

Temozolomide and Thalidomide in the Treatment of Glioblastoma Multiforme

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Abstract. *Objective: The aim of this study was to assess efficacy and toxicity of temozolomide given alone or in combination with thalidomide, an anti-angiogenetic drug, in patients with newly diagnosed glioblastoma multiforme (GBM). Patients and Methods: 46 patients with histologically proven GBM were eligible for inclusion. Twenty-three patients (15 males and 8 females) received temozolomide on a conventional schedule; 23 patients (12 males and 11 females) received temozolomide on the same schedule and thalidomide was dose-adjusted in each individual patient based on their tolerance. Results: The median survival time was 12 months for temozolomide and 13 months for temozolomide + thalidomide. Conclusion: The administration of temozolomide in association with thalidomide after radiotherapy (RT) does not offer an advantage over temozolomide alone in adults with newly diagnosed GBM. The two therapeutic strategies produce similar results for survival, but the latter regimen shows a moderate increase in toxicity.*

The treatment of high-grade glioma aims at improving the neurological deficits and increasing the survival time while maintaining the best quality of life. Despite the use of integrated therapeutic approaches (surgery, radiotherapy, and chemotherapy), recent data report survival ranging from 9 to 15 months from the diagnosis (18).

In most patients steroids improve the neurological deficit within a few days. However, because of harmful side-effects and possible negative interference with chemotherapy (20), the minimum effective dose should be prescribed and stopped as soon as possible during the course of the disease.

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Key Words: Glioblastoma, chemotherapy, temozolomide, thalidomide.

According to the practice parameters of the American Academy of Neurology, anticonvulsant drugs (AEDs) should not be prescribed systematically and are recommended only as prophylaxis in patients who have already had seizures (4). AEDs can also induce severe side-effects and interfere with other drugs commonly used in these patients, mainly the chemotherapeutic agents (13, 19).

Phase II trials in malignant gliomas frequently include heterogeneous patient populations and use different endpoints to evaluate chemotherapy efficacy, such as response rate or progression-free survival (PFS-6). Although PFS-6 has been recently deemed the most reliable measure of tumor control, it is influenced by assessment procedures and toxicities of drugs (mainly AEDs and steroids). All these confounding factors justify the well-known selection bias present in uncontrolled brain tumor trials (7).

Angiogenesis is one of the major pathological features of malignant gliomas. The down-regulation of thrombospondin, an angiogenesis inhibitor, and the overexpression of factors that promote new vascular formation, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (b-FGF) and platelet-derived growth factor (PDGF), have been identified in malignant gliomas (6, 12). Therefore the requirement for the abundant vascular supply, exhibited by malignant gliomas, becomes a possible treatment target. Among the antiangiogenic agents, thalidomide, which inhibits the angiogenic activity of b-FGF and of tumor necrosis factor alpha (TNF- α), could be suitable for this purpose. There are a few reports on the use of thalidomide in the treatment of malignant gliomas, mainly at the time of recurrence, showing some clinical efficacy (3, 9, 14). These studies have suggested starting the treatment at the earliest stage with thalidomide in combination with an alkylating agent. These considerations and the promising preliminary data from patients with high-grade gliomas treated with temozolomide (11, 16, 21) have prompted the further evaluation of this new concept based on the combination of an antiangiogenic drug with an alkylating agent in patients

with newly diagnosed GBM. Temozolomide and thalidomide have different mechanisms of antitumor activity, non-overlapping side-effect profiles and are both well-tolerated. Thalidomide may act as a cytostatic agent to prevent tumor progression supported by neovascular formation, while temozolomide may act as a cytotoxic agent, inhibiting residual glioma cell growth and providing tumor control (16, 21). In addition, thalidomide produces an improvement of cytopenias typical of myelodysplastic syndrome, resulting in the reduction or elimination of transfusion dependence in some patients (15). Drowsiness, constipation and fatigue are common adverse effects (seen in up to 75% of patients) (15). Peripheral neuropathy and skin rash are seen in 30%. A few patients experience bradycardia and thrombotic events. Despite the high frequency of adverse effects, the most severe, leading to treatment discontinuation, are observed only in 10-15% of patients (15).

In the present paper, the clinical efficacy and safety of temozolomide with and without thalidomide in newly diagnosed GBM patients after radiotherapy was investigated. The primary endpoint of this study was overall survival.

Patients and Methods

Patient eligibility and entry criteria. Adult patients with newly diagnosed, histologically proven supratentorial GBM, with no history of relevant comorbidity or pregnancy were enrolled; patients had adequate hematological, renal, and hepatic function; histopathological examination was performed by two independent expert neuropathologists to exclude an oligodendroglial component; all patients were required to give written informed consent. All the patients were entered on the study between January 1999 and December 2001.

Treatment and clinical evaluation. All patients were treated with conventional 60 Gy LINAC radiotherapy (RT), delivered in 2 Gy fractions over six weeks, started within five weeks after surgery. At admission, each patient was invited to receive temozolomide and thalidomide in combination (group A), after careful explanation of the potential benefits and risks of the two drugs. Patients who refused the combined treatment received monotherapy with temozolomide and served as controls (group B). Both drugs were administered orally until unacceptable toxicity or clinical and radiological progression of the disease. Temozolomide was administered according to the conventional schedule one month after completion of RT. Thalidomide was given orally at bedtime every night starting on day 7 after the start of RT. Patients started with 100 mg daily and the dose was increased every week until a final dose of 600-1200 mg was achieved, if well tolerated, or 200-400 mg, in the case of adverse effects. The minimum follow-up was two months, starting from the target thalidomide dose (range 2-18 months). All the patients were evaluated for toxicity and response to therapy and followed until death. The extent of surgery was determined using the preoperative and the first postoperative (72-96 hours) contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI).

Clinical and hematological controls were performed monthly or whenever necessary, while assessments of response were performed

at the end of RT and every eight weeks thereafter. Steroids (up to 16-24 mg/day dexamethasone during the terminal phase) and AEDs were added to the treatment schedule according to patients' specific needs.

Statistical methods. The median survival time in each treatment group was assessed using Kaplan-Meier estimates and 95% confidence intervals. Differences were tested for significance with the log-rank test. The two treatment groups were compared in the entire sample and in subgroups defined by age at diagnosis (> or <60 years), extent of resection (total vs. subtotal), tumor side, and use of enzyme-inducing AEDs. Multivariate analysis was not performed, given the small sample size.

Safety assessment. Drug toxicity was graded according to the World Health Organization (WHO) toxicity criteria.

Results

General characteristics of the sample and main toxicity data. Forty-six patients with GBM were eligible for inclusion and consented to enter the study. A summary of the patient characteristics is shown in Table I. Except for a predominance of men in group A, the demographic and clinical features of the two treatment groups were fairly similar.

A summary of the adverse treatment events is shown in Table II. Compared to patients receiving temozolomide, none of whom had adverse events, those with the drug combination had a number of reactions, the commonest being drowsiness and fatal thrombo-embolic events. By contrast, marked myelosuppression was observed in 13% of patients in group A and 9% of patients in group B.

Survival. Figure 1 depicts the Kaplan-Meier survival estimates of patients in the two treatment groups. The median survival time was 12 months and 13 months for group A and B ($p=ns$). For the patients receiving the combination treatment, the cumulative time-dependent survival was 96%, 70%, 22% and 4% at 6, 12, 18, and 24 months. The corresponding values for those receiving temozolomide alone were 83%, 48%, 26% and 0%. The two treatment modalities were followed by a fairly similar survival even when the patients were stratified by age at diagnosis, extent of resection and enzyme-inducing AEDs (Figure 2 a, b, d). In contrast, as shown in Figure 2c, patients with GBM located in the right hemisphere showed a survival advantage over patients with left-sided lesions: median 30 vs. 22 months with a $p=0.046$ significance.

Discussion

The growth of solid neoplasms depends on angiogenesis to sustain the metabolic needs of the tumor cells, thus providing a potential target for cancer therapy. GBM is a

Table I. Patient characteristics.

Characteristics	All patients (n=46)	Group A (TMZ) (n=23)	Group B (TMZ+THAL) (n=23)
Gender			
Male	27 (59%)	15	12
Female	19 (41%)	8	11
Male/Female ratio	1.4:1	1.9:1	1.1:1
Age at diagnosis			
Median	56.5	54	59
Mean	57	53	54
Range	(28-70)	(32-66)	(28-70)
Location and side			
T	10 (22%)	5 L	5 L
F	4 (9%)	2 R	2 R
F-T	20 (43%)	10 (6 L - 4 R)	10 (6 L - 4 R)
F-T-P-O	12 (26%)	6 R	6 R
Preoperative symptoms			
HICP	24 (52%)	11	13
Epilepsy	9 (20%)	4	5
Focal deficits	13 (28%)	8	5
Extent of surgery			
Gross total resection	11 (24%)	6	5
Subtotal resection	32 (70%)	16	16
Biopsy	3 (6%)	1	2
N cycles/month* [median range]	5 (2-24)	5 (3-24)	5 (2-16)
Overall survival (months) [median range]	13 (4-30)	12 (4-23)	13 (4-30)

Refer to the number of TMZ cycles and/or months of continuous-concomitant thalidomide assumption. T: temporal; F: frontal; O: occipital; L: left; R: right; HICP: high intracranial pressure; TMZ: temozolomide; THAL: thalidomide.

tumor type suitable for probing angiogenesis inhibition as target therapy. This approach has prompted several studies that reported some slight benefit of thalidomide on tumor growth in patients with recurrent high-grade gliomas (3, 9, 14). A combined approach potentially counteracts the selective pressure on hypoxia-resistant malignant tumor cells, circumvents endothelial resistance induced by local cytoprotective response and enhances the delivery of cytotoxic agents by normalizing vascular physiology. In the most recent clinical trial, Chang and co-workers (2) studied the combination of temozolomide, thalidomide and radiotherapy in 67 newly-diagnosed GBM patients. They concluded that this strategy was relatively well-tolerated with favorable survival outcome in comparison with a historical cohort of patients with and without adjuvant chemotherapy. In the study conducted by Morabito and co-workers (10), one of the 18 patients with recurrent GBM had a minimal response and eight showed stable disease. The median time to progression and the median overall

Table II. Adverse treatment events.

Adverse events	All patients 46 (%)	Group A TMZ 23 (%)	Group B TMZ+THAL 23 (%)	Statistical analysis
Fatal thrombo-embolism	4 (9%)	0	4 (17%)	ns
Rash	2 (4%)	0	2 (9%)	ns
Drowsiness	6 (13%)	0	6 (26%)	<i>p</i> =0.02
Constipation	2 (4%)	0	2 (9%)	ns
CTC myelo-suppression III°-IV°	5 (11%)	3 (13%)	2 (9%)	ns

TMZ: temozolomide; THAL: thalidomide; CTC: common toxicity criteria.

survival for responders were respectively 25 and 36 weeks. These results are similar to previous studies in which thalidomide showed modest antitumor activity in patients with recurrent malignant gliomas (3, 9).

Baumann *et al.* (1) evaluated the combination of temozolomide (200 mg/m² a day for five days, every 28 days) with thalidomide (200 mg/day) in 44 pretreated GBM patients. Nineteen patients (43%) received only thalidomide, and 25 patients (57%) had a combination of thalidomide and temozolomide. The median survival was 103 weeks and the median time to progression was 36 weeks in patients receiving combined therapy, compared with a median survival of 63 weeks and a median time to progression of 17 weeks for patients receiving thalidomide alone (1). The study suggested a possible benefit of combining temozolomide with thalidomide. In contrast, a North American Brain Tumor Consortium (NABTC) study of temozolomide with thalidomide in recurrent malignant gliomas did not demonstrate prolonged survival (5).

Temozolomide alone and the combination of temozolomide with thalidomide produced similar therapeutic results on the total survival time in newly diagnosed GBM patients in our trial. Nevertheless, in this homogeneous series from a single institution, even a subgroup analysis of age, extent of resection, localization of tumour and AEDs status failed to show any significant therapeutic advantage. These observations do not support the possibility of achieving a better response by combining cytotoxic and antiangiogenic therapy in young patients, who typically present with a genetically different "from progression-GBM" compared to older "de novo-GBM" patients. This was not a randomized clinical trial. For this reason, our conclusions should be considered only speculative. In addition, the sample was small and the possibility of a high β error cannot be excluded. However, this study had several advantages, which include the comparability of the demographic, clinical and pathological

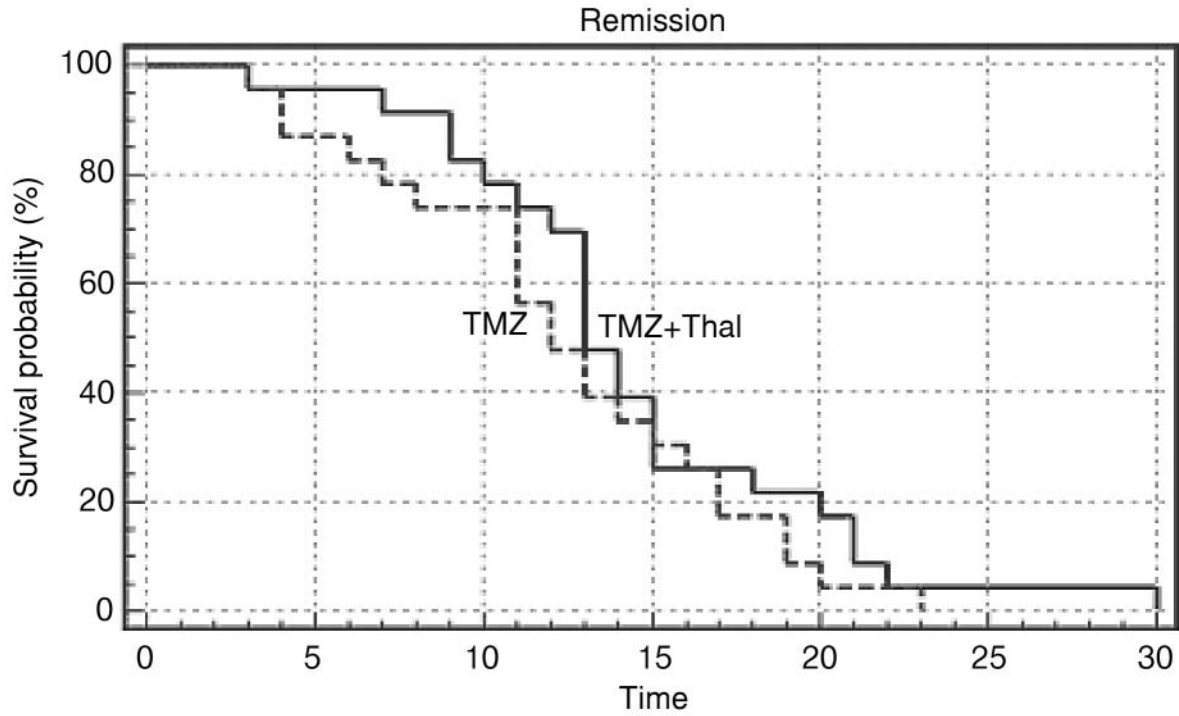


Figure 1. Kaplan Meier survival estimates in patients receiving temozolomide (TMZ) and temozolomide and thalidomide in combination (TMZ + Thal).

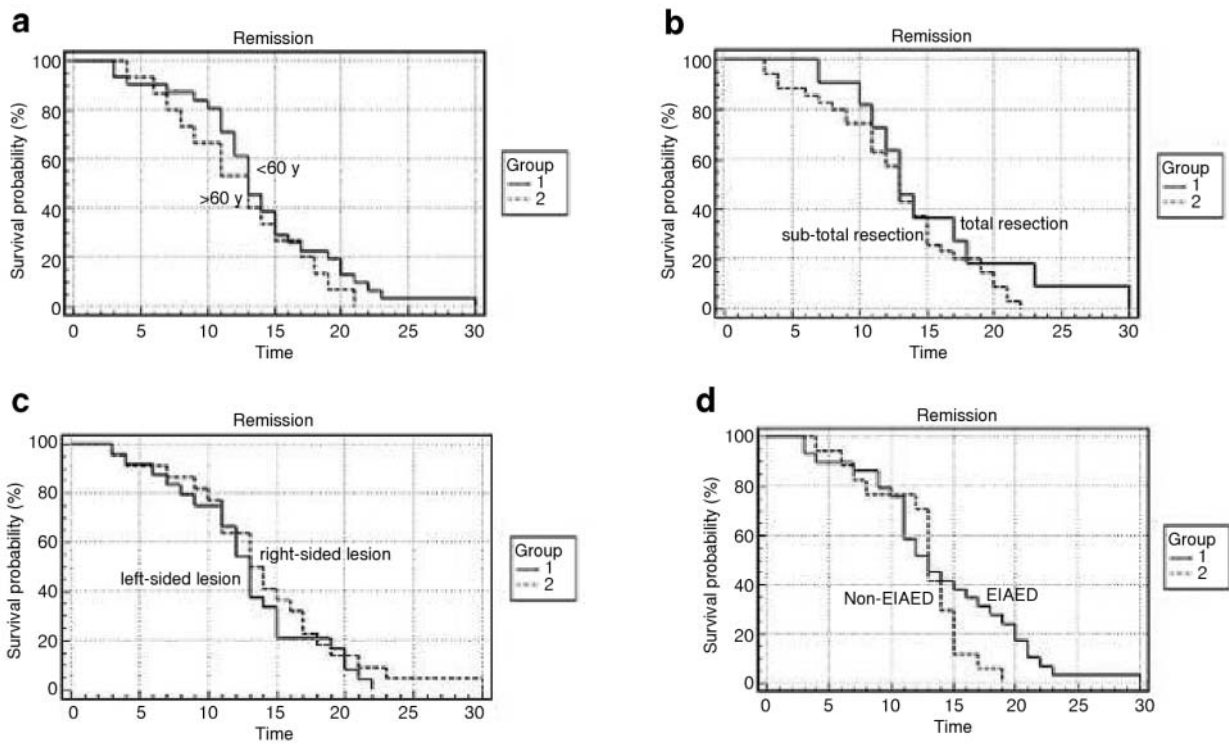


Figure 2. Kaplan Meier survival estimates by treatment group and a, age; b, extent of resection; c, side of resection; and d, use of enzyme-inducing AEDs.

features of the two treatment groups and the choice of overall survival as the primary end-point in patients who refused further active treatments at relapse.

In our study, the association with thalidomide implied a moderate increase of toxicity compared to temozolomide alone. Tolerability of treatment is a major issue for patients who undergo chemotherapy. In this respect, drowsiness, constipation and thromboembolism are a major concern. The incidence of thromboembolic events deserves particular attention as the risk of venous thromboembolism is increased throughout the course of malignant gliomas even in non-paretic limbs and beyond the peri-operative phase (8) and is reported in up to 25-30% of patients (1, 3).

The combination of RT with agents that act on the vasculature has clear theoretical advantages (17). As the modes of action and target cell populations are different, the agents should be additive or even synergistic without overlapping toxicity. Specifically, the poorly vascularized regions of tumors become hypoxic and resistant to radiation, but they may be selectively affected by the antiangiogenic agent. However, it is also theoretically possible that any reduction in vascularity caused by these agents will render tumors more resistant to subsequent RT. The exact sequencing of these modalities may therefore be crucial. More preclinical data are needed before we can assume that these new agents will enhance the effects of radiation in a predictable manner.

At present, temozolomide alone in the concomitant and adjuvant schedule seems to be the best available choice in GBM patients, because of its fairly good tolerability and efficacy.

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Received November 1, 2006

Revised January 15, 2007

Accepted February 2, 2007