Phase 2 study of BCNU and temozolomide for recurrent glioblastoma multiforme: North American Brain Tumor Consortium study¹

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The purpose of this study was to evaluate the activity, measured in terms of progression-free survival (PFS) and response rates, of 1,3-bis(chloro-ethyl)-1-nitrosourea (BCNU) plus temozolomide in adult patients with recurrent glioblastoma multiforme. The phase 2 dose and schedule for this trial was BCNU 150 mg/m² i.v. followed in 2 h by temozolomide 550 mg/m² as a single oral dose. Treatment was repeated every 6 weeks for up to 8 cycles unless tumor progression was documented. The

primary end point was PFS at 6 months (PFS-6). Response was a secondary end point, measured by MR imaging, neurological status, and steroid requirements prior to each 6-week cycle. The median age of eligible patients was 53, and 89.5% had no prior chemotherapy. All patients were evaluable for toxicity and time to progression. The PFS-6 was 21%. Overall survival was 68% at 6 months and 26% at 1 year. The MRI response for 36 patients was 2 partial responses, 2 minor responses, 19 cases of stable disease, and 13 immediate progressions. Median survival was 34 weeks, and median PFS was 11 weeks. Toxicity was primarily myelosuppression; no toxic deaths occurred. Historical phase 2 study data in this patient population show a PFS-6 of 15%. Recent data for use of temozolomide alone have shown a PFS-6 of 21%. We conclude that BCNU plus temozolomide when used in these doses and schedule has only modest activity, with significant toxicity, and appears to be no more effective than single-agent temozolomide. *Neuro-Oncology* 6, 33–37, 2004 (Posted to *Neuro-Oncology [serial online]*, Doc. 03-030, October 29, 2003. URL <http://neuro-oncology.mc.duke.edu>; DOI: 10.1215/S1152 8517 03 00030 9

Received June 26, 2003; accepted August 26, 2003.

¹ This study was supported by the following grants: CA62399, CA62422, CA62412, CA62407, CA62455, CA62405, CA62426, CA62399, and CA62421 as well as the GCRC grants M01-RR00079, M01-RR00633, M01-RR00056, M01-RR00042, and M01-RR03186.

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³ Abbreviations used are as follows: AGT, O⁶-alkylguanine-DNA alkyltransferase; BCNU, 1,3-bis(chloro-ethyl)-1-nitrosourea; DCLO, carbon monoxide diffusion capacity; GBM, glioblastoma multiforme; MTD, maximum tolerated dose; PFS, progression-free survival.

The treatment of recurrent glioblastoma multiforme (GBM)³ has been largely unsuccessful, and new treatment strategies are necessary (Fine, 1994). We previously reported our results using the combination of BCNU and temozolomide in a phase 1 study for patients with recurrent malignant glioma (Schold et al., 2000). The recommended phase 2 dose and schedule were 1,3-bis(chloro-ethyl)-1-nitrosourea (BCNU) 150 mg/m² i.v. followed in 2 h by temozolomide 550 mg/m² by mouth repeated every 6 weeks. The rationale for studying this combination was based on preclinical models that suggested therapeutic synergy as well as schedule-dependent toxicity. Plowman et al. (1994), using a human glioma xenograph model in athymic mice, reported that the use of temozolomide given 2 h before BCNU was more likely to cause the mice to die from the toxicity of the treatment than was treating animals in the reverse sequence. However, the therapeutic benefit was similar. The human phase 1 trial evaluated both schedules, namely, temozolomide given prior to or following BCNU. The maximum tolerated dose (MTD) for both drugs, when BCNU was given first, was 1 dose level higher than for the reverse sequence, when temozolomide was given before BCNU. Because higher doses of both drugs were tolerated in this sequence, we began a phase 2 trial using this sequence. This report details our results for the combination in patients with recurrent GBM. The objectives of this study were to evaluate the activity, measured in terms of progression-free survival (PFS), to estimate the response rate of BCNU plus temozolomide in recurrent GBM, and to further assess toxicity of this regimen. The primary end point was PFS at 26 weeks.

Patients and Methods

Eligible patients had to be aged 18 years or older with a documented recurrent or progressive grade IV astrocytoma including GBM or gliosarcoma, which required an increase in tumor size on sequential imaging by at least 25%, measured by cross-sectional diameters of the enhancing lesion. All patients had to have measurable or evaluable disease. If on steroids, the dose had to be stable for at least 72 h prior to registration. Patients with prior treatment that included interstitial brachytherapy or radiosurgery had to have confirmation of true tumor progression based upon glucose PET imaging or surgical confirmation. All pathology was confirmed centrally at the University of California at San Francisco. Prior radiation had to be completed at least 6 weeks before treatment, and no more than one prior chemotherapy was allowed. Prior treatment with a nitrosourea or temozolomide was not allowed. The on-study Karnofsky performance status had to be 60 or greater. Baseline laboratory requirements included the following minimum values.

White blood cell count >3500/mm³
 Absolute neutrophil count >1500/mm³
 Platelets >125,000/mm³
 Hemoglobin >9 g%

Serum creatinine <1.5 mg/dl
 Serum bilirubin <1.5 mg/dl
 Serum glutamic-oxaloacetic transaminase <2 times the institutional upper normal limit
 Carbon monoxide diffusion capacity (DLCO) of >80% of the expected value

Patients were excluded if they were pregnant or nursing or had a concurrent diagnosis of cancer within the preceding 5 years, excluding adequately treated squamous cell or basal cell carcinoma of the skin, in situ cervical cancer, or other stage I or II cancer from which the patient was currently in complete remission. All patients were informed of the investigational nature of this study and had to give and sign written informed consent in accordance with institutional and federal guidelines. Eligible patients were registered with the Data Management Center of the North American Brain Tumor Consortium prior to treatment. Patients were treated as follows.

- BCNU 150 mg/m² given intravenously day 1, 2 h prior to temozolomide
- Temozolomide 550 mg/m² given orally on day 1
- Treatment cycle repeated every 6 weeks for up to 8 treatment cycles

Patients were retreated every 6 weeks as long as the absolute neutrophil count was at least 1500/mm³, the platelet count was >100,000/mm³, and all nonhematologic toxicity resolved to grade 1 or less. Toxicity was assessed by using the NCI Common Toxicity Criteria version 2.0 (NCI, 1999). Treatment could be delayed up to 3 weeks to allow recovery from toxicity. Doses of both drugs were reduced by 25% for reversible grade 3 or grade 4 toxicity. Patients who developed grade 3 or grade 4 nonhematologic toxicity following one dosage reduction (excluding nausea or vomiting) were removed from the protocol treatment. For repeat grade 3 or grade 4 hematologic toxicity, patients could be retreated with an additional 25% dosage reduction. Further dose reduction was not allowed. Treatment was discontinued at the completion of 8 cycles or after progression of disease or unacceptable toxicity. The latter included grade 3 or 4 nonhematologic toxicity after 1 dose reduction or irreversible grade 2 or greater toxicity. A greater than 3-week delay in treatment or a reduction in the DLCO to less than 80% was also cause for discontinuation of treatment. Imaging studies were done after each cycle (every 6 weeks), and DLCO measurements were done every other cycle of treatment.

Tumor progression was defined as an increase of greater than 25% of the size of measurable tumor, or clear worsening of evaluable disease, or the appearance of any new lesion, or failure to return for evaluation due to death or deteriorating clinical condition. A partial response required measurable disease to decrease by at least 50%; a complete response required complete disappearance of all measurable and evaluable disease. Minor response required a decrease in tumor size by at least 25% but less than 50%. All responses had to be in the setting of a stable or decreasing dose of steroids, and patients had to be neurologically stable. Patients who

had a response by imaging criteria but were on higher doses of steroids were considered to have stable disease. All claimed responses were centrally reviewed at the University of California at San Francisco.

The primary end point was progression within 26 weeks. The historical values for comparison are from a database of 375 patients with recurrent high-grade glioma enrolled in previous phase 2 studies (Wong et al., 1999). The Kaplan-Meier estimate of the proportion of patients remaining free from progression at 26 weeks for both GBM and anaplastic gliomas was 21% (95% CI, 16%–27%). The PFS at 6 months for recurrent GBM was 15%. A Simon's optimal 2-stage design was used targeting a 20% improvement, alpha at 10% and beta at 10%. The hypothesis tested was $H_0: P \leq 0.2$ versus $H_1: P \geq 0.4$, where P is the probability of response (i.e., remaining free from progression for 26 weeks). The first stage would enroll 17 patients. If <4 of the 17 were progression-free at 6 months, accrual would stop. If >3 of the 17 were progression-free at 6 months, an additional 20 patients would be enrolled. If more than 10 of the 37 patients were progression-free at 6 months, the treatment would be considered of interest and worthy of further study. Up to 10% overaccrual was allowed to ensure at least 37 eligible, treated patients.

Results

A total of 41 patients were registered. Table 1 describes the patient characteristics. Of these, 3 were considered ineligible. One had anaplastic astrocytoma on central pathology review, and 2 additional cases were entered too soon after the completion of radiation therapy. Of the 38 eligible patients, all were evaluable for toxicity assessment and time to progression; 2 patients were not evaluable for tumor response on MR imaging. The median age was 53 years (range 32–70 years); 23 patients were males (60.5%). Only 4 patients had been treated with prior chemotherapy.

No patient died from toxicity. Table 2 describes grade 3 and grade 4 toxicity. A total of 84 courses of chemotherapy were given, 53 at full dose, 28 with 1 dose reduction, and 3 with 2 dose reductions. All patients were treated at full dose for cycle 1. Because 13 patients had immediate progression, the remaining 25 patients were subject to dose reduction for toxicity; thus, dose reductions occurred only in patients with stable or responding disease. Dose reductions took place, therefore, in 31 of the remaining 46 courses delivered beyond cycle 1. There were 27 grade 4 toxic events, all due to myelosuppression, including 1 neutropenic infection. There were no grade 3 or greater pulmonary complications of treatment.

At the completion of the first stage, with >3 of 17 patients progression-free at 6 months, the decision was made to complete the accrual. Of the 38 evaluable patients, 21% were progression-free at 6 months (95% CI, 11%–39%). The median PFS was 11 weeks (95% CI, 7–15 weeks). In the 36 patients evaluable for response, there were 2 partial responses (5.5% response rate),

2 minor responses, and no complete responses. The overall median survival was 34 weeks (95% CI, 28–49 weeks). Overall survival at 26 weeks and 52 weeks was 66% (95% CI, 52%–83%) and 24% (95% CI, 13%–42%), respectively. As a comparison, the historical database describes the PFS at 6 months as 15% (95% CI, 10%–19%), with a median PFS of 9 weeks (95% CI, 8–10 weeks) and a median overall survival of 25 weeks (95% CI, 21–28 weeks) (Wong et al., 1999).

Discussion

When used in these doses and this schedule, BCNU plus temozolomide has only modest activity and does not appear to offer an advantage compared to the use of temozolomide, or possibly BCNU, alone. The major toxicity was myelosuppression, and although it was tolera-

Table 1. Characteristics of the phase 2 study patients

Characteristic	No. of Patients
Enrolled	41
Ineligible	3
Evaluable for progression/toxicity	38
Evaluable for MRI response	36
Median age (range)	53 (32–70)
Males/Females	23/15
Karnofsky performance status (eligible patients)	
100	5 (13.2%)
90	8 (21.1%)
80	15 (39.5%)
70	9 (23.7%)
60	1 (2.6%)
Histology (eligible patients)	
Glioblastoma multiforme	36
Gliosarcoma	2
Prior chemotherapy	
Zero regimens	34
One regimen	4

Table 2. Grade 3 and grade 4 toxicity

Name of Event	Number of Events	
	Grade 3	Grade 4
Anemia	2	0
Constipation	1	0
Elevated LDH	2	0
Fatigue	2	0
Granulocytopenia	2	10
Neutropenic infection	0	1
Non-neutropenic infection	1	0
Leukopenia	6	6
Lymphocytopenia	1	0
Thrombocytopenia	13	10

ble, dose reductions were common, and there was more toxicity caused by the combination than by single-agent temozolomide.

The prognosis of patients with recurrent malignant glioma is poor, and thus there is an intense interest in investigating new agents or combinations in this population. Temozolomide is an orally bioavailable imidazotetrazine derivative of decarbazine (Stevens and Newlands, 1993). The active metabolite is monomethyl triazenoimidazole carboxamide, and cytotoxicity is primarily due to methylation at the O⁶ position of guanine. Temozolomide also acts as an inhibitor of DNA mismatch repair and can induce apoptosis (Friedman et al., 1997). In phase 2 studies for recurrent anaplastic gliomas other than GBM, a PFS at 6 months of 46% was reported, with a complete response plus partial response rate of 35% (Yung et al., 1999). A randomized phase 2 study comparing temozolomide with procarbazine in the setting of recurrent GBM resulted in a PFS at 6 months of 21% for patients treated with temozolomide compared to 8% for those treated with procarbazine (Yung et al., 2000). BCNU has been used for both newly diagnosed and recurrent malignant glioma, with reported response rates ranging from 30% to 50% in recurrent disease. However, many of those studies were done in the 1970s, prior to the introduction of MR imaging, using different criteria to declare response than is typically used today. A recent meta-review of the treatment of patients with recurrent high-grade glioma revealed that chemotherapy studies that used nitrosoureas significantly extended time to tumor progression compared to those using other drugs (Huncharek and Muscat, 1998). BCNU forms a chloroethyl adduct at the O⁶ position of guanine, whereas temozolomide appears to act by methylation at this site. Both the methyl and chloroethyl adducts are repaired by the DNA repair protein O⁶-alkylguanine-DNA alkyltransferase (AGT). The mechanism of synergy of BCNU and temozolomide is unknown. High levels of AGT can be protective of the cytotoxic effects of temozolomide or BCNU. Pretreatment with drugs that react with AGT may render a tumor cell more sensitive to the subsequent exposure of an alkylating agent such as BCNU. The synergistic toxicity on bone marrow function of the dosing schedule in which temozolomide is given prior to BCNU may be explained, in part, by this sequence of depletion or inhibition of AGT prior to BCNU treatment. A potential therapeutic effect in tumor cells may also occur.

We previously reported our results in a phase 1 study that evaluated the toxicity of temozolomide given just prior to or following BCNU (Schold et al., 2000). Because of the preclinical studies showing synergistic therapeutic effects of the combination with either schedule, but potentially more toxicity when temozolomide was given 2 h prior to BCNU, the study design evaluated both schedules. When BCNU was given prior to temozolomide, the MTD was one dosage level higher than that with the reverse sequence of temozolomide given prior to BCNU. Pharmacokinetic parameters of temozolomide were unaffected by the treatment schedule, so the difference in the MTD was felt to be due to a biologic

effect rather than a pharmacokinetic sequence interaction. The preclinical model also suggested therapeutic superiority of the sequence in which BCNU was given first. The recommended phase 2 dose was 150 mg/m² of BCNU given prior to 550 mg/m² of temozolomide. In the phase 1 trial, there were 5 claimed partial responses in 24 evaluable patients with GBM. However, central radiological review of responses was not required and was not done in that study, and thus these responses cannot be confirmed. The current phase 2 study has only 2 confirmed partial responses. Although the 6-month PFS of 21% appears to be slightly superior to that of our historical database of 15%, the 95% confidence intervals overlap, and it does not appear to improve upon the reported 6-month PFS of 21% with temozolomide alone. Indeed, because of the added toxicity of the combination of BCNU with temozolomide compared to the minor toxicity of temozolomide alone, the overall benefit of the combination does not appear to warrant the significant risk of toxicity.

One potential explanation for these results may be the consequence of using a single oral dose of temozolomide rather than using the daily $\times$ 5 days schedule of temozolomide. While the current study was ongoing, the Institute for Drug Development, Cancer Therapy and Research Center (The University of Texas Health Science Center at San Antonio) was conducting a phase 1 study of the combination, using a 5-day schedule of temozolomide given prior to or following BCNU (Hammond et al., 2000). That study enrolled more patients with metastatic tumors than the North American Brain Tumor Consortium phase 1 trial, but otherwise was similar in design. Toxicity was also reported to be less when BCNU was given prior to temozolomide. The total dose of temozolomide was higher with the 5-day schedule (up to 750 mg/m² over the 5-day cycle) compared with the one oral dose of 550 mg/m² in the current trial. A phase 2 trial in recurrent malignant glioma using the combination of BCNU followed by a 5-day schedule of temozolomide has not been reported, and thus it is unknown if this schedule has clinical benefit compared to a single oral dose of temozolomide. The Radiation Therapy Oncology Group recently opened a phase 1/3 study in patients with newly diagnosed anaplastic glioma (RTOG 98-13). The phase 1 study treated patients with the combination of BCNU and temozolomide, given concurrently with radiation. The plan was to further evaluate the toxicity of this combination before considering the phase 3 question that would randomize 1 group of patients to BCNU alone, another to temozolomide alone, and a third group to BCNU plus temozolomide. In this study, BCNU was given at a dose of 200 mg/m² i.v. followed by a 5-day schedule of temozolomide at a dose of 150 mg/m²/day. Because of excessive toxicity of the combination, the planned arm using both drugs was abandoned, and the current study randomizes to BCNU alone versus temozolomide alone.

When temozolomide is used in combination with BCNU, either in a single dose or in a 5-day schedule, the doses of both drugs must be lowered. In our study, a significant number of dose reductions were required after

cycle 1 of treatment. This reduction in dose intensity of both drugs may also impact efficacy. Efforts to minimize systemic toxicity are ongoing by exploring delivery systems that allow direct exposure of BCNU into brain tumor or brain adjacent to tumor following resection. The significant myelosuppression caused by BCNU given systemically is thus reduced, and this delivery technique allows higher systemic doses of temozolomide. One such effort includes the use of copolymers impregnated with BCNU (Gliadel wafers: Aventis Pharmaceuticals, Parsippany, N.J.) placed in a resection cavity after surgery. The wafers are designed to deliver up to 61.6 mg of BCNU by local delivery. Temozolomide is then given systemically. This strategy decreases the risk of myelosuppression due to BCNU and would allow greater doses of temozolomide. Phase 1 studies reveal no dose-limiting toxicity of temozolomide at 200 mg/m²/day for 5 days (Rich et al.,

2001). Efficacy will ultimately have to be evaluated in both phase 2 and phase 3 trials.

Combination chemotherapy in newly diagnosed or recurrent malignant glioma has not been shown to improve efficacy beyond that seen with single-agent chemotherapy (Fine, 1994; Huncharek and Muscat, 1998; Wong et al., 1999). Many combination studies, like the current trial, report added toxicity without the benefit of increased efficacy. A listing of all those studies is beyond the scope of this manuscript. This study, unfortunately, can be added to that list.

In conclusion, the combination of BCNU and temozolomide used in the doses and schedules for this study is only modestly active, has significant toxicity, and does not appear to offer an advantage over the use of single-agent temozolomide alone. Further research testing other schedules or delivery systems is needed before the combination is used in this patient population.

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