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ORIGINAL REPORT

# Phase I Trial of Lenalidomide in Pediatric Patients With Recurrent, Refractory, or Progressive Primary CNS Tumors: Pediatric Brain Tumor Consortium Study PBTC-018

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## ABSTRACT

### Purpose
A phase I trial of lenalidomide was performed in children with recurrent, refractory, or progressive primary CNS tumors to estimate the maximum-tolerated dose (MTD) and to describe the toxicity profile and pharmacokinetics.

### Patients and Methods
Lenalidomide was administered by mouth daily for 21 days, repeated every 28 days. The starting dose was 15 mg/m$^2$/d orally, and the dose was escalated according to a modified continuous reassessment method. Correlative studies included pharmacokinetics obtained from consenting patients on course 1, day 1, and at steady-state (between days 7 and 21).

### Results
Fifty-one patients (median age, 10 years; range, 2 to 21 years) were enrolled. Forty-four patients were evaluable for dose finding, and 49 patients were evaluable for toxicity. The primary toxicity was myelosuppression, but the MTD was not defined because doses up to 116 mg/m$^2$/d were well-tolerated during the dose-finding period. Two objective responses were observed (one in thalamic juvenile pilocytic astrocytoma and one in optic pathway glioma) at dose levels of 88 and 116 mg/m$^2$/d. Twenty-three patients, representing all dose levels, received ≥ six cycles of therapy. Pharmacokinetic analysis demonstrated that the lenalidomide area under the concentration-time curve from 0 to 24 hours and maximum plasma concentration increased with dosage over the range studied.

### Conclusion
Lenalidomide was tolerable in children with CNS tumors at doses of 116 mg/m$^2$/d during the initial dose-finding period. The primary toxicity is myelosuppression. Antitumor activity, defined by both objective responses and long-term stable disease, was observed, primarily in patients with low-grade gliomas.

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## INTRODUCTION

Tumors of the CNS are the most common solid tumors of childhood, representing approximately 18% of all childhood cancers.[1] The overall 5-year survival rate for this population is approaching 75%, but brain tumors, particularly malignant gliomas, remain the leading cause of death from solid tumors in children.[2] Although some tumors are amenable to surgery, radiation, and cytotoxic chemotherapeutic agents, others are resistant, and new approaches are needed.

Lenalidomide (CC5013, Revlimid; Celgene, Summit, NJ) is a potent structural and functional thalidomide analog that belongs to a class of agents known as immunomodulatory drugs. In preclinical testing, lenalidomide demonstrates antiangiogenic, proapoptotic, and anti-inflammatory activities in addition to its immunomodulatory effects.[3-7] This agent is approved by the US Food and Drug Administration for the treatment of patients with myelodysplastic syndrome associated with a del(5q) cytogenetic abnormality and, in combination with dexamethasone, for the treatment of multiple myeloma. Lenalidomide is being evaluated in a number of adult solid tumors, including lymphomas,[8] renal cell carcinoma,[9] melanoma, and CNS tumors.[10] Although the exact antitumor mechanism is not completely understood, lenalidomide has direct effects on tumor cells, effects

on the tumor microenvironment, and immunomodulatory effects that include alteration of ligand-induced cellular responses, modulation of cytokine responses, altered production of growth factors, and costimulation of T-cell activation.[11,12]

Clinical trials of lenalidomide have been performed in adults using several different schedules.[10,13-17] Common adverse effects include neutropenia, thrombocytopenia, GI toxicities, skin toxicity, and fatigue.[16-19] Myelosuppression is the most common toxicity and the dose-limiting toxicity (DLT) and is more frequently observed at doses $\geq$ 50 mg/m$^2$/d. Other toxicities are generally mild, although a possible increased risk of thrombosis has been reported.[10,20] In the phase I dose-escalation trial of lenalidomide in adults with recurrent CNS tumors, a predetermined maximum dose of 40 mg daily for 21 days followed by a 1-week rest was well-tolerated.[10] Children with recurrent, refractory, or progressive primary CNS tumors were treated with lenalidomide to estimate the maximum-tolerated dose (MTD), describe toxicities, and evaluate pharmacokinetics in this population.

## PATIENTS AND METHODS

### Eligibility

Patients $\leq$ 21 years old with recurrent, refractory, or progressive primary CNS tumors were eligible. Patients were required to have a performance score (Lansky or Karnofsky) of $\geq$ 60; be able to swallow capsules; and have adequate bone marrow function with absolute neutrophil count (ANC) $\geq$ 1,000/$\mu$L, hemoglobin $\geq$ 8 g/dL, and platelets $\geq$ 100,000/$\mu$L. Patients with overt renal, hepatic, or pulmonary disease; patients at risk for thromboembolic events (ie, history of thromboembolic event unrelated to central line or family history of thrombophilia); and patients who were pregnant or breast-feeding were excluded.

The institutional review boards of each participating Pediatric Brain Tumor Consortium institution approved the protocol before initial patient enrollment, and continuing approval was maintained throughout the study. Patients or their legal guardians gave written informed consent, and assent was obtained as appropriate at the time of enrollment.

### Treatment Regimen and Dose Escalation

Lenalidomide was supplied by the Pharmaceutical Management Branch of the National Cancer Institute's Cancer Therapy Evaluation Program (CTEP). Eligible patients received lenalidomide capsules orally daily for 21 days followed by a 7-day rest. The dose-escalation schema is provided in Table 1. No intrapatient dose escalation was allowed.

### Definition of MTD and DLT

Dose escalation followed a modified continual reassessment method.[21] Using this method, the MTD was defined as the dose at which the model estimated 25% of patients would experience a DLT. Toxicity data from the first treatment course (ie, 28 days) was used to determine the MTD. Toxicities were graded according to the Cancer Therapy Evaluation Program common toxicity criteria version 3.0. Nonhematologic DLT was defined as any grade $\geq$ 4 toxicity, any grade 3 toxicity (with the exception of nausea or vomiting controlled by antiemetics, hepatotoxicity that returned to $\leq$ grade 1 within 7 days, and fever/infection of $<$ 5 days in duration), any grade 2 toxicity that persisted for more than 3 days and required treatment interruption, and any adverse event that required treatment interruption for more than 3 days and recurred on rechallenge. Hematologic DLT was defined as grade 4 neutropenia ($<$ 500/$\mu$L) or thrombocytopenia ($<$ 25,000/$\mu$L) occurring during the dosing period, grade 4 neutropenia of $\geq$ 5 days in duration occurring during the 7-day rest period, the requirement for two or more platelet transfusions for platelet counts less than 50,000/$\mu$L during the first course, or $\geq$ 1 week delay in starting subsequent cycles as a result of neutropenia or thrombocytopenia.

### Dose Modification for Toxicity

Lenalidomide was held for ANC less than 500/$\mu$L or platelet count less than 25,000/$\mu$L during the dosing period until the ANC returned to $\geq$ 1,000/$\mu$L and the platelet count was $\geq$ 100,000/$\mu$L. Patients with hematologic DLT were treated on the next lowest dose level for subsequent courses. Patients who experienced a second hematologic DLT after dose reduction were removed from treatment. Lenalidomide was also held for patients who experienced a nonhematologic DLT until the toxicity returned to baseline or $\leq$ grade 1. These patients were subsequently treated on the next lower dose level. A patient was removed from treatment if the same toxicity recurred and met the definition of DLT after dose reduction or if the toxicity did not return to baseline after 7 days of withholding the drug.

### Definition of Response

Complete response was defined as complete resolution of all tumor and mass effect, on a stable or decreasing dose of corticosteroids, accompanied by a stable or improving neurologic examination and maintained for at least 6 weeks. Partial response was defined as a $\geq$ 50% reduction in tumor size based on the area calculated using the maximal perpendicular cross-sectional measurements on magnetic resonance imaging (MRI), on a stable or decreasing dose of corticosteroids, accompanied by a stable or improving neurologic examination and maintained for at least 6 weeks. Stable disease was defined as a neurologic examination that was at least stable, a maintenance corticosteroid dose that was not increased to maintain neurologic function, and MRI/computed tomography imaging that did not meet the criteria for partial response or progressive disease. Progressive disease was defined as progressive neurologic abnormalities or worsening neurologic status not explained by causes

**Table 1.** Dosage-Escalation Schema for Lenalidomide

| Dose Level | Lenalidomide Dosage (mg/m$^2$/d for 21 days) | No. of Patients Entered | No. of Patients Assessable for Toxicity | No. of DLTs |
|---|---|---|---|---|
| 1 | 15 | 4 | 3 | 0 |
| 2 | 20 | 4 | 4 | 1 |
| 3 | 25 | 3 | 4* | 0 |
| 4 | 32 | 4 | 2* | 0 |
| 5 | 40 | 3 | 3 | 0 |
| 6 | 52 | 3 | 3 | 0 |
| 7 | 68 | 7 | 6 | 1 |
| 8 | 88 | 4 | 3 | 0 |
| 9 | 101 | 5 | 4 | 0 |
| 10 | 116 | 14 | 12 | 0 |

Abbreviation: DLTs, dose-limiting toxicities.
*One patient entered at dose level 4 was mistakenly dosed at 25 mg/m$^2$/d. Although evaluable at the 25 mg/m$^2$/d dose level, an additional patient was enrolled at 32 mg/m$^2$/d.

unrelated to tumor progression, the appearance of a new lesion, or a greater than 50% increase in the bidimensional measurement on MRI over the smallest sum observed. Because lenalidomide is a cytostatic agent and a lag time may exist between the initiation of therapy and antitumor effect, patients were allowed to remain on therapy if the tumor had increased up to 50% in size from baseline unless they exhibited significant clinical symptoms from any degree of tumor enlargement. Tumor measurements were determined by the treating institution.

### Pharmacokinetics

Lenalidomide pharmacokinetic studies were performed in consenting patients on day 1 and between days 7 and 21 of course 1. To measure the lenalidomide disposition, serial blood samples (2 mL) were collected in heparinized tubes before the dose and at 1, 2, 4, 8, and 24 (± 2) hours after administration. Samples were processed by solid-phase extraction, and their lenalidomide concentrations were analyzed using a high-performance liquid chromatography/mass spectroscopy method.[22] The lower limit of quantitation was 5.0 ng/mL, the interday coefficient of variation was ≤ 3.8%, and the intraday coefficient of variation was ≤ 4.5%.

Lenalidomide concentration-time data were modeled by nonlinear mixed-effects modeling as implemented in NONMEM VI.[23] A one-compartment model (ADVAN 2) was fit to plasma concentration-time data from all individuals simultaneously using first-order conditional estimation with interaction. After estimation of the population parameters, individual pharmacokinetic parameters were obtained using a post hoc analysis. Pharmacokinetic parameters estimated included apparent volume of the central compartment, elimination rate constant, and absorption rate constant. Apparent oral clearance and half-life were calculated by standard equations, and the area under the concentration-time curve (AUC) for each patient was calculated by integration of the simulated concentration-time data from model estimates. The time to maximum concentration and maximum concentration were reported from the observed plasma concentration data.

## RESULTS

### Patient Characteristics

Fifty-one patients with progressive, refractory, or recurrent primary CNS tumors were enrolled between February 2005 and February 2008 (Table 2). Five patients were not assessable for estimating the MTD for the following reasons: rapidly progressive disease (n = 2), noncompliance (n = 1), missed doses as a result of unrelated urosepsis (n = 1), and withdrawal because of difficulty swallowing capsules (n = 1). Eight additional patients were enrolled at the highest dose level to better characterize the toxicity profile; two of these patients were not assessable for toxicity because of withdrawal of consent before starting therapy or because laboratory tests were not performed as required by protocol. Therefore, decisions to dose escalate were based on the toxicities from 38 patients during the dose-finding period, with six additional patients treated at the highest dose level. The number of patients entered at each dose level is listed in Table 1.

**Table 2.** Patient Demographics and Clinical Characteristics

| Demographic or Clinical Characteristic | No. of Patients |
|---|---|
| Enrolled | 51 |
| Assessable | 44 |
| Age, years | |
| Median | 10.4 |
| Range | 2.7-21.6 |
| Sex | |
| Male | 26 |
| Female | 25 |
| No. of prior chemotherapy regimens (n = 49) | |
| Median | 3 |
| Range | 0-7 |
| Craniospinal XRT | 8 |
| Prior thalidomide | 4 |
| Diagnosis | |
| HGG | 6 |
| BSG | 2 |
| LGG | 26 |
| Glioma, NOS | 1 |
| PNET/MBL | 6 |
| EP | 9 |
| Other | 1 |

Abbreviations: XRT, radiation therapy; HGG, high-grade glioma; BSG, brainstem glioma; LGG, low-grade glioma; NOS, not otherwise specified; PNET/MBL, primitive neuroectodermal tumor/medulloblastoma; EP, ependymoma.

### Toxicity

Two DLTs were observed. One occurred at dose level 2 (20 mg/m$^2$/d) and consisted of grade 4 chest pain and elevated troponin levels in a 15-year-old girl subsequently found to have factor V Leiden heterozygosity and lupus anticoagulant. The second DLT occurred in a patient on dose level 7 (68 mg/m$^2$/d) and consisted of grade 4 fatigue. On investigation, this patient was found to have increased intracranial pressure and disease progression. No other DLTs occurred in the dose-finding period.

The most common toxicity observed during the dose-finding period was myelosuppression, which was observed in more than 50% of patients during course 1 and was generally mild (grades 1 and 2). Neutropenia, lymphopenia, anemia, and thrombocytopenia were observed at all dose levels (Table 3). Most episodes were ≤ grade 2, although one of three patients at 52 mg/m$^2$/d, one of six patients at 68 mg/m$^2$/d, and four of 12 patients at 116 mg/m$^2$/d had grade 3 neutropenia. Other common adverse effects included metabolic and electrolyte laboratory abnormalities; GI toxicity including nausea, vomiting, diarrhea, and constipation; fatigue; rash; muscle cramping; and headache. With the exception of the two DLTs, no grade ≥ 4 toxicities occurred during course 1.

Although the dose-finding period was defined during course 1, 34 patients received more than one course of therapy, 23 patients received ≥ six courses, and 10 patients received ≥ 12 courses, allowing assessment of long-term tolerability. Of note, 13 of 29 patients discontinued therapy between courses 4 and 18 for adverse events rather than disease progression. The most common chronic toxicity was myelosuppression. Although patients who discontinued treatment because of toxicity represented all dose levels, withdrawal secondary to toxicity was more common at the higher dose levels, with seven of 13 patients treated at the 116 mg/m$^2$/d dose level discontinuing therapy between courses 3 and 11 for myelosuppression (Appendix Tables A1 and A2, online only).

### Responses

Forty-seven patients were evaluable for response. Two partial responses were observed, including a patient with juvenile pilocytic astrocytoma treated at 88 mg/m$^2$/d who received 18 courses and a patient with an optic pathway glioma treated at the 116 mg/m$^2$/d dose level who received 11 courses. Both patients were removed from the study as a result of myelosuppression. Fifty-two percent of patients (n = 23), primarily patients with low-grade gliomas,

  

**Table 3.** Toxicities Experienced by at Least 10% of Patients During the Dose-Limiting Toxicity Evaluation Period (course 1)

| Toxicity | Total No. of Patients With Toxicity | Grade (No. of patients) | | | |
|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 |
| Leukocytes (total WBC) | 24 | 13 | 10 | 1 | 0 |
| Neutrophils/granulocytes (ANC/AGC) | 24 | 5 | 13 | 6 | 0 |
| Fatigue (asthenia, lethargy, malaise) | 14 | 9 | 4 | 0 | 1 |
| Hemoglobin | 14 | 13 | 1 | 0 | 0 |
| Lymphopenia | 14 | 10 | 3 | 1 | 0 |
| Platelets | 12 | 12 | 0 | 0 | 0 |
| Pain | 11 | 7 | 2 | 2 | 0 |
| ALT | 7 | 4 | 2 | 1 | 0 |
| Rash/desquamation | 6 | 6 | 0 | 0 | 0 |
| Diarrhea | 5 | 5 | 0 | 0 | 0 |
| Potassium, serum low (hypokalemia) | 5 | 5 | 0 | 0 | 0 |
| Dizziness | 2 | 1 | 0 | 1 | 0 |
| Cardiac ischemia/infarction | 1 | 0 | 0 | 0 | 1 |
| Cardiac troponin I | 1 | 0 | 0 | 0 | 1 |

Abbreviations: ANC, absolute neutrophil count; AGC, absolute granulocyte count.

had long-term (≥ six courses) stable disease. Of note, the 12-month progression-free survival (PFS) rate for patients with low-grade glioma was 67% ± 13%.

### *Pharmacokinetics*

Plasma samples were collected from 23 consenting patients, but only 18 patients had adequate data for pharmacokinetic modeling (eg, five patients only had a predose sample and one other sample). Of the 23 consenting patients, 10 had studies between days 15 and 21. A representative lenalidomide plasma concentration-time plot is shown in Figure 1. A summary of the lenalidomide pharmacokinetic parameters determined on course 1, day 1 in relation to lenalidomide dosage is presented in Table 4. The median lenalidomide plasma half-life and apparent oral clearance were 2.5 hours (range, 0.9 to 4.2 hours) and 11.4 L/h/m$^2$ (range, 5.1 to 33.9 L/h/m$^2$), respectively. The lenalidomide AUC from 0 to 24 hours and maximum concentration increased with the actual lenalidomide dosage administered over the dosage range studied (Figs 2A and 2B). In the subset of patients with repeat studies, no accumulation was observed, which was expected given the relatively short half-life.

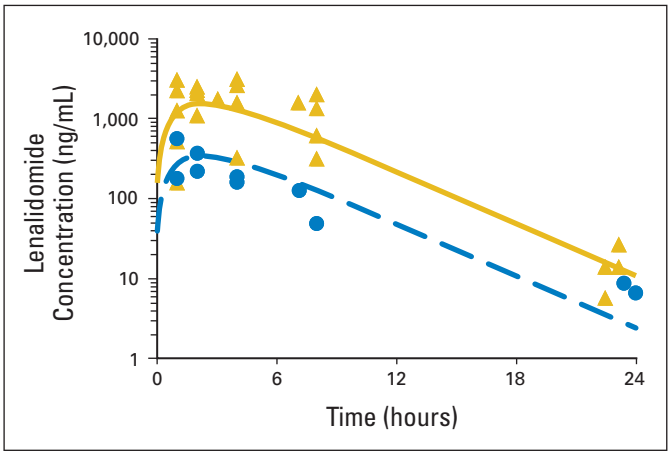


**Fig 1.** Concentration-time curve for lenalidomide at the 25 mg/m$^2$ dosage (blue circles, n = 2) and 116 mg/m$^2$ dosage (gold triangles, n = 5). The lines are from the population model–predicted concentrations at those dosages (dashed blue line for 25 mg/m$^2$ and solid gold line for 116 mg/m$^2$).

## DISCUSSION

Lenalidomide is well tolerated in pediatric patients with CNS tumors at doses up to 116 mg/m$^2$/d. The MTD was not established. The major toxicity observed in our study was myelosuppression, similar to the adult trials. There was no clear dose relationship with acute toxicity. However, long-term tolerability and toxicity may be dose limiting.

Previous investigational studies of lenalidomide have not clearly established a dose relationship with acute toxicity. Several of the early studies were performed in patients with bone marrow disease or in a population that was heavily pretreated, complicating the assessment of myelosuppression as a primary toxicity. In a phase I clinical trial of lenalidomide in patients with heavily pretreated multiple myeloma (including autologous stem-cell transplantation in 15 of 24 patients) treated for 28 days at doses of 5 to 50 mg/d, one patient treated at 10 mg/d had a DLT characterized by grade 3 leukopenia and neutropenia; no other DLTs were observed in the first course of therapy, including in 13 patients treated at 50 mg/d.[24] However, 12 of 13 patients treated at 50 mg/d developed grade 3 or 4 myelosuppression after day 28. In a study of adult patients with advanced cancers, 20 heavily pretreated patients were enrolled and tolerated lenalidomide doses up to 50 mg/d.[19] The majority of adverse events were classified as grade 1 or 2, and no serious adverse events were attributed to lenalidomide therapy. In a phase I trial of lenalidomide in adults with recurrent ovarian and primary peritoneal carcinoma, patients were treated with 25 mg/d for 21 days of a 28-day cycle.[14] Twenty patients were enrolled and received 70 completed cycles of therapy. The majority of events were grade 1 or 2. No grade 4 toxicities were observed.

In a dose-escalation study of lenalidomide, adults with solid tumors (primarily melanoma and renal cell carcinoma) received daily lenalidomide doses of 5 to 150 mg/d.[17] Adverse events, including myelosuppression, were not obviously related to dose. In a study of

**Table 4.** Summary of Lenalidomide Pharmacokinetic Parameters From Course 1, Day 1

| Dosage ($mg/m^2$) | No. of Patients | Pharmacokinetic Parameters | | | | | |
|---|---|---|---|---|---|---|---|
| | | $C_{max}$ (ng/mL) | $T_{max}$ (hours) | $AUC_{0\to24}$ (ng/mL · h) | $AUC_{0\to\infty}$ (ng/mL · h) | $t_{1/2}$ (hours) | Cl/F ($L/h/m^2$) |
| 20 | 3 | | | | | | |
| Median | | 224 | 2.0 | 1,584 | 1,599 | 3.3 | 12.6 |
| Range | | 210-275 | 1.0-2.1 | 1,032-1,711 | 1,033-1,730 | 2.1-3.3 | 12.4-19.9 |
| 25 | 2 | 225, 544 | 1.0, 2.0 | 1,796, 1,845 | 1,834, 1,846 | 1.9, 4.1 | 13.1, 14.9 |
| 32 | 1 | 993 | 1.0 | 2,656 | 2,657 | 1.81 | 13.2 |
| 40 | 2 | 532, 1,050 | 1.0, 2.0 | 2,503, 2,752 | 2,507, 2,752 | 0.9, 2.4 | 15.0, 15.5 |
| 52 | 1 | 858 | 8.0 | 9,996 | 10,328 | 4.2 | 19.9 |
| 68 | 2 | 372, 1,650 | 1.9, 2.0 | 1,968, 10,731 | 1,970, 10,914 | 2.8, 3.9 | 6.4, 33.8 |
| 88 | 2 | 1,410, 2,530 | 2.0, 2.0 | 8,713, 10,883 | 8,775, 10,886 | 2.1, 3.2 | 7.8, 10.1 |
| 116 | 5 | | | | | | |
| Median | | 2,540 | 4.0 | 15,673 | 15,771 | 2.6 | 7.3 |
| Range | | 1,950-3,060 | 1.1-7.9 | 11,055-19,760 | 11,072-20,167 | 2.1-3.1 | 5.8-10.3 |

Abbreviations: $C_{max}$, maximum plasma concentration; $T_{max}$, time of maximum plasma concentration; $AUC_{0\to24}$, area under the plasma concentration-time curve from 0 to 24 hours; $AUC_{0\to\infty}$, area under the plasma concentration-time curve from time 0 to infinity; $t_{1/2}$, half-life; Cl/F, apparent oral clearance.

adults with refractory metastatic cancer, dosing for 21 of 28 days was better tolerated.[22] Doses up to 35 mg/d (21 days on, 7 days off) were well tolerated, and the authors concluded that tolerability to myelosuppression may be better in patients without hematologic malignancies. In a phase I study in adults with recurrent high-grade gliomas,[10] lenalidomide 40 mg/d for 21 days was well tolerated, and no MTD was defined. Myelosuppressive events consisted of one episode of grade 2 leukopenia at dose level 1 (2.5 $mg/m^2$/d for 21 days, with a 7-day rest) and one episode of grade 3 neutropenia at dose level 1.

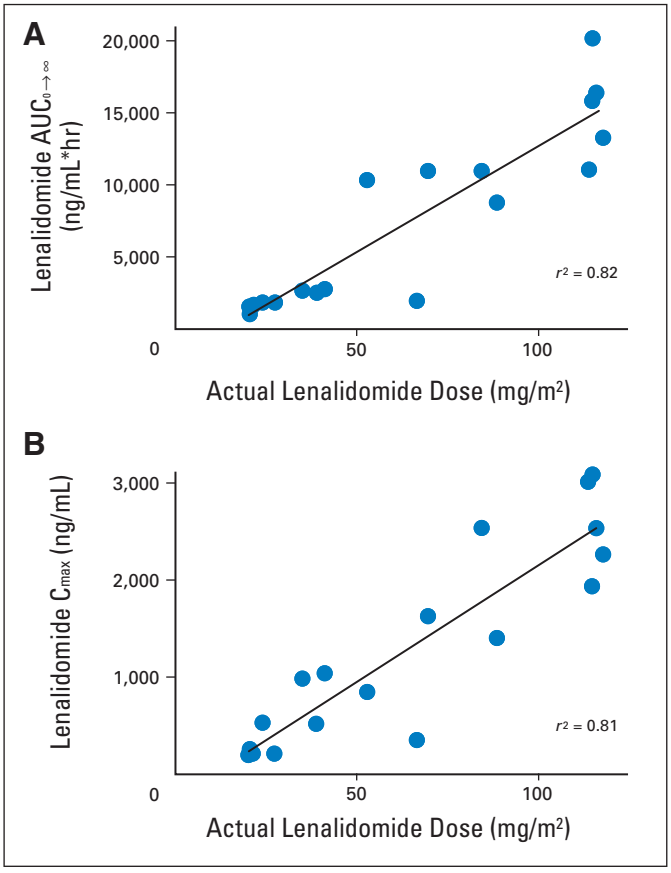


**Fig 2.** Plot of lenalidomide exposure (area under the curve [AUC] and maximum concentration [$C_{max}$]) versus actual dosage. Exposure to lenalidomide (A) AUC from time 0 to infinity ($AUC_{0\to\infty}$) and (B) $C_{max}$ increases with actual lenalidomide dosage ($mg/m^2$/d). Each blue circle represents an AUC or $C_{max}$ value for a patient.

A phase I study of lenalidomide was recently performed by the Children's Oncology Group in pediatric patients with relapsed or refractory solid tumors or myelodysplastic syndrome (ADVL0319).[25] The primary objectives were to determine the MTD and recommended phase II dose for children with refractory solid tumors and describe the toxicities in this population. Doses up to 70 $mg/m^2$/d for 21 days followed by a 7-day rest were evaluated. Although six episodes of DLT were observed, they were sporadic and not clearly associated with dose. The MTD was not reached. The majority of patients on this study did not receive more than one course of therapy.

The disposition of lenalidomide in children was similar to that observed in adults.[10,24] Absorption was relatively slow, with a time to maximum concentration ranging from 2 to 4 hours (1 to 4 hours in adults). In adults, the lenalidomide systemic exposure (AUC from time 0 to infinity) increased with dosage,[10] but a relationship only up to 20 $mg/m^2$ has been reported. In the present study, we observed a linear relationship between lenalidomide systemic exposure (AUC from time 0 to infinity) and lenalidomide actual dosage up to a dosage of 116 $mg/m^2$. Similarly, we observed a relationship with lenalidomide maximum concentration and actual dosage, which has been observed in adult studies. As with other oral drugs studied in children, we observed a wide range (approximately six-fold) in lenalidomide apparent oral clearance.

Early-phase clinical trials of noncytotoxic (eg, antiangiogenic) agents in patients with brain tumors are complicated by several issues. Conventional end points in phase I trials are defined by predetermined toxicity criteria to define an MTD or, more recently, by biologic end points to define a biologically effective dose. Standard phase I studies are designed to best identify acute, rather than long-term, toxicities. Antiangiogenic agents frequently have little acute toxicity and may need to be administered chronically. They may be effective at doses well below the MTD, and therefore, dose escalations to the MTD may be unnecessary. However, defining a biologically effective dose is

  

difficult because there is a lack of validated biologic surrogate markers. In the case of lenalidomide, this is further complicated by the lack of complete understanding of its antitumor mechanisms.

There is preliminary evidence of activity of lenalidomide in this population, particularly in patients with progressive low-grade gliomas who had a 12-month PFS rate of 67% ± 13% on this study. Although this could be attributed to the inconsistent growth rates of these tumors, all patients had recurrent, refractory, or progressive disease at study entry, and this 12-month PFS rate compares favorably to other studies in this population.[26] It is unclear whether this antitumor activity is dose related, although there is some suggestion that this is the case given that the two objective responses occurred at the higher dose levels (88 and 116 mg/m$^2$/d). The exact antitumor mechanism of action is unknown, although potential mechanisms have been identified, including induction of apoptotic signals[27] and inhibition of angiogenesis.

In summary, lenalidomide is relatively well tolerated in pediatric patients with recurrent, refractory, and progressive CNS tumors at doses up to 116 mg/m$^2$/d, particularly in the acute setting, although long-term toxicity may be limiting. No MTD was defined. As in adult studies, the primary toxicity was myelosuppression. Lenalidomide seems to have activity in this patient population. It is unclear whether toxicity and antitumor activity are dose related. Further trials of lenalidomide in the pediatric brain tumor population are planned.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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