Temozolomide as an Alternative to Irradiation for Elderly Patients with Newly Diagnosed Malignant Gliomas

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BACKGROUND. The optimal treatment for elderly patients (defined as patients 70 years of age or older) with malignant gliomas (MG) remains controversial. Some physicians advocate withholding therapy following diagnosis based on the observation that elderly patients do not tolerate adjuvant radiotherapy. The availability of temozolomide (TMZ), a new alkylating agent with antiglioma efficacy, offers another potential therapeutic option for these patients. The drug can be administered orally at home with minimal morbidity.

METHODS. The authors retrospectively reviewed a cohort of 86 consecutive elderly MG patients from three institutions, 32 of whom received monthly TMZ in lieu of radiation.

RESULTS. Initial Karnofsky performance score was the only predictor of survival in this cohort. No difference in survival was noted between these two groups. Toxicity was minimal in the chemotherapy-treated group and a higher percentage of patients receiving chemotherapy died at home.

CONCLUSIONS. The authors concluded that TMZ is as effective as irradiation as a treatment of elderly patients with MG. It is an alternative and, perhaps, a superior therapeutic option to irradiation, based on its ease of administration and low morbidity. ***Cancer* 2003;97:2262–6.** © *2003 American Cancer Society.*
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Age has such a striking negative influence on survival[1–5] that it may outweigh any benefits of treatment for elderly patients with malignant glioma (MG). Although radiotherapy (RT) has been the foundation of postoperative treatment for more than two decades,[6,7] its value for the older patient with MG remains less clear.

RT may be less effective in prolonging survival of the elderly patient with MG because it is either less effective against the tumor or more toxic to the normal brain. Therefore, RT may be more toxic for the elderly patient because of a limited cerebral reserve.[8] Elderly patients are also more susceptible to RT-induced leukoencephalopathy, brain atrophy, and, ultimately, dementia due to the presence of preexisting vascular changes. The higher incidence of risk factors such as hypertension, diabetes mellitus, and atherosclerosis also predisposes the elderly to vascular injury, the pathologic substrate of radiation-induced brain injury.[9] The poor tolerability and limited efficacy of RT in elderly patients, coupled with the mandate to provide high-quality care and longer survival, provide strong justification for exploring alternative therapies.

Chemotherapy has not been advocated as an alternative treat-

TABLE 1
Demographics of Patient Cohort

Characteristics	Entire group (n = 86)	RT cohort (n = 54)	TMZ cohort (n = 32)	P value RT vs. TMZ
Mean age (SD) [range]	73.8 (4.12) [70–91]	73.3 (3.76) [70–87]	74.5 (4.64) [70–91]	0.2066
Male (%)	53 (62)	32 (59)	21 (66)	0.6489
Mean KPS (SD) [range][a]	67.7 (13.34) [40–70]	67.41 (12.16) [40–90]	67.67 (15–33) [50–90]	0.8111
Image confirmed total resection (%)	16 (18.6)	11 (20.3)	5 (15.6)	0.7757
GBM (%)	84 (98)	54 (100)	30 (94)	0.1357
Survival; mos (median, range)	5 (0.3–30+)	4.1 (0.3–22.5)	6 (0.7–30+)	
One-yr survival rate (%)	10.31	9.26	11.88	0.1983 (log rank test)

RT: radiotherapy; TMZ = temozolomide; KPS: Karnofsky performance score; SD: standard deviation; GBM : glioblastoma multiforme.
[a] Assessed postoperatively.

ment for elderly patients because MGs are chemoresistant[10,11] and the side effects of chemotherapeutic strategies are severe.[12–14] However, the recent availability of less toxic oral agents that can be administered at home may be one way of improving a patient's quality, if not quantity, of life. Temozolomide (TMZ; Schering-Plough, Kenilworth, NJ) is an oral alkylating agent with 100% oral bioavailability.[15] It has modest activity against MG at first recurrence[16,17] and is well tolerated in patients with newly diagnosed MG.[18] When TMZ became commercially available in 1999, we offered our elderly patients with newly diagnosed MGs the choice of receiving RT or TMZ in lieu of irradiation. Our initial results are favorable, albeit retrospective, and show that elderly patients receiving adjuvant TMZ survive at least as long as those receiving adjuvant irradiation.

MATERIALS AND METHODS

We retrospectively analyzed all consecutively treated MG patients who were older than 70 years of age. These patients were referred to the authors between 1991 and 2002. Patients were referred from the Southwestern Vermont Cancer Center (n = 42), the University of Southern California (n = 38), and the University of Massachusetts (n = 6). Patient-related data were obtained from institutional neurooncology databases and, when necessary, from patients' charts. All patients had histologically verified glioblastoma multiforme (GBM; n = 84) or anaplastic astrocytomas (n = 2). Postoperative contrast-enhanced magnetic resonance image scans obtained within 48 hours of surgery assessed the extent of tumor resection. Patients who were not treated with any postoperative therapy were excluded. All patients were treated with either standard fractionated external beam radiation (180 centigrays [cGy] daily fractions, total tumor dose 60 grays (Gy)) or with monthly TMZ. Since 1999, all patients were offered this choice of treatment. Approximately 40% of patients and their families selected TMZ over irradiation. Regular surveillance post-RT imaging was not performed in this elderly cohort. Consequently, no data are available regarding radiographic response.

Eight-six patients were identified, 54 (63%) of whom received RT as initial therapy. Temozolomide was administered as first-line treatment to 32 patients (37%) at a dosage of 150 mg/m^2 every day for 5 days every 28 days in 11 patients and at a dosage of 200 mg/m^2 for at least one cycle in 21 patients. In the event of lowered blood counts, dose adjustments were made according to published recommendations.[16,17]

Records were reviewed and data were obtained on patients' demographics, postoperative Karnofsky performance scores (KPS), age, gender, extent of operation, histology, tumor location, and survival time since the day of diagnosis. Survival rates were calculated using the Kaplan–Meier method. A log rank test was used to compare survival outcomes between the two treatment groups. A multivariate Cox proportional hazards regression model was used to test the effect of age, gender, KPS, extent of surgery, and treatment on overall survival.

RESULTS

Table 1 summarizes the significant demographic characteristics of this patient cohort. There was no statistically significant difference in either mean age (73.34 years $\pm$ 3.8 vs. 74.5 years $\pm$ 4.6, P = 0.21) or KPS at the time of diagnosis (67.4 $\pm$ 12.2 vs. 68.1 $\pm$ 15.3, P = 0.81) between the 54 patients who received RT and the 32 patients who received TMZ. Stratification of KPS by treatment assignment was as follows: RT: KPS $<$ 50, 9 patients; KPS 60–70, 30 patients; KPS $\geq$ 80, 15 patients; TMZ: KPS $<$ 50, 7 patients; KPS 60–70, 14 patients; KPS $\geq$ 80, 11 patients. Except for two patients

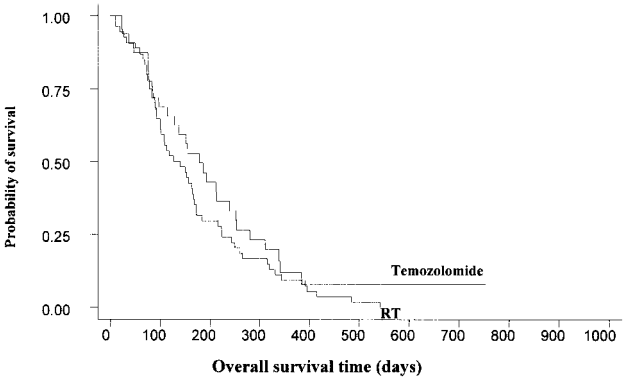

FIGURE 1. Patient survival as a function of treatment ($P = 0.20$, log rank test). RT: radiotherapy.

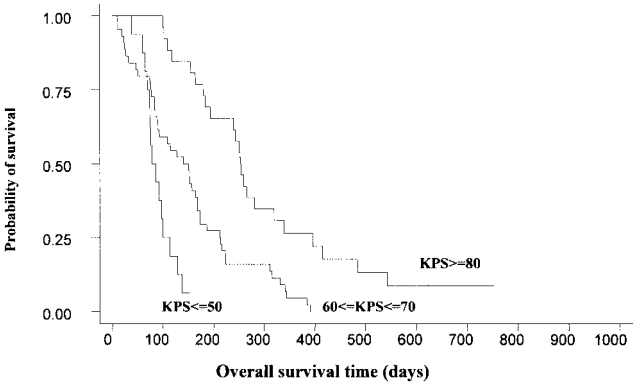

FIGURE 2. Patient survival as a function of postoperative Karnofsky performance score (KPS; $P < 0.0001$, log rank test).

(2.3%), both of whom received TMZ to treat anaplastic astrocytomas, all histologic diagnoses were GBM.

Thirty-two patients received a median of 3.5 cycles of TMZ (range, 1–12 cycles). The only toxicity noted with TMZ was occasional myelosuppression that required a delay in the next cycle or a dose reduction in five patients (15.6%). No patient required transfusions and none developed neutropenic fever. Two patients, who were age 80 years and 91 years, respectively, at the time of diagnosis, completed 12 cycles of TMZ. The 80-year-old patient, who was diagnosed in June 2000 with a right temporal lobe anaplastic astrocytoma after a biopsy was performed, had a KPS of 100 as of August 1, 2002. Fifteen of 54(27.7%) patients did not complete irradiation, 10 due to tumor progression and 5 due to toxicity.

The median survival for the entire cohort was 5 months. Only 10.3% of patients survived 1 year. Median survival times for the TMZ and RT groups were 6 months and 4.1 months, respectively, and the 1-year survival rates were 11.9% and 9.3%. The difference in survival between the two groups was not statistically significant (Fig. 1, $P = 0.198$, log rank test) and did not appreciably change when the two patients with anaplastic astrocytoma were excluded from the analysis. The differences in survival among subgroups of KPS were statistically significant (Fig. 2, $P < 0.0001$, log rank test for equality of survival functions). A multivariate Cox proportional hazards regression model was used to test the effect of age, gender, extent of surgery, postoperative KPS, and treatment group on overall survival. A postoperative KPS of 60 or 70 (hazards ratio = 0.329, $P = 0.001$) and a KPS $\geq$ 80 (hazards ratio = 0.119, $P < 0.0001$) were protective factors compared with a KPS less than or equal to 50. The hazards ratios for age (0.98, $P = 0.44$) and treatment (i.e., TMZ compared with RT; 0.74, $P = 0.21$) were not significantly different between the two groups.

Place of death was determined for 82 patients (95%). Seventy-five percent of patients receiving TMZ died at home compared with 61% of those receiving RT. This difference was not statistically significant ($P = 0.423$, chi-square analysis).

DISCUSSION

A dramatic increase in the incidence of central nervous system tumors has occurred among the elderly population.[19–23] Studies indicate that the diagnostic rate of primary brain tumors has nearly doubled in the 65–74-year-old population and has more than doubled in 75–84-year-old patients.[24] At the same time, the size of the elderly population has increased (i.e., both the population and the age-specific incidence are increasing). Therefore, the treatment of MGs in the elderly represents an increasingly frequent challenge for the physician.

The most important adverse prognostic factor in patients with MG is advanced age. Patients older than 60 years at the time of diagnosis survive for significantly shorter periods than patients who are younger than 45 years.[4,25–29] Several possibilities may explain this difference, including increased perioperative and postoperative morbidity and mortality due to underlying diseases, worse performance status, and more aggressive tumors.[10,11,30–32] Because age is not a significant prognostic factor in GBM patients who are not treated postoperatively,[10] decreased survival reflects more of an inherent resistance to treatment rather than a difference in growth rate.

Except for a few studies, the elderly patient cohort has been ignored in the literature.[33] According to these studies,[8,34–38] elderly patients have poor survival, with median survival ranging from 4 to 6 months. Occasionally, some patients do much better with RT. Several analyses also suggested that patients

with good postoperative performance status had better survival. These studies recommended RT for elderly patients with good performance status.

However, RT is not a trivial treatment for the elderly patient. Even when treatment volumes are decreased, patients frequently worsen during treatment and have to make daily trips to the hospital to receive treatment draining. For all these reasons, physicians are inclined to withhold treatment so as to maximize patients' quality of life. Published studies indicate that up to 50% of elderly patients may not receive treatment.[34,36,39] Therefore, an agent that was well tolerated, was equally as effective as RT, and could be administered easily would represent an attractive alternative to irradiation. Although the findings presented in this study are retrospective and uncontrolled, they demonstrate that TMZ is as effective as conventional RT for older patients with MG, and is better tolerated. However, a randomized clinical trial would be required to substantiate this assertion.

At least two interpretations might explain the equivalence of survival between patients treated with RT and those treated with TMZ. Either TMZ is as effective as RT or neither is effective. In support of treatment being effective is the overall median survival of 5 months in this cohort, which is longer than the period reported for supportive care only (i.e., 1–3.5 months).[6,37] However, this benefit is relatively modest. Therefore, the results of this study cannot exclude the possibility that both treatments are ineffective.

Nevertheless, elderly patients are able to tolerate TMZ chemotherapy well and maintain excellent performance status for several months. Such a result is unusual with RT. After RT, elderly patients almost always complain of excessive fatigue and frequently develop increased neurologic deficits. It is noteworthy that the two elderly patients with anaplastic astrocytomas in this cohort who received TMZ had prolonged survival with maintenance of independent living. The absence of any morbidity in these two patients suggests a particular role for TMZ in this special subset of elderly patients with nonglioblastomatous MGs.

There are strong clinical, economic, and social imperatives for determining the optimal age-specific treatment approach for this tumor. A randomized, controlled trial is the best way to obtain that information, but such a trial would be difficult to conduct for a number of reasons. First, a large number of patients would be required for such a study. Even if the magnitude of the difference in the 1-year survival rate between the TMZ and RT treatment arms in our study (11.9% vs. 9.3%, a 27% relative increase) is real, more than 2000 patients per treatment arm (assuming a two-sided α of 0.05 and 80% power) would be required to show a significant difference, assuming a 10% 1-year survival rate in the RT group. Second, elderly patients are accrued rarely to clinical trials.[12–14,39] Finally, even a scrupulously designed and executed trial might show no difference in survival outcome between treatment arms. Despite these obstacles, a randomized trial would be ideal. Currently, two randomized European trials (a Nordic trial and a French trial) are evaluating the role of RT (conventionally fractionated or hypofractionated) versus TMZ in the treatment of elderly patients with MG. In the meantime, we believe, based on our study, that it is appropriate to offer TMZ to elderly patients with newly diagnosed MG as an alternative to cranial irradiation as a first-line therapy.

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