A Phase I Trial of Lenalidomide in Patients with Recurrent Primary Central Nervous System Tumors

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Abstract

**Purpose:** Inhibition of angiogenesis represents a promising new therapeutic strategy for treating primary malignant brain tumors. Lenalidomide, a potent analogue of the antiangiogenic agent thalidomide, has shown significant activity in several hematologic malignancies, and therefore we chose to explore its tolerability and activity in patients with primary central nervous system tumors.

**Experimental Design:** A phase I interpatient dose escalation trial of lenalidomide in patients with recurrent primary central nervous system tumors was conducted.

**Results:** Thirty-six patients were accrued to the study, of which 28 were evaluable for toxicity, the primary end point of the trial. We show that lenalidomide can be given safely up to doses of 20 mg/m^2^, with the only toxicity being a probable increased risk of thromboembolic disease. Pharmacokinetic studies reveal good bioavailability, linear kinetics, and no effects of enzyme-inducing antiepileptic drugs on the metabolism of lenalidomide. No objective radiographic responses were seen in any of the treated patients. In the group of 24 patients with recurrent glioblastoma, the median time to tumor progression was 2 months and only 12.5% of patients were progression-free at 6 months.

**Conclusion:** Lenalidomide is well tolerated in patients with recurrent glioma in doses up to 20 mg/m^2^. Treatment may be associated with an increased risk of thromboembolic disease. Preliminary data suggest that single agent activity may be limited in patients with recurrent glioblastoma at the doses evaluated although larger studies will be needed to confirm these observations.

Despite recent advances in neurosurgery, radiotherapy, and chemotherapy, the prognosis of patients with malignant gliomas remains poor (1). With the failure of most standard cytotoxic agents to dramatically alter the course of this disease, there is an increasing interest in developing new therapeutics with novel mechanisms of action.

Preclinical and clinical studies have shown that gliomas are highly angiogenic and that antiangiogenic therapy represents a potentially promising new therapeutic strategy (2–7). Thalidomide was one of the first oral antiangiogenic agents evaluated in patients with recurrent malignant gliomas (8). As a single agent, thalidomide showed cytostatic activity against gliomas, as reflected by stabilization of disease in some patients (9). Unfortunately, “responses” to thalidomide were generally short-lived, leading to the search for similar but potentially more clinically active agents.

Lenalidomide (Revlimid, CC-5013) is a potent thalidomide analogue based on *in vitro* anti-inflammatory and immuno-modulatory assays (10–13). Lenalidomide has shown significant antitumor activity in patients with multiple myeloma and myelodysplastic syndrome with chromosome 5q deletions (14–18). Secondary to lenalidomide safety profile, proven activity in several other cancers, and the possible antiglioma activity of thalidomide, we elected to evaluate lenalidomide in patients with recurrent gliomas.

**Patients and Methods**

**Study population and eligibility criteria.** Patients 18 years or older with histologically confirmed diagnosis of progressive or recurrent primary central nervous system tumors who had failed prior radiation therapy were eligible for the study. Evaluable disease on magnetic resonance imaging scan, a Karnofsky performance status of ≥60%, and normal hematologic, liver, and renal function were required. The number or types of prior treatment regimens was not an exclusion criterion except for patients who had prior therapy with thalidomide. All participants signed a written informed consent approved by the National Cancer Institute Institutional Review Board.

**Treatment.** Each 4-week treatment cycle consisted of lenalidomide administered p.o. once daily for 3 weeks followed by a 1-week rest period. A complete physical and neurologic examination was done...
every 2 weeks for the first cycle and every 4 weeks thereafter. A magnetic resonance imaging scan was done before each cycle to assess response. Patients with stable or responding disease based on clinical and radiographic assessment continued on to an additional cycle of treatment. Three patients per dose level were treated, and if no dose-limiting toxicity (DLT) occurred, three subsequent patients were enrolled in the next higher dose. If, however, a DLT was encountered, three more patients would be added to that group. The maximum tolerated dose was considered to have been exceeded in the event of two DLTs (any drug-related nonhematologic grade ≥3 or hematologic grade ≥4 toxicity) in any given dose level. The six dose levels were 2.5, 5, 8, 11, 15, and 20 mg/m²/d. Based on existing data showing severe and life-threatening neutropenia with doses >40 mg/d, the maximum total daily dose was predetermined to be <40 mg. DLT was defined for only the first cycle of therapy (4 weeks) and patients had to have at least 4 weeks of treatment to be evaluable for toxicity and DLT.

Patients were stratified into those not on enzyme-inducing antiepileptic drugs (EIAED; group A) and those on EIAED (group B), with each group proceeding through dose escalation independently. After the pharmacokinetic data from patients on the second dose level revealed that EIAEDs had no effects on lenalidomide metabolism, the protocol was amended to place all subsequent patients into a single stratum.

Pharmacokinetic evaluation. Serial blood samples for the determination of lenalidomide were collected on the 1st and 15th days of the first cycle. Plasma concentrations of lenalidomide were measured using a high-performance liquid chromatography-mass spectrometry method and analyzed as previously described (19).

Statistical considerations. The primary endpoint was to evaluate the toxicity and pharmacokinetics of lenalidomide in this dose-escalating phase 1 study. Using the dose escalation scheme described above, the probability of escalating to the next dose level, based on the true rate of DLT at the current dose, is given by the following (each group was considered independent of the other):

<table>
<thead>
<tr>
<th>True toxicity at a given dose</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of escalating</td>
<td>0.91</td>
<td>0.71</td>
<td>0.49</td>
<td>0.31</td>
<td>0.17</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Thus, if the true underlying proportion of DLTs is 50% at the current dose, there was a 17% chance of escalating to the next dose. The progression-free survival (PFS) and overall survival rate were estimated according to the method of Kaplan and Meier.

Pharmacokinetic analysis. Twenty-four patients had complete pharmacokinetic sampling done (Table 1). There was no statistically significant difference in dose-normalized AUC0–∞ (P = 0.8) evident between the patients on EIAEDs and those who were not, and thus the EIAED and non-EIAED treatment groups were combined for further pharmacokinetic and other analyses. No difference (P = 0.27) was observed in CI/F (and dose-normalized AUC0–∞) as dose increased. In the dose range investigated (2.5-20 mg/m²), lenalidomide exhibited apparent linear pharmacokinetics. Linear regression analysis indicated a dose-proportional increase in AUC0–∞ with a good correlation (Fig. 1). The lenalidomide concentration-time profiles were very similar between patients (Fig. 2) and were characterized by a rapid absorption with mean Tmax of 1.0 h and a monophasic decline with mean terminal half-life of 3.9 h.

Toxicities. Seven patients experienced clinical and radiographic progression before their first 4-week evaluation and were therefore evaluable for toxicity but not maximum tolerated dose determination. The drug was generally very well tolerated with only one observed DLT (see Table 2). There were only two episodes of grade 2 thrombocytopenia, one episode each of grade 2 and grade 3 neutropenia. The one grade 3 neutropenia occurred in a patient previously treated with high-dose

### Table 1. Mean (SD) pharmacokinetic variable estimates of lenalidomide

<table>
<thead>
<tr>
<th>Variables</th>
<th>2.5</th>
<th>5</th>
<th>8</th>
<th>11</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0–∞ (ng·h/mL)</td>
<td>316</td>
<td>622</td>
<td>385</td>
<td>923</td>
<td>1055</td>
<td>942</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>89.8</td>
<td>114</td>
<td>109</td>
<td>229</td>
<td>409</td>
<td>210</td>
</tr>
<tr>
<td>Tmax* (h)</td>
<td>0.9</td>
<td>1.5</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>3.2</td>
<td>4.5</td>
<td>2.3</td>
<td>5.6</td>
<td>2.2</td>
<td>3.5</td>
</tr>
<tr>
<td>CI/F (mL/min/m²)</td>
<td>169</td>
<td>206</td>
<td>451</td>
<td>258</td>
<td>247</td>
<td>354</td>
</tr>
<tr>
<td>Vd/F (L/m²)</td>
<td>38.9</td>
<td>50.5</td>
<td>85.1</td>
<td>89.5</td>
<td>45.8</td>
<td>77.8</td>
</tr>
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*Tmax values are median (range).
chemotherapy and autologous bone marrow support. Mild to moderate fatigue was seen in 13 patients. The only clinically significant infection was a case of herpes zoster keratoconjunctivitis. There were five cases of venous thrombosis (18% of evaluable patients) including a case of retinal vein thrombosis in the patient on lenalidomide for the longest time (24 months). Adverse events did not seem to be dose related.

Clinical efficacy. Twenty-seven of 36 patients completed the first 3 weeks of treatment and were therefore evaluable or maximum tolerated dose determination. Of the nine patients not evaluable, seven had rapid disease progression, one had a DLT (herpes zoster), and one required a non–brain tumor and non–study-related surgical procedure.

No patient had an objective radiographic response. The 6-month PFS for all 27 evaluable patients was 14.8% [95% confidence interval (CI), 6.0-36.6%; Fig. 3A]. The median time to progression for this group of patients was 1.74 months (95% CI, 1.6-3.4) and the overall 6-month survival for all evaluable patients was 45.8% (95% CI, 30.1-69.8%; Fig. 3B). The median survival time was 5.95 months (95% CI, 4.4-11.4).

The 24 patients with glioblastoma, 17 of whom where evaluable for response, represented a more homogeneous subgroup to study. The 6-month PFS of these patients was 17.7% (95% CI, 6.3-49.3%) and the median time to progression is 1.84 months (95% CI, 1.7-4.6; Fig. 4A). The 6-month overall survival was 47.1% (95% CI, 28.4-77.9%) with a median survival of 5.95 months (95% CI, 4.4-11.4; Fig. 4B). Seven glioblastoma multiforme patients were not evaluable for the primary end points of this study because they had disease progression before the end of the first cycle. If we include these patients in the overall tumor efficacy cohort, the overall 6-month PFS was 12.5%. There was no apparent correlation between clinical outcome and dose of lenalidomide or pharmacokinetic profiles.

Discussion

Thalidomide has been evaluated in a number of phase II trials in patients with recurrent high-grade gliomas and in patients with newly diagnosed glioblastomas in combination with and following standard fractionated radiotherapy (9, 20–22). There was a suggestion of some antiglioma activity with a few minor radiographic responses and several cases of prolonged disease stabilization in patients with recurrent gliomas. In patients with newly diagnosed glioblastoma, overall median survival was equivalent to that seen when carmustine is used in the postradiation adjuvant setting. The lack of clear convincing evidence of significant antiglioma activity, yet the hint of some clinical benefit, has led to the search for drug combinations incorporating thalidomide and more potent thalidomide analogues.

Lenalidomide is a potent IMiDS (immunomodulatory drugs), a class of drugs that are structural and functional analogues of thalidomide. Lenalidomide has more immunomodulating and antiangiogenic activities than thalidomide in various preclinical assays (10, 12, 23, 24). The precise antiangiogenic mechanism of lenalidomide is unclear, although it has been shown that lenalidomide can inhibit vascular endothelial growth factor–, basic fibroblast growth factor–, and tumor necrosis factor-α–induced endothelial cell migration (11). Additionally, it has been suggested that thalidomide analogues like lenalidomide can inhibit tumor- and stroma cell–mediated secretion of vascular endothelial growth factor and basic fibroblast growth factor in preclinical models of multiple myeloma (25). Thus, lenalidomide is a drug of interest to investigate in patients with malignant gliomas.

Lenalidomide has shown significant activity in multiple myeloma and in myelodysplasia with chromosome 5q deletion (18). Dose and toxicity information from these trials may not, however, be relevant to brain tumor patients because bone marrow reserve is generally normal in these patients compared with those with hematologic malignancies. To this end, at least two single agent phase I trials of lenalidomide in patients with solid tumors have partially been reported.

Bartlett et al. (13) conducted a phase I trial of lenalidomide in patients with solid tumors using an intrapatient weekly dose escalation schema of 2 mg/d escalating to 50 mg/d over 4 weeks, although treatment was formally suspended after 4 weeks secondary to toxicity. Thus, dose versus toxicity data were difficult to determine. Tobnya et al. (17) conducted a phase I trial of lenalidomide in patients with refractory solid tumors using a more standard modified Fibonacci design with dose escalation from 5 to 40 mg/d. The investigators observed a significant incidence of grade 1 and grade 2 fatigue, rash, nausea, myalgias, and neutropenia. A number of grade 3 and 4 toxicities, including neutropenia, resulted in modifying the
treatment regimen to administering lenalidomide for 21 days on a 28-day cycle.

Based on these and other trials showing that continuous dosing and higher doses of lenalidomide are not well tolerated, we designed our phase I trial to use the accepted 21 days on and 7 days off dose administration schedule. Our pharmacokinetic analysis revealed that lenalidomide exhibited rapid absorption and displayed relatively good linear kinetics relative to the dose administered and AUC. Additionally, no accumulation of drug in the plasma was observed after multiple doses due to the short terminal half-life of the agent. Finally, EIAEDs, known to induce CYP450 enzymes such as CYP3A4, did not have any effect on lenalidomide metabolism or exposure.

We found that lenalidomide was well tolerated at all doses evaluated. Despite the relatively high doses of lenalidomide used in this trial, we did not observe the neutropenia commonly reported in other trials of lenalidomide. This likely reflects the fact that most glioma patients are less heavily pretreated with chemotherapy and thus have relatively better bone marrow reserve than patients with multiple myeloma and myelodysplastic syndrome, those patients most commonly treated with lenalidomide.

Despite the immunosuppressive activity of lenalidomide, we did not see any significant clinical infections except for one case of herpes zoster of the trigeminal nerve. This infection, however, occurred in a patient on long-term, high-dose glucocorticoids, and thus the relationship of the infection to lenalidomide is uncertain. We did, however, observe five cases of venous thrombosis in patients treated with lenalidomide. Although thalidomide and lenalidomide are known to increase the risk of thromboembolic events in other disease settings, glioma patients are at inherent high risk of developing thromboembolic events independent of treatment (26). Thus, it is impossible to know for certain whether lenalidomide contributed to any of the thrombotic events observed in this trial. Nevertheless, the fact that 18% of patients experienced a thromboembolic event during their relatively short duration of exposure to lenalidomide is of concern and strongly suggests a possible contribution of lenalidomide to the high thrombotic rate seen in this trial.

Twenty-four glioblastoma patients with good performance status (i.e., potentially phase II trial eligible) were treated on this trial, allowing us to carry out an exploratory efficacy analysis of the data despite the fact that the trial was not formally designed to evaluate the antitumor efficacy of lenalidomide. Because there were no objective radiographic responses and no clear improvement in patient symptoms, PFS in conjunction with clinical stability was our major determinant of clinical benefit. As shown in Fig. 3A, the median PFS for all evaluable glioblastoma patients was 1.84 months and the 6-month PFS was 17.7%. If one includes all patients with glioblastoma, including those who had tumor progression during the first cycle, the 6-month PFS was 12.6% (Fig. 4A). This compares to a historical 15% and 9% 6-month PFS for patients accrued to phase I/II single institution and cooperative group trials of drugs subsequently determined to be inactive in glioblastoma, respectively (27, 28). Thus, these preliminary data are not encouraging for the antitumor activity of lenalidomide for recurrent glioblastoma.

The lack of objective radiographic responses and a 6-month PFS of 12.5% are disappointing; however, it remains plausible that a study with a larger cohort of less heavily pretreated patients might give a more favorable outcome. Nevertheless, there are few data to suggest that prior exposure to standard chemotherapeutic agents (almost exclusively alkylating agents) lessens one’s likelihood of responding to an antiangiogenic agent. Indeed, one of our few long-term responders was one of our most heavily pretreated patients, having had four prior chemotherapeutic regimens before his enrollment on this trial.

In addition to prior extensive prior treatment, another possible explanation for the low response rate is that most patients were treated at a dose of lenalidomide below the
maximum tolerated dose. Nevertheless, a true dose-response relationship was not seen in our cohort of patients and has never been shown for thalidomide or lenalidomide. Indeed, one of the few long-term stable disease patients in this study was treated at our lowest dose (2.5 mg/m²). Given that all patients on this trial were treated at doses of lenalidomide that have proved active in lenalidomide-sensitive tumors, there is little compelling data to believe that dose escalations higher than the 20 mg/m² we achieved in this trial would result in greater clinical benefit. Nevertheless, given the preliminary nature of our efficacy data, a larger formal phase II trial of lenalidomide in less heavily pretreated patients using the 20 mg/m² dose, or a higher dose as yet to be established, might be considered reasonable.

We were unable to identify any radiographic or clinical variables that could allow us to prospectively identify patients likely to benefit from lenalidomide. Because the true in situ antitumor and antiangiogenic mechanism of action of lenalidomide remains obscure, no obvious biological end points could be evaluated. Recently, it has been suggested that peripheral endothelial cell and endothelial cell progenitor cells may be surrogate end points of angiogenesis in vivo; however, these assays had not been identified at the time this trial was conducted. The utility of such assays may represent a potential area of exploration should additional trials of lenalidomide be conducted in patients with recurrent glioma.

The minimal antitumor efficacy of lenalidomide observed in our trial suggests that if lenalidomide ultimately does prove to have significant clinical activity, trials with large numbers of patients will likely be required to definitively show such modest activity in a statistically rigorous way. The extensive monetary and patient resources necessary for such a trial might be better used on definitive trials of other more highly active antiangiogenic agents that have recently shown significant radiographic responses and clinical benefit in ongoing clinical trials of patients with recurrent gliomas (i.e., bevacizumab). A more promising approach for the development of lenalidomide in gliomas might be to consider trials of lenalidomide in combination with other chemotherapeutic agents (i.e., temozolomide and nitrosoureas), although additive myelosuppression may ultimately limit the utility of such combinations.

In summary, lenalidomide is generally well tolerated in patients with recurrent primary central nervous system tumors at doses up to and including 20 mg/m², with the only major toxicity being an increased risk of thromboembolic disease. Although confirmatory phase II data may be necessary, lenalidomide does not seem to be a highly effective single agent for patients with recurrent glioblastoma at the doses evaluated. Trials of lenalidomide in combination with other agents may be worth exploring.

Fig. 3. A, PFS for all evaluable patients with 95% CIs. B, overall survival for all evaluable patients with 95% CIs.

Fig. 4. A, PFS for evaluable glioblastoma multiforme (GBM) patients with 95% CIs. B, overall survival for evaluable glioblastoma multiforme patients with 95% CIs.

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References

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