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# A Multi-Center Phase Ib Study of Oxaliplatin (NSC#266046) in Combination With Fluorouracil and Leucovorin in Pediatric Patients With Advanced Solid Tumors

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***Background.*** Platinum agents have been used for a variety of cancers, including pivotal use in pediatric tumors for many years. Oxaliplatin, a third generation platinum, has a different side effect profile and may provide improved activity in pediatric cancers. ***Procedure.*** Patients 21 years or younger with progressive or refractory malignant solid tumors, including tumors of the central nervous system were enrolled on this multi-center open label, non-randomized Phase 1 dose escalation study. The study used a standard 3 + 3 dose escalation design with 2 dose levels (85 and 100 mg/m$^2$) with an expansion cohort of 15 additional patients at the recommended dose. Patients received oxaliplatin at the assigned dose level and 5-fluorouracil (5-FU) bolus 400 mg/m$^2$ followed by a 46-hour 5-FU infusion of 2,400 mg/m$^2$ every 14 days. The leucovorin dose was fixed at 400 mg/m$^2$ for all cohorts. ***Results.*** Thirty-one evaluable patients were enrolled, 8 at 85 mg/m$^2$ and 23 at 100 mg/m$^2$ for a total of 121 courses. The median age was 12 years (range 2–19 years). The main toxicities were hematologic, primarily neutrophils and platelets. The most common non-hematologic toxicities were gastrointestinal. Stable disease was noted in 11 patients (54% of evaluable patients) and 1 confirmed partial response in a patient with osteosarcoma. ***Conclusions.*** The maximum planned dose of oxaliplatin at 100 mg/m$^2$ per dose in combination with 5-FU and leucovorin was safe and well tolerated and in this patient population. This combination demonstrated modest activity in patients with refractory or relapsed solid tumor and warrants further study. Pediatr Blood Cancer 2013;60:230–236. © 2012 Wiley Periodicals, Inc.

**Key words:** chemotherapy; 5-fluorouracil; FOLFOX; oxaliplatin; pediatrics; Phase 1

## INTRODUCTION

Platinum agents have been widely used in the treatment of many pediatric tumors including, neuroblastoma, hepatoblastoma, Wilms tumor, non-Hodgkin lymphomas, germ cell tumors, and the majority of sarcomas, and brain tumors for many years. Oxaliplatin is a potentially attractive agent for use in a variety of pediatric malignancies due to its unique properties and the known activity of platinums in many pediatric tumors. Oxaliplatin (*trans*-l-1,2-diaminocyclohexane oxalatoplatinum) is a novel antineoplastic platinum derivative with a 1,2-diaminocyclohexane [DACH] carrier ligand. Like other platinums, oxaliplatin exerts its cytotoxic effects through the formation of DNA adducts that block both DNA replication and transcription, resulting in cell death in actively dividing cells as well as the induction of apoptosis [1]. Like cisplatin, oxaliplatin reacts with DNA, forming mainly platinated intra-strand links with two adjacent guanines or a guanine adjacent to an adenine [2]. However, DACH-platinum adducts formed by oxaliplatin are bulkier and apparently more effective at inhibiting DNA synthesis [1,3] and are more cytotoxic than *cis*-diamine-platinum adducts formed from cisplatin and carboplatin [1,4]. Oxaliplatin also has been shown to be active in cisplatin resistant cells [5,6].

Compared to other platinum compounds, oxaliplatin possesses a different and attractive side-effect profile. Specifically, oxaliplatin is associated with less ototoxicity and thrombocytopenia when compared to cisplatin and carboplatin. This profile is particularly attractive for patients with central nervous system (CNS) tumors who are at an increased risk for CNS hemorrhage with thrombocytopenia, who may already have significant limitations in the function of other cranial nerves. It is also attractive for use in very young patients who may have significant delays in speech and language acquisition if their hearing is damaged by ototoxic therapy. The dose limiting toxicity of oxaliplatin in adults is peripheral neuropathy (paresthesias and dysethsesias worsened by exposure to cold) that is usually reversible [7–9]. In pediatric Phase 1 single agent studies of oxaliplatin, DLTs included peripheral neuropathies (paresthesias and dysethesias), myelosupression, and sepsis [10–13]. Thrombocytopenia was also a common finding and myelosupression was also seen in pediatric trials combining oxaliplatin with chemotherapy [12,14]. In contrast to other platinum compounds, no ototoxicity was observed and no grade 2–4 renal toxicity was seen in the pediatric Phase 1 studies [10–11,13].

Two single agent Phase 1 trials with oxaliplatin in pediatric patients have been conducted to date. A Phase 1 single agent study by St. Jude Children's Research Hospital determined the (maximally tolerated dose) MTD to be 130 mg/m$^2$ when oxaliplatin was given on an every 3-week schedule and 85 mg/

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$m^2$ given every 2 weeks [13]. Another Phase 1 study conducted in France by Geoerger and colleagues evaluated a dose-intensive schedule of single agent oxaliplatin administered weekly for 3 weeks out of a 4-week cycle. The MTD and the recommended Phase 2 dose was 90 mg/$m^2$ on this intensive weekly schedule. No ototoxicity was noted in the 45 patients treated on this protocol. Two patients had confirmed partial responses (4.7%) and stable disease was reported in seven patients (16.3%) [11]. A Phase 2 pediatric study of single agent oxaliplatin in relapsed/refractory brain tumors conducted by the Pediatric Brain Tumor Consortium demonstrated similar toxicities with limited tumor response (3 of 43 patients with partial response, and 16% with stable disease greater than 3 months) in a population with previous platinum exposure [10]. Similar response rates among other solid tumors were seen in the Children's Oncology Group (COG) Phase 2 of oxaliplatin [15]. More recently, responses have been seen in Phase 1 pediatric studies when oxaliplatin was combined with irinotecan or etoposide [12,14].

Oxaliplatin is frequently combined with 5-fluorouracil (5-FU) and leucovorin (LV) infusions for adults with CRC, and this combination has shown greater anticancer activity when compared to prior combination regimens in stage 3 CRC. Using the regimen developed by de Gramont for patients with CRC, oxaliplatin, and LV are given as a 2-hour infusion with LV at a dose of 200 mg/$m^2$ followed by a loading dose of 5-FU given as a 400 mg/$m^2$ bolus [8]. The 5-FU loading dose is then followed by a dose of 5-FU of 600 mg/$m^2$ delivered over 22 hours via at a constant drug infusion rate. The 5-FU/LV bolus and infusion is repeated for a total of 48 hours with the entire regimen being repeated every 2 weeks. The various combination regimens containing oxaliplatin/5-FU/leucovorin have been termed ''FOLFOX'' based permutations of the individual components. The FOLFOX4 regimen was shown to be effective in patients with stage II and III newly diagnosed CRC. This and similar regimens containing irinotecan or capecitabine rather than 5-FU are considered to be within the standard of care for a variety of CRC patients. These regimens now include combinations incorporating anti-EGFR (cetuximab, panitumumab) or anti-angiogenic therapies [7,8,16–20].

One of this study's investigators had anecdotal but positive experience using oxaliplatin alone, the FOLFOX6 regimen, or oxaliplatin + thiotepa (THIOX) in nine pediatric patients with highly refractory recurrent malignancies. Disease stabilization and response were noted, including a durable complete response (CR) in the one patient with colorectal cancer, an 18-month CR in a patient with relapsed metastatic medulloblastoma, and 4 sustained stable diseases in CNS tumor patients of 6–19 months in duration. Given these results with use of an outpatient regimen, a modified FOLFOX6 combination regimen schedule [21] (oxaliplatin 85 mg/$m^2$ as a 2-hour infusion Day 1; LV 400 mg/$m^2$ as a 2-hour infusion Day 1; followed by a loading dose of 5-FU, 400 mg/$m^2$ IV bolus, then 2,400 mg/$m^2$ 5-FU via ambulatory pump over 46 hours Days 1 and 2) was proposed. The associated potential for decreased toxicity and greater ease of administration when compared to the FOLFOX4 regimen in adults without evidence of decreased efficacy [21] made the FOLFOX6 more attractive. Additionally, while FOLFOX based regimens are routinely used for adults with colorectal cancer, little data exists for pediatric and adolescent patients CRC, a group for whom the outcome is often poor, and there are few, if any trials. Another group for whom FOLFOX6 regimen is attractive is children with hepatoblastoma, where the current standard of care includes 5-FU and cisplatin, and there are limited retrieval options available. We conducted this multi-center open label, non-randomized Phase 1 dose escalation study to explore whether the modified FOLFOX6 regimen was a feasible and safe treatment option for patients with relapsed or refractory malignancies.

## MATERIALS AND METHODS

### Patient Selection

Patients were $\leq$21 years of age with histologically confirmed malignant solid tumors, including tumors of the central nervous system that had progressed despite standard therapy or for which no effective standard therapy existed. Additional criteria included: Eastern Cooperative Oncology Group performance status of $\leq$2 for patients age 16 and older; Karnofsky $\geq$40% for patients $>$10 years of age; or Lansky Play Scale $\geq$40 for children $\leq$10 years of age; patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, surgery, or radiotherapy prior to entering this study; no myelosuppressive chemotherapy within 3 weeks; no nitrosoureas or mitomycin C within 6 weeks; no biologic agents or PEGylated GCSF (Neulasta$^{TM}$) within 14 days; no retinoids or conventional growth factors within 7 days; no local radiation therapy or major surgical procedures within 4 weeks; no craniospinal irradiation or irradiation to $\geq$50% of the pelvis or other substantial bone marrow irradiation including total body irradiation within 6 months; no stem cell transplant within 3 months; no current immunosuppressive therapy; no evidence of active graft versus host disease; steroids at a stable or decreasing dose for $\geq$7 days prior to study entry and no more than 4 mg of dexamethasone (or equivalent) per day. Patients must have had a life expectancy greater than 8 weeks; no persistent toxicities from previous therapies $\geq$ grade 2; females of childbearing potential needed a negative serum pregnancy test; central venous access. Informed consent; and assent as appropriate was obtained according to federal and institutional guidelines. The study protocol was approved by the institutional review board or independent ethics committee at each participating site and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and all local and federal regulatory guidelines. Each patient's parent or legal guardian provided written informed consent, with patient assent as appropriate to institutional requirements.

### Drug Administration

Oxaliplatin was provided by the Division of Cancer Treatment and Diagnosis (DCTD) of the National Cancer Institute as a sterile powder or solution. 5-FU and leucovorin were commercially obtained. The initial doses for this protocol were oxaliplatin 85 mg/$m^2$ and 5-FU bolus 400 mg/$m^2$ followed by a 46-hour 5-FU infusion of 2,400 mg/$m^2$ given every 14 days. The leucovorin dose was fixed at 400 mg/$m^2$ for all cohorts. There was no intra-patient dose escalation.

The 5-FU dosing remained fixed for the dose escalation with a single planned oxaliplatin dose escalation to 100 mg/$m^2$. If de-escalation was required, there was also a dose level-1 of oxaliplatin 65 mg/$m^2$, 5-FU bolus 320 mg/$m^2$, 5-FU infusion 2,000 mg/$m^2$/46 hours with a fixed leucovorin dose of 400 mg/$m^2$.

This study used a 3 + 3 dose escalation design with patients enrolled in standard cohorts of three until dose-limiting toxicity (DLT) was observed in the first course. Patients with CNS tumors and those with non-CNS solid tumors were enrolled on parallel cohorts and evaluated for dose escalation separately, as there was concern that the possible neurotoxicity noted with oxaliplatin could affect the toxicity attributions in patients with CNS tumors and underlying neurological changes. Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. DLT was defined as (i) non-hematologic toxicity $\geq$ grade 3 despite maximal medical management (excluding transaminitis, alopecia, diarrhea, nausea, or vomiting that resolved by the end of the course); (ii) grade 4 neutropenia lasting $>$7 days or associated with fever $\geq$38.5°C; (iii) grade 4 thrombocytopenia lasting $>$7 days; (iv) grade 3 or 4 thrombocytopenia with significant bleeding episode requiring platelet transfusion; or (v) treatment delay greater than 14 days due to hematologic toxicity. The MTD was to be defined as the dose level below which two or more of three to six patients experienced DLT during the first course of therapy (three cycles or 6 weeks). To confirm tolerability, an additional 15 patients were then enrolled at dose level 2 as MTD was not reached. Patients received successive courses of protocol therapy until they withdrew consent, exhibited progressive disease, developed intercurrent illness that prevented further administration of treatment, experienced unacceptable adverse event(s), were unable or unwilling to comply with study requirements, or if study discontinuation was in their best interest. If a patient experienced DLT other than the defined or anticipated toxicities including pre-existing neurologic toxicity or the oxaliplatin-associated syndrome of laryngopharyngeal dysesthesia, the dose of study drugs were reduced by one dose level for all subsequent treatment courses. For patients who had defined/expected non-DLT toxicities, there were specific protocol guidelines for re-dosing or dose reduction of oxaliplatin or 5-FU. There were no further dose reductions below dose level-1.

## Pre-Treatment and Follow-Up Clinical Assessments

Within 7 days prior to starting protocol therapy, a complete history and physical, a list of concomitant medications, laboratory studies, and serum pregnancy test (in all females of childbearing potential) were obtained. An extent of disease evaluation with tumor measurements based on radiologic studies appropriate for the disease (CT, MRI, bone scan) were obtained within 4 weeks prior to the start of protocol therapy. Based on recommended standard care for adults treated with oxaliplatin at the time, a chest X-ray was performed at study entry. Echocardiogram or MUGA were also obtained within 4 weeks prior to treatment. On therapy disease evaluations, tumor measurements and chest X-rays (if CT was not performed as part of tumor assessment) were performed every 6 weeks. Complete physical exams, including height, weight, performance status, intercurrent medical history and current medications, and serum chemistries were obtained every 2 weeks. Complete blood counts with differential were collected weekly. Disease evaluations were performed after every three courses (6 weeks) of treatment using Response Evaluation Criteria in Solid Tumors (RECIST) Criteria [22]. All responses (CR, PR) were confirmed 4–6 weeks after the scan showing the initial response. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks. Patients who did not complete the full 6 weeks of therapy were not considered to be evaluable for response.

## Pharmacokinetic Sampling and Platinum Measurements

Heparinized blood samples (7 ml per time point) for determination of platinum in plasma ultrafiltrate were obtained at 1 and 120 minutes after the start of oxaliplatin infusion, then 24 and 48 hours after completion of infusion, and 1 week following the completion of the first dose of oxaliplatin. The same pharmacokinetic (PK) sampling schedule was then repeated on course 2/Day 1 prior to the second oxaliplatin infusion to evaluate for any evidence of accumulation. This limited sampling strategy was designed to obtain population PKs for the initial ''rapid'' decline (1 and 120 minutes), the ''intermediate'' phase (hour 24 and 48), and the ''long terminal'' phase of drug elimination (1 week and pre-course 2). Samples were not drawn from a line in which oxaliplatin was administered. The sample tubes were inverted gently to mix and then placed immediately on ice to minimize hemolysis prior to centrifugation.

Plasma ultrafiltrate was prepared on site by centrifugation at 1,000$g$ $\times$ 10 minutes at 4°C using 1 ml Amicon Centrifree Micropartition Systems filters (Millipore Corporation, Billerica, MA). The blood pellet was discarded and the plasma ultrafiltrate was centrifuged on a fixed rotor system at 3,000$g$ $\times$ 30 minutes at 4°C, and then frozen at $-$20°C or colder until shipped to the reference lab for processing. PKs were measured using a validated flameless atomic absorption spectrophotometric method previously described [23]. Platinum concentration versus time data were analyzed using previously validated non-compartmental methods by the Langrange function program [24]. AUC and half-life calculations were carried out using SAAM II software, version 2.0 (The Epsilon Group, Charlottesville, VA).

## RESULTS

Thirty-one patients received 121 courses of the modified FOLFOX regimen (Table I); all were assessable for toxicity. Eighty-seven percent of patients had a performance status of 80 or greater at time of enrollment. Sarcomas and CNS tumors were the most common tumor types enrolled (35% each). Tables I and II illustrate patient characteristics and courses listed by dose levels. Ninety percent of patients on study had received prior chemotherapy with a median of 4 prior regimens.

## Hematologic Toxicity

Hematologic toxicity as seen in adults was also noted with this regimen. Neutropenia predominated over thrombocytopenia (Table III). Grade 3 or 4 neutrophils were noted in 37 of 121 cycles overall (31%). The median duration of grade 3 or 4 neutropenia was 7 days (range 1–19) with 18 lasting $<$7 days. Grade 4 neutrophils lasting over a week resulted in dose reduction in one patient, lasting 14 days. This was noted in cycle 4 (after the DLT window) and was associated with grade 3 platelets. 5-FU was dose reduced in one patient with grade 4 neutrophils lasting 14 days. As this was outside of the DLT window and 5-FU is known to have effect on the neutrophil count, the decision was made to modify the 5-FU. Treatment delays due to neutropenia up

**TABLE I. Patient Characteristics**

| | |
|---|---|
| Patients enrolled | 33 |
| Evaluable patients | 31 |
| Male:female | 18:13 |
| Median age (range in years) | 12 (2–19) |
| Median courses per patient (range) | 1 (1–4) |
| Performance status (Karnofsky or Lansky play score) | |
| 50 | 3 (10%) |
| 70 | 1 (3%) |
| 80 | 6 (19%) |
| 90 | 8 (26%) |
| 100 | 13 (42%) |
| Prior therapy | |
| Chemotherapy | 28 (90%) |
| Radiation therapy | 17 (55%) |
| Surgery | 29 (94%) |
| Immunotherapy | 7 (23%) |
| Hormonal therapy | 0 |
| Tumor types | |
| CNS[a] | 11 (35%) |
| Hepatoblastoma | 4 (13%) |
| Sarcoma | 11 (35%) |
| Other[b] | 5 (16%) |

[a]Tumor types included ependymoma (3), medulloblastoma (2), chordoma (2), one patient each with diffuse pontine glioma, high grade glioma and atypical teratoid/rhabdoid tumor (AT/RT), and one with tumor not otherwise specified (NOS). [b]One patient each with carcinoid, lymphoepithelioma, adenocarcinoma of the liver, hepatocellular carcinoma, and neuroblastoma.

to 14 days (range 2–14 days) were required in 13 of 121 cycles (11%).

Grade 3 or 4 platelets occurred in 14 of 121 cycles (12%), and lasted a mean of 7 days (range 1–35). One patient required two separate dose reductions due to grade 3 platelets. Treatment delays due to thrombocytopenia occurred in 12 patients lasting up to 35 days (range 7–35 days). Most patients had more than 1 delay for thrombocytopenia during their therapy. Only 1 CNS tumor patient required delay in therapy for low platelets. Thrombocytopenia was dose limiting in one patient treated at dose level 2, who had simultaneous grade 1 neutropenia. Bleeding events were reported in four patients, three patients with grade 1 hemorrhage (2 nose, 1 stoma), and one patient with grade 3 hemorrhage, nose. This was associated with concurrent grade 3 thrombocytopenia.

## Non-Hematologic Toxicity

The most common toxic effects were mild to moderate gastrointestinal complaints (Table IV). Fifty-seven percent of patients had grade 1 or 2 vomiting with 63% experiencing grade 1–3 vomiting. Peripheral neuropathy was also common with 50% of patients experiencing grade 1 or 2 neuropathy, but only one patient had grade 3 peripheral neuropathy. Isolated grade 3 occurrences of hypokalemia, hyperglycemia, dehydration, fever without neutropenia, abdominal pain, hypotension, hyponatremia, dypsnea, and febrile neutropenia were reported. Only two patients experienced a grade 4 non-hematologic toxicity. One patient had grade 4 hypokalemia, which was transient, easily reversible and did not require on-going therapy. The other patient had grade 4 hyponatremia was associated with grade 4 vomiting and SIADH. This patient had a CNS tumor and was discontinued from treatment for progressive disease. The oxaliplatin dose was reduced for chest tightness in one patient and was reduced for laryngeal dysesthesia in two patients. The only treatment delay secondary to non-hematologic toxicities was in one patient who complained of dysesthesia on the day of infusion and was dose decreased and delayed 3 days. There were no allergic reactions to any of the study regimen components.

Five patients had grade 1 creatinine elevations (all solid tumor patients), one preexisting, all brief, and self-limiting. Two patients had auditory, ear (not related) complaints reported. No ototoxicity was reported, however audiograms were not followed on this study. Twenty-three of 31 patients (74%) experienced at least one grade 3 or 4 adverse event over all 121 courses considered possibly, probably, or definitely related to oxaliplatin and/or fluorouracil; over half (12) of these patients had non-DLT hematologic toxicity only.

## Dose Modifications

Sixteen patients (52%) required delay in re-treatment due to toxicity in the previous cycle, primarily non-DLT, hematologic delays. Ten of the 16 patients required delays over 1 week at some period during their therapy. Overall 5 of 31 patients (16%) required oxaliplatin dose reductions due to toxicity, one required 2 separate dose reductions during a total of nine cycles. One patient also had reduction in the 5-FU dosing in addition to the decrease in oxaliplatin and additionally one had reduction of the 5-FU dose alone.

## Preliminary Evidence of Anti-Tumor Activity

Eleven of the 24 patients evaluable for disease status (46%) had stable disease at first disease response assessment, including two CNS tumor patients at dose level 2 (chordoma and ependymoma) who had stable disease for 6 and 8 weeks of therapy, respectively. One patient with diffuse pontine glioma (dose level 1) at first evaluation had response with 85% tumor necrosis, but had significant clinical deterioration and died of complications related to radiation-induced necrosis. Two of 4 hepatoblastoma patients had stable disease for 12 (dose level 2) and 24 (dose level 1) weeks, the 24-week response was confirmed. There was one confirmed partial response in a patient with osteosarcoma treated

**TABLE II. Enrollment and Dose Escalation Scheme**

| Cohort | Oxaliplatin (mg/m$^2$) | Number of patients | Number of courses delivered | Number of patients with DLT |
|---|---|---|---|---|
| 1 | 85 | 8 | 30 | 0 |
| 2 | 100 | 23 | 91 | 1 (grade 3 platelets) |
| Total | | 31 | 121 | 1 |

**TABLE III. Number of Hematologic Toxicity Occurrences by Dose Level in 121 Courses**

| | | Hemoglobin grade | | | ANC grade | | | Platelets grade | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cohort (n) | Oxaliplatin (mg/m$^2$) | 1–2 | 3 | 4 | 1–2 | 3 | 4 | 1–2 | 3 | 4 | Patients with DLT |
| 1 (8) | 85 | 15 | 0 | 1 | 8 | 7 | 3 | 11 | 4 | 0 | 0 |
| 2 (23) | 100 | 37 | 4 | 0 | 17 | 16 | 11 | 42 | 9 | 1 | 1 (grade 3 platelets) |
| Total | | 52 | 4 | 1 | 25 | 23 | 14 | 53 | 13 | 1 | |

at dose level 2 which lasted 24 weeks. Five of 11 (45%) treated sarcoma patients had stable disease or better lasting 12–24 weeks; two were confirmed. A single patient with carcinoid tumor also demonstrated stable disease for 12 weeks.

## Pharmacokinetics

Plasma samples for PK analysis were obtained from all patients enrolled. Analysis was performed on eight complete sample sets, as shown in Table V. The maximum plasma concentrations of oxaliplatin ultrafiltrate were observed 2 hours after administration at both dose levels, with 36.9% (SD 13.9%) being ultrafilterable. The mean maximum plasma concentration ($C_{max}$) was 0.288 μg/ml at the 85 mg/m$^2$ dose level and 0.294 μg/ml at the 100 mg/m$^2$ dose level. The mean ultrafilterable platinum area under the curve was 6.29 μg/ml hours (±3.77) at the 85 mg/m$^2$ dose level and 8.17 μg/ml hours (±5.43) at the higher dose level. Mean free platinum clearance (ml/minute) was 200.3 (SD 13.02, CV 65%). The median half-life was 116.7 hours across both dose levels with a wide degree of inter-patient variation (range 79.2–211.4 hours) but without obvious differences between dose levels.

## DISCUSSION

This study was designed to evaluate the feasibility and dosing of oxaliplatin when combined with 5-FU and LV in a standard FOLFOX regimen in pediatric patients with relapsed and/or refractory cancer. Adult studies have shown the effectiveness of this combination in GI malignancies in particular. The rationale for this study was based on anecdotal reports of pediatric tumor responses to similar regimens and the effectiveness of other platinum-based chemotherapies in a variety of pediatric cancers [25–30]. This regimen was generally well tolerated in a population of heavily pretreated patients. In this trial, the maximum planned dose of oxaliplatin at 100 mg/m$^2$ per dose in combination with 5-FU and leucovorin was well tolerated and defined as safe and tolerable in this patient population. This is notable as patients enrolled on the COG Phase 1 study of oxaliplatin in combination

**TABLE IV. Non-Hematologic Toxicity for all Dose Levels***

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Vomiting | 9 (30%) | 5 (16.7%) | 6 (20%) | 0 |
| Nausea | 11(36.7%) | 6 (20%) | 2(6.7%) | 0 |
| Neuropathy; sensory | 12 (40%) | 3 (10%) | 1 (3.3%) | 0 |
| Hypophosphatemia | 10 (33.3%) | 3 (10%) | 2 (6.7%) | 0 |
| AST, elevated | 11 (36.7%) | 3 (10%) | 0 | 0 |
| Hypokalemia | 11 (36.7%) | 0 | 1 (3.3%) | 1 (3.3%) |
| Fatigue | 8 (26.7 %) | 4 (13.3%) | 0 | 0 |
| ALT, elevated | 11 (36.7%) | 0 | 0 | 0 |
| Hypoalbuminemia | 8 (26.7%) | 3 (10%) | 0 | 0 |
| Hypocalcemia | 9 (30%) | 2 (6.7%) | 0 | 0 |
| Diarrhea | 9 (30%) | 2 (6.7%) | 0 | 0 |
| Hyperglycemia | 7 (23.3%) | 3 (10%) | 1 (3.3%) | 0 |
| Hyponatremia | 9 (30%) | 0 | 1 (3.3%) | 1 (3.3%) |
| PTT, elevated | 8 (26.7%) | 0 | 0 | 0 |
| Pain, headache | 6 (20%) | 2 (6.7%) | 0 | 0 |
| Alkaline phosphatase, elevated | 6 (20%) | 0 | 0 | 0 |
| Bicarbonate, low | 4 (13.3%) | 2 (6.7%) | 0 | 0 |
| Fever without neutropenia | 4 (13.3%) | 1 (3.3%) | 1 (3.3%) | 0 |
| Pain, abdomen | 4 (13.3%) | 1 (3.3%) | 1 (3.3%) | 0 |
| Hypotension | 3 (10%) | 0 | 1 (3.3%) | 0 |
| Dyspnea | 1 (3.3%) | 1 (3.3%) | 1 (3.3%) | 0 |
| Hemorrhage, nose | 2 (6.7%) | 0 | 1 (3.3%) | 0 |
| Dehydration | 0 | 0 | 1 (3.3%) | 0 |
| Febrile neutropenia | 0 | 0 | 1 (3.3%) | 0 |
| SIADH | 0 | 0 | 0 | 1 (3.3%) |

*Grade 1 or 2 toxicities occurring in ≥20% of patients. All grade 3 or 4 toxicities.

**TABLE V. Oxaliplatin Pharmacokinetics**

| Parameter | 85 mg/m$^2$ dose (n = 4) | 100 mg/m$^2$ dose (n = 4) |
|---|---|---|
| $C_{max}$ (μg/ml) | 0.288 | 0.294 |
| AUC (μg/ml hour) | 6.29 | 8.17 |
| SD (μg/ml hour) | 2.77 | 4.43 |
| Clearance (ml/minute) | 200.3 ml/minutes, SD 13.1, CV 65% | |
| $T_{½}$ (hours) | 116.7 hours (range 79.2–211.4 hours) | |

with irinotecan required dose reductions in both drugs due to excessive toxicity [12].

Similar to studies in adults and the single agent oxaliplatin pediatric study, the DLT was myelosuppression [13]. All patients who experienced a hematologic DLT were heavily pretreated with multi-agent chemotherapy, as were nearly all of the patients enrolled on this study. For all tumors, the hematologic side effects were overall relatively brief and self-limiting. Non-hematologic effects were typically mild and similar to those seen with oxaliplatin alone. Patients treated with weekly oxaliplatin had a relatively high incidence of grade 1–2 peripheral neuropathy (paresthesias and dysesthesia) [11], similar to that seen in our regimen with every 14-day infusions. Additionally, there were no DLTs associated with the neuropathy on this study. The eleven CNS patients who were treated did not appear to have increased neurologic toxicities but also had decreased platelet toxicities compared to the solid tumor group on this regimen. This decrease in platelet toxicities may be due to the CNS patients receiving fewer myelosuppressive regimens prior to participation on study compared to patients with non-CNS solid tumors. Oxaliplatin associated laryngospasm was seen in two patients on this study, with one requiring a dose reduction.

The limited PK data obtained showed similar properties to the identified PK parameters seen in adults, although with a slightly lower $C_{max}$ despite higher doses tested [31,32] and in children [10,15], with similar AUC, clearance, and half-life. Our limited data set did not suggest any evidence of accumulation, enhanced toxicity or altered metabolism based on the results obtained and did not suggest any alterations in oxaliplatin PK in children when combined with 5-FU and leucovorin compared to single agent oxaliplatin parameters published previously.

Nine of 23 patients (39%) experienced either stable disease through at least 6 weeks of therapy or in the case of one patient, confirmed partial tumor response. All of these patients had extensive prior treatment. While the patient with the partial response was treated at the higher dose level (oxaliplatin 100 mg/m$^2$), disease stabilization was seen in patients treated at both dose levels. Significant proportions of patients with sarcoma (5 of 11) or hepatoblastoma patients (2 of 4) had stable disease. This is similar to the activity seen in the many early phase pediatric trials of both single agent and combination studies. Most pediatric patients who experienced stabilization of disease or better following treatment with oxaliplatin were patients with sarcomas [10–14]. An additional factor that may be associated with lower response rates in early phase clinical trials is the enrollment of heavily pretreated patients with aggressive refractory disease.

Based on this study, oxaliplatin and 5-FU given in a FOLFOX regimen with oxaliplatin dosed at 100 mg/m$^2$, LV at 200 mg/m$^2$, and 5-FU at 2,400 mg/m$^2$/48 hours is a feasible therapy with relatively minor side effects in children with refractory solid tumors, including CNS tumors. This study did not define an MTD. However, it was not designed to evaluate doses that would exceed the recommended doses being used in adults with cancer. Importantly, ototoxicity and bleeding events were not observed during this study.

This regimen does require continuous infusion 5-FU. While proven feasible, in pediatrics the continuous infusion is not convenient to administer. Additionally, 5-FU, like a number of other chemotherapy agents, has been subject to variable supply and availability recently. Further study of oxaliplatin either in this regimen or with alternative combinations to determine its anticancer effect in children is warranted, as its side effect profile is manageable. In addition, newer data regarding microsatellite instability or mismatch repair may also guide future treatment decisions [33–36]. Patients with defective mismatch repair may not only not benefit from 5-FU but may have enhanced toxicity with this agent. While mismatch repair assays were not widely available at the time of inception of the study, they may aid decision-making regarding use of 5-FU containing regimens in the future.

Platinum compounds have played an important role in the successful treatment of pediatric cancers over the past 30 years and next generation agents that have reduced toxicity along with less risk of resistance may prove to have better effectiveness. Due to the bulky DNA adduct formation of oxaliplatin, this is an attractive mechanism to overcome potential chemotherapy resistance. Many of the patients who responded this regimen had received prior platinum compounds suggesting that this agent may provide improved sensitivity. Additionally, combinations with anti-angiogenic agents and other small molecule inhibitors could also be of interest with this regimen, similar to adult strategies [16–20,37]. As the molecular profiling of tumors becomes more common, cancer therapy can be more accurately directed to target inhibition of oncogenically active pathways.

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