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Medical Treatment of Pediatric Low-Grade Glioma

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Low-grade glioma (LGG) is the most common brain tumor in children and has excellent long-term survival. With an excellent survival rate, the choice of treatment involves careful consideration of minimizing late toxicity from surgery, radiation, and chemotherapy. Surgery, radiation therapy, and chemotherapy can be used as monotherapy or in combination, providing different therapeutic ratios and complications. As a result, establishing the selection of ideal therapies has been a controversial area, presenting challenges. Recent advances in understanding molecular characteristics of pediatric LGG affect classification and treatment approaches. This review aims to overview recent developments in medical treatment in pediatric LGG.

Keywords Low grade glioma; Pediatric brain tumor; Chemotherapy; Target therapy.

INTRODUCTION

Low-grade glioma (LGG) is the most common brain tumor in children, accounting for approximately 30% of pediatric brain tumors [1-3]. Pediatric LGGs (pLGG) are heterogeneous neoplasms, including tumors of primarily glial histology and tumors of mixed neuronal-glial morphology [4]. Most LGGs in children are pilocytic astrocytoma (65%), followed by LGGs not otherwise specified in 21% of cases. The long-term survival is excellent, over 90%, but the progression-free survival (PFS) is only approximately 50%, and these patients require adjuvant therapy [5]. Surgical resection is important for the management of pLGG, and complete resection is the most favorable predictor of survival in patients with pLGG. In patients where gross tumor removal cannot be achieved, the progression of the tumor has been treated with adjuvant chemotherapy and radiation. Therefore conventional therapies, including surgical resection, radiotherapy, and chemotherapy, often provide long-term neurological and endocrine complications [6].

Recent molecular data has emerged to suggest that pLGG near universally upregulates the *RAS*-mitogen-activated protein kinase (*RAS/MAPK*) pathway [7-9]. The 5th edition of

WHO Classification of Central Nervous System Tumors, published in 2021, introduces the change in the classification of gliomas into adult-type and pediatric-type diffuse gliomas according to molecular and genetic differences, and the pediatric glioma is further divided into low-grade and high-grade gliomas [3]. Despite clinical and molecular distinctions between those diffuse gliomas that primarily occur in adults (termed "adult-type") and those that occur primarily in children (termed "pediatric-type"), pediatric-type tumors may sometimes occur in adults, particularly young adults, and adult-type tumors may more rarely occur in children. The pediatric low-grade group includes 4 entities that feature diffuse growth in the brain, and molecular work-up helps to characterize the lesion as one type or the other. Pediatric type diffuse LGGs expected to have good prognoses has three new tumors: 1) diffuse astrocytoma, *MYB* or *MYBL1*- altered, 2) polymorphous low grade neuroepithelial tumor of the young (PLNTY), and 3) diffuse LGG-MAPK altered. Five well-established tumors are classified to circumscribed astrocytic gliomas in which the tumor–non-tumor border is comparatively sharper, including 1) pilocytic astrocytoma, 2) pleomorphic xanthoastrocytoma, 3) subependymal giant cell astrocytoma, 4) chordoid glioma, and 5) astroblastoma, *MN1*-altered. Many of the circumscribed astrocytic gliomas share several morphological and molecular features with pediatric-type diffuse LGGs such as MAPK-activating alterations. Circumscribed astrocytic gliomas are relatively common in children, but can also occur in young adults [3].

TREATMENT OF pLGG

The mainstay of therapy for progressive or symptomatic pLGG is surgical resection [10]. Gross total resection (GTR) of tumors often requires no further therapy, and even subtotal resection may lead volume reduction and long-term tumor quiescence [8].

Several studies have shown that GTR correlates with increased PFS and overall survival (OS) in pLGG [5,11]. Around 40% of all LGG patients can be cured by complete neurosurgical resection and second-look operation is highly recommended for patients with a postoperative residual or recurrent tumor [12,13]. For the recurrent pLGGs, two thirds required subsequent therapies such as surgery, radiotherapy or chemotherapy. Unfavorable prognostic factors for OS include subtotal resection, young age, and unfavorable tumor location as brainstem or optic pathway [14-16].

Historically, radiation therapy has been used in the up-front and salvage treatment of pLGG. However, traditional photon radiotherapy is associated with several long-term adverse effects including cognitive decline, endocrine dysfunction, growth abnormalities, vascular damage, and secondary malignancies [6,17-20]. Thus, radiotherapy is generally reserved for older pLGG patients and for whom have progressive or refractory diseases after surgery, chemotherapy and/or targeted agents.

Newer radiation modalities including conformal radiation and proton beam radiotherapy have allowed sparing of normal brain regions that is exposed to low and intermediate doses of radiation compared to conventional photon radiotherapy.

CONVENTIONAL CHEMOTHERAPY OF pLGG

Chemotherapy has been considered for young children with progressive or incompletely resected pLGG to delay radiotherapy and recurrent tumors in unfavorable location infeasible surgery. This is especially important in children with neurofibromatosis type-1 (NF-1) who are at increased risk of pLGG, typically optic pathway glioma for high risk of secondary malignancy due to their germline mutation. The most commonly used chemotherapy regimens for pLGGs are carboplatin plus vincristine and/or etoposide, a combination of thioguanine, procarbazine, lomustine (CCNU) and vincristine (TPCV) or vinblastine monotherapy. Temozolomide, the treatment of choice for adult diffuse gliomas, is not effective standard therapy for pLGG [21]. Chemotherapy regimens in newly-diagnosed pLGG showed 50%−80% of 3-year PFS [14,15,22-25]. The use of chemotherapy to manage newly diagnosed LGG was first introduced in the 1980s. Procarbazine, 6-thioguanine, dibromodulcitol, CCNU, and vincristine regimen given to 42

pediatric patients showed 78% of 5-year survival rate [24]. Twenty-three patients of this group had juvenile pilocytic astrocytomas, 11 had astrocytomas, one had oligodendroglioma, one had ganglioglioma, and six had radiographically diagnosed LGGs. Phase II study of carboplatin single therapy in 81 children with progressive LGG had 64% of 3-year PFS and 84% of OS [25]. One of the largest studies, the German multicenter, cooperative Hirntumorstudien (HIT)-LGG-1996 study reported long-term follow-up result of 1,032 patients, and 668 children were under observation and 363 had started adjuvant treatment, as either chemotherapy or radiotherapy [12]. Vincristine+carboplatin (VC) chemotherapy was administered to 216 children including 55 patients with NF-1. Compared with the radiotherapy group, the patients in the chemotherapy group were younger and more often had NF-1. Best tumor responses were complete remission (CR) in 3.8%, partial remission (PR) in 31.6%, and overall response/stable disease (SD) in 56.5%, while 8.1% had tumor progression during follow-up period. In this report, NF-1 status was positive predictor for OS in children treated with chemotherapy. The European comprehensive treatment strategy for childhood LGG, the International Society of Pediatric Oncology Low Grade Glioma (SIOP LGG) Committee reported a randomized controlled study in the non-NF1 group by adding etoposide to the standard VC combination and the addition of etoposide to VC did not improve PFS or OS [15]. The other randomized trial comparing VC versus TPCV regimen showed a trend of higher 5-year PFS without statistical significance [14]. Through these two studies, VC recommended as standard first-line therapy [22]. Vinblastine monotherapy is also recommended according to the result with low toxicity and comparable PFS to previous chemotherapy studies including VC regimen [23]. The two currently recommended standard therapies are VC for 81 weeks or a weekly IV administration of vinblastine for 70 weeks [26].

THE GENOMIC LANDSCAPE OF pLGG

Genomic profiling studies have confirmed pLGGs to be distinct from adult LGGs and proved pLGGs have somatic driver genetic alterations that result in activation of the MAPK pathway [7,27,28]. Diffuse astrocytoma, *MYB*-altered or *MYBL1*-altered is defined as having *MYB* or *MYBL1* alterations, and angiocentric gliomas also commonly have *MYB* fusions. In both tumors, these alterations trigger MAPK pathway activation. Polymorphic PLNTY neoplasm includes histological components including oligodendrogliomas, gangliomas, pilocytic astrocytomas, dysembryoplastic neuroepithelial tumors, and pleomorphic xanthoastrocytomas. PLNTY is characterized by MAPK-activating mutations in *BRAF*, *FGFR2*, *FGFR3* or even *NTRK* alterations. Diffuse LGG, MAPK path-

way alterations are similar to the other previously mentioned tumors, and while other MAPK activating driver mutations are also found, tumor progression is mainly caused by *BRAF* mutations or *FGFR1* alterations [4,29]. They are all amalgamated by MAPK pathway activation and *IDH* mutations or lack of *IDH* mutations in histone-encoding genes.

MAPK activation resulting in downstream activation of the mTOR pathway is predominant in pLGG and offers a useful target for therapy [30]. Rearrangements affecting the genes *BRAF* and *KIAA1549* are the most frequent alterations in all pLGGs [7,27,28]. *KIAA1549-BRAF* rearrangements results in constitutive activation of the *BRAF* kinase with downstream activation of MAPK signaling. *BRAF^{V600E}* mutations are also tumorigenic driver particularly in the group of ganglioglioma and pilocytic astrocytoma [7,29] and are associated with worse outcome when accompanying alterations of *CDKN2A* [31,32].

TARGETED TREATMENTS FOR pLGG

Various agents that target the MAPK pathway, such as MEK or BRAF inhibitors are currently attempted in pLGGs and encouraging results has been recently reported [33-37]. Dabrafenib and vemurafenib of those agents, is expected to improve clinical outcomes with few adverse events and good tolerance in patients with *BRAF*-mutated gliomas [35,36,38-42].

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. Early reports showed dramatic responses to dabrafenib and vemurafenib in infants and children with recurrent LGG that harbor *BRAF^{V600E}* mutations [38-40,42], and led to multi-institutional phase I/II trials of these agents in children with recurrent *BRAF^{V600E}* mutated LGG. Thirty-two children with pLGG on dabrafenib have been revealed 13 PR and 1 CR with an overall RR of 44% and 85% of 1-year PFS [36,43]. Phase I trial of vemurafenib in children with recurrent or refractory gliomas containing the *BRAF^{V600E}* mutation also showed 1 CR, 5 PR, and 13 SD [44].

Despite high initial response rates, developing resistance to BRAF inhibitors has reported from melanoma trials, and the reason of this resistance is explained by reactivation of the MAPK pathway [45]. Combination therapy of BRAF inhibitors and MEK inhibitors that inhibit MAPK pathway demonstrated overcome of BRAF inhibitor resistance, and superiority over a BRAF inhibitor alone in CNS tumors including glioma [35,46].

To evaluate the efficacy and safety of dabrafenib in combination with trametinib for pediatric gliomas, a nationwide phase II pediatric study is progress (NCT02684058) and the result of interim analysis is reported [47]. In the LGG cohort, median

follow-up was 32.2 months and 9 (69%) of 13 patients had an objective response including one complete response, six partial responses, and two minor responses. The most common grade 3 or worse adverse events was fatigue, headache, and neutropenia. Dabrafenib plus trametinib showed clinically meaningful activity in patients with *BRAF^{V600E}* mutation-positive recurrent or refractory LGG and *BRAF^{V600E}* testing could potentially be adopted in clinical practice for patients with glioma.

The other drug that has been actively studied is selumetinib, MEK1/2 inhibitor. Promising preclinical data, led to the phase I and II trial of selumetinib in children with recurrent and refractory pLGG [48,49]. In the phase 1 study, 37% of 38 eligible patients completed all 26 cycles of protocol treatment with at least SD and 2-year PFS was 69%±9.8%. Rash, increased amylase/lipase and mucositis were the main dose limiting toxicities [48]. In the next phase II study (NCT01089101), the result of the children with PA harboring either one of the two most common BRAF aberrations (*KIAA1549-BRAF* fusion or the *BRAF^{V600E}* mutation), and NF-1 associated LGG was reported [49]. Selumetinib was given orally at the recommended phase 2 dose of 25 mg/m^2 twice daily in 28-day courses for up to 26 courses. Among 25 eligible and evaluable patients with PA, 9 (36%) of 25 patients achieved a sustained partial response, and the median follow-up for the 11 patients who had not had a progression event was 36 months. In the group of NF-1 associated LGG, 10 (40%) of 25 patients achieved a sustained partial response and median follow-up was 48 months for the 17 patients without a progression event. The most common grade 3 or worse adverse events were elevated creatine phosphokinase and maculopapular rash. Throughout these trials, selumetinib was considered being an alternative to standard chemotherapy for the patients with recurrent or progressive BRAF aberrated PA and NF-1 associated LGG. Two Children's Oncology Group phase 3 studies (NCT03871257 and NCT04166409) comparing standard chemotherapy (carboplatin and vincristine) to selumetinib in patients with newly diagnosed pLGG both with and without NF1 are ongoing.

Trametinib is another oral MEK-1/2 inhibitor, and several clinical trials are ongoing as single therapy or combination therapy (NCT05180825, phase II study comparing a daily trametinib to weekly vinblastine during 18 courses of 4 weeks each; NCT04485559, phase I trial studying the side effects and best dose of trametinib and everolimus in treating pediatric and young adult patients with LGG; NCT03363217, a phase 2, open-label, oral administration of trametinib). Another oral MEK inhibitors, binimetinib (MEK-162) and cobemitinib have completed or progressed phase 1 trials in children with recurrent, refractory or progressive pLGG and other BRAF-mutated recurrent pediatric solid tumors which are Ras/Raf pathway activated malignancies [50]. Therapies targeting the mTOR

pathway, such as everolimus, are also currently being tested evaluating everolimus in children with recurrent/progressive pLGG [51,52]. The phase 2 study of everolimus showed the results of 2 PR, 10 SD without CR in 23 children with recurrent and/or progressive pLGGs.

CONCLUSION

Aside from 'watch and waiting' when the tumor is low-grade and has gross total or near-total resection, the optimal adjuvant treatments for those pLGG remain unclear. Early results of new radiation therapy and MAPK-targeted agents have been quite promising in the children with LGG. Novel target agents such as BRAF inhibitors and MEK inhibitors have demonstrated high response rates, good PFS and relatively tolerable toxicity. Nevertheless, many questions regarding targeted therapies remain unanswered, such as the proper duration of therapy, durability of response, late toxicities and the use of these agents as up-front therapy or in combination with other agents. Hence, until now, chemotherapy with CV or vinblastine or focal radiotherapy in selected cases (in older children with relatively localized tumors) remains standard therapy. Further clinical trials will respond better answers to standardize and customize treatment protocols for pLGGs.

Ethics Statement

Not applicable

Availability of Data and Material

The data generated or analyzed during the current study are available in the PubMed database.

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Conflicts of Interest

The author has no potential conflicts of interest to disclose.

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