Alternative Chemotherapeutic Agents: Nitrosoureas, Cisplatin, Irinotecan

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KEYWORDS

• Glioblastoma • Glioma • Chemotherapy • Cisplatin
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CHEMOTHERAPY FOR HIGH-GRADE GLIOMA

Before Food and Drug Administration (FDA) approval of temozolomide (TMZ, Temodar) for the treatment of high-grade gliomas in 2005, the mainstay of treatment focused on the use of cisplatin, irinotecan, and nitrosoureas alone and in combination. Decades of experience with these chemotherapies coupled with meta-analyses that provide evidence of significant improvement in survival when added to surgery and radiotherapy have established a position for chemotherapy in the treatment regimen of malignant gliomas.[1,2] With the establishment of TMZ concomitant with radiotherapy and adjuvant TMZ as the standard of care for the initial treatment of glioblastoma multiforme (GBM), the role for these chemotherapies has changed to that of one at the time of recurrence or progression.[3] In this article, the authors focus on the use of cisplatin, irinotecan, and the nitrosoureas in the era of TMZ and bevacizumab (Avastin). The assessment of outcomes across clinical trials is notoriously difficult. To facilitate some meaningful level of comparison, an effort was made to include like outcomes, such as overall survival (OS) and progression-free survival at 6 months (PFS-6), in addition to the radiographic response.

CISPLATIN

Cisplatin (CDDP) is a platinum-based inorganic metal complex that acts as a DNA-intercalating agent forming DNA intrastrand and interstrand cross-links, along with DNA-protein cross-links. Apoptosis and cell growth inhibition are induced as a result of the cross-links. Cisplatin has been shown to have antitumor activity against several human malignancies. The use of CDDP in brain tumors stems from its ability to cross the blood-brain barrier.[4,5] Before the advent of TMZ, researchers investigated cisplatin's use in the treatment of malignant gliomas, primarily in concert with other chemotherapeutic agents and radiotherapy.

Upfront Treatment with Cisplatin

- Cisplatin has a long history of therapeutic use in high-grade gliomas. In clinical use, cisplatin is often given in combination with other chemotherapies. In 1992 Yung and colleagues[5] conducted a single-arm study to test the efficacy of using alternating courses of 1,3-bis(2-chloroethyl)-1 nitrosourea (BCNU, carmustine) and CDDP in conjunction with radiation therapy after surgical resection to treat primary malignant

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glioma. Patients with histologic diagnosis of GBM, anaplastic astrocytoma, and anaplastic oligodendroglioma underwent surgical resection or biopsy. Radiotherapy was initiated over 6 to 7 weeks, and chemotherapy was started during the first week of radiotherapy. A total of 33 patients entered the analysis, with a median time to tumor progression of 32 weeks for patients with glioblastoma and 50 weeks for those with anaplastic glioma. Median survival time was 55 weeks for glioblastoma and 110 weeks for anaplastic glioma.[5] The 18-month survival rate was 55% overall. The results of this study suggested that BCNU alternating with CDDP in conjunction with radiotherapy is safe and also indicated that there may be benefits in OS over radiotherapy with BCNU alone.

- Lassen and colleagues[6] investigated the use of CDDP as part of a combination therapy for newly diagnosed GBM. This study was a single-arm phase II trial examining the efficacy of a combination of cisplatin, BCNU, and etoposide, followed by radiation. All patients underwent tumor resection, and then chemotherapy was started 2 to 4 weeks after surgery. The primary end point of the study was response to chemotherapy using the MacDonald criteria.[7] Radiographic partial response was achieved by 32% of patients, 39% had stable disease, and 29% had progressive disease. Complete response was not achieved in any patient. Median time to progression was 7.6 months and median survival was 11.4 months.[6] The investigators concluded that although the survival benefit fell short of historical data, a potential benefit from the regimen used in the study was the shorter total treatment time of preradiation chemotherapy making it potentially less cumbersome.
- In 2009 Silvani and colleagues[8] conducted a retrospective study examining the clinical effectiveness of using the combination of CDDP and BCNU as the first-line management of GBM. One hundred sixty patients received chemotherapy and radiotherapy in a tandem fashion. After chemotherapy, radiotherapy was administered at 1.8 to 2.0 Gy/d to a total of 60 Gy. The next cycle of chemotherapy was started after radiotherapy was completed and subsequent cycles started every 6 weeks for a total of 5 cycles. Patients in this study had a median PFS of 7.6 months and median OS of 15.6 months. Although the survival results of the study are comparable with those of Stupp and colleagues[3] with TMZ, regarding the clinical benefit of cisplatin and BCNU, the toxicities were comparably worse.[8] The results of this large trial of CDDP in GBM are compared in **Table 1**.

Cisplatin Toxicity

The main difficulty in the use of cisplatin is its toxicity profile. Hematologic side effects are the most common and tend to be the most severe. Hematologic toxicity was significant with grade 4 leukopenia and thrombocytopenia occurring in 10% and 57% respectively.[6] Ototoxicity is also frequent, making this a drug that must be used with caution. Clinically significant hearing loss and tinnitus can be seen in 13% to 19% of patients at 6 months after treatment with cisplatin, with 36% having evidence of sensorineural hearing loss on audiogram testing.[10]

IRINOTECAN

The prodrug irinotecan (CPT-11; Camptosar; 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyl-20-S-camptothecin) is a water soluble alkaloid derivative of camptothecin that is extracted from the Chinese tree, *Camptotheca acuminata*.[11] Irinotecan is largely metabolized in the liver by carboxylesterase enzymes to the active 7-ethyl-10-hydroxycamptothecin (SN-38), which functions

Table 1
Comparison of cisplatin-based chemotherapies in high-grade gliomas

Trial	Tumor Type	Timing of Treatment	Number of Patients	Chemotherapy	Median PFS (wk)	Median OS (wk)
Yung et al,[5] 1992	Grade III/IV	Upfront	33	BCNU + CDDP	50/32	110/55
Shinoda et al,[9] 1997	GBM	Upfront	30	CDDP	16	60
Lassen et al,[6] 1999	GBM	Upfront	27	BCNU + CDDP + Etoposide	30.4	45.6
Silvani et al,[8] 2009	GBM	Upfront	160	BCNU + CDDP	30.4	62.4

as a topoisomerase I inhibitor.[12,13] The inhibition of the enzyme produces DNA damage via interference with DNA transcription, replication, and repair.[14] Activity against central nervous system (CNS) tumors was initially demonstrated by Hare and colleagues[15] using xenografts derived from childhood and adult high-grade gliomas.

Irinotecan in Recurrent Disease

- The use of irinotecan as a single agent has had mixed results and is complicated by interactions with CYP inducers. A prospective phase II study by Chamberlain[14] of CPT-11 in 40 patients with recurrent supratentorial GBM failed to show a tumor response to treatment although the dosages used, 400 to 500 mg/m^2 every 3 weeks, were suboptimal.[14] Anticonvulsant medications with cytochrome P450–inducing features upregulate chemotherapy catabolism.[14] It was suggested that the dosages used may have been insufficient because more than 60% of patients were on anticonvulsant therapy.
- Only 48% of patients enrolled in the Friedman and colleagues'[11] phase II study of recurrent or progressive malignant gliomas received enzyme-inducing antiepileptic drugs. In this population of 80% GBM, the 60 patients enrolled experienced a median time to tumor progression of 12 weeks and a median estimated survival of 43 weeks. Confirmed partial responses on magnetic resonance imaging were seen in 15% of patients, whereas stable disease was achieved in 55% of radiographic responses.[11]

Enzyme-Inducing Antiepileptic Drugs Affect the Dosing of Irinotecan

- The effects of receiving enzyme-inducing antiepileptic drug (EIAED) therapy were taken into account in the phase II North American Brain Tumor Coalition (NABTC) study in recurrent malignant gliomas treated with irinotecan.[16] Irinotecan was administered at 350 mg/m^2 every 3 weeks in those not on EIAED therapy and 750 mg/m^2 in those on EIAED therapy until progression or a total of 12 months of treatment. Patients with GBM accounted for 75% of 51 total patients enrolled. Overall, 17.6% of the patients were PFS-6. A partial radiographic response was seen in 5.8%, stable disease in 33%, and immediate progression was seen in 58.8% of the group.[16] The predetermined PFS-6 efficacy of at least 30% was not met, leading the study investigators to conclude that efficacy was not established in this population.[16]
- In the New Approaches to Brain Tumor Therapy (NABTT) 97-11 study, they attempted to mitigate the varied doses of prior trials and the influence of EIAED therapy by treating at the maximum tolerated dose (MTD) of irinotecan for those patients on EIAED therapy (group A) and those who were not (group B).[17] Group A was treated with an infusion of 411 mg/m^2 every week for 4 consecutive weeks out of a 6-week cycle, whereas group B received 117 mg/m^2. The primary end point was the radiographic response: 6% experienced a complete response, there were no partial responses, 28% had stable disease, and another 28% experienced disease progression during treatment. Median PFS was 7.3 months, PFS-6 was 56%, and median OS was 10.4 months.[16] Phase I of this trial was closed after 18 patients because of the failure to meet the minimum requirement of more than 2 responses.[17]

Irinotecan Toxicity

- Common toxicities seen in single-agent CPT-11 were diarrhea, nausea and vomiting, and neutropenia.[11,15,17] In CNS disease, toxicities were less frequently seen than in colorectal studies of similar doses because of the increased metabolism of CPT-11 caused by the CYP450-inducing antiepileptic drugs with subsequent increases in irinotecan clearance.[11,14] The frequency of grade 3/4 diarrhea was 33.7% and grade 3/4 neutropenia was 28% in colorectal studies.[18] In those patients treated at the MTD, grade 3/4 toxicities were encountered in 67% of patients.[17] Anticholinergic symptoms are frequently seen and commonly pretreated with atropine during infusion. The equivocal efficacy data on single-agent CPT-11 led to postulation about its role in combination therapy with newer treatments.

Irinotecan in the TMZ Era

With the statistically significant survival benefits of the alkylating agent, TMZ, along with minimal toxicity, the Stupp regimen has become the standard care for newly diagnosed GBM.[3] The role of irinotecan in addition to TMZ has been investigated in the NABTT study along with the pharmacokinetics of the combination in patients receiving EIAED therapy.[12]

- In this dose-escalation study of irinotecan combined with TMZ, the starting dose of irinotecan was 350 mg/m^2, which was escalated in 50 mg/m^2 increments to 550 mg/m^2. The MTD in the study was 500 mg/m^2.[12] Twenty-six out of 33 patients had GBMs, one was diagnosed with gliosarcoma and the remainder of the patients had anaplastic gliomas. Radiographic complete response was seen in 6%, partial response in 19%, stable disease in 36%, and progressive disease in 39%.[12]
- Quinn and colleagues[19] studied the use of TMZ plus irinotecan in 42 newly diagnosed patients with GBM before treatment with radiotherapy at the end of cycle number 3 in a phase II trial. Irinotecan was infused on days 1, 8, 22, and 29 of each cycle, with those on EIAED therapy receiving 325 mg/m^2 and 125 mg/m^2 for those not receiving EIAED therapy. The radiographic response consisted of 19% partial responses and 50% with stable disease.[19] Median PFS was 3.1 months and median OS was 13.8 months. Disappointingly, the study failed to meet the predetermined response rate of greater than or equal to 26% required to proceed with a phase III trial and had grade 3/4 adverse events of up to 36%.[19] Of interest, the level of O^6-methylguanine-DNA methyltransferase (MGMT) expression in this study failed to show a statistically significant relationship between PFS and OS as would be expected from treatment with TMZ.

Irinotecan in the Bevacizumab Era

The introduction of the humanized immunoglobulin G_1 monoclonal antibody that selectively inhibits vascular endothelial growth factor, bevacizumab, has changed the way chemotherapies, such as irinotecan, are used. FDA approval for bevacizumab in the recurrent setting was established in 2009 based on response data from the following study.

- The prospective phase II trial by Vrendenburgh and colleagues[20] evaluated bevacizumab plus irinotecan in 35 patients with recurrent GBM initially treated with radiotherapy and concurrent TMZ. Two dosing schedules were used, most patients received bevacizumab at 10 mg/kg and irinotecan every 2 weeks, with those on EIAEDs receiving 340 mg/m^2 and those not on EIAEDs receiving 125 mg/m^2. There was no difference between the 2 groups statistically. A radiographic partial response was seen in 57% of patients by the Macdonald criteria.[7] The median PFS was 24 weeks and median PFS-6 was 46%, far exceeding the predetermined 20% decision rule for effectiveness. The 6-month OS was 77% and the median OS was 42 weeks.[20]
- The benefit of bevacizumab alone or in combination with CPT-11 was evaluated by Friedman and colleagues[21] in a phase II, multicenter, noncomparative trial in recurrent glioblastoma. The PFS-6 rates were 42.6% and 50.3%, and the median OS times were 9.2 months and 8.7 months, respectively, for bevacizumab alone and bevacizumab/CPT-11 groups.

NITROSOUREAS

Nitrosoureas are alkylating agents that function by cross-linking DNA. As a group, the high lipid solubility of nitrosoureas promotes crossing of the blood-brain barrier. Before TMZ, radiotherapy plus nitrosoureas was the standard of care for the treatment of GBM.[22] The most commonly used nitrosoureas in clinical practice today are 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosurea (CCNU, lomustine) and BCNU. In a meta-analysis of properly randomized trials comparing radiotherapy alone with radiotherapy plus chemotherapy consisting largely of nitrosoureas in high-grade gliomas established a role for chemotherapy in the treatment regimen of gliomas after it was shown that chemotherapy significantly improved outcomes.[2] There was a statistically significant increase in PFS (overall hazard ratio [HR] of 0.83) (P<.0001) and a significant increase in OS (HR of 0.85) (P<.0001) seen with the addition of chemotherapy.[2] Nitrosoureas are commonly used as modern, standard second-line chemotherapies and are frequently relegated to the standard arm in randomized phase II trials against novel agents. Multiple nitrosourea-based polychemotherapy regimens have largely been unsuccessful in increasing efficacy as compared with single-agent nitrosourea chemotherapy.

CCNU

The chemotherapy CCNU is a derivative of 1-methyl-1-nitrosourea. CCNU is a lipid-soluble, nonionized, aqueous insoluble, oral chemotherapy that, because of high lipid solubility, is able to pass the blood-brain barrier.[23] With a wide spectrum of antitumor activity, CCNU was eventually used to treat brain tumors. CCNU is one of the few

chemotherapeutic agents that are FDA approved in the treatment of GBM.

- The benefits of CCNU in place of and in addition to radiation were explored in an early randomized trial by Reagan and colleagues.[24] Sixty-three patients with high-grade gliomas at a single institution were randomized into 3 groups receiving radiotherapy alone, CCNU, or combined radiation therapy and CCNU. The group receiving chemotherapy alone experienced the lowest OS with a median 6.6 months survival. Those receiving radiotherapy consisting of whole brain irradiation had a median survival of 11.5 months. Lastly, the combined radiation and chemotherapy group demonstrated a median survival of 12.0 months.[24]
- In the phase II study by Rosenblum and colleagues,[23] patients were treated with 130 mg/m^2 every 6 weeks, and a remission rate of 37% for all patients was seen. This finding compared favorably with remission rates of 40% to 50% that were seen in earlier studies with BCNU. The results of CCNU therapy in several trials are illustrated in **Table 2**.

CCNU in the TMZ Era

- The use of CCNU plus TMZ was evaluated in the study by Herrlinger and colleagues[25] in 31 patients with newly diagnosed glioblastoma given chemotherapy concomitant with radiotherapy. The median PFS was 9 months and the PFS-6 was 61.3%, which was higher than the predefined efficacy criteria of 53.3%. The median survival time was 22.6 months, with 71% of patients surviving at 1 year and 44.7% surviving at 2 years.[25]

MGMT Methylation Status

- The association of MGMT promoter methylation with a favorable outcome in patients with glioblastoma treated with the alkylating agent TMZ has been well described.[28] MGMT methylation status was available for the determination by methylation-specific polymerase chain reaction in 19 tumors in the Herrlinger study.[25] The favorable methylation of MGMT was associated with significantly longer PFS and median survival times. The PFS was 19 months in those tumors with methylated MGMT as compared with 6 months in those with unmethylated tumors (P = .014).[25] The median survival time was not reached in the methylated MGMT group at 24 months as compared with 12.5 months in those unmethylated tumors.[25] These findings support the presumed similar effects on survival for nitrosoureas seen with TMZ and MGMT promoter methylation, given both agents affect the O^6-position of guanine.

CCNU Toxicity

- Early studies with CCNU in malignant brain tumors in 26 consecutive patients admitted to the Baltimore Cancer Research Center between 1970 and 1971 show that CCNU is well tolerated.[23] Immediate toxic effects, beginning 4 to 6 hours after treatment, consisted of nausea and vomiting in 70% of patients. Infrequent anorexia and rare fatigue were noted. Transient thrombocytopenia begins after the first week and reaches a nadir in the third week, before recovering to near baseline values by the fifth week. Treatment-limiting and dose-limiting delayed hematological toxicity were encountered. Nearly half of the

Table 2
Results of various trials using CCNU in GBM

Trial	Tumor Type	Timing of Treatment	Number of Patients	Chemotherapy	Median PFS (wk)	Median OS (wk)
Reagan et al,[24] 1976	HGG	Upfront	63	CCNU	—	46
Herrlinger et al,[25] 2006	GBM	Upfront	31	CCNU + TMZ	36.0	90.4
Wick et al,[26] 2010	GBM	Recurrent	266	CCNU (vs enzastaurin)	6.4	28.4
Ballman et al,[27] 2007	GBM	Upfront	1348	CCNU + others[a]	21.2	40.8

[a] Ballman et al is a pooled analysis of 11 North Central Cancer Treatment Group (NCCTG) trials for newly diagnosed GBM.

patients developed mild transient elevations of transaminases, alkaline phosphatase, and lactate dehydrogenase in nearly one-half of the patients.[23] The toxicity of CCNU is largely hematologic and cumulative in nature.

- When CCNU was given concomitantly with TMZ, the dose was adjusted for hematologic toxicity in 12.9% of the patients.[25] The World Health Organization grade 4 leukopenia was seen in 10% of the patients, thrombocytopenia in 16%, and anemia in 3%. One case of grade 2 pulmonary fibrosis was seen; 12.9% of the patients developed elevation of transaminases to levels consistent with drug-induced hepatitis.[25]

BCNU

BCNU is an intravenously administered nitrosourea that functions as an alkylating agent at the O^6 position of guanine, forming cross-linking between DNA strands resulting in impairment in DNA duplication and protein transcription.[13] A meta-analysis of several studies involving BCNU has demonstrated a statistically significant PFS and OS improvement in the treatment of GBM.[1,2] BCNU is one of the few chemotherapeutic agents that are FDA approved in the treatment of GBM.

BCNU Comparison with Temozolomide

- In a retrospective analysis of BCNU versus TMZ in newly diagnosed patients with GBM, Vinjamuri and colleagues[29] reported on the use of BCNU given intravenously every 8 weeks at 200 mg/m^2 for a maximum of 8 cycles concomitant with radiation in comparison with TMZ given concomitant with radiotherapy and adjuvantly up to 2 years. The median PFS for the 2 groups was not significant, with a median PFS of 7.7 months in the BCNU group and 5.2 months in the TMZ group ($P = .8$). Median OS curves were significantly different, with 11.5 months in the BCNU group and 15.9 months in the TMZ group. The BCNU and TMZ groups had a 1-year survival of 44% and 64% respectively. The 2-year survival for BCNU was 9% and 36% for TMZ.[29]

BCNU in Recurrent Disease

- Reithmeier and colleagues[30] recently investigated the use of BCNU in recurrent GBM after the initial treatment with radiotherapy and TMZ. This retrospective analysis looked at 35 patients with recurrent or progressive GBM treated with BCNU 80 mg/m^2 on days 1 through 3 every 8 weeks for a maximum of 6 cycles. Radiographic complete responses were not seen in any patient, 5.7% had a partial response, 54.3% were observed to have stable disease, and 31.4% developed progressive disease after the first cycle of BCNU. Median PFS was 11 weeks, PFS-6 was 13%, median OS was 22 weeks, and 6-month OS was 43%.[30]
- In a multicenter Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO) trial, the use of BCNU plus irinotecan was evaluated in recurrent or progressive GBM after first-line TMZ chemotherapy and radiotherapy.[13] BCNU 100 mg/m^2 was intravenously given every 6 weeks with irinotecan 175 mg/m^2/wk for 4 out of 6 weeks for a maximum of 8 cycles in a total of 42 patients. There were no radiographic complete responses, 21.4% partial responses, and 50% exhibited stable disease. The median time to progression was 17 weeks and the PFS-6 was 30.3%. The median survival time was 11.7 months, with 71% of patients alive at 6 months and 44.1% alive at 12 months[13]

BCNU Toxicity

- Sclerosis of the veins is a frequent long-term sequelae of administration of intravenous BCNU.[22] Fatigue and lethargy are common and can be seen as a cause of treatment discontinuation even in the absence of tumor progression. Grade 4 pulmonary toxicities complicate treatment in 5% of cases treated with BCNU.[31] Decreased carbon monoxide diffusing capacity was seen in 14.3% of patients, with one case of acute pulmonary reaction seen in one study of 49 patients.[29]

BCNU WAFERS

BCNU wafers (poly[carboxyphenoxy-propane]sebacic acid) anhydride (Gliadel) wafers contain BCNU at 3.85% concentration. Biodegradable BCNU wafers are implanted into the tumor resection cavity at the time of surgery whereby they slowly release BCNU over a 2- to 3-week period.[32] The surgeon may implant up to 8 wafers in the resection cavity, depending on the cavity size. Based on the phase III trial by Westphal and colleagues,[32] BCNU wafers became the only interstitial chemotherapy approved for malignant glioma.

Use of BCNU Wafer Alone

- In the prospective, randomized, placebo-controlled, multicenter, multinational, double-blind trial, the effectiveness of BCNU wafers was assessed in 240 patients at the time of the first surgical resection with an intraoperative abnormality of the malignant glioma.[32] Study patients received standard radiation to the tumor site; however, systemic chemotherapy was prohibited. Median survival time was 13.9 months for the BCNU wafer group and 11.6 months for the placebo group, a statistically significant difference. The median survival within the GBM subgroup treated with BCNU wafers was 13.5 months compared with 11.4 months in the placebo wafer group, a difference that was not statistically significant. PFS was not statistically different between both treatment groups.[32]
- The long-term follow-up by Westphal and colleagues[33] followed the same group of 240 patients with malignant glioma to assess the 1-, 2-, and 3-year event rates. The proportion surviving at the 3-year point was statistically significant at 9.2% in the BCNU group versus 1.7% in the placebo wafer group. In the GBM subgroup, the median survival was 13.1 months in the BCNU wafer-treated group compared with 11.4 months in the placebo group, a non-statistically significant difference even after Cox proportional hazards model was performed to account for possible prognostic factor imbalances between the groups (**Fig. 1**).[33]

Use of BCNU Wafer with Chemotherapy

- The initial trials using BCNU wafers prohibited the use of adjuvant chemotherapy. The single-institution retrospective study by McGirt and colleagues[34] evaluated the added benefit of concomitant TMZ in addition to BCNU wafers after primary resection of GBM. All patients underwent surgical resection and adjuvant radiotherapy. Patients treated before the initiation of the Stupp protocol TMZ at the institution were evaluated and compared with those who received TMZ in addition to BCNU wafers placed at surgery. The median OS in the radiation + TMZ + BCNU wafer group was significantly improved compared with the radiation + BCNU wafer group: 21.3 months versus 12.4 months. The 2-year OS was 39% versus 18% respectively for the treatment group as compared with the control and was independently associated with improved OS. However, when surgery was controlled for with only those patients with gross total resection receiving radiation + TMZ + BCNU wafers were compared with those receiving radiation + TMZ, the median survival was not significant.[34]

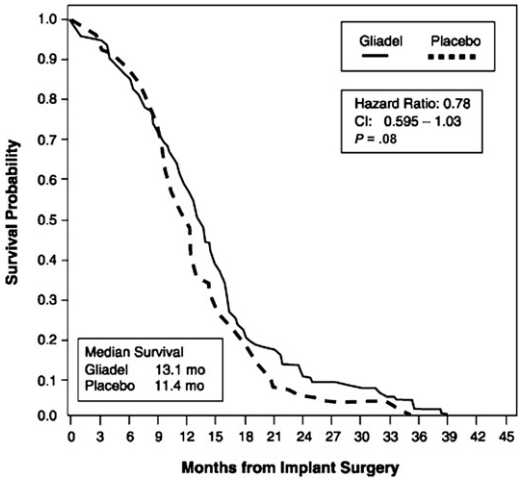

Fig. 1. GBM population. Survival curve for the subset 207 patients with GBM. The median survival time was not significantly increased among the GBM subset ($P = .08$). CI, confidence interval. (*Data from* Westphal M, Ram Z, Riddle V, et al. Gliadel wafer in initial surgery for malignant glioma: long-term followup of a multicenter controlled trial. Acta Neurochir 2006;148: 269–75. Used with permission Springer publishing.)

BCNU Wafer Toxicity

- BCNU wafers are generally well tolerated with adverse events profile similar to that of the placebo group in the Westphal and colleagues[32] randomized, double-blind, placebo-controlled trial. Only intracranial hypertension is seen more often in the BCNU wafer group, occurring as a late event generally greater than 6 months after implantation. Seizures, intracranial infections, and healing abnormalities were not seen more commonly in the BCNU wafer group than the placebo wafer group.[32] When added to TMZ and radiation, BCNU wafers resulted in significantly increased incidence of myelosuppression: 23% versus 0%.[34] In the era of antiangiogenic treatments, such as bevacizumab, with well-described impairments in healing, caution should be exercised in combining these 2 treatments.

FOTEMUSTINE

Fotemustine (diethyl-1-[3-(2-chloroethyl)-3-nitrosoureido]-ethylphosphonate) is a third-generation chloroethylnitrosourea, historically used less frequently than CCNU or BCNU. The agent is highly lipophilic, readily crossing the blood-brain barrier owing to the addition of the phosphoalanine carrier group.[31] Clinical studies suggest a role for fotemustine in the treatment of progressive GBM.[31] The activity of this agent has been evaluated in the TMZ era in recurrent GBM trials.[31,35,36] The activity of various chemotherapies in the recurrent GBM after the initial standard of care treatment with radiotherapy and concomitant TMZ are shown in **Table 2**.

Fotemustine Use in Recurrent GBM

- Scoccianti and colleagues[35] evaluated the fotemustine in 27 patients with recurrent glioblastoma pretreated with temozolomide. There were radiographic partial responses in 29.6% of patients, stable disease in 18.5%, and 51.8% showed disease progression. The median PFS was 5.7 months, PFS-6 was 48%, and PFS at 1 year was 18.5%. Median survival from the time of first recurrence was 9.1 months and median OS was 21.2 months. Survival from the first diagnosis at 1 year and 2 years were 92.5% and 46% respectively.[35]
- Recurrent GBM was treated with fotemustine 100 mg/m^2 infused on days 1, 8, and 15, followed by a 4- to 6-week rest period during induction. Maintenance fotemustine therapy was administered at 100 mg/m^2 every 3 weeks until progression.[36] Fifty patients were enrolled with 2% complete responses, 16% partial responses, 44% stable disease, and 38% progressive disease. A measure of efficacy control Complete Response + Partial Response + Stable Disease (CR+PR+SD) was 62%. The median PFS was 6.1 months, the PFS-6 was 51.5%, and the PFS at 1 year was 35.5%. The median survival from time of first relapse was 8.1 months, median OS was 24.5 months, and survival at 1 year and 2 years from diagnosis were 80.7% and 51.0%, respectively (**Table 3**).[36]

Fotemustine and MGMT Methylation Status

- Brandes and colleagues[31] evaluated fotemustine in recurrent or progressive glioblastoma in 43 patients. On radiographic review, 7.1% experienced partial responses, 34.9% had stable disease with a disease control rate (PR+SD) of 42.5%. The disease control rate was statistically greater in patients who were MGMT methylated (75.0%) compared with the unmethylated MGMT promoter (34.6%). The median PFS was 1.7 months, the PFS-6 was 20.9%, and median OS was 6 months.[31]

Fotemustine Toxicity

- Fotemustine was well tolerated in general, with grade 2 transaminase elevations in 4%, grade 3 thrombocytopenia in 8%, grade 3 anemia in 2%, grade 3 lymphopenia, and grade 4 neutropenia in 2%.[36] Grade 3/4 toxicities were found in 14% of cases. Toxicities increased to grade 3/4 thrombocytopenia in 20.9% and grade 3/4 neutropenia in 16.3% during the induction phase of the treatment.[31]

Table 3
Chemotherapies in GBM after initial treatment with radiotherapy and concomitant TMZ

Trial	Tumor Type	Timing of Treatment	Number of Patients	Chemotherapy	Median PFS (wk)	Median OS (wk)
Brandes et al,[13] 2004	GBM	Recurrent/ progressive	42	BCNU + CPT-11	17.0	46.8
Reithmeier et al,[30] 2010	GBM	Recurrent	35	BCNU	11	22
Brandes et al,[31] 2009	GBM	Recurrent/ progressive	43	Fotemustine	6.8	24.0
Scoccianti et al,[35] 2008	GBM	Recurrent	27	Fotemustine	22.8	36.4
Fabrini et al,[36] 2009	GBM	Recurrent	50	Fotemustine	24.4	32.4

SUMMARY

Irinotecan, cisplatin, and nitrosoureas have a long history of use in brain tumors, with demonstrated efficacy in the adjuvant treatment of malignant gliomas. In the era of TMZ with concurrent radiotherapy given as the standard of care, the use has shifted to that of treatment at progression or recurrence. Now with the widespread use of bevacizumab in the recurrent setting, irinotecan and other chemotherapies are seeing use in combination and alone in the recurrent setting. Despite future advancements in biologic and targeted agents, the activity of these chemotherapeutic agents in brain tumors will likely ensure a place in the armamentarium of neuro-oncologists for years to come.

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