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Phase I Clinical Trial of Ifosfamide, Oxaliplatin and Etoposide (IOE) in Pediatric Patients with Refractory Solid Tumors

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Summary

Oxaliplatin, although related to cisplatin and carboplatin, has a more favorable toxicity profile and may offer advantages in combination regimens. We combined oxaliplatin, ifosfamide, and etoposide (IOE) and estimated the regimen's maximum tolerated dose (MTD) in children with refractory solid tumors. Dose-limiting toxicity (DLT) and MTD were assessed at 3 dose levels in a 21-day regimen: day 1, oxaliplatin 130 mg/m^2 (consistent dose); days 1-3, ifosfamide 1200 mg/m^2/day (level 0) or 1500 mg/m^2/day (levels 1 and 2) and etoposide 75 mg/m^2/day (level 0 and 1) or 100 mg/m^2/day (level 2). Course 1 filgrastim/pegfilgrastim was permitted after initial DLT determination, if neutropenia was dose-limiting. Seventeen patients received 59 courses. Without filgrastim (n=9), DLT was neutropenia in two patients at dose level 1. No DLT was observed after adding filgrastim (n=8). There was no ototoxicity, nephrotoxicity >grade 1 or neurotoxicity >grade 2. One patient experienced a partial response and 9 had stable disease after two courses. In conclusion, the IOE regimen was well tolerated. Without filgrastim, neutropenia was dose-limiting with MTD at ifosfamide 1200 mg/m^2/day and etoposide 75 mg/m^2/day. The MTD with filgrastim was not defined due to early study closure. Filgrastim allowed ifosfamide and etoposide dose escalation and should be included in future studies.

Keywords

oxaliplatin; ifosfamide; etoposide; phase I trial; solid tumors

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Introduction

Cisplatin and carboplatin are widely used in the treatment of children with solid tumors, including combinations with ifosfamide and etoposide (ICE).[1-3] However, cisplatin and carboplatin cause significant ototoxicity, nephrotoxicity and dose-limiting myelosuppression.[4,5] Oxaliplatin (trans-l-1,2-diaminocyclohexane (DACH) oxalatoplatinum) is a platinum compound shown by preclinical and clinical studies to exert activity against multiple tumors, without the toxicities that typically accompany cisplatin or carboplatin.[6-8] With its DNA-crosslinking DACH-platinum adducts, oxaliplatin differs from cisplatin in its activation of signal transduction, DNA repair, and drug disposition.[6,7] In preclinical models, its antitumor activity parallels that of cisplatin, and it can be active against tumors with primary or acquired cisplatin resistance.[6-11] Oxaliplatin has cytotoxicity against a range of cancers, including colorectal and ovarian cancer, neuroblastoma, osteosarcoma, and germ cell tumors.[8-10,12,13] In adults, oxaliplatin is approved by the U.S. Food and Drug Administration for use in front-line regimens for colorectal cancer,[14,15] and phase III trials of oxaliplatin-based regimens for various adult malignancies are ongoing.[16-18] The predominant dose-limiting toxicity (DLT) in adults is sensory neurotoxicity, which appears to improve over time and may be amenable to therapy; no ototoxicity or nephrotoxicity has been observed.[14,19-21]

In children, oxaliplatin has been studied in single-agent phase I/II trials[22-25] and in combination with etoposide,[26] irinotecan,[27] gemcitabine,[28] doxorubicin,[29] and fluorouracil with leuocovorin.[30] Oxaliplatin has been well tolerated, without significant nephrotoxicity or ototoxicity.[22-31] As a single agent, its DLT is acute neurotoxicity, and its maximum tolerated dose (MTD) in children is 130 mg/m^2 when administered intravenously every 3 weeks.[22] Given the broad use of the ICE regimen and the potential of combining ifosfamide and etoposide with a less toxic agent, we conducted a phase I study to estimate the MTD of oxaliplatin combined with ifosfamide and etoposide (IOE) in children with refractory solid tumors.

Materials and Methods

Eligibility

Patients ≤21 years of age with recurrent solid tumors unresponsive to therapy or without known effective therapy were eligible if they met the following criteria: Karnofsky/Lansky score >50%; CNS tumor–related neurologic deficits stable for ≥2 weeks; life expectancy >8 weeks; recovery from acute effects of previous treatment; no myelosuppressive chemotherapy for ≥3 weeks (6 weeks if nitrosurea); no biologic agent(s) for ≥7 days; no craniospinal, whole pelvis, or total body irradiation for ≥3 months; no substantial bone marrow radiation for >6 weeks; no focal radiation for metastases for >2 weeks; no allogeneic stem cell transplantation for ≥6 months; no active graft vs. host disease; and no growth factors for >1 week. Indicators of adequate organ function were also required: absolute neutrophil count (ANC) >1000/μL; hemoglobin >8 g/dl; platelets >100,000/μL (transfusion-independent); hyperbilirubinemia grade ≤1; ALT elevation and hypoalbuminemia grade ≤2; normal serum creatinine or GFR ≥80 ml/min/1.73m^2; <50 urine RBCs/HPF; normal magnesium and calcium; potassium, sodium, and phosphate

abnormalities grade ≤1 (supplements permitted); normal electrocardiogram with SF >27%; EF >50% on echocardiogram; no resting dyspnea or exercise intolerance; room air O_2 saturation >94%; no seizures or seizures controlled by non-enzyme-inducing anticonvulsants; and peripheral neuropathy grade ≤1. Patients were excluded if they were receiving anticancer/experimental therapy; had uncontrolled infection; had previously received oxaliplatin; had life-threatening platinum hypersensitivity; or were pregnant or breastfeeding.

The protocol (ClinicalTrials.gov NCT00101205) was approved by the St. Jude Institutional Review Board. Informed consent was obtained from parents or legal guardians and patient assent was obtained as appropriate.

Drug Administration and Study Design

Therapy was given every 21 days. Oxaliplatin (Eloxatin [Sanofi-Aventis], supplied by the National Cancer Institute Cancer Therapy Evaluation Program [NSC 266046, IND 57004]), was reconstituted in 250 to 500 mL of sterile water with 5% dextrose and infused over 2 hours intravenously on day 1, after hydration achieved urine specific gravity ≤ 1.010 and antiemetics were given. Etoposide was infused over 1 hour on days 1-3 (immediately after oxaliplatin on day 1). Ifosfamide was infused over 1 hour after etoposide on days 1-3; MESNA was given before and 3 and 6 hours after ifosfamide. IV hydration was given at 200 mL/m^2/hour for 6 hours after chemotherapy on days 1-3, and then continued at 100 mL/m^2/hour until 24 hours from start of chemotherapy.

Since the dose-intensity of oxaliplatin has been shown to be a critical factor in combination studies with other agents[32] we chose to maximize the dose-intensity of oxaliplatin in this study by fixing the oxaliplatin dose and escalate ifosfamide and etoposide in a stepwise fashion. Oxaliplatin was administered at 130 mg/m^2/day, its MTD when given every 21 days as a single agent and in the two-drug regimen with etoposide.[22,26] Due to the potential increased myelosuppression with the addition of ifosfamide to oxaliplatin and etoposide, the starting dose of etoposide in our three-drug regimen was one dose level below its MTD in the two-drug regimen.[26] Thus, the first dose level comprised ifosfamide 1500 mg/m^2/day and etoposide 75 mg/m^2/day; this ifosfamide dose comprised a conventional dose used in pediatric combination protocols.[1] The second dose level comprised ifosfamide 1500 mg/m^2/day and etoposide 100 mg/m^2/day. If necessary, a reduced dose (dose level 0) comprised ifosfamide 1200 mg/m^2/day and etoposide 75 mg/m^2/day. Each MESNA dose was equivalent to 25% of the ifosfamide dose. DLT was assessed during course 1, in which filgrastim/pegfilgrastim support was withheld in the initial cohort. No dose-limiting neutropenia had been observed in the two-drug regimen with oxaliplatin and etoposide[26] at the maximum doses in this study; however, if neutropenia was dose-limiting upon addition of ifosfamide, the effect of filgrastim/pegfilgrastim support on DLT would be assessed during course 1 in the subsequent cohort. Filgrastim/pegfilgrastim would start on day 4 (filgrastim 5 mcg/kg/day until ANC >2000/μL, or single-dose pegfilgrastim administered SC, using 6 mg in patients >45 kg and 100 mcg/kg in patients ≤45 kg). In both the initial and subsequent cohorts, filgrastim/pegfilgrastim could be used from course 2 onward as clinically indicated, similar to the phase II oxaliplatin study.[25]

A conventional phase I dose-escalation design was used; there was no intra-patient dose escalation. If one of three patients in a cohort experienced DLT, the cohort was expanded to six patients; if two of three patients experienced DLT, patients were treated at the next lower dose level. If filgrastim was added to course 1, three additional patients were treated at a given dose level. Courses were repeated in the absence of progressive disease or DLT. The MTD was defined by DLT during course 1 as the maximal dose at which no more than one patient experienced DLT.

Patient Evaluation

Evaluations included clinical history, physical examination, serum electrolytes, and renal and liver function tests (baseline, weekly during course 1, and before each course thereafter). Complete blood counts were obtained twice weekly during course 1 and weekly thereafter. Electrocardiogram, echocardiogram, and hearing tests were conducted at baseline, after course 1, and then after every third course. Females of childbearing age were tested for pregnancy before each course.

Toxicities were assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 [33] with oxaliplatin-specific sensory neuropathy grading.[22] DLTs during course 1 were defined as grade 4 neutropenia or thrombocytopenia >7 days, and any nonhematologic toxicity ≥ grade 3, excluding selected grade 3 toxicities: nausea and vomiting, hepatotoxicity that returned to grade ≤1 before course 2, fever or infection, and electrolyte abnormalities. Toxicity that prevented initiation of course 2 within 28 days after starting course 1 was considered dose-limiting.

Disease evaluation with imaging was completed within 2 weeks before enrollment, after course 2, and then after every third course. Patients without measurable disease were monitored for recurrence. Documented responses were reassessed after the next course for confirmation. Response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [34] with the exception of CNS malignancies. For patients with brain tumors, complete response (CR) was defined as the disappearance of all measurable lesions on magnetic resonance imaging (MRI), partial response (PR) was defined as a ≥50% reduction in the summed product of the maximum perpendicular dimensions of measurable lesions on MRI, and progressive disease (PD) was defined as an increase >25% in this product for any lesion, appearance of new lesions, worsening neurologic status not otherwise explained, or requirement for increased corticosteroids to maintain neurologic stability. Stable disease (SD) was a response not meeting the criteria for other categories at the time of defined disease evaluations as compared to baseline. CR, PR, and SD required stable or decreasing corticosteroid doses and stable neurologic status.

Results

Between March 2009 and September 2011, 19 patients were enrolled; two were in-evaluable (one withdrew consent; one needed radiotherapy and withdrew before starting treatment). Seventeen evaluable patients (Table 1) received 59 courses (median 2; range 1-7). All had measurable or evaluable disease at enrollment, including four of eight neuroblastoma patients with bone marrow involvement. Patients were heavily pretreated; 15 (88%) had

received radiotherapy; patients received a median of three prior chemotherapy regimens; 13 (76%) previously received cisplatin (median cumulative dose for twelve patients with data available 440 mg/m^2); 8 (47%) previously received carboplatin (median cumulative dose 2060 mg/m^2); 11 (65%) received either platinum agent with ifosfamide and/or etoposide.

Toxicity

Of the first 3 patients treated at dose level 1, two developed a DLT (grade 4 neutropenia >7 days). Three patients then enrolled at dose level 0; one developed grade 4 neutropenia for >7 days, constituting DLT; the cohort was expanded by three patients, and no additional DLT was observed. Without filgrastim, the MTD was established as oxaliplatin 130 mg/m^2 on day 1, ifosfamide 1200 mg/m^2/day on days 1-3, and etoposide 75 mg/m^2/day on days 1-3 (Table 2).

Eight patients were enrolled after filgrastim was added to course 1 (three at dose level 0, three at dose level 1, two at dose level 2). The study was stopped before complete accrual at dose level 2 (with ifosfamide 1500 mg/m^2/day, etoposide 100 mg/m^2/day) due to slow accrual and withdrawal of sponsor-supplied oxaliplatin; therefore, the regimen's MTD with filgrastim support could not be accurately defined. However, no DLTs were experienced by patients receiving course 1 filgrastim.

Grade 3 and 4 toxicities are summarized in Table 3. Three patients discontinued therapy due to toxicity (grade 3-4 myelosuppression in all, grade 3-4 hypokalemia in two). Grade 4 neutropenia and grade 4 thrombocytopenia occurred in approximately half of all courses. Febrile neutropenia (one patient) was the only nonhematologic grade 4 toxicity. Grade 2 sensory neuropathy was observed in 3 patients (throat sensitivity to cold food/drink, transient slurring of speech that resolved with slowed oxaliplatin infusion with peripheral dysesthesia, and cold sensitivity with peripheral dysesthesia, respectively); two of these patients completed 2 to 3 additional courses with neuropathy ≤ grade 1. No ototoxicity, nephrotoxicity, or chronic neuropathy were noted; one patient experienced transient grade 1 serum creatinine elevation.

Antitumor Activity

One PR was confirmed in a patient with recurrent medulloblastoma previously treated with cisplatin; PR was maintained from course 2 to course 5 before the patient withdrew to pursue other therapy. SD was seen in nine patients (6 neuroblastoma, 2 rhabdomyosarcoma, 1 carcinoma) after 2 courses with a median duration of 16 weeks. All but one of these nine patients had previously been treated with platinum agents (five had received both cisplatin and carboplatin); the one patient not treated with platinum had received both ifosfamide and etoposide. Two of these nine patients experienced unconfirmed PR; PR was documented on two occasions (16 days apart) after course 4 in a neuroblastoma patient with progressive disease at study enrolment, but he electively withdrew before confirmation; the second patient, with rhabdomyosarcoma refractory to seven previous regimens, had a PR after course 5 but disease progression after course 6. Both of the patients treated at the highest IOE dosage (with filgrastim support) tolerated five courses.

Discussion

This first pediatric phase I study of ifosfamide, oxaliplatin, and etoposide (IOE) demonstrates that the regimen is tolerable and modestly active in selected heavily pre-treated patients. The MTD of the combination, without filgrastim support, is oxaliplatin 130 mg/m^2 (day 1), ifosfamide 1200 mg/m^2/day (days 1-3) and etoposide 75 mg/m^2/day (days 1-3) and the dose limiting toxicity is neutropenia. Single-agent oxaliplatin was reported to most frequently cause grade 3 or 4 myelosuppression,[23,24] and our cohort not only received oxaliplatin with two myelotoxic agents but had been heavily pre-treated (most had received radiotherapy, platinum agents, and ifosfamide or etoposide). Despite myelosuppression, only two patients experienced transient grade 3 infection while neutropenic, and only one had grade 4 febrile neutropenia.

Given the expected myelosuppression, our study was designed to secondarily assess the effect of filgrastim support during course 1. Notably, filgrastim allowed five patients to be safely treated above the MTD established without filgrastim support. It is likely that a higher MTD with filgrastim would have been confirmed after treatment of several additional patients, allowing ifosfamide and etoposide doses closer to those conventionally used in pediatrics and analogous to doses well tolerated in adults. In the one adult prospective study of oxaliplatin with ifosfamide and etoposide as second-line therapy, minimal toxicity was seen among the 34 patients with Hodgkin lymphoma who received 3 planned courses of oxaliplatin 130 mg/m^2 on day 1, ifosfamide 1500 mg/m^2 on days 1-3, and etoposide 150 mg/m^2 on days 1-3, every 21 days, with filgrastim support. Three cases of grade 4 hematologic toxicity, but no nonhematologic toxicity, were observed.[35] Similarly, we encountered no sensory neuropathy above grade 2, no ototoxicity, and no nephrotoxicity.

The IOE regimen achieved tumor control (PR or SD) in 10 of 17 patients with refractory solid tumors, 9 of whom had previous platinum exposure. Our review of all reported prospective pediatric studies of oxaliplatin-containing regimens (Table 4) documented responses in patients similar to those in our study and included children with medulloblastoma, neuroblastoma, rhabdomyosarcoma, and carcinoma.[23,24,26-29]

Despite widespread interest in oxaliplatin for adult malignancies, its development in pediatrics is uncertain. Of the 274 oxaliplatin-containing interventional studies currently recruiting on ClinicalTrials.gov, only six include pediatric patients.[36] The tempered enthusiasm for oxaliplatin in pediatrics may reflect the somewhat disappointing responses to single-agent oxaliplatin in children.[22-25] Importantly, however, although single-agent oxaliplatin produced objective response rates of only 20% in adults with colorectal cancer,[37] response rates more than doubled when it was used in combination regimens, which have now become standards of care.[14,19] Furthermore, when oxaliplatin was directly compared with cisplatin or carboplatin prospectively in adults with advanced tumors, similar efficacy and less hematologic and nonhematologic toxicity were documented in oxaliplatin-containing regimens.[38-41] In the current era of competing priorities in protocol and drug development, scarce funding, and few eligible patients, randomized pediatric trials comparing the efficacy or toxicity of ICE and IOE are unlikely to be supported. However, the IOE regimen is well tolerated and has antitumor activity in pediatric patients, including

those previously treated with ICE. We therefore propose that this combination be considered as a treatment alternative for patients with refractory disease, or those with platinum-sensitive tumors who are unable to tolerate treatment with cisplatin or carboplatin.

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Table 1

Characteristics of 17 Eligible Patients

Characteristic	No.	%
Median (range) age at diagnosis, y	4 (1-19)	
Median (range) age at enrollment, y	7 (2-21)	
Sex		
Male	12	71
Female	5	29
Race		
White	13	76
Black	2	12
Other	2	12
Diagnosis		
Neuroblastoma	8	47
Rhabdomyosarcoma	3	18
Medulloblastoma	2	12
Atypical teratoidrhabdoid tumor	1	6
Carcinoma of unknown primary site	1	6
Ewing sarcoma	1	6
Osteosarcoma	1	6
Previous therapy		
Median (range) no. of chemotherapy regimens	3 (1-7)	
Cisplatin or carboplatin (both)	14 (7)	82 (41)
Ifosfamide	9	53
Etoposide	12	71
ICE regimen	4	24
Radiation	15	88

Abbreviation: ICE, ifosfamide, cisplatin or carboplatin, and etoposide

Table 2

Dose Levels and Dose-limiting Toxicity

Dose Level	Oxaliplatin mg/m^2(day 1)	Ifosfamide mg/m^2/day (days 1,2,3)	Etoposide mg/m^2/day (days 1,2,3)	No. of patients (No. evaluable)	DLT (No. of patients)
1	130	1,500	75	4 (3)	Neutropenia (2)
0	130	1,200	75	6 (6)	Neutropenia (1)
0+filgrastim	130	1,200	75	4 (3)	None
1+filgrastim	130	1,500	75	3 (3)	None
2+filgrastim	130	1,500	100	2 (2)	None

Abbreviation: DLT, dose-limiting toxicity

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Table 3

Grade 3 and 4 Toxicities

	Course 1 (N = 17)		Course 2-7 (N= 42)	
Toxicity	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Hematologic				
Thrombocytopenia	4	3	8	25
Neutropenia	2	9	6	18
Leukopenia	5	5	7	11
Anemia	1	2	20	2
Non-hematologic				
Hypokalemia	1		6	
Febrile neutropenia	2		3	1
Hypophosphatemia	2		2	
Vomiting	1		3	
Infection	3			
Diarrhea	2		1	
Hemorrhage			2	
Allergic reaction/hypersensitivity			1	
Anorexia			1	
AST elevation			1	
Hyponatremia	1			
PTT Elevation			1	

Abbreviation: N, total number of courses

Table 4

Pediatric Tumors Reported to Respond to Oxaliplatin*

Tumor	Study Phase (No. evaluable)[a]	Best Response
Medulloblastoma		
	Phase I (5)[22]	1 SD
	Phase II (15)[24]	2 PR
	Phase I + etoposide (3)[26]	1 CR
	Phase II + gemcitabine (14)[28]	1 CR[b], 6 SD
	Current Phase I (2)	1 PR
Neuroblastoma		
	Phase I (6)[22]	1 SD
	Phase I (18)[23]	1 PR[c]
	Phase I + etoposide (3)[26]	2 SD
	Phase I + irinotecan (1)[27]	1 SD
	Phase I + doxorubicin (3)[29]	1 CR, 1 PR, 1 SD
	Phase II (10)[25]	3 SD
	Phase II + gemcitabine (12)[28]	5 SD
	Current Phase I (8)	6 SD[d]
Rhabdomyosarcoma		
	Phase I (1)[22]	0[e]
	Phase I + irinotecan (2)[27]	1 CR
	Phase I + doxorubicin (2)[29]	0[e]
	Phase II (10)[25]	0[e]
	Phase II + gemcitabine (12)[28]	1 PR
	Current Phase I (3)	2 SD[f]
Nasopharyngeal carcinoma		
	Phase II (4)[25]	0[e]
	Phase I + doxorubicin (1)[29]	1 CR

[a] Oxaliplatin was given alone unless otherwise indicated.

[b] PR after course 4, CR after course 7.

[c] Stable disease data unavailable.

[d] One had unconfirmed PR after course 4 before elective withdrawal.

[e] All had progressive disease.

[f] One had PR after course 5 and PD after course 6.

* Tumors with at least one PR or CR are included in this table

Abbreviations: CR, complete response; PR, partial response; SD, stable disease