Original article

Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse

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Summary

Background: Recurrent glioblastoma multiforme (GBM) is resistant to most therapeutic endeavors, with low response rates and survival rarely exceeding six months. There are no clearly established chemotherapeutic regimens and the aim of treatment is palliation with improvement in the quality of life.

Patients and methods: We report an open-label, uncontrolled, multicenter phase II trial of temozolomide in 138 patients (intent-to-treat [ITT] population) with glioblastoma multiforme at first relapse and a Karnofsky performance status (KPS) ≥ 70. One hundred twenty-eight patients were histologically confirmed with GBM or gliosarcoma (GS) by independent central review. Chemotherapy-naïve patients were treated with temozolomide 200 mg/m^2/day orally for the first five days of a 28-day cycle. Patients previously treated with nitrosourea-containing adjuvant chemotherapy received 150 mg/m^2/day for the first five days of a 28-day cycle. In the absence of grade 3 or 4 toxicity, patients on the 150 mg/m^2 dose schedule were eligible for a 200 mg/m^2 dose on the next cycle.

Results: The primary endpoint was six-month progression-free survival assessed with strict radiological and clinical criteria. Secondary endpoints included radiological response and Health-related Quality of Life (HQL). Progression-free survival

at six months was 18% (95% confidence interval (CI): 11%–26%) for the eligible-histology population. Median progression-free survival and median overall survival were 2.1 months and 5.4 months, respectively. The six-month survival rate was 46%. The objective response rate (complete response and partial response) determined by independent central review of gadolinium-enhanced magnetic resonance imaging (MRI) scans was 8% for both the ITT and eligible-histology populations, with an additional 43% and 45% of patients, respectively, having stable disease (SD). Objectively assessed response and maintenance of a progression-free status were both associated with HQL benefits (characterized by improvements over baseline in HQL domains). Temozolomide had an acceptable safety profile, with only 9% of therapy cycles requiring a dose reduction due to thrombocytopenia. There was no evidence of cumulative hematologic toxicity.

Conclusions: Temozolomide demonstrated modest clinical efficacy, with an acceptable safety profile and measurable improvement in quality of life in patients with recurrent GBM. The use of this drug should be explored further in an adjuvant setting and in combination with other agents.

Key words: chemotherapy, glioblastoma multiforme, gliosarcoma, quality of life, temozolomide, tumor response

Introduction

Glioblastoma multiforme (GBM) is a primary malignant brain neoplasm characterized by poor differentiation, with such features as vascular proliferation, necrosis, and pseudopalisading. Despite aggressive first-line therapy, consisting of surgery, radiation therapy and adjuvant chemotherapy, the tumors invariably recur and the median survival is 9–12 months.

There are no clearly established chemotherapeutic regimens for the treatment of recurrent GBM. Nitro-

soureas are considered the most effective agents [1], although there are no reliable comparative data. The choice of chemotherapeutic regimen for patients who received previous therapy with nitrosoureas is particularly restricted. Because of cumulative bone marrow toxicity and the perceived development of chemoresistance, patients relapsing after previous chemotherapy are often treated with investigational agents. In this setting chemotherapeutic strategies in patients with recurrent GBM have used platinum [2–4], procarbazine [5, 6], tamoxifen [7], and various combinations [8–13]. The

response rates reported are up to 20%–30% with short progression-free intervals and a median survival rarely exceeding six months. Because of these poor results, chemotherapy for recurrent GBM can only be considered a palliative treatment. In such a palliative context, investigational chemotherapeutic agents should be required to demonstrate functional improvement and enhanced quality of life with validated Health-related Quality of Life (HQL) instruments [14, 15].

Temozolomide is a new, orally administered, second generation imidazotetrazine derivative. It is degraded spontaneously at physiological pH to the cytotoxic species 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC), and unlike dacarbazine, does not require hepatic activation [16]. Treatment with temozolomide results in the formation of N^7- and O^6-methylguanine, and O^3-methyadenine DNA adducts, although the O^6-methylation product is probably the cytotoxic entity since tumors that have a high content of the enzyme O^6-methyguanine-DNA-methyl transferase that repair the lesion tend to be resistant to therapy [17].

The efficacy of temozolomide has been evaluated in phase I [18], and phase II trials [19–21] in patients with recurrent malignant glioma In patients with recurrent anaplastic astrocytoma (AA), temozolomide has also demonstrated antitumor efficacy, a favorable toxicity profile, and significant quality of life improvements [22]. We report a single arm phase II study of the palliative efficacy of temozolomide in patients with recurrent GBM.

Patients and methods

Study design

This multicenter phase II trial was designed to evaluate the antitumor activity and safety profile of temozolomide in patients with supratentorial GBM at first relapse. Twenty-six international centers participated in the study. The phase II trial design was similar to that recently reported for AA at first relapse [22]. Data were compared with those from an historical database of patients treated with investigative regimens at the University of California San Francisco. This database includes 16 phase II trials with protocols similar to that in the current trial. The primary purpose of this database was to describe the outcome of 'ineffective' therapies. Agents that provide less than 10% progression-free survival at six months were deemed 'ineffective'. Consequently, the primary endpoint for efficacy chosen in the study was progression-free survival at six months. estimated from the start of treatment with temozolomide to the occurrence of disease progression defined as the onset of tumor regrowth detected on imaging. Based on the initial review of the historical database, 10% progression-free survival at six months was chosen as the lower limit of efficacy. A minimum of 100 eligible patients were to be enrolled, so that for a hypothetical progression-free survival of 20% at 6 months for temozolomide, the 95% CI would range from 12 2% to 27.8%. The secondary endpoints were overall survival and objective response rate based on central review assessment and palliative benefit in terms of improvement in HQL scores and neurologic function.

Patient eligibility

Patients eligible for enrollment were 18 years of age or older, with histologically proven supratentorial GBM at first relapse, evidence of

tumor recurrence or progression more than 12 weeks after completion of radiotherapy, and a KPS ⩾ 70. An independent central pathology review of all histologies was conducted by Dr Janet Bruner, Department of Pathology, University of Texas, MD Anderson Cancer Center, Houston, Texas. Gliomas were classified according to the three-tiered system of Nelson and Burger [23, 24]. Histologic criteria included the presence of diffusely infiltrating malignant astrocytoma with necrosis. In most cases, mitotic activity and microvascular proliferation were also present. Pseudopalisading necrosis was a required histologic feature only for those tumors biopsied after radiation therapy. Eligible histologies included GBM and gliosarcoma (GS) and were based on the most recent histology prior to enrollment. Patients had to show unequivocal evidence of first tumor recurrence or progression by gadolinium (Gd)-enhanced magnetic resonance imaging (MRI) or contrast-enhanced axial computed tomography (CT) after failing a conventional course of radiation therapy and not more than one course of adjuvant nitrosourea-containing chemotherapy. Multifocal disease was allowed. Required hematologic and chemistry parameters were as follows: absolute neutrophil count (ANC) ⩾ 1500/mm^3, platelet count ⩾ 100,000/mm^3, hemoglobin ⩾ 10 g/dl or 100 g/l, BUN and serum creatinine < 1.5 times the upper limit of normal (ULN), total and direct serum bilirubin < 1.5 times the ULN, SGOT or SGPT < 3 times the ULN, and alkaline phosphatase < 2 times the ULN. Patients were to have been on a non-increasing dose of steroids for at least 7 days prior to pretreatment MRI and study start and for at least 72 hours prior to study drug administration, to have a life expectancy > 12 weeks, and to have provided written consent.

Treatment

Temozolomide was administered orally, for the first five days of a 28-day cycle. Chemotherapy-naïve patients were given daily doses of 200 mg/m^2 temozolomide on therapy days. Patients previously treated with nitrosourea-containing chemotherapy were started on temozolomide 150 mg/m^2 daily on therapy days and were allowed to escalate the dose to 200 mg/m^2 in the next cycle in the absence of any grade 3 or 4 toxicity. Fasting four hours prior to and two hours after administration was required.

The initiation of a new treatment cycle was based upon strict hematologic criteria. An ANC and a platelet count ⩾ 1500/mm^3 and ⩾ 100,000/mm^3, respectively, were required; otherwise, chemotherapy was delayed and counts were reassessed weekly for up to four weeks until these levels were reached. Administration of growth factors to boost the ANC for the purpose of study drug administration was not allowed, but rescue with granulocyte colony stimulating factor (G-CSF) in the case of grade 4 neutropenia was acceptable. Prophylactic antiemetics were permitted as needed. Only the lowest steroid dose required to ensure neurologic stability was recommended. Patients continued treatment for a maximum of one year or until unacceptable toxicity and/or disease progression occurred.

Patient evaluation

Objective tumor assessment was performed by Gd-enhanced MRI according to a strictly defined protocol. MRI scanning was performed at trial entry within two weeks before first chemotherapeutic treatment and after every second course of chemotherapy. Copies of all scans were centrally reviewed at Johns Hopkins University, Baltimore, Maryland, by Dr Nancy Yue. The assessment of tumor response was based on criteria defined by Macdonald et al. [25] and carried out by the central reviewer using Gd-enhanced MRI scans in the context of steroid use, with supporting neurologic evaluation. The assessment of patients following debulking surgery was confined to those with early post-surgical MRI where residual nodular masses could be distinguished from post-surgical effects.

Neurologic evaluation, which was performed at each study visit, was based on changes in signs and symptoms from the previous examination. Relative changes were graded as definitely better (+2), possibly

Table 1. Demographics and characteristics of patients in the intent-to-treat population.

Parameter	Number of patients (%)
Age (years)	
Median	54
Range	24–77
Sex	
Male	85 (62)
Female	53 (38)
Karnofsky performance status	
100	7 (5)
90	39 (28)
80	33 (24)
70	59 (43)
Prior treatment	
Prior radiation therapy	138 (100)
Prior chemotherapy	40 (29)
Prior surgery at initial diagnosis	123 (89)
Prior surgery at first relapse	18 (13)
Median time to first relapse (months (range))	
From initial diagnosis	8.1 (1.1–80.2)
From end of radiation therapy	5.6 (0.4–75.6)
From surgery at first relapse to study drug	0.8 (−1.5–23.5)[a]
Histologies	
Glioblastoma multiforme	126 (91)
Gliosarcoma	2 (1.5)
Anaplastic astrocytoma	3 (2)
Anaplastic oligoastrocytoma	1 (1)
Low-grade gliomas	2 (1.5)
Histologies not available	4 (3)

[a] One patient had surgery 1.5 months *after* registration.

better (+1), unchanged (0), possibly worse (−1), or definitely worse (−2).

Adverse events during treatment or up to 30 days after initiation of therapy were scored according to the NCIC–CTC scale. Abnormal laboratory values were recorded as serious adverse events only if they caused hospitalization, transfusion of blood products or discontinuation of therapy.

The impact of therapy on patients' quality of life was assessed with a self-administered HQL questionnaire. In some instances, however, proxy completions of HQL forms were assessed. These included the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life (QLQ-C30) [14, 26] with 3 additional questions (hence QLQ-C30 [+3]) and a 20-question brain cancer module (BCM-20) [15]. Questionnaires were administered on the first day of the first cycle of therapy and at every visit thereafter. QLQ-C30 scores were converted to a scale of 0 to 100. A change of ⩾ 10 was considered clinically significant and an improvement of ⩾ 10 was defined as a favorable response in HQL domain [27] For the six HQL concepts related to functioning included in the QLQ-C30, higher values represent better functioning. For the nine disease-related symptoms commonly experienced by patients with cancer and that are included in the QLQ-C30, higher values represent a greater degree of symptom severity. For the disease-specific concepts included in BCM-20, higher scores represent worse disease-related symptoms.

Statistical analyses

The product limit method of Kaplan–Meier was used to estimate the progression-free survival and event-free survival at six months with a 95% CI. Large sample CIs based on the normal distribution were used when $n > 30$ and the binomial CIs were calculated when $n < 30$.

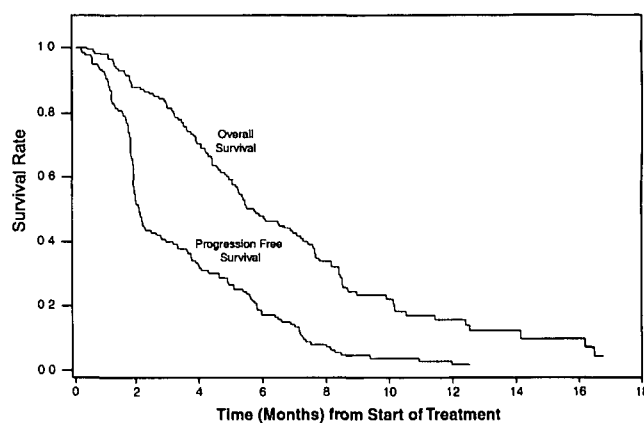All efficacy analyses were carried out on the intent-to-treat (ITT)

Figure 1 Kaplan–Meier analysis of time-related efficacy parameters in patients with GBM at first relapse treated with temozolomide.

population with additional analyses performed on the eligible-histology population. A Cox regression model was used to assess the potential influence of baseline characteristics on progression-free survival and overall survival. Subgroup analyses were based on age, time from initial diagnosis to first relapse, time from end of radiation treatment to first relapse and baseline Karnofsky performance status (KPS). Cut-off points were selected to obtain approximately 50% of the patients in each category.

Results

Patient characteristics

From March 22, 1995 to March 25, 1996, 26 international centers enrolled 138 patients (ITT population) in the trial. One hundred twenty-eight patients (93%) had GBM or GS (eligible-histology population) on central pathology review. Six of one hundred thirty-eight ITT patients did not receive temozolomide; therefore, the safety population included one hundred thirty-two patients. The characteristics of the ITT population of patients with GBM and GS eligible for chemotherapy at first relapse are shown in Table 1. The median age was 54 years. All patients had a KPS over 70. Twenty-nine percent had received nitrosourea-based adjuvant chemotherapy. Most patients (113; 82%) had single lesions, 89% of which were measurable. Tumor size (the product of two perpendicular diameters) and tumor volume ranged from < 1 to 60 cm^2 and < 1 to 180 cm^3, respectively. Eighteen patients (13%) underwent surgery at the time of relapse. The characteristics of patients in the eligible histology population were similar.

Therapeutic efficacy

Nineteen percent (95% CI: 12%–26%) and 18% (95% CI: 11%–24%) of patients, respectively, in the ITT and eligible-histology populations were progression-free at six months. The median progression-free survival was 2.1 months. The six-month survival rate was 46% with a median overall survival 5.4 months (Figure 1). The progression-free and survival results were identical for each population.

Table 2. Prognostic value of various factors on progression-free survival and overall survival by Cox analysis (backward regression method).

Variable	Subgroup	Patients (n)	Median PFS (months)	P-value	Median OS (months)	P-value
Overall	ITT	138	2.1	NS	5.4	NS
	GBM/GS	128	2.1		5.4	
Age	> 50	90	2.0	0.89	5.4	0.23
	< 50	48	2.8		5.2	
Sex	Male	85	1.9	0.14	5.2	0.21
	Female	53	2 8		7.2	
Prior chemotherapy	Yes	40	2.1	0.34	5.9	0.35
	No	98	2.2		5.3	
Surgery at ID	Yes	123	2.1	0.83	5.4	0.29
	No	15	2.1		5.1	
Time from ID to FR	> 8 months	76	2.6	0.03[a]	7.0	0.04[a]
	< 8 months	62	1.9		4.4	
Baseline KPS	> 80	46	2.4	0.43	7.0	0.13
	≤ 80	92	2.0		5.1	

Abbreviations: PFS – progression free survival; OS – overall survival; ID – initial diagnosis; FR – first relapse; RT – radiation therapy; KPS – Karnofsky performance status.
[a] Statistically significant.

A Cox regression analysis was performed to identify prognostic factors for progression-free survival and overall survival in the ITT population. Time from initial diagnosis to first relapse was the only independent predictor of progression-free survival (P = 0.03) and overall survival (P = 0.04) (Table 2).

As determined by independent central review, objective response to single agent temozolomide was modest and similar in each patient population. In the ITT population, 8% (11 of 138) of patients had either a CR (2 of 138) or a PR (9 of 138); 60 patients (43%) had stable disease. In the eligible histology population, 8% (10 of 128) of patients had either a CR (2 of 128) or a PR (8 of 128) and 57 patients (45%) had stable disease (Table 3).

Exposure to temozolomide

The 132 patients treated with temozolomide received a total of 538 cycles of therapy, 72% of which were administered at the 200 mg/m²/day dose and 24% at the 150 mg/m²/day dose. The median number of cycles administered was 3 (range 1–14). Seventy-four percent of cycles were administered on time (≤ 30 days cycle length), thirteen percent were thirty-one to thirty-five days long, nine percent were thirty-six to forty-two days long, and four percent were longer than forty-two days. Only 10% of cycles were dose reduced.

Adverse events

Adverse events observed in ≥ 2% of patients are shown in Table 4. The most common adverse events were grade 1–2 nausea and vomiting (26% and 24%, respectively) with few grade 3–4 events (4% in each case). These values, however, represent emesis without prior pre-medication, since there was no formal antiemetic policy in this trial. Administration of conventional antiemetics

Table 3. Objective response rates to temozolomide treatment at first relapse in patients with glioblastoma multiforme or gliosarcoma (eligible population) and patients with other brain tumors.

Independently assessed histology	Independently assessed quality of response		
	Complete response (CR) n (%)	Partial response (PR) n (%)	Stable disease (SD) n (%)
GBM/GS (eligible histology)	2/128 (2)	8/128 (6)	57/128 (45)
Others	0/10 (0)	1/10 (10)	3/10 (30)
Total (ITT population)	2/138 (2)	9/138 (6)	60/138 (43)

upon emesis stopped further vomiting. If 5-HT₃ antagonists were used preventively, vomiting did not occur. Grade 3–4 hematologic toxicity occurred in a limited proportion of patients as thrombocytopenia (10%), leukopenia (7%), and neutropenia (4.5%). The toxicity resolved with one dose level reduction. Three patients discontinued treatment due to adverse events.

Quality of life

Of the 138 patients entered in the trial, 12 had no baseline HQL data and were therefore excluded from the HQL analysis. Twenty-two patients were eligible for the HQL analysis as six-month progression-free survivors. The baseline HQL profiles were similar for patients who had progressed at six months and for those alive and progression-free at six months. HQL scores of patients achieving a response (CR, PR) were compared with those of the other patients. HQL responses (improvement in score ≥ 10) were more common among the 10 CR/PR patients than among those with progressive disease, with the most improvement recorded in global

Table 4. Treatment-related adverse events reported in ≥ 2% of patients during all cycles of temozolomide administration.

Adverse events (Aes)	Number of patients (%) (grade 1–2)	Number of patients (%) (grade 3–4)
Patients with AEs	62 (47)	33 (25)
Thrombocytopenia	2 (1.5)	13 (10)
Leukopenia	1 (1)	9 (7)
Neutropenia	1 (1)	6 (4.5)
Anemia	3 (2)	2 (1 5)
Asthenia	4 (3)	3 (2)
Fatigue	16 (12)	3 (2)
Fever	8 (6)	1 (1)
Headache	9 (7)	2 (1.5)
Confusion	2 (1.5)	2 (1.5)
Convulsions	1 (1)	2 (1.5)
Dizziness	3 (2)	–
Hemiparesis	1 (1)	2 (1.5)
Paresis	1 (1)	2 (1.5)
Somnolence	12 (9)	–
Anorexia	12 (9)	1 (1)
Constipation	6 (5)	–
Diarrhea	5 (4)	–
Dyspepsia	3 (2)	–
Stomatitis	3 (2)	–
Nausea	34 (26)	5 (4)
Vomiting	32 (24)	5 (4)
Alopecia	5 (4)	–
Petechia	10 (8)	–
Rash	4 (3)	–
Oral candidiasis	5 (4)	–
Pulmonary infection	2 (1 5)	2 (1.5)

HQL and motor dysfunction scores (Figure 2). Improvements were also noted in a proportion of patients with SD and in some progressing patients. Restriction of the analysis to patients with baseline functioning scores < 90 or symptoms scores > 10 (i.e., excluding 21 patients with normal scores) resulted in a magnification of the HQL response. Among patients who achieved an objective clinical response, 75% improved their motor dysfunction scores, 60% improved their global HQL, and 57% and 20%, respectively, experienced an improvement in communication deficit and visual disorder scores.

Ninety percent of patients achieving an objective response experienced an HQL response in at least one domain compared with fifty-eight percent of those with SD and fifty-two percent of those with PD. The proportion of patients experiencing an HQL response in three or more HQL domains was also higher in responding patients than in patients with either SD or PD (Table 5).

The HQL benefit was assessed in the 22 patients who remained progression-free at 6 months. The mean changes from baseline in QLQ-C30 (+3) functioning and symptom scores, and in BCM-20 symptom scores are shown in Figure 3.

The use of steroids to alleviate symptoms was monitored in order to exclude the potential influence on HQL independent of chemotherapy. Whereas 30% of HQL responders did increase concomitant steroid usage during the first six months of treatment, at least 60% did not or even reduced their steroid intake. Five patients in this latter category discontinued steroid usage entirely.

Discussion

The aim of chemotherapy in patients with recurrent malignant glioblastoma is to offer a palliative benefit in terms of improvement in neurologic function and HQL, or to prevent neurologic deterioration and worsening of HQL ideally with prolongation of survival. This is hoped to be achieved by reducing disease burden and delaying tumor progression.

We evaluated the therapeutic efficacy of single-agent temozolomide, an oral imidazotetrazine recently introduced for the management of malignant glioma at recurrence [19, 21, 22, 28, 29]. Patients with GBM at first relapse were evaluated for response using imaging and functional indices. The primary endpoints were progression-free survival and functional/palliative benefits using a validated instrument of HQL measurement.

The objective response rate according to imaging data was 8%, and 45% of patients had SD. This represents an objective assessment based on central radiology review. Similar results were reported in a previous Cancer Research Campaign (CRC) study where the majority of patients had GBM [30]. Although these results may appear disappointing, there is no published data of a large homogeneous cohort of patients with GBM histology alone treated at first recurrence. The published data usually combines AA and GBM, and the apparently more favorable response rates and survival times are not applicable to patients with GBM alone, as AA is associated with higher response rates [1]. In addition, radiologic endpoints are difficult to assess and are confounded by many factors, making conventional response criteria unreliable [25, 31]. Nevertheless, response rates in patients with recurrent GBM are low and of short duration with most patients achieving temporary disease stabilization.

The primary efficacy end-point in the present study was defined as six-month progression-free survival. A review of the literature suggested that an agent demonstrating a six-month progression-free survival of 10% or greater would be considered active [32, 33]. However, reliable data on a selected population of patients with GBM alone is not available. The six-month progression-free survival of 18% (95% CI: 11%–26%) in patients with confirmed GBM is above the limit of 10% set before the study was initiated and, as such, suggests activity of temozolomide. The time to progression and median overall survival of 2.1 months and 5.4 months, respectively, are comparable to results reported in the literature for various combination regimens. The time from initial diagnosis to first recurrence/disease progression was the only independent prognostic factor for progression-free survival and survival. It suggests that shorter progression-free interval indicates a biologically more aggressive disease.
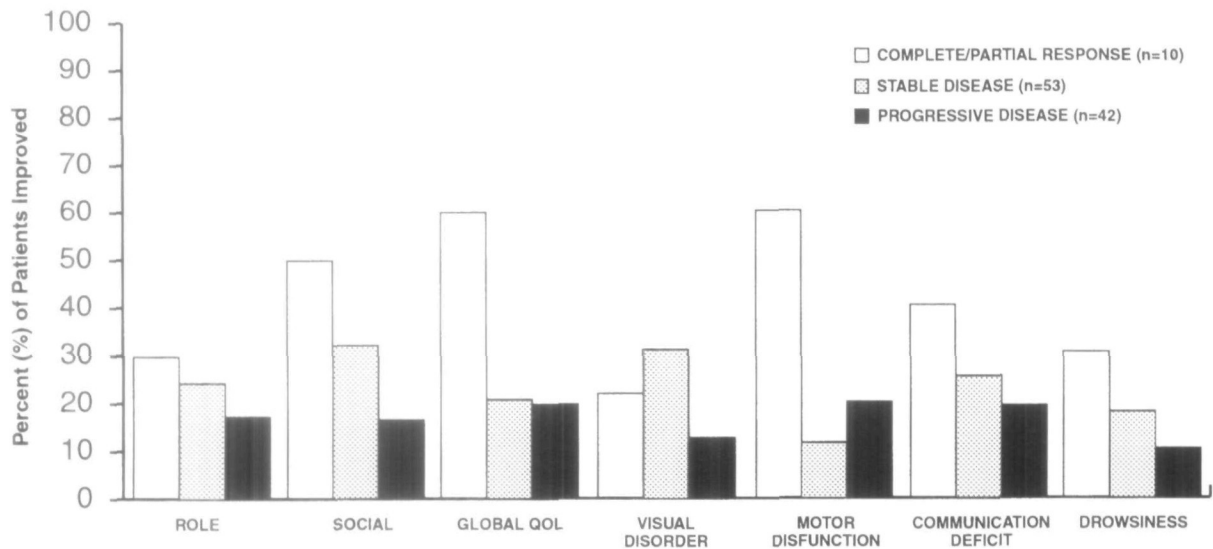
Figure 2. Frequency of HQL responses as a function of patient clinical response.

Table 5. Number of responses in selected QLQ-C30 (+3) functioning domains and BCM20 symptoms domains as a function of clinical response to temozolomide therapy in patients with malignant glioma.

Clinical response	Number of patients	Number (%) of patients with improved functioning and symptom domains (population per number of improved domains)				
		No improvement	Improved in one or more domains	Improved in two or more domains	Improved in three or more domains	Improved in four or more domains
CR + PR	10	1 (10)	9 (90)	8 (80)	4 (40)	3 (30)
SD	53	22 (42)	31 (58)	23 (43)	15 (28)	9 (17)
PD	42	20 (48)	22 (52)	12 (29)	7 (17)	4 (10)
Total	105	43 (41)	62 (59)	43 (41)	26 (25)	16 (15)

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

Temozolomide has a favorable toxicity profile and is well tolerated. Grade 4 thrombocytopenia, which occurred in only 4% of therapy cycles in a limited number of patients was fully reversible. Grade 3–4 nausea and vomiting were virtually eliminated with standard antiemetics. By contrast, nitrosoureas cause delayed and prolonged myelosuppression, which is cumulative [34].

The goal of a palliative treatment is to reduce tumor burden and improve, or at least prevent, the deterioration of HQL. The QLQ-C30 (+3) and BCM-20 [14, 15, 26] used in this trial evaluate a range of domains (global HQL, physical, role, cognitive, emotional and social functioning) and disease- and treatment-related signs and symptoms were selected as appropriate domains for evaluation in this group of patients. Temozolomide improved HQL function scores over baseline in patients who achieved an objective radiologic response and to a lesser extent in those with SD. This was accomplished without a concomitant increase in steroid use in the majority of patients. However, the contribution of steroids to the improvement in HQL scores cannot be ruled out. The results suggest that radiologic response correlates with clinical/HQL improvement. However, palliative benefit is seen in a larger proportion of patients than indicated by radiologic response alone.

In conclusion, temozolomide has modest single-agent activity in patients with GBM at first relapse. The favorable safety profile and the efficacy suggest that temozolomide should be assessed further to optimize its effectiveness, by exploring its pharmacokinetic profile. It should also be tested in combination with O^6-methyl-guanine-DNA methyl transferase (AGT) inhibitors and together with other agents. The ultimate aim should be to develop an effective regimen that could be tested in an adjuvant setting. Currently the efficacy of adjuvant temozolomide is being assessed in multicenter, randomized trials of the EORTC and the Radiation Therapy Oncology Group (RTOG).
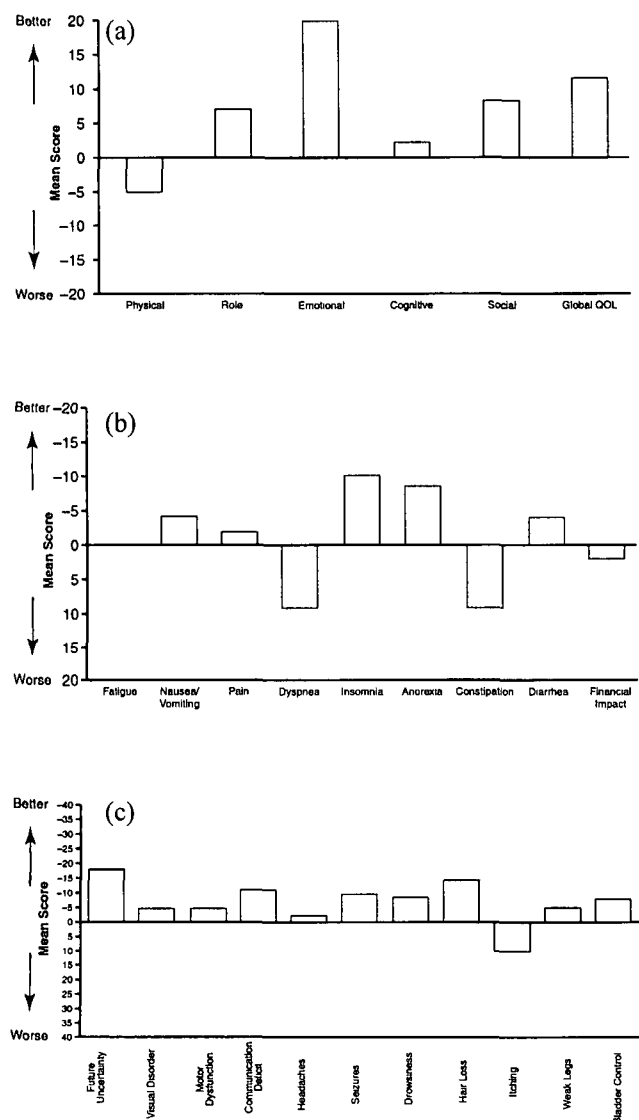
Acknowledgement

Figure 3 Mean change from baseline in progression-free survivors at six months in QLQ-C30 functioning scores (a) and symptom scores (b) and in BCM20 scores (c).

*Appendix

The following individuals also contributed patients to the study: H. Kostron, Clinic Innsbruck, Austria; J. Cebon, Austin and Repatriation Medical Centre, Heidelberg, Australia; M. Findlay, Royal Prince Alfred Hospital, Camperdown, Australia; J. G. Villemure, Institut Neurologique de Montreal, Quebec, Canada; D. Stewart, Ottawa Regional Center, Ottawa, Ontario, Canada; H.S. Poulsen, Rigs-hospitalet, Copenhagen, Denmark; O. Chinot, Hopital de la Timone, Marseille, France; E. Bouffet, Centre Regional Raymond Bernard, Lyon, France; M. Bamberg and W. Hoffmann, Klinikum der Eber-hardt-Karls-Universität, Tübingen, Germany; J -C. Tonn, Universität Würzburg, Würzburg, Germany; R. Engenhart-Cabillic, Klinikum der Ruprecht-Karls-Universität Heidelberg, Heidelberg, Germany; M. Santos-Ortega, Sanatorio San Francisco de Asis, Madrid, Spain; A. Malmstrom, University Hospital, Linköping, Sweden; R. Herrmann, Kantonsspital Basel, Basel, Switzerland; C. Zielinski, University Clinic Vienna, Vienna, Austria; L. Dávila-Maldonado, Hospital Angeles, Mexico City, Mexico.

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