Phase II trial of irinotecan and thalidomide in adults with recurrent glioblastoma multiforme

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This phase II study aimed at determining the efficacy and safety of irinotecan combined with thalidomide in adults with recurrent glioblastoma multiforme (GBM) not taking enzyme-inducing anticonvulsants (EIACs). Adult patients (≥18 years) with recurrent GBM with up to three relapses following surgery and radiation therapy were eligible for this trial. The primary end point was rate of progression-free survival at 6 months (PFS-6); secondary end points were response rate, overall survival, and toxicity. Patients were treated in 6-week cycles with 125 mg/m^2 irinotecan weekly for 4 weeks followed by 2 weeks off treatment and 100 mg of thalidomide daily increased as tolerated to 400 mg/day. Of 32 evaluable patients, 8 (25%) were alive and progression free at 6 months. The median PFS was 13 weeks. One patient experienced a complete response, one a partial response, and 19 stable disease. Median overall survival time from entry into the study was 36 weeks, and the 1-year survival rate was 34%. Adverse events (grade 3 or 4) included diarrhea, abdominal cramps, lymphopenia, neutropenia, and fatigue. Two of the four deaths that occurred were possibly due to treatment-related toxicity. The combination of irinotecan, a cytotoxic agent, and thalidomide, an antiangiogenic agent, shows promising activity against recurrent GBM in patients not receiving EIACs and warrants further study. The results also provide support for similar strategies using combination therapies with newer targeted antiangiogenic agents to generate effective therapies against malignant gliomas.
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Glioblastoma multiforme (GBM) is associated with significant morbidity and a disproportionately high rate of mortality. For patients with newly diagnosed GBM, chemoradiation therapy followed by adjuvant treatment with temozolomide provides a survival advantage over radiation therapy alone.[1] However, tumor recurrence is the norm, with a median time to progression (TTP) ranging from 9 to 14 weeks. For most patients with recurrent GBM, there is no approved standard of care, and these patients survive only a few months after tumor progression. New strategies that can selectively target the biology of tumors are clearly needed.

Neoangiogenesis and proliferation are recognized fea-

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tures of recurrent GBM and are logical targets for therapy.[2] However, single-agent trials with antiangiogenic agents against malignancies have shown disappointing activity or unacceptable toxicity. Preclinical data suggest that certain antiangiogenic agents can increase vascular perfusion in tumors by decreasing edema and reducing interstitial pressure. This can potentially improve the delivery of concurrently used cytotoxic agents to the tumor, resulting in improved efficacy.[3] Consequently, strategies that combine cytotoxic and antiangiogenic approaches to target the tumor in two distinct ways critical to its biology could maximize the potential of these agents.

Irinotecan, a topoisomerase I inhibitor, has demonstrated activity against several malignancies, including gliomas,[4] although its activity against recurrent GBM has been modest[5,6] and associated with side effects, including diarrhea.[7] In studies of colorectal cancer,[8,9] the combination of irinotecan with the antiangiogenic agent thalidomide showed antitumor activity; in addition, thalidomide ameliorated the gastrointestinal side effects of irinotecan. Although it is not efficacious when used alone against recurrent malignant gliomas,[10–12] the antiangiogenic activity of thalidomide, mediated by inhibition of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), and with its immunomodulatory effects mediated through cytokine modulation and costimulation of partially activated T cells, remains of interest in combination strategies against gliomas.

We hypothesized that the antiangiogenic effect of thalidomide combined with the cytotoxic activity of irinotecan would improve progression-free survival (PFS) in patients with recurrent GBM. We also hypothesized that the combination would be well tolerated because of the nonoverlapping toxic effects of these agents and the anticipated reduction of irinotecan's gastrointestinal side effects by thalidomide. To test our hypotheses, we conducted a phase II study of thalidomide and irinotecan in adult patients with recurrent GBM.

Patients and Methods

Eligibility

Adult patients (≥18 years) with a KPS score of ≥70 and an estimated life expectancy of >8 weeks who had histologically proven supratentorial GBM or gliosarcoma were eligible for this trial. Patients were required to have prior radiation therapy and unequivocal evidence of tumor recurrence or progression by MRI on a stable or decreasing steroid dose. Treatment for up to two prior relapses was permitted. Patients who had undergone a recent resection of a recurrent tumor were eligible even if they did not have radiologically measurable or evaluable disease, provided they had completely recovered from the surgery. Recovery from side effects of prior cytotoxic or cytostatic therapies was also required. Concurrent treatment with enzyme-inducing anticonvulsants (EIACs) was not allowed because of the impact of these agents on irinotecan metabolism. Patients were required to have adequate bone marrow, hepatic, and renal function. All patients were required to comply with the System for Thalidomide Education and Prescribing Safety Program (S.T.E.P.S. program, Celgene Corporation, Summit, NJ, USA) and to abide by its mandatory requirements for pregnancy testing and birth control. Patients with a history of cancers, other than nonmelanoma skin cancer or carcinoma in situ of the cervix, were eligible for this trial only if they were in complete remission and had not required therapy within the previous 3 years. Patients with serious medical conditions, prior treatment with irinotecan, or grade 2 or higher peripheral neuropathy were ineligible for this trial, as were those who were pregnant or lactating. The trial was approved by our institutional review board, and all the patients who participated provided written informed consent.

Treatment Plan

Six consecutive weeks of treatment was considered one cycle. Irinotecan was administered as a 90-min intravenous infusion at a dose of 125 mg/m^2 weekly for 4 weeks followed by 2 weeks of rest. Thalidomide was administered concurrently for a total of 42 days: each cycle at a dose of 100 mg/day for 1 week and then increased weekly by 100 mg/day, provided no side effects were noted, to a final dose of 400 mg/day. A 1-week "wash out" period was required for patients who were switched from EIACs to nonenzyme-inducing anticonvulsants (NEIACs) before beginning treatment.[13] In addition, all patients received warfarin (1 mg daily) for the duration of therapy to reduce the risk of venous thromboembolism (VTE) associated with the combination of thalidomide and cytotoxic agents.[14]

For subsequent treatment cycles, drug doses were individually titrated based on toxicity. If grade 3 or higher toxic effects as measured by the National Cancer Institute Common Toxicity Criteria version 3.0 (NCI-CTC) were observed, treatment was held up for at least 2 weeks and subsequently restarted at a lower dose level. For thalidomide, the dose was reduced by 100 mg for each grade 3 or higher toxic effect to a minimum of 100 mg/day. The irinotecan dose was reduced by 25 mg/m^2 per dose to a minimum of 75 mg/m^2. The decision regarding which agent should be dose reduced was guided by the type of adverse event observed.

Evaluation at Baseline and during Study

Disease progression was confirmed radiologically by a baseline contrast-enhanced MRI. Patients underwent a baseline history and physical examination, including neurologic examination, prior to treatment initiation; this was repeated before each subsequent treatment cycle or as clinically indicated. Pretreatment tests included assessment of complete blood count with differential and platelet counts, which was repeated every 2 weeks and before each new cycle during treat-

ment. Serum chemistry and anticonvulsant levels were obtained at baseline and repeated before each cycle of treatment. As mandated by the S.T.E.P.S. Program, all women of reproductive age with regular menstruation were required to complete a pregnancy test before each treatment cycle, and those with irregular menstruations, every 2 weeks. A quantitative sensory test (QST) was performed on all patients at baseline and after every two cycles to identify any peripheral neurotoxic effects associated with thalidomide. In addition to the above-mentioned MRI, dynamic contrast-enhanced MRI was performed at baseline and after every cycle of treatment. The routine use of granulocyte colony-stimulating factor was not permitted unless symptomatic neutropenia was observed.

Response Criteria

The primary end point was PFS at 6 months (PFS-6). PFS time was defined as the duration from the date of registration to the date of disease progression, as determined by MRI; neurologic deterioration (when radiological data could not be obtained); or death.

Response to treatment was determined by MRI using bidimensional measurement of enhancing lesions based on criteria proposed by Macdonald et al.[15] A complete response (CR) required disappearance of all contrast-enhancing disease and no evidence of new lesions. A partial response (PR) was defined as a decrease of >50% of the baseline sum of measurable contrast-enhancing lesions with no progression of evaluable disease and no new lesions. Patients with stable disease (SD) were those who had neither CR nor PR but no disease progression. For patients with CR or PR, the response was confirmed by an additional scan done at least 4 weeks after the scan indicating response. Disease progression was defined as a ⩾25% increase in the sum of the products of all measurable lesions, clear worsening of evaluable disease, or the appearance of a new lesion.

Evaluation of Toxicity

All patients were evaluated and graded for toxic effects using the NCI-CTC version 3. In addition, when the trial had accrued 50% of the total planned number of patients, accrual was stopped for 6 weeks and an interim toxicity analysis was performed. The analysis revealed no unexpected findings in the rate or type of adverse events, allowing the trial to continue to full accrual.

Statistical Design

A single-stage phase II trial design was used and the results compared with historical data obtained from a database of 225 patients who had recurrent GBM and had been enrolled in eight previous phase II trials in which none of the treatments were considered effective.[16] The proportion of patients who remained alive and progression free at 6 months in the control population was 15%. The hypothesis tested was H0: $p < p0$ versus H1: $p > p1$, where p was the probability of remaining alive and progression free at 6 months (PFS-6). Based on our control population, $p0$ was set to 15% to discard a treatment that might be significantly worse than the aggregate value from the control population, and $p1$ was set to 35% to demonstrate an absolute improvement of 0.2 relative to the control treatments. These parameters led to a single-stage design with a total of 32 patients. The treatment would be declared a success if more than seven patients had PFS > 6 months (with $\alpha = 11\%$ and $\beta = 8.9\%$).

To accomplish the secondary objectives, the distribution of time to progression or death (PFS) and time to death was calculated with the Kaplan-Meier method. The proportion of patients in each of the response categories (CR, PR, and SD) was computed.

Results

Patient Characteristics

Between November 2003 and February 2005, 33 patients with recurrent GBM were registered in this trial. One patient declined to participate in the trial before treatment was initiated; the remaining 32 patients were included in this analysis. The patient characteristics are listed in Table 1. Eleven patients had failed more than one type of chemotherapy regimen before entering this trial. Twenty-seven patients had received prior treatment with temozolomide, and eight had also been previously treated with nitrosoureas (Table 2).

Treatment Efficacy

Eight of the 32 patients were alive and progression free at 6 months after treatment with thalidomide and irinotecan. Using the Kaplan-Meier method, the estimated PFS-6 rate was 25% (95% confidence interval [CI],

Table 1. Patient characteristics

Characteristic	No. of Patients (%)
Age	
Median (range)	46.5 (21–65) years
Gender	
Men	24 (75)
Women	8 (25)
KPS score	
100	5 (15.6)
90	12 (37.5)
80	11 (34.4)
70	4 (12.5)
Prior treatment	
Surgery	32 (100)
Gross total resection	8 (25)
Subtotal resection	21 (65.6)
Biopsy	3 (9.4)
Radiation therapy	32 (100)
Chemotherapy	32 (100)

Table 2. Chemotherapy regimens administered prior to study entry

Prior Treatments	No. of Patients (%)
Number of prior treatments	
One prior regimen	20 (62.5)
Two prior regimens	8 (25)
Three prior regimens	4 (12.5)
Type of treatment	
Temozolomide only	13 (40.6)
Temozolomide + isotretinoin	5 (15.6)
Temozolomide + tipifarnib	5 (15.6)
Temozolomide + PEG-interferon	2 (6)
Temozolomide + gefitinib	2 (6)
Erlotinib	4 (12.5)
Procarbazine, lomustine, vincristine	4 (12.5)
Carmustine	5 (15.6)
Other	6 (18.7)

Abbreviation: PEG, polyethylene glycol.

14%–46%) and the median PFS time was 13 weeks (95% CI, 10–24 weeks) (Fig. 1). The best responses included CR in one patient, PR in one (Fig. 2), and SD in 19. Characteristics of the eight patients who survived progression free for at least 6 months are shown in Table 3. Four patients died during or shortly after participating in the trial. The median overall survival time from time of entry into the study was 36 weeks (95% CI, 24–56 weeks), and the overall survival rate at 1 year was 34% (95% CI, 21%–56%) (Table 3).

One patient had a CR but was unable to continue participation in the trial because of treatment-related side effects. However, treatment was continued off-protocol at an irinotecan dose of 50 mg/m^2 weekly, which she was able to tolerate. After 13 months of overall treatment, the patient elected to discontinue therapy because of persistent low-grade fatigue, but remained alive and progression free.

Toxicity and Treatment Tolerance

The most common toxicities in this study without considering grade or relationship to treatment were neutropenia, diarrhea, fatigue, headache, lymphopenia, anemia, constipation, abdominal pain, electrolyte disturbances (including hypokalemia, hypomagnesemia, hypophosphatemia, and hyponatremia), hyperglycemia, and dizziness; the majority of these were grade 1 or 2 events. Of the 32 patients, 25 experienced treatment-related toxic effects. The most frequent grade 3 adverse events included leukopenia/neutropenia (18 patients) and diarrhea with abdominal cramping or abdominal pain (14 patients). Grade 4 adverse events included neutropenia in two patients and lymphopenia, seizure, VTE, and lymphopenia in one patient each. Four patients had VTE, of whom only one had a grade 4 event. Grade 1 and 2 toxicities included nausea, dehydration, dizziness, myelotoxicity, elevated transaminase levels, and abnormal electrolyte levels. Five patients discontinued therapy because of treatment-related toxic effects (two due to intercurrent illnesses and three due to decline in quality of life due to grade 3 toxic effects). These patients had been on the study treatment for a median of 17 weeks (range, 4.4–31.1 weeks) before treatment was discontinued. Of the four deaths that occurred during or shortly after participation in the trial, two were considered unrelated to treatment (and possibly due to tumor progression). Of the two patients whose deaths were possibly treatment related, one developed grade 3 diarrhea and dehydration requiring hospitalization, with an MRI scan showing no evidence of tumor progression. Because of continued neurologic decline, this patient was discharged to a home hospice and died shortly thereafter. The other patient received one cycle of chemotherapy but was hospitalized after developing neutropenic fever. After being discharged, she developed acute abdominal pain due to peritonitis secondary to a perforated colonic diverticular pouch and died shortly thereafter of septic shock.

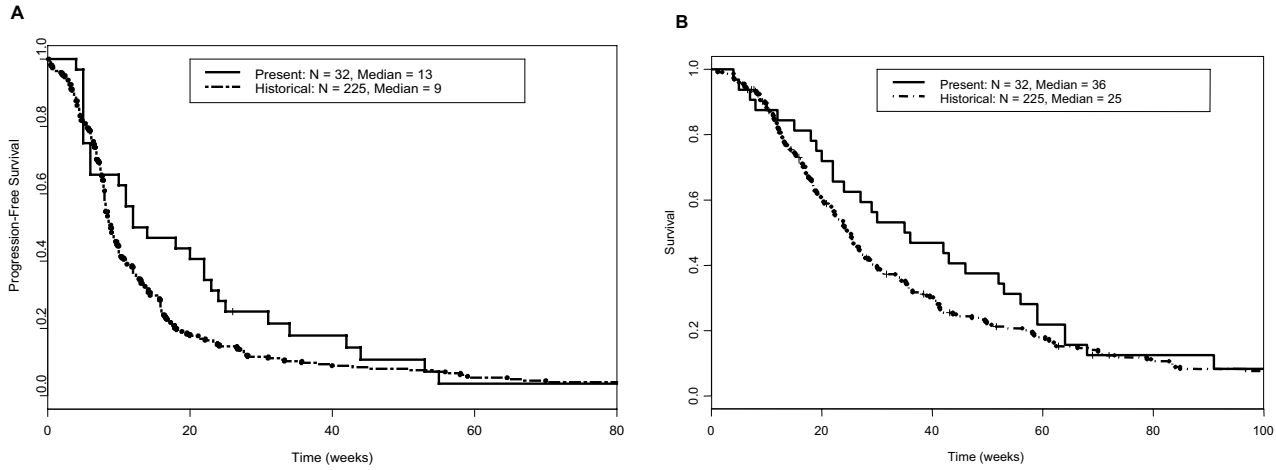

Fig. 1. Kaplan-Meier curves for progression-free survival (A) and overall survival (B).

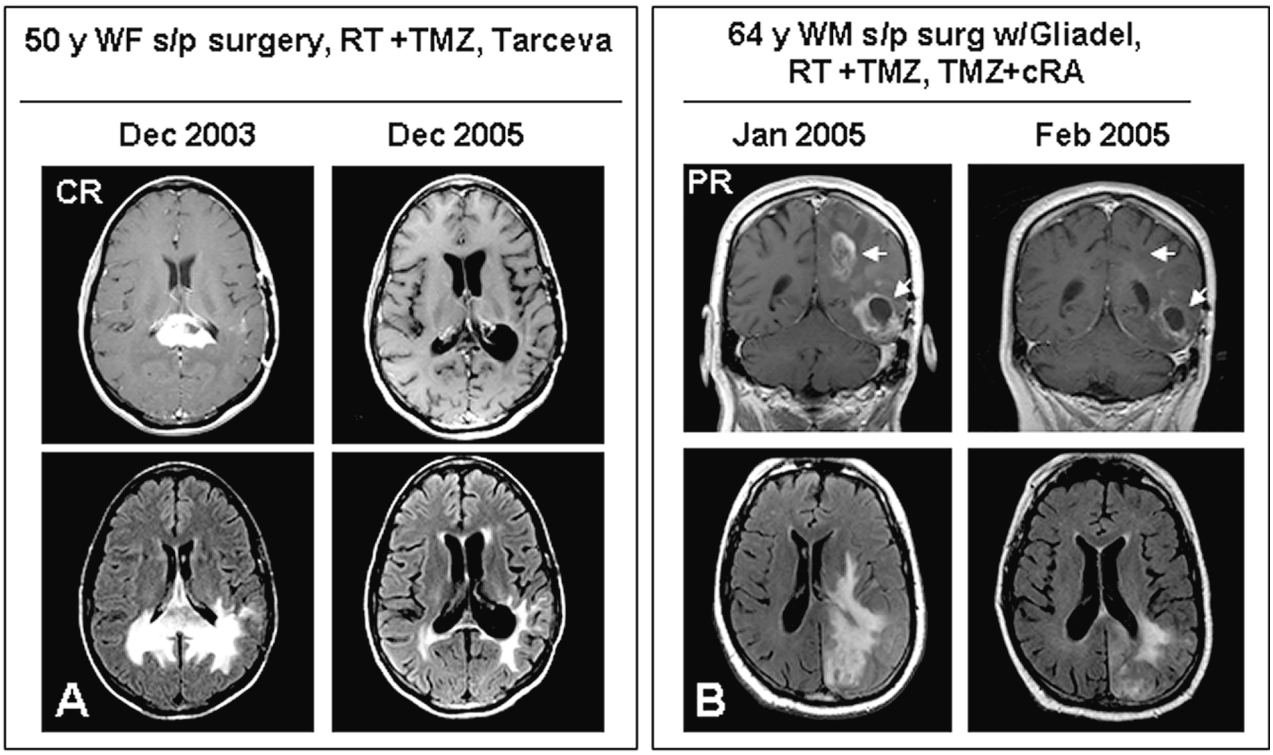

Fig. 2. MR images showing response to treatment with irinotecan and thalidomide in patients with glioblastoma multiforme. (A) Complete response in a 50-year-old woman in whom prior treatments with radiotherapy (RT), temozolomide (TMZ), and erlotinib (Tarceva) had failed. (B) Partial response in a 64-year-old man in whom prior treatments with radiotherapy, temozolomide, and isotretinoin (13-*cis*-retinoic acid, cRA) had failed.

Discussion

The combination of irinotecan and thalidomide used in the present study to treat patients with recurrent GBM showed a PFS-6 rate that is superior to that observed in historical controls, with 8 of the 32 patients being progression free at 6 months. Some of our patients experienced prolonged PFS and increased duration of overall survival. Adverse events related to irinotecan necessitated dose reductions in several patients, including some who had durable responses, suggesting that a lower starting dose of irinotecan may be more appropriate.

Several trials have studied the effects of single-agent irinotecan therapy against malignant gliomas. Friedman et al.[17] reported radiological responses in 17% and SD in 54% of patients with recurrent GBM using a treatment regimen with irinotecan similar to ours. Cloughesy et al.[18] reported a response rate of 14% and a median survival time of 24 weeks in patients with recurrent malignant gliomas when irinotecan was given once every 3 weeks. Prados et al.[19] reported a PFS-6 rate of 16% with irinotecan given every 3 weeks to patients with recurrent GBM (with separate arms for patients on NEIACs and EIACs) and concluded that single-agent irinotecan was

Table 3. Characteristics of patients who were alive and progression-free for at least 6 months

Patient Age, Years	PFS, Weeks	Survival, Weeks[a]	Subsequent Treatment (Status at Last Follow-up)
31	26	106+	None (PF)
50	31	59	Resection, cRA, dose-dense TMZ[b]
47	34	64	None (hospice)
21	42	64	6-TG + carmustine, dose-dense TMZ
46	44	68	TMZ + cRA, procarbazine
63	53	53	None (hospice)
34	55	69+	Irinotecan + bevacizumab (PF)
49	90	104+	Dose-dense TMZ (PF)

Abbreviations: PFS, progression-free survival; PF, progression free; cRA, 13-*cis* retinoic acid; TMZ, temozolomide; 6-TG, 6-thioguanine.

[a]Measured from date of registration to present trial.

[b]Defined as TMZ administered at 150 mg/m^2/day on days 1–7 and 15–21 of a 28-day cycle.

Table 4. Progression-free and overall survival

Survival Measure	Median Survival, Weeks (95% CI)	Rate of Survival, Weeks, % (95% CI)		
		13 Weeks	26 Weeks	52 Weeks
Overall	36 (24 to 56)	84 (73–98)	62 (48–81)	34 (21–56)
Progression-free	13 (10 to 24)	50 (35–71)	25 (14– 46)	12 (5–31)

Abbreviation: CI, confidence interval.

ineffective for treating recurrent GBM. Batchelor et al.[20] reported similar findings in a two-stage phase II study that was terminated after the first stage due to lack of activity. Thus, single-agent irinotecan therapy appears to have limited activity in patients with recurrent GBM.

In previous studies of thalidomide administered as a single agent to patients with malignant gliomas (grade III or IV), PR rates of 6% and SD rates of 33% were reported.[10,11] Marx et al.[12] reported a 5% PR rate and a 42% disease stabilization rate in patients with recurrent GBM who received thalidomide at escalating doses similar to that in the present study. These results were considered indicative of the limited activity of thalidomide against malignant gliomas.

Using a combination of irinotecan and carmustine, Reardon et al.[21] reported objective responses (one CR and four PRs) and a median TTP of 11.3 weeks in patients with recurrent malignant gliomas (including 28 with recurrent GBM), concluding that the combination was comparable in activity to single-agent irinotecan but with more frequent toxic effects. In contrast, another phase II trial of the same combination in patients with recurrent GBM on EIACs who had failed temozolomide was reported to have 9 PR and 21 SD, with a PFS-6 rate of 30.3% and a median TTP of 17 weeks.[22] Irinotecan combined with temozolomide showed a PFS-6 rate of 38%–39% in patients with recurrent GBM.[23,24] Thalidomide combined with temozolomide was reported by Groves et al.[25] to have an objective response rate of 7% and a PFS-6 rate of 24%. The relevance of these results for patients with recurrent GBM who fail first-line temozolomide remains uncertain. However, combination strategies appear to be superior to single-agent therapies; this was also seen in our study, in which irinotecan combined with thalidomide appeared to be more active than either agent alone in patients who had previously failed first-line therapy with temozolomide.

Although no unexpected treatment-related toxic effects were noted, several patients experienced grade 3 toxic effects that caused delays in treatment. Myelotoxicity effects, fatigue, and gastrointestinal effects were the most frequent side effects seen, but were well controlled with dose reductions. The expected reduction of diarrhea with the use of thalidomide was not seen in the majority of patients; this could have been due to the gradual dose escalation schedule of thalidomide used in this study. All patients were required to take low-dose warfarin to reduce the risk of VTE, which has been reported with the combination of thalidomide and cytotoxic agents.[26] Of the four (12.5%) patients who developed a deep vein thrombosis, three also had pulmonary embolism; all these patients received therapeutic anticoagulation and were able to continue treatment without additional adverse effects. The frequency of VTE observed in this study was less than that observed in other studies, which have reported incidence rates ranging from 24% to 31%.[27,28] These results suggest that the addition of low-dose warfarin may have conferred protection against VTE, although the number of patients was too small to draw any definite conclusions. Our results are similar to those from a previous study,[14] which found that low-dose warfarin (1–2 mg daily) was as effective as higher doses in reducing the incidence of VTE associated with thalidomide, while reducing the risk of bleeding. We observed no symptomatic or asymptomatic intracranial or intratumoral bleeding in this study in spite of the use of low-dose warfarin in all patients.

Given that EIACs increase the clearance and reduce the plasma concentrations of irinotecan and its metabolite, SN-38,[29] in an unpredictable manner, we restricted trial enrollment to patients who were not taking EIACs. The availability of several new NEIACs made it feasible for us to switch our patients on EIACs to NEIACs without compromising seizure control.

Being accessible to oncologists and with well-recognized and manageable adverse events, the combination of irinotecan and thalidomide may provide an option for patients who fail first-line therapy with temozolomide. In addition, newer analogues of thalidomide, such as lenalidomide, that are significantly more potent are also attractive candidates for treatment strategies against GBMs. On the basis of the results of the present study and those reported by Fine et al.[30] showing that lenalidomide is active against GBM, we have initiated a phase I/II trial of lenalidomide in combination with irinotecan in patients with recurrent GBM that will begin patient accrual shortly. Such strategies combining cytotoxic and novel signal transduction agents that target tumor biology bear promise in providing viable therapeutic options for patients with GBM.

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