Can We Afford To Add Chemotherapy to Radiotherapy for Glioblastoma Multiforme? Cost-Identification Analysis of Concomitant and Adjuvant Treatment with Temozolomide until Patient Death

Jean-Blaise Wasserfallen, M.D., M.P.P.[1]
Sandrine Ostermann, Ph.D.[2]
Alessia Pica, M.D.[3]
René-Olivier Mirimanoff, M.D.[3]
Serge Leyvraz, M.D.[2]
Jean-Guy Villemure, M.D.[4]
Roger Stupp, M.D.[2]

[1] Health Technology Assessment Unit, University Hospital Center of Vaud, Lausanne, Switzerland.

[2] Multidisciplinary Oncology Center, University Hospital Center of Vaud, Lausanne, Switzerland.

[3] Radiation Oncology Service, University Hospital Center of Vaud, Lausanne, Switzerland.

[4] Neurosurgery Service, University Hospital Center of Vaud, Lausanne, Switzerland.

The authors thank Ralph Crott, M.D., for his critical review of an earlier version of the article.

Address for reprints: Jean-Blaise Wasserfallen, M.D., M.P.P., Health Technology Assessment Unit, University Hospital Center of Vaud, Rue du Bugnon 46, CH-1011 Lausanne, Switzerland; Fax: (011) 41 213141818; E-mail: jean-blaise.wasserfallen@chuv.hospvd.ch

Received June 22, 2004; accepted July 26, 2004.

BACKGROUND. Adding temozolomide (TMZ) to standard radiotherapy as a first-line therapy for glioma may increase costs to a disproportionate degree compared with the resulting survival benefits.

METHODS. Forty-six consecutive patients (28 males and 18 females; median age, 52 years; age range, 24–70 years) received concomitant TMZ with radiotherapy for 6 weeks followed by adjuvant TMZ for 6 cycles, and they were followed until disease recurrence and then until death. The authors assessed the costs associated with the four phases of treatment from a hospital-centered perspective.

RESULTS. Treatment was discontinued early in 3 patients, 9 patients, and 15 patients during concomitant TMZ, before adjuvant TMZ, and during adjuvant TMZ, respectively. Karnofsky index values varied between 85% (at the beginning of treatment) and 76% (at the end of treatment). The nature of care after disease recurrence was diverse. Overall survival ranged from 1.4 months to 64.3 months (median, 15.8 months) and was better if surgical debulking could be carried out before treatment. Global costs amounted to €39,092 ± €21,948 (concomitant TMZ, €14,539 ± €4998; adjuvant TMZ, €13,651 ± €4320; follow-up, €6363 ± €6917; and recurrence, €12,344 ± €18,327), with 53% of these costs being related to the acquisition of TMZ; this represented an eightfold increase in cost compared with radiotherapy alone.

CONCLUSIONS. TMZ may be an effective but costly adjuvant outpatient therapy for patients with glioblastoma multiforme. Definite cost-effectiveness/utility must be assessed in a randomized Phase III trial. ***Cancer* 2004;101:2098–105.**

KEYWORDS: chemotherapy, economics, glioblastoma, quality of life, radiotherapy.

Glioblastoma multiforme (GBM), the most malignant type of brain tumor, accounts for 15–20% of all primary brain tumors but < 2% of all adult malignancies. Despite surgery and/or radiotherapy, the prognosis for patients with GBM remains poor, with a median overall survival of only 9–12 months.[1–3] The use of adjuvant chemotherapy remains controversial for patients with GBM,[4] and no survival benefit was shown in a large randomized trial.[5]. Nevertheless, a metaanalysis based on individual patient data[6] suggested a 5% absolute increase in 2-year survival linked to the addition of chemotherapy. At present, chemotherapy usually is reserved for the purely palliative treatment of patients who have recurrent disease.[7,8]

Temozolomide (TMZ), a novel alkylating agent, recently has been introduced to the clinical setting. It has demonstrated some degree of

DOI 10.1002/cncr.20619
Published online 23 September 2004 in Wiley InterScience (www.interscience.wiley.com).

clinical activity (albeit modest) in patients with melanoma[9] and in patients with recurrent high-grade glioma.[10,11] Compared with procarbazine, TMZ improved health-related quality of life in patients with recurrent GBM.[12] In patients with anaplastic astrocytoma at first recurrence, TMZ yielded a high single-agent response rate, a favorable safety profile,[13] and improved health-related quality of life.[14] However, the treatment of tumors at a late stage of disease is complicated by cellular resistance to the agents that are used and frequently results in only short exposure to chemotherapy due to tumor progression. High intratumoral levels of O^6-methylguanine DNA methyltransferase (MGMT), an enzyme that mends TMZ-induced methylations of the position of the guanine nucleic acid,[15] have been linked to TMZ resistance. Different drug administration schedules have been proposed to overcome this phenomenon, including continuous TMZ administration.[16]

When new agents or treatment modalities are introduced to the clinic, attention should focus not only on efficacy and safety but also on costs and on the relation between cost and effectiveness. This is of particular importance for agents with high acquisition costs, such as TMZ. Only one study evaluated TMZ from an economic perspective in patients with metastatic melanoma. That post hoc economic analysis demonstrated that using TMZ instead of dacarbazine required expenditure of an additional $37,000 per life-year or $101 per day of life gained (the incremental cost-effectiveness ratio).[17] To our knowledge, however, none of the published studies on brain tumor treatment directly examined the issue of cost. The United Kingdom National Institute for Clinical Excellence (NICE) published guidelines that focused on the use of TMZ in the treatment of patients with recurrent GBM and extrapolated drug acquisition costs from the survival data observed in a randomized controlled study that compared TMZ with procarbazine.[18] That report concluded that, except in the context of a randomized controlled trial, TMZ should not be recommended as first-line chemotherapy for patients who have experienced failure following standard treatment, which involves surgery (when feasible) plus radiotherapy. In contrast, TMZ was identified as a possible treatment option at the time of first recurrence or disease progression for patients who have experienced failure following first-line chemotherapy with other agents. The use of TMZ in adjuvant chemotherapy was not considered.[18]

In an ongoing effort to improve the outcomes of patients who are treated for GBM, the use of TMZ in the early stages of disease as a concomitant and adjuvant treatment option (in conjunction with radiotherapy) has been suggested. The preliminary results of a pilot Phase II study conducted at our institution (University Hospital Center of Vaud, Lausanne, Switzerland) are promising[19] and await confirmation in a large randomized trial. Prospective economic analyses conducted alongside Phase II clinical trials allow identification of the most important cost items to be collected in subsequent Phase III trials. The current report analyzes the effectively incurred costs associated with this novel therapeutic option from the time of the pilot study until patient death, leading to a realistic estimation of additional costs expected to arise due to advances in drug therapy.

MATERIALS AND METHODS

The clinical results of a Phase II study that involved 64 patients and assessed the benefit of concomitant and adjuvant TMZ administration along with standard radiotherapy for patients with newly diagnosed GBM were published recently.[19] The 46 consecutive patients who were treated at our institution and for whom detailed and complete cost data were available were included in the current economic analysis. Details of the treatment protocol, patient characteristics, and outcomes have been reported previously.[19] In brief, TMZ (75 mg/m^2 per day) was administered 1 hour before irradiation for 6 weeks and was followed, after a 4-week interval, by adjuvant TMZ (200 mg/m^2 per day) for 5 days once every 28 days for up to 6 cycles. Radiotherapy involved conformal (3-dimensional planning) irradiation with the use of 6–18-megavolt linear accelerators. The total dose to the primary tumor volume was 60 grays (Gy) delivered in 30 daily fractions of 2 Gy. Supportive care during the concomitant TMZ treatment phase included pentamidine inhalations for *Pneumocystis carinii* pneumonia prophylaxis twice during concomitant therapy and antiemetics as needed during concomitant and adjuvant TMZ. Patient monitoring consisted of medical visits, blood tests (every week during concomitant treatment and the first cycle of adjuvant treatment, and monthly thereafter), and brain imaging studies (magnetic resonance images or computed tomography scans) every other month to detect recurrent disease. During follow-up, patients were seen monthly, and blood tests and brain imaging studies were performed every other month or according to clinical need until patients developed recurrent disease. After recurrence, all treatment and follow-up decisions were left to the clinician's discretion. The protocol was approved by the local ethics committee, and all patients provided written informed consent.

Quality of life was not formally assessed in the current trial. We used Karnofsky performance status

(KPS)[20] and Eastern Cooperative Oncology Group (ECOG) performance status[21] at each visit as surrogate measures. It has been shown that these physician-based health status measures are closely correlated with each other;[22] in addition, it has been shown that KPS serves as a relatively good proxy for quality of life.[23] Missing single values on specific dates were imputed using the mean of the preceding value and the value that immediately followed. The values observed at the beginning and at the end of each treatment phase and during the follow-up period were compared using paired *t* tests. Statistical significance was assumed when P was < 0.05.

The analysis was censored, regardless of treatment phase or follow-up period, upon the emergence of clinical and/or radiologic evidence of disease recurrence or on December 31, 2003, for patients who were still in their follow-up period. The cost analysis was based on effectively incurred resource use, which was assessed using detailed prospective data. It did not include the costs of the initial surgical procedure performed to establish the diagnosis. Cost assessment singled out the 4 distinct periods of treatment and follow-up: Period 1, radiotherapy and concomitant TMZ; Period 2, adjuvant TMZ; Period 3, follow-up (from the end of TMZ treatment until disease recurrence); and Period 4, care after disease recurrence until patient death.

The cost of hospitalization was computed at a fixed rate for acute or palliative care, with this computation based on the cost effectively incurred for such a treatment at our institution. Personnel costs linked with outpatient visits were computed as *wages* $\times$ *time* and were extracted from the hospital information system. The costs of drugs, brain imaging studies, and laboratory tests were computed as billing prices and were extracted from published price lists. Radiotherapy costs were composed of costs associated with initial evaluation and treatment planning and costs associated with each session administered. Only direct medical costs were considered from a hospital-centered perspective. Unit costs are displayed in Table 1.

Costs were computed for each of the four periods and are reported as mean costs $\pm$ standard deviations. For the follow-up and recurrence periods, monthly costs were computed to take into account the individually variable durations of these periods. In addition, a total cost was computed for each patient and was averaged over the whole cohort. Finally, TMZ acquisition costs were computed for each patient, for each treatment period, as a proportion of the cost of both concomitant and adjuvant periods, and also as a proportion of global cost. Swiss francs (CHF) were converted into Euros (€) at an exchange rate of 0.67 (€1.00 = 1.50 CHF = £0.626 = $0.9).

TABLE 1
Unit Costs for Temozolomide Treatment

	Cost (€)
Personnel (per hr)	
Physician	32.6
Nurse	27.6
Radiologic technician	27.6
Drugs	
TMZ	
250 mg	280.2
100 mg	123.5
20 mg	25.7
5 mg	8.0
Pentamidine 300 mg aerosol	220.4
Metoclopramide	
50 mg i.v.	14.1
10 mg orally administered	0.7
Alizapride 50 mg orally administered	0.2
Ondansetron	
4 mg orally administered	9.4
8 mg orally administered	15.7
Radiology	
CT for radiotherapy planning	511.2
MRI	555.9
Laboratory tests	
Blood count	9.6
Complete blood count	16.0
Radiotherapy	
Planning	966.7
Session	33.3
Hospital (per day)	
Acute care	233.3
Palliative care	166.7

TMZ: temozolomide; i.v.: intravenously administered; CT; computed tomography; MRI: magnetic resonance imaging.

RESULTS

Patient and Treatment Characteristics

There were 28 men and 18 women, with a median age of 52 years (range, 24–70 years), in the study cohort. Thirty-five patients (76%) underwent surgical debulking (63% underwent complete resection); 11 patients (24%) had inoperable tumors due to extent or localization, and their diagnoses were established by stereotactic biopsy only.

Detailed resource use during the four periods is summarized in Table 2. Three patients (6.5%) stopped receiving concomitant TMZ early during the course of radiotherapy (due to disease progression in 2 patients and to chronic viral hepatitis in 1 patient). Thirteen patients (28%) required hospitalization in an acute care setting for a mean of 5 days (range, 1–95 days),

TABLE 2
Distribution of Resources Used during the Different Periods of Temozolomide Treatment and Follow-Up until Patient Death[a]

Type of resource	Concomitant TMZ (n = 46)	Adjuvant TMZ (n = 35)	Follow-up (n = 19)	Recurrence (n = 43)	Total (n = 46)
Period duration (mos)	2.4 ± 0.6	4.5 ± 1.7	18.5 ± 19.7	9.1 ± 9.9	22.0 ± 18.4
TMZ treatment duration (days)	41.0 ± 8.0	23.0 ± 9.0	—	—	59.0 ± 17
Radiotherapy duration (days)	31.0 ± 3.0	—	—	—	31.0 ± 3.0
Medical visits (no.)	8.9 ± 4.1	9.0 ± 4.1	5.3 ± 5.5	8.0 ± 9.8	25.4 ± 14.8
Brain imaging scans (no.)	3.4 ± 1.5	2.7 ± 1.1	5.4 ± 4.9	2.7 ± 3.9	10.3 ± 6.6
Laboratory tests (no.)	14.2 ± 9.0	14.0 ± 7.7	4.8 ± 4.7	10.6 ± 14.2	36.7 ± 20.3
Hospitalization (days)					
Acute care	5.5 ± 16.3	3.9 ± 7.7	5.0 ± 12.4	2.1 ± 6.6	12.5 ± 20.4
Palliative care	3.8 ± 14.9	2.9 ± 10.0	11.6 ± 29.1	8.9 ± 24.2	19.1 ± 48.1

TMZ: temozolomide.
[a] All table entries are mean values ± standard deviations.

and 5 patients (11%) required hospitalization in a palliative care setting for 4–90 days.

Eleven patients (24%) did not receive adjuvant TMZ (the 3 patients who stopped receiving concomitant TMZ treatment and 8 other patients for the following reasons: disease progression in 3 cases, a significant decrease in performance status in 2 cases, patient decision in 1 case, and *Pneumocystis carinii* infection in 2 cases). Sixteen patients (35%) stopped receiving adjuvant TMZ treatment prematurely—i.e., before completing all 6 planned cycles (due to disease progression in 13 cases, second surgical intervention in 1 case, a decrease in performance status in 1 case, and patient decision in 1 case). Nineteen patients (41.5%) completed all planned therapy. Twelve of those patients (34%) required hospitalization in an acute care setting for a mean of 4 days (range, 1–29 days), and 3 (3%) required hospitalization in a palliative care setting for 21–48 days.

Treatment was tolerated well by most patients, and toxicity, if present, was primarily hematologic.[19] Quality of life, as assessed using the KPS and ECOG scales, was minimally and transiently impaired during both concomitant TMZ and adjuvant TMZ (KPS, 84.1 ± 14.0 before and 76.4 ± 17.3 after concomitant TMZ; ECOG performance status, 0.7 ± 0.7 before and 1.1 ± 0.9 after concomitant TMZ; KPS, 81.2 ± 12.2 before and 77.0 ± 16.7 after adjuvant TMZ; ECOG performance status, 0.9 ± 0.7 before and 1.2 ± 0.9 after adjuvant TMZ).

Analysis of the follow-up period (before disease recurrence), which lasted for 0.5–59.7 months (median, 8.7 months), involved 19 patients. Three of these patients (16%) required hospitalization in an acute care setting for 23–44 days, and 3 other patients required hospitalization in a palliative care setting for 45–101 days.

Forty-three patients developed recurrent disease. Among them, 23 patients (53%) received chemotherapy (12 patients received daily TMZ for 3–6 weeks; 5 patients received a combination of TMZ and irinotecan; 7 patients received combined procarbazine, lomustine, and vincristine; and 7 other patients received chemotherapeutic or immunotherapeutic agents). Eight patients received multiple treatments. Eight of 23 patients (34%) required hospitalization in an acute care setting for 1–35 days, and 6 of those patients (14%) required hospitalization in palliative care setting for 45–115 days.

At the time of the current analysis, 3 patients (6.5%) were still alive without evidence of recurrent disease after follow-up periods of 47 months, 26 months, and 21 months, respectively. On the whole, the patient attrition rate was linear over the entire observation period.

Costs Associated with Radiotherapy, TMZ Treatment, Follow-Up, and Disease Recurrence

The distribution of observed costs for the various TMZ treatment phases is summarized in Table 3. TMZ treatment had an average cost of €20,952 and was 8 times more expensive than radiotherapy alone. Drug-acquisition costs represented 54% and 75% of the concomitant and adjuvant costs, respectively. Most of the costs during the follow-up period were attributable to hospitalization and brain imaging studies, and most of the costs that arose during the recurrence period were attributable to hospitalization in a palliative care setting and additional chemotherapy.

Altogether, the total cost of care for patients with GBM ranged from €10,893 to €125,275, with a median of €34,362; 55% of this cost was attributable to TMZ acquisition. These costs amounted to a median of

TABLE 3
Distribution of Costs during the Different Periods of Temozolomide Treatment and Follow-Up until Patient Death

	Cost (€)[a]				
Type of cost	Concomitant TMZ (n = 46)	Adjuvant TMZ (n = 35)	Follow-up by month (n = 19)	Recurrence by month (n = 43)	Total (n = 46)
Period duration (mos)	2.4 ± 0.6	4.5 ± 1.7	18.5 ± 19.7	9.1 ± 9.9	22.0 ± 18.4
Radiotherapy	2478 ± 92	—	—	—	2478 ± 92
Medical visits	119 ± 54	113 ± 57	5 ± 4	11 ± 10	334 ± 197
TMZ/chemotherapy	7411 ± 1667	9808 ± 4089	0	674 ± 1131	23,645 ± 19,544
Pneumocystis prophylaxis	430 ± 449	0	0	0	430 ± 449
Antiemetics	5 ± 10	255 ± 288	0	2 ± 4	200 ± 223
Brain imaging	1992 ± 844	1558 ± 625	227 ± 160	131 ± 147	5951 ± 3805
Laboratory tests	197 ± 117	213 ± 116	6 ± 6	17 ± 15	543 ± 310
Hospital care	1907 ± 4796	1369 ± 2842	592 ± 1684	902 ± 1937	6110 ± 10,581
Total	14,539 ± 4998	13,651 ± 4320	831 ± 1756	1736 ± 1936	39,092 ± 21,948

TMZ: temozolomide.
[a] Mean ± standard deviation.

€2307 per month of survival, or €27,684 per year of survival.

The Impact of MGMT Status and Surgical Debulking

The methylation status of the MGMT promoter was assessed in 28 resection specimens[15] and was identified as being positive in 21 patients and negative in 7 patients.[24] Inactivation of the MGMT gene by promoter methylation was associated with increased survival.[24] Relative to the 7 patients without MGMT methylation, the 21 patients who tested positive for a methylated MGMT promoter had no difference in outcome, except for a statistically significantly longer follow-up period before they developed recurrent disease (19.6 ± 17.7 months vs. 2.3 ± 1.7 months; P = 0.049). They incurred higher costs of care during follow-up (€4793 ± €3848 vs. €636 ± €633; P = 0.049), but their average monthly costs did not differ. In contrast, the 28 patients for whom surgical debulking was possible, compared with the 11 patients who could not undergo surgery and therefore underwent biopsy only, had dramatically different outcomes: they received more TMZ cycles before developing recurrent disease and thus had longer adjuvant periods (144 ± 50 days vs. 80 ± 24 days; P = 0.032), and they survived for a longer period after the diagnosis of disease recurrence (10.9 ± 10.7 months vs. 4.1 ± 4.7 months; P = 0.014). Consequently, their total cost of care was higher (€41,744 ± €22,132 vs. €30,665 ± €19,983; P = 0.059), but their cost per month of survival was lower (€2289 ± €1542 vs. €4688 ± €2200; P = 0.001), as they required less hospitalization in spite of greater TMZ use. Distributions of the different costs incurred by these two patient groups are summarized in Table 4.

DISCUSSION

The current pilot Phase II study showed that concomitant and adjuvant TMZ administration in conjunction with radiation treatment for patients with newly diagnosed GBM prolonged survival. This treatment regimen was well tolerated, as KPS, a proxy for quality of life, decreased only slightly during both the concomitant and adjuvant treatment periods. In addition, this decrease was transient and disappeared between the two treatment periods for most patients, with KPS remaining stable until the development of recurrent disease. For the 46 patients in the current single-institution cohort, the additional cost of using TMZ as concomitant and adjuvant treatment agent until disease recurrence amounted to €20,952, an 8-fold increase compared with standard radiation treatment alone. Fifty-three percent of total expenses for care until death were attributable to drug acquisition. The cost-effectiveness and cost-utility ratios of this new treatment remain to be computed in a randomized controlled trial. If survival were to increase by 4 months in our healthcare system, as is suggested by the related clinical study,[19] then this additional cost would fall slightly above the commonly accepted upper limit of $50,000 per life year gained.[25]

Nevertheless, adjuvant TMZ chemotherapy may possess significant advantages over other conventional chemotherapy options; specifically, it can be administered orally and on an outpatient basis, two features that are highly valued by patients.[26] TMZ is

TABLE 4
Distribution of Survival and Costs in the Different Periods of Treatment and Follow-Up by Type of Surgical Treatment: Biopsy versus Debulking

	Biopsy (n = 11)		Surgical debulking (n = 35)		
Treatment	**Mean**	**SD**	**Mean**	**SD**	***P* value**
Concomitant TMZ					
Duration (days)	77.5	29.7	72.0	10.4	0.919
Total cost (€)	16,751	6865	13,843	4137	0.308
Adjuvant TMZ					
Duration (days)	80.2	24.2	144.2	50.5	0.032
Total cost (€)	11,135	3867	13,975	4325	0.130
Follow-up					
Duration (mos)	3.9	1.5	20.2	20.1	0.004
Total cost (€)	21,850	6274	4541	4225	0.012
Monthly cost (€)	5781	637	248	138	0.012
Recurrence					
Duration (mos)	4.1	4.7	10.9	10.7	0.014
Total cost (€)	5882	6203	14,565	20,561	0.241
Monthly cost (€)	2223	2800	1569	1561	0.794
Total					
Duration (mos)	8.3	6.3	26.3	18.8	< 0.001
Total cost (€)	30,655	19,983	41,744	22,133	0.059
Medical visits (€)	244	168	362	199	0.053
Drugs (€)	10,246	5274	27,856	20,519	< 0.001
TMZ (€)	9658	5155	24,502	15,892	< 0.001
Brain imaging (€)	2636	1648	6993	3700	< 0.001
Laboratory tests (€)	297	214	620	297	0.002
Hospitalization (€)	14,752	16,648	3394	5909	0.014
Monthly cost (€)	4688	2200	2289	1542	0.001

SD: standard deviation; TMZ: temozolomide.

tolerated well, with $< 10\%$ of patients experiencing any significant side effects. In a randomized Phase II trial involving patients with recurrent GBM, TMZ was compared with procarbazine, another oral alkylating agent.[10] Efficacy in both arms was similar, with a modest increase in survival at 6 months for patients receiving TMZ (60% vs. 44%; $P = 0.019$), translating into a median survival advantage of 6 weeks, which was not statistically significant. However, there was a clear advantage in terms of quality of life for TMZ-treated patients;[12] quality of life improved until disease recurrence in five of seven dimensions of the European Organization for Research and Treatment of Cancer Quality-of-Life (EORTC-QLQ-C30)[27] and Brain Cancer Module (BCM20)[28] questionnaires for patients in the TMZ arm, whereas the procarbazine group experienced deterioration in all seven dimensions. Based on these results, NICE[18] found that the additional cost of TMZ treatment would amount to $51,546 per life year gained and $63,118 per quality-adjusted life year gained.

Another British report assessed the total costs of care for patients with GBM. It showed that, with 75% of the costs being incurred during the initial treatment period,[29] total costs ranged from £1978 to £26,980 per patient, and median costs decreased sequentially as brain tumor prognostic group (according to the Medical Research Council system) went from more favorable to less favorable.[30] Because the mean length of hospitalization was 40 days, inpatient care amounted to the largest share of costs (£7210), followed by surgery (£1296), and radiotherapy (£1173) (Bloor K, unpublished data). In this setting, it becomes especially important to assess whether the administration of TMZ as concomitant and adjuvant therapy, compared with administration of TMZ at the time of recurrence, is associated with improved survival and does not merely add cost with little accompanying benefit. The detailed analysis of resource use in the current study allowed us to estimate the cost of this combined treatment modality in a specific healthcare system.

Our analysis has some limitations. First, it represents a single-center experience involving a small number of patients (with no control group) who belong to a single healthcare system. Second, although KPS is a relatively good proxy for quality-of-life assessment[23] and is used frequently by clinicians to assess their patients, it focuses on physical activity and does not take into account 1) other dimensions that usually

are included in the quality-of-life assessment[31] and 2) patients' preferences. With these limitations in mind, the KPS was used only as a surrogate for quality of life in the current pilot study. Third, the protocol called for brain imaging every other month, compared with every 3 months or even less frequently in common medical practice. With increasing experience, the frequency and intensity of surveillance will diminish, and costs will decrease accordingly. Fourth, cost data were censored on December 31, 2003, for the 3 patients who were without evidence of disease progression, which may have biased cost estimates. However, because the median follow-up for these 3 patients exceeded the median follow-up for the overall cohort, it is unlikely that cost figures were underestimated. Complete assessment of survival, costs, and quality of life will have to be undertaken in a prospective, randomized study. With such additional information, the true value and cost-effectiveness of this novel treatment strategy can be determined.

Because overall survival is short for patients with GBM, and because their alternative treatment options are limited, the advantages of treating patients with TMZ at the time of initial diagnosis must be compared with withholding the use of this therapeutic agent until patients develop recurrent disease. This comparison must take into account the benefits in terms of both survival and quality of life, and it must also assess the costs of illness until death.

Alternatively, selecting the patients who are most likely to benefit from this treatment strategy may decrease the additional cost to acceptable levels. As was suggested by the current study, assessment of MGMT methylation status may help to identify patients who are less likely to benefit from this novel treatment option.[24] Surgical debulking at the time of diagnosis remained the strongest predictive factor in the overall patient population.

Finally, the limit of $50,000 per life year gained can be challenged from an equity perspective: it would be unfair to deny potentially effective treatment to patients who are suffering from illnesses associated with a high fatality rate only because of high drug acquisition costs when at the same time, patients who are suffering from long-lasting chronic conditions are granted treatment that amounts, over time, to a much larger share of our limited healthcare resources.

REFERENCES

1. Chamberlain MC, Kormanik PA. Practical guidelines for the treatment of malignant gliomas. *West J Med.* 1998;168:114–120.
2. Walker MD, Alexander E, Hunt WE, et al. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. *J Neurosurg.* 1978;49:333–343.
3. Kristiansen K, Hagen S, Kollevold T, et al. Combined modality therapy of operated astrocytomas Grade III and IV. Confirmation of the value of postoperative irradiation and lack of potentiation of bleomycin on survival time: a prospective multicentre trial of the Scandinavian Glioblastoma Study Group. *Cancer.* 1981;47:649–652.
4. Levin VA, Silver P, Hannigan J, et al. Superiority of post-radiotherapy adjuvant chemotherapy with CCNU, procarbazine, and vincristine (PCV) over BCNU for anaplastic gliomas: NCOG 6G 61 final report. *Int J Radiat Oncol Biol Phys.* 1990;18:321–324.
5. Medical Research Council Brain Tumor Working Party. Randomized trial of procarbazine, CCNU and vincristine in the adjuvant treatment of high grade astrocytoma. A Medical Research Council trial. *J Clin Oncol.* 2001;19:509–518.
6. Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet.* 2002;359:1011–1018.
7. Wong ET, Hess KR, Gleason MJ, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto Phase II clinical trials. *J Clin Oncol.* 1999;17:2572–2578.
8. Rodriguez LA, Levin VA. Does chemotherapy benefit the patient with a central nervous system glioma? *Oncology (Huntingt).* 1987;1:29–36.
9. Middleton MR, Grob JJ, Aaronson N, et al. Randomized Phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol.* 2000;18:158–166.
10. Yung WK, Albright RE, Olson J, et al. A Phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. *Br J Cancer.* 2000;83:588–593.
11. Brada M, Hoang-Xuang K, Rampling R, et al. Multicenter Phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. *Ann Oncol.* 2001;12:259–266.
12. Osoba D, Brada M, Yung WK, Prados M. Health-related quality of life in patients treated with temozolomide versus procarbazine for recurrent glioblastoma multiforme. *J Clin Oncol.* 2000;18:1481–1491.
13. Yung WK, Prados MD, Yaya TR, et al. Multicenter Phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. *J Clin Oncol.* 1999;17:2762–2771.
14. Osoba D, Brada M, Yung WK, Prados MD. Heath-related quality of life in patients with anaplastic astrocytoma during treatment with temozolomide. *Eur J Cancer.* 2000;36:1788–1795.
15. Friedman HS, McLendon RE, Kerby T, et al. DNA mismatch repair and O^6-alkylguanine-DNA alkyltransferase analysis and response to Temodal in newly diagnosed malignant glioma. *J Clin Oncol.* 1998;16:3851–3857.
16. Brock CS, Newlands ES, Wedge SR, et al. Phase I trial of temozolomide using an extended continuous oral schedule. *Cancer Res.* 1998;58:4363–4367.
17. Hillner BE, Agarwala S, Middleton MR. Post hoc economic analysis of temozolomide versus dacarbazine in the treatment of advanced metastatic melanoma. *J Clin Oncol.* 2000; 18:1474–1480.
18. Dinnes J, Cave C, Huang S, Major K, Milne R. The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma. London: Queen's Printer and Controller of Her Majesty's Stationery Office, 2001.

19. Stupp R, Dietrich PY, Ostermann Kraljevic S, et al. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. *J Clin Oncol.* 2002;20:1375–1382.
20. Karnofsky DA, Abelmann WH, Craver LF, et al. The use of nitrogen mustards in the palliative treatment of carcinoma. *Cancer.* 1948;1:634–656.
21. Zubrod CG, Schneiderman M, Frei E, et al. Appraisal of methods for the study of chemotherapy of cancer in man: comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. *J Chronic Dis.* 1960;11:7–33.
22. Verger E, Salamero M, Conill C. Can Karnofsky performance status be transformed to the Eastern Cooperative Oncology Group scoring scale and vice versa? *Eur J Cancer.* 1992;28A:1328–1330.
23. Mackworth N, Fobair P, Prados MD. Quality of life self-reports from 200 brain tumor patients: comparisons with Karnofsky performance scores. *J Neurooncol.* 1992;14:243–253.
24. Hegi ME, Diserens AC, Godard S, et al. Clinical trial substantiates the predictive value of O-6-methylguanine-DNA methyltransferase promoter methylation in glioblastoma patients treated with temozolomide. *Clin Cancer Res.* 2004;10:1871–1874.
25. Goldman L, Gordon DJ, Rifkind BM, et al. Cost and health implications of cholesterol lowering. *Circulation.* 1992;85:1960–1968.
26. Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol.* 1997;15:110–115.
27. Aaronson NK, Ahmedzai S, Bergman B, et al. The EORTC QLQ-C30: a quality of life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85:365–376.
28. Osoba D, Aaronson N, Muller M, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer specific instruments. *Qual Life Res.* 1996;5:139–150.
29. Silverstein MD, Cascino TL, Harmsen WS. High-grade astrocytomas: resource use, clinical outcomes and cost of care. *Mayo Clin Proc.* 1996;71:936–944.
30. Latif AZ, Signorini D, Gregor A, Whittle IR. The costs of managing patients with malignant glioma at a neuro-oncology clinic. *Br J Neurosurg.* 1998;12:118–122.
31. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. *Ann Intern Med.* 1993;118:622–629.