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ORIGINAL REPORT

Phase I Study of Weekly Oxaliplatin in Relapsed or Refractory Pediatric Solid Malignancies

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
To explore feasibility, maximum-tolerated dose (MTD), and recommended dose (RD) for phase II studies of weekly oxaliplatin for the treatment of relapsed or refractory pediatric solid malignancies.

Patients and Methods
Eligible patients were 6 months to 21 years old, had a diagnosis of a solid malignancy, and had experienced treatment failure with at least two or more previous lines of therapy. The phase I study was multicentric, open-label, and nonrandomized. It foresaw two phases: a dose-escalation phase (comprising six levels) to find the RD and an extension at the RD to evaluate the cumulative toxicity. Oxaliplatin was administered intravenously over 2 hours on days 1, 8, and 15 of a 28-day cycle.

Results
Forty-five patients were enrolled: 29 patients in the dose-escalation phase and 16 patients in the extension at the RD. Median age was 9.5 years (range, 2.8 to 20.0 years) and 7.8 years (range, 1.8 to 19.2 years), respectively. The dose-limiting toxicities during the first treatment cycle were grade 3 (G3) sepsis at 50 mg/m^2, G3 dysesthesia at 90 mg/m^2, and G3 dysesthesia and G3 paresthesia at 110 mg/m^2, thus the MTD and RD was 90 mg/m^2. No case of ototoxicity was reported. Stable disease was reported in seven patients (16.3%), and confirmed partial response was observed in two patients (4.7%), one with neuroblastoma and one with osteosarcoma.

Conclusion
Oxaliplatin administered in a weekly schedule has an acceptable safety profile, different from cisplatin and carboplatin, and shows activity in children with relapsed or refractory solid tumors, suggesting further investigation in pediatric malignancies.

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INTRODUCTION

Oxaliplatin-based chemotherapy is a standard for adjuvant and advanced treatment of colorectal cancer in adults.[1-3] Like other platinum compounds, oxaliplatin forms platinum-DNA adducts, leading to cell death.[4] In addition, it is active in cell lines with acquired or intrinsic cisplatin resistance and in tumors resistant to first line platinum-based therapy.[5,6]

Cisplatin and carboplatin are key chemotherapeutic components in a variety of pediatric malignancies but are associated with severe renal or neuronal toxicities, myelosuppression,[7] and ototoxicity,[8-11] the latter possibly leading to a poor quality of life, especially for children.

Oxaliplatin exhibits a different toxicity profile, mainly related to sensory neuropathy, which generally resolves over time.[12] Lack of renal and ototoxicity would be an important benefit and may potentially allow platinum dose intensification. Furthermore, a weekly schedule of oxaliplatin given at a lower total dose may enable prolonged exposure to active compound and reduce adverse effects.

To explore whether weekly oxaliplatin is a feasible treatment option for relapsing or refractory pediatric solid malignancies, we conducted a multicenter, open-label, noncomparative, nonrandomized phase I study.

PATIENTS AND METHODS

Eligibility

Eligibility criteria included patient age of 6 months to 21 years; histologic or cytologic diagnosis of solid malignancy; two or more previous lines of chemotherapy and/or no effective treatment available; life expectancy ≥ 6 weeks; no concomitant anticancer or investigational drug;

Eastern Cooperative Oncology Group performance status ≤ 2 or Lansky play score more than 50%; completion of anticancer therapy ≥ 4 weeks before study entry; no clinical evidence of peripheral sensory or motor neuropathies; adequate bone marrow; AST/ALT ≤ 2.5× the upper limit of normal (ULN); bilirubin ≤ 1.5× the ULN; creatinine less than 3× the ULN for age; no organ toxicity, including ototoxicity grade ≥ 2; and informed consent signed. The protocol was approved by institutional review board/independent ethics committee.

Treatment Design

The study was articulated in two phases: a dose-escalation phase to determine the maximum-tolerated dose (MTD) and the recommended dose (RD) and an extension to evaluate activity and cumulative toxicity at the RD. Dose escalation was started at 40 mg/m^2 (80% of adult RD intensity/wk), then escalated to 50, 60, 75, 90, and 110 mg/m^2. For each dose level, at least three patients were to be treated. If none developed a dose-limiting toxicity (DLT), the next patient received the following dose level. If at least one developed a DLT, up to three additional patients were to be treated at the same dose. If two or more DLTs occurred at a given dose level, escalation was stopped, leading to three additional patients treated at the previous dose level. Intrapatient dose-escalation was not allowed. MTD and RD were thus defined as the dose level immediately below the dose at which at least two patients experienced DLT during cycle 1. In the extension phase, at least 10 patients were to receive no fewer than four cycles at the RD to evaluate cumulative toxicity.

Oxaliplatin was administered intravenously over 2 hours on days 1, 8, and 15 of a 28-day cycle. Antiemetic treatment, including anti-5-HT$_3$ with corticosteroids, was allowed. Treatment was to be continued until disease progression, unacceptable toxicity, patient or parental refusal, or treatment delay of more than 3 weeks.

Toxicity

A DLT was defined as grade 4 neutropenia lasting more than 7 days, grade 4 thrombocytopenia (< 10.0 × 10^9/L) lasting more than 7 days, documented infection during grade 4 neutropenia, any grade 3 or worse nonhematologic toxicity (except grade 3 nausea/vomiting in absence of optimum antiemetic treatment, transient AST/ALT, fever, or mucositis), grade 2 peripheral neuropathy not resolved before initiation of the following cycle, or life-threatening toxicity.

Adverse events and laboratory variables were assessed using the National Cancer Institute Common Toxicity Criteria version 2.0, with the exception of neurotoxicity, which was graded to an oxaliplatin neurotoxicity scale: grade 1, paresthesias/dysesthesias, possibly cold-induced, interfering with function; grade 2, paresthesias/dysesthesias interfering with function but not with activities of daily living; grade 3, paresthesias/dysesthesias with pain or functional impairment and also interfering with activities of daily living; and grade 4, paresthesias/dysesthesias that are disabling or life-threatening. An audiometric test was conducted every four cycles.

If a grade 4 neutropenia or grade 3 to 4 thrombocytopenia occurred on day 8 or day 15, treatment was omitted. The next cycle began at day 29 after recovery to ≤ grade 2 neutropenia and ≤ grade 2 thrombocytopenia. In case of nonhematologic toxicity, treatment was delayed until less than grade 1 or recovery. Paresthesias/dysesthesias were required to be ≤ grade 2 before the next cycle. No treatment was administered in case of grade ≥ 2 sensory neuropathy on days 8 or 15. In the event of pharyngolaryngeal dysesthesia, the infusion duration was to be increased from 2 to 6 hours. Doses that were reduced for toxicity were not re-escalated. If grade 4 toxicity kept persisting despite dose reduction, treatment was to be discontinued, but safety and efficacy evaluations were to be continued.

Neurophysiologic Evaluation

Neurophysiologic evaluation was performed at baseline and after at least four cycles of treatment or if neurologic toxicity occurred. It consisted of comprised measurement (Viking II and Spirit machines; Nicolet Biomedical Sarl, Trappes, Yvelines, France) of conduction velocity in the median nerve and somesthetic-evoked potentials (SEPs) in the median and posterior tibial nerves. For each test, at least two recordings were obtained and the results were compared with previously established normative laboratory values (M. Mayer, personal communication, August 2005).

Pharmacokinetics

Blood samples for plasma and plasma ultrafiltrate (PUF) platinum concentrations were collected at selected collection times during cycle 1 and immediately before starting cycle 2. Five mL of blood were drawn and immediately centrifuged at 1,000 × *g* for 10 minutes at 4°C. A total of 500 μL of plasma was removed and frozen for total platinum analysis. Two mL of the remaining plasma was loaded onto Amicon micropartition filters (Millipore S.A., Saint-Quentin, France) and centrifuged at 2,000 × *g* for 30 minutes (4°C). The protein-free ultrafiltrate was stored at −20°C until analysis. Platinum concentrations were determined using a validated Inductively Coupled Plasma Mass Spectrometry method that measures atomic platinum with a limit of quantification of 1 ng/mL for PUF.

Oxaliplatin-associated platinum concentrations in PUFs were analyzed using a noncompartmental pharmacokinetic analytic method (WINNonlin Professional, version 4.01; Scientific Consultant, Apex, NC). Maximum concentrations (C_{max}) were obtained directly from experimental observations. The area under the concentration-time curve (AUC) from time 0 to 48 hours ($AUC_{0\text{-}48\ hours}$) was calculated using the trapezoidal method. The AUC from time 0 to infinity was calculated as a function of time from 0 to the real time t_{last}, with time corresponding to the last concentration above the limit of quantification (AUC_{last}) plus (last concentration [C_{last}]/slope of the regression line of the terminal phase of the plasma concentration versus time curve, on a semi-logarithmic scale [λz]). AUC values were retained only if the percent of extrapolated AUC was less than 10%. The plasma clearance (CL) was calculated as dose/AUC. The volume of distribution at steady-state (Vss) was calculated as CL times the mean residence time (MRT = AUMC/AUC − t/2; where t is the infusion duration and AUMC is the area under the curve of moments calculated using the trapezoidal method).

In addition, PUF platinum terminal half-life ($t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$) was calculated by compartmental analysis (WINNonlin Professional, version 4.01). Best fit was assessed by visual analysis of residuals. A three-compartment model best fitted the PUF concentration-versus-time data after multiple dosing. A weighted least squares computation (1/y^2) was used for PUF.

Tumor Response

Tumor response was assessed according to WHO criteria[13,14] every two cycles. Objective responses were to be confirmed at 4 to 6 weeks. Efficacy parameters included complete response (CR), partial response (PR), duration of response (time from CR or PR to disease progression), and progression-free survival (PFS; time from first treatment to disease progression, death, or cutoff date).

RESULTS

Patient Characteristics

Twenty-nine patients were enrolled in the dose-escalation phase, and 16 patients were enrolled in the extension phase (Table 1). Median age at enrollment was 9.5 years and 7.8 years, respectively. The majority of patients had Eastern Cooperative Oncology Group performance status 0 to 1, metastatic disease, and had experienced relapse after prior therapy (median, two chemotherapy regimens, with nearly all including platinum compounds). Overall, 46% of patients had bone and 36% had bone marrow involvement.

In the dose-escalation phase, 28 patients were treated and were assessable for efficacy and safety. One patient was not treated because of organ toxicity (audiometric test grade 3). One patient received only partial cycle 1 at 75 mg/m^2 because of early tumor progression and was thus not assessed for DLT.

Table 1. Patient Characteristics

Variable	Dose-Escalation Phase		Extension at the RD	
	No.	%	No.	%
No. of patients	29		16	
Male	17	58.6	7	43.8
Age at inclusion, years				
Median	9		7	
Range	2-19		1-9	
ECOG or equivalent Lansky play score				
0-1	25	86.2	14	87.5
2	4	13.4	1	6.3
Not evaluated	0	0	1	6.3*
Prior treatment				
Chemotherapy	29	100	16	100
Carboplatin	17	58.6	13	81.3
Cisplatin	22	75.9	13	81.3
Radiation therapy	19	65.5	9	56.3
No. of prior chemotherapy regimens				
Median	2		2	
Range	1-10		1-8	
Type of cancer				
Neuroblastoma	11	37.9	7	43.8
Osteosarcoma	6	20.7	2	12.5
Ewing's tumor	2	6.9	2	12.5
Nephroblastoma	2	6.9	1	6.3
Rhabdomyosarcoma	2	6.9	0	0
Germ cell tumor	2	6.9	1	6.3
Brain tumors	3	10.0	1	6.3
Hepatoblastoma	1	3.4	0	0
Other malignant tumor	0	0	2	12.5
Disease status at study entry				
Relapse	26	89.7	13	81.3
No. of relapses				
1	14	48.3	6	37.5
2	9	31.0	3	18.8
3+	3	10.0	4	25.0
Missing	3	10.3	3	18.8
Refractory after first-line therapy	3	10.0	3	18.7
Metastatic	18	62.1	10	62.5
Nonmetastatic	11	37.9	6	37.5
Time since initial diagnosis, months				
Median	24		31	
Range	5-135		8-60	

Abbreviations: RD, recommended dose; ECOG, Eastern Cooperative Oncology Group.
*Patient not treated.

In the extension, 15 patients were treated with oxaliplatin 90 mg/m^2 and were assessable for efficacy and safety. One patient discontinued because of disease progression before baseline measurements and did not receive study treatment. One patient received only partial cycle 1 treatment because of tumor progression and early death and was not assessed for DLT.

DLTs

During the first treatment cycle, one of six patients experienced dose-limiting grade 3 sepsis at 50 mg/m^2; of three patients treated at 110 mg/m^2, one patient had grade 3 dysesthesia and one had grade 3 paresthesia. Therefore, the dose was de-escalated to 90 mg/m^2, where one of six patients treated experienced grade 3 dysesthesia (Appendix Table A1, online only). The MTD and RD for the oxaliplatin phase II study was established as 90 mg/m^2 administered as a 2-hour infusion on days 1, 8, and 15 of a 28-day cycle. Furthermore, during cycle 2, four patients with neuroblastoma experienced dose-limiting grade 3 thrombocytopenia, of whom two patients also experienced grade 4 neutropenia, one patient experienced grade 3 dehydration after vomiting, and one patient experienced grade 3 laryngospasm.

Safety

A total of 59 cycles were administered (median, two cycles/patient; range, one to six cycles) during the dose-escalation phase, and 28 cycles (median, two cycles/patient; range, one to four cycles) were administered in the extension phase at the RD. The mean cumulative normalized dose was 389 mg/m^2 (range, 120 to 1,220 mg/m^2) and 425

Table 2. Adverse Events Occurring in ≥ 10% of Patients in Either Phase of the Study*

Adverse Event	Dose-Escalating Phase (n = 28)		Extension at the RD (n = 15)	
	All Grades (%)	Grades 3 to 4 (%)	All Grades (%)	Grades 3 to 4 (%)
Any event	100.0	82.1	100.0	73.3
Paresthesia	50.0	3.6	60.0	6.7
Abdominal pain	39.3	10.7	13.3	0.0
Pyrexia	35.7	3.6	40.0	6.7
Asthenia	28.6	0.0	20.0	0.0
Thrombocytopenia	28.6	28.6	40.0	26.7
Headache	25.0	7.1	6.7	0.0
Vomiting	25.0	3.6	26.7	13.3
Diarrhea	21.4	0.0	26.7	0.0
Cough	17.9	0.0	6.7	0.0
Dysesthesia	17.9	7.1	0.0	0.0
Nausea	17.9	0.0	6.7	0.0
Arthralgia	14.3	0.0	0.0	0.0
Bone pain	14.3	14.3	20.0	0.0
Dysesthesia pharynx	14.3	0.0	6.7	0.0
Pain in extremities	14.3	0.0	13.3	13.3
Anorexia	10.7	0.0	20.0	6.7
Chest pain	10.7	0.0	6.7	0.0
Hyperesthesia	10.7	0.0	6.7	0.0
Paresthesia mucosal	10.7	0.0	0.0	0.0
Pruritus	10.7	0.0	6.7	0.0
Anemia	7.1	7.1	13.3	13.3
Muscle cramps	7.1	0.0	13.3	0.0
Back pain	3.6	0.0	20.0	6.7
Pain, not specified	3.6	3.6	13.3	6.7
Peripheral sensory neuropathy	0.0	0.0	13.3	0.0
Superior vena cava occlusion	0.0	0.0	13.3	13.3

Abbreviation: RD, recommended dose.
*Graded according to National Cancer Institute Common Toxicity Criteria version 2.0.

mg/m^2 (range, 180 to 1,080 mg/m^2) in the dose-escalation and extension phases, respectively. Seven patients (three patients during dose-escalation and four patients at the RD) had received cumulative oxaliplatin doses greater than 500 mg/m^2 (range, 720 to 1,220 mg/m^2). Six patients (21%) and three patients (20%) in the dose-escalation and RD phases, respectively, had treatment delays of more than 5 days, most because of adverse events. Twenty-three patients (82%) and 11 patients (73%) in the dose-escalation and RD phases had a grade 3 to 4 adverse event, respectively.

Adverse events are listed in Table 2. During the dose-escalation phase, the most common toxicities reported were all grades paresthesia (50%), abdominal pain (39%), and pyrexia (36%). During extension at the RD, the most common toxicities reported were all grades paresthesia (60%), pyrexia (40%), and thrombocytopenia (40%). Grade 3 to 4 thrombocytopenia was reported in 27% of all patients. Grade 1 creatininemia was noted at baseline or during study treatment in seven patients; none experienced grade 2 to 4 renal toxicity. No case of ototoxicity was observed in all six patients receiving four or six treatment cycles as determined by audiometric test (five patients) or clinically (one patient).

Treatment was stopped mostly as a result of disease progression in both study phases (82% and 73%, respectively), and there was one early death. Three patients in each phase (11% and 20%, respectively) discontinued treatment because of adverse events: prolonged grade 3 to 4 thrombocytopenia, including delaying treatment more than 3 weeks (two patients with relapsing metastatic neuroblastoma in cycle 2), one patient with neurotoxicity after cycle 1, and one patient with allergic reaction at the first administration of cycle 4. Two patients stopped treatment, thus undergoing surgery, one patient on investigator's decision.

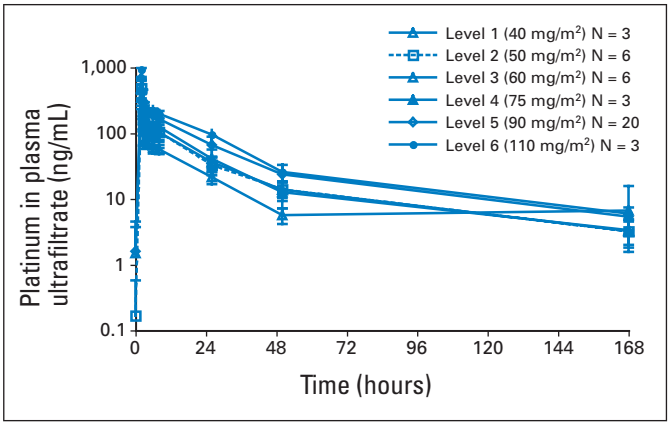

Fig 1. Platinum concentration-time profiles in plasma ultrafiltrate (mean ± standard deviation) from 0 to 168 hours and 0 to 26 hours after the first infusion.

Neurophysiologic Evaluation

Thirty-four of 45 patients underwent a neurophysiologic evaluation before oxaliplatin administration. Three of six patients who had received four or more complete cycles of study treatment had a second evaluation 2 to 4 weeks after the last oxaliplatin dose and cumulative doses of 720, 900, and 1,220 mg/m^2. One evaluation was performed after two cycles and a cumulative dose of 480 mg/m^2 in a child that had experienced dose-limiting dysesthesia at 110 mg/m^2. None of the four children reported clinical symptoms at the time of neurophysiologic evaluation.

The amplitude of the response in the sensory axons of type II fibers was reduced after treatment in two patients who had received 900 and 1,220 mg/m^2(50% and 36% reductions compared with the initial amplitudes). Both patients had evidence of pre-existing electrophysiologic alterations in sensory axons of type II fibers (88% of the lower limit of normal and at the lower limit of normal). No changes were observed in the two children who received 480 and 720 mg/m^2. Electrophysiologic changes in motor nerves were not observed.

Median nerve SEPs showed an alteration in the type I fibers of all four patients; however, at baseline, in three children, the SEP amplitudes were already reduced compared with normal values, and they remained stable after oxaliplatin treatment. Similar results were observed for posterior tibial nerve SEPs: one patient had normal (144% of the lower limit of normal) amplitude at baseline, which decreased to 33% of initial value after 1,220 mg/m^2 of oxaliplatin treatment. The other three patients had subnormal amplitudes at baseline; one of whom underwent a further marked decrease after 720 mg/m^2 oxaliplatin treatment.

Pharmacokinetics

Because of irreversible binding of platinum complexes to plasma protein and erythrocytes, PUF platinum is considered to represent all the platinum species with antitumor and toxic properties after administration of oxaliplatin.

Forty-one patients were analyzed for pharmacokinetic parameters. Thirty-one of 36 patients having PUF samples available were assessed for PUF platinum clearance. Platinum was highly bound to plasma proteins, with a plasma binding of 66.5% ± 9% (mean ± standard deviation) at the end of infusion, 86.8% ± 4.2% at 1 hour, and 98.1% ± 1.6% at 168 hours. Comparative mean (± standard

Table 3. Pharmacokinetic Parameters for Platinum Ultrafiltrate After the First Infusion (first cycle)

Parameter	Escalation Level and Dosage						
	1 (40 mg/m^2)	2 (50 mg/m^2)	3 (60 mg/m^2)	4 (75 mg/m^2)	5 (90 mg/m^2)	6 (110 mg/m^2)	Overall
C_{max}, ng/mL							
No. of patients	3	6	4	3	17	3	NA
Mean	344	481	489	669	696	926	
SD	82.2	143	171	400	287	45.8	
$AUC_{0\text{-}48h}$, ng · h/mL							
No. of patients	3	6	4	3	17	3	NA
Mean	1,830	3,020	2,990	3,120	4,880	6,370	
SD	262	764	624	1,340	1,240	1,090	
$AUC_{0\text{–}inf}$, ng · h/mL							
No. of patients	2	5	4	2	16	2	NA
Mean	2,242	4,351	4,102	4,788	6,669	7,910	
SD	390	947	910	2,133	1,786	232	
CL, L/h/m^2							
No. of patients	2	5	4	2	16	2	31
Mean	8.97	5.87	7.15	8.62	7.13	6.8	7.07
SD		1.47	1.45		1.67		1.93
Vss, L/m^2							
No. of patients	2	5	4	2	16	2	31
Mean	340	230	300	373	294	278	292
SD		54	85		73		171
$t_{1/2\alpha}$, h							
No. of patients	3	5	3	2	13	2	28
Mean	0.161	0.168	0.193	0.378	0.248	0.133	0.220
SD	0.038	0.101	0.080		0.226		0.170
$t_{1/2\beta}$, h							
No. of patients	3	5	3	2	13	2	28
Mean	10.6	9.61	13.4	10.3	10.8	13.4	11.0
SD	2.10	2.63	2.66		4.89		3.75
$t_{1/2\gamma}$, h							
No. of patients	3	5	3	2	13	2	28
Mean	337	281	224	390	282	390	297
SD	318	319	98.7		281		270

Abbreviations: C_{max}, maximum concentration; NA, not applicable; SD, standard deviation; AUC, area under the concentration-time curve; CL, plasma clearance; Vss, volume of distribution at steady-state; $t_{1/2}$, terminal half-life.

deviation) platinum concentrations in PUF (0 to 168 hours and 0 to 26 hours), after the first infusion, are shown in Figure 1. Table 3 lists the main PUF pharmacokinetic parameters. PUF clearance was dose-independent (Kruskal-Wallis test, $P = .3366$), whereas AUC increased linearly with dose (Appendix Fig A1, online only). In two of the three patients experiencing neurologic DLT, pharmacokinetic samples were available. Both patients had high AUCs, although higher levels were found in patients where no DLT was observed. PUF clearance corrected for body-surface area did not seem different according to age groups (Appendix Fig A2, online only).

Pretreatment evaluation of glomerular filtration rate (GFR), as measured by ^{51}EDTA clearance, was available in 22 patients. PUF clearance was linearly correlated to GFR (r^2, 0.81; $P < .0001$). Clearance can be estimated by the following equation: Cl (L/h) = (1.47 × GFR) + 0.87 (Fig 2). This confirms that in children, the main mechanism of platinum excretion is through the kidney and that extrarenal clearance accounts for approximately 10% of the clearance rate. Data over time showed no significant increase in C_{max} levels on days 8 and 15 (Appendix Table A2, online only).

Efficacy

Forty-three patients (28 patients in the dose-escalation phase and 15 patients in the extension phase) were assessable for response. Tumor control (CR + PR + SD) occurred in nine patients (20.9%; 95% CI, 10% to 27%). The median PFS was 1.8 months in both parts of the study (95% CI, 1.3 to 1.9 months, and 95% CI, 1.2 to 2.1 months, respectively). The best overall response (CR + PR) rate was 4.7% (95% CI, 0% to 16%), comprising two confirmed PRs. One patient with a pleural osteosarcoma metastasis experienced a PR after one cycle at 110 mg/m^2 (Appendix Fig A3, online only). The second patient with a lumbo-aortal neuroblastoma experienced a PR after two cycles at 110 and 90 mg/m^2. Both patients had received 600 mg/m^2 of cisplatin before study treatment.

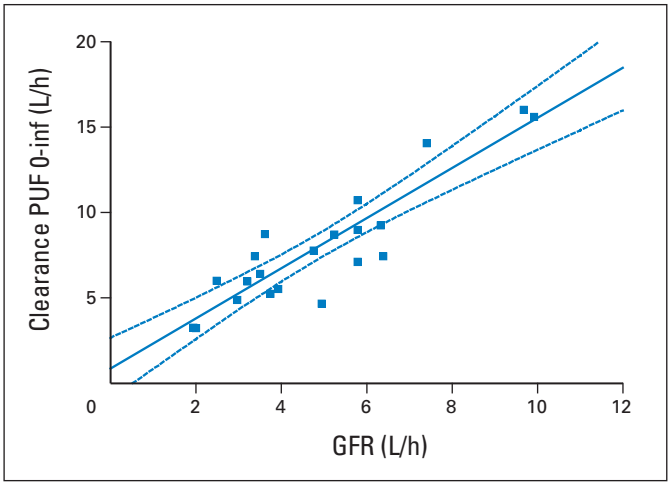

Fig 2. Correlation of free platinum plasma clearance with pretreatment glomerular filtration rate (GFR) in 21 children treated with oxaliplatin. (——), linear regression line; (– – – –), 95% CIs. Mean ± SE = 1.47 ± 0.16 for the slope and 0.87 ± 0.86 for the γ intercept. Correlation coefficient $r^2 = 0.81$, $P < .0001$. PUF, plasma ultrafiltrate.

DISCUSSION

The MTD and RD of oxaliplatin for phase II clinical studies in children is 90 mg/m^2 given as a 2-hour infusion, administered weekly for 3 consecutive weeks of a 4-week cycle. Despite the fact that eligible patients carried advanced disease and were heavily pretreated with myelosuppressive/neurotoxic compounds and radiotherapy, all doses of oxaliplatin were tolerable. As for adults,[15,16] and recently for children,[17,18] we detected a high incidence of peripheral sensory neuropathy (paresthesia and dysesthesia), which resolved over time. Although the second phase of the study aimed to achieve more information on cumulative toxicity, this failed as a result of rapid disease progression in most children. Nevertheless, six patients received cumulative doses between 720 and 1,220 mg/m^2. No cumulative neurologic toxicity was reported, and further investigation is needed.

Similar to the study of Fouladi et al,[18] a high rate of grade 3 to 4 thrombocytopenia was observed. Most of these children had metastatic neuroblastoma and had received intensive prior treatment. Nausea and vomiting were generally mild. This may be attributed to the concomitant use of 5-HT$_3$ antagonists (received by 98% of patients), which suggests that these adverse effects can be easily managed with standard antiemetic medications. DLTs were sepsis at 50 mg/m^2, dysesthesia at 90 mg/m^2, and dysesthesia and paresthesia at 110 mg/m^2. Neither renal nor ototoxicity was observed in systematically performed audiometric evaluations after prolonged treatment.

Pharmacokinetic evaluations showed that for a 2.75-fold increase in oxaliplatin dose (40 mg/m^2 to 110 mg/m^2), mean C_{max} and AUC of platinum in PUF increased by approximately 2.69- and 3.53-fold, respectively. The pharmacokinetic parameters C_{max}, AUC_{0-48}, and AUC after oxaliplatin infusion seem to be similar to values observed in adults[19] and those reported recently in two studies in children with every 2 weeks or every 3 weeks oxaliplatin administrations.[17,18]

Electrophysiologic evaluations indicate a high incidence of cumulative neurotoxicity on type I and II fibers owing to prior treatments. No evidence of oxaliplatin toxicity was observed on the axons of peripheral motor nerves or on those of central pathways. Data of the four patients who underwent both pre- and post-treatment neurophysiologic evaluations showed evidence of oxaliplatin toxicity on the axons of peripheral sensory type II fibers; however, the neurophysiologic alterations were subclinical.

In the present study, the weekly schedule allowed higher dose-intensity compared with the every 2 weeks or every 3 weeks schedules commonly used (67.5 mg/m^2/wk *v* 42.5 and 43.3 mg/m^2/wk, respectively). However, because of the long half-life of oxaliplatin,[18] the weekly schedule was limited by increasing neurotoxicity and thrombocytopenia.

Tumor control was achieved in nine patients, with confirmed PRs reported for two patients at the 110 mg/m^2 dose level, which was, however, the dose level above the MTD. Considering the advanced disease stage and high level of previous platinum therapy in this population, the efficacy of single-agent oxaliplatin should be further explored, particularly in osteosarcoma and neuroblastoma.

In conclusion, single-agent oxaliplatin administered in a weekly schedule demonstrated acceptable safety (similar to that reported for adults) and activity in pediatric relapsed or refractory solid malignancies. The profile of oxaliplatin seems to be distinct from that of cisplatin and carboplatin in that it is not associated with cumulative renal or

ototoxicities. Further investigations are warranted to establish its potential in the treatment of childhood malignancies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

