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A Phase I Study of Oxaliplatin and Doxorubicin in Pediatric Patients With Relapsed or Refractory Extracranial Non-Hematopoietic Solid Tumors

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Background. The combination of a platinum agent and anthracycline has shown activity in pediatric solid tumors. This trial evaluated the maximum tolerated dose (MTD) and dose limiting toxicities (DLT) of oxaliplatin combined with doxorubicin in pediatric patients with recurrent solid tumors. ***Methods.*** Oxaliplatin was administered on day 1 and Doxorubicin on days 1–3 of each 21 day course. The study utilized a standard 3 + 3 dose escalation design. Three dose levels were evaluated: (1) oxaliplatin 105 mg/m^2 and doxorubicin 20 mg/m^2; (2) oxaliplatin 130 mg/m^2 and doxorubicin 20 mg/m^2; and (3) oxaliplatin 130 mg/m^2 and doxorubicin 25 mg/m^2. Dexrazoxane was administered at 10 times the doxorubicin dose prior to doxorubicin infusion. ***Results.*** Seventeen patients were enrolled. Dose level 1 was the determined MTD. Grade 2 cardiac DLT was seen in one of six patients on dose level 1, grade 4 thrombocytopenia in two of five patients on dose level 2, and one each of grade 2 cardiac and grade 4 thrombocytopenia in five patients on dose level 3. Cardiac DLT was only noted in patients with prior exposure to both anthracycline and chest radiation. No grade 3 or 4 neurotoxicity or mucositis was seen. Objective responses were noted in two patients with neuroblastoma and one each of mixed germ cell tumor, thymic neuroendocrine carcinoma, and nasopharyngeal carcinoma. ***Conclusions.*** Oxaliplatin 105 mg/m^2 on day 1 combined with doxorubicin 20 mg/m^2 days 1–3 was the MTD. This combination shows sufficient activity to justify further studies in select pediatric tumors. Pediatr Blood Cancer 2013;60:1103–1107. © 2013 Wiley Periodicals, Inc.

Key words: children; doxorubicin; oxaliplatin; phase I; recurrent; refractory; relapsed; solid tumors

INTRODUCTION

Doxorubicin combined with a platinum agent has been used in the treatment of many pediatric cancers including osteosarcoma, hepatoblastoma, neuroblastoma, and advanced soft tissue sarcoma [1–3]. Ototoxicity and nephrotoxicity caused by cisplatin, and myelosuppression caused by carboplatin limit their therapeutic use [4]. Oxaliplatin is a platinum derivative with a 1, 2-diaminocyclohexane (DACH) carrier ligand. Oxaliplatin is more potent than cisplatin *in vitro* requiring fewer DNA adducts to achieve an equal level of cytotoxicity [5]. It has shown efficacy in preclinical studies against many tumor cell lines, including some that are resistant to cisplatin and carboplatin [6–10]. The activity of oxaliplatin is not hindered by loss of mismatch repair and replicative bypass which confer resistance to cisplatin [11]. In prior trials, children treated with oxaliplatin did not have significant renal or ototoxicity, and oxaliplatin caused less myelosuppression when compared to carboplatin [12–16]. The maximum tolerated dose (MTD) in children as a single agent was 130 mg/m^2 administered intravenously every 21 days. Sensory neuropathy was the main dose limiting toxicity (DLT) [12].

Doxorubicin is used in the frontline treatment of a variety of childhood hematological malignancies and solid tumors. It is also active in patients who were previously exposed to anthracyclines [17,18]. Combining doxorubicin and oxaliplatin has the potential advantage of being active across multiple childhood cancers while avoiding the ototoxicity and nephrotoxicity of cisplatin. This combination is well tolerated and has demonstrated significant antitumor activity in adults with advanced ovarian cancer, hepatocellular carcinoma, and gastric cancer [19–22]. We conducted a phase I study of oxaliplatin and doxorubicin in children with refractory extra-cranial solid tumors. Dexrazoxane was used as a cardio-protectant in an attempt to reduce the cardiac side effects of doxorubicin, since it was expected that several eligible patients would have prior anthracycline exposure.

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MATERIALS AND METHODS

Patient Eligibility

Patients ≤21 years of age with a histologically confirmed extra-cranial solid tumor which was refractory to conventional therapy, body weight ≥10 kg, a Karnofsky or Lansky performance score of >50%, and with an expected life expectancy of ≥8 weeks were eligible. Organ function requirements were as follows: peripheral blood neutrophil count (ANC) ≥750/μl, platelet count ≥75,000/μl (transfusion-independent), Hemoglobin ≥8 g/dl; ANC ≥ 500/μl, platelet count ≥50,000/μl (transfusion-independent) in patients with bone marrow involvement;

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normal serum creatinine for age or a glomerular filtration rate of $\geq$70 ml/min/m^2; left ventricular shortening fraction of $\geq$28% by echocardiogram or ejection fraction of $\geq$55% by MUGA scan; bilirubin level $\leq$1.5 $\times$ upper limit for age, alanine aminotransferase $\leq$ grade 2. Patients must have recovered from toxic effects of prior therapy; and not received (1) myelosuppressive therapy within 2 weeks (6 weeks if nitrosurea); (2) biological agent within 2 weeks; (3) small-port palliative radiotherapy within 2 weeks; (4) total body, craniospinal or hemi-pelvic radiation within 6 months; (5) autologous or allogeneic stem cell transplant in the previous 6 months; (6) hematopoietic growth factors within 1 week. Patients who had previously received oxaliplatin or cumulative anthracycline (doxorubicin equivalent) dose of >450 mg/m^2 were ineligible. Pregnant or breast feeding females, and patients with uncontrolled infection were excluded.

Written informed consent was obtained from all patients prior to enrollment. The institutional review board at Children's Hospital Los Angeles approved conduct of this study (CCI-06-00092).

Study Design

Oxaliplatin and doxorubicin were administered over three dose levels (Table I). A standard 3 + 3 phase I dose escalation study design was used. A minimum of three evaluable patients were to be treated at each dose level. In the absence of DLT, patients were enrolled in the next dose level. If 1 of three patients had a DLT, the cohort was expanded to include six patients. If $\geq$2 patients experienced DLT, MTD was exceeded and further enrollment at that dose level was stopped. MTD was defined as the highest dose level at which $\leq$1 of 6 patients experienced a DLT. Only DLT that occurred during the first course were used to determine the MTD.

Oxaliplatin was reconstituted in 250–500 ml of water with 5% dextrose and administered intravenously over 2 hours on day 1 of a 21 day course. Doxorubicin was administered by rapid drip intravenous infusion over 15 minutes on days 1, 2, and 3. Dexrazoxane was administered at 10 times the dose of doxorubicin prior to doxorubicin infusion on days 1, 2, and 3. Doxorubicin infusion was begun within 30 minutes of completion of dexrazoxane. Patients received granulocyte colony stimulating factor (G-CSF) 5 μg/kg/day subcutaneously starting on day 4 and continued until ANC > 2,000/μl. Patients could receive a maximum of eight courses in the absence of disease progression. Doxorubicin was discontinued once a cumulative lifetime dose of 750 mg/m^2 was reached and oxaliplatin monotherapy was administered for the remaining courses.

Patient Evaluation

A medical history, physical examination, renal, and liver function tests serum electrolytes were obtained prior to study enrollment, weekly during the first course of treatment and prior to each course thereafter. Complete blood counts (CBC) were obtained three times a week during first course and twice a week starting with the second course. Echocardiogram was obtained prior to each course and at completion of therapy.

Toxicities were graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. Hematological DLT was defined as grade 4 neutropenia or grade 4 thrombocytopenia lasting >7 days or myelosuppression which caused delay in chemotherapy for >14 days. Any grade 3 or grade 4 non hematological toxicity was considered a DLT with the specific exclusion of (1) grade 3 or 4 nausea and vomiting responding to antiemetics; (2) grade 3 serum transaminase elevation which returned to $\leq$ grade 1 before next course; (3) grade 3 infection or grade 3 or 4 fever. In addition, cardiac shortening fraction <25%, grade 2 dysesthesia that persisted through the beginning of next course, and grade 1 pharyngolaryngeal dysesthesia that lasted more than 7 days were considered dose limiting. Response evaluation criteria in solid tumors (RECIST) was used to assess tumor response at the end of course 1, and at the end of every other course thereafter. Responses were required to be sustained for a minimum of two consecutive imaging evaluations.

RESULTS

Patient Characteristics

Between August 2006 and October 2009, 17 patients were enrolled (Table II). Patients received 59 courses of therapy (median, 1 course; range 1–8 courses). Twelve patients had received a platinum agent or doxorubicin in the past; 8 of the 12 had received both. Median cumulative anthracycline exposure prior to study entry was 150 mg/m^2 (range: 0–450 mg/m^2).

Toxicity

There were no deaths due to toxicity. One of the initial three patients enrolled on dose level 1 had dose limiting cardiac toxicity (Table I). This patient was asymptomatic and received two additional courses on protocol without doxorubicin. None of the additional three patients enrolled at this level developed a DLT. The first three patients enrolled on dose level 2 did not experience a DLT and the dose was further escalated to dose level 3. Dose limiting cardiac toxicity and thrombocytopenia were observed in two of the first five patients treated at dose level 3. Since dose level 3 exceeded MTD, dose level 2 was expanded to enroll three additional patients. Two of these three patients had dose limiting thrombocytopenia. The third patient did not have study mandated CBC checks during course 1, and was not fully evaluable for hematological DLT. There were no non-hematological DLT at

TABLE I. Dose Levels and Dose-Limiting Toxicity

Dose level	Oxaliplatin, mg/m^2/dose (day 1)	Doxorubicin, mg/m^2/dose (days 1-3)	No. treated	No. of DLTs	DLT (no. of patients)
1	105	20	6	1	Cardiac (1)
2	130	20	6	2	Thrombocytopenia (2)
3	130	25	5	2	Cardiac (1), thrombocytopenia (1)

DLT, dose-limiting toxicity.

TABLE II. Patient Characteristics (N = 17)

Characteristic	No. of patients (%)
Age at enrollment (years)	
Median	13.8
Range	2.9–20.4
Gender	
Male	8 (47)
Female	9 (53)
Diagnosis	
Osteosarcoma	4 (24)
Neuroblastoma	3 (18)
Rhabdomyosarcoma	2 (12)
Germ cell tumor	1 (6)
Nasopharyngeal carcinoma	1 (6)
Dentritic cell sarcoma	1 (6)
Wilms tumor	1 (6)
Neurofibrosarcoma	1 (6)
Thymic carcinoma	1 (6)
Ewing sarcoma	1 (6)
Hepatocellular carcinoma	1 (6)
Prior therapy	
No. of chemotherapy regimens	
Median (range)	2 (0–6)
Prior platinum therapy	10
Prior anthracycline therapy	10
Prior radiotherapy	9
Prior Bone Marrow Transplant	5

TABLE III. Grades 3 and 4 Toxicities

	Course 1 (N = 17)		Courses 2–8 (N = 42)	
Toxicity	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	5	3	9	8
Leukopenia	3	9	4	11
Neutropenia	1	12	5	14
Thrombocytopenia	1	11	10	17
ALT	1		2	
Cardiac	1			
Colitis			1	
Fever Neutropenia	4		8	4
Hemorrhage			1	
Hypoalbuminemia			1	
Hypokalemia			1	
Hyponatremia			1	
Infection	3		1	1
Nausea	1			
Vomiting	2			

N, total number of courses.

this dose level. Dose level 1 (oxaliplatin 105 mg/m^2 and doxorubicin 20 mg/m^2/day for 3 days) was determined to be the MTD.

Both patients who developed dose limiting cardiac toxicity had been previously treated with both anthracycline and chest irradiation. The cumulative anthracycline dose at the time of cardiac toxicity in the two patients was 235 mg/m^2 (dose level 1) and 300 mg/m^2 (dose level 3), respectively. Two of the three patients with dose limiting thrombocytopenia had prior autologous bone marrow transplants (1 each at dose levels 2 and 3).

Grades 3 and 4 hematological and non-hematological toxicities are summarized in Table III. Fever and neutropenia occurred in greater than 10% of the courses. Other non-hematological toxicities were hypokalemia, elevated transaminase, hypophosphatemia, pain, and vomiting. None of the patients experienced pharyngolaryngeal dysesthesia. Transient grades 1–2 sensory neuropathy was observed in 14 courses in eight patients. Cumulative neurotoxicity was not observed in four patients who completed all eight courses. None of the patients experienced grades 3 or 4 mucositis.

Antitumor Activity

All patients had measurable disease by RECIST at study entry. Six patients developed progressive disease at the end of course 1 and were removed from protocol therapy (Table IV). Two patients were removed from protocol therapy due to progressive disease after 3rd and 5th courses, respectively. Another patient had progressive disease at the end of eight courses. One patient with stable disease was removed from protocol therapy by the treating oncologist after three courses to pursue other therapies. One patient with metastatic nasopharyngeal carcinoma treated at MTD achieved complete remission following three courses and completed all eight courses. This patient continues to be in remission 4 years after end of treatment without further therapy. Another patient with neuroblastoma treated at dose level 2 achieved complete remission. This patient was also removed from protocol therapy by the treating physician after five courses to pursue other treatments. Both these patients had received cisplatin in the past. Partial responses were seen in patients with neuroblastoma, testicular germ cell tumor, and thymic neuroendocrine carcinoma.

DISCUSSION

In our cohort of heavily pre-treated pediatric patients, oxaliplatin 105 mg/m^2 administered intravenously over 2 hours every 3 weeks and doxorubicin 20 mg/m^2/day given over 3 days together with dexrazoxane every 3 weeks with myeloid growth factor support was the MTD. Cardiac and hematological toxicity were the dose limiting toxicities. Decrease in cardiac shortening fraction occurred in two patients who had received previous anthracyclines, albeit with lower cumulative doses. Both these patients had previously been exposed to chest radiation where the heart was included in the radiation field. Cardiac irradiation is known to increase the risk of cardiomyopathy following anthracycline exposure [23].

The combination of oxaliplatin and liposomal doxorubicin was studied in a phase I study in adults with advanced ovarian cancer [19]. Oxaliplatin 120 mg/m^2 and doxorubicin 40 mg/m^2 administered on day 1 every 3 weeks was the MTD. Neutropenia and thrombocytopenia were dose limiting. Hematologic toxicity was expected in our heavily pretreated patient population. Grades 3 and 4 thrombocytopenia in up to 27% of courses has been reported in previous studies with oxaliplatin in children [14,16]. Minimal myelosuppression was observed when oxaliplatin was combined with protracted irinotecan schedule [15]. MTD for oxaliplatin was 40 mg/m^2 administered on days 1 and 8 with irinotecan at a dose of 15 mg/m^2 on days 1–5 and 8–12 of each 21-day course. Dose limiting neutropenia was observed when oxaliplatin was combined with etoposide [24]. We report higher

TABLE IV. Tumor Response

Tumor type	Dose level	No. of courses	Response after course 1	Best response
Osteosarcoma	1	1	PD	PD
Rhabdomyosarcoma	1	3	PR	PD
Germ cell tumor	1	5	PR	PR
Nasopharyngeal carcinoma	1	8	SD	CR
Osteosarcoma	1	8	SD	SD
Dentritic cell sarcoma	1	1	PD	PD
Wilms tumor	2	1	PD	PD
Rhabdomyosarcoma	2	1	PD	PD
Neurofibrosarcoma	2	8	SD	SD
Osteosarcoma	2	1	PD	PD
Neuroblastoma	2	2	PR	PR
Neuroblastoma	2	3	SD	SD
Thymic carcinoma	3	8	PR	PR
Ewing sarcoma	3	1	SD	SD
Osteosarcoma	3	1	PD	PD
Hepatocellular carcinoma	3	2	SD	SD
Neuroblastoma	3	5	SD	CR

PD, progressive disease; CR, complete response; SD, stable disease; PR, partial response.

rates of grades 3 and 4 thrombocytopenia (66%), and grade 4 anemia in our study when compared to previous studies. Use of doxorubicin and dexrazoxane may have contributed to the excess hematological toxicity in our study [25]. Pharyngolaryngeal dysesthesia or acute neurotoxicity requiring slowing of oxaliplatin infusion was not seen in our study. In the pediatric phase I trial of oxaliplatin administered every 3 weeks, pharyngolaryngeal dysesthesia was dose limiting at 160 mg/m^2 [12]. In a subsequent phase II study of oxaliplatin, pharyngolaryngeal dysesthesia or neurosensory symptoms were observed in less than 2% of the 351 courses administered [13]. Geoerger et al. [16] reported pharyngolaryngeal dysesthesia in 14% of courses and neurosensory symptoms in 18% of courses when oxaliplatin was administered in a weekly schedule. Recently, Macy et al. reported 50% incidence of peripheral neuropathy (grades 1 and 2) with FOLFOX regimen when oxaliplatin (85–100 mg/m^2) was administered every 2 weeks [26].

Oxaliplatin as a single agent showed limited antitumor activity in pediatric phases I and II studies [12,13]. No objective responses were observed in the pediatric phase I study [12]. Of the 113 patients treated in the single agent phase II study of oxaliplatin, only one patient with ependymoma achieved a partial response [13]. No responses were seen in patients with other cancer types including neuroblastoma, germ cell tumors, and nasopharyngeal carcinoma. This is similar to adult trials where oxaliplatin used as a single agent in patients with colorectal cancer showed a response rate of 20% [27]. In a subsequent randomized trial, the response rate in colorectal cancer patients treated with fluorouracil and leucovorin increased significantly (22% vs. 50%) when oxaliplatin was added [28]. Fifty-five percent of adults with advanced ovarian cancer responded to combination of oxaliplatin and liposomal doxorubicin [19]. Two complete responses and three partial responses were observed in our study; two at the MTD. This is higher than previous combinations of oxaliplatin with etoposide or irinotecan in children [15,24]. The patient with metastatic nasopharyngeal carcinoma achieved long-term remission without radiation therapy using this regimen. Objective responses were seen in two patients with neuroblastoma despite prior exposure to cisplatin, high dose carboplatin and doxorubicin. In conclusion, combination of oxaliplatin and doxorubicin is tolerable and shows sufficient activity to justify further studies in select pediatric cancers.

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