Original Article

Phase 1 Study of an Oxaliplatin and Etoposide Regimen in Pediatric Patients With Recurrent Solid Tumors

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BACKGROUND: The combination of a platinating agent and etoposide has induced responses in various pediatric tumors. The study estimated the maximum tolerated dose (MTD) of an oxaliplatin and etoposide regimen in children with recurrent solid tumors. **METHODS:** Oxaliplatin was administered on Day 1 and etoposide on Days 1 to 3 of each 21-day course. Cohorts of 3 to 6 patients were enrolled at 3 dose levels: 1) oxaliplatin at a dose of 130 mg/m^2 and etoposide at a dose of 75 mg/m^2, 2) oxaliplatin at a dose of 130 mg/m^2 and etoposide at a dose of 100 mg/m^2, and 3) oxaliplatin at a dose of 145 mg/m^2 and etoposide at a dose of 100 mg/m^2. Calcium and magnesium infusions were used at dose level 3 in an attempt to escalate the oxaliplatin dose past the single-agent MTD. **RESULTS:** The 16 patients received a total of 63 courses. At dose level 1, dose-limiting epistaxis, neuropathy, and neutropenia occurred in 1 of 6 patients. No dose-limiting toxicity (DLT) occurred at dose level 2 (n = 6). At dose level 3, 2 of 4 patients experienced dose-limiting neutropenia; none experienced grade 3 or 4 acute neuropathy. Six patients required prolongation of the oxaliplatin infusion because of acute sensory neuropathy. Responses were observed in patients with medulloblastoma (1 complete response) and pineoblastoma (1 partial response); 3 others with atypical teratoid rhabdoid tumor, ependymoma, and soft tissue sarcoma had prolonged disease stabilization. **CONCLUSIONS:** The MTD of this regimen was found to be oxaliplatin at a dose of 130 mg/m^2 given on Day 1 and etoposide at a dose of 100 mg/m^2/d given on Days 1 to 3. Neutropenia was found to be the DLT. Calcium and magnesium infusions did not allow escalation of the oxaliplatin dose. The combination was well-tolerated and demonstrated antitumor activity. **Cancer 2009;115:655–64. © 2008 American Cancer Society.**

KEY WORDS: clinical trial, phase 1, oxaliplatin, etoposide, child, adolescent.

Responses to the combination of a platinating agent with etoposide have been reported for a variety of pediatric tumors, including medulloblastoma,[1-4] neuroblastoma,[5-7] Wilms tumor,[8,9] germ cell tumor,[10,11] rhabdomyosarcoma,[9,12,13] and retinoblastoma.[14] Carboplatin, which is much less ototoxic[15-18] and nephrotoxic[19-21] than cisplatin, is now used to treat many pediatric tumors. However, carboplatin is

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significantly myelotoxic, inducing thrombocytopenia that often requires platelet transfusions and that can cause severe hemorrhagic complications.[22-26] Therefore, platinating agents that may offer equivalent antitumor activity and a more acceptable spectrum of toxicity are of interest.

Oxaliplatin, *trans*-l-1,2-diaminocyclohexane (DACH) oxalatoplatinum, is a platinum agent that forms DACH-platinum adducts with DNA.[27] In preclinical models, oxaliplatin is comparable to cisplatin in efficacy and is active against several cisplatin-resistant cell lines.[28-30] The cytotoxicity of oxaliplatin in cisplatin-resistant cells may be due to the poor recognition of the DACH-containing adducts by cellular DNA repair pathways.[27,31-33] In clinical trials, oxaliplatin has been reported to cause little ototoxicity, nephrotoxicity, or myelosuppression.[34-40] Therefore, oxaliplatin may be useful in sparing patients who require a platinating agent from the toxicities of cisplatin, and also may be effective in patients whose tumors are refractory to cisplatin. Furthermore, if oxaliplatin can be safely combined with etoposide, the combination may be as potent as the combination of cisplatin or carboplatin with etoposide.

As noted above, the combination of a platinating agent and etoposide is active against many tumor types. In vitro, cisplatin and etoposide demonstrate at least additive and, in some systems, supra-additive, cytotoxicity.[41-43] The cellular mechanism of this interaction is unclear, but it is postulated that inhibition of topoisomerase II by etoposide decreases the ability of the cell to repair the DNA damage caused by cisplatin (as demonstrated with the combination of cisplatin and another topoisomerase II inhibitor, novobiocin[44]). When etoposide was combined with topotecan in a colon cancer xenograft model,[45] pretreatment with topotecan was found to increase cellular levels of topoisomerase II and increase sensitivity to etoposide. When topotecan was removed, the levels of topoisomerase II returned to baseline as did the etoposide sensitivity. In addition, in a model of mouse mammary carcinoma, increased levels of topoisomerase II were found to be correlated with increased etoposide sensitivity.[46] In colon carcinoma cell lines, treatment with oxaliplatin caused an increase in topoisomerase II levels.[47] This effect of oxaliplatin on topoisomerase II levels may increase the sensitivity of tumor cells to the effects of etoposide, producing a clinically synergistic regimen similar to the combinations of cisplatin with etoposide.

The most common toxicity caused by oxaliplatin is peripheral sensory neuropathy, both acutely, around the time of the infusion, and chronically, with higher cumulative doses.[48] The acute neuropathy that is most often dose-limiting is pharyngolaryngeal dysesthesia (tingling, numbness, and a sensation of having a lump in the throat). This sensation is often accompanied by dysesthesia/paresthesia in the extremities and is exacerbated by exposure to cold temperatures.[49] Acute sensory neuropathy was the dose-limiting toxicity (DLT) in both of the pediatric phase 1 trials of oxaliplatin.[36,40] To our knowledge the mechanism of oxaliplatin-related neuropathy has not been entirely elucidated to date, but there is evidence that the oxalate molecule released during the metabolism of oxaliplatin may affect the function of neuronal voltage-gated Na^+ channels.[50,51] Carbamazepine, which is a Na^+ channel blocker, can ameliorate this acute neurotoxicity without significant pharmacokinetic interactions with oxaliplatin.[52] However, because carbamazepine can induce cytochrome P450 enzymes, there is a risk of significant pharmacokinetic interaction when administered with etoposide.[53] Other investigators have used calcium and magnesium infusions to chelate the oxalate and thereby reduce oxaliplatin-related sensory neuropathy.[53]

We conducted a pediatric phase 1 trial of the combination of oxaliplatin and etoposide using an oxaliplatin dose that was previously determined to be safe in children (130 mg/m^2 every 3 weeks).[40] Because treatment with oxaliplatin may increase topoisomerase II levels and thereby increase etoposide sensitivity, oxaliplatin was administered first on Day 1 with etoposide given on Days 1 to 3. There are several platinum and etoposide regimens described in children.[1-5,9,12] We chose a 3-day regimen of etoposide to decrease the risk of toxicity because there is no clear benefit to a 5-day regimen. Calcium and magnesium infusions were used with oxaliplatin doses higher than the single-agent maximum tolerated dose (MTD) in an attempt to advance the oxaliplatin dose by ameliorating oxaliplatin-related neurotoxicity.

MATERIALS AND METHODS

Eligibility

Patients $\leq$21 years of age with a histologically verified solid tumor that was refractory to conventional therapy, a

Karnofsky or Lansky performance score ≥50%, and life expectancy >8 weeks were eligible for enrollment if they had recovered from the acute toxic effects of prior therapy; had no evidence of active graft-versus-host disease; and had not received 1) myelosuppressive therapy within 3 weeks (nitrosourea within 6 weeks); 2) hematopoietic growth factors or biologic (antineoplastic) agents within 1 week; 3) small-port palliative radiotherapy within 2 weeks; 4) total body, craniospinal, or whole-pelvis radiation within 3 months; 5) other substantial bone marrow radiation within 6 weeks; 6) allogeneic stem cell transplantation within 6 months; or 7) previous oxaliplatin exposure. Organ function requirements were as follows: for bone marrow, an absolute neutrophil count (ANC) ≥1000/μL, a platelet count ≥100,000/μL (transfusion-independent), and a hemoglobin ≥8 g/dL (bone marrow involvement with tumor allowed if criteria met); for renal function, a normal serum creatinine level for age or a glomerular filtration rate ≥80 mL/min/1.73 m^2, serum potassium and sodium abnormalities ≤ grade 1 (supplementation allowed), and normal serum magnesium and calcium values (supplementation allowed); for hepatic function, hyperbilirubinemia ≤ grade 1, hypoalbuminemia ≤ grade 2, and alanine aminotransferase elevation ≤ grade 2; for cardiac function, a normal electrocardiogram and shortening fraction ≥27% by echocardiography; for pulmonary function, no dyspnea at rest, no exercise intolerance, and oxygen saturation >94% on room air; and for the nervous system, seizure disorders absent or well controlled and peripheral neurotoxicity ≤ grade 1. Pregnant or breastfeeding patients were excluded, and agreement to use effective contraception was required if patients were of reproductive age. Patients receiving other investigational agents, anticancer agents, or anticonvulsants that interact with CYP3A (ie, phenytoin, carbamazepine, oxcarbazepine, phenobarbital) were excluded. Additional exclusion criteria were uncontrolled infection and life-threatening hypersensitivity to platinum-containing agents.

Written informed consent was obtained from patients, parents, or legal guardians, with assent as appropriate. The protocol was approved by the St. Jude Institutional Review Board.

Drug Administration and Study Design

Oxaliplatin (Eloxatin; Sanofi-aventis, Bridgewater, NJ [supplied by the Cancer Therapy Evaluation Program (CTEP), the National Cancer Institute (NCI), Bethesda, MD (NSC 266046, IND 57,004)]), was reconstituted in 250 to 500 mL of sterile water with 5% dextrose and infused intravenously over 2 hours after an antiemetic. Etoposide, obtained from commercial suppliers, was infused intravenously over 1 hour daily for 3 days, beginning immediately after the oxaliplatin infusion.

The initial dose level was oxaliplatin at a dose of 130 mg/m^2 and etoposide at a dose of 75 mg/m^2/day. The second dose level was oxaliplatin at a dose of 130 mg/m^2 and etoposide at a dose of 100 mg/m^2/day. The third dose level was oxaliplatin at a dose of 145 mg/m^2 and etoposide at a dose of 100 mg/m^2/day. To explore whether the latter dose of oxaliplatin, which is greater than the single-agent MTD, could be tolerated, calcium and magnesium infusions were administered to ameliorate oxaliplatin-associated neurotoxicity.[53] Calcium chloride at a dose of 10 mg/kg (maximum dose, 1 g) was infused over 30 minutes, and magnesium sulfate at a dose of 25 mg/kg (maximum dose, 1 g) was then infused over 30 minutes before each oxaliplatin infusion and after etoposide infusion on Day 1. The calcium infusions were not given if the patient's serum calcium concentration was ≥10.5 mg/dL; the magnesium infusions were omitted if the serum magnesium was ≥2 mEq/L. There was no intrapatient dose escalation. Patients with reversible grade 3 toxicity (with the exception of acute dysesthesia) or grade 4 electrolyte or hematologic toxicity (lasting >7 days) could continue on protocol therapy with a reduction to the next lower dose level. For patients treated at dose level 1, the dose of oxaliplatin was reduced to 100 mg/m^2. Patients with grade 3 acute dysesthesia, including pharyngolaryngeal dysesthesia, received subsequent doses infused over 6 hours. If the dysesthesia recurred, then the dose of oxaliplatin was decreased by 1 dose level. Recurrent toxicity requiring a second dose reduction resulted in removal from protocol therapy.

At least 3 evaluable patients were treated at each dose level. If 1 of 3 patients at a given level experienced a DLT, 3 more were accrued at that level. If ≥2 of these patients experienced DLT, the MTD was exceeded and the next 3 patients were treated at the next lower dose level. The MTD was the dose level at which no more than 1 patient experienced DLT and was 1 level less than the dose level at which ≥2 of 3 to 6 patients

experienced a DLT. A minimum of 6 patients were treated at the MTD.

Patient Evaluation

A medical history, physical examination, serum electrolytes, and renal and liver function tests were obtained for each patient before enrollment, weekly during the first course of therapy, and before each subsequent course. Routine complete blood counts were obtained twice weekly during the first course and weekly thereafter. Female patients of childbearing age were tested for pregnancy before each course. Echocardiography, electrocardiography, and audiography were performed before enrollment, after the first course, and at completion of study therapy.

Adverse events were assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE; version 3.0).[54] A nonhematologic DLT was defined as any grade 3 or 4 nonhematologic toxicity in the first course that was attributable to protocol therapy, with the exclusion of grade 3 nausea and vomiting, grade 3 liver enzyme elevation that returned to $\leq$ grade 1 before the next course, and grade 3 fever or infection. A hematologic DLT was defined as grade 4 neutropenia or thrombocytopenia lasting $>$7 days in the first course. Any persistent toxicity attributable to the chemotherapy that prevented the initiation of the second course within 28 days after the start of the first course was considered to be dose-limiting.

Patients underwent disease-appropriate evaluations for response within 2 weeks before study entry, after the second course of therapy, and after every third course thereafter. If a patient had a documented response, studies were repeated after the next course. Patients without measurable or evaluable disease at study entry were monitored for disease recurrence. Tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST),[55] with the exception of brain tumors.

For patients with brain tumors, complete response (CR) was defined as the disappearance of all demonstrable tumor on magnetic resonance imaging (MRI) and negative cerebrospinal fluid (CSF) cytology. A partial response (PR) was defined as a $\geq$50% reduction in the sum of the product of the maximum perpendicular dimensions of all measurable lesions on MRI, with no new lesions and stable to improving CSF cytology. Progressive disease (PD) was defined as worsening neurologic status not explained by other causes, an increase $>$25% in the product of the maximum perpendicular dimensions of any lesions, evidence of new lesions, or a requirement for increasing doses of corticosteroids to maintain a stable neurologic status. Stable disease (SD) was defined as a response that did not meet the criteria for any of the other categories. CR, PR, and SD designations required a stable or decreasing dose of corticosteroids accompanied by stable or improving neurologic status.

Table 1. Characteristics of the 16 Protocol Patients

Characteristic	No.	%
Age at enrollment, y		
Median	8	
Range	1-18	
Sex		
Male	11	69
Female	5	31
Race		
White	13	81
Black	1	6
Other	2	13
Diagnosis		
Ependymoma	5	31
Neuroblastoma	3	19
Medulloblastoma/supratentorial PNET	3	19
Atypical teratoid rhabdoid tumor	1	6
Osteosarcoma	1	6
Pineoblastoma	1	6
Malignant peripheral nerve sheath tumor	1	6
Wilms tumor	1	6
Prior therapy		
Chemotherapy	14	88
Median no. of agents (range)	6.5 (2-14)	
Median no. of regimens (range)	3 (1-8)	
Radiation	13	81

PNET indicates primitive neuroectodermal tumor.

RESULTS

From December 2004 to December 2006, 16 patients were enrolled, all of whom were evaluable for toxicity (Table 1). All patients had measurable or evaluable disease, except 1 with a fourth recurrence of atypical teratoid rhabdoid tumor (ATRT) who underwent macroscopic total resection before study entry. A total of 63 courses of therapy were administered (median, 3 courses; range, 1-13 courses).

Table 2. Dose-limiting Toxicity

	Dose Level, mg/m^2/d		No. Treated	No. of DLTs	DLT (No. of Patients)
	Oxaliplatin	Etoposide			
1	130	75	6	1	Epistaxis (1), neuropathy (1), neutropenia (1)
2	130	100	6	0	None
3*	145	100	4	2	Neutropenia (2)

DLT indicates dose-limiting toxicity.
* Given with calcium and magnesium infusions.

Toxicity

Of the first 3 patients treated at dose level 1, 1 experienced dose-limiting grade 3 pharyngolaryngeal dysesthesia at the time of completion of the 2-hour oxaliplatin infusion (Table 2). These symptoms resolved within 30 minutes. The same patient experienced prolonged grade 4 neutropenia and grade 3 epistaxis while thrombocytopenic during the first course of treatment. He tolerated a second course with a reduced oxaliplatin dose infused over 6 hours; however, he was removed from protocol therapy for PD after the second course. None of the subsequent 5 patients treated at dose level 1 experienced a DLT. At dose level 2, none of the first 3 patients experienced a DLT. At the third dose level, 1 of 3 initial patients experienced dose-limiting neutropenia. The fourth patient enrolled also experienced dose-limiting neutropenia, indicating that the MTD had been exceeded, and that level was closed to accrual. Three additional patients were subsequently enrolled at dose level 2 and did not experience a DLT. Thus, dose level 2 (130 mg/m^2 of oxaliplatin and 100 mg/m^2/day $\times$3 of etoposide) was the MTD.

Two patients experienced serious toxicities that occurred after the first course of treatment and therefore were not considered dose-limiting. One patient with ependymoma experienced a life-threatening anaphylactic reaction followed by a generalized seizure. After multiple anticonvulsants, he required intubation for apnea and admission to the intensive care unit. He recovered and was removed from protocol therapy. Another patient with neuroblastoma, who had received a nonmyeloablative allogeneic bone marrow transplant, developed grade 3 diarrhea during course 2 that improved with loperamide. During his response evaluation at the end of the course, pneumatosis intestinalis was noted incidentally. He was admitted to the hospital and treated with intravenous antibiotics, bowel rest, and parenteral fluid support. The radiographic findings resolved within 3 weeks. No infectious etiology was identified. The patient was removed from protocol therapy.

Table 3. Hematologic Toxicities

Toxicity*	Course 1 (N = 16)			Courses 2-13 (N = 47)		
	Grade			Grade		
	2	3	4	2	3	4
Anemia	5	1	1	25	9	
Leukopenia	4	6	3	14	12	4
Neutropenia	2	5	7	6	16	16
Thrombocytopenia	1	1	3		12	7

* Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

The hematologic toxicities are summarized in Table 3. The median duration of grade 4 neutropenia was 7 days (range, 2 days-14 days) and the median duration of grade 4 thrombocytopenia was 6 days (range, 2 days-8 days).

The most common grade 3 nonhematologic toxicities were sensory neuropathy, vomiting, hypophosphatemia, and diarrhea (Table 4), all of which had an incidence of $<$10%. None of the patients treated at dose level 3 (an oxaliplatin dose greater than the single-agent MTD) in conjunction with calcium and magnesium infusion experienced dose-limiting pharyngolaryngeal dysesthesia. Six patients (1 at dose level 1, 4 at dose level 2, and 1 at dose level 3) required a reduced oxaliplatin infusion rate because of acute sensory neuropathy during or immediately after a dose. The patients tolerated subsequent

Table 4. Nonhematologic Toxicities

Toxicity*	Course 1 (N = 16)		Courses 2-13 (N = 47)	
	Grade		Grade	
	3	4	3	4
Allergic reaction/hypersensitivity†				1
Anorexia			2	
Dehydration			1	
Diarrhea			3	
Febrile neutropenia			2	
Hypoglycemia			1	
Hemorrhage (nose)	1			
Sensory neuropathy	1		4	
Hypophosphatemia	1		4	
Hypokalemia			1	
Vomiting			4	

*Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).
†Patient with grade 4 allergic reaction also experienced grade 4 laryngeal edema and grade 4 hypoxia.

courses without recurrence of the acute neuropathy. There was no evidence of ototoxicity. No patient had a significant increase in serum creatinine.

Antitumor Activity

Of the 16 patients, 7 experienced PD during the first 2 courses and withdrew from the study. The patient with recurrent ATRT without evaluable disease, whose previous therapy had included cisplatin and etoposide, had a sustained disease-free interval through 11 courses. She developed disease recurrence 3 months after electively withdrawing from therapy. Two patients had prolonged confirmed SD. One patient with recurrent ependymoma experienced SD for 14 courses and continued to have stable residual disease at the time of last follow-up, 15 months after electively withdrawing from therapy. The other patient, who had high-grade metastatic sarcoma, experienced SD for 5 courses, then chose to pursue other therapy. Two patients, 1 with neuroblastoma and 1 with ependymoma, achieved SD after 2 courses of therapy but developed PD after 5 courses. Another neuroblastoma patient had SD after 2 courses but was then removed from protocol therapy due to toxicity. A patient with recurrent pineoblastoma sustained a PR through 5 courses of therapy (Fig. 1) but withdrew due to worsening myelosuppression. One patient with recurrent medulloblastoma maintained CR through 8 courses until the patient voluntarily withdrew from the study (Fig. 2). Both patients with objective responses had previously been treated with cisplatin and etoposide. The patient with the PR had previously received carboplatin as well.

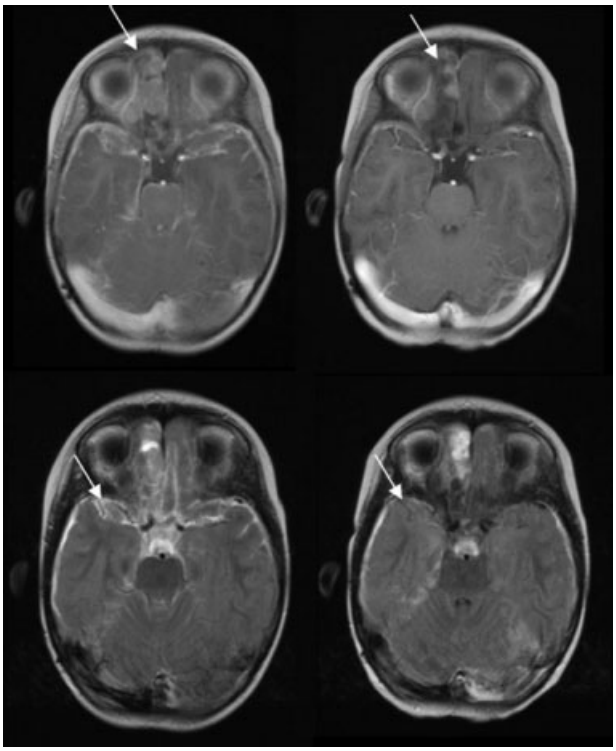

FIGURE 1. Magnetic resonance imaging (MRI) of a partial response of recurrent pineoblastoma to the oxaliplatin and etoposide regimen. Before the initiation of therapy, (*Top*) postcontrast axial T1 and (*Bottom*) postcontrast fluid attenuation inversion recovery (FLAIR) MRI scans showed a metastasis in the (top left) right cribriform region and (top left and bottom left) diffuse leptomeningeal tumor within sulci and basilar cisterns (arrows). (Bottom left) Some enhancement within the cerebrospinal fluid was also noted on the postcontrast FLAIR image. A decrease in the size of (top right) the solid metastasis and (bottom right) the extent of diffuse leptomeningeal tumor occurred with therapy.

DISCUSSION

The MTD of the 2 agents in this combination regimen was oxaliplatin at a dose of 130 mg/m^2 (Day 1) and etoposide at a dose of 100 mg/m^2/d (Days 1-3). The most common DLT was neutropenia lasting >7 days. Grade 4 neutropenia occurred in 37% of all courses and grade 4 thrombocytopenia in 16%. However, there were no

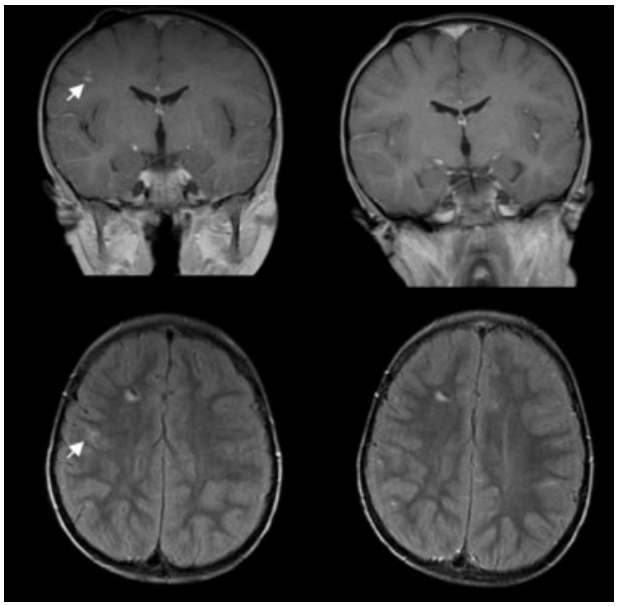

FIGURE 2. Magnetic resonance imaging (MRI) of a complete response of recurrent medulloblastoma to the oxaliplatin and etoposide regimen. (*Top*) Coronal postcontrast T1-weighted MRI scans show a (left, arrow) focal metastasis deep within a sulcus in the right frontal lobe that (right) resolves after therapy. (*Bottom*) Postcontrast fluid attenuation inversion recovery (FLAIR) MRI scans show the same focal metastasis (left) before and (right) after therapy.

significant infectious complications reported during the periods of neutropenia and only 2 episodes of febrile neutropenia. Other notable toxicities included acute sensory neuropathy associated with oxaliplatin; this toxicity was ameliorated by reducing the oxaliplatin infusion rate. Although cumulative neuropathy is well described in patients receiving oxaliplatin, none of our patients withdrew from the study due to worsening neurologic symptoms. Of the 4 patients who electively withdrew, 3 did so because they were enjoying a good quality of life and wished for a respite from chemotherapy. The fourth patient disliked the avoidance of cold beverages. None of these patients found the toxicity of therapy too burdensome.

The most common DLT of oxaliplatin given every 3 weeks in the single-agent pediatric phase 1 study was acute sensory neuropathy, including pharyngolaryngeal dysesthesia, at a dose of 160 mg/m^2.[40] This toxicity appeared to improve with concomitant carbamazepine; however, carbamazepine caused significant toxicity in 1 patient. Because intravenous calcium and magnesium infusion were reported to reduce the incidence and severity of acute oxaliplatin-related neurotoxicity,[53] we attempted to advance the dose of oxaliplatin beyond the single-agent MTD by using this approach. It is unclear whether these infusions were helpful: 5 of 15 patients receiving a dose of 130 mg/m^2 and 1 of 4 patients receiving a dose of 145 mg/m^2 required reduction of the oxaliplatin infusion rate due to acute neurotoxicity. This rate of acute neurotoxicity is similar to the pediatric single-agent phase 1 trial in which 2 of 8 patients experienced grade 3 acute neurotoxicity in the first course at a dose of 130 mg/m^2 administered over 2 hours.[40] After accrual to this study was completed, a randomized study of calcium and magnesium infusions in patients with colorectal cancer receiving oxaliplatin was terminated because of decreased tumor response in the group randomized to receive the infusions[56]; however, those results were not confirmed by an independent radiology review.[57] We did not find that the use of calcium and magnesium infusions allowed escalation of the oxaliplatin dose with this regimen. Neither should carbamazepine be used for this purpose because it interacts pharmacokinetically with etoposide.[58] In 1 study, patients with a specific polymorphism of glyoxylate aminotransferase, an enzyme involved in oxalate metabolism, appeared to have a higher risk of acute neurotoxicity.[59] In the future, pharmacogenomics may help physicians to predict which patients are at increased risk of oxaliplatin-associated toxicity. Because there are no studies addressing the efficacy of a 6-hour oxaliplatin infusion, the best approach appears to be an initial infusion of oxaliplatin over 2 hours, with a reduction of the infusion rate in patients who experience acute neurotoxicity.

The combination of oxaliplatin and etoposide demonstrated potential evidence of antitumor activity, especially in patients with central nervous system (CNS) malignancies. Three patients with recurrent embryonal tumors (medulloblastoma, ATRT, and pineoblastoma, respectively), all of whom had previously been treated with cisplatin and etoposide, had significant clinical benefit with the combination regimen; 2 patients achieved objective responses and a third had a sustained disease-free interval after surgical resection. An additional patient with ependymoma had SD through 14 courses of therapy. The reported response rate for pediatric patients with recurrent embryonal brain tumors was approximately 5% in a phase 2 study of oxaliplatin alone[39] and 17.1% for

single-agent etoposide.[60] Although our patient cohort was small, the objective response rate of 40% (2 of 5 patients) reported in patients with recurrent embryonal brain tumors shows promise, and toxicity was manageable. Notably, both patients with objective responses had failed after treatment with regimens that contained both cisplatin and etoposide. With the reported lack of ototoxicity or nephrotoxicity, 2 of the significant long-term toxicities in cancer survivors treated with cisplatin,[61-63] the regimen of oxaliplatin and etoposide deserves further evaluation. A formal phase 2 study would be needed to determine whether this combination produces better response rates than either agent alone.

Overall, this regimen appears safe and the antitumor effects, especially in embryonal CNS malignancies, warrant further evaluation. Support with filgrastim may ameliorate the most common toxicity, neutropenia. Future studies may include a phase 2 study of oxaliplatin and etoposide, especially in children with brain tumors. We also plan to assess the addition of ifosfamide to this regimen, beginning 1 dose level below the MTD due to the potential for an increased incidence of neutropenia.

Conflict of Interest Disclosures

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