Systemic Chemotherapy in Brain Gliomas

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Gliomas constitute the most common and difficult to treat primary brain tumors, accounting for over 50% of all primary central nervous system tumors. The glioblastoma is by far the most frequently occurring and most malignant of the glial tumors, with a median patient survival of 15 months. Current treatment involves maximal surgical resection followed by radiotherapy with concomitant and adjuvant chemotherapy. However, over the last decade much has changed regarding the role of chemotherapy in gliomas. This is the result of several trials that reported survival benefit with a combination of agents and the incorporation of molecular genetic markers as predictors of response to chemotherapy. Herewith we discuss the chemotherapy regimens currently used for glioma treatment as well as the associated toxicities and try to provide an insight into future advancements.

24.1 Introduction

Gliomas constitute the most common primary brain tumors, accounting for over 50% of all primary central nervous system (CNS) tumors and including tumors of astrocytic, oligodendroglial, and ependymal lineage. Among gliomas, astrocytomas occur predominantly in the cerebral hemispheres and less commonly in the cerebellum, brainstem, spinal cord, and optic pathways [1, 2]. Oligodendroglial tumors usually are localized to the cerebral hemispheres. Ependymal tumors are more likely to occur in an infratentorial location such as the floor of the fourth ventricle in children, the spinal cord and cauda equina in adults, and much less commonly in the supratentorial compartment [3].

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High-grade gliomas (WHO grades III and IV) and especially glioblastomas are among the most difficult cancers to treat, with a dismal prognosis and poor response to chemotherapeutics [4]. This has been attributed to the blood-brain barrier (which forms a pharmacologic sanctuary), the expression of multidrug resistance proteins in malignant cells and associated capillaries [5], the genetic, molecular, and metabolic heterogeneity of glioma cells [1], a resistance mechanism to commonly used alkylating agents, and the ability of tumor cells to evade immune surveillance [6]. Furthermore, tumor stem cells within malignant gliomas have been linked to glioma development, perpetuation, and resistance to both chemotherapy and radiation, accounting for the failure of conventional therapies and tumor recurrence [7]. In addition, chemotherapy and radiation therapy may trigger several signal transduction pathways and toxic events to the tumor cells, such as direct DNA damage which apart from cell death can lead to mutations in the surviving tumor cells that might result in therapy-driven evolution of recurrent gliomas [8]. Herewith we discuss how to treat an individual patient with glioma, the chemotherapeutic drug-related toxicities and their management, and other potential useful approaches for glioma treatment that may emerge in the near future.

24.2 Systemic Chemotherapy for Brain Gliomas: Strategy and Technique

Because glioma cells infiltrate widely in the brain ahead of or independent of new vessel formation (angiogenesis), drug delivery can be highly compromised unless chemotherapeutic agents have a molecular weight of less than 600 Da in order to cross the blood-brain barrier [4]. The blood-brain barrier is formed by brain endothelial cells, which are connected by tight junctions and extremely high electrical resistivity that tend to keep the brain extracellular fluid free of complex organic compounds such as those found in many anticancer drugs.

K. Fountas, E. Z. Kapsalaki (eds.), *Epilepsy Surgery and Intrinsic Brain Tumor Surgery*,
https://doi.org/10.1007/978-3-319-95918-4_24

In addition to size and charge concerns, another shortcoming of the anticancer agents is the severe side effects on normal tissues and/or because their pharmacokinetics and biotransformation are too fast to permit distribution of chemotherapeutic agents at therapeutic levels within most tumors [9].

24.3 Low-Grade Astrocytoma

Based on the latest WHO 2016 classification, diffuse astrocytomas are now categorized into isocitrate dehydrogenase (IDH) wildtype, IDH-mutant, and not otherwise specific (NOS) in cases in which IDH evaluation cannot be performed [10]. The incidence of these tumors decreases progressively from childhood into late adult life. Although they have a prolonged natural history, indolent behavior, and may not need immediate therapy, these tumors always recur and often dedifferentiate into anaplastic astrocytomas or glioblastomas. Since it is difficult to perform prospective clinical trials with astrocytoma patients because they constitute a small number of glioma patients, gross total excision for both diagnostic and therapeutic purposes is the treatment of choice. Radical excision reduces the risk of malignant transformation. Patients over 40 years of age in need of subtotal excision of a tumor over 6 cm, the presence of neurologic deficits, and diffuse astrocytoma subtype have been associated with unfavorable outcomes, but further treatment had a beneficial effect in these patients [11].

Adjuvant radiotherapy for a total dose of 50.4 Gy is the accepted standard of care, since higher or lower doses were found to have similar effect to the higher dose with less toxicity [12, 13]. Thus, from a survival viewpoint, radiation following surgery is of value, especially for patients with three or more of the above risk factors. What is debatable, however, is whether the impairment in cognitive and emotional function secondary to irradiation for low-grade astrocytoma is worth the increase in lifespan. In this decision-making process, patient age, life-style expectations, and potential effects on cognitive and emotional function need to be considered for each patient.

Mounting evidence from molecular and genetic profiling of low-grade gliomas have resulted in more accurate prognosis assessment. The effectiveness of PCV (procarbazine, lomustine [CCNU] and vincristine) was assessed by RTOG 9802 (a phase III trial that randomized adults with low-grade glioma (LGG) to fractionated radiotherapy with or without six cycles of PC) and showed a substantial improvement in overall survival in the PCV arm (13.3 versus 7.8 years) [14]. Temozolomide (TMZ), owing to its favorable side-effect profile, may be effective in treating progressive WHO grade II astrocytomas. Repeat surgery was suggested for patients with wild-type IDH1 regardless of the histopathologic diagnosis. Although complete tumor resection is generally the goal in the management of these lesions, this can prove difficult to achieve because tumor margins may blend into the surrounding brain tissue. Nonetheless, recent evidence has shown that the median survival of low-grade astrocytomas is 7–10 years [15].

The author's approach has been to treat adults with contrast-enhanced low-grade astrocytomas with radiotherapy and chemotherapy postoperatively. This is based on three clinical observations: (1) in patients over 15 years, survival is inversely correlated to age at diagnosis; (2) noncontrast-enhanced low-grade astrocytomas have a better prognosis than contrast-enhanced low-grade astrocytomas (3.9 versus. 7.8 years' survival); and (3) 70% of patients with contrast-enhanced low-grade astrocytomas who received postoperative chemotherapy and irradiation survived nearly 7 years.

When low-grade astrocytomas first recur, approximately 50% have the original low-grade histology, while the rest recur as more aggressive anaplastic astrocytomas or glioblastomas [11].

24.4 Anaplastic Astrocytomas and Glioblastomas

Based on the latest WHO 2016 classification, anaplastic astrocytomas are now categorized into IDH-mutant, IDH-wildtype, and NOS categories. IDH-mutant cases have a more favorable outcome [10]. In anaplastic astrocytomas, the gains of treatment have been much greater. Standard therapy entails adjuvant radiotherapy up to 60 Gy after surgical excision. However, chemotherapy instead of radiotherapy may be used in some cases, especially when the long-term cognitive effects of radiotherapy are of concern. Upon recurrence, chemotherapy with either TMZ or PCV may be used. Recent evidence showed no difference in time to failure if chemotherapy or radiation was administered first and no significant difference between PCV or TMZ chemotherapy [16].

Based on the latest WHO 2016 classification glioblastomas are now categorized into IDH-wildtype, the most frequent (nearly 90% of cases) of which correspond to primary glioblastoma; IDH-mutant, which corresponds more frequently to secondary glioblastoma; and glioblastoma NOS, in cases in which IDH evaluation cannot be performed [10]. The role of surgery in glioblastoma is mainly cytoreduction, to relieve mass effect, to obtain tissue for establishing diagnosis, and to assess the tumor's molecular profile (LOH 1p/19q, MGMT promoter methylation, IDH mutation). Furthermore, the extent of resection has a prognostic significance [17]. An improvement in progression-free survival (PFS) and increase in the complete resection rate has been

verified when surgery is performed by 5-amino-laevulinic acid (5-ALA), a fluorescence that marks the tumor under blue light [18]. Gliadel wafer-bearing carmustine (BCNU) can be applied in situ only for patients in whom 90% or more of the tumor has been resected. This exposes the remaining tumor cells to a much greater concentration of BCNU compared to systemic administration. In a study, carmustine wafers increased median survival from 11.6 to 13.8 months in patients with newly diagnosed glioblastoma (GBM) [19]. However, in recurrent tumors carmustine wafers had no survival benefit.

The Stupp protocol consisting of external beam radiation and concomitant TMZ has become the gold standard. The use of a radiation dose of 60 Gy in conventional daily fractions of 1.7–2.0 Gy is based on data from clinical studies and on the radiation tolerance of normal brain tissue. Higher total doses by conventional (to 70 Gy) or hyperfractionated (to 80 Gy) regimens did not increase survival. Trials using 1.6–2.0 Gy three times per day have been conducted, but none has shown a survival benefit [20]. Concomitant TMZ consists of 75 mg/m^2/day, 7 days per week until the end of radiation therapy. One month later, six cycles of adjuvant chemotherapy starts. Every cycle consists of 5 days of TMZ repeated every 28 days. The dose is 150 mg/m^2/day for the first cycle and increases up to 200 mg/m^2/day in the following cycles. In a phase III trial of dose-dense TMZ at 100 mg/m^2, days 1 through 21 of a 28-day cycle showed no significant benefit compared to standard dosing in both PFS or overall survival (OS) [21]. With the Stupp protocol the median survival was 14.6 months compared to 12.1 months with radiotherapy alone. The 5-year survival rate was 9.8% compared to 1.9% with radiotherapy alone. The authors extend TMZ chemotherapy after the standard 6-month regimen until tumor recurrence. This has resulted in one study in an increase of the median survival from 16.5 to 24.6 months [22]. In the first phase II glioblastoma study that used this approach, TMZ achieved a 21% PFS at 6 months [2]. The addition of 13-*cis*-retinoic acid to TMZ improved PFS_6 to 32%; the addition of marimastat, a matrix metalloprotease inhibitor, moved PFS_6 to 39%. For BCNU with thalidomide PFS_6 was 27% [2].

Antioangiogenesis agents such as bevacizumab have been administered in addition to standard treatment for newly diagnosed GBM (AVAglio study), but although it showed improved PFS, there was no significant improvement in OS. Furthermore, the rate of adverse events was higher with bevacizumab than with placebos [23]. However, a retrospective analysis of AVAglio data reported that patients with IDH1 wild-type primary glioblastoma had better OS from first-line bevacizumab treatment than from placebo (17.1 versus 12.8 months) [24]. The addition of bevacizumab to standard glioblastoma treatment prolongs PFS and OS for patients with progressive disease who do not receive second-line therapy [25]. Another antioangiogenic agent, cilengitide, in a phase III trial showed no increase in either PFS or OS.

Assessment of MGMT status has a prognostic significance and assists in patient management. Patients with MGMT promoter methylation had 23.4 months median survival compared to 12.6 months in the nonmethylated group. The Stupp protocol in the unmethylated group increased survival from 11.8 to 12.6 months. Thus, alternative treatments for patients with nonmethylated MGMT are proposed as part of ongoing clinical trials. Recently, a phase II study, the GLARIUS trial, explored the efficacy of bevacizumab plus irinotecan as an alternative to TMZ in primary glioblastomas with nonmethylated MGMT. The primary end point was the PFS rate at 6 months. The results showed that PFS was increased from 42.6% with TMZ to 79.3% with bevacizumab plus irinotecan. Thus, PFS was prolonged for 3.7 months. However, no difference in OS was found, and this was attributed to the high crossover rate [26].

Another important issue constitutes the finding from several uncontrolled retrospective case series and a post-hoc analysis of an association between valproic acid (VPA) use and increased survival in patients with newly diagnosed glioblastomas.

A recent combined analysis of the effect of antiepileptic drug use and overall survival was performed in the pooled patient cohort of four randomized clinical trials. The results showed no difference in patients' outcomes between VPA and levetiracetam [27].

Since treatments for glioblastoma add little to survival, especially for the elderly, quality-of-life issues need to be addressed in this group. This is particularly true for patients over 60 years of age in whom median survivals are closer to 35 weeks [2]. This is not to say that surgery should not be carried out aggressively but is rather to express caution about expectations from radiation and chemotherapy. Patients over 70 years of age with reasonable Karnofsky performance status should receive hypofractionated radiotherapy such as 40 Gy in 2.66 Gy fractions over 3 weeks. Preliminary evidence suggests that concurrent and adjuvant TMZ might also be of benefit [28]. As with glioblastoma patients, age is an important variable that negatively influences survival of anaplastic astrocytoma patients. Unlike glioblastoma patients, however, chemotherapy can increase survival substantially.

24.5 Oligodendroglioma and Anaplastic Oligodendroglioma

Based on the WHO 2016 classification, the diagnosis of oligodendroglioma and anaplastic oligodendroglioma mandates the identification of both an IDH gene family mutation and combined whole arm losses of 1p and 19q (1p/19q

codeletion). NOS oligodendrogliomas are histologically typical oligodendrogliomas without the capability of testing IDH and 1p/19q codeletion. The term oligoastrocytomas is now strongly discouraged [10].

Regarding treatment, after surgical resection chemotherapy is the primary treatment modality. Radiotherapy is usually reserved for anaplastic transformation if it occurs. Chemotherapy with PCV given on a 29-day cycle (repeated every 6 weeks) is a standard treatment. Two randomized controlled trials reported that chemoradiotherapy with PCV doubled the median survival of patients with 1p/19q codeleted tumors compared to radiotherapy alone [29, 30]. Cairncross et al. [30] have conducted a series of consecutive phase II studies to examine the rate and duration of response of anaplastic oligodendrogliomas to PCV. Among 24 eligible patients, 38% achieved complete responses (CRs), 38% partial responses (PRs), and 17% stable disease (SD). The median time to progression was less than 25 months for CRs, 14 months for PRs, and 6.8 months for SD patients. Recent analysis showed that patients with 1p/19q noncodeleted IDH-mutated tumors also lived longer after chemoradiotherapy with PCV [31].

TMZ for recurrent anaplastic oligoastrocytoma also showed some efficacy [32–34]. In an EORTC study of 35 oligodendroglioma and oligoastrocytoma patients treated at first recurrence with TMZ, 29% had a CR, 26% a PR, and 31% SD; the 54% of responding patients had a median time to progression of 13.2 months; and the PFS_{12} for all patients was 40% [2]. Van Den Bent and colleagues found that 50% of oligodendroglioma and oligoastrocytoma patients initially responded to PCV chemotherapy, and of 28 patients 25% of oligodendroglioma patients at recurrence responded to TMZ with a median time to progression of 8 months [2].

24.6 Systemic Chemotherapy–Associated Complications: Avoidance and Management

The majority of chemotherapy regimens may produce toxicities that require reduction of dosages or cessation of the responsible chemotherapeutic agent. At times if the toxicity is not recognized early it cannot be reversed, further affecting the quality of life of the patient. Although several compounds have been reported as neuroprotective agents, few have been shown to be active against the chemotherapy-induced toxicity.

24.6.1 Temozolomide

Although TMZ shows many types of toxicities, the majority of them represent either grade 1 or 2 and are tolerable for patients. Fatigue, anemia, leukopenia, thrombocytopenia, and gastrointestinal troubles such as nausea and vomiting are exceedingly common [35, 36]. These may affect the quality of life of patients and thus aggressive monitoring of gastrointestinal toxicities and administration of prophylactic antiemetics may be needed. More toxicities are usually observed in concurrent chemoradiotherapy than in chemotherapy alone.

24.6.2 Vincristine

Vincristine is a neurotoxic agent and can produce dose-dependent and cumulative peripheral neuropathy. Among the most common symptoms and signs are paresthesias, loss of tendon reflexes, and progressive weakness. Less frequently reported are sensory impairment, cranial nerve palsies, gastrointestinal disturbances, and autonomic dysfunctions, including orthostatic hypotension, atonic bladder, and erectile dysfunction. In addition, the efferent olivocochlear system is usually affected by vincristine [37]. Seizures may also occur, and bihemispheric lucencies on brain MRI may be found. However, the latter are reversible after cessation of vincristine [38]. Abducens nerve palsy can be also a presenting sign of a toxic neuropathy associated with vincristine use [39].

24.6.3 Lomustine (CCNU)

Lomustine is an alkylating nitrosourea compound and highly lipid-soluble agent that can cross the blood-brain barrier. Chemotherapy-associated toxicity with this agent is generally mild, is more pronounced in females, and does not increase in older patients. The usual toxicities are gastrointestinal disturbances, hematologic toxicities, and renal impairment that may resolve after discontinuation [40].

24.6.4 Antiangiogenic Therapy

Bevacizumab, a recombinant humanized IgG1 monoclonal antibody, is the first antiangiogenic agent approved for clinical use in brain tumors; however, several treatment-associated toxicities have been reported. Hypertension and proteinuria are frequent toxicities. A three-fold increase of any grade hypertension by low-dose (<10 mg/kg/dose) bevacizumab has been reported, whereas high-dose (≥10 mg/kg/dose) bevacizumab increased such incidence by 7.5-fold [41]. Management of hypertension in these cases should follow the general guidelines for hypertension treatment. Other risk factors associated with hypertension should be assessed, but a single antihypertensive agent is typically sufficient to reduce blood pressure within normal limits [42]. Reversible posterior leukoencephalopathy syndrome has also been associated with antiangiogenic therapy and usually mani-

fests with headaches, confusion, and seizures. Cortical blindness is not a rare sequela. Hyperintensities predominating in the white matter can be seen in brain imaging. Symptoms can be reversible upon cessation of the agent. Another devastating toxicity is the increased risk of both systemic and intracerebral hemorrhage, which are common within the first 5 months of treatment. In a meta-analysis that included 12,617 patients, bevacizumab was associated with an increased risk of hemorrhage (RR 2.48 [95% confidence interval (CI)], 1.93–3.18) compared with the controls [43]. Antiangiogenic therapy also compromises wound healing and has been associated with bowel perforation.

24.7 Future Developments in Systemic Chemotherapy for Brain Gliomas

In human gliomas, expression of hepatocyte growth factor (HGF) receptor (HGFR or MET) was found in up to 29% of cases and is associated with higher grade and more serious clinical outcome. The anaplastic lymphoma kinase (ALK) is a tyrosine kinase that can potentially function as an oncogene. High-grade tumors such as glioblastomas and anaplastic oligodendrogliomas showed an increased expression of ALK relative to normal brain tissues [44]. This is important since crizotinib, an orally available ATP-competitive selective inhibitor of ALK and MET tyrosine kinases, can inhibit tyrosine phosphorylation on these receptors at nanomolar concentrations. Currently a phase Ib study evaluating the safety and activity of crizotinib with TMZ and radiotherapy in newly diagnosed glioblastomas is under way.

The *BRAFV600E* mutation occurs frequently in tumors such as pleomorphic xanthoastrocytomas, gangliogliomas, and pilocytic astrocytomas. It is found less frequently in glioblastoma. Inhibitors of B-Raf protein kinase activity may serve as efficacious drugs for treating patients with *BRAF V600E*-positive GBM. A case of complete response in a *BRAF V600E*-mutated pediatric glioblastoma to vemurafenib (BRAF inhibitor) therapy has been reported [45]. However, more studies are needed to explore the incidence of *BRAFV600E* mutation in this tumor type.

TRAIL is a proapoptotic molecule that induces apoptosis to varying degrees in different tumor cell types and to a lesser degree in normal cells. Furthermore, several agents have been found that sensitize cancer cells to TRAIL-mediated apoptosis [46]. TRAIL requires systemic delivery because of its short half-life. Over the last years recombinant human TRAIL/Apo2L has been tested in phases I, II, and III clinical trials. Regarding toxicity, this agent exhibited minimal adverse effects, and peak serum concentrations were identical to those seen with preclinical antitumor efficacy. Nevertheless, the clinical results were not encouraging. Thus, combination treatments are under way with this agent [47].

p38α Mitogen-activated protein kinase (MAPK) is activated in cancer cells and plays a pivotal role in tumor growth, invasion, metastasis, and resistance to chemotherapy. LY2228820 is a potent and selective inhibitor of the α- and β-isoforms of p38 MAPK and reduces phosphorylation of its cellular target, MAPK-activated protein kinase 2. In several in vivo cancer models, LY2228820 produced significant tumor growth delay in several cancers such as melanoma, non–small cell lung cancer, and glioma [48]. Currently a Phase I/II Study of LY2228820 with radiotherapy plus concomitant TMZ in the treatment of newly diagnosed glioblastoma is recruiting patients [ClinicalTrials NCT02364206].

Epidermal growth factor receptor (EGFR) overexpression and/or amplification can be found in up to 40% of primary GBM cases, the most frequent being the EGFRvIII. Cetuximab, a chimeric monoclonal antibody against EGFRvIII, failed to be more effective than bevacizumab and irinotecan alone in recurrent GBM [49]. ABT-414, an ABT-806 monomethyl auristatin F conjugate, has exhibited in vitro and in xenograph models of selective activity for cancer cells that overexpress wild-type or mutant forms of EGFR [50]. Based on these promising results a randomized phase II study of the EORTC Brain Tumor Group (EORTC Protocol 1410-BTG) study comparing ABT-414 alone or ABT-414 plus TMZ versus lomustine or TMZ for recurrent GBM is currently recruiting patients.

Conclusion

In this chapter we have referenced primarily newer articles and used our own experience to supplement the literature. Certainly, improvements in survival have been made in the treatment of gliomas over the last years. However, radiotherapy and chemotherapy have an impact on surviving patients, causing intellectual and emotional impairment because of toxicity to the CNS. Hopefully, in the near future more specific and selective therapies may emerge that will achieve better tumor control and less toxicities. Until then, we must be thoughtful, creative, and compassionate in our care of brain tumor patients so that we match patients with the most effective treatment that can help them achieve a long life with minimal toxicity.

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