Novel therapies for pediatric low grade glioma

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Purpose of review
Current biological findings provide new insights into the genetics driving growth of low-grade gliomas in pediatric patients. This has provided new targets for novel therapies. The purpose of this paper is to review novel therapies for pediatric low-grade gliomas that have been published in the past 24 months.

Recent findings
Low-grade gliomas are often driven by mitogen activated protein kinase (MAPK) alterations either with BRAF V600E point mutations or BRAF fusions. Current advances have also highlighted novel fusions of fibroblast growth factor receptor (FGFR), myeloblastosis family of transcription factors (MYB), meningioma 1 tumor suppressor (MN1), neurotrophic receptor kinase family of receptors (NTRK), Kristen RAS (Rat Sarcoma Virus) oncogene homolog in mammals (KRAS), Receptor tyrosine kinase ROS proto oncogene 1 (ROS1), protein kinase C alpha (PRKCA), and platelet derive growth factor receptor (PDGFR) amplification. Novel therapies have been employed and are showing encouraging results in pediatric low-grade gliomas. Current trials are underway with newer generation pan RAF inhibitors and mitogen activated protein kinase - kinase (MEK) inhibitors. Other early phase clinical trials have provided safety data in pediatric patients targeting FGFR fusion, NTRK fusion, PDGFR amplification and ROS1 mutations.

Summary
Historical treatment options in pediatric low-grade gliomas have utilized surgery, radiation therapy and conventional chemotherapy. Recently greater insight into their biology has found that alterations in MAPK driven pathways are often the hallmark of tumorigenesis. Targeting these novel pathways has led to tumor control and shrinkage without the use of conventional chemotherapy. Caution should be taken however, since these treatment options are still novel, and we do not fully appreciate the long-term effects. Nonetheless a new era of targeted medicine is here.

Keywords
BRAF inhibitors, mitogen activated protein kinase/ERK pathway, MEK inhibitors, pediatric low-grade gliomas, targeted therapy

INTRODUCTION

Pediatric low-grade gliomas are the most common central nervous system (CNS) neoplasm in children and young adults [1–3]. They account for up to one third of all CNS tumors in these age groups [4]. These tumors are most commonly sporadic but predisposition to these tumors can be associated with syndromes including neurofibromatosis type 1 (NF1) and tuberous sclerosis [5▪,6]. Although overall survival rates are very favorable, they can be associated with increased intracranial pressure depending on anatomical location or seizures in up to 25% of patients [7▪,8,9]. In tumors involving the optic pathways, vision loss can often be the first sign of tumor burden requiring treatment [5▪]. They are often surgically resectable resulting in high cure rates, however they may not be amenable to surgical resection depending on their location, infiltrative nature or metastatic lesions [2,4]. Other modalities of treatment have included conventional chemotherapy as well radiation therapy [4,10]. Although many are surgically resectable, in large cohort studies up to 50% may have some remaining tumor burden, and up to 30% will require some form of nonsurgical treatment [11]

The most recent edition of the World Health Organization (WHO) classification of CNS tumors divides low-grade gliomas into two broad categories depending on their histological features, being defined as either circumcised or diffuse in nature [12], This further leads to molecular sub classifications often affecting the MAPK signaling pathway and downstream mTOR activation [8,7▪]. In the era

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KEY POINTS

- The mitogen activated protein kinase/extracellular signal regulate kinase pathway plays an important role in the pathogenesis of the majority of pediatric low-grade gliomas.
- Since pediatric low-grade glioma is a chronic disease, it is important to emphasize quality of life and function when deciding treatment options.
- Although there are increasing options for targeted therapy, several questions remain including how best to use these drugs as single agents and in combination, the optimal schedule and duration of therapy, as well as potential long term side effects.

of precision medicine, the sub classification of diffuse low-grade glioma will include diffuse astrocytoma, myeloblastosis family of transcription factors (MYB) or MYB1 altered, angiocentric glioma, polymorphous low-grade neuroepithelial tumor of the young (PLTNY) and diffuse low-grade gliomas, MAPK altered [13]. Fibroblast growth factor receptor (FGFR) fusions, MYB-QKI fusions and more rarely neurotrophic receptor kinase family of receptors (NTRK) and Kristen RAS (Rat Sarcoma Virus) oncogene homolog in mammals (KRAS) alterations are noted in some tumors serving as potential targets upstream of the MAPK pathway [3,14]. BRAF and mitogen activated protein kinase - kinase (MEK) activation can be seen in circumscribed gliomas, including BRAF–KIAA1549 fusion events as well as BRAF V600E mutations. Within NF1 predisposition we expectedly see the loss of neurofibromin induced inhibition of the MAPK pathway. Other rare events include upstream activation of receptor tyrosine kinases as NTRK or FGFR and also parallel pathways involving mTOR such as seen in tuberous sclerosis and resulting in sub ependymal giant cell astrocytomas [3,15]. The third classification of low-grade gliomas identified as glioneuronal and neuronal tumors also show great heterogeneity but with common drivers again being MAPK alterations with BRAF fusion events as well V600E point mutations. Other rare mutations include NTRK fusions and FGFR mutations or fusions again manifesting as alterations of the MAPK pathway, offering therapeutic targets either upstream or downstream of the pathway in cases of resistance [3,7▪,15]. Much overlap can be seen in the underlying drivers, however anatomical location and histology still differentiate the clinical course. For example, in ganglioglioma, a well differentiated slow growing glioneuronal neoplasm, gross total resection achieving 5 year and 10-year EFS of 65–80% and 57%, higher than other pediatric low-grade gliomas. Location importantly also plays a role with supratentorial sites faring better than infratentorial [16]. Current trials within the Children's Oncology Group (COG), Pediatric Brain Tumor Consortium (PBTC) and Pediatric Neuro Oncology Consortium (PNOC) as well as others are exploring inhibitions of these MAPK signaling pathways to assess for clinical efficacy in progression-free survival and overall survival [3]. This manuscript will review results of several novel treatment regimens which have been published in the past 2 years.

TARGETED THERAPY

Seminal studies in the past two decades, outlining the pathogenesis of pediatric low-grade gliomas, have implicated RAS–RAF–MAPK pathway activation as a driver for tumorigenesis. Our current understanding of RAF mutations divides these into class I mutations, which are activating point mutations resulting in persistent activation of BRAF and activation of MEK 1/2 activity. Class II mutations involve RAF fusions, such as with KIAA1549, resulting in RAS independent dimerization and activation of MEK 1/2. Class III mutations involve point mutations on RAF that enhance its activation via binding to RAS that would be otherwise inappropriate [17,18]. BRAF V600 mutations causing inappropriate MEK 1/2 is detected in 15–20% of pediatric low-grade gliomas and often indicates a poorer prognosis to conventional chemotherapy [19▪▪].

In the first phase I/II study assessing Trametinib, a target of MEK 1/2 with or without Dabrafenib (ClinicalTrials.gov identifier: NCT02124772) in pediatric low-grade gliomas with a BRAF V600 point mutation, 13 patients were treated with Trametinib monotherapy and 36 were treated with dual therapy including Dabrafenib. Two patients were diagnosed with high grade glioma. Progression free survival (PFS) was noted to be 16.4 months in the trametinib monotherapy group vs. 36.9 months in the combination dabrafenib plus trametinib group [20▪].

This was a seminal trial with important findings that was then followed up with another phase II trial comparing Dabrafenib plus Trametinib with conventional chemotherapy composing of Carboplatin and Vincristine as front-line therapy in pediatric patients with low-grade gliomas harboring a BRAF V600 mutation. (Funded by Novartis; ClinicalTrials.gov number, NCT02684058.) In the phase II trial, 110 patients were randomized in a 2 : 1 fashion to receive dabrafenib plus trametinib vs. chemotherapy. Overall response based on Response Assessment in Neuro-Oncology (RANO) criteria at 18.9 months was 47% in the dabrafenib plus trametinib arm vs.

11% of those treated with chemotherapy with responses in the former group occurring mostly by 4 months. Progression-free survival was noted to be significantly longer at 20.1 months in the dabrafenib plus trametinib arm vs. 7.4 months in the chemotherapy arm. In patients that had a low-grade glioma adjacent to the optic chiasm, visual acuity importantly was noted to be improved in the dabrafenib plus trametinib arm at 34% vs. 11% in the chemotherapy arm [19▪▪].

In a small cohort study of 11 pediatric and young adult patients with progressive low-grade gliomas and glioneuronal tumors, trametinib monotherapy was effective in prolonging time to progression [21]. Three patients did not respond to monotherapy and five patients with a partial or minor response had a median time to response up to 21 months, indicating a more aggressive phenotype. Importantly only six patients had molecular evaluation with three having a BRAF:KIAA1549 fusion, one somatic NF1 mutation, one germline NF1 mutation as well as five with known histology of pilocytic astrocytoma but no molecular findings. It is important to note the rationale for use of Trametinib in this study, even without molecular confirmation, as MAPK alteration is extremely likely in low-grade gliomas.

Another MEK 1/2 inhibitor Selumetinib was approved by the FDA in Neurofibromatosis I patients with inoperable plexiform neurofibromas resulting in a 3-year PFS of 84% [22]. Trials assessing for activity of Selumetinib in non-NF1 recurrent or progressive low-grade gliomas have revealed responses though not quite as impressive as the NF1 experience. Selumetinib is currently being investigated as upfront therapy in two phase III COG trials in a randomized fashion vs. conventional chemotherapy Carboplatin and Vincristine both in NF1 associated low-grade gliomas and in non NF1 or V600E mutated low-grade gliomas.

Common side effects of the MEK inhibitors can include weight gain in up to 57% of patients or even weight loss in 19% of patients. Weight adjustments are made as necessary to dosing but even in grade 3 weight gain there is no dose decrease [23]. Other side effects can include paronychia secondary to drug induced neutrophilic lobular panniculitis [24] diarrhea, CPK elevation and skin dryness as well as reports of cardiomyopathy in adults but not currently reported in children [19▪▪].

Although targeted therapies appear promising, there is noted resistance to MEK inhibitors, and progressive disease can be noted in up to 28% of patients while undergoing treatment. Such resistance is thought to be secondary to activation of parallel pathways as well as possible recruitment of immune suppressive microglia. Pathway activation scoring systems have been developed in preclinical models to better assess transcriptomics data, thus driving models for the next generation of drug development [25].

Once therapy with dabrafenib/trametinib is completed there is a subset of patients that will have fast tumor regrowth, defined as growth >25% within three months of stopping therapy. In small studies, 76.5% of patients have experienced rapid progression with a median time of 2.3 months [26,27]. However up to 90% of patients will respond if rechallenged. This is not unusual and had also been seen with conventional chemotherapy. The mechanism is not fully known but early preclinical models seem to suggest this may be due to accumulation of upstream activators. Current terminology has not been fully recognized for rebound, regrowth or resistance but current expert consensus includes the following: Resistance is to be defined as growth while on MAPK inhibitor therapy, defined as >25% based on RAPNO pediatric low-grade glioma criteria; Rebound is to be defined as >25% growth of an existing lesion within 3 months of stopping therapy; Regrowth is then also defined as >25% growth or a new lesion 6 months after stopping therapy [27].

The underlying biology of all three is different in that rebound is not thought to occur secondary to intrinsic resistance of the tumor, compared to either intrinsic or acquired resistance in progressive or refractory disease [28]. Interestingly there is preclinical evidence for immune dysregulation as a potential driver of resistance. In BT-40 cell lines which are derived from juvenile pilocytic astrocytomas driven by BRAF V600E and co-occurring CDKN2A/B deletion there is no rebound growth noted when withdrawing conventional chemotherapy but significant increase in the dabrafenib treated cells. Furthermore, there was noted increased microglial attractions in the tumor micro environment once MAPK inhibition was withdrawn, suggesting a role for microglia in the increased mass size on MRI as well as potential immune suppression [26].

Early type I RAF inhibitors such as Dabrafenib are not indicated as monotherapy in BRAF fusion driven tumors and may in fact cause paradoxical tumor growth if not combined with a MEK 1/2 inhibitor. Newer agents thus have been undergoing clinical trials and approval targeting BRAF fusion as monotherapy. Most recently Tovarafenib a new type II pan RAF inhibitor received approval by the FDA for relapse/refractory pediatric low-grade gliomas targeting BRAF fusion. In the phase 2 trial totaling 137 patients, the overall response rate was 51% based on RAPNO criteria, median duration of response was 13.8% and median time to response

was 5.3 months. Adverse events included decrease in growth velocity, hair color changes, anemia, elevated CPK and fatigue [29▪▪]. The current phase III study will randomize patients to Tovarafenib vs. standard of care chemotherapy. Standard of care will include regiments based on COG carboplatin/vincristine, SIOP carboplatin/vincristine and vinblastine, with a patient target of 400 [30].

Parallel pathways targeting mTOR have also been explored, with a PNOC0001 phase II single arm study assessing the use of Everolimus in recurrent or progressive low-grade glioma. Sixty-five patients of whom 60% had mTOR pathway activation, were treated with Everolimus with a median number of previous therapy regimens of two. Interestingly rare BRAF fusion events were noted to be more aggressive and more commonly seen in midline lesions. When seen in younger infants this portends a worse prognosis. Overall survival (OS) at 6 months for the entire cohort was at 100% and 91.9% at 24 months. Median PFS was at 11.1 months based on site review and not central review [31].

Recently investigators have begun to explore the use of targeted therapy for tumors harboring alterations in the FGFR family which make up the second largest group of sporadic pediatric low-grade gliomas [7▪]. A phase 2 international study of Erdafitinib, a potent FGFR1–4 tyrosine kinase inhibitor, for patients 12 years of age and older with solid tumors with FGFR alterations showed clinical benefit. However, safety and clinical efficacy data in the pediatric population are limited since there were only two patients less than 18 years of age enrolled on this trial [32]. In another report, three pediatric patients, two with posterior fossa ependymomas and one with a low-grade glioma with an FGFR1 internal tandem duplication, were treated with erdafitinib. Following 6 months of therapy, the child with the low-grade glioma had a decrease in the tumor volume and enhancement which then remained stable for another 6 months after therapy was discontinued [33]. One of the largest experiences using erdafinitinib in pediatric patients has been reported by COG as part of the National Cancer Institute (NCI)-COG Molecular Analysis for Therapy Choice (MATCH) trial. Eligible subjects were between 1 and 21 years of age and had tumors that were shown to have FGFR 1/2/3/4 activating alterations. Six of 11 children with previously treated low grade gliomas/glioneuronal tumors had partial response or stable disease with a median duration of stable disease of 6.5 months following therapy with Erdafitinib. The therapy was fairly well tolerated. The most common treatment-related adverse events included hypophosphatemia, nail changes and infections which have previously been reported in adults treated with Erdafitinib [34]. However, it will be important to continue to monitor the use of FGFR inhibitors in children as a single institution retrospective study recently reported slipped capital femoral epiphyses in 3 of 7 children and increased linear growth velocity [35].

Although much work has been done in the treatment of the more common low-grade gliomas such as pilocytic astrocytomas, newer classification of low-grade tumors such as MYB/MYBL1 are not often treated utilizing molecular targets. However, with conventional therapy of GTR or NTR, 5-year EFS has been shown to be 81.3% ± 8.3% and OS 96.4% ± 4.1%. Surgical resection and conventional chemotherapy remain the mainstay of treatment, however markers of pERK1/2 and pS6 have been increased, indicating activation of MAPK and mTOR pathways, suggesting a rationale for targeted therapy [36].

ALTERNATIVE DRUG OPTIONS

Alternative therapies include use of the pan VEGF inhibitor Bevacizumab in refractory/progressive cases of low-grade gliomas. In a meta-analysis up to half of patients may achieve stability of disease with 8% showing progression [37]. In a small cohort of patients with progressive optic pathway gliomas, when assessing response of therapy based on visual acuity and visual field, it was noted that 14 of 17 patients had a stable or improved visual acuity or visual field. The median time to improvement was 2.7 months [38]. In a larger multicenter trial assessing 33 patients with optic pathway gliomas, visual acuity stabilized in 74.4% of patients and improved in 20.5% of patients while visual field stabilized in 15.4% and improved in 73.1% of patients. PFS was 70.9% at 18 months and 38% at 36 months [39]. In another cohort of 6 patients with cervicomedullary brainstem low- grade gliomas, retrospective review of the use of Bevacizumab was found to be efficacious in all six patients with signs of radiographic response most consistently on post gadolinium T1 weighted imaging. All six patients had improvement in cranial nerve deficits and at mean follow up of 7 months all patients were clinically stable without progressive disease [40].

NOVEL LOCALIZED THERAPY

Previous methods of nonsurgical treatment have included photon therapy; however, this has fallen to much less use due to long term cognitive effects and more chemotherapeutic options. Other nonsurgical methods include focused ultrasound utilizing circulating microbubbles and low intensity sound waves to disrupt the blood brain barrier,

further enhancing targeted drug delivery to localized sites. [2]. The limited research that exists appears to show feasibility to such a novel approach and this procedure may also play a role in acquiring of liquid biopsy samples [41]. As many pediatric low-grade gliomas harbor common fusions in BRAF as well as point mutations involving V600E, liquid biopsies are currently being explored as a noninvasive technique for diagnostics and confirmation of therapeutic targets [42].

Laser interstitial thermal therapy (LITT) is another option being explored for local control of pediatric low-grade gliomas [43]. This treatment involves stereotactic placement of an optic fiber which delivers focused laser energy into the tumor. This approach may be helpful for deep-seeded, noncystic small tumors. To date, this approach has only been performed at a limited number of centers. Additional experience on a larger scale will need to be obtained in order to determine the efficacy of this approach, the ability to obtain diagnostic tissue, potential complications and long-term effects.

CONCLUSION

Our current understanding of the molecular landscape has created a paradigm shift in our treatment of pediatric low-grade gliomas, with novel therapies being assessed for clinical efficacy [44]. Although information regarding tolerability and responses has been documented, many questions remain how best to incorporate these new therapeutic options in the treatment of pediatric low-grade gliomas. Along with a shift in treatment, early phase clinical trials in pediatric low-grade gliomas have undergone changes in endpoint assessment based on radiological as well as clinical criteria. For example, in optic pathway gliomas, vision screening and symptomatic resolution is paired with radiographic improvement based on modified imaging criteria in pediatric low-grade gliomas that may better evaluate 2-dimensional changes [45,46]. As further studies undergo assessment based on changing criteria, it will be prudent to compare historical studies carefully.

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Conflicts of interest

There are no conflicts of interest.

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