A phase II study of extended low-dose temozolomide in recurrent malignant gliomas^{1,2}

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Temozolomide is an effective agent in the treatment of recurrent malignant gliomas. The standard dosage is 150-200 mg/m² per day for 5 days in a 28-day cycle. A prior phase I study established a chronic daily temozolomide dose that significantly increased the total dose administered and suggested a superior response rate. In a prospective phase II trial, we treated 35 patients with recurrent malignant gliomas with temozolomide 75 mg/m² per day for 42 consecutive days in a 70-day cycle. Median age was 55 years (range, 27-73 years) and median Karnofsky performance score was 70 (range, 60-90). Twenty-eight (79%) patients had glioblastoma multiforme, 3 (9%) anaplastic astrocytoma, 2 (6%) anaplastic oligodendroglioma, and 2 (6%) anaplastic oligoastrocytoma. All but one had prior radiotherapy, and 27 had prior chemotherapy. There were 2 partial (anaplastic astrocytoma) and 3 minor (glioblastoma multiforme) radiographic responses; 17 patients had progressive disease at the end of the first cycle. In 55 cycles of temozolomide, there were 8 episodes of asymptomatic drug-related grade 3 toxicity: 6 lymphopenia, 1 neutropenia, and 1 thrombocytopenia. Median progression-free survival and overall survival were 2.5 and 8.7 months (2.3

and 7.7 months in glioblastoma multiforme patients). At 6 months, progression-free survival and overall survival rates were 27% and 67% (19% and 60% in glioblastoma multiforme). Quality of life scores did not change significantly during treatment. We conclude that the extended low-dose schedule of temozolomide is well tolerated in heavily pretreated patients; however, our results do not support an improved rate of response or survival. *Neuro-Oncology* 4, 39-43, 2002 (Posted to *Neuro-Oncology* [serial online], Doc. 01-038, November 27, 2001. URL <neuro-oncology.mc.duke.edu>)

The treatment of recurrent malignant gliomas represents a therapeutic challenge. Even with maximum treatment at initial diagnosis, malignant gliomas have a dismal prognosis. Standard management is optimal surgical resection followed by involved field radiotherapy. The role of chemotherapy is controversial because median survival is not improved, although a minority of patients may have prolonged survival. A recent randomized clinical trial failed to show any benefit (Medical Research Council Brain Tumor Working Party, 2001), but a prior meta-analysis of published randomized trials demonstrated a modest survival benefit for patients receiving adjuvant chemotherapy after radiotherapy (Fine et al., 1993).

Temozolomide is an oral alkylating agent with 100% bioavailability (Newlands et al., 1992). It spontaneously converts the active metabolite, 5(3-methyltriazen-1-yl)imidazole-4-carboximide, which alkylates the O6 (and N7) position of guanine. It is well tolerated and has modest activity against GBM⁴ and anaplastic astrocytoma at first relapse (Yung et al., 1999, 2000).

Experimentally and in vivo, temozolomide is schedule dependent (Stevens et al., 1987). Recent studies in recur-

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⁴Abbreviations used are as follows: CI, confidence interval; FACT-BR, functional assessment of cancer therapy with brain subscale; GBM, glioblastoma multiforme; QOL, quality of life.

rent malignant gliomas used 150 to 200 mg/m² per day for 5 days in a 28-day cycle (Yung et al., 1999, 2000). However, a phase-I study of low-dose continuous temozolomide defined a maximum tolerated dosage of 75 mg/m² per day for 42 days in a 70-day cycle (Brock et al., 1998). This regimen provides 2.1-fold greater drug exposure over 4 weeks with comparable toxicity compared with the standard 200 mg/m² dose. There was no evidence of drug accumulation and, furthermore, this extended schedule may deplete O⁶-alkylguanine DNA alkyltransferase levels, a potential mechanism of drug resistance. Therefore, this treatment schedule may have improved efficacy as a result of increased drug exposure and decreased drug resistance without having an increase in treatment-related toxicity.

Chemotherapy frequently affects the health-related QOL but this is not routinely studied in brain tumors. Considering the significant toxicity and modest benefit associated with chemotherapy, some authors have suggested that QOL should be used as one of the outcome measures in brain tumor trials (Osoba et al., 2000a, 2000b). Therefore, we designed a phase II study to determine more explicitly the efficacy and toxicity of this treatment schedule in patients with recurrent malignant glioma and included major end points such as radiographic response, survival, and QOL assessment.

Methods

This was a single-institution phase-II study of patients with recurrent malignant glioma (World Health Organization grades III and IV). Eligibility criteria included histopathologic diagnosis of GBM, gliosarcoma, high-grade glioma, anaplastic astrocytoma, anaplastic mixed glioma, or anaplastic oligodendroglioma (histopathology acceptable from either the original surgery or surgery at recurrence); age ≥ 18 years; Karnofsky performance score ≥ 60 ; and unequivocal evidence of tumor progression or recurrence on contrast-enhanced MRI. Patients were excluded if they had received temozolomide or dacarbazine previously, were pregnant or lactating women, were patients with known human immunodeficiency virus seropositivity, or were patients with another active malignancy. Prior chemotherapy or radiation therapy had to be completed at least 4 weeks before enrollment, 8 weeks if the patient had prior stereotactic radiosurgery. Patients had to have adequate bone marrow (absolute neutrophil count $>1500/\text{mm}^3$, platelet count $>100,000/\text{mm}^3$, hemoglobin $>10\text{g/dl}$), renal function (blood urea nitrogen and serum creatinine both <1.5 times upper limit of normal), hepatic function (total and direct bilirubin both <1.5 times the upper limit of normal, serum glutamic oxaloacetic transaminase and serum glutamic pyruvate transaminase both <3 times the upper limit of normal, and alkaline phosphatase <2 times the upper limit of normal). The Memorial Sloan-Kettering Cancer Center Institutional Review Board approved the study design, and informed consent was obtained from all patients.

All patients had a baseline contrast-enhanced brain MRI, neurologic examination, and laboratory tests; pathology of all patients was reviewed. FACT-BR was

administered at study entry and at the end of each cycle (Weitzner et al., 1995). Repeat MRI and neurologic examination were performed prior to each cycle of temozolomide.

Temozolomide was administered in a fasting state at the same time every day for 42 days at a dosage of 75 mg/m² per day; a 28-day rest period followed. Patients were monitored weekly with complete blood counts and monthly with physical examinations and serum chemistries. Hematologic and nonhematologic adverse reactions were graded using the National Cancer Institute Common Toxicity Criteria. Grades 1 and 2 toxicities were treated symptomatically. Treatment-related grades 3 or 4 toxicity required a 25-mg/m² per day reduction in the dosage of temozolomide. Any further grades 3 or 4 toxicity required withdrawal from the study.

Radiographic response, the primary end point of this study, was assessed every 8 weeks using gadolinium-enhanced MRI; standard definitions of response were adapted from Macdonald et al. (1990). Complete response was defined as the total disappearance of measurable tumor. Partial response was defined as at least a 50% reduction in the tumor size as measured by the product of the greatest length and maximum width of all contrast-enhancing lesions. These parameters had to be met on 2 serial MRI scans separated by at least 4 weeks to qualify for either a complete response or a partial response; the patient must have been neurologically stable, and on stable or decreasing doses of corticosteroids. Progressive disease was defined as 25% or more increase in the tumor size. Lack of either tumor response or progression constituted stable disease. Secondary end points were time to progression, overall survival, and QOL. A 10% change in FACT-BR was considered significant.

A modified 2-stage phase II design was used to assess the primary end point, radiographic response (Fleming, 1982). This required 2 or more responses (complete response + partial response) in the first 20 adequately treated patients in order to accrue the planned sample size of 35; if fewer than 2 responses were seen in the first 20 patients, the trial would be stopped for lack of efficacy. This design will detect a response rate of 20% with 91% probability and a 7% probability of early termination. The Kaplan-Meier product limit method was used to analyze survival data (Kaplan and Meier, 1958); all patients were considered in the survival and time-to-progression analysis in an intent-to-treat fashion. Time to progression was calculated from date of study entry to the day of radiographic progression or last follow-up. Overall survival was calculated from day of study entry to the day of death or last follow-up. A paired 2-sample *t* test was used to compare the means in FACT-BR analysis.

Results

Thirty-five patients, 25 men and 10 women, were enrolled between September 1999 and February 2001 (Table 1). Twenty-eight patients (79%) had GBM. Median age was 55 years (range, 27 to 73 years). All patients had resection at initial diagnosis; all but 1 had

Table 1. Patient characteristics

Variable	Value
Sex	
Men, <i>n</i>	25
Women, <i>n</i>	10
Median age, yrs	55 (range, 27-73 yrs)
Median KPS	70 (range, 60-90)
Histology	
Glioblastoma multiforme	28
Anaplastic astrocytoma	3
Anaplastic oligodendroglioma	2
Anaplastic oligoastrocytoma	2
Prior radiotherapy	34
Prior chemotherapy	27

Abbreviation: KPS, Karnofsky performance score.

Table 2. Adverse reactions to low-dose temozolomide

	Grade 1 (<i>n</i> = 50)	Grade 2 (<i>n</i> = 14)	Grade 3 (<i>n</i> = 8)
Thrombocytopenia	10	1	1
Neutropenia	0	2	1
Lymphopenia	1	7	6
Hemoglobin	13	1	0
Constipation	6	0	0
Fatigue	6	0	0
Nausea	2	1	0
Vomiting	2	2	0
Liver			
ALP	4	0	0
ALT	5	0	0
AST	1	0	0

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase.

prior radiotherapy; and, no patient had prior radio-surgery or gamma knife treatment. Twenty-seven patients had received prior chemotherapy, mostly nitrosourea based (23/27). The median number of prior chemotherapy cycles given was 3, and 3 patients had more than 1 prior regimen. No patient had been treated with Gliadel wafers or other local chemotherapy or immunotherapy.

In 55 cycles of chemotherapy, there were no grade 4 adverse events, and grade 3 adverse events occurred in 8 patients: 6 episodes of lymphopenia and 1 episode each of thrombocytopenia and neutropenia (Table 2). No intervention was required. Two patients withdrew from the study before receiving any treatment.

The objective response rate observed was 6% (2/35). Both responses were seen in patients with anaplastic astrocytoma. One progressed at 6 months and was still alive after 9 months of follow-up. Seventeen (49%) patients with GBM progressed by the end of the first cycle. All other patients had stable disease, including 3 GBM patients with minor radiographic responses. Two of these 3 patients progressed after 4.7 and 9.1 months, 1

Fig. 1. Kaplan-Meier progression-free survival curves for all (small dash), GBM (continuous), and other grade 3 gliomas (large dash).

was alive with progressive disease at 19.1 months, and the other died at 8.9 months. Three patients remain active on the study: 2 have GBM (4 cycles each), and 1 has anaplastic astrocytoma (8 cycles).

Median overall progression-free survival was 2.5 months (95% CI, 2.2-4.5); median progression-free survival in GBM was 2.3 months (95% CI, 2.1-3.9; Fig. 1) and in other gliomas was 7 months (95% CI, 2.7-not reached). Progression-free survival at 6 months was 27%: 19% for GBM and 57% for other gliomas (Table 3). Median overall survival was 8.7 months (95% CI, 6.1-14.7; Fig. 2). GBM patients had a median survival of 7.7 months (95% CI, 4.2-13.9), and median survival has not been reached for other glioma patients (95% CI, 7.4-not reached). At 6 months, 67% of patients were alive (60% GBM and 100% of other glioma).

At the end of the first cycle, 13 patients had stable disease. FACT-BR scores for these patients were stable in 7, improved in 3, and deteriorated in 3. Karnofsky performance score improved in 9 and was stable in 4. In these 13 patients, there was no difference between mean FACT-BR at baseline and during stable disease (128 versus 125, $P = 0.9$). Postprogression FACT-BR scores were available in 17 patients: 9 were stable, 5 deteriorated, and 3 showed improvement. There was no difference in the mean FACT-BR score at baseline and at progression in these 17 patients (119 versus 113, $P = 0.4$). Of all the patients whose disease ultimately progressed, 8 patients had more than 2 cycles of temozolomide. In these 8 patients, FACT-BR mean scores during stable disease and after progression were not different (132 versus 125, $P = 0.5$).

Discussion

The dosing regimen in our study was based on the results of a phase I study that suggested improved efficacy with a 41% objective radiographic response in glioma patients (Brock et al., 1998). Although we could not reproduce the response rate reported in the phase I study, the combined response rate (partial response + stable disease) of 49% in our study is comparable to that reported for the 5-day regimen (Yung et al., 2000). In our study, 2 partial responses were seen in patients with anaplastic astrocy-

Table 3. Survival of patients treated with extended low-dose temozolomide

Survival	Extended low dose (<i>n</i> = 35) ^a	5-Day regimen (<i>n</i> = 209) ^b	Other phase II (<i>n</i> = 375) ^c
Median PFS (months) ^d			
All	2.5 (2.2, 4.5)		2.3
GBM	2.3 (2.1, 3.9)	3.1	2.1
Grade III	7.0 (2.7, NR)	5.4	3
6-Month PFS (%)			
All	27		21
GBM	19	21	15
Grade III	57	46	31
Median OS (months) ^d			
All	8.7 (6.1, 14.7)		6.9
GBM	7.7 (4.2, 13.9)	7.3	5.8
Grade III	NR (7.4, NR)	13.6	10.8
6-Month OS (%)			
All	67		55
GBM	60	60	
Others	100	75	

Abbreviations: PFS, progression-free survival; NR, not reached; OS, overall survival.

^aData are means for 28 GBMs and 7 grade 3 tumors.

^bData are means for 112 GBMs and 97 grade 3 tumors (Yung et al., 1999, 2000).

^cData are means for 225 GBMs and 150 grade 3 tumors (Wong et al. 1999).

^dNumbers in parentheses are the 95% CI.

Fig. 2. Kaplan-Meier overall survival curves for all (small dash), GBM (continuous), and other grade 3 gliomas (large dash).

toma. Sixteen patients had stable disease, including 3 with GBM who had a minor response (<50% reduction in tumor size). Furthermore, this treatment was well tolerated and there was no adverse impact on QOL.

Conventional chemotherapeutic agents, including temozolomide, have at best only a modest effect on the survival of patients with malignant gliomas. By increasing the total dosage delivered and potentially depleting one of the enzymes critical for drug resistance, we hoped to improve survival with the continuous low-dose schedule. However, median and 6-month progression-free survival and overall survival were similar to those rates reported using the standard 5-day regimen (Bower et al., 1997; Yung et al., 2000). There was no difference in outcome if patients who withdrew from the study were excluded from the analysis. Six patients in our study received 3 or more cycles of temozolomide: 3 had

anaplastic astrocytoma, 2 had GBM, and 1 had anaplastic oligoastrocytoma. There were too few patients with anaplastic astrocytoma and anaplastic oligoastrocytoma to reach any definitive conclusions as to whether this dosing regimen may merit further study in patients with grade 3 glioma.

Compared with other phase II studies for recurrent malignant glioma, our patient population was fairly typical. Wong et al. (1999) summarized the patient characteristics and prognostic factors of more than 300 patients with recurrent malignant glioma enrolled on phase II clinical trials. Our patients were slightly older (55 versus 45 years) and had a slightly worse median Karnofsky performance score (70 versus 80). The most important prognostic factor identified by Wong et al. (1999) was histology, and 80% of our patients had GBM as compared with a typical GBM proportion of 60%. Therefore, the most appropriate comparison can be made between the GBM patients enrolled on our trial and other trials reporting specific outcomes by histology as shown in Table 3.

In malignant glioma patients, every effort should be made to maintain QOL by choosing the most effective and least toxic treatment. We assessed QOL by administering the FACT-BR questionnaire (Weitzner et al., 1995). It is self administered and consists of a general version of FACT (Cella et al., 1993) with the addition of a brain subscale. The FACT-BR is particularly sensitive to change in clinical status over time and may be useful in assessing response to treatment. The FACT-BR assesses physical, emotional, functional, and social well-being and relationship to the doctor. The brain subscale consists of 20 additional questions regarding neurocognitive function. Temozolomide was previously reported to be associated with stable or improved QOL in patients with stable dis-

ease (Osoba et al., 2000a, 2000b). In this study, most patients who completed the questionnaire maintained their FACT-BR scores during both stable and progressive disease, suggesting that this extended treatment schedule did not have an adverse impact on QOL for these patients. Interestingly, we did not see significant postprogression deterioration in the FACT-BR scores. This may be secondary to early detection of asymptomatic progression in some patients or an insensitivity of the FACT-BR to detect neurologic deterioration relative to a patient's perceived QOL.

This extended low-dose schedule of temozolomide was well tolerated. There were no grade 4 and only 8 grade 3 adverse reactions (Table 3); none of the grade 3 adverse reactions required intervention or hospitalization. Grade 3 lymphopenia occurred in 6 patients, and

grade 3 neutropenia occurred in 1 patient. A high incidence of lymphopenia has been previously reported with temozolomide (Bower et al., 1997), with an increased rate of *Pneumocystis carinii* infection (Stupp et al., 2000). However, no patient in this study developed *P. carinii* pneumonia.

Chronic temozolomide dosing, as used in this study, is well tolerated, and using it achieved comparable outcome to that reported for the 5-day regimen. However, the total dose administered was higher compared with the 5-day regimen, and, consequently, this regimen incurs higher costs. Low-dose extended-use temozolomide may be most useful (or efficacious) when given in conjunction with radiotherapy (Stupp et al., 2000), but our data do not support routine use in recurrent malignant gliomas.

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