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REVIEW

Critical appraisal of temozolomide formulations in the treatment of primary brain tumors: patient considerations

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Abstract: Chemotherapy is assuming an increasingly important role in the treatment of malignant gliomas, of which temozolomide (TMZ) is a key part. TMZ belongs to a class of second-generation imidazotetrazinone prodrugs that exhibit linear pharmacokinetics and do not require hepatic metabolism for activation to the active metabolite. New intravenous (iv) TMZ formulations have recently been approved based on studies of bioequivalence between iv and oral TMZ. The efficacy of TMZ was initially evaluated in patients with recurrent disease but phase II and III trials in newly diagnosed gliomas are available. The results of a large phase III trial that compared RT alone vs RT concomitant with oral TMZ created a new standard of adjuvant treatment. Efficacy data for iv TMZ on which its approval was based are those extrapolated from clinical trials with oral TMZ. No comparative data are available on the differences in tolerability and patient satisfaction between oral and iv formulations of TMZ, or for quality of life. New oral formulations could encourage the adherence of patients to treatment. Although patients presumably would prefer oral treatment, iv formulations may be an alternative in noncompliant patients or patients for whom good adherence could not be expected.

Keywords: temozolomide, brain tumors, new formulations, patient considerations, chemotherapy, glioblastoma

Current treatment for malignant glioma

Malignant gliomas account for approximately 70% of the 22,500 new cases of malignant primary brain tumors that are diagnosed in adults in the United States each year.[1] The annual incidence of malignant gliomas is approximately 5 to 8 cases per 100,000 people. Glioblastomas (GBM) account for approximately 60% to 70% of malignant gliomas, anaplastic astrocytomas for 10% to 15%, and anaplastic oligodendrogliomas and anaplastic oligoastrocytomas for 10%. Malignant gliomas are associated with a high morbidity and mortality. Despite optimal treatment, the median survival is only 12 to 15 months for patients with GBM and 2 to 5 years for patients with anaplastic gliomas.[2]

The standard therapy for newly diagnosed malignant gliomas involves surgical resection when feasible, radiotherapy (RT), and chemotherapy. Malignant gliomas cannot be completely eliminated surgically because of their infiltrative nature, but patients should undergo maximal surgical resection whenever possible. Surgical debulking reduces the symptoms from mass effect and provides tissue for histologic diagnosis and molecular studies. The value of surgery in prolonging survival is controversial, but patients who undergo extensive resection probably have a modest survival advantage.[3]

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Radiotherapy is the mainstay of treatment for malignant gliomas. The addition of RT to surgery increases survival among patients with GBM from a range of 3 to 4 months to a range of 7 to 12 months. Conventional RT consists of 60 Gy of partial-field external-beam irradiation delivered 5 days per week in fractions of 1.8 to 2.0 Gy.[4]

Chemotherapy is assuming an increasingly important role in the treatment of malignant gliomas. Although early studies of adjuvant chemotherapy for malignant gliomas with the use of nitrosoureas failed to show a benefit, 2 meta-analyses have suggested that adjuvant nitrosourea-based chemotherapy results in a modest increase in survival (a 6% to 10% increase in the 1-year survival rate).[5,6] In 2005, the results of a large phase III clinical trial conducted by The European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) created a new standard of adjuvant treatment.[7] This study compared RT alone (60 Gy over a period of 6 weeks) with RT and concomitant treatment with oral temozolomide (TMZ) 75 mg/m^2 of body-surface area per day for 6 weeks, followed by adjuvant TMZ therapy (150 to 200 mg/m^2 per day for 5 days every 28 days for 6 cycles), in patients with newly diagnosed GBM. The combination of RT and TMZ as compared with RT alone, increased the median survival (14.6 months vs 12.1 months, $P < 0.001$). In addition, the survival rate at 2 years among the patients who received RT and TMZ was significantly greater than the rate among the patients who received RT alone (26.5% vs 10.4%). As a consequence, the TMZ regimen was rapidly adopted as the new standard of care for patients with newly diagnosed GBM who met the inclusion criteria (age younger than 70 years and good performance status) of EORTC/NCIC trial.

In general, chemotherapy for recurrent malignant gliomas is more effective for anaplastic gliomas than for GBM. The efficacy of TMZ was initially demonstrated in patients with recurrent disease. Two pivotal phase II studies with identical entry criteria were conducted for patients with GBM and with anaplastic astrocitoma.[8,9] These studies suggested an increase in progression-free survival at 6 months (6PFS) compared with a historical database (Table 1). On the basis of the results of these studies, TMZ 150 to 200 mg/m^2 per day for 5 days every 28 days rapidly became the standard therapy for relapsed malignant gliomas in adult patients.

New TMZ formulations have recently been approved by the European Medicines Agency (EMEA) and Food and Drug Administration (FDA): oral (140 and 180 mg capsules) and intravenous (iv) (100 mg vial).[10,11]

The purpose of this article is to review the evidence available about TMZ and its formulations in the treatment of primary brain tumors in terms of safety and efficacy, and to provide arguments for discussion on the election of optimal treatment from the patient's point of view, with consideration of adherence to treatment, quality of life and patient preferences.

Pharmacology of temozolomide

Temozolomide belongs to a class of second-generation imidazotetrazinone prodrugs that undergo spontaneous conversion under physiological conditions to the active alkylating agent 5-(3-methyl)1-triazen-1-yl-imidazole-4-carboxamide (MTIC). Thus, TMZ does not require enzymatic demethylation in the liver for activation. This fact contributes to its highly reproducible pharmacokinetic properties in comparison with other alkylating agents such dacarbazine and procarbazine. However this spontaneous conversion to MTIC is dependent on pH. The methylation of DNA seems to be the principal mechanism responsible for the cytotoxicity of TMZ to malignant cells. TMZ is spontaneously converted to MTIC, the active metabolite. MTIC is degraded to the methyldiazonium cation, which transfers the methyl group to DNA, and the final degradation product, 5-aminoimidazole-4-carboxamide (AIC), which is excreted via the kidneys.[12] Temozolomide transfers a methyl group to 3 sites: N^7-guanine, N^3-adenine and O^6-guanine. The toxic lesion is believed to be the O^6-guanine adduct, which leads to a lethal cycle of DNA mismatch repair if the adduct is not removed by the DNA repair protein, O^6-alkylguanine-DNA alkyltransferase (AGT).[13]

Phase I studies

The pharmacokinetic and pharmacodynamic properties of TMZ in adults have been characterized adequately in 5 phase I trials using a daily schedule for 5 days and in 1 phase I trial using a daily dose for a continuous 6- or 7-week period and in 2 phase I trials conducted on pediatric cancer patients.[14–19] Newlands et al initially studied iv TMZ at doses of 50 to 200 mg/m^2 and it was subsequently given orally up to 1200 mg/m^2.[14] Temozolomide exhibited linear pharmacokinetics with increasing dose. Myelotoxicity was dose limiting. Temozolomide activity was schedule dependent and therefore oral administration was studied as a daily for 5 days schedule using total doses between 750 and 1200 mg/m^2 in 42 patients. The recommended dose for phase II trials was 150 mg/m^2 oral for 5 days for the first course, and if no major myelosuppression was detected on day 22 of the 4-week

cycle, the subsequent courses could be given at 200 mg/m^2 for 5 days on a 4-week cycle. A subsequent phase I study has been conducted to evaluate the plasma pharmacokinetics of TMZ administered as an extended continuous oral schedule and to compare total plasma exposure over 7 weeks with the conventional 5-day regimen.[17] Twenty-four patients with varying tumor types (17 of 24 gliomas) received TMZ that was administered at 50 mg/m^2/day, increasing by 25 mg/m^2/day/cohort until at 100 mg/m^2/day grade 4 myelotoxicity forced dose reductions to 85 mg/m^2/day, then to 75 mg/m^2/day. At 75 mg/m^2/day the regimen was extended to 7 weeks, allowing the future potential combination with RT for primary gliomas. Hematological toxicities did not exceed grade 2 in 10 patients receiving 75 mg/ m^2/day TMZ. Peak plasma TMZ concentrations were obtained 30 to 90 minutes after oral administration. Elimination in plasma was best described by a monoexponential equation with an elimination half-life of 96 ± 16 minutes. No plasma accumulation of TMZ occurred. The area under the TMZ plasma vs time curve (AUC) was noncumulative between the first and last week of the schedule. Temozolomide administration of 75 mg/m^2/day over a 7-week period permits a 2.1-fold greater drug exposure over 4 weeks in comparison with the 5-day schedule of 200 mg/m^2/day repeated every 28 days. Temozolomide (75 mg/m^2/day) for 7 weeks is the recommended starting dose for further assessment of this schedule.

Dosage forms

At present there are more than 20 oral antineoplastic agents which are being used in cancer care.[20] Temozolamide was commercialized in 1999 with several dose-presentations: 5 mg, 20 mg, 100 mg and 250 mg. Some of them were changed in 2008 in order to make the compliance easier by simplifying the oral regimens. Two new doses were approved, 140 mg and 180 mg, and the 250 mg capsules were withdrawn in Europe. Patients treated concomitantly with RT at a dose higher than 140 mg/day seem to be obviously benefited after availability of 140 mg tablets, simplifying oral treatment and diminishing the probability of toxicity or insufficient dosing through a mistake.

Intravenous TMZ obtained EMEA authorization on February 17, 2009.[10] The approved therapeutic indications are the same as the oral ones: "adult patients with newly-diagnosed GBM concomitantly with RT and subsequently as monotherapy treatment and children from the age of 3 years, adolescents" and "adult patients with malignant glioma, such as GBM or anaplastic astrocytoma, showing recurrence or progression after standard therapy". FDA approved iv TMZ on February 27, 2009, as 100 mg powder for injection.[11] The indications and usage provided on label information are: "newly diagnosed GBM concomitantly with radiotherapy and then as maintenance treatment", also "refractory anaplastic astrocytoma and patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine". No available data of the studies on which the approval is based have been published in peer-review journals. As recorded on label information, bioequivalence studies have been performed and have established that an infusion over 90 minutes delivers equivalent TMZ dose and exposure to both TMZ and MTIC as does the corresponding TMZ capsules. Regarding toxicity, the adverse events newly reported due to iv formulation were: pain, irritation, pruritus, warmth, swelling and erythema at infusion site, petechiae and hematoma. The number of patients in the two studies reported on label is 35.

Pharmacokinetics

Pharmacokinetic studies of TMZ have consistently shown linear pharmacokinetics with the AUC increasing in proportion to the dose. After oral administration to adult patients, TMZ is absorbed rapidly with t_{max} between 0.5 and 1.5 hours. The good bioavailability (100%) after oral administration allows oral administration of the drug. After absorption, TMZ was rapidly converted to the active substance, MTIC, and subsequently to AIC. Mean t_{max} values for MTIC were 1.5 to 2.0 hours after a single dose, and mean t_{max} of AIC was 2.5 hours. Mean AUC values ranged from 14.3 to 15.5 μg/h/mL for a dose of 100 mg/m^2 to 176 μg/h/mL for a dose of 1000 mg/m^2. The effect of gastric pH and ingestion of food on pharmacokinetic properties and oral bioavailability has also been evaluated. Administration of TMZ with food resulted in a 33% decrease in C_{max} and 9% decrease in AUC.[16] Although the clinical significance of these changes is unclear, TMZ should be administered in the fasting state. Administration of TMZ with ranitidine did not result in alterations in the extent of absorption of TMZ.[21]

A phamacokinetic study has been performed comparing oral and iv TMZ in 19 patients with primary central nervous system malignancies. Intravenous TMZ at 150 mg/m^2 over 90 minutes was bioequivalent to 150 mg/m^2 oral TMZ with respect to both C_{max} and AUC of TMZ and MTIC. The mean C_{max} and AUC values for TMZ and MTIC were 7.3 μg/mL and 276 ng/mL, respectively. The same values for oral TMZ were 7.5 and 282, respectively. The mean AUC values for TMZ and

Table 1 Phase II trials of standard and dose dense temozolomide administration schedules for recurrent malignant gliomas

Study	Dose mg/m²	Dose intensity mg/m²/week	Schedule	Tumor type	No. of patients	RR %	6PFS %	OS months	Grade 3–4 hematological toxicity (no. of patients)	Grade 3–4 nonhematological toxicity (no. of patients)
Standard treatment										
Yung et al[8]	150–200	250	5/28	AA	111	35	46	5.4	1 anemia 3 neutropenia 3 leukopenia 10 thrombocytopenia	16 nausea 10 vomiting 10 headache 9 asthenia 7 fatigue
Yung et al[9]	150–200	250	5/28	GBM	112	5.3	21	2.9	1 anemia 4 neutropenia 1 leukopenia 8 thrombocytopenia	3 nausea 3 vomiting 2 headache 1 constipation 3 fatigue
Dose-dense dosing schedules										
Wick et al[28]	150	525	7/14	GBM	39	5.1	43	–	1 grade 4 anemia 3 neutropenia 1 febrile neutropenia 6 thrombocytopenia	2 nausea 4 fatigue
Tosoni et al[29]	75	400	21/28	GBM	51	–	–	–	52% of patients any grade lymphocytopenia 1 grade 5 hematological toxicity	1 herpes zoster concomitant with grade 2 lymphocytopenia 3 infections concomitant with grade 3 lymphocytopenia 1 fungal penumonia concomitant with grade 4 lymphocytopenia 1 grade 5 infection concomitant with grade 4 pancytopenia 1 grade 5 pulmonary thromboembolism
Chinot et al[30]	150	525	7/17	GBM	29	24	–	6,1	6 thrombocytopenia 6 lymphocytopenia 5 neutropenia 5 leukopenia 1 grade 3 febrile neutropenia	3 grade 3 febrile neumonitis with lymphocytopenia 2 grade 3 febrile neumonitis with neutropenia 1 grade 4 pulmonary embolism 2 grade 3 infection whitout neutropenia 1 grade 3 constipation 1 grade 3 asthenia
Wick et al[31]	150	525	7/14	GBM, LGGs, AA, AOA, Other	64	15	43,8	–	1.2% of patients neutropenia 1.8% of patients lymphocytopenia 10.4% of patients thrombocytopenia	–

Neyns et al[32]	100	525	21/28	AA	15	13	56	12,9	53% of patients lymphocytopenia 47% of patients lymphocytopenia	1 herpes zoster concomitant with grade 3 lymphocytopenia 1 grade 5 *P. carinii* pneumonia concomitant with grade 4 lymphocytopenia
Perry et al[36]	50	350	28/28	GBM	21	–	17	–	lymphocytopenia	
				GBM	14	–	57	–		
				AA	14	–	42	–		
Berrocal et al[33]	85	446	21/28	AA and GBM	39	5.1	20	5.9	7% of patients thrombocytopenia 3.5% of patients neutropenia	–

Abbreviations: AA, anaplastic astrocytoma; AOA, anaplastic oligoastrocytomas; GBM, glioblastoma multiforme; LGG, low-grade gliomas; other, meningioma, ependimoma, sarcoma; OS, overall survival; 6PFS, progression-free survival at 6 months; RR, respone rate.

MTIC were 24.6 μg/h/mL and 891 ng/h/mL after iv TMZ and 23.4 μg/h/mL and 864 ng/h/mL after oral TMZ.[10,11]

Efficacy studies

Recurrent anaplastic gliomas

Temozolomide was evaluated in a phase II study involving patients who had previously been treated with nitrosoureas; the study showed a 35% response rate (RR), and 6PFS was 46% and 5.2 months of median PFS (MPFS).[8] A randomized phase II trial comparing oral procarbazine with TMZ in recurrent GBM showed a 5.4% RR and a 21% 6PFS[9]. These studies suggested an increase in 6PFS compared with a historical database. The EORTC conducted 2 phase II trials evaluating single-agent, standard-schedule TMZ as first- and second-line therapy in patients with recurrent or progressive anaplastic oligodendroglioma and oligoastrocytoma.[22,23] A RR of 53% (26% complete responses) and 25% were observed in first- and second-line chemotherapy, respectively. Most patients that responded to second-line therapy had also responded to first-line procarbazine, lomustine, and vincristine (PCV) chemotherapy but some patients that do not respond to PCV may still respond to TMZ. The NOA-04 phase III, multicenter, open-label trial compared the efficacy and safety of RT vs chemotherapy (PCV or TMZ) in 318 patients with newly diagnosed, supratentorial anaplastic gliomas (AG).[24] At occurrence of unacceptable toxicity or progressive disease (PD), patients in RT arm were treated with one of the chemotherapy regimens (1:1 randomization) while patients receiving chemotherapy were switched to RT. Median time-to-treatment failure (TTF), MPFS, and overall survival (OS) did not differ between arms.

At the time of this review the optimal treatment of AG is controversial and, while the standard of care in most centers is still radiotherapy, in other centers TMZ is routinely associated with RT in this setting. The results of the NOA-4 study suggested that initial therapy in all AG patients could be either TMZ or RT alone but ongoing trials are currently evaluating the role of RT plus concomitant TMZ. In addition, patients with an astrocytic tumor (52.6% of cases) had a worse TTF than oligoastrocytic (33.2%) or oligodendroglioma tumors (14.2%). Oligoastrocytic tumors share the same favorable prognosis of pure oligodendroglioma. The combination of 1p/19q chromosome deletion and the hypermethylation of the *MGMT* gene promoter bear a large risk reduction for TTF and MPFS irrespective of histology and treatment.

In conclusion, in this study the presence of an oligodendroglial component in tumors was as strong favorable

prognostic factor as combined 1p/19q deletion. MGMT promoter methylation was associated with prolonged PFS also in the RT arm.

Newly diagnosed GBM

In 2002, Stupp et al reported a pilot trial combining TMZ and RT.[25] Treatment consisted of surgical debulking to the extent feasible or biopsy followed by standard focal RT (a total dose of 60 Gy in 30 daily fractions of 2 Gy) with daily TMZ (75 mg/m²/day) administered concomitantly during the whole period of RT for 49 days at most. After a 4-week break, patients received up to 6 cycles of adjuvant oral TMZ (150–200 mg/m²) for 5 days every 28 days. Encouraging results with a median survival of 16 months (95% CI, 11 to 21 months) and a 2-year survival rate of 31% (95% CI, 19% to 44%) in this phase II trial led to the randomized phase III trial by EORTC and NCIC. In 2005, the indications for TMZ use were expanded for use in the adjuvant treatment of newly diagnosed GBM based on the interim results of this randomized phase III trial [7]. The final results of this trial have recently been published in *Lancet Oncology*.[26] Patients were randomized to receive either standard RT (n = 286), or standard RT plus concomitant daily TMZ, followed by adjuvant TMZ (n = 287) with the same schedule as previous phase II study. At the time of this final analysis, 532 (93%) had died after a median follow-up of 61 months. Survival was significantly greater in the TMZ group than in the RT alone group throughout follow-up. Overall survival was 27.2% at 2 years, 16.0% at 3 years, 12.1% at 4 years, and 9.8% at 5 years with TMZ, vs 10.9%, 4.4%, 3.0%, and 1.9% with RT alone. A benefit of combined therapy was recorded in all clinical prognostic subgroups, including patients aged 60–70 years. Methylation of the O^6-methylguanine-DNA methyltransferase (MGMT) promoter was the strongest predictor for outcome and benefit from TMZ chemotherapy. In conclusion, benefits of adjuvant TMZ with RT lasted throughout 5 years of follow-up. A few patients in favorable prognostic categories survived longer than 5 years and *MGMT* methylation status identifies patients most likely to benefit from the addition of TMZ.

A second randomized trial was also published in 2005.[27] It used a dose intensification schedule of TMZ in the adjuvant phase involving 150 mg/m² of TMZ on days 1 to 5 and 15 to 19. In the concomitant phase TMZ was administered using a standard 75 mg/m². RT was administered to both arms at a dose of 60 Gy over 6 weeks. Randomization was adequate but the trial was not blinded and did not include a placebo. One hundred thirty patients with newly diagnosed GBM were randomly assigned (110 assessable patients). Median time to progression was 10.8 months in the TMZ group and 5.2 months in the RT alone group ($P = 0.0001$). One-year PFS rate was 36.6% in the TMZ group and 7.7% in the RT alone group. Median OS time was also significantly better in TMZ group vs the RT alone group (13.4 vs 7.7 months, respectively; $P < 0.0001$), as was the 1-year OS at 56.3% vs 15.7% ($P < 0.0001$), respectively.

Efficacy data of iv TMZ which have been approved are those extrapolated from clinical trials with oral TMZ.[10,11]

Different schedules of TMZ administration

Even though the only 2 formally approved administration regimens are the 5 daily dose schedule and the low-dose daily administration regimen in combination with RT, a number of other different regimens have been used (Table 1). The dose-dense schedules allow a significant increase in the dose intensity (over 2-fold TMZ exposure) and deplete MGMT, mitigating a potential mechanism of TMZ resistance.[28–33] However, improved efficacy of these schedules remains to be demonstrated and continuous TMZ exposure may induce profound lymphocytopenia. The results of a randomized trial that compared PCV regimen vs TMZ (5-day or 21-day schedule) for recurrent high-grade glioma have been reported.[34] A total of 447 patients were randomized 2:1:1 to PCV, TMZ 200 mg/m² for 5 days (TMZ-5), and TMZ 100 mg/m² for 21 days (TMZ-21). Both TMZ schedules were repeated every 28 days for up to 9 cycles or until progression. Median follow-up was 12 months. Overall survival for PCV vs TMZ was 6.7 months vs 7.2 months, hazard ratio (HR) = 0.91 (0.74–1.11) $P = 0.35$. Overall survival for TMZ-5 vs TMZ-21, HR = 1.32 (0.99, 1.75) $P = 0.056$. Progression-free survival for TMZ-5 vs TMZ-21, HR = 1.38 (1.04, 1.82) $P = 0.023$. While TMZ did not show a clear benefit over PCV, the comparison of the 2 TMZ schedules demonstrated that the TMZ-21 regimen was inferior to TMZ-5.

A randomized phase II trial was conducted comparing dose-dense 7/14 TMZ and metronomic TMZ in 51 patients with newly diagnosed GBM following surgery and concurrent TMZ and RT. The OS was 11.2 months in patients receiving the metronomic schedule and the median survival was not reached for the dose-dense TMZ schedule. Median PFS was 3.8 months for the metronomic group and 6.8 months for the dose-dense group. Although these results are preliminary, early analysis indicates that the dose-dense TMZ regimen may be better than metronomic TMZ.[35] So the currently available data and clinical experience do not

support the use of alternative TMZ regimen outside specific protocols and clinical investigation.

Temozolomide rechallenge in recurrent malignant glioma

Temozolomide is well tolerated and may have activity despite prior TMZ exposure. Perry et al reviewed their experience with a continuous TMZ schedule (50 mg/m^2 daily), given at progression after conventional 5-day TMZ. Patients were reported in 3 groups:[36] Group 1, included 21 patients with GBM after progression on conventional TMZ; Group 2, included 14 patients with GBM at first recurrence after completion of standard concomitant and adjuvant TMZ; and Group 3, included 14 patients with other AG at second relapse on conventional TMZ. In Group 1, the 6PFS was 17%. In Group 2, with a median disease-free interval after adjuvant TMZ of 3 months (range 2–10) the 6PFS was 57%. In Group 3, 6PFS was 42%. Toxicity was mild and lymphocytopenia was common but no serious opportunistic infections were identified. Despite their retrospective condition, these results demonstrate that administration of TMZ as rechallenge is an active regimen if there is an interval >2 months after adjuvant prior TMZ therapy. Nevertheless, some of these cases could represent a pseudoprogression phenomenon. Wick et al have conducted another retrospective review of 80 patients with 90 recurrent glioma rechallenged with TMZ.[37] Some patients experiencing PD during TMZ therapy were rechallenged with alternative TMZ regimens. Other group of patients was rechallenged after stable disease in a TMZ-free interval and they were evaluated separately. The 6PFS was 48% in patients with anaplastic gliomas (12/25) and 27.7% in those with GBM (14/47). The 6PFS for patients switched during TMZ were 16.7 and 26.3% in the anaplastic glioma and GBM groups respectively and 57.9% and 28.6% in the same groups when only patients rechallenged after a TMZ-free interval of at least 8 weeks were considered. Relevant hematological toxicity (NCI-CTC grade 3–5) was observed in 22 of 90 rechallenged patients, and relevant nonhematological toxicity in 10 of 90 patients of the same group.

Low-grade glioma

Low-grade glioma may respond to chemotherapy. Response rates of over 40% to 60% to TMZ chemotherapy have been reported in 2 reports of patients treated for progressive low-grade glioma.[38,39] However, inclusion in these trials was based on initial histology, and the presence of contrast enhancement in 60% to 70% of the patients and the confirmed transformation into anaplastic glioma in over 50% of the operated patients clearly indicates that most patients had a higher-grade tumor and that the observed RRs are in accordance with earlier reports. There are 2 reports of TMZ administration (standard schedule) to patients with previously untreated low-grade glioma.[40,41] Objective RRs were 10% and 17%, respectively, with a 14% to 48% rate of minor responses or clinical improvement. These results suggest that TMZ does have activity for lower-grade glioma. However, whether there is an advantage in treating these patients with upfront chemotherapy for 12 months or longer compared with initial RT is currently the subject of a randomized EORTC/NCIC trial.

Neoadjuvant setting

High RRs with first-line TMZ chemotherapy immediately after surgery or biopsy and before RT have been reported. Gilbert et al reported on 36 GBM patients receiving standard-dose TMZ for up to 4 cycles.[42] An overall RR of 42% with a MPFS of 4 months and OS of 13 months were observed. A phase II study with neoadjuvant combination chemotherapy of TMZ plus cisplatin on 40 newly diagnosed GBM showed a RR of 45% (95% CI, 27%–58%) and OS of 12.5 months.[43] Overall survival is comparable with the standard sequence of TMZ and RT followed by TMZ. One phase II trial evaluated the administration of TMZ in 32 elderly patients with a median age of 75 years.[40] The RR was 31% (95% CI, 14%–48%) and the OS was 6.2 months, comparable with the 5.2 to 5.6 months recently reported for RT alone.[44] A randomized trial by the Nordic Neuro-Oncology Group comparing RT with a standard dose of TMZ is ongoing.

Combination with other agents

TMZ in combination with other alkylating agents (eg, BCNU), has been tested and schedule-dependent toxicity is to be expected due to fact that repair of the DNA damage induced by both agents depends on MGMT. Phase II trials of TMZ in combination with other agents are summarized in Table 2.[45–47] At the time of this review, no combination has demonstrated superiority to monotherapy in phase III setting. Studies are under way to evaluate the combination of TMZ with biotherapy agents in the treatment of malignant glioma such as metalloproteinase inhibitor marimastat, thalidomide and cis-retinoic acid. All have showed modest evidence of activity in patients with recurrent GBM.[48–50] A phase II trial showed the safety and feasibility of the adjunction of cilengitide to the standard regimen of TMZ and concomitant RT, followed by TMZ maintenance.[51] Overall survival was

promising, notably in the patients with a methylated *MGMT* gene promoter. Recently a worldwide randomized phase III trial has been launched. Patients with a methylated gene promoter are eligible for randomization between standard TMZ/RT + TMZ, vs the same standard regimen enhanced by the addition of cilengitide.

Recently a phase II trial of bevacizumab (10 mg/kg every 2 weeks) in combination with TMZ (75 mg/m^2/day) and RT in 70 patients with newly diagnosed GBM has been presented.[52] After completion of RT patients are then placed on a maintenance phase of bevacizumab (10 mg/kg every 2 weeks) and TMZ (150–200 mg/m^2/day 5 days out of every 28) until progression or 24 months. There were grade 3–4 hematological and nonhematological toxicity (Table 2). Median progression free survival was 13 months and OS was 25 months. Despite a good theoretical rationale for all regimens, the available data from these phase II trials do not allow for any firm conclusions with regard to increased activity. A phase III study starts now to answer this question.

Safety and tolerability

In phase I, the dose-limiting toxicity of the drug was thrombocytopenia. Grade 3–4 thrombocytopenia occurred in 10% of the 138 patients in a phase II study of TMZ at 200 mg/m^2/day for 5 days every 28 days for chemonaïve GBM patients and 150 mg/m^2/day for 5 days every 28 days for pre-treated patients, which was allowed to escalate to 200 mg/m^2 if no grade 3 or 4 toxicity was observed in first cycle, with 7% of leukopenia and 4.5% of neutropenia.[53] Nonhematologic toxicity was observed only in 8% of patients, with grade 3–4 nausea and vomiting without prior antiemesis medication. When studied in combination with cranial RT, TMZ at 75 mg/m^2/day 7 days a week concomitant with 60 Gy of RT, grade 3–4 neutropenia occurred in 4 patients (6%), and grade 3–4 thrombocytopenia in another 4. Forty-nine patients (79%) experienced grade 3–4 lymphocytopenia.[25] In this study, 3 patients who were receiving corticosteroids and presented grade 3–4 neutropenia and lymphocytopenia needed hospitalization and treatment interruption and 2 of these developed *Pneumocystis carinii* pneumonia. The same study explored adjuvant TMZ at 200 mg/m^2/day for 5 days every 28 days for 6 cycles. Grade 3–4 neutropenia or thrombocytopenia occurred in 2% and 6% of cycles, respectively. Nonhematologic toxicities were rash and moderate to severe fatigue during concomitant treatment in 2 patients at grade 3 and in 1 patient in adjuvant setting. Interestingly, on MRI, signs of leukoencephalopathy without clinical symptoms were observed among the 14 patients that were alive longer than 18 months. One of these patients showed intracranial hypertension, refractory seizures and loss of vision 33 months after beginning RT. Another patient showed memory loss and hemiplegia 17 months after beginning RT.

In the less selected phase III setting, patients were randomized to receive RT alone vs RT concomitant with TMZ followed by 6 cycles of adjuvant TMZ. Four percent of patients in the concomitant arm (12/287) experienced grade 3–4 neutropenia and 3% (9/287) grade 3–4 thrombocytopenia. Fourteen percent of patients presented any type of grade 3–4 hematological toxicity, 4% presented grade 3–4 neutropenia and 11% presented grade 3–4 thrombocytopenia during adjuvant TMZ treatment.[7] Severe infections were observed in 9 patients of the TMZ plus RT arm (3%) but 6 patients treated only with RT (2%) presented severe infections, too. Thirty-three percent of patients in the combination arm experienced grade 3–4 fatigue, and 26% in the control arm. There were 28 thromboembolic events, 16 in RT group and 12 in the combination group. Two patients presented opportunistic pneumonia, one in each arm. Another two patients died because of cerebral hemorrhage without coagulation alteration or thrombocytopenia, both in the combination arm. No late toxicity was observed with a median follow-up of 28 months. The dosing regimens tested in order to prolong the exposition to TMZ in compressed and extended dosing schedules summarized in Table 1 showed induction of profound lymphocytopenia and severe secondary infections.

However no opportunistic infection was reported, possibly due to *P. carinii* pneumonia prophylaxis administered to patients if they were found to have grade 3 or more lymphocytopenia, as was done in one of the studies mentioned.[31]

Mechanisms of resistance

The mechanisms of resistance to TMZ evaluated in preclinical studies are the enzyme AGT, the deficiency in the mismatch repair pathway and the base excision repair pathway. Of these mechanisms, AGT plays a primary role in resistance to TMZ and other alkylating agents by removing the alkyl groups from the O^6 position of guanine, in effect reversing the cytotoxic lesion of TMZ. Several preclinical studies have examined methods for reducing the resistance to alkylating agents such as TMZ. O^6-benzylguanine and lomeguatrib are potent inhibitors of AGT-mediated resistance to DNA. Preclinical studies suggest a role for these agents in increasing the therapeutic index of TMZ, and phase I trials have been reported.[54–57] Another possible

Table 2 Phase II trials of temozolomide in combination

Study	Phase	Agent	Dose	TMZ	Tumor type	No. of patients	Activity 6PFS (%, 95% CI)	Toxicity
Barrié et al[45]	II	BCNU	150 mg/m^2 day 1	110 mg/m^2/day 5 days every 42 days	GBM	40	Median PFS was 7.4 months	15% of patients grade 3–4 hematological (thrombocytopenia and neutropenia) and pulmonary
Brandes et al[46]	II	Cisplatin	75 mg/m^2 day 1	130 mg/m^2 bolus followed 70 mg/m^2 twice daily for 5 days	GBM	50	34, 23–50	15% of patients grade 3–4 myelosupression
Quinn et al[47]	II	Irinotecan	125 or 325 (if receiving or not enzyme-inducing antiepileptic drugs) mg/m^2/day days 1, 8, 22 and 29 every 42 days	200 mg/m^2/day 5 days every 42 days	GBM	42	Median PFS was 3.1 months	14% of patients grade 3–4 hematological toxicities 10% of patients grade 3–4 nonhematological toxicities 5% of patients grade 5 toxicities (intracranial hemorrhage and renal failure)
Groves et al[48]	II	Marimastat	50 mg days 8 to 28 every 28 days	150 to 200 mg/m^2/day 1 to 5 every 28 days	GBM	44	39	47% joint and tendon pain
Chang et al[49]	II	Thalidomide	Started on day 7 of RT at 200 mg and escalated by 100–200 mg every 1–2 weeks depending on patient tolerance, to a maximum of 1200 mg daily	150 mg/m^2/day daily for 5 days every 4 weeks Radiation: 60 Gy delivered in 2 Gy fractions over 42 days	GBM	77	45, 33–57	Grade 3–4 neutropenia (n = 8), thrombocytopenia (n = 11), rash (n = 6), constipation (n = 1), fatigue (n = 6)
Jaeckle et al[50]	II	13-cis-retinoic acid	100 mg/m^2/day, days 1 to 21, every 28 days	150 or 200 mg/m^2/day, days 1 through 5, every 28 days	GBM, AG	88	43, 33–54	Grade 3–4 granulocytopenia (1.8%), thrombocytopenia (1.4%), and hypertriglyceridemia (1.2%)
Lai et al[52]	II	Bevacizumab	10 mg/kg every 2 weeks during RT Maintenance: 10 mg/kg every 2 weeks	75 mg/m^2/day Radiation: 30 × 200 Gy over 42 days Maintenance: 150 to 200 mg/m^2/day 1 to 5 every 28 days	GBM	70	Median PFS was 13 months	Grade 3–4 hematological toxicity (43% lymphopenia, 7% thrombocytopenia) Grade 3–4 nonhematological toxicity (8 hypertension, 12 venous thromboembolism, 3 ischemic stroke, 5 seizure, 1 intracranial hemorrhage, 6 proteinuria, 4 wound breakdown/infection, 4 gastrointestinal bleeding/perforation, 7 hyponatremia, 1 fatigue)

Abbreviations: AG, anaplastic glioma; GBM, glioblastoma multiforme; 6PFS, progression-free survival at 6 months; RT, radiotherapy; TMZ, temozolomide.

mechanism of resistance to TMZ is the base excision repair pathway. Studies have shown that treatment of human tumor cells with TMZ induced an increase in the activity of poly (ADP-ribose) polymerase (PARP), and the inhibition of PARP has been reported to enhance the cytotoxicity of methylating agents.[58] A phase I trial evaluated the safety and pharmacokinetic–pharmacodynamic profile of AGO14699, a PARP inhibitor, in combination with TMZ.[59]

MGMT and resistance to temozolomide in gliomas

MGMT gene on chromosome band 10q26 encodes a ubiquitous DNA repair enzyme, present in normal human tissues. This enzyme, MGMT, removes and accepts alkyl groups from the O^6 position of methylguanine without affecting DNA integrity. This is called a suicide enzyme because by doing that, MGMT inactivates itself irreversibly. MGMT plays a key role in reverting lethal DNA damage induced by TMZ, and thus neutralizing the cytotoxic effect. Furthermore, preclinical studies have shown that in the absence of this enzyme, cells are more susceptible to TMZ. High levels of MGMT in the tumor are associated with resistance to TMZ and other alkylating agents. Different methods have been described to measure MGMT levels in tumors. The protein can be detected by immunohistochemistry (IHC), and also the enzyme activity can be measured by high-performance liquid chromatography (HPLC). Promoter methylation status can be assessed by different methods. A retrospective study has been recently published analyzing the role of IHC as a clinical biomarker. The authors do not recommend the use of anti-MGMT immunohistochemistry as a routine biomarker for diagnostic purposes because of observer variability and lack of association with the MGMT promoter methylation status and survival.[60] A methylation-specific polymerase chain reaction assay (MSP-PCR) shows high sensitivity and specificity. This method requires a small amount of DNA and can be extracted from paraffin-embedded tissue or from cryopreserved tissue samples.[61] The presence of a methylated *MGMT* allele is only due to tumor cells. Until future validation, this test cannot yet be considered for routine clinical decision. Other assays are now under evaluation, such as *MGMT* hypermethylation analysis using methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA).[62] The potential value of *MGMT* hypermethylation evaluation by MS-MLPA was recently shown in a small group of patients with a GBM treated with TMZ. Nevertheless, further evaluation is needed to establish its clinical value. Epigenetic silencing of *MGMT* by promoter hypermethylation is present in approximately 40% of primary GBM and represents the main mechanism to reduce *MGMT* expression and diminish the DNA repair activity. Moreover, it has been shown to be an independent predictor of response to alkylating chemotherapy in patients with newly diagnosed GBM treated with RT and concomitant TMZ and adjuvant TMZ.[63] In this study TMZ only benefited patients with a methylated *MGMT* gene promoter. TMZ treated patients with a nonsilenced *MGMT* gene had an OS and PFS similar to patients who initially received radiotherapy alone. These results can give the impression that patients without *MGMT* promoter methylation should not be treated with alkylating chemotherapy. However, these patients had at least a minor benefit from TMZ and other alternative strategies are currently not available outside clinical trials.[64,65] Nevertheless it is important to note that this analysis was performed retrospectively, and therefore these results require prospective validation. The accrual of a trial by RTOG and EORTC (RTOG 0525/EORTC 26052-22053) is actually closed. In this study patients with newly diagnosed GBM are stratified by *MGMT* methylation status before randomization to a TMZ schedule (standard daily dose for 5/28 days or a 21/28 days dose-dense regimen). Data from this study are expected at the end of 2009.

Health-related quality of life in patients treated with temozolomide

An important goal to evaluate the usefulness of any treatment in cancer is the ability to maintain or improve the patient's quality of life. The tools used to determine how the general quality of life is affected by cancer are the health-related quality of life (HRQOL) self-report questionnaires. The most used tests are the Quality of Life Core-30 (QLQ-C30) and the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaires, both supplemented with modules designed to specifically assess symptoms due to brain cancer (QLQ-BN20 and FACT-Br).[66–69] These instruments are well validated and have robust psychometric properties as a result of rigorous testing and development in several international cancer clinical trials. These questionnaires measure quality of life status in a multidimensional way, providing several scales of symptoms and functional domains of patient's life. The effect of TMZ treatment over quality of life has been well assessed in patients with high grade gliomas, mainly GBM, and more recently in patients with low grade gliomas.

The randomized trial of RT alone vs RT with concomitant and adjuvant TMZ conducted by EORTC-NCIC was also focused on the evaluation of quality of life.[7,70] In this study, at baseline HRQOL scores were the same for both groups.

During subsequent assessments, groups did not differ significantly for any of the 7 preselected scales analyzed. The addition of performance status and type of surgery data to the analysis did not change the results. This trial allows us to conclude that adding concomitant and adjuvant TMZ to RT does not adversely affect HRQOL, although the sample calculation was not based on detecting changes in HRQOL. Two phase II studies had been performed to evaluate the efficacy of TMZ after GBM recurrence where HRQOL was also considered as a secondary end point.[7–9] Joint results of HRQOL for these two works were reported in a separate publication.[71,72] This work showed that before disease progression, patients treated with TMZ had an improvement in most of preselected HRQOL domains analyzed compared with their pretreatment scores. Conversely, patients treated with procarbazine reported deterioration in HRQOL that was independent of whether or not the disease had progressed. Baseline scores between the two treatment arms were similar. Patients with disease progression, independent of treatment, experienced a decline in HRQOL domains assessed. Only 1 study has been carried out to determine whether TMZ treatment affects quality of life of patients with recurrent anaplastic astrocytomas and anaplastic oligoastrocytomas.[72] This study showed that scores in seven preselected domains were maintained or improved in patients who did not have disease progression and a gradual decrease in scores as progression neared and worse than baseline scores at time of progression. The results of an interim analysis about HRQOL in a phase II trial in newly diagnosed low grade gliomas have been recently reported.[73] Patients treated in this study showed either no significant changes or improvement in HRQOL scores at each cycle of TMZ compared to their own baseline scores. However, despite the good overall compliance rate of questionnaires (71%–85%), patients who progressed and those who had intolerable side effects that needed cessation of therapy were not included in the analysis.

A small phase II trial that was performed in progressive low grade gliomas to assess benefits of TMZ in recurrent low-grade gliomas showed that an improvement of HRQOL scores in 1 or more items was more frequent in patients with radiological response to treatment than in patients with stable or progressive disease.[39]

In summary, the schedule and adverse effects of TMZ do not deteriorate the patients' quality of life in newly diagnosed or recurrent glioblastomas (level I evidence). The main factor implied in the decrease HRQOL scores in these patients is tumour progression. In high grade gliomas, TMZ seems to present the same effect in quality of life, although we have less studies available (level II evidence). Currently, there is little available evidence of TMZ in low-grade gliomas, although the preliminary results are encouraging. The main criticisms in the quality of life studies available are: in the design of studies the sample calculation is based on OS and not on HRQOL scores and each study selects some arbitrary scales to analyze and none make any comment about cognitive or language status of patients and their ability to understand the questionnaires. Moreover, we should not forget that the analyzed group of patients corresponds to a trial-selected population that could not reflect the tolerance to this treatment in general population.

Adherence and patient preferences

It has been generally believed that cancer patients were always compliant to treatment. But nowadays, the number of oral compounds is increasing in oncology and some studies have showed that adherence must be focused and followed. To our knowledge, little information is published in oncology on the incidence of nonadherence, which ranges from 25% to 98%.[74] Nonadherence can have multiple consequences such as inducing the physician to attribute progression of the disease to a lack of activity of the drug, and increasing the consumption of healthcare resources.[75] In a recent study, the factors associated with poor adherence in 169 patients with chronic myeloid leukemia who were treated with imatinib were: demographic variables such as age, living alone and being male; treatment variables such as duration of treatment and different combinations for a dose; and the patient–physician relationship.[76] The same risk factors have been published in the recommendations of the Spanish AIDS groups, including adverse events secondary to treatment.[77] When feasible, on-site pharmacies and consultations with a pharmacist should be encouraged because they may facilitate adherence.[78]

There are no published studies about adherence to TMZ, but adherence of patients treated with this drug could be compromised by several factors, such as consequences of tumor resection and the complexity of treatment regimen. In any case, these data would be relevant to eventually choosing the better treatment for any individual patient, as iv formulations are available if predictors of poor adherence are present.

Liu et al studied the advanced cancer patient's preferences between oral and parenteral treatment.[79] Of 103 assessable patients, 92 preferred oral chemotherapy, 10 preferred iv chemotherapy, and 1 had no preference. Patient preferences were not associated with age, sex, site of primary cancer, or previous chemotherapy experiences. Major reasons for preferring oral chemotherapy were convenience, problems

with iv access or needles, and a better environment for medication (taking medication at home). Studies comparing clinical efficacy and safety of oral and parenteral forms of the same drug are not common. Data are available for colon, breast and lung cancer patients.[80–83] To date, all but one of the studies based on patient surveys have showed a preference for oral over parenteral treatments and there is little question that oral regimens are more convenient for patients, as long as efficacy is guaranteed.

After assuming that oral and iv formulations of TMZ are bioequivalent in terms of pharmacokinetics, toxicity and efficacy, the question raised is about their advantages and disadvantages. Oral chemotherapy offers advantages for patient convenience in terms of flexibility of timing and location of administration, which can lead to potential reductions in the use of healthcare resources. There are few concerns about the bioavailability of oral TMZ used during fasting. As the oral administration of chemotherapy results in prolonged drug exposure, the scientific community has explored extended schemes in order to enlarge the time of drug exposure and avoid resistance to TMZ. First comparative results are now available. This approach does not appear to show any advantage for iv formulations. From the patient's point of view, there are neither comparative available data on the differences of tolerability and patient satisfaction between oral and iv formulations of TMZ, nor quality of life data. One of potential problems arising from oral administration of chemotherapy is the lack of treatment compliance. Data on compliance are limited and there is no study with TMZ, but interestingly the main clinical importance of iv formulations could be the treatment of noncompliant patients or patients for whom good adherence could not be expected, such as children or adolescents.

Conclusions

The best treatment available for GBM includes surgery if possible, RT and chemotherapy with TMZ. Toxicity of TMZ, which particularly consists of myelotoxicity, is manageable. Alternative TMZ regimens are being tested, especially extended ones, in which profound lymphocytopenia has been observed and severe opportunistic infections should be prevented, but they are not recommended outside clinical trials. In spite of a robust biological rationale, MGMT testing is not yet incorporated in routine clinical practice due to lack of definitive validation. Oral TMZ formulations are well established and new oral formulations can encourage the adherence of patients to treatment. Intravenous formulations may be an alternative if needed, although patients presumably would prefer oral treatment. For patients, TMZ treatment is beneficial, tolerable, preserves quality of life and is easy to administer.

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Disclosures

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