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ORIGINAL REPORT

Efficacy and Tolerability of Temozolomide in an Alternating Weekly Regimen in Patients With Recurrent Glioma

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ABSTRACT

Purpose
Evaluation of toxicity and efficacy of an alternating weekly regimen of temozolomide administered 1 week on and 1 week off in patients with recurrent glioma.

Patients and Methods
Ninety adult patients with recurrent gliomas accrued in one center received chemotherapy with temozolomide at 150 mg/m^2/d (days 1 through 7 and 15 through 21 every 4 weeks) with individual dose adjustments according to hematologic toxicity.

Results
A total of 906 treatment weeks were delivered. Grade 4 hematotoxicity according to the Common Terminology Criteria for Adverse Events (CTCAE; version 3.0) was observed in 24 treatment weeks (2.6%). CTCAE grade 4 lymphopenia eventually developed in 11 patients (12%). There were neither cumulative lymphopenias nor opportunistic infections. The progression-free survival (PFS) rate at 6 months for glioblastoma patients was 43.8%. The median PFS in these patients was 24 weeks (95% CI, 17 to 26 weeks), the median survival time from diagnosis of progression was 38 weeks (95% CI, 30 to 46 weeks), and the 1-year survival rate from progression was 23%. *O^6-methylguanine DNA methyltransferase* (*MGMT*) gene promoter methylation in the tumor tissue was not associated with longer PFS (log-rank $P = .37$).

Conclusion
These data imply that the alternating weekly schedule is feasible, safe, and effective and clearly warrants investigation in randomized studies. Compared with more protracted low-dose temozolomide schedules, the 1-week-on/1-week-off schedule may be less toxic. We provide preliminary evidence that this dose-dense schedule is also active in patients with tumors lacking *MGMT* gene promoter methylation.

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INTRODUCTION

Progression-free survival (PFS) with primary treatment has been 7.2 and 10.8 months in the experimental arms of the recent randomized trials implementing temozolomide (TMZ) as part of the standard of care for newly diagnosed glioblastoma. Salvage therapies in these studies added another 7.4 and 3.3 months.[1,2] These observations highlight the importance of second-line treatment to improve overall survival and illustrate that current treatment concepts can be improved. Interestingly, patients who were stable for a longer time after primary TMZ treatment may have another prolonged stabilization on second-line TMZ therapy.[3,4] Moreover, evidence from single-arm trials suggests that TMZ administered in dose-dense regimens may be more efficacious than in conventional dosing schedules.[5,6] Alternative dosing schedules that deliver more prolonged exposure may result in higher cumulative doses than the standard 5-day regimen and may deplete tumor-derived O^6-methylguanine DNA methyltransferase (MGMT) in tumor cells, thus sensitizing tumor cells to the toxic effects of TMZ.[7,8] In an Italian series, protracted low-dose TMZ at 75 mg/m^2 for 3 of 4 weeks was surprisingly toxic, resulting in cumulative lymphopenia and opportunistic infections.[9] The PFS rate with this regimen in recurrent glioblastoma was 30% in chemotherapy-naive patients.[10] Conversely, the clinical experience with the alternating weekly regimen of 1 week on and 1 week off in 39 patients with recurrent glioblastoma suggests a relatively low incidence of lymphopenia. Moreover, this regimen produced a response rate of 9.5%, a 6-month PFS rate of 43%, and a median PFS of 21 weeks (approximately 5 months), which is superior to the data reported on the standard 5-day

dosing regimen[8,11] and the 3-weeks-on/1-week-off regimen.[10] Meanwhile, dose-dense TMZ regimens are already widely used to treat primary and secondary CNS tumors including sarcomas, ependymomas, and brain metastases, although published toxicity and efficacy data are largely lacking.

In contrast to the reported 3-weeks-on/1-week-off series and to the majority of patients in our first series,[5,11] radiochemotherapy has now become standard first-line treatment for patients with glioblastoma. There has been a lack of data carefully analyzing toxicity, efficacy, and the impact of MGMT status on PFS in a 1-week-on/1-week-off TMZ administration schedule in patients pre-exposed to chemotherapeutic agents. We therefore performed a new phase II trial enrolling 64 patients with glioblastoma, mainly pretreated with radiochemotherapy, plus 26 patients with other primary brain tumors to assess its safety profile and efficacy.

PATIENTS AND METHODS

Patients

This prospective nonrandomized phase II study of TMZ in a 1-week-on/1-week-off regimen (TMZ 1 week on/1 week off) was initiated on December 15, 2003, and closed to accrual on January 15, 2006. The local ethics committee at the University of Tübingen (Tübingen, Germany) approved the study. All patients gave written informed consent. The main inclusion criteria were prior histologic diagnosis of supratentorial glioma, prior radiotherapy with or without one regimen or more of chemotherapy, unequivocal evidence of recurrence or progression by cranial computed tomography (CCT) or magnetic resonance imaging (MRI), age more than 17 years; Karnofsky performance score (KPS) of 60 or more, recovery from toxic effects of prior radiotherapy or other therapies, and no alterations in bone marrow reserve, liver function, or renal function. Nonglioma brain tumor patients were treated off study according to the protocol. Toxicity data of these patients are included in this report.

Treatment and Surveillance

TMZ was administered orally at 150 mg/m^2 on days 1 through 7 and 15 to 21 of 28-day cycles for a maximum of 12 cycles. The start of each new cycle required that all hematologic toxicity assessed according to the Common Terminology Criteria for Adverse Events (CTCAE; version 3.0) from the previous cycle had resolved to grade 2 or less and that all nonhematologic toxicity had recovered to grade 0 or 1. If recovery had not occurred by the last day of the week off from TMZ, the subsequent week of TMZ was delayed until these criteria were met. No dose escalations were allowed. Dose reductions for hematologic toxicity were applied in 25-mg/m^2 steps. If the counts were less than 2×10^9/L for leukocytes or less than 75×10^9/L for platelets, TMZ was reduced by 25 mg/m^2 for the next week. A reduction by 50 mg/m^2 (two dose levels) was necessary if the leukocyte counts were less than 2×10^9/L and the platelet counts less than 75×10^9/L. If more than a two-dose-level reduction was necessary for the continuation of treatment of any patient (< 100 mg/m^2 daily dose), the patient was withdrawn from the study. The dose was re-escalated in steps of 25 mg/m^2 when, after a former dose reduction, the lowest counts for leukocytes were more than 2×10^9/L and for platelets more than 75×10^9/L for two subsequent weeks. When lymphopenia of grade 3 or worse occurred, a *Pneumocystis carinii* pneumonia prophylaxis was administered. In addition, patient treatment was halted when grade 4 lymphopenia occurred.

Toxicity monitoring was performed on all patients during all cycles according to the CTCAE scale every month. Safety parameters included all laboratory and hematologic abnormalities, neurological history and examination, and adverse events reported by patients. Quality-assurance measures included ongoing (per protocol timetable) monitoring of protocol compliance and response reviews.

During the trial, the patients underwent MRI every 3 months. PFS with TMZ and overall survival were calculated from the date recurrent or progressive tumor was diagnosed. Tumor progression was defined according to the Macdonald criteria.[12] Further, neurotoxicity, regarded as evolving T2 abnormalities during the treatment with TMZ, was evaluated on consecutive MRI scans.

End Points and Statistical Analysis

The primary end points were acute toxicity in the whole cohort and PFS at 6 months in the glioblastoma population. Secondary end points were median PFS and median survival time (MST) after TMZ had been commenced at recurrence. PFS and MST for nonglioblastoma patients were observed. PFS and MST were calculated according to the Kaplan-Meier method starting from the day of diagnosis of recurrence or progression on MRI.

TMZ was approved as a treatment for recurrent malignant glioma on the basis of a study showing that conventional dose TMZ results in a PFS at 6 months (PFS-6) of 21%.[8] We wanted to test whether the alternating weekly (1-week-on/1-week-off) regimen of TMZ resulted in an improvement of 21% patients with PFS-6 of more than 20%. We concluded that 64 patients in a single-arm study would give us acceptable error rates for testing our hypothesis and acceptable precision for estimation. To declare success, 28 successful treatments (patients alive and progression free at 6 months) of 64 patients (target: at least 43%) were needed. We performed a two-sided Fisher's exact test to test for significance of the outcome in our study compared with the standard regimen.[8] Further patients with progressive gliomas have been included in the safety analysis, and efficacy data are reported.

MGMT Analysis

Genomic DNA was extracted from formalin-fixed, paraffin-embedded tumor samples.[13] MGMT promoter methylation status was analyzed by methylation-specific polymerase chain reaction (PCR). One microgram of genomic DNA from each case and appropriate reference samples were treated with sodium bisulfite.[14] The primer sequences used to detect methylated MGMT promoter sequences were 5′-GTTTTTAGAACGTTTTGCGTTTCGAC-3′ and 5′-CACCGTCCCGAAAAAAAACTCCG-3′. This primer combination allows for the amplification of a 122–base pair (bp) fragment from methylated DNA. The primer sequences used to detect unmethylated MGMT promoter sequences were 5′-TGTGTTTTTAGAATGTTTTGTGTTTTGAT-3′ and 5′-CTACCACCATCCCAAAAAAAAACTCCA-3′. This primer combination allows for the amplification of a 129-bp fragment from unmethylated DNA. Each PCR product was separated on 2% agarose gels. As positive control sample, we used genomic DNA from a glioma with known MGMT hypermethylation.[15] Genomic DNA extracted from non-neoplastic brain tissue served as unmethylated control sample. In addition, a control reaction without any template DNA was performed together with each PCR experiment.

RESULTS

Patient Characteristics

Ninety patients (nine with a low-grade gliomas [LGGs], nine anaplastic astrocytomas [AAs], two anaplastic oligoastrocytomas [AOAs], two meningiomas, three ependymomas, one sarcoma, and 64 glioblastomas) were accrued between December 2003 and January 2006. All patients had a recurrent tumor and experienced treatment failure with standard therapy at that time. Of note, combined radiochemotherapy with concomitant and adjuvant TMZ[1] was not standard-of-care until June 2005. Detailed characteristics are provided for the glioblastoma patient cohort (Table 1). All patients screened were accrued, and all patients were assessable for toxicity.

Treatment

A total of 906 treatment weeks of TMZ were delivered. The median number of treatment weeks delivered was 24 for patients with LGG (range, 5 to 51 treatment weeks), 9 for AA and AOA (range, 7 to 91 treatment weeks), 17.5 (range, 3 to 24 treatment weeks) for the mixed-tumor cohort, and 15.5 (range, 4 to 73 treatment weeks) for glioblastoma patients. The dose of TMZ was modified in 26 patients.

Table 1. Characteristics of Patients With a Glioblastoma (n = 64) in the Trial of Alternating Weekly TMZ

Characteristic	No.	%
Age, years		
Median	51	
< 40	7	11
40-59	35	54
≥ 60	22	35
Sex		
Male	20	
Female	44	
Karnofsky performance score		
60-80	18	28
90-100	46	72
Median time from initial diagnosis, weeks	37	
Prior debulking surgeries		
1	41	64
≥ 2	19 (4 patients with 3 prior surgeries)	30
Prior therapy		
RT	64 (3 re-RT)	100
CT*	41	64

Abbreviations: TMZ, temozolomide; RT, radiotherapy; CT, chemotherapy.
*Prior chemotherapy: 22 patients were chemotherapy naive; 30 had prior nimustine/teniposide in analogy to Weller et al,[17] three had prior PCV, and nine prior lomustine/TMZ.[4] Two patients received two prior chemotherapies.

TMZ was discontinued prematurely in 13 patients (14.4%). All dose adjustments or discontinuations were necessary for acute or prolonged hematotoxicity. Nonhematologic toxicity did not lead to dose adjustments or premature cessation of TMZ. Three of the 13 patients who discontinued prematurely could have continued after recovery of the bone marrow, but decided not to continue on TMZ.

Toxicity

Nine hundred six treatment weeks were assessable for acute toxicity. CTCAE grade 4 neutropenia was observed in 0.1% of courses and CTCAE grade 4 thrombocytopenia in 0.7% of courses. CTCAE grade 4 anemia was not seen in the entire study. Acute grade 3 and 2 toxicities are summarized in Table 2. Overall, 13 (14.4%) of 90 patients experienced hematologic CTCAE grade 4 toxicity. However, there were no opportunistic infections or toxic deaths in the study. Because of the recent data on lymphopenia with dose-intense TMZ regimens,[9,10,16] particular attention was paid to the lymphocyte counts. Twenty-nine patients entered the study with CTCAE grade 1 or 2 lymphopenia, and two patients had grade 3 or 4 lymphopenia at baseline. In total, 61 (68%) of 90 patients eventually showed lymphopenia. Of note, in contrast to the toxicity data reported for the 3-weeks-on/1-week-off (21 of 28 days) TMZ regimen at 75 mg/m^2,[9] lymphopenia in this study was not cumulative. Further, toxicity did not differ between low- and high-grade tumors ($r = 0.16$; $P > .05$) or between patients pretreated with chemotherapy or chemotherapy-naive patients ($r = 0.2$; $P > .05$). Especially, pre-exposure to nitrosoureas did not predict toxicity of TMZ ($r = 0.18$; $P > .05$). On the other hand, CTCAE grade 3 or 4 toxicity did not predict a longer PFS (≥ 6 months; $r = 0.25$; $P > .05$). Importantly, no relevant hints for neurotoxicity, irrespective from the pretreatment, were detected clinically or on regular MRI imaging with this TMZ regimen.

Table 2. Hematologic Toxicity Per Week in 906 Treatment Weeks

	%		
Criterion	Grade 2	Grade 3	Grade 4
Neutrophils	7.6	1.1	0.1
Lymphocytes	1.6	1.1	0.7
Platelets	5.9	8.5	1.9

NOTE. Grade based on National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Therapeutic Efficacy

The PFS-6 was 62.5% for the low-grade (n = 9) and 46% for the anaplastic glioma (n = 11) patients. It was 17% for patients with ependymoma (n = 3), meningioma (n = 2), and sarcoma (n = 1). All 64 patients with a glioblastoma were assessable for outcome assessment. Of 45 patients with measurable tumor, one patient had complete response (2%) and six patients partial response (13%). No responses were seen in the patients with other histologies. The median PFS was 24 weeks (range, 4 to 78 weeks; 95% CI, 17 to 26 weeks; Fig 1). PFS-6 was 43.8% and PFS at 12 months (PFS-12) was 12.5%. PFS-6 was thus higher than 43% (28 of 64 patients), which was needed to meet the predefined efficacy criteria. Nine patients (14%) were entered onto the study after treatment in the Universitätsklinikums Tübingen (UKT) -03 trial[4], indicating that dose-dense TMZ after TMZ and nitrosoureas treatment is feasible. The PFS in these patients did not differ from the general cohort. MST from diagnosis of progression was 38 weeks (range, 5 to 99 weeks; 95% CI, 30 to 46 weeks), the 1-year survival rate from progression was 23%. Testing for the impact of the different primary treatments, radiotherapy only, lomustine/TMZ plus radiotherapy within the UKT-03 study[4] and any other chemotherapy, mainly nimustine/teniposide plus radiotherapy,[17] revealed a trend toward better median PFS in the patients pretreated within the UKT-03 study (27 weeks; range, 17 to 73 weeks; 95% CI, 17 to 72 weeks) compared with the other groups (radiotherapy: median, 24 weeks; range, 4 to 50 weeks; 95% CI, 15 to 27 weeks; radiochemotherapy: median, 17 weeks; range, 4 to 78 weeks; 95% CI, 8 to 27 weeks) that does not reach statistical significance.

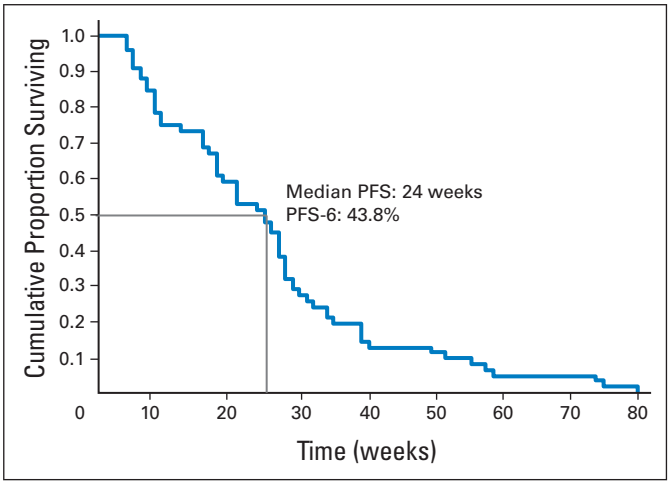

Fig 1. Progression-free survival (PFS) in the 64 patients with a glioblastoma of the alternating weekly temozolomide trial.

MGMT Methylation Status and Survival

Tumor specimens of 36 patients with a glioblastoma were available for analysis of *MGMT* promoter methylation. Seventeen patients had a methylated *MGMT* promoter and 19 patients did not. Using the log-rank test, PFS did not significantly differ with regard to the methylation of the *MGMT* promoter. The median PFS was 19 weeks with an unmethylated and 27 weeks with a methylated *MGMT* promoter ($P = .22$). The PFS-6 was 34% with an unmethylated and 52% with a methylated *MGMT* promoter. Looking at the MST from diagnosis also, no difference was found between patients harboring a tumor with an unmethylated (77 weeks; 95% CI, 56 to 102 weeks) or methylated *MGMT* promoter (71 weeks; 95% CI, 53 to 82 weeks).

DISCUSSION

This study demonstrates that the alternating weekly (1-week-on/1-week-off) TMZ regimen is feasible and effective in patients with recurrent gliomas, confirming the toxicity and efficacy data obtained in the previous smaller series.[5,11] Furthermore, within the limitations of the sample size available for *MGMT* testing, this is the first study to our knowledge to suggest that MGMT depletion, which is potentially achieved with the alternative dosing schedule, may circumvent the disadvantage of an unmethylated *MGMT* gene promoter.

The PFS-6 of 43.8% in the glioblastoma patients in the current study is clinically meaningful and superior to the data obtained in the TMZ registration trial (PFS-6: 21%)[8] and a large meta-analysis on phase II trials in recurrent glioblastoma (PFS-6: 15%),[18] as well as the competing 3-weeks-on/1-week-off regimen.[10] To exclude that data were biased towards favorable outcome because of the relatively high number of chemotherapy-naive patients entered onto the study, we performed a log-rank test for the effect of no prior chemotherapy versus prior chemotherapy. Absence of prior chemotherapy did not correlate with better outcome in the recurrent setting ($r = 0.26$; $P > .05$). On the other hand, patients with a PFS of more than 1 year after treatment at recurrence were found only in the groups that had received combined primary treatment supporting previous data.[1] Most importantly, our data support the notion that patients who were stable for a longer time after primary TMZ therapy may have another prolonged stabilization on second-line therapy with TMZ.[3] Thus, patients who benefit from primary TMZ chemotherapy can or even should undergo treatment with TMZ at recurrence.

The concept of enhanced MGMT depletion with alternative TMZ dosing regimens was most rigorously tested by Tolcher et al,[7] if only in peripheral blood rather than tumor tissue. In this study, MGMT activity was measured in peripheral blood mononuclear cells (PBMC) during treatment with TMZ, indicating that prolonged exposure to TMZ may effectively deplete cells of MGMT activity and may increase their sensitivity to alkylating agents. To date, however, no data on the depletion of MGMT in tumor cells in situ exposed to TMZ have been published to our knowledge. Several studies using TMZ at a 3-weeks-on/1-week-off (21 of 28 days) schedule at recurrence in malignant glioma[6,10] or at a 1-week-on/1-week-off schedule both neoadjuvant and adjuvant in nonresectable glioblastoma[19] have investigated alternative dosing schedules for TMZ. These alternative regimens increasing the duration of exposure and the cumulative dose of TMZ have been shown to effectively deplete MGMT activity in PBMCs.[7] Which regimen will provide the best balance of enhanced antitumor activity with acceptable hematologic toxicity, however, remains to be determined. Although analyzed in only a subset of patients, the current TMZ 1-week-on/1-week-off study is the first to demonstrate that patients with MGMT-active glioblastoma might benefit from the dose-dense regimen. The PFS-6 in this subgroup (26%) is still superior to the TMZ registration trial (21%)[8] and the phase II trial meta-analysis (15%).[18] According to novel data, this is not true for the 3-weeks-on/1-week-off TMZ regimen.[10] Whether this can be reproduced in randomized trials remains to be analyzed.

Dose-dense regimens are clearly more toxic than conventional dosing schedules. Hematologic toxicity in the French phase II trial required careful monitoring; 24% of patients developed WHO grade 3 or 4 thrombocytopenia, 14% had grade 4 granulocytopenia, and 14% had grade 4 lymphopenia. In addition, five patients developed interstitial pneumopathy, and six patients required dose reductions. It was also unclear whether this regimen is superior to the standard 5-day schedule.[19]

An Italian phase II study investigated the safety of temozolomide at 75 mg/m^2 on the 21-of-28-days schedule in 51 patients with different gliomas. This regimen led to cumulative lymphopenia of 25% in patients up to three cycles and 91% in patients with more than nine cycles. Of note, the regimen increased the risk of opportunistic infections.[9,10] A small Belgian phase II trial has also examined the 21-of-28-days schedule at a dose of 100 mg/m^2 in 17 patients with recurrent AA and AOA. In addition to a high incidence of grade 3 and 4 lymphopenia in 12 and four patients, respectively, there were two suspected opportunistic infections.[6] In contrast, cumulative toxicity and opportunistic infections were not seen in the TMZ 1-week-on/1-week-off study, although the incidence of grade 2 to 4 lymphopenia per patient was similar (52.9% in the 21-of-28-days regimen[9] *v* 56%). However, lymphopenia in the 1-week-on/1-week-off regimen is short in duration (Table 2). Therefore, it appears that, in addition to regular lymphocyte counts in all dose-dense regimens, a prophylaxis against opportunistic infections may be required when using the 3-weeks-on/1-week-off but not the 1-week-on/1-week-off of regimen. Further, most careful dose adjustments are mandatory in all regimens. A likely explanation for the difference in the occurrence of opportunistic infections might be the duration of lymphopenia. It has been suggested that lymphopenia from chronic exposure to TMZ is a function of days of TMZ exposure, dose intensity, and number of months a patient has been receiving the drug.[20] In this respect, 1-week-on/1-week-off TMZ is probably more tolerable. Because the efficacy of this regimen is also promising and the data imply activity in patients with an unmethylated *MGMT* promoter, this regimen should be further evaluated in a phase III trial and should induce efforts to analyze the predictive value of *MGMT* promoter methylation prospectively.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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