Cost of temozolomide therapy and global care for recurrent malignant gliomas followed until death

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Effectiveness and costs of care and treatment of recurrent malignant gliomas are largely unknown. In this study, 49 patients (32 males, 17 females; mean age, 49; age range, 23–79) were treated with temozolomide (TMZ) for recurrent or progressive malignant gliomas after standard radiation therapy. Cost assessment (payer's perspective) singled out treatment for first recurrence and all costs of care until death. We computed personnel costs as wages; drugs, imaging, and laboratory tests as prices; and hospitalizations as day rates. Patients were administered a median of five TMZ cycles at recurrence. Drug acquisition costs amounted to €2206 per cycle (76% of total costs). Seven patients showed no second recurrence (two are still alive), 16 received no further chemotherapy and died after 3.9 months, and 26 received second-line chemotherapy. After the second progression, median survival was 4.0 months (95% confidence interval, 1.8–6.1). Overall monthly costs of care varied between €2450 and €3242 among the different groups, and median cost-effectiveness and cost utility ranged from €28,817 to €38,450 and from €41,167 to €53,369 per life of year and per quality-adjusted life-year gained, respectively. We conclude that despite high TMZ drug acquisition costs, care of recurrent malignant gliomas is comparable to other accepted therapies. *Neuro-Oncology 7, 189–195, 2005 (Posted to Neuro-Oncology [serial online], Doc. 04-068, February 24, 2005. URL http://neuro-oncology.mc.duke.edu; DOI: 10.1215/S1152851704000687)*

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[2] Abbreviations used are as follows: AA, anaplastic astrocytoma; CCNU, lomustine; GBM, glioblastoma multiforme; MRC, Medical Research Council; PCV, procarbazine, CCNU, and vincristine; TMZ, temozolomide.

Malignant gliomas are a heterogeneous group of primary brain tumors, including glioblastoma multiforme (GBM),[2] gliosarcomas, anaplastic astrocytomas (AA), and anaplastic oligoastrocytomas. Glioblastoma multiforme, the most malignant form of primary brain tumors, represents 15% to 20% of all adult brain tumors and about 2% of all cancers. Despite surgery and/or radiotherapy, the prognosis of these patients remains poor, with a median overall survival of 9 to 12 months only for GBM and 18 to 24 months for AA (Chamberlain and Kormanik, 1998; Kristiansen et al., 1981; Walker et al., 1978). The use of adjuvant chemotherapy remains controversial (Levin et al., 1990), and no survival benefit has been shown in a recent randomized trial (MRC Brain Tumour Working Party, 2001). A recent meta-analysis based on individual patient data (Stewart et al., 2000) nevertheless suggests a 5% increase in two-year survival in patients receiving chemotherapy. Chemotherapy is usually reserved for the treatment of recurrent disease with a purely palliative objective (Rodriguez and Levin, 1987; Wong et al., 1999).

Temozolomide (TMZ), an alkylating agent, has recently been introduced to the clinic. It has demonstrated modest activity in patients with melanoma (Middleton et al., 2000) and recurrent high-grade glioma (Brada et al., 2001; Yung et al., 2000). Compared with procarbazine, TMZ improved health-related quality of life in patients with recurrent GBM (Osoba et al., 2000a). In AA at first recurrence, TMZ showed a high single-agent response

rate, a favorable safety profile (Yung et al., 1999), and improved health-related quality of life (Osoba et al., 2000b). Finally, concomitant and adjuvant TMZ administration with standard radiation therapy showed promising survival benefit (Stupp et al., 2002).

When new drugs or treatment modalities are introduced to the clinic, attention should focus not only on efficacy and safety but also on cost-effectiveness. This is of particular importance for drugs with high acquisition costs. To date, only one study evaluated TMZ from an economical perspective. This post hoc economic analysis in advanced metastatic melanoma showed that the incremental cost-effectiveness ratio using TMZ over dacarbazine amounted to $37,000 per life-year, or $101 per day of life gained (Hillner et al., 2000). None of the studies on brain tumor treatment looked at the issue of costs.

The cost of treating a disease is made of several components. It includes the cost of establishing the diagnosis, the cost of initial therapy, the cost of follow-up, and the cost of treatment for recurrence and supportive care. However, efficacy of any treatment in glioblastoma at recurrence is frequently short-lived and observed in a few patients only. Despite this reality, the commitment of physicians to their patients, coupled with the despair of these patients, leads them to try various treatments with marginal benefits, but substantial costs. On the other hand, disease progression requires support, and palliative care until patient death may also require substantial resources.

We therefore wanted to assess the true total costs of treating patients with GBM at first recurrence. All patients were initially treated with TMZ at standard doses within a clinical trial. Resource utilization was prospectively collected and extended until the patient's death.

Patients and Methods

Forty-nine patients were enrolled in a clinical trial and treated with TMZ as first-line chemotherapy (Stupp et al., 1998) for recurrent or progressive malignant gliomas (GBM or AA/anaplastic oligoastrocytoma) and were prospectively followed until death. These 32 men and 17 women were on average 49 years old (range, 23–79). Initial treatment included surgery or biopsy and standard fractionated radiotherapy. Recurrence was documented by clinical signs or symptoms and/or tumor progression on MRI.

The observation period was divided into two periods. Period 1 extended from the beginning to the end of TMZ treatment for first recurrence, and period 2 extended from the end of TMZ treatment or progression or second recurrence until the patient's death or, for the two patients still alive, date of last follow-up visit (September 9, 2003).

At first recurrence, patients were treated with TMZ, 200 mg/m^2 per day for five days every four weeks, until progression, toxicity, or patient refusal, for a maximum of two years. In a case of further progression or a second recurrence, treatment was left to the physician's discretion. Subsequent chemotherapy, if any, consisted of TMZ administered continuously at 75 mg/m^2 per day $\times$ 6 weeks (continuous schedule [Brock et al., 1998]), or other drugs such as irinotecan, topotecan, tamoxifen, carmustine, lomustine (CCNU), fotemustine, or combination chemotherapy with procarbazine, CCNU, and vincristine (PCV).

Follow-up consisted of medical visits, blood tests, and MRI every other month to detect further relapse, or more frequently if dictated by clinical condition. The protocol had been approved by the local ethics committee, and all patients gave written informed consent.

For the purpose of this analysis, patients were allocated into five groups: (1) disease progression free, (2) no further chemotherapy, (3) continuous TMZ schedule, (4) continuous TMZ schedule followed by other drugs, and (5) other drugs only.

Survival data were computed by the Kaplan-Meier method. The cost analysis was based on effectively incurred resource utilization, which was determined from the detailed prospective data that were collected. Personnel costs were computed as salary $\times$ time and were extracted from the hospital information system. Costs for drugs, imaging, and laboratory tests, which were based on data retrieved from patients' charts, were computed as billing prices extracted from published price lists. The length of hospitalization was also retrieved from patients' charts, and its cost was computed at a fixed rate for acute or palliative care, based on the cost effectively incurred for such a treatment at our institution. All costs were computed with 2001 cost figures, from a hospital perspective. Unit costs are displayed in Table 1. Swiss francs were converted into euros at the 2001 exchange rate of 0.64 (1 € = 1.565 CHF = 0.626 £ = 0.9 US$).

In this study, quality of life was not formally assessed. We used Karnofsky performance status (Karnofsky et al., 1948) and Eastern Cooperative Oncology Group scales (Zubrod et al., 1960) at each visit as a surrogate. These physician-based health status measures were shown to be highly correlated (Verger et al., 1992), and in addition, the Karnofsky index was shown to provide a good proxy for quality of life (Mackworth et al., 1992). Missing single values at a specific date were imputed by using the mean of the previous and following data. The area under the curve was computed for each patient, in order to determine a mean value, which in turn was used for computing a cost-utility ratio.

Total costs of treatment and survival of the first-recurrence period and the follow-up period were computed separately for each patient, and monthly costs were computed by dividing this total cost by the number of months spent in each of these two periods. A cost-effectiveness ratio was computed for each patient. These different values were then grouped by type of treatment, and the median value of each group was taken as the group cost-effectiveness ratio. A 95% confidence interval was also computed. These cost figures were then weighted by the individual mean health status measure in order to compute a cost-utility ratio for each group,

Table 1. Unit costs for temozolomide treatment (euros)*

Treatment	Euros
Personnel (per visit)	
Physician	7.3
Nurse	6.0
Drugs	
TMZ 250 mg	280.2
TMZ 100 mg	123.5
TMZ 50 mg	25.7
TMZ 20 mg	8.0
BCNU 100 mg	109.8
CCNU 40 mg	5.5
CCNU 10 mg	1.8
CPT-11 100 mg	310.2
CPT-11 40 mg	146.5
Fotemustine 200 mg	655.3
Procarbazine 50 mg	0.5
Topotecan 4 mg	464.5
Topotecan 1 mg	145.2
Tamoxifen 20 mg	1.4
Tamoxifen 10 mg	0.9
Vincristine 2 mg	44.1
Vincristine 1 mg	25.7
Radiology	
MRI	555.9
Laboratory tests	
Blood count	9.6
Complete blood count	16.0
Hospital day	
Acute care	217.2
Palliative care	164.2

Abbreviations: BCNU, carmustine; CCNU, lomustine; CPT-11, irinotecan; TMZ, temozolomide.

*Swiss francs were converted into euros at the 2001 exchange rate of 0.64 (1 € = 1.565 CHF = 0.626 £ = 0.9 US$).

according to the same methodology as described for cost-effectiveness. Difference in costs between the five different treatment groups as determined by the kind of treatment received at the end of the first-recurrence treatment was analyzed with the Mann-Whitney U-test. Statistical significance was assumed at $P < 0.05$.

Results

Period 1

Treatment duration for first recurrence was on average 5.1 months (range, 0.2–16.3 months), and the median number of TMZ cycles administered was 5 (range, 1–17 cycles). The detailed numbers of treatment months, medical visits, blood tests, and MRI as well as TMZ dose are displayed as means ± SD in Table 2. During this treatment period, 11 patients required hospitalization in an acute care setting for a median of eight days (range, 1–36 days), and 10 patients required hospitalization in a palliative care setting for a median of 31 days (range, 3–152 days). Quality of life, as measured with the Eastern Cooperative Oncology Group scale, did not change between the beginning and the end of this treatment phase, and its median value remained at 1 (range, 0–3).

The corresponding costs for the different resources used are also displayed in Table 2. First recurrence was characterized by an average cost of €4242 per month, with a wide variation between patients. Acquisition costs for TMZ amounted to an average of 76% of the total costs of treating first recurrence (median, 85%; range, 13%–92%).

Period 2

The median of the survival times after stop of first-recurrence treatment or progression or second recurrence was 3.6 months (range, 0.1–38.5 months). The average cost per patient amounted to €10,762 (range, €0–€70,694), of which 29% were drug acquisition costs (range, 0%–95%). Average cost by month of survival amounted to €2290 by patient.

Seven patients did not show any evidence of recurrent disease on MRI after a median follow-up of 4.1 months (range, 0.7–38.5 months). Five of them died: three patients with clinical disease progression but stable disease or partial remission on MRI and two patients with hematological toxicity and treatment cessation. Three of these patients needed hospitalization in palliative care, one for 438 days. Their use of resources is displayed as means ± SD in Table 3, and the corresponding costs are

Table 2. Distribution of resource utilization and costs during treatment of first recurrence with TMZ standard intermittent schedule (observation period 1)

Resource	Number of Times Resource Was Used (mean ± SD)	Cost in Euros (mean ± SD)
Treatment duration (months)	5.1 ± 3.7	
Number of TMZ cycles	5.4 ± 3.9	
Medical visits (n)	9.9 ± 6.5	127 ± 83
Laboratory tests (n)	16.8 ± 12.1	233 ± 175
MRI (n)	2.9 ± 2.4	1,622 ± 1,312
TMZ (mg)	8,914.8 ± 6,913.5	11,915 ± 9,495
Hospitalizations		
Acute care (days, n = 11)	11.8 ± 12.2	2,460 ± 2,530
Palliative care (days, n = 10)	49.1 ± 54.4	7,724 ± 8,564
Total		16,026 ± 11,002
Cost by month		4,242 ± 5,217
Percent TMZ		76.0 ± 20.8

Table 3. Distribution of resource utilization in the follow-up period until death (observation period 2)

Resource Utilization (mean ± SD)	No Recurrence (n = 7)	No Treatment (n = 16)	Continuous TMZ (n = 13)	Continuous TMZ + Other Drugs (n = 7)	Other Drugs (n = 6)
Survival (months)	11.6 ± 14.6	3.9 ± 6.9	6.7 ± 5.8	7.6 ± 2.8	2.6 ± 0.9
ECOG score (at the beginning of period)	1.8 ± 0.5	2.4 ± 1.5	1.1 ± 1.1	0.6 ± 0.5	1.4 ± 1.3
Medical visits (n)	2.3 ± 2.4	1.1 ± 2.3	5.5 ± 4.8	12.6 ± 9.1	2.8 ± 1.6
Laboratory tests (n)	1.4 ± 1.0	1.2 ± 1.4	8.8 ± 8.6	19.9 ± 10.0	2.5 ± 1.6
MRI (n)	1.4 ± 2.3	0.4 ± 1.0	1.7 ± 1.6	3.1 ± 2.0	0.7 ± 0.8
Drug treatment (days)	0	0	56.4 ± 47.9	123.0 ± 36.5	25.5 ± 13.9
Hospitalizations (days)					
Acute care	0	2.9 ± 9.0	3.8 ± 6.0	11.1 ± 10.2	3.8 ± 5.1
Palliative care	69.9 ± 162.8	25.9 ± 40.1	19.0 ± 21.3	26.9 ± 24.8	29.3 ± 23.6

Abbreviations: ECOG, Eastern Cooperative Oncology Group; TMZ, temozolomide.

Table 4. Distribution of costs in the follow-up period until death, euros (mean ± SD), observation period 2

Type of Cost	No Recurrence (n = 7)	No Treatment (n = 16)	Continuous TMZ (n = 13)	*P*	Continuous TMZ + Other Drugs (n = 7)	Other Drugs (n = 6)	*P*
Survival (months)	11.6 ± 14.6	3.9 ± 6.9	6.7 ± 5.8		7.6 ± 2.8	2.6 ± 0.9	†††
Medical visits	29 ± 31	14 ± 29	71 ± 61	*	161 ± 117	36 ± 20	
Laboratory tests	26 ± 18	24 ± 26	166 ± 154	*	349 ± 174	50 ± 37	††
MRI	794 ± 1,278	208 ± 570	941 ± 890		1,747 ± 1,085	371 ± 454	†
Drug treatment	0	0	8,890 ± 7,066	**	16,244 ± 7,187	560 ± 772	†††
Hospitalizations							
Acute care	0	598 ± 1878	800 ± 1251		2,319 ± 2,117	798 ± 1,065	
Palliative care	10,356 ± 25,832	3,229 ± 4,733	2,768 ± 3,363		4,225 ± 3,901	3,382 ± 2,093	
Total	11,204 ± 26,261	4,073 ± 5,133	13,636 ± 9,400	*	25,045 ± 8,877	5,196 ± 3,474	††
Cost by month	2,125 ± 4,457	1,627 ± 1,855	2,642 ± 1,295		3,607 ± 1,679	1,958 ± 1,116	

*$P < 0.05$ between patients treated with TMZ alone (n = 13) and TMZ in combination with other drugs (n = 7).

**$P < 0.005$ between patients treated with TMZ alone (n = 13) and TMZ in combination with other drugs (n = 7).

†$P < 0.05$ between patients treated with other drugs (n = 6) and patients treated with TMZ either alone or followed by other drugs (n = 20).

††$P < 0.01$ between patients treated with other drugs (n = 6) and patients treated with TMZ either alone or followed by other drugs (n = 20).

†††$P < 0.001$ between patients treated with other drugs (n = 6) and patients treated with TMZ either alone or followed by other drugs (n = 20).

displayed in Table 4. Two of the patients are still alive after 52.7 and 37.5 months, respectively.

Sixteen patients did not receive further cytotoxic therapy after progression or after a second recurrence was diagnosed. Three of them needed hospitalization in acute care for a median of seven days (range, 3–36 days), and 10 of them needed hospitalization in palliative care for a median of 21 days (range, 5–113 days). The median of the survival times in follow-up period was altogether 1.4 months (range, 0.1–28.5 months).

Twenty-six patients received second-line chemotherapy. In 20 patients, a continuous administration schedule of TMZ alone (13 patients) or in combination (seven patients) was prescribed. The first group received an average of 1.3 TMZ cycles of six weeks (range, 0.7–5.0 cycles), and the second group received an average of 2.0 TMZ cycles of six weeks (range, 1.0–3.0 cycles). Other drugs included irinotecan (three patients), CCNU or PCV (two patients each), and tamoxifen or fotemustin (one patient each). The median of the survival times in follow-up period was 3.8 months (range, 1.4–22.1 months) for the first group of patients and 6.7 months (range, 4.1–12.3 months) for the second group. Acquisition costs for TMZ amounted to 64% of total costs in each of these two groups.

Six patients of the group treated only with continuous TMZ needed hospitalization in acute care for a median of 6.5 days (range, 2–20 days), and 11 of them were in palliative care for a median of 22 days (range, 1–68 days). Of the group treated with continuous TMZ and other drugs, six patients required hospitalization in acute care for a median of eight days (range, 5–26 days), and five were in palliative care for a median of 43 days (range, 5–56 days).

Finally, six patients were treated exclusively with other drugs: PCV (three patients), carmustine (one patient), topotecan (one patient). These patients were followed for a median of 2.6 months (range, 1.2–3.9). Three patients

Table 5. Summary of survival, health status, cost distribution, and cost-effectiveness/cost-utility ratios for entire observation period (euros)

Type of Cost (mean ± SD)	No Recurrence (n = 7)	No Treatment (n = 16)	Continuous TMZ (n = 13)	Continuous TMZ + Other Drugs (n = 7)	Other Drugs (n = 6)	*P*
Survival (months)	18.6 ± 18.8	8.2 ± 9.3	12.6 ± 6.1	12.0 ± 1.4	6.7 ± 2.7	***
Health status[a]	63.6 ± 9.9	60.6 ± 15.6	72.3 ± 18.2	83.6 ± 6.3	8.3 ± 16.9	
First recurrence	26,398 ± 13,873	14,475 ± 11,864	15,947 ± 9,649	11,656 ± 5,058	13,331 ± 7,802	
Follow-up	11,204 ± 26,261	4,073 ± 5,133	13,636 ± 9,400	25,045 ± 8,877	5,196 ± 3,474	***
Total	37,603 ± 28,664	18,548 ± 12,166	29,583 ± 12,752	36,701 ± 8,788	18,527 ± 10,140	*
Cost per month	3,242 ± 2,532	3,232 ± 2,167	2,450 ± 618	3,100 ± 856	2,668 ± 549	
Cost-effectiveness ratio						
Median	28,817	33,528	32,453	38,450	31,809	
Mean	38,906	38,781	29,397	37,203	32,018	
95% CI	10,801–67,011	24,927–5,636	24,918–33,876	27,703–46,702	25,100–38,937	
Cost-utility ratio						
Median	41,167	53,369	41,200	48,062	45,688	
Mean	66,161	73,590	44,888	44,948	51,777	
95% CI	15,052–117,271	36,467–110,713	31,989–57,787	32,603–57,293	25,092–78,462	

Abbreviations: CI, confidence interval; TMZ, temozolomide.

[a]As measured by the area under the Karnofsky curve over the whole period.

*$P < 0.05$ between patients treated with other drugs (n = 6) and patients treated with TMZ either alone or followed by other drugs (n = 20).

**$P < 0.01$ between patients treated with other drugs (n = 6) and patients treated with TMZ either alone or followed by other drugs (n = 20).

***$P < 0.005$ between patients treated with other drugs (n = 6) and patients treated with TMZ either alone or followed by other drugs (n = 20).

needed hospitalization in an acute care setting, and four were in palliative care for a median of five days (range, 5–13 days) and 23 days (range, 8–37 days), respectively. The detail for resources used by these different groups of patients is displayed as means ± SD in Table 3, and the detail for the corresponding costs appears in Table 4.

Total Survival and Costs Until Death

Table 5 provides the summary of survival, health status, and costs over the entire period from diagnosis of first recurrence until death. Survival was significantly longer in patients receiving continuous TMZ with or without other drugs than in other patients ($P = 0.001$), reflecting mainly patient selection. Altogether, TMZ treatment amounted to an average of €16,316 (median €12,745; range, €1749–€49,165), or an average of 61% of total cost of care (median, 62%; range, 8%–90%).

A statistically significant difference in health status ($P = 0.004$) was observed between patients allocated to any treatment as compared with the others. As a consequence, treatment intensity was highest in these groups, translating into higher total costs. However, when transformed into monthly costs, these costs did not differ by treatment group. Taking these differences into account, median cost-effectiveness ratios among the different patient groups extended from €28,817 to €38,450 per life-year gained. When we included quality of life, as measured by Karnofsky health status, cost-utility ratios leveled off between the different groups and ranged between €41,167 and €53,369 per quality-adjusted life-year gained.

Discussion

This study showed that TMZ treatment for first recurrence of malignant gliomas was well tolerated and efficient, but expensive, mainly because of high drug acquisition cost. Oral administration of TMZ on an outpatient basis is an advantage that is highly valued by patients (Liu et al., 1997).

Attribution of patients to different treatment groups at the time of second recurrence was dependent on their health status and prior response to therapy. Continuous TMZ was administered to patients with a more favorable profile and resulted in prolonged survival as compared with other groups. This was also true for patients to whom additional chemotherapy was prescribed as third-line treatment. As a consequence, these two groups incurred higher additional cost due to TMZ acquisition cost. However, because it conferred longer survival, this additional treatment translated into only a modest increase in monthly cost of treatment, and hence into cost-effectiveness ratios that were still within the accepted limit of US $50,000/life-year gained (Goldman et al., 1992). This is even more pronounced when quality of life was taken into account to compute cost-utility ratio: Because of TMZ's low toxicity, the difference that was initially observed between the different groups leveled off.

Economic analyses published on standard radiation treatment of malignant gliomas showed that 75% of the costs were incurred during the initial treatment period (Silverstein et al., 1996). Total costs of care ranged from US $2900 to $39,680 per patient (Latif et al.,

1998). Because the mean length of hospital stay was 40 days, inpatient care amounted to the largest share (US $10,570), followed by surgery (US $1900) and radiotherapy (US $1720) (Bloor et al., 1998). In this setting, it becomes especially important to assess whether TMZ administration at the time of recurrence can bring a cost-effective additional benefit. On the basis of current evidence demonstrating an increase in progression-free survival at a cost of only £700–£1000 per progression-free week, the National Institute for Clinical Excellence (London) recommended that TMZ be administered at the time of first recurrence (Dinnes et al., 2001). This report underlined the fact that no data are yet available on the impact of TMZ on costs associated with global care of malignant glioma recurrence. Our results bring a partial answer to this important question. In the specific setting of this study, costs of first-recurrence treatment with standard TMZ administration amounted to an average of 65% of total costs of care (median, 67%; range, 13%–100%), of which 76% were TMZ acquisition costs. These findings indicate that final deterioration was linked with substantial resource use, especially if TMZ was administered continuously at a later stage of disease. In our study, TMZ acquisition costs amounted to 64% of total costs in these groups of patients. Therefore, targeting TMZ treatment to patients likely to benefit from it is of paramount importance.

Our study has some limitations. It involved only a limited number of patients, many of whom had received primary therapy elsewhere and were referred for chemotherapy at recurrence. In order to overcome differences in accounting and unit costs between the different health care systems involved, cost data were extrapolated to all patients from data available at our center. In our institution, all patients were treated by the same physician (R.S.), and thus differences in treatment allocation should have been minimal and should not influence cost analysis. However, practice variations exist both within and between countries that may affect both outcome and costs (Fisher et al., 2003a, b). As a consequence, the results of our study may be only partially applicable to other health care systems. Second, although the Karnofsky index has been shown to be a relatively good proxy for quality of life assessment (Verger et al., 1992) and is frequently used by clinicians to assess the performance status of their patients, it focuses on physical activity and does not take into account the other dimensions usually included in the quality-of-life assessment (Guyatt et al., 1993) or the patient's preferences. With these limitations in mind, it was used only as a first quality-of-life assessment. Full assessment of quality of life will have to be included in a prospective randomized study.

Finally, as overall survival is short in this disease and alternative treatment options are limited, the additional benefit of early administration of TMZ must be considered, assessed, and prospectively compared. Such a study should incorporate a full cost analysis as well as a quality-of-life assessment in order to provide a definite answer on the place of TMZ treatment for gliomas. It is indeed of paramount importance that the true value of a specific treatment and its related costs be known, to allow for rational allocation of limited health care resources and to prevent denial of access because of high drug acquisition cost to a potentially clinically effective treatment for patients who might benefit from it.

References

Bloor, K., Drummond, M.F., Brada, M., and Rampling, R. (1998) High grade gliomas: Clinical outcomes, resource use and cost of care. Memorandum. University of York, Centre for Health Economics, Heslington, York, U.K.

Brada, M., Hoang-Xuang, K., Rampling, R., Dietrich, P.Y., Dirix, L.Y., Macdonald, D., Heimans, J.J., Zonnenberg, B.A., Bravo-Marques, J.M., Henriksson, R., Stupp, R., Yue, N., Bruner, J., Dugan, M., Rao, S., and Zaknoen, S. (2001) Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. *Ann. Oncol.* **12**, 259–266.

Brock, C.S., Newlands, E.S., Wedge, S.R., Bower, M., Evans, H., Colquhoun, I., Roddie, M., Glaser, M., Brampton, M.H., and Rustin, G.J. (1998) Phase I trial of temozolomide using an extended continuous oral schedule. *Cancer Res.* **58**, 4363–4367.

Chamberlain, M.C., and Kormanik, P.A. (1998) Practical guidelines for the treatment of malignant gliomas. *West. J. Med.* **168**, 114–120.

Dinnes, J., Cave, C., Huang, S., Major, K., and Milne, R. (2001) The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: A rapid and systematic review. *Health Technol. Assess.* **5**, 1–73.

Fisher, E.S., Wennberg, D.E., Stukel, T.A., Gottlieb, D.J., Lucas, F.L., and Pinder, E.L. (2003a) The implications of regional variations in Medicare spending. Part 1: The content, quality, and accessibility of care. *Ann. Intern. Med.* **138**, 273–287.

Fisher, E.S., Wennberg, D.E., Stukel, T.A., Gottlieb, D.J., Lucas, F.L., and Pinder, E.L. (2003b) The implications of regional variations in Medicare spending. Part 2: Health outcomes and satisfaction with care. *Ann. Intern. Med.* **138**, 288–298.

Goldman, L,. Gordon, D.J., Rifkind, B.M., Hulley, S.B., Detsky, A.S., Goodman, D.W., Kinosian, B., and Weinstein, M.C. (1992) Cost and health implications of cholesterol lowering. *Circulation* **85**, 1960–1968.

Guyatt, G.H., Feeny, D.H., and Patrick, D.L. (1993) Measuring health-related quality of life. *Ann. Intern. Med.* **118**, 622–629.

Hillner, B.E., Agarwala, S., and Middleton, M.R. (2000) Post hoc economic analysis of temozolomide versus dacarbazine in the treatment of advanced metastatic melanoma. *J. Clin. Oncol.* **18**, 1474–1480.

Karnofsky, D.A., Abelmann, W.H., Craver, L.F., and Burchenal, J.H. (1948) The use of the nitrogen mustards in the palliative treatment of carcinoma: With particular reference to bronchogenic carcinoma. *Cancer* **1,** 634–656.

Kristiansen, K., Hagen, S., Kollevold, T., Torvik, A., Holme, I., Nesbakken, R., Hatlevoll, R., Lindgren, M., Brun, A., Lindgren, S., Notter, G., Andersen, A.P., and Elgen, K. (1981) 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* **47**, 649–652.

Latif, A.Z., Signorini, D., Gregor, A., and Whittle, I.R. (1998) The costs of managing patients with malignant glioma at a neuro-oncology clinic. *Br. J. Neurosurg.* **12**, 118–122.

Levin, V.A., Silver, P., Hannigan, J., Wara, W.M., Gutin, P.H., Davis, R.L., and Wilson, C.B. (1990) Superiority of post-radiotherapy adjuvant chemotherapy with CCNU, procarbazine, and vincristine (PCV) over BCNU for anaplastic gliomas: NCOG 6G61 final report. *Int. J. Radiat. Oncol. Biol. Phys.* **18**, 321–324.

Liu, G., Franssen, E., Fitch, M.I., and Warner, E. (1997) Patient preferences for oral versus intravenous palliative chemotherapy. *J. Clin. Oncol.* **15**, 110–115.

Mackworth, N., Fobair, P., and Prados, M.D. (1992) Quality of life self-reports from 200 brain tumor patients: Comparisons with Karnofsky performance scores. *J. Neurooncol.* **14**, 243–253.

Middleton, M.R., Grob, J.J., Aaronson, N., Fierlbeck, G., Tilgen, W., Seiter, S., Gore, M., Aamdal, S., Cebon, J., Coates, A., Dreno, B., Henz, M., Schadendorf, D., Kapp, A., Weiss, J., Fraass, U., Statkevich, P., Muller, M., and Thatcher, N. (2000) Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J. Clin. Oncol.* **18**, 158–166.

MRC Brain Tumour Working Party (2001) Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: A Medical Research Council Trial. *J. Clin. Oncol.* **19**, 509–518.

Osoba, D., Brada, M., Yung, W.K.A., and Prados, M. (2000a) Health-related quality of life in patients treated with temozolomide versus procarbazine for recurrent glioblastoma multiforme. *J. Clin. Oncol.* **18**, 1481–1491.

Osoba, D., Brada, M., Yung, W.K.A., and Prados, M.D. (2000b) Health-related quality of life in patients with anaplastic astrocytoma during treatment with temozolomide. *Eur. J. Cancer* **36**, 1788–1795.

Rodriguez, L.A., and Levin, V.A. (1987) Does chemotherapy benefit the patient with a central nervous system glioma? *Oncology* **1**, 29–36.

Silverstein, M.D., Cascino, T.L., and Harmsen, W.S. (1996) High-grade astrocytomas: Resource use, clinical outcomes and cost of care. *Mayo Clin. Proc.* **71**, 936–944.

Stewart, L.A., Burdett, S., and Souhami, R.L. (2000) Chemotherapy for high-grade glioma: A meta-analysis using individual patient data from randomized clinical trials (RCTs). *Proc. Annu. Meet. Am. Soc. Clin. Oncol.* 650 (abstract).

Stupp, R., Maeder, P., Maillard, I., Pica, A., Wurm, R., Hungerbühler, H.P., Villemure, J.G., Baumert, B., Büttner, W., de Tribolet, N., Lejeune, F., Mirimanoff, R.O., and Leyvraz, S. (1998) Improved outcome with chemotherapy with temozolomide for recurrent glioblastoma and anaplastic astrocytoma. *J. Neurooncol.* **39**, 151 (abstract).

Stupp, R., Dietrich, P.Y., Ostermann Kraljevic, S., Pica, A., Maillard, I., Maeder, P., Meuli, R., Janzer, R., Pizzolato, G., Miralbell, R., Porchet, F., Regli, L., De Tribolet, N., Mirimanoff, R.O., and Leyvraz, S. (2002) Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. *J. Clin. Oncol.* **20**, 1375–1382.

Verger, E., Salamero, M., and Conill, C. (1992) Can Karnofsky performance status be transformed to the Eastern Cooperative Oncology Group scoring scale and vice versa? *Eur. J. Cancer* **28** (suppl. A), 1328–1330.

Walker, M.D., Alexander, E., Jr., Hunt, W.E., MacCarty, C.S., Mahaley, M.S., Jr., Mealey, J., Jr., Norrell, H.A., Owens, G., Ransohoff, J., Wilson, C.B., Gehan, E.A., and Strike, T.A. (1978) Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. *J. Neurosurg.* **49**, 333–343.

Wong, E.T., Hess, K.R., Gleason, M.J., Jaeckle, K.A., Kyritsis, A.P., Prados, M.D., Levin, V.A., and Yung, W.K. (1999) Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J. Clin. Oncol.* **17**, 2572–2578.

Yung, W.K.A., Prados, M.D., Yaya-Tur, R., Rosenfeld, S.S., Brada, M., Friedman, H.S., Albright, R., Olson, J., Chang, S.M., O'Neill, A.M., Friedman, A.H., Bruner, J., Yue, N., Dugan, M., Zaknoen, S., and Levin, V.A., for the Temodal Brain Tumor Group (1999) Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligo-astrocytoma at first relapse. *J. Clin. Oncol.* **17**, 2762–2771.

Yung, W.K., Albright, R.E., Olson, J., Fredericks, R., Fink, K., Prados, M.D., Brada, M., Spence, A., Hohl, R.J., Shapiro, W., Glantz, M., Greenberg, H., Selker, R.G., Vick, N.A., Rampling, R., Friedman, H., Phillips, P., Bruner, J., Yue, N., Osoba, D., Zaknoen, S., and Levin, V.A. (2000) A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. *Br. J. Cancer* **83**, 588–593.

Zubrod, C.G., Schneiderman, M., Frei, E., III, Brindley, C., Gold, G.L., Shnider, B., Oviedo, R., Gorman, J., Jones, R., Jr., Jonsson, U., Colsky, J., Chalmers, T., Ferguson, B., Dederick, M., Holland, J., Selawry, O., Regelson, W., Lasagna, L., and Owens, A. (1960) Appraisal of methods for the study of chemotherapy of cancer in man: Comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. *J. Chron. Dis.* **11**, 7–33.