Temozolomide in the Treatment of Recurrent Malignant Glioma

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BACKGROUND. Options for chemotherapy at the time of recurrence in patients with malignant glioma are limited. The authors describe the efficacy and safety results of their institution's open-label, compassionate-use protocol of temozolomide for patients with recurrent malignant glioma.

METHODS. Patients with recurrent malignant glioma at any time during recurrence were treated with oral temozolomide at a dose pf 150 mg/m^2 per day on a 5-day schedule every 28 days. If this dose was tolerated, then escalation to 200 mg/m^2 was allowed. Clinical evaluations and assessments of tumor response were performed every 2 months. All patients or their surrogates signed approved Institutional Review Board consent forms.

RESULTS. Among 213 patients who were treated, 33% had Grade 3 tumors, and 67% had Grade 4 tumors. The overall objective response rate was 16% in both of these patient groups; and an additional 51% and 30% of patients with Grade 3 and Grade 4 tumors, respectively, had stable disease as their best response. The 6-month progression-free survival rates were 41% and 18% for patients with Grade 3 and Grade 4 tumors, respectively. The median survival was 49 weeks for patients with Grade 3 tumors and 32 weeks for patients with Grade 4 tumors. The major toxicity was hematologic toxicity. In multivariate analysis, the Karnofsky performance score was a significant predictor of survival for patients with Grade 4 tumors.

CONCLUSIONS. Temozolomide was well tolerated in patients with recurrent malignant glioma and had modest efficacy, even at the time of multiple recurrences. ***Cancer* 2004;100:605–11.** © *2003 American Cancer Society.*

KEYWORDS: chemotherapy, temozolomide, recurrent malignant glioma, survival.

The treatment of patients with malignant glioma remains the biggest challenge for the neurooncologist. Despite maximal safe surgical debulking and radiation treatment, overall survival (OS) for the average patient remains poor.[1–5] Several chemotherapeutic agents, most notably the nitrosoureas, have been used successfully in trials for the treatment of malignant glioma.[2,6–8] A number of trials with new agents are underway in search of improved treatment efficacy.[9–15] Moreover, despite initial successful treatment, most patients develop recurrent disease. Chemotherapy regimens for patients at the time of recurrence remain palliative, with median survival 6–8 months.

Temozolomide is an alkylating agent that has shown clinical efficacy in the treatment of a variety of malignant tumors.[16] Preliminary studies showed excellent bioavailability from oral dosing and significant penetration into the central nervous system, whereas Phase I trials revealed a well-tolerated side-effects profile.[17] Phase II studies have yielded promising results regarding the treatment of

patients with new diagnoses and recurrences of malignant glioma.[9,11,18]

Before the accelerated approval of temozolomide by the United States Federal Drug Administration in 1999 specifically for use in patients with anaplastic astrocytoma at first recurrence, an open-label, *compassionate-use* study of this agent was performed. We further define the efficacy and side effects of temozolomide in the treatment of patients with recurrent malignant glioma at the time of any recurrence. The study objectives were to determine the overall response rate, time to disease progression (DP), and OS of patients with recurrent malignant glioma who were treated with temozolomide.

MATERIALS AND METHODS

We report on an open-label, compassionate-use protocol trial for patients at the University of California–San Francisco (San Francisco, CA) with recurrent malignant glioma between March 1997 and October 1999.

Patient Eligibility

Patients were eligible for enrollment at the time of any recurrence. Inclusion criteria included a histologically confirmed supratentorial malignant glioma at diagnosis (histologic types included anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic mixed glioma, or glioblastoma), a Karnofsky performance status (KPS) score ≥ 70, age > 18 years, failure of standard radiotherapy, completion of radiation treatment > 12 weeks before the initiation of temozolomide, and a life expectancy > 12 weeks. If patients received radiosurgery or brachytherapy as part of their prior therapy, then histologic confirmation of recurrence or metabolic imaging consistent with recurrent tumor was recommended but was not mandated given the compassionate nature of this protocol. Each patient was required to have evaluable, enhancing disease on a gadolinium-enhanced magnetic resonance image (MRI) scan and adequate hematologic, renal, and liver parameters, consisting of an absolute neutrophil count (ANC) $> 1500/mm^3$; platelets $> 100{,}000/mm^3$; hemoglobin ≥ 10 g/dL; blood urea nitrogen, creatinine, total bilirubin, and direct bilirubin levels < 1.5 times the upper normal laboratory value; and aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels ≤ 3 times the upper normal laboratory value. Any number of prior surgical resections or chemotherapy regimens, except for dacarbazine or temozolomide, were allowed. Pregnant or nursing women and patients who were positive for the human immunodeficiency virus or with known acquired immunodeficiency syndrome-related illness were excluded. All patients or their surrogates signed an approved Institutional Review Board consent form.

Treatment Regimen

Temozolomide was provided by Schering-Plough Corporation (Kenilworth, NJ) and was administered once per day for 5 consecutive days in a fasting cycle. The cycle was repeated every 28 days provided that adequate hematologic parameters (ANC $> 1500/mm^3$ and platelet count $> 100{,}000/mm^3$) were met. The initial dose of temozolomide was 200 mg/m^2 per day orally for patients who had received no prior chemotherapy and 150 mg/m^2 per day for patients who had received prior chemotherapy. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria (CTC) grading system. Dose reductions were based on Grade 3 or 4 myelosuppression, down to a minimum dose of 100 mg/m^2 per day. All nonhematologic CTC Grade 2, 3, and 4 toxicities had to be resolved to at least Grade 1; and any elevations in transaminase or alkaline phosphatase levels had to be decreased to below the inclusion criteria level prior to repeat dosing. Dose escalation for the patients starting at 150 mg/m^2 per day was performed to the maximum of 200 mg/m^2 per day in the absence of Grade 3 or 4 myelosuppression. Patients continued to receive therapy with temozolomide until tumor progression, unacceptable toxicity, patient refusal, or a maximum of 1 year of therapy.

Evaluation of Response

Response was assessed on serial, gadolinium-enhanced MRI scans performed at the end of every two cycles. Lesions were compared between consecutive scans. A complete response (CR) was defined as resolution of all enhancing disease, whereas a partial response (PR) described a reduction $> 50\%$ in lesion size using bidimensional measurements. Disease progression (DP) indicated an increase in lesion size $> 50\%$. In addition, increasing doses of steroids with neurologic worsening also were considered DP, even in the absence of radiographic worsening.

The time to DP and survival were measured from the start of the study. Response duration was measured from the first documentation of either a PR or a CR until documentation of DP. Time-to-event estimation was performed using the method of Kaplan and Meier. Proportional hazards models were used to evaluate clinical factors that we believed would affect outcome.

TABLE 1
Patient Characteristics Based on Histology (N = 213)

Characteristic	Grade 3 (33%)	Grade 4 (67%)
Age (yrs)		
Median	42	53
Range	19–69	18–78
Median KPS	80	80
Median time from diagnosis to treatment (wks)	108	36
Prior treatment		
Radiation alone (%)	18	49
Nitrosourea (%)	77	44

KPS: Karnofsky performance status.

TABLE 2
Response Rates to Temozolomide by Histology

	No. of patients (%)	
Response	Grade 3	Grade 4
CR	1 (1)	1 (1)
PR	11 (15)	21 (15)
SD	36 (51)	43 (30)
PD	23 (32)	77 (54)

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

RESULTS

Patient Characteristics

Two hundred thirteen patients (136 males) were enrolled in the study. There were 142 patients with Grade 4 lesions (138 glioblastoma multiforme [GM] and 4 gliosarcomas), and 71 patients with Grade 3 malignant glioma. Of the patients with Grade 3 tumors, 75% had anaplastic astrocytoma histology, 24% had mixed histology, and 1% had anaplastic oligodendroglioma histology. The median age at enrollment in the study was 42 years (range, 19–69 years) for patients with Grade 3 tumors and 53 years (range, 18–78 years) for patients with Grade 4 tumors. The median KPS was 80 for both patient groups.

The median time from initial diagnosis to treatment with temozolomide was 108 weeks for patients with Grade 3 tumors and 36 weeks for patients with Grade 4 tumors. Excluding surgery, the mean number of prior treatments was two. Radiation therapy was the only prior treatment in 18% of patients with Grade 3 tumors and in 49% of patients with Grade 4 tumors, whereas 77% of patients with Grade 3 tumors and 44% of patients with Grade 4 tumors had received prior nitrosourea chemotherapy either in the adjuvant setting or at the time of recurrence. A median of 2 chemotherapy cycles were administered (range, 1–8 cycles). Patient characteristics based on histology are summarized in Table 1.

Efficacy

There was an overall objective response rate of 16% for all patients, with a CR rate of 1% each in patients with Grade 4 and Grade 3 tumors. Thirty percent of patients with Grade 4 tumors and 51% of patients with Grade 3 tumors had disease stabilization as their best response (Table 2). For patients with Grade 3 tumors, the median duration of response was 21 weeks, with 1 patient still in response at 266 weeks. The median duration of response for the patients with Grade 4 tumors was 10 weeks. One patient had no follow-up available after determination of response. Only one other patient did not experience failure by 44 weeks, and that patient experienced failure at 87 weeks. All patients were included in the analysis of progression-free survival (PFS) and OS. Seven patients with Grade 3 tumors were censored for time to DP. Two patients were lost to follow-up at 46 weeks and 115 weeks. The other 4 patients were progression free at 187 weeks, 204 weeks, 280–284 weeks, and 315 weeks. Four patients with Grade 4 disease were censored for time to tumor progression. Two patients were censored (at 5 weeks and 58 weeks, respectively) because they went on to receive other therapy without progression. Two patients were lost to follow-up, at 10 weeks and 38 weeks, respectively. Ten patients with Grade 3 tumors were censored for survival. Three patients were lost to follow-up, at 29 weeks, 46 weeks, and 50 weeks, respectively. The remaining patients were alive at the time of the current report, with follow-up ranging from 187 weeks to 315 weeks. Four patients with Grade 4 tumors were censored for survival: those patients were lost to follow-up at 10 weeks, 38 weeks, 64 weeks, and 117 weeks, respectively. The overall 6-month PFS rate was 41% for patients with Grade 3 tumors and 18% for patients with Grade 4 tumors. The 6-month OS rate was 75% for patients with Grade 3 tumors and 60% for patients with Grade 4 tumors. The median OS was 49 weeks for patients with Grade 3 tumors and 32 weeks for patients with Grade 4 tumors (Table 3). Kaplan–Meier estimates of progression and survival for patients with Grade 3 and 4 tumors patients are depicted in Figures 1 and 2.

Multivariate regression analysis was used to evaluate whether patient characteristics at the time the study started were predictive of either time to progression or survival for the patients with Grade 4 tumors. The variables considered were KPS, age, time from diagnosis, number of prior therapies, and whether the

TABLE 3
Progression and Survival by Histology

Characteristic	Grade 3	Grade 4
Median TTP in wks (range)	21 (15–29)	10 (9–14)
Median OS in wks (range)	49 (33–65)	32 (27–36)
Six-month PFS (%)	41	18
Six-month OS (%)	75	60

TTP: time to tumor progression; OS: overall survival; PFS: progression-free survival.

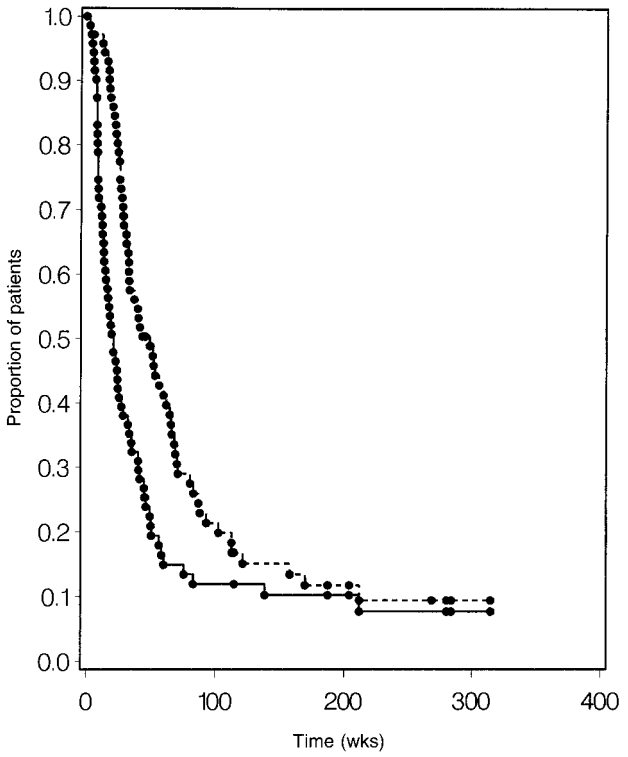

FIGURE 1. Kaplan–Meier estimates of disease progression (solid lines) and survival (dashed lines) for patients with Grade 3 glioma.

patient had previously received nitrosoureas. The various predictors and their associated *P* values are listed in Table 4. The KPS score was the only statistically significant predictor of survival. No factors were identified that were significant in predicting the time to DP ($P > 0.5$ in all patients). The limited numbers of patients and events precluded multivariate analysis in the patients with Grade 3 tumors.

Toxicity Results

Temozolomide was tolerated well with limited serious toxicities. There was 9% Grade 3 and 16% Grade 4 hematologic toxicity with myelosuppression, 2% Grade 3 gastrointestinal upset, 1% Grade 3 hepatic toxicity, and 4% Grade 3 fatigue (Table 5).

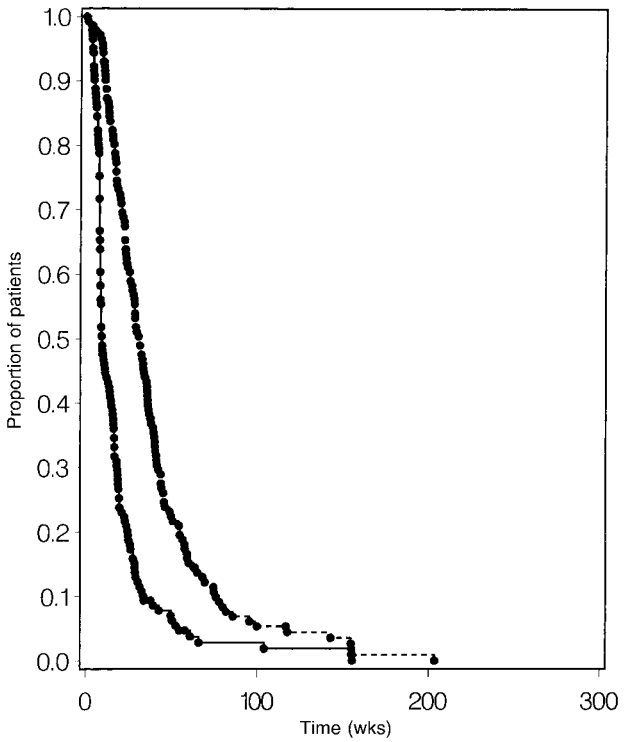

FIGURE 2. Kaplan–Meier estimates of disease progression (solid lines) and survival (dashed lines) for patients with Grade 4 glioma.

TABLE 4
Predictor Variables and Significance Levels from Multivariate Analysis

Predictor	Hazard ratio (95% CI)	*P* value
Survival (Grade 4 glioma)		
KPS	0.978 (0.960–0.997)	0.02
Prior nitrosourea	0.858 (0.573–1.284)	0.46
Age at treatment (yrs)	1.004 (0.987–1.021)	0.67
Wks from diagnosis (log-transformed)	1.073 (0.806–1.428)	0.63
No. of prior therapies	1.033 (0.84–1.27)	0.76
Time to tumor progression (Grade 4 glioma)		
KPS	0.997 (0.978–1.016)	0.72
Prior nitrosourea	1.153 (0.767–1.735)	0.49
Age at treatment (yrs)	1.004 (0.978–1.016)	0.60
Wks from diagnosis (log-transformed)	0.954 (0.722–1.260)	0.74
No. of prior therapies	1.006 (0.828–1.223)	0.95

95% CI: 95% confidence interval; KPS: Karnofsky performance status.

DISCUSSION

The current trial, which involved 213 patients with recurrent malignant glioma, demonstrated the effi-

TABLE 5
Toxicities by Grade of Severity

Toxicity	No. of patients (%)	
	Grade 3	Grade 4
Hematologic	22 (9)	40 (16)
Nausea/emesis/diarrhea	5 (2)	0 (0)
Allergy	3 (1)	0 (0)
Constipation	5 (2)	0 (0)
Hepatic toxicity	3 (1)	0 (0)
Fatigue	10 (4)	0 (0)

cacy and safety of temozolomide treatment at the time of any recurrence. These results confirm the findings of previous Phase II trials of temozolomide in patients with malignant glioma at the time of recurrence.[9,11,18–23]

Although the current study allowed enrollment at any time during recurrence, and although $>$ 50% of patients previously had experienced treatment failure following chemotherapy, our results were comparable to the results of temozolomide use at first recurrence. The response rate for patients with Grade 3 tumors in the current study was 16%, less than the 35% rate reported by the Temodol Brain Tumor Group (TBTG).[9] However, the percentage of patients with stable disease was 51% in the current study, compared with 26% in the TBTG study, and the sum of response and disease stabilization rates was 67% in the current study, compared with 61% in the TBTG study. The median time to progression and the median OS for our patients with Grade 3 tumors were 4.5 months and 14.9 months, respectively, similar to the 5.4 months and 13.6 months reported in the TBTG study. The 6-month PFS and OS rates of 41% and 75%, respectively, in our study also were similar to the respective rates of 46% and 75% reported in the TBTG study.

With respect to the efficacy of temozolomide in patients with Grade 4 tumors, we demonstrated a median PFS of 10 weeks[20] with a 6-month OS rate of 60%, similar to the 12.4 weeks and 60% reported by the trial of temozolomide for patients with GM at first recurrence.[11] The combined response and disease stabilization rate of 55% among patients in the current study with Grade 4 lesions also was similar to the 63% rate reported in a smaller study of temozolomide in patients with newly diagnosed GM,[19] the 40% rate reported in a study of patients at the time of second recurrence, and the 44% rate[20] reported in a study of temozolomide in patients with GM at any time during recurrence.[22]

Our results compare favorably with the results yielded by more traditional, nitrosourea-based combination chemotherapy treatment regimens for patients with recurrent malignant glioma (response and stabilization rates $\leq$ 60%[24–28]) and with the results yielded by monotherapy regimens, including procarbazine (stabilization rate, 27–57%[29,30]) and carboplatin (combined response and stabilization rate, 48%[31]). Regarding aggregate outcomes in Phase II trials involving patients with recurrent glioma, our combined response rate of 16% was better than the 9% reported previously, as was the case with PFS and OS rates.

Multivariate regression analysis indicated that KPS was the only statistically significant predictor of survival at the time of any recurrence in patients with Grade 4 lesions, regardless of the number of prior chemotherapy regimens. This finding suggests that, contrary to current practice, patients with Grade 4 lesions who have experienced failure with multiple prior chemotherapy regimens but who have maintained a good KPS score should not automatically be excluded from temozolomide treatment.

The optimal treatment dosing of temozolomide has been explored in other, more recent studies. Continuous daily temozolomide administration may lead to a persistent depletion of methylguanine-DNA methyltransferase, the main resistance pathway to temozolomide. A recent study using continuous daily temozolomide concomitant with radiation therapy in patients with newly diagnosed glioblastoma showed improved results with 58% 1-year survival and 31% 2-year survival without a significant increase in toxicity.[21] That cohort was compared with the Radiation Therapy Oncology Group recursive partitioning analysis.[32] Khan et al. also evaluated a similar dosing schedule in patients with recurrent malignant glioma, and although it was well tolerated, improvements in rate of response and survival were not demonstrated.[33] To date, no study has addressed the efficacy between various temozolomide schedules at the time of recurrence.

The current study had several shortcomings. The patient population was mixed, with some patients treated at first recurrence and others treated after experiencing failure with multiple prior chemotherapy regimens. This feature may have biased our results, because some multiply recurring tumors may be especially resistant to chemotherapy. There also may be a bias with respect to time from diagnosis to enrollment, because patients with longer survival were able to try (and possibly experience failure with) more chemotherapy regimens. The absence of centralized pathology review also may have skewed the distribution of Grade 3 and Grade 4 lesions. Despite these short-

comings, the current study reproduces results from previous studies and suggests that temozolomide is an effective treatment for patients with malignant glioma at any time during recurrence.

In conclusion, the treatment of malignant glioma at recurrence remains a significant challenge in neurooncology. Chemotherapy appears to be a promising alternative for both adjuvant treatment and treatment of recurrent disease. Temozolomide has demonstrated efficacy similar to, if not better than, that of nitrosourea regimens in the treatment of malignant glioma at initial diagnosis and at first recurrence. Our findings support the efficacy of temozolomide at any time during recurrence.

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