

A North American brain tumor consortium (NABTC 99-04) phase II trial of temozolomide plus thalidomide for recurrent glioblastoma multiforme

Morris D. Groves · Vinay K. Puduvalli · Susan M. Chang · Charles A. Conrad · Mark R. Gilbert · Ivo W. Tremont-Lukats · Ta-Jen Liu · Pamela Peterson · David Schiff · Timothy F. Cloughesy · Patrick Y. Wen · Harry Greenberg · Lauren E. Abrey · Lisa M. DeAngelis · Kenneth R. Hess · Kathleen R. Lamborn · Michael D. Prados · W. K. Alfred Yung

Received: 28 June 2006 / Accepted: 20 July 2006 / Published online: 22 September 2006
© Springer Science+Business Media B.V. 2006

Abstract

Background Laboratory and clinical data suggest that the anti-angiogenic agent, thalidomide, if combined with cytotoxic agents, may be effective against recurrent glioblastoma multiforme (GBM).

Objectives: To determine 6-month progression-free survival (6PFS) and toxicity of temozolomide plus thalidomide in adults with recurrent GBM.

Patients and methods Eligible patients had recurrent GBM after surgery, radiotherapy, and/or adjuvant chemotherapy. Temozolomide was given at 150–200 mg/m²/day on days 1–5 of each 28-day cycle. Thalidomide was given orally at 400 mg at bedtime (days 1–28) and increased to 1,200 mg as tolerated. Patients were evaluated with magnetic resonance imaging scans every 56 days. The study was designed to detect an increase of the historical 6PFS for GBM from 10 to 30%.

Results Forty-four patients were enrolled, 43 were evaluable for efficacy and safety. The study population included 15 women, 29 men; median age was 53 years (range 32–84); median Karnofsky performance status was 80% (range 60–100%). Thirty-six (82%) patients were chemotherapy-naïve. There were 57 reports of toxicity of grade 3 or greater. Non-fatal grade 3–4 granulocytopenia occurred in 15 patients (34%). The objective response rate was 7%. The estimated probability of being progression-free at 6 months with this therapy is 24% [95% confidence interval (C.I.) 12–38%]. The median time to progression is 15 weeks (95% C.I. 10–20 weeks). There was no observed correlation between serum levels of vascular endothelial growth factor, basic fibroblast growth factor, and IL-8 and the 6PFS outcome.

Conclusion This drug combination was reasonably safe, but with little indication of improvement compared to temozolomide alone.

M. D. Groves (✉) · V. K. Puduvalli · C. A. Conrad · M. R. Gilbert · I. W. Tremont-Lukats · T.-J. Liu · P. Peterson · K. R. Hess · W. K. A. Yung
Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, 1400 Holcombe, 431, Houston, TX 77030, USA
e-mail: mgroves@mdanderson.org

S. M. Chang · K. R. Lamborn · M. D. Prados
The University of California, San Francisco, CA, USA

D. Schiff
The University of Pittsburgh Medical Center, Pittsburgh, PA, USA

T. F. Cloughesy
University of California, Los Angeles, CA, USA

P. Y. Wen
Dana Farber/Brigham and Women's Cancer Center, Boston, MA, USA

H. Greenberg
University of Michigan, Ann Arbor, MI, USA

L. E. Abrey · L. M. DeAngelis
Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Keywords Glioblastoma multiforme · Clinical trial · Controlled · Temozolomide · Thalidomide · Angiogenesis inhibitors · Vascular endothelial growth factor · Basic fibroblast growth factor · Interleukin 8

Introduction

Glioblastoma multiforme (GBM) is a rapidly growing, malignant astrocytic tumor with high morbidity and mortality [1]. The current management of GBM is based on cytoreduction through surgery, radiotherapy, and chemotherapy [2]. Despite this multidisciplinary approach to treatment, median patient survival is approximately 12 months. Two meta-analyses have confirmed that systemic chemotherapy provides a small yet statistically significant survival benefit [3, 4]. The most commonly used agents in these studies were nitrosourea-based drugs.

In recurrent GBM, the median time to progression (MTP) in a study of 225 patients treated with various chemotherapy regimens (none of which were considered particularly effective) was 9 weeks and the 6-month progression-free survival (6PFS) was 15% [5]. *N,N'*-Bis(2-chloroethyl)-*N*-nitrosourea (BCNU), when used in patients with recurrent GBM results in a time to progression (TTP) and 6PFS of 13.3 weeks and 17.5%, respectively [6]. Single-agent TMZ in GBM at first recurrence resulted in an objective response rate of 5.4%, median TTP of 12.4 weeks, and a 6PFS of 21% [7].

TMZ is a cytotoxic alkylating agent with modest efficacy in patients with recurrent high-grade gliomas, including GBM; it is relatively well-tolerated and has an acceptable safety profile [7–13]. It demonstrated a better 6PFS, overall survival (OS), and overall quality of life compared to procarbazine in GBM patients [7].

Thalidomide (*N*-phthalylglutamic acid imide) is a biological response modifier that may interfere with angiogenesis through several potential mechanisms [14, 15]. These include: inhibiting the expression of the $\alpha v\beta 3$ and $\alpha v\beta 5$ integrin receptors [16], inhibiting production or activity of TNF-alpha [17], basic fibroblast growth factor (bFGF) [18–20], vascular endothelial growth factor (VEGF) [20], vascular cell adhesion molecule-1 [15–21], and E-selectin [15–21].

A robust blood supply is critical to the progression of high-grade gliomas [22]. This is reflected in tumors by the overexpression of VEGF [23], bFGF [24, 25], TGF- β [23], the PDGFs [26], and the downregulation of the angiogenesis inhibitor, thrombospondin [25–27]. Based upon its *in vitro* and *in vivo* anti-angiogenic effects, we chose to combine thalidomide with TMZ in recurrent GBM looking for prolongation of 6PFS. Here we present the results of this multicenter study.

Materials and methods

Eligibility

Eligible patients had a histologically proven diagnosis of GBM or gliosarcoma with unequivocal progression by magnetic resonance imaging (MRI) scan. Pathological material was not centrally reviewed, but original pathological material was reviewed by the neuropathologist at each participating NABTC institution and met criteria to be classified as World Health Organization grade IV GBM. Eligible patients had progression after radiation therapy (RT); no more than one adjuvant chemotherapy; no more than one treatment with chemotherapy for recurrence, no prior TMZ or thalidomide, and a baseline brain MRI/CT scan within 14 days prior to registration. Patients must have recovered from the toxic effects of prior therapy and be at least 2 weeks from vincristine, 6 weeks from nitrosoureas, and 3 weeks from other chemotherapies. In addition, patients had to be ≥ 18 years old with a life expectancy ≥ 8 weeks and a Karnofsky performance status (KPS) ≥ 60 ; normal renal, liver, and bone marrow function; further, no evidence of pregnancy, active use of contraception methods, and written informed consent were required to participate in the study. Patients were excluded if they did not fulfill any of the inclusion criteria, or had an active infection, a concurrent illness obscuring toxicity or dangerously altering drug metabolism, or a history of any other cancer (except non-melanoma skin cancer and carcinoma *in situ* of the cervix), unless in complete remission and off therapy for that disease for > 3 years.

Endpoints

The primary endpoint for evaluable patients in this study was the proportion of patients surviving without evidence of disease progression at least 6 months from the date of first drug dose (6PFS). The secondary endpoints included MTP, OS, radiographic response, and change in serum levels of bFGF, VEGF, and IL-8 before and after treatment, and toxicity of the therapy. Patients were evaluable for response if there was bidimensional, measurable enhancing disease on baseline MRI scans and had initiated treatment with TMZ and thalidomide. Assuming no increase in steroid dose in the preceding evaluation, complete response (CR) was the total disappearance of the tumor by neuroimaging. Partial response (PR) was a decrease of $\geq 50\%$ in the product of two diameters in the enhancing tumor. Minor response (MR) was a decrease of $< 50\%$ in the product of two diameters in the enhancing tumor. Stable disease (SD)

meant no change in the scan, and progressive disease was a >25% increase in tumor area. Toxicity was graded according to the National Cancer Institute Toxicity Criteria, Version 2.0.

Assays

Enzyme-linked immunosorbent assays (ELISA) were performed to measure VEGF, IL-8, and bFGF on stored serum samples from patients enrolled in the study. Samples were collected prior to beginning therapy and prior to each new course of therapy (every 28 days) and stored at -80°C . ELISA assays were performed according to the manufacturer's (R&D Systems, Minneapolis, MN, USA) instructions.

Treatment plan

Patients took TMZ 150–200 mg/m² orally once a day for five consecutive days every 28 days. The starting dose for chemotherapy-naïve patients was 200 mg/m²/day; patients who had previous chemotherapy started at 150 mg/m²/day. Patients received thalidomide 400 mg orally at bedtime for 28 consecutive days. Thalidomide dose was adjusted upward to 1,200 mg/day if patients were able to tolerate increased doses. Subsequent courses of TMZ and thalidomide were administered every 4 weeks unless the patient had not recovered from treatment-related adverse events from a previous course. Treatment continued until recurrence or progression, unacceptable toxicity, or to a maximum of 24 courses.

Statistical considerations

The historical values for comparison are from a database of 225 patients with recurrent GBM enrolled in eight previous phase II studies [5]. The overall proportion of patients with GBM remaining alive and free from progression at 6 months was 15% [95% confidence interval (C.I.) 10–19%]. The lower bound of this C.I. was selected as the level of no interest with the level of interest being a success rate of 30%. The intent was to enroll 40 patients and declare success if 6 or more patients were progression-free at 6 months, providing an $\alpha = 0.1$ and $\beta = 0.05$. Because the trial permitted entry of more than 40 patients to allow for possible ineligible patients, the final patient number differed from what was intended. Therefore the results are presented in the form of a point estimate and C.I.s. The method of Kaplan and Meier was used to estimate TTP. For the purpose of assessment of 6PFS, a patient was considered a failure if they

were not known to have been a success. For the purpose of the Kaplan–Meier estimate, patients not known to have progressed by the end of the study or prior to alternative therapy were censored as of the last on-protocol assessment date.

Results

Seven participating institutions enrolled 44 patients. Patient registration began on 16th June 2000, and ended on 11th December 2000. The demographic and treatment characteristics of enrolled patients are summarized in Table 1. All patients had recurrent GBM after surgery (gross total or subtotal resection in 94% of cases) followed by external beam RT without concurrent chemotherapy. Eight of these patients had also been treated with chemotherapy before recurrence or at progression prior to enrollment in this study. Six patients had a KPS of 60, while the rest scored 70 or above at trial registration. One patient refused treatment after enrollment and was not evaluable for response and survival. All patients received the maximum dose of TMZ except three, who received a dose of 150 mg/m². The median of the highest daily dose of thalidomide for all patients was 600 mg; the lowest dose was 200 mg and the highest dose was 1,200 mg.

Progression-free survival

Forty-three patients were evaluable and included in the analysis. All but two patients have progressed. One

Table 1 Distribution of demographic variables in NABTC99-04

Variable	N
Number of patients	44
Median age in years (range)	53 (32–84)
Median KPS (range)	80 (60–100)
Gender (M/F, n)	29/15
≥1 previous chemotherapy (%)	8 (18)
<i>Extent of initial resection (%)</i>	
Gross total or subtotal	55
Partial	39
Biopsy	6
<i>Accrual by center</i>	
MD Anderson Cancer Center	17
University of California, San Francisco	10
University of Pittsburgh Medical Center	7
University of California, Los Angeles	5
Dana Farber Cancer Institute	3
University of Michigan	1
Memorial Sloan-Kettering Cancer Center	1

KPS Karnofsky performance score

of those that did not progress died on study. Death was thought to be due to pulmonary embolism and not tumor progression. This patient is considered a failure for the primary analysis. For the estimation of TTP, and the associated Kaplan–Meier curves, this patient is censored for time of progression at time of death (9 weeks). Nine patients had times of progression occurring after 26 weeks. One patient was declared to have progressed at 27.6 weeks due to scan timing. The remaining times of progression were 34, 43, 45, 46, 48, 54, 81, and 103 weeks with one patient censored 172 weeks after starting the study. The original goal for defining success was 6 patients out of 40. We had 10 out of 43 (23%, 95% C.I. 12–38%) progression-free at 6 months. If a 90% one-sided C.I. were used—consistent with the original selection of alpha of 0.1 and a planned one-tailed test—the lower bound for that C.I. would be 15%. The Kaplan–Meier estimate of the probability of being progression-free at 6 months with this therapy is 24% and the Kaplan–Meier curve of progression-free survival is depicted in Fig. 1. The MTP is 15 weeks (95% C.I. 10–20 weeks).

Radiographic response

In the 43 patients evaluable for radiographic response (one patient never initiated treatment after enrollment), the median time to response was 56 days. There were no CRs. Three patients (7%) had a PR, three (7%) had a MR, 19 (44%) had SD, and 18 (42%) progressed through treatment.

Serum growth factor assays

Based upon another study evaluating thalidomide in glioma [28] we chose to look for change in serum levels

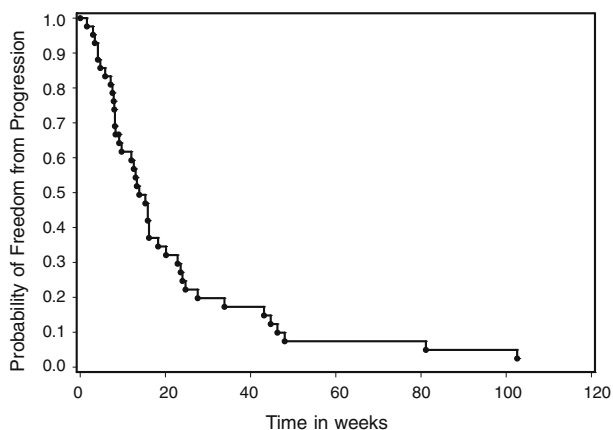


Fig. 1 Kaplan–Meier curve of progression-free survival, $n = 43$

of markers at 4 weeks after enrollment. Baseline and follow-up levels of VEGF, bFGF, and IL-8 were available from 20 patients. The remainder of the patients either did not have initial or follow-up samples available or the samples were outside the sample time window determined to be the most informative. Median baseline serum VEGF level was 366 pg/ml (range 62–815 pg/ml), and median change from baseline was –22 pg/ml (range 0 to +651). Median baseline serum bFGF level was 10 pg/ml (range 1.6–25.1 pg/ml) and the median change from baseline was 0.67 pg/ml (range 0–86.9 pg/ml). Median baseline serum IL-8 level was 0.0 pg/ml (range 0–187.2 pg/ml), and the median change from baseline was 0 pg/ml (range 0–82.8 pg/ml). There was no indication of an association of any of the tested serum growth factor levels with outcome.

Adverse effects

Safety data are reported for the 43 patients who received the treatment. There was one patient death while on study, felt not to be treatment-related. Two other deaths were recorded within 30 days after discontinuation of the study drugs. These were also felt not to be treatment-related. Most adverse effects were grades 1–2. There were ten reports of grade-4 toxicity. The adverse effects by organ and grade are in Table 2.

Discussion

Based upon the known modest efficacy of TMZ and the potential anti-angiogenic properties of thalidomide, we chose to study this combination in patients with recurrent GBM. The results indicate an improved outcome compared to the 10% success rate that was to be excluded. Based on the results of this trial a study using this combination plus radiotherapy was subsequently initiated and has been reported [29]. In that trial the combination showed some efficacy, but no indication that thalidomide added to the efficacy of TMZ alone. It appears that the same is true for treatment of recurrent GBM, since TMZ alone resulted in an estimated 6-month PFS rate of 21% in GBM patients treated at time of first relapse [7]. While in this study patients could have had up to one prior chemotherapy, it does not appear that the addition of thalidomide to TMZ adds substantially to the success of TMZ alone in recurrent GBM. Thus, we consider that while some modest efficacy was seen in this trial, this combination of agents, at this dose and schedule, is not worthy of further investigation in the setting of recurrent GBM.

Table 2 Treatment-related toxicity

Toxicity	Grade					Total
	1	2	3	4	5	
Thrombocytopenia	13	5	1	1		20
Neutropenia	11	4	11	4		30
Neurological ^a	6	13	9	1		29
Gastrointestinal ^b	9	18	3	1		31
Fatigue	4	15	3			22
Headache	7	4	1			12
Thrombosis			7	1		8
Skin	8	3	1			12
Laboratory ^c	6	6	4			16
Other ^d	8	6	4	2	3 ^e	23
Total	72	74	44	10	3	203

Each patient counted only once at level of worst toxicity in each category.

^a Includes (grade 3 or greater): confusion, decreased consciousness, motor changes, depression, weakness, syncope, seizure.

^b Includes (grade 3 or greater): abdominal pain, constipation, diarrhea.

^c Includes (grade 3 or greater): elevated liver enzymes, hypokalemia, hyponatremia.

^d Includes (grade 3 or greater): bleeding, constitutional symptoms, fever, infection, pneumonitis, second malignancy (felt unrelated to treatment).

^e All constitutional symptoms (all grade 5 toxicities felt unrelated to treatment).

Further, analysis of plasma levels of VEGF, bFGF, and IL-8 did not show any correlation with efficacy as had been previously demonstrated [28].

There have now been four prospective phase II studies evaluating thalidomide either as a single agent or in combination with other anti-neoplastic treatments in patients with recurrent GBM from which outcome data can be extracted [28, 30, 31]. Results from these studies and the current report are summarized in Table 3. In terms of toxicity, we identified 54 discrete grade 3 or 4 toxicities in 30 of 43 patients (70%) as compared to the 50% incidence of grade 3 or 4 toxicities in adult anaplastic glioma patients treated at recurrence [32].

In the present trial, the radiographic response rate was about the same as that published previously for single-agent thalidomide in recurrent disease [28]. And the 6PFS was close to that for the thalidomide plus BCNU combination reported for recurrent disease

[31]. The study’s primary endpoint, 6PFS, was higher than our historical comparator value of 15% [5], and slightly improved over the results of single-agent TMZ in recurrent GBM (21%) [7].

The present study was conceived prior to the availability of data on the use of radiotherapy plus concomitant and adjuvant TMZ in GBM [33] and the accompanying suggestion of the influence of the O6-methylguanine-DNA methyltransferase (MGMT) gene promoter hypermethylation on survival outcomes [34]. These data have changed the standard of care for the newly diagnosed GBM patient such that essentially all newly diagnosed GBM patients are now treated with TMZ along with their radiotherapy followed by at least 6 months of TMZ as maintenance. Because of this change in standard of care, studies such as the one reported here are now infeasible due to patients’ prior TMZ exposure. Although, as the MGMT promoter hypermethylation issue is sorted out, there may be a

Table 3 Phase II studies evaluating thalidomide as a single agent or combined with cytotoxic chemotherapy for recurrent GBM

Author	Patient #	Add'l Tx	OR%	6-month PFS	PFS/TTP (weeks)
Fine et al. [28]	39 (25 GBM)	None	6% PR 6% MR 33% SD	4%	10
Marx et al. [30]	42	None	5% PR 42% SD	18%	11
Fine et al. [31]	40 (38 GBM)	BCNU	22% OR	27.5%	14.8
Current study	43	TMZ	7% PR	24%	15

OR% objective response percentage, PFS progression-free survival, TTP time to progression

role for higher dose or more chronic dose TMZ with or without additional agents in the setting of recurrent GBM.

Taken as a whole, this and the other phase II studies reported to date demonstrate that thalidomide has only minimal single-agent activity, and may modestly augment the effects of the cytotoxic agents BCNU and TMZ in patients with recurrent GBM. These improvements are small and could be due to small sample sizes or institution accrual biases. Further, this possible benefit comes at the price of an increase in grade 3 and 4 toxicities. The apparent minimal beneficial effect of thalidomide, even though clearly inadequate, still leaves open the possibility of its study in GBM patients. Combination studies of thalidomide with other anti-angiogenic agents targeting alternative pro-angiogenic pathways might show synergy and more efficacy. Further, newer thalidomide-like molecules with less systemic toxicity, may allow for higher dosing and potentially better anti-angiogenic and anti-glioma activity. Lastly, a more complete understanding of glioma biology and the mechanisms of action of thalidomide and its congeners may assist in choosing patients with a higher likelihood of experiencing benefit from this class of agents.

Acknowledgments This study was supported under the following grants: CA62412, CA16672 (M.D. Groves, V.K. Puduvalli, C.A. Conrad, M.R. Gilbert, I.W. Tremont-Lukats, T-J. Liu, P. Peterson, K.R. Hess, W.K. Alfred Yung), CA62399, CA62422, M01-RR00079 (S.M. Chang, K.R. Lamborn, M.D. Prados), U01CA62407-08 (P.Y. Wen), U01CA62405, M01-RR00056 (D. Schiff), U01 CA62399, M01-RR0865 (T.F. Cloughesy), U01CA62399, M01-RR00042 (H. Greenberg), 5-U01CA62399-09 (L.E. Abrey, L.M. DeAngelis).

References

- Levin VA, Leibel SA, Gutin PH (2001) Neoplasms of the central nervous system. In: DeVita VTJ, Hellman S, Rosenberg SA (eds) *Cancer principles and practice of oncology*, 6th edn. Lippincott, Williams and Wilkins, Philadelphia, pp 2100–2160
- Grossman SA, Batatra JF (2004) Current management of glioblastoma multiforme. *Semin Oncol* 31:635–644
- Fine HA, Wen PY, Maher EA, Viscosi E, Batchelor T, Lakhani N, Figg WD, Purow BW, Borkowf CB (1993) Phase II trial of thalidomide and carmustine for patients with recurrent high-grade gliomas. *J Clin Oncol* 21:2299–2304
- Stewart LA (2002) Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomized trials. *Lancet* 359:1011–1018
- Wong ET, Hess KR, Gleason MJ, Jaeckle KA, Kyritsis AP, Prados MD, Levin VA, Yung WK (1999) Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol* 17:2572
- Brandes AA, Tosoni A, Amista P, Nicolardi L, Grosso D, Berti F, Ermanni M (2004) How effective is BCNU in recurrent glioblastoma in the modern era? A phase II trial. *Neurology* 63:1281–1284
- Yung WK, Albright RE, Olson J, Fredericks R, Fink K, Prados MD, Brada M, Spence A, Hohl RJ, Shapiro W, Glantz M, Greenberg H, Selker RG, Vick NA, Rampling R, Friedman H, Phillips P, Bruner J, Yue N, Osoba D, Zaknoen S, Levin VA (2000) A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. *Br J Cancer* 83:588–593
- Yung WK (2001) Future directions for temozolomide therapy. *Semin Oncol* 28:43–46
- Osoba D, Brada M, Yung WK, Prados M (2000) Health-related quality of life in patients treated with temozolomide versus procarbazine for recurrent glioblastoma multiforme. *J Clin Oncol* 18:1481–1491
- Murray JJ, Greco FA, Wolff SN, Hainsworth JD (1983) Neoplastic meningitis—marked variations of cerebrospinal fluid composition in the absence of extradural block. *Am J Med* 75(2):289–294
- Theodore WH, Gendelman S (1981) Meningeal carcinomatosis. *Arch Neurol* 38(11):696–699
- King D, Goodman J, Hawk T, Boles ETJ, Sayers MP (1975) Dumbbell neuroblastomas in children. *Arch Surg* 110(8):888–891
- Huang TY, Arita N, Ushio Y, Hayakawa T, Yamada K (1994) Pharmacokinetics of intrathecal 1-(4-amino-2-methyl-5-pyrimidinyl) methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride in rats. *J Neurooncol* 19(3):245–250
- Teo SK, Stirling DI, Zeldis JB (2005) Thalidomide as a novel therapeutic agent: new uses for an old product. *Drug Discov Today* 10:107–114
- Teo SK (2005) Properties of thalidomide and its analogues: implications for anticancer therapy. *AAPS J* 7:E14–E19
- List AF (2005) Emerging data on IMiDs in the treatment of myelodysplastic syndromes (MDS). *Semin Oncol* 32:S31–S35
- Moreira AL, Sampaio EP, Zmuidzinis A, Frindt P, Smith KA, Kaplan G (1993) Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. *J Exp Med* 177:1675–1680
- Gelati M, Corsini E, Frigerio S, Pollo B, Broggi G, Croci D, Silvani A, Boiardi A, Salmaggi A (2003) Effects of thalidomide on parameters involved in angiogenesis: an in vitro study. *J Neurooncol* 64:193–201
- Neben K, Moehler T, Egerer G, Kraemer A, Hillengass J, Benner A, Ho AD, Goldschmidt H (2001) High plasma basic fibroblast growth factor concentration is associated with response to thalidomide in progressive multiple myeloma. *Clin Cancer Res* 7:2675–2681
- Li X, Liu X, Wang J, Wang Z, Jiang W, Reed E, Zhang Y, Liu Y, Li QQ (2003) Thalidomide down-regulates the expression of VEGF and bFGF in cisplatin-resistant human lung carcinoma cells. *Anticancer Res* 23:2481–2487
- Geitz H, Handt S, Zwingerberger K (1996) Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade. *Immunopharmacology* 31:213–221
- Kaur B, Tan C, Brat DJ, Post DE, Van Meir EG (2004) Genetic and hypoxic regulation of angiogenesis in gliomas. *J Neurooncol* 70:229–243
- Jensen RL (1998) Growth factor-mediated angiogenesis in the malignant progression of glial tumors: a review. *Surg Neurol* 49:189–195

24. Morrison RS, Yamaguchi F, Saya H, Bruner JM, Yahanda AM, Donehower LA, Berger M (1994) Basic fibroblast growth factor and fibroblast growth factor receptor I are implicated in the growth of human astrocytomas. *J Neurooncol* 18:207–216
25. Brat DJ, Kaur B, Van Meir EG (2003) Genetic modulation of hypoxia induced gene expression and angiogenesis: relevance to brain tumors. *Front Biosci* 8:d100–d116
26. Reigstad LJ, Varhaug JE, Lillehaug JR (2005) Structural and functional specificities of PDGF-C and PDGF-D, the novel members of the platelet-derived growth factors family. *FEBS J* 272:5723–5741
27. Harrigan MR (2003) Angiogenic factors in the central nervous system. *Neurosurgery* 53:639–660
28. Fine HA, Figg WD, Jaeckle K, Wen PY, Kyritsis AP, Loeffler JS, Levin VA, Black PM, Kaplan R, Pluda JM, Yung WK (2000) Phase II trial of the antiangiogenic agent thalidomide in patients with recurrent high-grade gliomas. *J Clin Oncol* 18:708–715
29. Chang SM, Lamborn KR, Malec M, Larson D, Wara W, Sneed P, Rabbitt J, Page M, Nicholas MK, Prados MD (2004) Phase II study of temozolomide and thalidomide with radiation therapy for newly diagnosed glioblastoma multiforme. *Int J Radiat Oncol Biol Phys* 60:353–357
30. Marx GM, Pavlakis N, McCowatt S, Boyle FM, Levi JA, Bell DR, Cook R, Biggs M, Little N, Wheeler HR (2001) Phase II study of thalidomide in the treatment of recurrent glioblastoma multiforme. *J Neurooncol* 54:31–38
31. Fine HA, Dear KB, Loeffler JS, Black PM, Canellos GP (2003) Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer* 71:2585–2597
32. Temodar (temozolomide) product information package insert. Schering Corp., Kenilworth, 2005
33. Stupp R, Mason WP, van den Bent MJ et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 352:987–996
34. Hegi ME, Diserens AC, Gorlia T et al (2005) MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 352:997–1003