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Review Article

Focus on Current and Emerging Treatment Options for Glioma: A Comprehensive Review

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ABSTRACT:

This comprehensive review delves into the current updates and challenges associated with the management of low-grade gliomas (LGG), the predominant primary tumors in the central nervous system. With a general incidence rate of 5.81 per 100,000, gliomas pose a significant global concern, necessitating advancements in treatment techniques to reduce mortality and morbidity. This review places a particular focus on immunotherapies, discussing promising agents such as Zotiraciclib and Lerapolturev. Zotiraciclib, a CDK9 inhibitor, has demonstrated efficacy in glioblastoma treatment in preclinical and clinical studies, showing its potential as a therapeutic breakthrough. Lerapolturev, a viral immunotherapy, induces inflammation in glioblastoma and displays positive outcomes in both adult and pediatric patients. Exploration of immunotherapy extends to Pembrolizumab, Nivolumab, and Entrectinib, revealing the challenges and variabilities in patient responses. Despite promising preclinical data, the monoclonal antibody Depatuxizumab has proven ineffective in glioblastoma treatment, emphasizing the critical need to understand resistance mechanisms. The review also covers the success of radiation therapy in pediatric LGG, with evolving techniques, such as proton therapy, showing potential improvements in patient quality of life. Surgical treatment is discussed in the context of achieving a balance between preserving the patient's

quality of life and attaining gross total resection, with the extent of surgical resection significantly influencing the survival outcomes. In addition to advancements in cancer vaccine development, this review highlights the evolving landscape of LGG treatment, emphasizing a shift toward personalized and targeted therapies. Ongoing research is essential for refining strategies and enhancing outcomes in the management of LGG.

6 **INTRODUCTION:**

Gliomas represent the most prevalent primary tumors in the central nervous system (CNS) across various age groups [1, 2]. Gliomas have a general incidence rate of 5.81 per 100,000 people, with older individuals having a threefold higher frequency than young children. Gliomas account for 29-35% of all central nervous system tumors in the adolescent and young adult (AYA) demographic (ages 15-39 years), with an incidence of 3.41 per 100,000 [3-5]. Gliomas continue to be a global concern, emphasizing the vital need to improve treatment techniques for lowering both mortality and morbidity, elevating it to the top of the neuro-oncology priority list. [6, 7]

Clinical care, therapeutic response, and outcomes differ significantly between pediatric and adult glioma patients. Children with high-grade gliomas (HGGs) have poor prognosis, with frequently limited long-term survival ranging from months to a few years after diagnosis [8, 9]. In contrast, pediatric patients with low-grade gliomas (LGG) have good overall survival (OS) [10, 11], despite significant tumor- and treatment-related morbidity [12] (Table 01). The increased likelihood of malignant transformation, which is extremely rare in children) adds to a less favorable prognosis in adults with low-grade gliomas [13, 14].

IMMUNOTHERAPIES

Despite advancements in surgery, radiotherapy, and chemotherapy for LGG, the disease remains incurable and often progresses to secondary malignant transformation. Immunotherapeutic strategies have demonstrated success in various cancers, including lung, skin, colon, and blood-related cancers (Figure 01). Given that

low-grade gliomas, particularly in younger patients, exhibit slower growth compared to high-grade gliomas, there is a suggestion that immunotherapies may be more effective due to the healthier immune systems of younger individuals, potentially leading to better treatment responses. Immunotherapies, including Zotiraciclib and Lerapolturev, exert their effects through distinct mechanism (**Table 02**)

Zotiraciclib:

Zotiraciclib, a potent CDK9 inhibitor, exhibits efficacy against glioblastoma by suppressing transcription and disrupting cellular energy production. Preclinical studies, both in vitro and in vivo, have revealed its synergistic effect with temozolomide (TMZ). In clinical trials, Zotiraciclib demonstrated the ability to cross the blood-brain barrier and suppress CDK9 activity in tumor tissues^[15]. This promising mechanism, targeting multiple glioblastoma survival pathways, positions Zotiraciclib as a potential therapeutic breakthrough^[16-19].

A two-stage, two-arm, randomized phase 1 clinical trial further investigated the potential of zotiraciclib in recurrent high-grade gliomas. This study included a comprehensive evaluation of pharmacokinetics, patient-reported outcomes, and a detailed examination of rapid-onset neutropenia. Despite this observed neutropenia, a thorough analysis concluded that it did not compromise patient safety, allowing the research and development of this novel CDK9 inhibitor to progress^[19].

Pembrolizumab or Nivolumab:

Immunotherapy has garnered significant interest as a potential treatment for glioblastoma (GBM). Nevertheless, a recent clinical study focusing on recurrent glioblastoma and employing PD-1 immune checkpoint inhibitors revealed that a minority of patients (8%) exhibited noticeable improvements in their condition^[20]. The mechanistic underpinnings of the variability in response patterns remain unclear.

Enhanced T cell infiltration in the tumor microenvironment and elevated mutational burdens in various cancer types have been associated with improved responses to anti-PD-1 therapy^[21-23]. However, GBM presents a more immunosuppressive tumor microenvironment and a lower burden of somatic mutations than melanomas or non-small cell lung cancer^[24]. Immunosuppression in GBM is facilitated by the expression

of PD-1 ligands (PD-L1/2) in tumor cells, leading to T cell exhaustion and apoptosis. The binding of PD-1 to the surface of cytotoxic T cells hampers their ability to mount an effective anti-tumor response. PD-1 inhibitor therapy disrupts this immune checkpoint, reinforcing the immune response against tumors^[23].

PD-1 inhibitors, such as pembrolizumab and nivolumab, have gained attention for glioblastoma treatment. However, recent clinical studies have revealed variable responses, necessitating deeper understanding of the underlying mechanisms. Glioblastoma's immunosuppressive microenvironment and lower mutation burden compared to other cancers pose challenges. Molecular-tailored strategies hold promise for optimizing patient selection for immunotherapy, although further testing is required to validate their efficacy^[25].

Lerapolturev:

Lerapolturev, a viral immunotherapy, operates via a unique mechanism. As a polio-rhinovirus chimera, it induces persistent type-I interferon-dominant inflammation in glioblastoma, leading to polyfunctional antitumor CD8+ T-cell responses. Clinical trials involving Lerapolturev for recurrent adult glioblastoma demonstrated a 16% survival rate of at least 36 months, with a manageable safety profile ^[26-29].

In pediatric high-grade gliomas, Lerapolturev showed promise, with no grade 3 or 4 toxicity observed in early trials. The safety of treatment at this dose allows for further trials, including patients as young as 9 years of age. Ongoing research is crucial to understand the immunological factors influencing the efficacy of Lerapolturev in pediatric versus adult high-grade gliomas^[30]. Our group's previous research in adults gained additional support from the inclusion of patients as young as 9 years old, including one individual with WHO grade 3 glioma^[30]. Moreover, pediatric high-grade gliomas typically exhibit significantly different molecular profiles compared to adult high-grade gliomas^[31]. However, whether immunological factors affecting viral immunotherapies, such as Lerapolturev, vary between pediatric and adult high-grade gliomas remains uncertain^[30].

Depatuxizumab:

Depatuxizumab (formerly ABT-806) is a humanized monoclonal antibody developed against epidermal growth factor receptor variant III (EGFRvIII) that also binds to wild-type EGFR at elevated levels^[32, 33]. ⁴ The antibody-drug conjugate (ADC) Depatuxizumab mafodotin (formerly ABT-414) connects the depatux to the cytotoxic payload monomethyl auristatin F (MMAF or mafodotin). Upon binding to activated EGFR, ADC is internalized, degraded in acidic compartments, and releases the toxin, causing cell death. Unlike other treatments, this direct cytotoxic effect does not rely on inhibition of EGFR signaling and avoids typical toxicities^[34]. Although unconjugated depatux is ineffective against GBMs, depatux-m demonstrates efficacy in GBM cell lines and models with EGFR amplification or EGFRvIII, showing effectiveness alone and in combination with radiotherapy and temozolomide^[35]. ADCs, including depatux-m, show promise in various cancers^[36], surpassing unconjugated monoclonal antibodies in efficacy, with numerous ADCs under investigation under diverse conditions^[37].

Despite promising preclinical and early clinical data, depatux-m has proven ineffective in treating GBM. This disappointing outcome may result from the emergence of resistant clones over time, negating any overall survival benefit^[38]. Limited penetration of depatux-m into large tumors and challenges in reaching intracranial tumors^[39], especially in the non-enhancing tumor region, underscore crucial lessons for future studies involving large molecules^[38]. Safety concerns with depatux-m were reversible, with adverse events, such as sensitivity to light and thrombocytopenia, being the most frequently observed.

Entrectinib:

Entrectinib, approved by both the FDA and EMA for tumors containing TRK or ROS1 fusions^[40], encounters a challenge in treating brain neoplasms due to the blood-brain barrier (BBB)^[35]. Effective targeted therapies for leptomeningeal disseminated tumors depend on their ability to penetrate this barrier. Although entrectinib, designed to cross the BBB, has demonstrated promise with a 79% objective response rate in various

solid tumors, including CNS tumors, information on its cerebrospinal fluid (CSF) penetrance in brain tumor patients is currently lacking^[41].

The potential therapeutic efficacy of entrectinib, a selective pan TRK inhibitor, has been explored in patients with leptomeningeal disseminated pediatric high-grade gliomas (pHGG) harboring NTRK or ROS1 fusions^[42, 43]. The STARTRK-NG trial reported positive radiographic responses in four pHGG patients treated with entrectinib, indicating promise for CNS tumors^[44, 45]. This study investigated the in vitro sensitivity of pHGG cell models to entrectinib and suggested potential combination therapies^[46]. The need for further studies to understand resistance mechanisms is emphasized, along with the generally well-tolerated nature of entrectinib. The observed CNS penetrance of entrectinib in a gliosarcoma patient has been discussed, highlighting its ability to cross the blood-brain barrier^[47]. The text also considers the combination of entrectinib with radiotherapy and suggests the importance of intrathecal therapy in cases of leptomeningeal dissemination^[41]. This conclusion underscores the need for comprehensive investigations and prospective clinical studies to establish the role of entrectinib and potential combination therapies in pHGG with ROS1/NTRK fusions.

ONC201 and Paxalisib:

ONC201, an oral small-molecule imipridone anticancer therapy, has demonstrated early clinical success in patients with Diffuse Intrinsic Pontine Glioma (DIPG)^[48] and recurrent H3K27M-mutant diffuse midline gliomas (DMG)^[49]. Investigations across various cancer types have shown that ONC201-induced apoptosis in cancer cells, independent of p53, occurs through an atypical integrated stress response involving the expression of the antitumor protein TRAIL. This mechanism has shown promise in hematological^[50], colorectal^[51], breast^[52], uterine cancers^[53], and glioblastoma^[54]. A sustained positive response was observed in a patient with secondary glioblastoma carrying an H3.3K27M mutation, prompting further exploration in patients with similar mutations, including those with DIPG^[54].

Studies have discussed the therapeutic benefits of combining ONC201, a dopamine receptor D2 antagonist^[55], with the blood-brain barrier-penetrant PI3K/Akt inhibitor,

paxalisib, for treating DIPG. Mechanistic insights indicate that ONC201, by decreasing tyrosine hydroxylase expression, exhibits global DRD2 antagonism, with ClpP identified as a crucial target that causes mitochondrial dysfunction and oxidative stress^[56]. The combination of paxalisib shows promising results in preclinical and preliminary clinical trials, leading to symptom resolution and tumor regression. Challenges related to immunologically cold tumor microenvironments in DIPG have been acknowledged, but potential changes in the epigenetic landscape and metabolic plasticity following ONC201 treatment may enhance immunogenicity^[57, 58]. The observed link between H3K27M mutations, metabolic changes, and the immune response highlights the complexity of DIPG treatment, presenting a potential avenue for the effective administration of therapy for glioblastoma^[59].

RADIATION THERAPY

Radiation therapy (RT) is a successful management method for pediatric low-grade gliomas (pLGG) using both initial and salvage treatment approaches. Historically, RT was the chosen initial therapy for quickly progressing or unresectable tumors, with 10-year PFS and OS rates of 70% and 80%, respectively^[60-62]. Furthermore, RT has been used as an adjuvant therapy, particularly when surgery is limited to partial resection or biopsy, particularly for tumors in the optic system, hypothalamus, deep midline tissues, and brainstem^[63, 64]. Adjuvant RT is suggested in cases of partial resection because PFS is greatly reduced^[65, 66]. However, there is a lack of agreement on its use, which is attributable in part to the paucity of randomized prospective studies^[67, 68].

For older children who have not responded to numerous systemic medications, RT is preferred as part of the care plan. Historically, postponing RT was motivated by concerns about RT-related toxicities such as cognitive impairment^[69, 70], endocrine dysfunction^[71], secondary malignancies^[72], vascular damage^[72, 73], and growth abnormalities^[74]. The severity of these symptoms is directly related to the location of the tumor and the patient's age, particularly in patients under the age of 10^[69, 72].

An institutional evaluation covering a median follow-up of 11 years found 8-year progression-free survival (PFS) and OS rates of 83% and 100%, respectively^[75]. Overall neurocognitive performance did not deteriorate in the trial; however,

significant cognitive impairment was noted in young children (under 7 years¹ old) and in patients who received high doses to the left temporal lobe or hippocampus. Higher dosages to the hypothalamus or pituitary caused endocrine disruption, and two patients developed Moya disease. The 5-year PFS and OS rates in a recently published prospective research including 174 pediatric patients with LGG who received proton treatment¹ were 84% and 92%, respectively, with a median follow-up of 4.4 years^[76]. Four patients experienced severe late toxicities, including brainstem necrosis, symptomatic vasculopathy, radiation retinopathy, and fatal secondary cancers. While acknowledging the relevance of radiation-related damage, it is vital to emphasize that recent research has yielded promising outcomes. The extended latency of toxicity should be considered in light of the rapid developments in the field^[77]. Concerns about RT-related toxicity originate mostly from long-term data collected from studies conducted during the 1970s and the 1990s using 2-dimensional RT methods that did not allow for accurate radiation dose administration. Significant technical progress has been achieved in reducing the radiation dose that reaches the normal structures surrounding the tumor. This began with the use of 3-dimensional conformal external beam RT (3D-CRT) and progressed in the 2000s with the advent of intensity-modulated RT (IMRT). Significantly, the introduction of proton therapy has reduced radiation exit dosage^[78, 79], contributing to its growing role in pediatric patients. Several studies have suggested that proton therapy might improve both patient quality of life and the cost-effectiveness of pediatric brain tumor treatment^[80, 81].

SURGICAL TREATMENT

The primary objective of glioma treatment is to strike a balance between preserving the patient's quality of life and improving PFS and OS^[82, 83]. The choice between oncological and surgical treatment depends on factors such as tumor size, location, and individual patient characteristics, including age and comorbidities^[82, 84, 85]. Patients aged > 40 years at diagnosis, those with incomplete resection, and those with wild-type IDH status are typically considered to be at increased risk. The conventional

treatment approach involves cytoreductive surgery to achieve gross total resection (GTR), followed by a combination of chemotherapy and/or radiation therapy^[86, 87].

The prognosis for gliomas, encompassing both LGG and HGG, is significantly influenced by the extent of surgical resection (EOSR) (**Table 03**). In LGG, EOSR is measured by the percentage of the FLAIR signal that is excised, whereas in HGG, it is determined by the removal of the percentage of enhancing tissue and the necrotic center. Extensive research on EOSR in LGG consistently shows that achieving GTR significantly improves survival rates, particularly among younger patients, classifying them as low-risk individuals compared to those who undergo only partial resection^[82-84].

Similarly, investigations into EOSR in HGG consistently demonstrated a strong correlation between the extent of resection and survival outcomes, assuming no surgery-related neurological morbidities^[88-90]. In most studies, the surgical goal is unequivocally defined as achieving GTR or complete tumor removal, typically amounting to 100% resection^[91].

Recent clinical investigations have explored the concept of subtotal resection for gliomas^[92]. This surgical approach aims to achieve GTR while simultaneously eliminating the FLAIR signal surrounding the necrotic and enhancing tumor mass in high-grade gliomas. Low-grade gliomas involve complete removal of the FLAIR signal along with additional radiographic extraction of the normal brain tissue adjacent to the tumor. Subtotal resection in LGG surgery was confirmed by observing that the resection cavity exceeded the initial FLAIR volume on the postoperative MRI at the three-month mark. Subtotal resection is considered justifiable when minimal neurological risks are involved, with the aim of eliminating invasive cells near the radiographic boundary^[93-95]. Evidence from clinical case series of glioblastoma multiforme and HGG presents a conflicting picture, as performing supra total resection may entail an increased risk of neurological function decline, despite potential improvements in PFS and OS^[92, 96]. Additionally, there has been increased focus on the utilization of laser interstitial thermal (LIT) treatment for brain tumors. Recent trials investigating LIT have shown that achieving a greater level of ablation,

including subtotal ablation, can lead to improved progression-free survival and overall survival outcomes in patients with HGG^[97, 98].

Intraoperative radiotherapy with a single high radiation dose administered following tumor resection, intraoperative radiotherapy (IORT), a novel and non-conventional form of radiotherapy, can eradicate any remaining tumor cells^[99]. A wide range of cancers, including breast, pancreatic, lung, and colon cancers, have been treated with IORT^[100-102]. The lack of a discernible increase in survival in IORT treatment reports for primary malignant gliomas has been ascribed to angle errors, low electrons, and small electron cones, which result in inadequate coverage of the target volume ⁵^[103]. A mobile IORT unit, INTRABEAM (Zeiss, Oberkochen, Germany), can deliver an equal dose of low-energy radiation in all directions within a tumor cavity, along with spherical irradiation. According to research, IORT with low-energy X-rays increases glioblastoma patients' survival rates without causing new problems ^[104]

Vaccine development:

Cancer vaccines targeting high-grade gliomas, predating COVID-19, are gaining momentum. Strategies include peptide-based vaccines, dendritic cells, viral vectors, and personalized neoantigen vaccines. They are also being explored for the treatment of LGG. For IDH-mutant LGG, adjuvants such as poly (I: C) and poly-ICLC enhance immune responses, collectively reflecting a determined push for glioma immunotherapy^[105]. To bolster the weak immune response in LGGs, synthetic double-stranded RNA molecules, such as polyinosinic acid homopolymers annealed to a polycytidylic acid homopolymer, have demonstrated potential ^[106]. They mimic viral infections and promote the release of interferon type 1 and other immune-boosting substances. Safely used as adjuvants with dendritic cells or peptide vaccines, they enhance therapeutic responses ^[106, 107].

CONCLUSION

In conclusion, advancements in LGG treatment span immunotherapies, targeted therapies, radiation, surgery, and vaccine strategies. Immunotherapies like Zotiraciclib and Lerapolturev show promise, while targeted therapies such as

Entrectinib and ONC201/Paxalisib combination demonstrate early success. Radiation therapy, evolving with proton therapy, remains crucial, and surgical approaches aim to achieve gross total resection. Cancer vaccines including synthetic RNA adjuvants have emerged. The evolving landscape underscores a shift toward personalized and targeted therapies, with ongoing research being essential for refining strategies and improving outcomes in LGG treatment.

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