A phase II study of temozolomide in patients with newly diagnosed supratentorial malignant glioma before radiation therapy

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Temozolomide is a novel second-generation oral alkylating agent with demonstrated efficacy and safety in patients with recurrent glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA). A multicenter phase II trial was conducted to determine the efficacy and safety of temozolomide before radiotherapy in patients with newly diagnosed GBM and AA. Fifty-seven patients (51 adult, 6 pediatric) with newly diagnosed supratentorial GBM or AA were treated with temozolomide (200 mg/m^2 per day for 5 consecutive days every 28 days) for a maximum of 4 cycles. All patients were then treated with external beam radiotherapy. Twenty-two patients (39%) achieved objective response, including 6 (11%) with complete response (CR) and 16 (28%) with partial response (PR). Additionally, 18 (32%) patients had stable disease (SD). Of 21 patients (18 adult, 3 pediatric) with AA, 2 (10%) achieved CR, 5 (24%) achieved PR, and 8 (38%) had SD. Among adult patients with AA, the median progression-free and overall survival rates were 7.6 and 23.5 months, respectively. Among 36 patients (33 adult, 3 pediatric) with GBM, 4 (11%) had CR, 11 (31%) had PR, and 10 (28%) had SD. The median progression-free and overall survival rates among adult patients with GBM were 3.9 and 13.2 months, respectively. Temozolomide was safe and well tolerated in adult and pediatric patients. Grades 3 and 4 adverse events were reported in 16 (28%) and 7 (12%) patients, respectively. Temozolomide was safe and effective in treating newly diagnosed GBM and AA before radiotherapy. This pre-irradiation treatment approach appears promising, but will require additional evaluation in comparative studies. *Neuro-Oncology 4, 261–267, 2002 (Posted to Neuro-Oncology [serial online], Doc. 02-009, July 12, 2002. URL <neuro-oncology.mc.duke.edu>)*

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[2]Abbreviations used are as follows: AA, anaplastic astrocytoma; CR, complete response; GBM, glioblastoma multiforme; Gd-MRI, gadolinium-enhanced magnetic resonance imaging; KPS, Karnofksy performance score; PR, partial response; SD, stable disease.

[3]Schering-Plough Research Institute (1999) Data on file. Protocol C94-138. Kenilworth, N.J.: Schering-Plough Research Institute.

Malignant gliomas, including GBMs[2] and AAs, are the most common primary brain tumors in adults, with a combined incidence of 5 to 8 per 100,000 population (Burger et al, 1985; Friedman et al, 2000). These high-grade malignant gliomas result in approximately 13,000 deaths annually in the United States (Greenlee et al, 2001). The current standard treatment for high-grade gliomas is surgery, followed by external beam radiation, with or without adjuvant chemotherapy (Azizi and Miyamoto, 1998). Although the effectiveness of adjuvant chemotherapy remains controversial, several studies, including a meta-analysis of 16

randomized trials, have concluded that adjuvant chemotherapy provides a survival benefit compared with radiotherapy alone (Fine et al, 1993; Levin et al, 1990; Solero et al, 1979). Despite this multidisciplinary approach, however, the median survival for patients with GBM remains < 1 year from initial diagnosis (Friedman et al, 2000). Most patients with malignant gliomas who initially respond to therapy will relapse, and the 2-year survival rates are only 8% to 12% for patients with newly diagnosed GBM and 38% to 50% for patients with newly diagnosed AA (Lesser and Grossman, 1993; Levin et al, 1997). The development of more effective chemotherapy agents should lead to improvements in survival.

Temozolomide is a novel alkylating agent with demonstrated activity in primary and recurrent gliomas (Newlands et al, 1992, 1996; O'Reilly et al, 1993). It is rapidly absorbed and highly bio-available after oral administration (Reid et al, 1997), and it crosses the blood-brain barrier and achieves effective concentrations in the CNS (Marzolini et al, 1998; Patel et al, 1995). In recently reported multicenter phase II trials, temozolomide (150 to 200 mg/m^2 per day for 5 consecutive days every 28 days) demonstrated efficacy in both recurrent AA and GBM (Yung et al, 1999, 2000). Temozolomide was very well tolerated in these trials: < 10% of patients experienced dose-limiting hematologic toxicity. The most common dose-limiting toxicities were thrombocytopenia and neutropenia (Brada et al, 1999). Importantly, temozolomide-induced myelosuppression is reversible and appears to be noncumulative (Dhodapkar et al, 1997).

Although the efficacy and tolerability of temozolomide in recurrent gliomas have prompted the evaluation of this promising new agent as front-line therapy for GBM and AA, the optimal use of chemotherapy in the front-line setting has not been established. The standard approach is to administer chemotherapy after radiotherapy; however, a number of studies have also investigated the activity of pre-irradiation chemotherapy using a variety of agents (Dazzi et al, 2000; Dropcho et al, 1992; Gilbert et al, 2000; Jeremic et al, 1999; Kirby et al, 1996; Recht et al, 1990). Patients in these studies received 1 to 4 courses of chemotherapy, and objective response rates ranged from 13% to 54%. Although most responses were partial, conversion to CR after radiotherapy has been documented (Dazzi et al, 2000). A particular advantage of this approach would be the treatment of very young pediatric patients, in whom radiotherapy can cause severe neurotoxic effects. In fact, Duffner et al. (1993) reported a 39% response rate among 102 evaluable patients < 3 years of age and demonstrated that radiotherapy could be delayed up to 1 to 2 years in approximately 40% of patients who remained free of progression for that time period.

The objective of this report is to update an earlier report of this study (Friedman et al, 1998) and to further assess the efficacy and safety of temozolomide in patients with GBM and AA in the front-line, pre-irradiation setting.

Patients and Methods

Patient Eligibility

Patients (≥ 4 years of age) with newly diagnosed and histologically proven supratentorial malignant glioma not requiring immediate radiation therapy were recruited between April 1996 and October 1999 at Duke University Medical Center, Durham, N.C.; The University of Texas M.D. Anderson Cancer Center, Houston, Tex.; University of California at San Francisco, San Francisco, Calif.; Emory University, Atlanta, Ga.; and Children's National Medical Center, Washington, D.C.[3] An Institutional Review Board approved the protocol at each study site, and the patients or the guardians of pediatric patients gave informed consent before participation. Histology was reviewed by the designated institutional pathologist according to the 3-tiered system of the World Health Organization, and specimens were forwarded for central review. Eligible histologies included GBM, gliosarcoma, and AA, and patients were required to have at least 1 contrast-enhancing lesion bidimensionally measurable (a minimum of 1.5 cm^2) by Gd-MRI within 72 h after surgical resection or > 14 days after surgery. If only a biopsy was performed, a scan had to be performed ≤ 14 days before temozolomide administration. Although surgical resection was not required, patients had to be treated within 28 days of a surgery or biopsy. Adequate laboratory values were required, including absolute neutrophil count ≥ 1500/mm^3 in adults and ≥ 1000/mm^3 in children; platelet count ≥ 100,000/mm^3; hemoglobin ≥ 9 g/dl; blood urea nitrogen, serum creatinine, and total serum bilirubin < 1.5 times the upper limit of laboratory normal; serum glutamic-oxaloacetic transaminase < 2.5 times the upper limit of laboratory normal; and alkaline phosphatase < 2 times the upper limit of laboratory normal. Patients were also required to have been on a stable dose of steroids for at least 7 days before the baseline scans, to have a life expectancy of > 12 weeks, and to have a KPS ≥ 70.

Patients were excluded if they had received prior chemotherapy, biologic therapy, radiation therapy, interstitial brachytherapy, or radiosurgery to the brain for the treatment of GBM, gliosarcoma, or AA. Patients who required immediate radiation therapy or who underwent a surgical resection for GBM or AA within 2 weeks of the start of treatment were excluded. In addition, patients who were neurologically unstable were excluded. Patients were not eligible if they were in poor medical condition because of nonmalignant systemic disease or acute infection treated with i.v. antibiotics, if they were vomiting frequently or had any medical condition that could interfere with the oral administration of temozolomide, or if they had previous or concurrent malignancies at other sites, with the exception of surgically cured carcinoma in situ of the cervix and basal or squamous cell carcinoma of the skin. Ineligible patients also included those with human immunodeficiency virus or acquired immuodeficiency disease–related illness, pregnant or lactating women, or patients not practicing an effective method of birth control.

Study Design

This was a phase II, multicenter, open-label study. Baseline evaluations were performed within 14 days of initiating temozolomide therapy and included a complete medical history, physical and neurologic examination, determina-

Table 1. Dose adjustment criteria

Nadir toxicity level	Nadir absolute neutrophil count/mm^3	Nadir platelets/mm^3	Temozolomide modification
0	≥ 2000	≥ 100,000	Dose unchanged from previous
1	1500-1999	75,000-99,999	Dose unchanged from previous
2	1000-1499	50,000-74,999	Dose unchanged from previous
3	500-999	25,000-49,999	Decreased dose to next lower dose level[a]
4	< 500	< 25,000	Decreased dose to next lower dose level[a]

[a]Dose levels (daily dose): 200 mg/m^2 per day, 150 mg/m^2 per day, 100 mg/m^2 per day.

tion of KPS, hematology test, clinical chemistry assessments, electrocardiogram, chest radiograph, and Gd-MRI of the brain. Hematologic tests were repeated within 21 days after the first dose of temozolomide, and baseline assessments were repeated before or on the first day of each subsequent cycle. After the final dose of temozolomide, all patients were observed for safety for a further 30 days. A physical and neurologic examination, vital signs, KPS, all laboratory tests, and Gd-MRI of the brain were all performed after each 28-day cycle. All patients alive at study completion were followed for disease progression and survival every 8 to 12 weeks for 2 years.

Treatment

Temozolomide was given orally at a dose of 200 mg/m^2 per day for 5 consecutive days every 28 days. Doses were based on body surface area calculated and rounded to the nearest 5 mg. Patients fasted for a minimum of 1 h before administration of temozolomide and continued fasting 1 h after administration. Cycles were repeated every 28 days up to a maximum of 4 cycles until occurrence of either unacceptable toxicity or evidence of disease progression. Patients were referred immediately after their final cycle of chemotherapy for radiation therapy. For patients with toxicity, the dose was modified as outlined in Table 1.

Clinical End Points and Statistical Methods

The primary study end point was the rate of objective response to temozolomide. Objective assessments of tumor response were based on major changes in tumor size on Gd-MRI scan compared with the baseline scan in light of steroid use and neurologic findings, as previously described by Macdonald et al. (1990). CR was defined as complete disappearance of enhancing tumor (measurable or nonmeasurable) on consecutive Gd-MRI scans, with stable steroid use for 7 days before each scan. PR was defined as ≥ 50% reduction in the sum of the products of the largest perpendicular diameters of contrast-enhancing measurable tumors on consecutive Gd-MRI scans with stable steroid use for 7 days before each scan. Progressive disease was defined as ≥ 25% increase in the sum of the products of the largest perpendicular diameters of contrast-enhancing measurable tumors or any new tumor on Gd-MRI scan.

The secondary end points were progression-free survival, 2-year overall survival, and safety and tolerability of treatment. Progression-free survival analysis included patients who progressed before radiotherapy. The number of pediatric patients was too small to allow meaningful survival conclusions to be drawn. Therefore, to prevent a decrease in the homogeneity of the adult population, pediatric patients were excluded from progression-free and overall survival analysis. The Kaplan-Meier method was used in the analysis of overall survival, and hematologic and nonhematologic toxicities were assessed using the National Cancer Institute Common Toxicity Criteria.

Table 2. Patient demographics and baseline disease characteristics

Characteristic	AA	GBM
Total number of patients	21	36
Number of patients < 18 yrs of age	3	3
Median age, yrs (range)	36 (5-80)	55 (16-71)
Sex, *n* (%)		
Male	11 (52)	23 (64)
Female	10 (48)	13 (36)
KPS, *n* (%)		
60	0	1 (3)
70	0	4 (11)
80	0	8 (22)
90	9 (43)	10 (28)
100	12 (57)	13 (36)
Median time from diagnosis, months (range)	0.8 (0.5-1.9)	0.8 (0.3-1.5)
Surgery at initial diagnosis, *n* (%)		
Biopsy	14 (67)	14 (39)
Subtotal resection	7 (33)	22 (61)
Prior treatment,[a] *n* (%)		
Chemotherapy	0	2 (6)
Radiation therapy	0	3 (8)

[a]For prior malignancies; not for GBM, gliosarcoma, or AA.

Results

Patient Characteristics

Patient demographics and baseline disease characteristics are outlined in Table 2. A total of 57 patients with a diagnosis of either AA (n = 21) or GBM (n = 36) were enrolled, including 6 pediatric patients. The median age of all patients with AA and GBM was 36 and 55 years,

Table 3. Patient response to temozolomide treatment

Patient subgroup	*n*	*n* (%) CR	PR	SD	CR + PR
Total	57	6 (11)	16 (28)	18 (32)	22 (39)
Histology					
AA	21	2 (10)	5 (24)	8 (38)	7 (33)
GBM	36	4 (11)	11 (31)	10 (28)	15 (42)
Extent of resection					
AA resection	7	1 (14)	0		
AA biopsy only	14	1 (7)	5 (36)		
GBM resection	22	4 (18)	5 (23)		
GBM biopsy only	14	0	6 (43)		
Adults (age ≥ 18 years)					
AA	18	2 (11)	5 (28)	6 (33)	7 (39)
GBM	33	3 (9)	11 (33)	8 (24)	14 (42)
Children/adolescents (age < 18 years)					
AA	3	0	0	2 (67)	0
GBM	3	1 (33)	0	2 (67)	1 (33)

respectively. Of the 6 pediatric patients (≥ 4 and < 18 years of age), 3 patients were diagnosed with AA (median age, 9 years), and 3 patients were diagnosed with GBM (median age, 16 years). All of the AA patients and most of the GBM patients (23 of 36 [64%]) had a KPS of ≥ 90. The median time from diagnosis to treatment with temozolomide was 0.8 months for both AA and GBM patients. Seven of 21 AA patients (33%) and 22 of 36 GBM patients (61%) underwent a subtotal surgical resection after initial diagnosis and before treatment with temozolomide, and the remainder underwent biopsy for diagnosis. Five patients received prior radiation or chemotherapy for unrelated diseases (not GBM or AA). Therefore, these patients were not excluded from the efficacy analysis.

Twenty-eight patients completed 4 cycles of temozolomide (10 AA patients and 18 GBM patients), including 1 patient with GBM who received 6 cycles of therapy. Twenty-nine patients discontinued therapy because of disease progression (n = 25), adverse events (n = 2), or withdrawal of consent (n = 2) after 1, 2, or 3 cycles and went on immediately to radiotherapy.

Response

Twenty-two (39%) patients achieved an objective response to temozolomide treatment (Table 3), including 6 (11%) patients with CR and 16 (28%) patients with PR. In addition, 18 (32%) patients had SD. Nine of these patients, who initially demonstrated an objective response or SD, progressed before completing all 4 cycles of temozolomide. In addition to the responses listed in Table 3 among patients with GBM, 1 patient had CR and 1 patient had PR after cycle 1, but both demonstrated evidence of disease progression on their next Gd-MRI scan after cycle 2. In addition, 6 patients had SD that was documented on only 1 scan. Fifteen (26%) patients failed to respond to temozolomide.

A subgroup analysis of responses among patients who had subtotal resection versus those who had only biopsy (Table 3) demonstrated that responses were seen with similar frequency in the two subgroups. Among 18 adult AA patients, 7 (39%) had an objective response and 6 (33%) had SD. Among the 3 pediatric AA patients, there were no objective responses, but 2 patients had SD. Within the group of 33 adult GBM patients, 14 (42%) had an objective response and 8 (24%) had SD. Of the 3 pediatric GBM patients, 1 patient had a CR and the remaining 2 patients had SD.

Survival

Median follow-up was 23.5 months (range, 14 to 38 months) for the entire patient population. Among the adult AA patients, median progression-free survival was 7.6 months, and median overall survival was 23.5 months (Fig. 1A). Likewise, for adult GBM patients, median progression-free and overall survival rates were 3.9 months and 13.2 months, respectively (Fig. 1B). The 2-year overall survival rates were 50% for adult AA patients and 18% for adult GBM

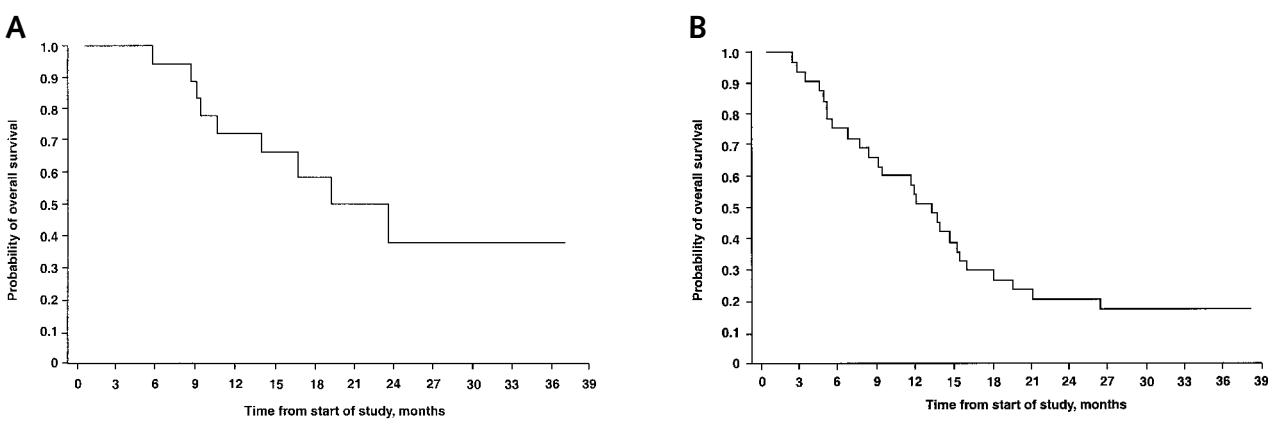

Fig. 1. Kaplan-Meier estimates of overall survival in patients ≥ 18 years of age with (A) anaplastic astrocytoma (n = 21) or (B) glioblastoma multiforme (n = 36) and treated with temozolomide.

Table 4. Summary of patients reporting grade 3 or 4 adverse events with temozolomide treatment

	n (%)	
Adverse event	Grade 3	Grade 4
Total	16 (28)	7 (12)
Constipation	3 (5)	0
Nausea	2 (4)	0
Thrombocytopenia	2 (4)	3 (5)
Anemia	0	1 (2)
Neutropenia	0	1 (2)
Ataxia	1 (2)	0
Impaired cognition	1 (2)	0
Convulsions	1 (2)	1 (2)
Speech disorder	1 (2)	0
Behavior disorder	1 (2)	0
Altered mental status	1 (2)	0
Somnolence	2 (4)	0
Suicide attempt	0	1 (2)
Hypotension	1 (2)	0
Asthenia	1 (2)	0
Back pain	1 (2)	0
Headache	4 (7)	0
Weight decrease	1 (2)	0
Syncope	2 (4)	0
Bradycardia	0	1 (2)
Bilirubinemia	1 (2)	0
Hyperglycemia	1 (2)	0
Apnea	1 (2)	0
Basal cell carcinoma	1 (2)	0
Urinary tract infection	1 (2)	0
Intracranial hemorrhage	1 (2)	0

patients. Survival analysis of the pediatric patients was not performed, because there were too few patients.

Safety

Temozolomide therapy was safe and well tolerated; 16 (28%) patients reported grade 3 adverse events, and 7 (12%) patients reported grade 4 adverse events (Table 4). The incidence of grade 3 and 4 hematologic toxicity was low, occurring in ≤ 5% of patients. Of the 7 (12%) grade 4 adverse events reported, 3 cases of thrombocytopenia, 1 case of bradycardia, and 1 case of neutropenia were considered related to temozolomide treatment. The most frequently reported serious nonhematologic adverse events involved the gastrointestinal system, including grade 3 constipation (5%) and nausea (4%) (Table 4). Grades 3 and 4 adverse events involving the central and peripheral nervous systems—including ataxia, impaired cognition, convulsions, and speech disorders—were reported in 5 patients (9%); however, these events were considered by the investigators to be unrelated to temozolomide. The safety profile in the 6 pediatric patients was similar to the overall patient population.

Table 5. Treatment discontinuation in patients with AA or GBM receiving temozolomide

	n (%)	
Patient subgroup	AA	GBM
Enrolled	21	36
Discontinued after		
1 cycle	6 (28)	8 (22)
2 cycles	5 (24)	7 (11)
3 cycles	0 (0)	3 (8)
Completed 4 cycles	10 (48)	18 (50)

Dose Reduction and Treatment Discontinuation

Six (11%) patients required dose reductions due to adverse events. Fifteen (26%) patients required dose delays; thrombocytopenia or neutropenia was responsible for 9 of these delays. Treatment completions and discontinuations are summarized in Table 5. Twenty-eight (49%) patients completed the study (4 cycles), 25 (44%) patients discontinued because of disease progression, 2 (4%) patients discontinued because of adverse events (grade 3 bilirubinemia in 1 patient and grade 4 neutropenia in 1 patient), and 2 (4%) patients withdrew consent. Of 4 patients with AA who discontinued after cycle 2, 2 patients discontinued because of disease progression and 2 patients had SD but refused further treatment. A review of these latter 2 cases showed that these patients were experiencing neurologic progression at the time of discontinuation. Of the 8 GBM patients who discontinued after cycle 1, 1 patient with PR discontinued because of grade 3 thrombocytopenia and grade 4 neutropenia.

Discussion

Clearly, patients with malignant gliomas would benefit from more effective and well-tolerated adjuvant chemotherapy agents. The effectiveness and tolerability of temozolomide in patients with recurrent gliomas (Yung et al, 2000) and AAs (Yung et al, 1999) prompted this multicenter phase II study, the aim of which is to confirm and extend the activity and safety of temozolomide in the pre-irradiation setting. This study also included a limited number of pediatric patients, our aim being to establish the safety and activity of temozolomide in children who could benefit from a well-tolerated chemotherapy regimen that would allow radiotherapy to be delayed. Unfortunately, the accrual goal for pediatric patients was not met, and this study is not adequate to fully assess the utility of pre-irradiation temozolomide in the pediatric population.

In this study, the objective response rate was 39%, including 6 (11%) CRs; an additional 32% of patients had SD (Table 3). Surprisingly, response rates were similar in patients with AA and GBM. The observation that a higher proportion of AA patients had only biopsy (67% versus only 39% of GBM patients) raised the possibility of sampling bias, in which case some of the AA patients may have had additional grade IV lesions. This prompted an analysis of responses in patients who had subtotal resection versus those who had only biopsy to determine

if this difference biased the response rate in favor of the GBM population. However, as shown in Table 3, responses were observed with similar frequency in the two subgroups, suggesting that this imbalance between the AA and GBM patients did not bias the results.

The response rates observed in this study compared favorably with published results of phase II studies investigating a variety of chemotherapy regimens in the pre-irradiation setting. These studies have predominantly demonstrated PRs in 13% to 54% of patients (Dazzi et al, 2000; Dropcho et al, 1992; Gilbert et al, 2000; Jeremic et al, 1999; Kirby et al, 1996; Recht et al, 1990). Several studies have investigated the activity of carmustine plus cisplatin (Dazzi et al, 2000; Gilbert et al, 2000; Recht et al, 1990). The highest response rates achieved with this regimen were recently reported by Dazzi et al. (2000). Among 18 patients (including 15 GBM patients) treated with carmustine (40 mg/m^2) plus cisplatin (40 mg/m^2) for 3 days every 3 to 4 weeks for up to 3 courses, 3 of 13 (23%) evaluable patients had CR, and 4 (31%) had PR. Moreover, 3 PRs were converted to CRs after radiotherapy (45 Gy). In a similar study, 47 patients with newly diagnosed GBM were treated with up to 3 cycles of carmustine and cisplatin by continuous i.v. infusion, and 22% of patients responded (Gilbert et al, 2000). However, this regimen was associated with significant (grade 3 or 4) hematologic and nonhematologic toxicities. Jeremic et al. (1999) also reported pre-irradiation therapy with carboplatin plus etoposide, which produced a 24% PR rate in 31 evaluable patients with only mild to moderate toxicities. These studies demonstrated the feasibility and safety of chemotherapy before radiotherapy and demonstrated high response rates. However, patients' disease status must be carefully monitored, as some patients will fail to respond, and other patients may progress early after an initial transient response to chemotherapy.

The use of pre-irradiation chemotherapy regimens may hold particular promise for pediatric patients in whom a delay in radiation therapy would spare the developing CNS from radiation-associated toxicity (Levin et al, 1997). In a large multicenter study in patients < 3 years of age with malignant brain tumors (although not AA and GBM), 39% of 102 evaluable patients had an objective response after only 2 cycles of cyclophosphamide plus vincristine (Duffner et al, 1993). Patients continued to receive chemotherapy for up to 1 or 2 years, depending on their age at diagnosis and response to treatment, before receiving radiotherapy. Approximately 40% of patients remained free of progression at 1 and 2 years; therefore, delaying radiation therapy for this period of time did not adversely affect outcome. Importantly, comparison of cognitive evaluations performed at baseline and after 1 year of chemotherapy revealed no deterioration in cognitive function. In the present study, temozolomide induced 1 CR, and 4 patients had SD during 4 months of therapy. These results suggest that temozolomide before radiation therapy should be investigated further in the pediatric population, either as a single agent or in combination with other agents; however, given the limited number of pediatric patients treated in this study, no conclusions can be drawn based on this experience.

Because AA is a less aggressive tumor than GBM and often responds better to chemotherapy, patients with AA usually have a longer median survival (2 to 4 years compared with < 1 year) than patients with GBM. However, the median overall survival of AA patients in this study was only approximately 2 years. This lower-than-expected survival rate in AA patients is likely due to the fact that most of these patients (67%) underwent only biopsy, indicating that their tumors were either advanced or inoperable at study entry. Of the 12 AA patients who underwent only biopsy, 2 patients had involvement of deep/diencephalic structures and 3 patients had tumors that crossed the midline. Therefore, many of the AA patients in this study had poor prognostic indicators. Moreover, the extent of resection was not controlled for in the survival analysis. It is also possible that some of the AA patients who underwent only biopsy may have had elements of GBM in lesions that were not sampled.

In addition to shorter-than-expected overall survival, the AA patients in this study had shorter-than-expected progression-free survival. This is likely due to the inclusion of a number of patients who progressed early before radiation therapy (52% of AA patients discontinued after 1 or 2 cycles due to disease progression). Among AA patients with SD, the duration of disease stabilization seemed to be shorter than for GBM patients who had SD. Among the 6 patients with stable AA, 2 remained stable for 12 weeks and 2 were stable for only 4 weeks. In addition, 2 patients who were categorized as having SD at the end of cycle 1 progressed at their next scan at the end of cycle 2. Therefore, although the number of patients is too small to allow conclusions to be drawn, it seems that a number of AA patients in this study had poor prognostic features.

This multicenter phase II trial demonstrated that temozolomide is an active and well-tolerated agent when given prior to radiation in patients with newly diagnosed GBM and AA and supports additional studies of temozolomide in the pre-irradiation setting, particularly in pediatric patients who could be spared radiation-associated neurotoxicity using this strategy. Specifically, it would be instructive to study the benefits of temozolomide when given for longer than 4 months in responding patients. Temozolomide can also be safely combined with radiotherapy (Stupp et al, 2002). Therefore, the study of temozolomide both prior to and concurrent with radiotherapy has been proposed. The favorable safety profile of temozolomide is a clear advantage compared with regimens containing a nitrosourea and/or cisplatin, and temozolomide appears to be as active as these alternative combination regimens in the front-line setting, although comparative trials are needed.

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