). In addition to determining the maximum tolerated dose of the combination in the phase 1 component, the secondary objectives include comparing event-free survival, response rate, toxicities, quality of life, and visual outcomes (in patients with OPG) between these 2 regimens. Although these trials are not yet complete and data are still forthcoming, they may all shed light on the potential benefits of combination therapies with anti-resistance agents, other targeted therapies, and chemotherapy. Other promising approaches that still require future clinical testing in pLGG include combinations of BRAF-targeting drugs with ERK inhibitors, immunotherapy, or senolytic agents.[34,103,104]

Other ongoing challenges include the balance of toxicity with therapeutic benefits of these new agents. For example, intermittent dosing and "drug holidays" have been utilized by some practitioners to minimize acute toxicity and the development of resistance with a goal of maintaining good response rates. Testing these concepts prospectively in clinical trials is challenging, and the pLGG community may have to rely somewhat on expertise, experience, and adult cancer trials until more robust prospective pLGG data are available. Preclinical modeling in melanoma evaluated 2 patient-derived xenograft models both treated with vemurafenib (a BRAF inhibitor) followed by an experimental schedule of 4 weeks on and 2 weeks off, compared to a standard continuous schedule. The intermittent regimen controlled tumor growth over 7 months of treatment, while the mice treated with a continuous schedule developed resistance after only 2 months of treatment.[105] Despite these encouraging preclinical data, phase 2 clinical trials in adults with melanoma testing intermittent dosing have thus far been discouraging. A randomized, phase 2 trial evaluated whether intermittent dosing of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) improves PFS in adults with metastatic and unresectable *BRAF*^{V600}-mutant melanoma.[106] Continuous dosing showed a statistically significant improvement in PFS compared to intermittent dosing, and there were no significant differences in overall survival or toxicity between the 2 regimens.[106] Another phase 2 adult melanoma trial compared a standard continuous schedule of vemurafenib (BRAF inhibitor) plus cobimetinib (MEK inhibitor) to an intermittent schedule in adults with advanced *BRAF*-mutant melanoma.[107] The trial revealed that the intermittent schedule did not have a superior PFS to the continuous schedule.[107] It is unclear if these findings in adult melanoma are relevant to pLGG given the distinct biology, resistance patterns, and natural history between these 2 diseases; however, at the very least, caution must be taken when testing alternative dosing regimens in pLGG. There are some ongoing clinical trials prospectively testing alternative dosing schedules of targeted therapies in children. PNOC will test both a continuous and intermittent dosing schedule of the combination of everolimus and trametinib in children with recurrent glioma (NCT04485559). There is also a trial testing intermittent selumetinib dosing, given twice daily for 5 out of 7 days, for children with NF1-associated tumors, such as OPG and plexiform neurofibromas (NCT03326388). These data are still forthcoming.

Finally, many practitioners are concerned that we do not yet know the complete spectrum of late effects when utilizing MAPK-targeted therapies in children. As most of these children will survive into adulthood, decreasing the risk of associated morbidities and late mortality is paramount.[3] In adults, BRAF inhibitor use is associated with the emergence of multiple skin tumors, both benign and malignant, including papilloma, keratoacanthoma, squamous cell carcinoma, and rarely, even new melanoma.[108,109] In addition, other secondary premalignant and malignant events have been reported, such as *RAS*-mutant leukemia, *RAS*-mutant colorectal cancer, and the development of gastric and colonic polyps.[110] It is thought that paradoxical MAPK activation from BRAF inhibitor-mediated homodimerization and heterodimerization of non-mutant RAF isoform leads to these secondary events.[108–110] Although this pattern of secondary effects has not yet been well documented in children using the same agents for pLGG, there are isolated reports. For example, on the phase 1 vemurafenib trial led by PNOC, one 13-y/o female developed facial lesions that later were biopsy confirmed to be squamous cell carcinoma.[9] There is a growing concern in the academic community that some of these effects could occur later in children, especially as they are exposed to more oncogenic environmental pathogens, like sun exposure and tobacco use. We also do not fully appreciate the full range of potential late effects attributable to MAPK-targeted therapies in developing children. For example, there may be possible late neurocognitive, cardiac, and pulmonary effects. Although these have not yet been described, long-term follow-up is still ongoing. Furthermore, the data collection of long-term, often very late, effects is very difficult with disjointed transition services to adult care.

Conclusions

Our understanding of pLGG has expanded tremendously over the last decade. We have not only come to recognize the primary molecular drivers of these tumors, but there are now effective strategies to target these molecular aberrations for therapeutic gain. We have also come to accept pLGG as a chronic illness of childhood that often requires multiple systemic therapies.[3] This understanding has led to a prioritization of functional outcomes to maximize the quality of life.

However, many challenges remain for the pLGG academic community as highlighted above. Other articles in this series dedicated to pLGG will focus on 3 specific major challenge topics: (1) preclinical pLGG models, (2) early-phase clinical trial development for pLGG, and (3) pLGG resistance, rebound, and recurrence. This continuum from preclinical investigation to clinical care is not only essential for our understanding of these tumors, but also offers the best implementation of international efforts to positively impact the lives of our patients with pLGG.

Keywords

MAPK/ERK pathway | overview | pediatric low-grade glioma | targeted therapy

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