

# Novel drugs in pediatric gliomas (Review)

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**Abstract.** Astrocytomas (gliomas) are the most common primary brain tumors among adults and second most frequent neoplasm among children. New ideas and novel approaches are being explored world over with aim to devise better management strategies for this deadly pathological state. We searched the electronic database PubMed for pre-clinical as well as clinical controlled trials reporting importance of various therapeutic drugs against gliomas. It was observed clearly that this approach of using therapeutic drugs is clearly evolving and has been observed to be promising future therapeutic avenue against gliomas. The searched literature on whole revealed that although gliomas are treated aggressively with surgery, chemotherapy and radiation, treatment resistance, drug toxicity and poor response rates among pediatric glioma patients, continue to drive the need to discover new and more effective chemotherapeutic agents. The present review is focused on the latest updates in therapeutic drugs against gliomas in pediatric patients. The important chemo-therapeutics discussed in this review included alkylating agents like temozolomide, derivatives of platinum, nitrosoureas, topoisomerases, angiogenesis inhibitors and cytomegalovirus as therapeutic agents.

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## 1. Introduction

Pediatric gliomas as the name suggests, are childhood tumors of a glial origin with heterogeneous nature (1). Gliomas have discrete molecular individualities, varying clinical attributes and varying levels of malignancy. Their histological profile mirrors those of adult gliomas but the frequency of occurrence of distinct molecular signatures sets them apart from adult gliomas (2,3). Such inherent differences in the biology of pediatric gliomas partly explain the reason for pediatric astrocytomas being unresponsive or having very low efficacies when administered with treatments tailored for adult gliomas.

## 2. Glioma therapy

The standard care of pediatric patients with gliomas involves the surgical resection of tumors coupled with adjuvant therapies such as radiation and chemotherapy, when relevant. Most often the choice of therapy is dictated by the patient's age, tumor location and tumor type. Patients with tumors having an indolent course such as optic pathway gliomas of Neurofibromatosis type 1, may be restricted to observation only since approximately 50% of these tumors fail to progress further (4). However, other tumors require an aggressive treatment modality in order to improve patient survival.

## 3. Surgery

Surgery remains the principal treatment for well-circumscribed resectable pediatric high- and low-grade astrocytomas (5,6). It is often recommended for tumors with distinct boundaries which are amenable to gross total or near total resection such as those that are peripherally located in the cerebellar and cerebral cortex (7). In general, surgical resection occasionally immensely decreases tumor volume, which is important to increase the efficacy of post-adjuvant treatments by radiation and/or chemotherapy on the residual unresected tumor. Surgical resection not only provides the tumorigenic tissues for histopathological diagnosis which is important for deciding follow-up therapies, but also decreases the size of the tumor

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mass, can prolong survival and sometimes can improve the overall quality of life for the patient (8).

With the exception of pilocytic astrocytomas, which have boundaries that are often well circumscribed, gliomas manifest predominantly a diffuse infiltrative behavior with no definitive boundaries. Therefore, complete resection is often not feasible even with the aid of sophisticated imaging and intraoperative techniques. Moreover, the surgical resection of brain tumors among children is often associated with the significant risk of morbidity and mortality. Examples of post-surgical complications include infections, bleeding, brain edema and stroke. Furthermore, neurological dysfunctions and even death can occur depending on which neighbouring functional neural networks at the resected tumor location are affected (9). Considering that some astrocytomas are located at eloquent regions of the brain where surgical resection may be more harmful than beneficial, and the fact that gross or even partial resection can never completely remove the tumor mass, other therapeutic options such as chemotherapy and radiotherapy must be utilized to improve the overall survival of the patient.

#### 4. Radiotherapy

Radiotherapy is recommended as a first-line therapy for some unresectable pediatric gliomas such as diffuse intrinsic pontine gliomas (DIPG) or as a post-operative treatment for residual disease (10). Generally, the procedure involves the use of CT and MRI in order to define the tumor boundaries. This is then followed by the localized administration of 36-52 Gy photons (X-ray beams) in 1.8 Gy fractionations to the glioma mass of the pediatric patient. Over the years, radiotherapy has undergone dramatic improvements as a therapeutic option for patients with brain tumors. For instance, the introduction of 3D treatment planning protocols which allows for a 30-40% reduction in volume of normal brain parenchyma exposed to irradiation compared to the 2D planning approach (11), could theoretically reduce long-term morbidity and radiation associated sequelae. The use of rigid head immobilization and stereotactic irradiation approaches including stereotactic convergence therapy, fractionated stereotactic convergence therapy, fractionated conformal radiotherapy and intensity modulated radiotherapy can also permit the delivery of homogeneously-focused irradiation fractionations to brain tumors of varying sizes, gradations and shapes (12). However, even though these advances have revolutionized radiotherapy, the physical property of X-rays including its high lateral side scatter and its toxic effect on normal tissues, which are proximal and distal to the targeted tumor mass, limits its use among pediatric patients who are younger than 3 years. Additionally, pediatric patients treated by radiotherapy are often at risk of developing secondary malignancies and often succumb to neurodevelopmental abnormalities including serious long-term neurocognitive and neuroendocrine sequelae.

#### 5. Chemotherapy

Chemotherapy is a common and the most basic therapeutic module for any type of cancer and is often administered concomitantly with radiotherapy. It is usually recommended

for children having disease progression after surgery and/or radiotherapy, as well as for those who are too young and therefore have been deferred from radiotherapy because of its associated toxicities (13). However, it must be noted that, no current Food and Drug Administration (FDA)-approved chemotherapeutic agents are promisingly effective for pediatric astrocytomas; even when used in conjunction with other chemotherapeutic agents. Furthermore, dismal results still remain from current clinical trials; hence necessitating the identification and characterization of new chemotherapeutic agents for the treatment of pediatric gliomas. Below is a review of the efficacy and safety of the most common therapeutic agents used for the treatment of pediatric gliomas.

#### 6. Alkylating agents

Alkylating agents include analogues of nitrogen mustards, nitrosoureas, platinum derivatives, thiopeta, and so on (14). They generally function by chemically modifying DNA with an alkyl group or by inducing monoadducts, intrastrand and interstrand crosslinks, which attenuates DNA replication leading to cell cycle arrest and apoptosis (15). Summarized below, are the findings from clinical trials involving the most commonly used alkylating agents investigated to treat pediatric gliomas.

*Temozolomide.* The alkylating imidazotetrazine derivative, temozolomide, eventually became an FDA approved chemotherapeutic drug in 1999 for the experimental treatment of adult patients with refractory anaplastic astrocytomas (16). However, ongoing clinical trials, including the landmark phase III trial conducted by the European Organization for Research and Treatment of Cancer, unfortunately noted that the adjuvant post-operative use of temozolomide and radiotherapy only had a modest improvement in <20% of the patients by increasing the median overall survival to 14.6 months for newly diagnosed glioblastoma patients, when compared to 12.1 months among similar patients treated by post-operative radiotherapy only (17,18). Since 2005, temozolomide has been the current recommended drug for the treatment of adult patients with glioblastoma multiforme (19). Temozolomide is administered orally, with a bioavailability of 96-100% and half-life of 1.8 h (20). At physiologic pH, temozolomide is converted to a reactive intermediate known as 5-(3-methyl-1-triazeno)imidazole-4-carboxamide (MTIC) which subsequently methylates the O6 or N7-position of guanine as well as the N3-position of adenine. If left unrepaired by the cellular machinery, cells become susceptible to undergo apoptosis (21).

*Clinical trials with temozolomide in pediatric glioma.* Several clinical trials involving panels of pediatric glioma patients were conducted to assess the efficacy and toxicity of temozolomide used alone or concomitantly with other chemotherapeutic agents and radiotherapy (22). However, only few pediatric patients showed signs of complete/partial response or disease stabilization when treated with temozolomide. Furthermore, adverse side effects are noted with the use of temozolomide, including thrombocytopenia, nausea, emesis, fatigue, myelosuppression, sepsis, pneumonia and

even death (23). Furthermore, a multicenter phase II clinical trial jointly conducted by the United Kingdom Children's Cancer Study Group and the French Society 20 for Pediatric Oncology showed only 12% of children with relapsed or progressive high-grade glioma, had a response to temozolomide administered daily at 200 mg/m<sup>2</sup> for 5 consecutive days. The response declines further to only 6%, when the same treatment is administered to children with progressive diffuse intrinsic brainstem glioma (24). Due to the limited efficacy of using temozolomide alone for the treatment of pediatric gliomas, other clinical trials have examined the concomitant use of this drug with other therapeutic agents. For instance, a clinical trial involving 14 pediatric glioblastoma and anaplastic astrocytoma cases showed that the post-operative adjuvant use of temozolomide with lomustine resulted in only one complete response and one partial response (26).

The futile efficacy of temozolomide in treating pediatric gliomas may be attributed to a number of factors including an increase in the expression of the HOX genes, deficiency in the mismatch repair pathway, the absence of O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation or even increased levels of MGMT protein expression in pediatric gliomas (26,27). Several strategies are currently being investigated to sensitize pediatric gliomas to temozolomide; the most common being to therapeutically inactivate MGMT.

## 7. Derivatives of platinum

*Carboplatin.* The platinum derived compound, carboplatin is among the most commonly used chemotherapeutic agents for the treatment of pediatric gliomas (28). Recent results showed that, the 5-year overall survival rate for using carboplatin and vincristine was 48%, which is significantly lower than 86% when pediatric low grade glioma patients were treated with thioguanine, procarbazine, lomustine and vincristine (29). Furthermore, children with DIPG and high grade gliomas did not show any significant improvements in overall survival when treated with carboplatin and etoposide or lobaradimil. The use of other platinum-based drugs such as cisplatin in combination with etoposide (30) had initially suggested some encouraging results among pediatric glioma patients. Nonetheless, platinum-based drugs are also confounded with adverse side effects including nephrotoxicity with cisplatin (31) and hypersensitivity with carboplatin (32), which limits their usefulness for treating pediatric patients with gliomas.

## 8. Nitrosoureas

Nitrosoureas function by establishing covalent interactions between DNA and proteins. This perturbs DNA repair, leading to cell cycle arrest and induction of apoptosis (33). Thus far, only carmustine (BCNU) and lomustine (CCNU), two nitrosoureas, have been clinically evaluated in pediatric glioma patients. For instance, a clinical trial conducted by the Children Cancer Group on 39 children diagnosed with malignant gliomas which examined the adjuvant use of eight drugs including BCNU, but no radiotherapy, noted a 24% response after two cycles of drugs with 51% of patients still being alive at 3 years (34). Recently, the French Society of Pediatric

Oncology noted a modest event-free 10-year survival rate of 13.3±9.4% in pediatric glioblastomas following the concomitant use of BCNU with cisplatin and VP16 (BCV) (33).

## 9. Topoisomerase inhibitors

Topoisomerases are required to establish and maintain the topology of DNA hence play pivotal roles during DNA replication, repair and transcription (36). Inhibition of topoisomerase in cancerous cells is therefore expected to affect the integrity of DNA, leading to the induction of cell death. Indeed, numerous inhibitors of topoisomerase I and II were developed (37), but only irinotecan, topotecan and etoposide were thus far examined in pediatric gliomas.

## 10. EGFR inhibitors

The epidermal growth factor receptor (EGFR) has materialized as an imperative target in the treatment of gliomas due to the fact that it is overexpressed in more than 40% of adult glioblastomas, and approximately 11% of pediatric glioblastomas (39). Recently, the Innovative Therapies for Children with Cancer European Consortium examined the efficacy and safety of the EGFR inhibitor, erlotinib, among children with recurrent or relapsed malignant gliomas, as well those with brainstem gliomas, using a dose of 125 mg/m<sup>2</sup> per day adjuvantly with radiotherapy (40). However, this study had a disappointing outcome of progression free survival in only 28% of subjects (40). A clinical study by Yalon *et al* (41) also investigated the daily administration of the mTOR inhibitor, rapamycin. The study, however, failed to show any efficacy of these two drugs for the treatment of pediatric low grade gliomas in 17/19 patients (41).

## 11. PDGFR- $\alpha$ inhibitors

The platelet-derived growth factor receptor (PDGFR)- $\alpha$  is an amplified and overexpressed genes in pediatric high-grade glioma (42). However, its relevance as a therapeutic target in pediatric gliomas remains to be investigated.

## 12. Angiogenesis inhibitors

Angiogenesis is a process whereby new vascular networks sprout from existing blood vessels but can also occur following the process of intussusception (43), vascular mimicry (that is, the development of blood channel linings from de-differentiated tumor cells), or even through the recruitment of circulating endothelial cells. Recent studies have focus on bevacizumab (avastin), a monoclonal antibody against the VEGF protein, for the management of glioblastoma multiforme (44). Among pediatric gliomas, bevacizumab was investigated as a single agent which could clinically improve the neurological responses of children with diffuse intrinsic gliomas when administered alone (45).

## 13. Cytomegalovirus as a therapeutic target in gliomas

Initially referred to as infectious agents with no relevance to human tumors, viruses are now well recognized as critical

mediators in the etiology and progression of human cancer (46). Consistent with the role of viruses in human tumors several studies have identified the human cytomegalovirus (HCMV) or its gene product in malignant gliomas (47,48). Data supporting HCMV tumor promoting function is further reinforced by compelling *in vivo* evidence demonstrating reduced survival time in Mut3 glioma mouse models infected with mouse cytomegalovirus compared to mock infected or herpes simplex virus 1 infected control. Moreover, glioblastoma patients with low-grade CMV infection have a 20-month increase in median overall survival rate and ~46.6 months increased in a two-year survival rate compared to those with high-grade CMV infection (49).

Promising findings have also been obtained using immunotherapeutic approaches against CMV in glioblastoma (50). These studies have demonstrated that, vaccination of a glioblastoma patient with autologous tumor lysate-pulsed dendritic cells can result in substantial CMV-specific T-cell immune response (51). Similarly, adoptive transfer of cytomegalovirus-specific T-cells in combination with temozolomide has been shown to result in long-term disease-free survival in a patient with glioblastoma by Crough *et al* (50). These findings collectively suggest CMV is an important therapeutic target in glioblastoma. Thus, strategies with the aim of blocking CMV-mediated oncogenesis are potentially useful for the treatment of patients with CMV-positive malignant glioma.

#### 14. Conclusion

Many therapeutic strategies are under investigation worldwide and most of them are being examined in different phases of clinical trials. However, application of these therapeutics as gold standard in pediatric gliomas remains to be implemented.

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