Phase II Study of Temozolomide without Radiotherapy in Newly Diagnosed Glioblastoma Multiforme in an Elderly Populations

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Supported by the Fondation Lionel Perrier.

The authors are deeply grateful to the following individuals who worked with us to prepare the article: Khe Huang-Xuan for review of responses, J. Cougnard for statistical analysis, Pr. J-Y Delattre for reviewing the article, and the Fondation Lionel Perrier for their support.

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Received August 6, 2003; revision received February 16, 2004; accepted February 24, 2004.

BACKGROUND. Currently, the survival of patients age > 70 years with glioblastoma multiforme (GBM) ranges from 4 months to 6 months, although radiotherapy and/or chemotherapy may prolong survival in certain subgroups. Temozolomide is an oral chemotherapeutic agent with efficacy against malignant gliomas and a favorable safety profile. This open-label, single-center, Phase II study was designed to evaluate the efficacy and safety of temozolomide as first-line chemotherapy and exclusive treatment in elderly patients with newly diagnosed GBM.

METHODS. Chemotherapy-naïve patients (age > 70 years) were treated with temozolomide at a dose of 150–200 mg/m^2 per day for 5 consecutive days of a 28-day cycle until they developed disease progression. No radiation therapy was administered. The primary endpoint was median overall survival (OS); secondary endpoints included progression-free survival (PFS) and toxicity.

RESULTS. Thirty-two patients (median age, 75 years; median Karnofsky performance status, 70) experienced a median OS of 6.4 months and a median PFS of 5.0 months. Of 29 patients who were assessed for response, 9 patients (31%) achieved a partial response, 12 patients (41%) maintained stable disease, and 8 patients (28%) developed progressive disease. Adverse events primarily were mild, with NCI CTC Grade 3–4 thrombocytopenia and neutropenia reported to occur in 6% and 9% of patients, respectively. No neurotoxicity was observed. Treatment delays and dose reductions occurred in 13% and 14% of cycles, respectively.

CONCLUSIONS. Temozolomide represents a safe, easily administered, and effective therapeutic approach for elderly patients with newly diagnosed GBM. ***Cancer* 2004;100:2208–14.** © *2004 American Cancer Society.*

KEYWORDS: temozolomide, glioblastoma multiforme, glioblastoma multiforme, elderly, first-line chemotherapy.

Recent evidence shows that the incidence of glioblastoma multiforme (GBM) has increased substantially in the elderly population over the past 20 years.[1–3] For example, some investigators have reported an increase of 5% per year in the portion of population age ≥ 65 years.[2] Another study showed that, although it remained relatively stable in the younger segment of the population, the incidence of GBM increased by > 20% in patients ages 70–74 years between 1980 and 1990.[1] Even more dramatic increases (from 30% to 254%) were observed in patients age ≥ 75 years. Improved diagnostic procedures may be responsible in part for the increased incidence of GBM, but they do not account for all of the changes.

It is particularly noteworthy that age has been recognized as a poor prognostic indicator in patients with malignant glioma.[4] Consequently, the majority of clinical studies do not include patients age

DOI 10.1002/cncr.20224
Published online 19 April 2004 in Wiley InterScience (www.interscience.wiley.com).

> 60 years (although a few studies have included patients up to age 70 years). This is unfortunate, because the subgroup of patients age > 70 years represents a distinct population in terms of toxicity and treatment compliance. Although data for this specific patient population are limited, it appears that the median survival ranges from 4 months to 5 months in patients age > 70 years.[4–6]

Treatment strategies for elderly patients with GBM remain a matter of debate, ranging from palliative care to aggressive strategies, including surgery, radiation therapy, and chemotherapy.[3,4,6] However, these strategies can be problematic in elderly patients. For example, radiation therapy requires particular compliance and is associated with significant cognitive impairments in the elderly population. Nitrosourea-based chemotherapies are associated with significant myelosuppression. In a retrospective study of 148 patients who received nitrosourea-based chemotherapy, age was a strong predictor of the risk of myelosuppressive complications, which occurred in approximately 35% of patients age > 60 years, compared with only 13–19% of patients age < 60 years($P = 0.03$).[7] In addition, response rates with nitrosourea-based chemotherapies are poor (≈ 5%), and there is little survival benefit in patients age > 60 years (≈ 5 months).[7] Finally, retrospective studies have suggested that the combination of surgical resection and radiation therapy provides only a modest survival benefit in patients age ≥ 65 years.[8,9]

Clearly, more effective and better tolerated treatments are needed for elderly patients with brain tumors. Temozolomide is a new, orally administered, second-generation alkylating agent that readily crosses the blood-brain barrier and has demonstrated efficacy in patients with malignant glioma.[10,11] Moreover, temozolomide has a favorable toxicity profile, with easily managed, noncumulative myelosuppression.[10,11] In addition, Gilbert and colleagues recently reported a response rate of 42% (a complete response [CR] was noted in 9% of patients) and a median survival duration of 13.2 months in 33 adult patients with GBM who were treated with temozolomide and were assessed for response before the initiation of radiation therapy.[12] Taken together, the results of these studies suggest that temozolomide may be an appropriate first-line, single-agent therapy for the treatment of GBM in patients age > 70 years. Thus, the current study was conducted to evaluate the efficacy and safety of temozolomide as first-line chemotherapy (without the use of radiation therapy) in elderly patients with newly diagnosed GBM.

MATERIALS AND METHODS

Patient Eligibility

Patients age > 70 years with newly diagnosed GBM, with a Karnofsky performance status (KPS) ≥ 60, and with an Eastern Cooperative Oncology Group (ECOG) performance status < 2 were eligible for inclusion in this Phase II study. At least 1 bidimensionally measurable target lesion (≥ 2 cm in greatest dimension) had to be present based on a magnetic resonance image or a computed tomography scan that was obtained within 2 weeks before the start of treatment. Concomitant corticosteroid therapy was allowed, provided that the patient had been on a stable or decreasing dose for a minimum of 2 weeks. All patients were required to have normal hematologic, liver, and renal function.

Patients who had received prior chemotherapy for GBM or brain irradiation and patients who had recurrent GBM were excluded from the study. Prior surgery for GBM (within the month before study enrollment) was allowed if postoperative imaging studies revealed a clearly limited target that measured at least 2 cm in greatest dimension.

Previous or current malignancies at other sites also were reasons for exclusion, with the exception of cone-biopsied cervical carcinoma and adequately treated basal or squamous cell skin carcinoma. Additional exclusion criteria included the presence of uncontrolled systemic disease or active infection or the presence of any psychological, familial, sociologic, or geographic condition that could result in noncompliance with the study protocol or the follow-up schedule.

Study participants were enrolled from May 1999 to September 2001. All patients provided written informed consent prior to study participation. The study protocol was approved by a local Institutional Review Board/Ethics Committee.

Study Design

Patients who were enrolled in this open-label, single-center, Phase II study received treatment with temozolomide at a dose of 150 mg/m^2 per day for 5 consecutive days every 28 days; the dose could be increased to 200 mg/m^2 if no toxicity was evident. No radiation therapy was allowed during the course of the study, and treatment continued until progressive disease (PD) occurred.

The primary endpoint was overall survival (OS) from the time of study inclusion. Secondary endpoints included response rates, duration of response, and progression-free survival (PFS) at 6 months. The criteria of Macdonald et al.[13] were used to determine treatment response; a CR and a partial response (PR)

had to be confirmed at 2 separate visits at least 1 month apart. In patients with stable disease (SD), confirmation was required at 2 visits at least 2 months apart. Independent reviews of all histology and response results were performed by a pathologist (K.M.) and a neurologist (K.H.-X.) at H. Pitie Salpetrière.

Changes in neurologic status were assessed using KPS and Mini-Mental State Examination (MMSE) scores. Safety and tolerability were measured using the National Cancer Institute Common Toxicity Criteria, version 2.

Statistical Methods

The Kaplan–Meier method was used to estimate OS and PFS in the intent-to-treat (ITT) population. Because data in that population are calculated from the time of diagnosis, OS and PFS were calculated from the time of surgery and the time of study inclusion. PFS and OS were then stratified by age ($>$ 75 years or $<$ 75 years), KPS at study entry (postsurgery; $>$ 60 or $<$ 60), median tumor size ($>$ 15.75 cm^2 or $<$ 15.75 cm^2), and type of response (CR, PR, or SD). Survival curves were compared using the log-rank test at an α level of 0.05.

RESULTS

Patients

Of 65 patients age $>$ 70 years with malignant gliomas at our center, 63 patients were referred directly for diagnosis and surgery in the month prior to study entry. Of these 63 patients, 32 patients met eligibility criteria and were enrolled in the study. Thirty-one patients were excluded from the study for various reasons: Eight patients had no biopsy because of either patient or surgeon refusal, generally in the context of poor general or neurologic status; 6 patients had histology other than GBM (e.g., mixed oligoastrocytoma or anaplastic astrocytoma); 8 patients refused treatment or received another form of therapy (i.e., radiotherapy and/or nitrosurea); and 9 patients with biopsy-confirmed GBM had poor general health (ECOG performance status $>$ 2) or neurologic status (KPS $<$ 60).

The median age of patients enrolled was 75 years, and the median KPS was 70. In all, 160 cycles of temozolomide treatment were administered (median, 4 cycles). Prior surgery included macroscopic total resection (n = 1 patient), partial resection (n = 6 patients), and biopsy only (n = 25 patients). Patient baseline clinical characteristics are shown in Table 1.

TABLE 1
Baseline Clinical Characteristics

Characteristic	No. of patients (%)
Age (yrs)	
Median (range)	75 (70–81)
Gender	
Male	15 (47)
Female	17 (53)
KPS	
Median (range)	70 (60–80)
60	14 (44)
70–80	18 (56)
Prior surgery	
Biopsy only	25 (78)
Partial resection	6 (19)
Macroscopic total resection	1 (3)
Initial MMSE	
Normal ($>$ 25)	12 (38)
Slightly altered (16–24)	8 (25)
Decreased ($<$ 16)	12 (38)
Steroid use at entry	29 (91)
Median tumor size (range) (cm^2)	15.75 (4.00–35.00)
Tumor location	
Temporal	8 (25)
Frontal	6 (19)
Bilobar	6 (19)
Midline	4 (13)
Parietal	4 (13)
Multifocal	2 (6)
Occipital	1 (3)

KPS: Karnofsky performance status; MMSE: Mini-Mental State Examination.

Efficacy

Twenty-nine patients were assessed for response to temozolomide, and 3 additional patients were not evaluable for a response (1 patient had no postoperative evidence of evaluable disease, 1 patient died of a pulmonary embolism before confirmation of PR, and 1 patient had an unconfirmed PR and died after 2 treatment cycles). Based on an ITT analysis, the median OS from the time of diagnosis was 6.4 months (Fig. 1), and the median PFS was 5.0 months (Fig. 2). The 6-month and 12-month survival rates were 60% (95% confidence interval [95% CI], 42–78%) and 25% (95% CI, 9–41%), respectively; and the 6-month and 12-month PFS rates were 44% (95% CI, 26–62%) and 15% (95% CI, 2–28%), respectively. When analyzed from the time of treatment initiation, OS was 6.2 months, and PFS was 4.5 months. When PD did occur, none of the patients received radiotherapy, and only a minority received additional chemotherapy (i.e., nitrosourea in four patients) after discontinuation of temozolomide.

A PR was observed in 9 patients (31%; 95% CI, 14–48%), 12 patients had SD (41%; 95% CI, 23–59%), and 8 patients had PD (28%; 95% CI, 12–44%). The median OS was 13.3 months in patients with PR, 6.4 months in patients with SD, and 4.5 months in patients with PD ($P < 0.001$). The median PFS was 9.2

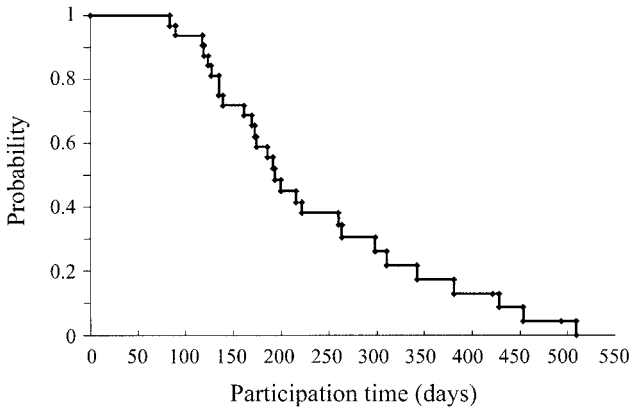

FIGURE 1. Kaplan–Meier analysis of overall survival.

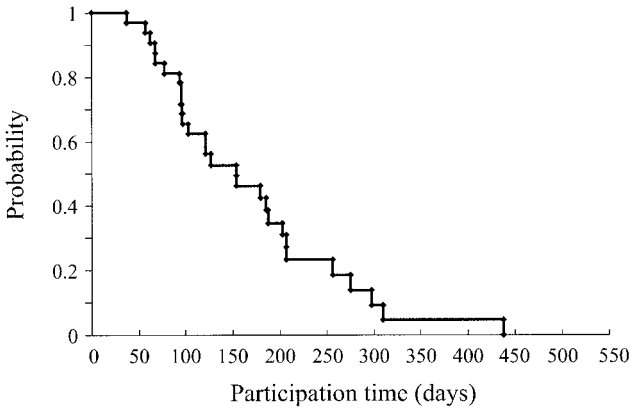

FIGURE 2. Kaplan–Meier analysis of progression-free survival.

months in patients with PR, 4.0 months in patients with SD, and 2.2 months in patients with PD ($P < 0.0001$). Of the nine patients who achieved a PR, five patients showed a response after two cycles of treatment, three patients responded after four cycles, and one patient responded after six cycles of temozolomide therapy.

Based on changes in KPS and MMSE scores, 50% of patients improved with temozolomide therapy, because a 1-level increase in KPS or a 5-point increase in MMSE score was accompanied by stable or decreased steroid dosage in 16 of 32 patients (50%). Of 29 patients who were receiving steroid therapy at the start of the study, 14 patients were able to have their steroid dosage decreased because of improved neurologic status, and an additional 3 patients discontinued steroid therapy completely before eventually experiencing disease progression.

Prognostic Factors

Of the potential factors affecting prognosis (i.e., age, KPS, tumor size, and type of surgery), only baseline tumor size, as estimated by radiographic evidence of the surface area of contrast enhancement, appeared to influence survival. In patients who had a median tumor size < 15.75 cm^2, OS was 8.7 months compared with 5.2 months in patients who had a median tumor size > 15.75 cm^2 ($P = 0.02$). However, PFS appeared to be unaffected by tumor size.

Although the type of surgery performed appeared to have no effect on OS or PFS, there were significant differences between the biopsy and surgery groups in terms of the number of patients in each group, making it difficult to draw meaningful conclusions. In the 7 patients who underwent surgery, the median OS was 8.8 months, compared with 6.3 months in the 25 patients who underwent biopsies. The absence of a significant P value for this comparison may have been due in part to the different numbers of patients in each group.

TABLE 2
Extent of Temozolomide Exposure

No. of treatment cycles received	No. of patients[a]
2	7
3–4	11
5–6	5
7–8	3
9–12	4

[a] Two patients remained on treatment after eight and nine cycles.

Safety

The majority of patients received the 150 mg/m^2 dose of temozolomide, which generally was tolerated well. Patients received a median of 4 cycles (range, 2–12 cycles) of temozolomide therapy (Table 2), and a total of 160 cycles were administered. Most adverse events noted during the 160 cycles of treatment were mild (Table 3), necessitating dose delays and dose reductions in only 13% and 14% of all cycles, respectively. Specifically, 12 patients (38%) had dose delays, and 4 patients (13%) required reductions in temozolomide doses during the study.

Grade 3 or 4 hematologic toxicities were minimal and included 2 patients (6%) with thrombocytopenia (both required platelet transfusions) and 3 patients (9%) with neutropenia (2 patients required therapy with granulocyte-colony stimulating factor). Nonhematologic Grade 3 or 4 adverse events included 2 patients with nausea and 1 patient each with fatigue and emesis. No neurotoxicity or other Grade 3 or 4 toxicities were observed. Grade 1 or 2 hematologic and nonhematologic adverse events included thrombocy-

TABLE 3
Incidence of Adverse Events

	No. of patients (%)	
Event	**Grade 1/2**	**Grade 3/4**
Hematologic		
Thrombocytopenia	17 (53)	2 (6)
Anemia	6 (19)	0 (0)
Neutropenia	4 (13)	3 (9)
Nonhematologic		
Fatigue	11 (34)	1 (3)
Nausea	10 (31)	2 (6)
Constipation	8 (25)	0 (0)
Emesis	6 (19)	1 (3)

topenia, anemia, neutropenia fatigue, nausea, constipation, and emesis (Table 3).

At the time of this analysis (last follow-up), 4 patients remained alive, 2 patients had PD, and 2 remained on treatment with confirmed PRs at 7 months and 8 months after diagnosis. Of the 28 patients who died, tumor progression was the primary cause of death ($n = 26$ patients). Two patients died of other causes, including 1 patient who had a pulmonary embolism that occurred 6 months after diagnosis (this patient had exhibited an unconfirmed PR 20 days earlier and was not considered evaluable for response) and 1 patient who died of cardiopulmonary disease 6 months after diagnosis (this patient had a confirmed PR). None of these deaths were considered related to treatment.

DISCUSSION

Investigators continue to explore chemotherapeutic regimens and combined treatment modalities in an effort to prolong survival and provide symptomatic relief for patients with GBM. Unfortunately, to our knowledge, few of these treatments have been studied in elderly patients, and the regimens that have been tested in the elderly appear to be associated with greater toxicity and reduced efficacy compared with their use in younger populations. No prospective randomized studies have addressed the question of optimal treatment of GBM in the elderly, and this issue continues to be debated.

Surgical resection has been a standard treatment option for patients with malignant gliomas. The advantages of cytoreductive surgery have been documented consistently in younger patients and include a correlation between the extent of tumor resection and the length of survival, decreases in intracranial pressure with subsequent improvement in neurologic function, increased susceptibility of remaining tumor cells to other treatment modalities, and the provision of tissue samples for accurate histologic diagnosis.[3] However, the results from retrospective studies suggest that prolongation of survival after surgery is minimal in patients age $>$ 65 years.[8]

It has been shown that the use of radiation therapy after surgical resection improves survival in elderly patients with malignant gliomas, particularly those with a good performance status.[5,6,14] However, the survival benefit after radiation therapy was significantly shorter in patients age $>$ 70 years compared with patients ages 65–70 years.[9] In addition, to our knowledge the optimal schedule for radiation therapy in the elderly has yet to be defined because of the potential for toxicity and the inconvenience of the standard schedule of 60 grays (Gy) in 30 fractions over 6 weeks. The limits of the efficacy of radiotherapy also were underlined in the study of Meckling et al., who studied 103 elderly patients with malignant gliomas and found that 19% of patients were unable to complete a full course of radiation therapy because of worsening neurologic status or death (mainly because of PD) or, in part, because of acute toxicity.[5] Many patients also are unhappy with the alopecia that accompanies radiation therapy. Finally, delayed central nervous system (CNS) toxicity after radiation therapy has been reported as a function of age.[15]

The optimal schedule of radiation therapy for the elderly has yet to be defined due to the potential for toxicity and the inconvenience of the standard schedule of 60 Gy in 30 fractions over 6 weeks, particularly when considering an estimated median survival of 5–6 months. Compliance can be an issue with conventional radiation therapy, because patients often must travel to receive multiple treatments. Hypofractionated radiation therapy (e.g., 50 Gy in 20 fractions over 4 weeks) has been evaluated as an alternative to conventional dosing regimens and appears to have similar efficacy in elderly patients with GBM, and it reduces the overall treatment time by $>$ 33% without an apparent increase in toxicity.[16] A shorter course of radiation (30 Gy in 6 fractions) also had efficacy comparable to that of conventional radiation therapy in patients age $>$ 60 years with malignant gliomas.[14] Thus, additional studies are needed not only to identify which elderly patients with malignant gliomas may be the best candidates for radiation therapy but also to define more clearly the optimal radiation schedule. In this regard, an ongoing randomized clinical trial in France conducted by the Association des NeuroOncologues d'Expression Francaise group will evaluate best supportive care versus radiotherapy. In addition, an ongoing, 3-arm Nordic trial will evaluate standard radiotherapy versus hypofractionated radio-

therapy (34 Gy in 10 fractions) versus temozolomide alone.

Several studies have investigated the role of chemotherapy in the treatment of primary brain tumors in elderly patients. Pierga et al. studied 30 patients age > 70 years with malignant gliomas who underwent surgery; received radiation therapy; and, in some patients, received reduced-dose chemotherapy: either carmustine (BCNU) or combined procarbazine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosurea, and vincristine (PCV).[17] The median survival was longer in the 12 patients who received chemotherapy (13.5 months) compared with patients who did not receive chemotherapy (6.2 months). However, patients were selected to receive chemotherapy because of their good performance status. In addition, 4 of 12 patients (33%) who received chemotherapy experienced World Health Organization Grade 3 or 4 hematologic toxicity.

Gilbert et al. studied a regimen of BCNU and cisplatin followed by standard radiotherapy in a subgroup of 17 patients age ≥ 65 years and reported a response rate of 76% with a median survival of 11.9 months.[18] Their small study population had better prognostic factors compared with the population in the current study, including a younger median age (71.6 years), better neurologic status (median KPS, 78.8), and more patients who underwent tumor resection (35% vs. 22%). However, this BCNU/cisplatin regimen has been associated with potentially serious adverse events, because 40 of 47 patients of all ages (85%) experienced Grade 3 and 4 toxicities.[19]

Temozolomide is an attractive chemotherapeutic option in patients with malignant gliomas. In addition to its ability to cross the blood-brain barrier and its proven efficacy against CNS malignancies,[10,11] temozolomide has a favorable safety profile and offers the convenience of oral administration. The results from several recent clinical trials evaluating temozolomide in the treatment of GBM in elderly patients, including the current study, are summarized in Table 4. Despite the advanced age (> 70 years) in the current study population, the response rates observed with single-agent temozolomide as first-line therapy for GBM (31% of patients achieved a PR with an additional 41% of patients who had SD) are promising. Temozolomide treatment also was associated with neurologic improvement that corresponded with decreased steroid dosage in 50% of patients. Moreover, temozolomide was tolerated well, with Grade 3 and 4 toxicities occurring in relatively few patients.

Although an earlier study by Gilbert et al.[12] of temozolomide in patients with newly diagnosed GBM reported a slightly higher response rate and longer median OS, that study was not restricted to an elderly population and raised a different question about the value of temozolomide in malignant gliomas when administered before radiotherapy. In that study, patients had better prognostic factors compared with patients in the current study, including a lower median age (55 years), a higher rate of tumor resection (61% vs. 22%), and better performance status at baseline (64% had a KPS ≥ 90). In addition, the patients in the study by Gilbert et al. also received radiotherapy as part of their treatment, so therefore the results in terms of survival cannot be compared directly.[12]

TABLE 4
Recent Clinical Studies of Temozolomide in Elderly Patients with Glioblastoma Multiforme

Study	Patients (*n*)	Age (yrs)	RT	CT	Response rate (%)	Median survival (mos)	One-yr survival (%)
Gilbert et al., 2002[12]	36	16–71	Yes	TMZ	42	13.2	18.0[a]
Brandes et al., 2003[20]	24		Yes	No	NR	11.2	31.6
	32	> 65	Yes	PCV	NR	12.7	56.3
	23		Yes	TMZ	NR	14.9	72.5
Glantz et al., 2003[21]	32	≥ 70[b]	No	TMZ	NR	6.0	11.88
	54		Yes	No	NR	4.1	9.26
Current study	32	> 70	No	TMZ	31	6.4	25.0

RT: radiotherapy; CT: chemotherapy; TMX: temozolomide; NR: not reported; PCV: procarbazine, lomustine, and vincristine.

[a] The 2-year survival rate was reported.

[b] Two patients had anaplastic astrocytoma.

Brandes et al. studied 79 consecutive patients who were referred between 1993 and 2000 who underwent surgery and received radiotherapy alone or with adjuvant chemotherapy using either PCV or temozolomide.[20] The median OS and the median time to disease progression were increased significantly in patients who received radiotherapy plus temozolomide (but not PCV) compared with radiotherapy alone. Grade 3–4 hematologic toxicity also was greater in the PCV arm compared with the temozolomide arm. Compared with the current study, patients who were treated with temozolomide in the study by Brandes et al. were younger (median age, 68 years), had better neurologic status (median KPS, 77 vs. 70), underwent surgery more (100% vs. 22%), and all received radiotherapy, which may account in part for the longer survival, particularly compared with other studies in that population. Further studies are needed to identify patients for whom temozolomide treatment may be more beneficial as an adjuvant to radiation therapy rather than as a single agent.

Similar to the results of the current study, survival in the temozolomide cohort in the retrospective study by Glantz et al. was 6 months, which was not different

statistically from the survival of patients who received radiotherapy alone (4.1 months). However, in the study by Glantz et al., no data were presented concerning response rates or neurologic improvement.[21]

In the current study, analysis of the potential factors affecting prognosis—age, KPS, tumor size, and type of surgery—revealed that only baseline tumor size was predictive of survival. Other studies conducted in elderly patient populations have shown conflicting results, with some reporting that age only[9]; age, neurologic function, and performance status[5,6]; or the extent of surgery[8] were predictive of survival. The lack of a clear relation in the current study between the response rate (and associated improvements in median OS and PFS) and the usual prognostic factors may indicate that other factors are better predictors of clinical outcomes in this patient population. In fact, there is evidence to suggest that specific genetic changes may be predictive of response in patients with oligodendrogliomas or astrocytomas.[22,23] However, to our knowledge to date, this has not been evaluated extensively in patients with GBM.

Temozolomide is a safe, effective, and convenient treatment for elderly patients with newly diagnosed GBM and may be an appropriate first-line, single-agent treatment in this population. In particular, patients age $\geq$ 70 years appear to be a distinct population that may benefit from less invasive treatment. The course of treatment for elderly patients requires careful consideration, and future studies will be necessary to determine the role of temozolomide with or without radiation therapy in the treatment of elderly patients with newly diagnosed GBM.

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