

Clinical Study

Combined thalidomide and temozolomide treatment in patients with glioblastoma multiforme

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Key words: antiangiogenic therapy, brain, chemotherapy, glioblastoma multiforme, survival, temozolomide, thalidomide, treatment

Summary

Objectives: Glioblastoma multiforme (GBM) may potentially be responsive to antiangiogenic therapies as these tumors are highly vascularized and overexpress angiogenic factors. Thalidomide exhibits antiangiogenic activity and may provide additive or synergistic antitumor effects when given concurrently with temozolomide, an alkylating agent. To further evaluate this new concept of combining an antiangiogenic with an alkylating agent, efficacy and tolerability of thalidomide alone and in combination with temozolomide were explored in a single-institution, nonrandomized open-label phase II study.

Patients and methods: Forty-four patients with GBMs, who received thalidomide for a period of at least three months, were evaluated for survival, time to tumor progression (TTP), and side effects. Microsurgical tumor extirpation and radiotherapy preceded chemotherapy. Nineteen patients (43%) received thalidomide only (T), and 25 patients (57%) had a combined chemotherapy of thalidomide and temozolomide (TT). Median thalidomide dosage was 200 mg/day. Median temozolomide dosage was 200 mg/m²/day for five days, in monthly cycles. Neuroradiological outcomes were assessed by a semiquantitative grading system.

Results: Median survival was 103 weeks (95% CI, 65–141 weeks) for TT-patients and 63 weeks (95% CI, 49–77 weeks) for T-patients ($p < 0.01$). Median TTP for the TT-group was 36 weeks (95% CI, 20–52 weeks) and 17 weeks (95% CI, 13–21 weeks) for the T-group ($p < 0.06$). Neuroradiologically, 14 patients (56%) of the TT-group and six (32%) of the T-group had evidence of stable disease on at least two successive neuroradiological follow-ups. Progressive disease was found in nine patients (36%) of the TT-group and in 13 (68%) of the T-group. In two patients (8%) of the TT-group, a response with tumor regression was found. Thalidomide and concurrent temozolomide were safe and well tolerated with mild to moderate toxicities.

Conclusions: The combination of thalidomide and temozolomide in the treatment of GBM appears to be more effective than that of thalidomide alone with respect to survival, TTP, and neuroradiological documentation of progression, stable disease or response. Further concurrent prospective studies of these agents in a larger group of patients with GBM will be required to establish the soundness of these intriguing observations.

Introduction

Malignant brain tumors with an incidence of 5 per 100,000 persons/year result in 17,000 new diagnoses each year in the United States. Among brain malignancies, glioblastoma multiforme (GBM) is the most frequent and aggressive tumor with a median survival of 40–70 weeks [1–4]. Little progress has been

made over the last decades in controlling high-grade gliomas despite intensive efforts and a multidisciplinary approach, including surgery, radiotherapy, and chemotherapy [5,6]. Among factors associated with longer survival and higher quality of life are age, Karnofsky performance scale (KPS) score, and extent of surgical resection [1,2,7,8], which can be improved by modern intraoperative imaging modalities.

Glioblastoma multiformes are highly vascularized and overexpress angiogenic factors [9], such as vascular endothelial growth factor and basic fibroblast growth factor [10], and may therefore be responsive to antiangiogenic therapies. As suggested by Folkman's group in 1994 [11], there is an apparent role for thalidomide in its antiangiogenesis function in combination with temozolomide, although not as a single agent. Several studies [12–14] suggested initiating thalidomide therapy at an earlier stage and in combination with an alkylating substance. This and promising preliminary data from patients with high-grade gliomas treated with thalidomide or temozolomide [15–17] prompted us to further evaluate this new concept of combining an antiangiogenic with an alkylating agent in a single-institution, nonrandomized open-label phase II study. Although there are currently more than 60 different antiangiogenic drugs studied in clinical trials [18], thalidomide was the only such agent available when we started our study in 1998.

There is no firm knowledge on the mode of action of thalidomide. The most important adverse effects besides teratogenicity include (in descending order) dose dependent somnolence, orthostatic hypotension, constipation, neutropenia, pruritic erythematous macular rash, and peripheral neuropathy [19]. These side effects necessitate cessation of thalidomide treatment in 10–15% of patients [20].

Temozolomide is an alkylating agent that has demonstrated clinical antitumor activity and is relatively well tolerated [15]. It shows superior results than other cytotoxic agents in the treatment of GBM [16,17] and was included in the standard care of our patients after being registered for the Swiss market in January 1999. Temozolomide has a favorable safety profile with minimal nonhematologic toxicities (nausea, vomiting, headache, fatigue, and constipation), permitting prolonged administration without cumulative myelosuppression (especially thrombocytopenia). Cessation of temozolomide treatment is necessary in fewer than 10% of patients.

Patients and methods

Patients

Patients (18–75 years) were eligible with histologically proven GBM (graded according to the World Health Organization (WHO) classification). Adequate bone marrow, liver, and renal functions were mandatory.

Patients participating in other studies or having any other active malignancy, active infection, or serious disease that would obscure toxicity were excluded. Exclusion of pregnancy by a negative pregnancy test at the beginning of the study was mandatory, and prevention of pregnancy by double contraception until six months after cessation of thalidomide therapy was required. All patients were asked to sign an informed consent according to the requirements of the ethical committee that had reviewed and approved the protocol. For neuroradiological evaluation of the effect of chemotherapy, duration of thalidomide therapy had to be at least three months.

Treatment

Patients received conventional treatment, including microsurgical tumor extirpation and postoperative radiotherapy, given as partial brain irradiation to a median total dose of 60 Gray (Gy). In cases with close relationship to functional cortex and white matter, stimulation mapping techniques were used during surgery to maximize resection and minimize morbidity, as well as to control seizures. If patients showed neurological deterioration during follow-up, reoperation was evaluated.

Not earlier than two weeks after surgery, usually following completion of radiotherapy, patients received 200 mg thalidomide/day, escalating by 100 mg every two weeks to a total of 600 mg/day if well tolerated. Treatment was continuous, and drug intake usually was at night before rest. To balance thalidomide dosage with quality of life, dosage was individually adjusted to minimize daytime somnolence. Patients undergoing reoperations were required to suspend thalidomide intake one week before until three weeks after surgery. Patients in the T-group received thalidomide only, whereas of January 1999, all patients (TT-group) additionally received temozolomide, administered orally (200 mg/m²/day for five days, repeated in cycles of 28 days) until unacceptable toxicity or tumor progression occurred.

Clinical evaluation

Clinical evaluation was performed 3, 7, 12, 18, and 24 months after initiation of surgery and allowed neurological examination with assessment of KPS scores and registration of possible side effects of chemotherapy.

Neuroradiological evaluation

Sequential MRIs (or CT scans in emergency) 3, 7, 12, 18, and 24 months after initiation of surgery were performed for neuroradiological follow-up. Since exact volumetric determination of tumor regrowth or regression may prove difficult, as further explained in the Discussion, a semiquantitative radiological grading system was developed and applied to assess postoperative brain tumor development as follows: tumor volumes were estimated preoperatively on contrast-enhanced T1-weighted MR images by calculating maximum length (X) and perpendicular width (Y) on axial sections and maximum height (Z) on coronal or sagittal sections perpendicular to this axial plane, using the formula $(X*Y*Z)*\pi/6$. This initial volume measurement was used as a baseline for comparison with follow-up images. To determine the extent of resection, routine contrast-enhanced CT scans, which were easier to obtain within the postoperative first 24 h, were performed for comparison with the preoperative images. Resections were assumed total (>98%) if there was no contrast-enhancing tumor visible, subtotal (90–98%) if there was minimal contrast enhancement present, and partial (<90%) if there was evidence of considerable remaining contrast-enhancing tumor.

The shape of recurring tumor was characterized on contrast-enhanced images by five grades, according to a typical growth pattern (Table 1, Figure 1) [7]. Grade 1 describes no enhancement of the resection cavity. Grade 2 describes circular enhancement along the resection border. Grade 3 describes nodular enhancement $\leq 100\%$ of primary tumor size; grade 3a: enhancement <50%, grade 3b: enhancement $\geq 50\%$. Grade 4 describes enhancement >100% of primary tumor size; grade 4a: enhancement <200%, grade 4b:

enhancement $\geq 200\%$. Grade 5 describes multifocal, multinodular enhancement, regardless of primary tumor size. On subsequent radiographic examinations, tumor behavior was either assessed as progressive disease (PD), stable disease (SD), or response with tumor regression (R), in accordance with proposed guidelines [21]. As previously suggested [21], only major changes in tumor size were recognized in our grading system; an increment of grade 3a to 3b or 4a to 4b was defined as increment of one grade (Table 2); PD was defined as an increase by at least two grades, as for example from grade 3a to 4a; SD was defined if follow-up scans showed the same grade or an increase or decrease by a single grade; R was defined as a decrease by at least two grades. Since tumor volume changes in grades 4 and 5 correspond to a more extensive growth or shrinkage than in grades 2 and 3, PD or R was defined by a change or decrement of grade 1.

Statistical methods

Primary endpoints were survival and time to tumor progression (TTP). For all patients, including patients with recurrent disease at the time of enrollment, survival was defined from time of diagnosis (same as time of operation, if not previous diagnostic biopsy) until death. TTP was determined as the interval during chemotherapy between smallest postoperative tumor size (including post-reoperation) and first observation of objective tumor progression or death related to tumor progression. For both variables, we had censored values (i.e. death or tumor progression, respectively, did not occur during the time of observation). We assessed median survival and median TTP in each group (T and TT) using a Kaplan–Meier estimate. To investigate the relationship of survival and TTP with various variables (such as group, age, KPS score, etc.), we used proportional hazard models (Cox regression models). We considered both multivariate models (to investigate the joint effect of several variables) and univariate models (to assess the effect of a single variable). If significant, the effect of a given variable on survival or on TTP was characterized by the exponential of its coefficient in these regression models. Such a value provides an estimation of the ratio between two risks for a binary variable (such as sex). For a continuous variable (such as age), it provides an estimation of the ‘increased risk’ when it increases by one unit.

For comparison of patients’ characteristics between the T- and the TT-group with respect to binary

Table 1. Grading system for neuroradiographic brain tumor behavior

Grade	Characteristics
1	No enhancement of resection cavity
2	Circular enhancement along resection border
3	Nodular enhancement $\leq 100\%$ of primary tumor size 3a: enhancement <50% 3b: enhancement $\geq 50\%$
4	Enhancement >100% of primary tumor size 4a: enhancement <200% 4b: enhancement $\geq 200\%$
5	Multifocal, multinodular enhancement, regardless of primary tumor size

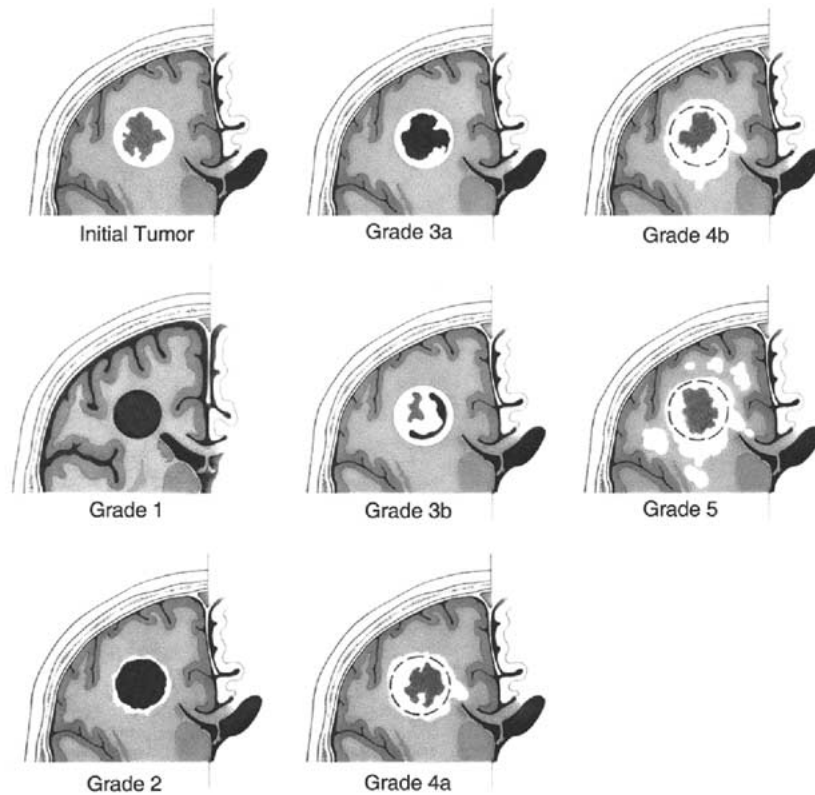


Figure 1. Schematic drawing illustrating the grading system for radiographic brain tumor behavior.

Table 2. Grouping of tumors according to their neuroradiographic behavior

Grade of previous radiographic examination	Grade of current radiographic examination						
	1	2	3a	3b	4a	4b	5
1	SD	SD	PD	PD	PD	PD	PD
2	SD	SD	SD	PD	PD	PD	PD
3a	R	SD	SD	SD	PD	PD	PD
3b	R	R	SD	SD	SD	PD	PD
4a	R	R	R	SD	SD	PD	PD
4b	R	R	R	R	R	SD	PD
5	R	R	R	R	R	R	SD

SD, stable disease; **PD**, progressive disease; **R**, tumor regression.

variables, we used Fisher's exact test. Comparison with respect to continuous variables was done using a Mann-Whitney test. Throughout the analysis, p -values smaller than 0.05 were considered significant. The StatView statistical software was used (version 5.0, 1998; SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Between July 1998 and August 2001, 44 patients (median age, 54 years), who had received thalidomide for at least three months, were enrolled in this trial. The predominance of male patients is partially related to the known sex distribution with a male:female ratio of 1.5:1 [22] and may additionally be caused by the requirement of double contraception until six months after cessation of thalidomide therapy for female patients. When entering the study, patients were differentiated into primary GBM (35 patients, 80%) and recurrent GBM (nine patients, 20%) (Table 3). Twenty-five patients (57%) had combined thalidomide and temozolomide treatment (TT-group), 19 patients (43%) had thalidomide only (T-group). Postoperative KPS score was ≥ 70 in 95% of our patients, three patients showed an improved, one a worsened KPS score. Twenty-four patients (54%) had a total tumor

Table 3. Patients characteristics

	All patients (n = 44)	T-group (n = 19)	TT-group (n = 25)
Sex			
Male	32 (73%)	16	16
Female	12 (27%)	3	9
Male : female ratio	2.7 : 1	5.3 : 1	1.8 : 1
Age at diagnosis			
Mean	51	55	48
Range	26–72	28–72	26–67
Median	54	57	48 ^a
Preoperative KPS score			
<70	4 (9%)	3	1
≥70	40 (91%)	16	24
Postoperative KPS score			
<70	2 (5%)	0	2
≥70	42 (95%)	19	23
Preoperative symptoms (more than one per patient possible)			
Epilepsy	22 (50%)	9	13
Headache	14 (32%)	4	10
Speech disorder	9 (20%)	7	2
Motor weakness	8 (18%)	4	4
Nausea/vomiting	7 (16%)	2	5
Mental alteration	6 (14%)	3	3
Ataxia	4 (9%)	1	3
Sensibility disorder	4 (9%)	2	2
Vertigo	4 (9%)	2	2
Visual impairment	4 (9%)	2	2
Hearing disorder	3 (7%)	1	2
Tiredness	2 (5%)	0	2
No symptoms	1 (2%)	0	1
Extent of tumor resection (neuroradiologically confirmed)			
Total	24 (54%)	9	15
Subtotal	18 (41%)	10	8
Partial	2 (5%)	0	2
Tumor stage			
Primary GBM	35 (80%)	18	17
Recurrent GBM	9 (20%)	1	8
Radiotherapy			
Partial brain irradiation	44 (100%)		
Stereotactic radiotherapy	10 (23%)	4	6
As part of postoperative radiotherapy	5 (11%)	4	1
In case of recurrence	5 (11%)	0	5
Reoperation for tumor recurrence during study time			
	19 (43%)	9	10

^a $p < 0.04$; KPS score, Karnowsky performance scale score; GBM, glioblastoma multiforme.

resection, 18 patients (41%) a subtotal tumor resection, and two patients (5%) a partial tumor resection. Nineteen patients (43%) were reoperated for tumor recurrence during the study, nine from the T-group

(47%) and 10 from the TT-group (40%). The median interval between first operation and first reoperation was 36 weeks (range, 9–77 weeks). One patient had a second reoperation after 77 weeks.

The two groups did significantly differ with respect to age (median age at diagnosis in the T-group, 57 years; 48 years in the TT-group; $p < 0.04$), but they were statistically uniform as to extent of resection (total resection in the T-group, 47%; 60% in the TT-group) as well as to KPS score (postoperative KPS score ≥ 70 in the T-group, 100%; 92% in the TT-group).

Thalidomide therapy was initiated after a median time of 16 weeks after diagnosis (range, 2–80 weeks). The median thalidomide dose was 200 mg/day (mean, 300 mg/day; range, 200–600 mg/day) with a median duration of continuous thalidomide treatment of 37 weeks (range, 14–113 weeks). The median number of completed temozolomide cycles was seven (range, 1–25 cycles).

All patients underwent radiotherapy of the partial brain (i.e. preoperative tumor area plus margin) with a median total dose of 60 Gy in 30 fractions. As part of postoperative irradiation, five patients (11%) received an additional stereotactic boost (20 Gy in four fractions) to a median total tumor dose of 80 Gy. The qualification criteria for a higher dose were preoperative tumor size < 4 cm in largest diameter, KPS score > 70 , and age < 65 years. Median interval between surgery and initiation of radiotherapy was four weeks.

Five patients (11%) received reirradiation in case of recurrence, given as fractionated stereotactic radiotherapy, with a median total dose of 20 Gy (range, 18–25 Gy; fraction size, 5 and 6 Gy). The qualification criteria for a stereotactic reirradiation were recurrent tumor size < 5 cm in largest diameter and KPS score > 70 .

Median interval between initiation of radiotherapy and initiation of thalidomide therapy was 12 weeks.

Survival and time to tumor progression

At the time of evaluation, 11 patients, 10 (40%) of the TT-group and one (5%) of the T-group, with a median age at diagnosis of 47 years, were still alive. Six of these 11 patients, five (20%) of the TT-group and one (5%) of the T-group, were still progression-free at the end of the study and had an ongoing median survival of 117 weeks and an ongoing median progression-free interval of 92 weeks.

For the entire study group, median survival was 72 weeks (95% CI, 66–78 weeks) with 98%, 79%,

and 31% of patients alive at 6, 12, and 24 months, respectively (Figure 2, Table 4). Median survival for patients of the TT-group was 103 weeks (95% CI, 65–141 weeks) and 63 weeks (95% CI, 49–77 weeks) for patients of the T-group. ($p < 0.01$) (Figure 3, Table 4). In the TT group, 96%, 88%, and 47%, in the T group, 100%, 69%, and 11% of patients were alive at 6, 12, and 24 months after diagnosis, respectively. The risk was estimated to be 2.5 times larger for the T-group. When including either age, KPS score, or extent of tumor resection as a covariate in the regression model, this

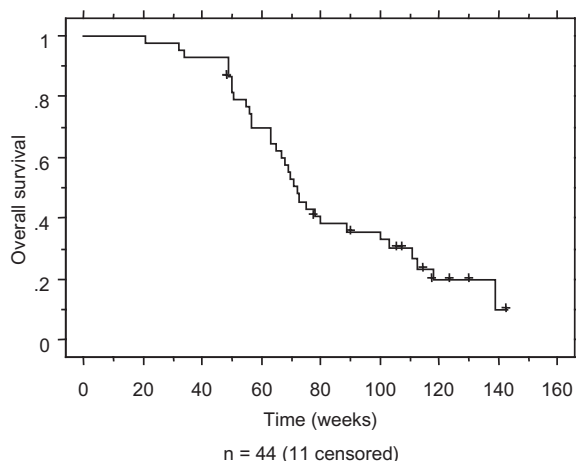


Figure 2. Overall survival from time of diagnosis of the whole study group.

Table 4. Median survival and TTP in relation to different patient groups

	Survival (in weeks)	TTP (in weeks)
Entire study group	72	26
Extent of resection		
Total	89 ^a	28
Subtotal	69	16
Treatment form		
Thalidomide-only	63	17
Thalidomide + temozolomide	103 ^b	36 ^c
Age at diagnosis >53		
Thalidomide-only ($n = 13$)	63	16
Thalidomide + temozolomide ($n = 9$)	103 ^d	17 ^e
Age at diagnosis ≤53		
Thalidomide-only ($n = 6$)	55	29
Thalidomide + temozolomide ($n = 16$)	111 ^f	36 ^g

^a $p < 0.08$, ^b $p < 0.01$, ^c $p < 0.06$, ^d $p = 0.57$, ^e $p = 0.06$, ^f $p < 0.0001$, ^g $p = 0.39$.

estimation was almost unchanged and still significant. Patients with total tumor resection showed a survival advantage over patients with subtotal or partial resection, with a median survival of 89 weeks versus 69 weeks ($p < 0.08$; Table 4). This statistically estimated risk was two times smaller, but not significant.

Median TTP was 26 weeks (95% CI, 13–33 weeks) for the whole study group, 36 weeks (95% CI, 20–52 weeks) for the TT-group, and 17 weeks (95% CI, 13–21 weeks) for the T-group (Figure 4). There was

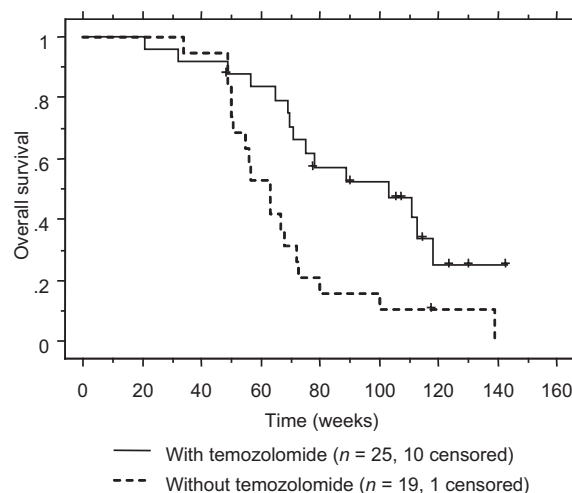


Figure 3. Overall survival from time of diagnosis for patients with thalidomide only and with combined thalidomide and temozolomide ($p < 0.01$).

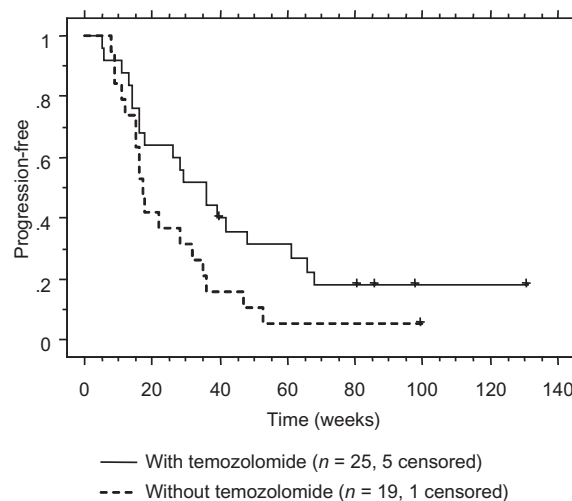


Figure 4. Time to tumor progression for patients with thalidomide only and combined treatment with temozolomide ($p < 0.06$).

a trend toward longer TTP for patients with combined chemotherapy ($p < 0.06$; Table 4). The risk was estimated to be 1.9 times larger for the T-group. When including either age, KPS score, or extent of tumor resection as a covariate in the regression model, this estimation was almost unchanged. Nine patients (20%), seven (16%) of the TT-group and two (5%) of the T-group, were progression-free for over one year (range, 53–131 weeks).

There was no statistical significance between survival or TTP and type of occurrence (primary or recurrent GBM), frequency of reoperations, total dose of radiotherapy, additional stereotactic boost, reirradiation in case of recurrence, interval between radiotherapy and initiation of thalidomide treatment, interval between initiation of thalidomide and initiation of temozolomide treatment, and dosage of thalidomide.

Neuroradiographic outcome

According to our neuroradiographic grading system described above in more detail, recurring tumor was characterized on contrast-enhanced images by a semiquantitative grading system (Tables 1 and 2, Figure 1).

Fourteen patients (56%) of the TT-group and six (32%) of the T-group had evidence of SD on at least two successive neuroradiological follow-ups (three months apart). PD was found in nine patients (36%) of the TT-group and in 13 (68%) of the T-group. In two patients (8%) of the TT-group, a response with tumor regression was found.

Toxicities

Fourteen patients (32%) showed daytime somnolence, which improved over time without dose reduction (Table 5). Although not clearly related to thalidomide, 11 patients (25%) showed thromboembolic complications during the study and among those were three patients with pulmonary embolism. These complications were independent of dosage of thalidomide. Six patients (14%) described paraesthesias, which led to a dose reduction in three patients.

In five of the TT-patients, mild myelosuppression (WHO grades 1 and 2) related to temozolomide, in one TT-patient, moderate leucopenia and thrombocytopenia (WHO grade 3) were observed.

Table 5. Side effects of therapy

Type	No. of patients
Thalidomide	44 (100%)
Daytime somnolence	14 (32%)
Thromboembolic complications	11 (25%)
Polyneuropathy	6 (14%)
Skin irritation	3 (7%)
Constipation	2 (5%)
Vertigo	2 (5%)
Tremor	2 (5%)
Headache	1 (2%)
Temozolomide	25 (57%)
Mild myelosuppression (WHO ^a grades 1 and 2)	5 (20%)
Moderate myelosuppression (WHO grade 3)	1 (4%)

^aWHO, World Health Organization.

Discussion

The biology of GBM mediated angiogenesis may potentially be responsive to antiangiogenic therapies as proposed in 1994 [11]. This concept has initiated several studies that have reported low effects of thalidomide (5–6% partial response, 33–42% SD) on tumor growth in patients with recurrent high-grade gliomas [12–14]. They also suggested initiating thalidomide therapy at an earlier stage and in combination with an alkylating substance.

As survival times among high-grade gliomas (anaplastic astrocytomas, WHO grade 3, and GBM, WHO grade 4) are heterogeneous, we included in this study only patients with GBM. These were further differentiated into primary (80%) and recurrent GBM (20%) and showed no statistically significant differences with regard to survival or TTP. Nevertheless, in this histologically homogeneous group, several subgroups have to be recognized: different age groups, KPS scores, and extent of resection, as well as the addition of a stereotactic boost after postoperative radiotherapy or fractionated stereotactic radiotherapy in case of recurrence. We have statistically analyzed these factors individually in reference to survival and TTP, and none of these parameters reached statistical significance in our patient population, except for a trend toward longer survival in patients with total resection ($p < 0.08$). This risk was estimated to be two times smaller.

When temozolomide became available in 1999, the study protocol was altered, and as of then, patients received combined therapy. Therefore, the

thalidomide-only arm (T-group) preceded the combined therapy arm (TT-group) in a sequential fashion. Nevertheless, treatment modalities, especially neurosurgical techniques and radiotherapy, remained the same during the study period. Except for the age variable ($p < 0.04$), the two groups did not significantly differ with respect to KPS score and extent of resection.

This is the first prospective study in a well defined group of patients with GBM comparing the effect of thalidomide with concurrent thalidomide and temozolomide therapy. The most notable finding is represented by the prolonged survival of patients receiving a combined therapy (TT-group), with a median survival of 103 weeks compared to 63 weeks of the thalidomide-only treated group ($p < 0.01$). The statistical risk estimate for the T-group was 2.5 times larger and did not change when including age, KPS score, or extent of tumor resection as covariates in the regression model. To further investigate the median age difference in the T- and TT-group, we divided the patients into two subgroups, ≤ 53 and > 53 years. In the age group ≤ 53 years, median age for T- and TT-patients was 46 and 44 years, respectively, median survival was 55 and 111 weeks, respectively. This finding was statistically highly significant ($p < 0.0001$). In the age group > 53 years, median age for T- and TT-patients was 60 and 59 years, respectively, median survival was 63 and 103 weeks, respectively ($p = 0.57$) (Table 4). These observations point to a possibly better response of combined chemotherapy and antiangiogenic therapy in young patients, which typically present with genetically different GBM compared to older patients. Median TTP for the TT-group was 36 weeks and 17 weeks for the T-group ($p < 0.06$). The risk for the T-group was estimated to be 1.9 times larger and did not change when including age, KPS score, or extent of tumor resection as covariates in the regression model.

Our results point to a possibly longer median survival as well as a longer TTP than the results of groups that previously studied the effect of thalidomide on similar patients [12–14] despite the fact that our participants received relatively low doses of thalidomide (mean, 300 mg/day). No convincing evidence of a dose–response relationship was found previously [19]. The observation that only a minority of patients has shown response to thalidomide suggests differences between these groups in the interaction of thalidomide with its receptor. It may be that preexisting vessels sufficiently provide tumor cells with their nutrients, particularly

at the tumor borders, the critical infiltrative zone [23], where thalidomide would not have an effect.

Whereas this study allows a comparison of the two treatment groups, T and TT, we cannot compare directly the TT-group to patients treated with temozolomide as a single adjuvant therapy. In recent studies with similar patient parameters, median overall survival was 64 weeks (concomitant radiation plus temozolomide followed by adjuvant temozolomide administered orally (200 mg/m²/day for five days, repeated in cycles of 28 days); all patients with GBM; median age, 52 years; KPS score > 80 , 64%) [17] and 34 weeks (extended low-dose temozolomide in recurrent malignant gliomas; 79% GBMs; median age, 55 years; median KPS score, 70; prior radiotherapy, 97%; temozolomide administered in a 70-day cycle) [24]. Compared to a median survival of 103 weeks in the TT-group in our study, this suggests a positive effect of the combined chemotherapy and antiangiogenic therapy. Thalidomide is not known to have antiproliferative or cytotoxic activity, but might act indirectly as an antiangiogenic or immunomodulatory drug [25].

Tolerability of treatment is a major issue for patients who undergo chemotherapy. In this respect, thalidomide alone and in combination with temozolomide was well tolerated (somnolence, 32%; polyneuropathy, 14%). Somnolence appeared to improve in most patients over two to three weeks. The dosage of thalidomide was adjusted according to the patient's potential of tachyphylaxis in order to minimize this side effect. Temozolomide also showed a favorable safety profile (mild (WHO grades 1 and 2) leucopenia or thrombocytopenia, 20%; moderate (WHO grade 3), 4%). Thromboembolic complications were seen in 25% of our patients. These complications were independent from thalidomide dosage and are not clearly related to this drug, although questioned in a patient group with dermatologic disorders [26]. Recent reports found thromboembolic complications in high-grade gliomas at a similar frequency [27,28].

Volume measurement of brain tumors on MR and especially CT images is of limited value due to substantial intra- and inter-observer variability in tracing the margins of a structure, especially after surgical treatment [29]. The determination of tumor volume by geometric methods is inaccurate, and therefore these are only adequate for comparing relative tumor sizes of follow-up scans of the same patient [30]. Especially, if tumor recurs alongside the resection cavity or sprouts

irregularly into it, exact estimations of tumor volumes are impossible. The proposed neuroradiographic grading system was felt to be useful and easy to apply in this patient group and fulfills the criteria for objective assessment of tumor behavior.

A prospective, randomized, double-blind phase II trial with these agents is under way to further elucidate and establish more soundness of these observations. Antiangiogenic agents, more selective and potent than thalidomide, will likely prove most valuable as part of a multimodality anticancer strategy rather than as a single therapeutic approach in the future.

Acknowledgements

We would like to thank Peter Roth for the scientific drawings and Grünenthal GmbH, Aachen, Germany, for supplying the thalidomide used in this study.

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