Phase I Clinical and Pharmacologic Study of Weekly Cisplatin and Irinotecan Combined with Amifostine for Refractory Solid Tumors

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ABSTRACT

Purpose: This Phase I study was designed primarily to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of irinotecan and cisplatin with and without amifostine in children with refractory solid tumors.

Patients and methods: Cisplatin, at a fixed dose of 30 mg/m², and escalating doses of irinotecan (starting dose, 40 mg/m²) were administered weekly for four consecutive weeks, every 6 weeks. After the MTD of irinotecan plus cisplatin was determined, additional cohorts of patients were enrolled with amifostine (825 mg/m²) support. Leukocyte DNA-platinum adducts and pharmacokinetics of cisplatin and WR-1065 (amifostine-active metabolite) were also determined.

Results: Twenty-four patients received 43 courses of therapy. The MTD for irinotecan administered in combination with cisplatin (30 mg/m²) was 50 mg/m². The DLTs of irinotecan were myelosuppression and thrombocytopenia. Toxicities associated with cisplatin were neutropenia and thrombocytopenia. With the addition of amifostine, at an irinotecan dose of 65 mg/m², cisplatin dose of 30 mg/m², the DLT was hypocalcemia. Although no objective responses were observed, six patients received at least three courses of therapy. The amounts of platinum adducts (mean ± SD) were 10 ± 20 molecules/10⁶ nucleotides. The maximum plasma concentrations (Cmax) for free cisplatin and WR-1065 were 4.5 ± 1.6 μM and ~89 ± 10 μM, respectively. The half-life (t1/2) for free plasma cisplatin was 25.4 ± 5.4 min. The initial t1/2 for plasma WR-1065 was ~7 min and terminal t1/2 ~24 min.

Conclusion: The combination of cisplatin and irinotecan administered weekly for 4 weeks in children with refractory cancer is well tolerated. Amifostine offers some myeloprotection, likely permitting ≥30% dose escalation for irinotecan, when administered in a combination regimen with cisplatin. However, effective antiemetics and calcium supplementation are necessary with the use of amifostine. Further escalation of irinotecan dosing, using these precautions for amifostine administration, may be possible.

INTRODUCTION

Irinotecan (Camptosar, CPT-11, 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin) is a water-soluble derivative of camptothecin, an alkaloid extracted from the Chinese tree Camptotheca acuminata (1). Its therapeutic effect is mediated by the active metabolite SN-38 (7-ethyl-10-hydroxycamptothecin), which is generated in the plasma and tissues (e.g., the liver, bowel mucosa, and tumors) by the catalytic activity of carboxylesterase that cleaves the water-solubilizing dipiperidino side chain (2). SN-38, in turn, interferes with the nicking-ligation reaction of topoisomerase I (a nuclear enzyme involved in DNA transcription, replication, and repair), preventing DNA ligation (3). Irinotecan was approved by the United States Food and Drug Administration in 1996 for the treatment of colorectal cancers refractory to 5-fluorouracil. The drug also has a broad spectrum of activity against pediatric solid tumors (4, 5). The DLTs of irinotecan are myelosuppression and diarrhea (produced by the effect of SN-38 on intestinal motility; Refs. 4 and 5). High doses of loperamide control diarrhea in most patients (6).

Cisplatin, cis-diaminedichloroplatinum (II), exerts its antitumor activity through binding to cellular DNA (7). When cisplatin enters the cell, it aquates, producing cationic species that bind to nitrogen atoms on the bases of DNA (8). Cisplatin binding alters the structure of DNA, affects its ability to act as a template in transcription, and promotes cell death by apoptosis (9, 10). Cisplatin also has a broad spectrum of antitumor activity and is included in standard front-line treatment regimens for a variety of adult and pediatric solid tumors. Cisplatin toxicities are cumulative. The primary DLTs of cisplatin are nephrotoxicity, peripheral neuropathy, and ototoxicity.

Amifostine [WR-2721, S-2-(3-aminopropylamino)ethyl phosphorothioic acid] is used to ameliorate some renal and bone
marrow toxicities (11). The drug is activated in the blood by alkaline phosphatase, producing the free thiol metabolite WR-1065 [WR-SH, S-2-(3 aminopropylamino)ethanethiol], which enters the cell by passive diffusion. The side effects of amifostine include hypotension, hypocalcemia, nausea, and vomiting (12). Guidelines for amifostine dosing, administration, and management of hypocalcemia are reported (13).

The different mechanisms of action, the lack of overlapping DLTs, and the broad spectrum of antitumor activity resulted in clinical trials to determine the MTD and DLTs of the combination of cisplatin and irinotecan administered to adults with refractory solid tumors (16–22). These studies demonstrated that the combination was well tolerated and effective. The DLTs were neutropenia, diarrhea, and cisplatin nephropathy.

Because cisplatin is widely used in pediatric tumors and the initial results of preclinical and early Phase I clinical studies suggest that irinotecan may have antitumor activity in a variety of pediatric solid tumors (1), we initiated a pediatric Phase I trial of this combination with and without amifostine. Cisplatin and irinotecan were given weekly for 4 weeks, followed by a 2-week rest. The cisplatin dose was fixed at 30 mg/m2, and the irinotecan dose was escalated in increments of ~30% (20). After the MTD of cisplatin plus irinotecan was determined, additional cohorts of patients were enrolled with amifostine (825 mg/m2) support. The study also included an estimation of the levels of leukocyte DNA-Pt adducts, the pharmacokinetics of cisplatin, and the pharmacokinetics of WR-1065.

### PATIENTS AND METHODS

#### Patient Population

Patients between 1 and 22 years of age with confirmed malignant solid tumors refractory to standard therapy were eligible for this trial. Other eligibility criteria included: (a) Karnofsky score ≥ 50% for patients >10 years old and Lansky play scale ≥ 50% for patients ≤10 years old; (b) life expectancy ≥ 8 weeks; (c) ≥3rd percentile weight for height; (d) serum albumin ≥ 2.5 grams %; (e) recovery from acute toxicity of previous therapy; (f) no significant systemic illness (e.g., uncontrolled infection); (g) no growth factors for ≥1 week before entry; (h) stable or decreasing doses of dexamethasone for ≥2 weeks before entry (for patients with CNS tumors); (i) no anticancer therapy for ≥3 weeks before entry (6 weeks for nitrosoureas); (j) no local radiation for ≥2 weeks before entry; (k) no craniospinal or ≥50% pelvic radiation for ≥6 months before entry; (l) no autologous or allogeneic bone marrow transplantation (without total body irradiation) for ≥6 months before entry; (m) no graft-versus-host disease; (n) ANC ≥ 1,000/mm3; hemoglobin concentration ≥ 8 grams/dl; (o) Pt count ≥ 100,000/mm3; (p) bilirubin ≤ 1.5 mg/dl; (q) SGPT less than or equal to twice the upper limit of normal; and (r) normal serum creatinine for age, or glomerular filtration rate.

Specific exclusion criteria were pregnancy, breast feeding, and therapy with anticonvulsants. For less heavily pretreated patients, the exclusion criteria also included more than two previous chemotherapy regimens, central axis radiation, bone marrow involvement with cancer, and previous bone marrow transplantation.

The study was approved by the institutional review board of each participating institution. Written informed consent was obtained for each patient before study entry.

Pretreatment evaluation included medical history, physical examination, performance status, tumor size, chest roentgenogram, complete blood count, serum electrolytes, creatinine, calcium, magnesium, phosphate, bilirubin, SGPT, total protein, albumin, and urinalysis. The same tests were done at least weekly thereafter. Complete blood count was done two to three times per week during myelosuppression. Tests of measurable disease, appropriate roentgenograms, bone marrow examination (if infiltrated), and audiogram were done before and every 6 weeks during treatment.

#### Treatment Plan

Cisplatin and irinotecan were administered weekly for four consecutive weeks, every 6 weeks. Courses were repeated every 6 weeks if there was no unacceptable toxicity or evidence of disease progression. The three treatment strata, irinotecan dose escalation schema, and treatment courses are shown in Table 1.

Cisplatin was administered i.v. at a fixed dose of 30 mg/m2 (mixed in 100 ml/m2 0.9% NaCl) over 60 min after 2 h of prehydration with 600 ml/m2 5% dextrose in 0.9% NaCl with 10 meq KCl/liter. Irinotecan was administered as a 90-min i.v. infusion immediately after cisplatin infusion. The starting dose of irinotecan was 40 mg/m2. The dosage was increased in

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**Table 1** Treatment strata, irinotecan dose escalation, and treatment courses

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Irinotecan (mg/m2)</th>
<th>Cisplatin (mg/m2)</th>
<th>No. of patients</th>
<th>Total no. of courses started</th>
<th>Total no. of courses completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (heavily pretreated without amifostine)</td>
<td>40</td>
<td>30</td>
<td>3</td>
<td>6</td>
<td>2a</td>
</tr>
<tr>
<td>II (less heavily pretreated without amifostine)</td>
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<td>30</td>
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<td>6</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>30</td>
<td>6</td>
<td>11</td>
<td>8b</td>
</tr>
<tr>
<td>III (less heavily pretreated with amifostine)</td>
<td>65</td>
<td>30</td>
<td>5</td>
<td>7</td>
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<td>Total</td>
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<td>24</td>
<td>43</td>
<td>34</td>
</tr>
</tbody>
</table>

* One course was completed at a irinotecan dose of 32 mg/m2.
* Two courses were completed at a irinotecan dose of 50 mg/m2.
subsequent cohorts to 50 and 65 mg/m². After administration of irinotecan, patients received two additional hours of hydration with 600 ml/m² 5% dextrose in 0.45% NaCl with 10 meq KCl/liter.

Amifostine (825 mg/m²; mixed in 100 ml/m² 0.9% NaCl) was infused i.v. over 15 min immediately before cisplatin in the cohort of patients enrolled after determination of the MTD for irinotecan administered with the fixed dose of cisplatin.

Criteria for starting a subsequent course of therapy included an ANC ≥ 1,000/mm³, Pt count ≥ 100,000/mm³, hemoglobin concentration ≥ 8 grams/dl, normal serum creatinine for age, total bilirubin ≤ 1.5 mg/dl, and SGPT less than or equal to twice the normal upper limit. Treatment doses within a course of therapy were held for any of the following: (a) ANC ≤ 500/mm³; (b) Pt count ≤ 50,000/mm³; (c) serum creatinine ≥ 150% of pretreatment value; or (d) any grade 2 or greater nonhematologic toxicity. Resumption of an interrupted course was permitted at a reduced irinotecan dosage when the toxicity resolved and the criteria for starting a new treatment course were met. In subsequent cycles of therapy, the irinotecan dosage was reduced to the previous dose level for an ANC ≤ 500/mm³ for > 7 days, Pt count < 20,000/mm³ for > 7 days, or reversible nonhematologic DLTs.

Supportive Care Measures. All patients were premedicated with ondansetron (0.15 mg/kg i.v. every 4 h × 2 or 0.45 mg/kg i.v. × 1). For patients with significant nausea and vomiting, diphenhydramine (0.5–1 mg/kg, maximum 50 mg) and ranitidine (1 mg/kg, maximum 50 mg) were recommended before amifostine infusion. Dexamethasone was not allowed as an antiemetic agent. Patients also received p.o. magnesium gluconate (3 grams/m²/day in three divided doses) or i.v. magnesium sulfate (30 mg/kg/24 h). Pneumocystis carinii prophylaxis [trimethoprim (150 mg/m²/day) plus sulfamethoxazole (750 mg/m²/day), pentamidine, or dapsone] was recommended.

Loperamide (1 mg followed by 0.5 mg every 2 h for children 1–6 years old, 2 mg followed by 1 mg every 2 h for children 6–8 years old, 3 mg followed by 1.5 mg every 2 h for children 8–12 years old, and 4 mg followed by 2 mg every 2 h for children > 12 years old) was administered at the first sign of poorly formed or loose stool or at the earliest onset of bowel movements that were more frequent than expected. Patients were allowed to stop loperamide only after being diarrhea free for ≥ 12 h. Early diarrhea (within the first 12 h of irinotecan) was treated with atropine (0.01 mg/kg, maximum of 0.4 mg/dose).

In patients who received amifostine, calcium levels (total and ionized) were monitored, and calcium was administered if amifostine-associated hypocalcemia was noted. Oral calcium carbonate, 20 mg/kg elemental calcium every 8 h × 3 starting the night before amifostine, was recommended for patients with precarious nutritional status, borderline pretherapy calcium levels, or preexisting renal tubular injury. Calcium supplements were given to all patients with hypocalcemia.

G-CSF was allowed only for patients with ANCs ≤ 500/mm³ and documented bacterial infections. Other antinecancer therapy was not allowed on the study.

Definitions of DLT and MTD. Toxicities were graded according to the Common Toxicity Criteria, version 2.0 (NIH, National Cancer Institute, 1999). A DLT was defined as any of the following adverse effects in 2 of 3–6 patients at a given dose level: (a) any grade III or IV nonhematologic toxicity with the specific exception of grade III nausea and vomiting, an elevated SGPT that returned to grade ≤ 1 before the next course, and grade III fever or infection; (b) grade IV neutropenia (ANC < 500/mm³) for > 7 days; (c) grade IV thrombocytopenia (Pt count < 10,000/mm³) for > 7 days or requiring at least two transfusions in 7 days or delaying treatment ≥ 14 days; (d) an inability to complete the first four treatment doses in 29 days; or (e) the failure to recover from toxicity by day 43.

Three patients were treated at each dose level. Up to 3 additional patients were treated at the same dose level if one of the 3 patients experienced DLT. A dose escalation was allowed if none of the 3 or 1 of the 6 patients experienced DLT during the first course of therapy. The DLTs were evaluated for all treatment cycles, although determination of MTD was performed based on toxicities during the first course only.

The MTD was defined as the dose level immediately below that at which 2 of 3–6 patients experienced DLT. No intrapatient dose escalation was allowed. The MTD was defined in both heavily pretreated and less heavily pretreated patients. After the MTD for irinotecan was determined, the amifostine stratum (stratum III) was opened at an irinotecan dose of 65 mg/m² (Table 1). Patients in this stratum were required to be less heavily pretreated.

Response Criteria. The criteria for response were: (a) complete response, resolution of all measurable tumors, and no appearance of new lesions for 3 weeks; (b) partial response, ≥ 50% decrease in the sum of products of maximum perpendicular diameters of all measurable lesions, no evidence of progression in any lesion, and no new lesions for 3 weeks; (c) SD, no evidence of progression in any lesion, and no new lesions for 3 weeks; (d) progressive disease, ≥ 25% increase in the sum of products of maximum perpendicular diameters of any measurable lesions, and/or the appearance of new lesions.

Leukocyte DNA-Pt Adducts. Leukocyte DNA-Pt adducts were determined on day 1 of the first course. Blood samples (~10 ml/time point from patients > 10 kg and ~5 ml from patients ≤ 10 kg) were drawn into EDTA tubes before cisplatin infusion, then at 0, 1, 2, and 4 h from the end of cisplatin infusion. Samples were centrifuged immediately at 4°C, and the plasma was removed. The blood cell pellets (containing theuffy coats) were stored at −20°C (storage at −70°C instead of −20°C gave the same yield; data not shown), shipped on dry ice, and processed immediately on arrival. Each sample was diluted with distilled water to 50 ml, mixed by inversions, placed on ice for ~5 min, and centrifuged at 2000 × g for 10 min. The supernatants were centrifuged, and the procedure was repeated twice. As described previously, the DNA was extracted from the leukocyte pellets, and atomic absorption spectroscopy was used to quantify the Pt adducts in the DNA (23).

Cisplatin Pharmacokinetics. Cisplatin pharmacokinetics were determined on day 8 of the first course. Blood samples (1 ml each) for plasma cisplatin determinations were drawn into EDTA tubes before cisplatin infusion, then at 0, 15, 30, 45, 60, and 90 min from the end of cisplatin infusion. The samples were centrifuged immediately at 4°C, and aliquots of the plasma were stored at −20°C. The remaining plasma was centrifuged in an Amicon Centrifree micropartition unit (30,000 molecular weight limit).
cutoff, catalogue 4104; Millipore, Billerica, MA) in a fixed-angle rotor (4°C, 2,000 × g) for 1 h. The ultrafilterates were stored at −20°, shipped on dry ice, and analyzed for cisplatin content immediately on arrival using atomic absorption spectroscopy as described previously (23).

Amifostine Pharmacokinetics. Amifostine pharmacokinetics were determined on day 14 of the first course. Blood samples (1 ml each) for amifostine metabolites were drawn into EDTA tubes that contained 10 mM (final concentration) monobromobimane before amifostine and then at 0, 1, 2.5, 5, 10, 15, 30, 60, and 120 min from the end of amifostine infusion. The samples were mixed by inversions for 3 min, stored at 4°C, shipped on wet ice, and processed immediately on arrival. A high-performance liquid chromatography technique described previously was used to quantitate amifostine metabolites (WR-1065 and its disulfide forms) in both the plasma and RBCs (24–26).

Pharmacokinetic Analyses. Pharmacokinetic analyses for nonprotein-bound (free) cisplatin and WR-1065 were performed using a nonlinear estimation program, Nonline (Statistical Consultants, Inc., Lexington, NY). The half-life (t1/2) was calculated by ln2/k, when k was the first-order rate constant for the dug decay (i.e., k was the slope of the plot of natural logarithm of drug concentration in μM versus time in minutes), as shown in Figs. 1 and 2.

RESULTS
Between December 1999 and June 2001, 43 courses of therapy were initiated in the 24 patients who participated in this trial. Thirty-four (79%) of the 43 courses were completed as planned (Table 1). Six courses (14%) were stopped early because of hematologic toxicity (five during the first course and one during a subsequent course), one (2%) because of progressive disease, one (2%) to allow for needed surgery, and one (2%) per the patient’s wish. All patients were assessable for toxicity and response. Patient characteristics are shown in Table 2, and the DLTs in the first course are shown in Table 3.

Cisplatin Plus Irinotecan without Amifostine. Dose-limiting thrombocytopenia and neutropenia occurred in 2 of the first 3 patients enrolled at the first irinotecan dose level (Table 3). All 3 patients were heavily pretreated, and thus the MTD of irinotecan was exceeded in heavily pretreated patients at 40 mg/m². Patient accrual was subsequently limited to less heavily pretreated patients (stratum II).

Six less heavily pretreated patients were subsequently treated at the first irinotecan dose level (40 mg/m²), 5 of whom completed the first course. One patient experienced dose-limiting thrombocytopenia (Table 3), and 1 had hypomagnesemia that responded to magnesium supplementation.

Escalation in the less heavily pretreated patients proceeded to the second irinotecan dose level (50 mg/m²). Four patients were accrued to this dose level, and all were able to complete the first course without DLT (Table 3).
Sandostatin (octreotide acetate).

Diarrhea (grade 4) occurred in 50% of the patients. Five patients received loperamide alone (1–4 days) and three loperamide (2–12 days) plus atropine (2–4 days). Two patients were hospitalized for the diarrhea and one received Sandostatin (octreotide acetate).

Table 3  DLTs in the first course at each irinotecan dose level

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Irinotecan (mg/m²)</th>
<th>Total no. of patients</th>
<th>No. of patients with DLT</th>
<th>DLTs</th>
</tr>
</thead>
</table>
| I       | 40                | 3                   | 2                       | Thrombocytopenia and neutropenia
| II      | 40                | 6                   | 1                       | Thrombocytopenia
| II      | 65                | 5                   | 2                       | None
| III     | 65                | 6                   | 0                       | Hypocalcemia

a Patients were unable to complete four treatment doses in 29 days because of the hematologic toxicities.
b One patient had a grade 4 hypocalcemia (serum calcium decreased from 9.8 to 4 mg/dL) and one a grade 3 hypocalcemia (serum calcium decreased from 9.8 to 6.9 mg/dL) and was associated with a serum albumin of 2.9 g/dL.

Escalation in the less heavily pretreated patients proceeded to the third irinotecan dose level (65 mg/m²). Six patients were accrued to this dose level, of whom 1 had dose-limiting neutropenia and another dose-limiting thrombocytopenia (Table 3). Grade 4 nausea and vomiting occurred in 1 patient, necessitating hospitalization for rehydration.

Thus, the MTD for irinotecan administered in combination with a fixed dose of cisplatin (30 mg/m²) weekly × 4 without amifostine was 50 mg/m²/dose for less heavily pretreated patients. No formal MTD was established for heavily pretreated patients, although the opening dose level of 40 mg/m² irinotecan was beyond MTD.

Cisplatin Plus Irinotecan with Amifostine. In an attempt to further escalate the irinotecan dosage, concomitant amifostine, at a fixed dose of 825 mg/m² (stratum III), was added to the combination regimen. Five patients were enrolled at the 65 mg/m² irinotecan dose level; however, 1 patient refused further treatment before completing an entire course. Six courses of therapy were initiated in the remaining 4 patients; 2 patients experienced amifostine-related hypocalcemia (Table 3). One patient had a grade 4 hypocalcemia ~22 h after the first amifostine dose and responded to calcium supplements. Another patient had a grade 3 hypocalcemia, which also responded to calcium supplements. Grade ≥2 hypocalcemia occurred in five of the seven courses. The hypocalcemia was asymptomatic in all patients. Nausea and vomiting (grade ≥2) occurred in six (85%) of the seven courses, necessitating hospitalization for rehydration in 1 patient. Asymptomatic hypokalemia (grade 3) occurred in 1 patient and was associated with grade 1 diarrhea and line infection.

In contrast to toxicities of cisplatin (30 mg/m²) plus irinotecan (65 mg/m²) without amifostine, there were no dose-limiting hematologic toxicities observed with concomitant amifostine support. None of the seven courses were associated with an ANC < 400/mm³ or a Pt count < 40 × 10⁹/mm³.

Diarrhea. Diarrhea (grade ≥3) occurred in 50% of the patients. Five patients received loperamide alone (1–4 days) and three loperamide (2–12 days) plus atropine (2–4 days). Two patients were hospitalized for the diarrhea and one received Sandostatin (octreotide acetate).

Leukocyte DNA-Pt Adducts. The leukocyte DNA-Pt adduct levels are shown in Table 5. Remarkable variability existed among the 15 patients studied, ranging from an undetectable level (4 patients) to 78 Pt molecules per 10⁶ nt (patient 2, who had bilateral hydronephrosis and t 1/2 for free plasma cisplatin of 43 min). The levels of Pt adducts did not correlate with response or toxicity.

Cisplatin Pharmacokinetics. The C max for total plasma cisplatin was [mean ± SD (n)] 7 ± 3.6(10) μM and nonprotein-bound (free) 4.7 ± 1.6(19) μM (i.e., ~65% of the total). The free plasma cisplatin had a single exponential decay in each patient [t1/2, 25.4 ± 5.4(19) min] (Table 5). In contrast, the total plasma cisplatin had a multiple exponential decay. The time course of total and free plasma cisplatin levels for patient 4 is shown in Fig. 1.

In patient 2, the t 1/2 for free plasma cisplatin was 43 min, which correlated with her bilateral hydronephrosis and high level of leukocyte DNA-Pt adducts (78 Pt molecules/10⁶ nt; Table 5). Thus, changes in renal function have an important

Response. Although no objective responses were observed, 6 patients received at least three courses (~18 weeks) of therapy, including 2 patients with Ewing’s sarcoma and 1 patient each with rhabdomyosarcoma, medulloblastoma, and hepatocellular carcinoma. SD was present in 15 of 24 patients (~63%) and 28 of the 43 courses (65%; Table 4).

Table 4  Patients with stable disease by tumor type

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>No. of patients with SD/ total no. of patients</th>
<th>Median no. of courses with SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewing sarcoma</td>
<td>4/7</td>
<td>2</td>
</tr>
<tr>
<td>Osteogenic sarcoma</td>
<td>0/4</td>
<td>0</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>3/4</td>
<td>2</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>3/3</td>
<td>1.5</td>
</tr>
<tr>
<td>Brain stem glioma</td>
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<td>1</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>1/1</td>
<td>3</td>
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<tr>
<td>Neuroblastoma</td>
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<tr>
<td>Total</td>
<td>15/24</td>
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</table>
Cisplatin and Irinotecan with Amifostine Support

Influence on cisplatin pharmacokinetics and pharmacodynamics. The $C_{\text{max}}$ for total plasma cisplatin of $\sim 7 \, \mu M$ (Table 5) represents only $\sim 7\%$ of the administered dose (calculated using cisplatin dose of $\sim 100 \, \mu mol/m^2$ and plasma volume of $\sim 1$ liter/m$^2$), confirming the rapid distribution and elimination of cisplatin.

**Amifostine Pharmacokinetics.** WR-1065 peaked in the plasma and RBC at the end of amifostine infusions with $C_{\text{max}}$ of 82–96 and 68–135 $\mu M$, respectively. WR-1065 also decayed from both compartments with similar initial ($t_{1/2}$, 6–8 min) and terminal ($t_{1/2}$, 20–28 min) half-lives (Table 6). The time course of plasma and RBC WR-1065 levels for patient 23 is shown in Fig. 2.

**DISCUSSION**

This is the first Phase I pediatric trial to evaluate the combination of cisplatin and irinotecan with and without amifostine support. The DLT of cisplatin and irinotecan administered weekly for four consecutive weeks every 6 weeks, in both heavily and less heavily pretreated patients, was myelosuppression (Table 3). The MTD of irinotecan when administered in combination with cisplatin (30 mg/m$^2$) was $<40 \, mg/m^2$ for heavily pretreated patients and 50 mg/m$^2$ for less heavily pretreated patients. These results are similar to the recent adult trial, showing the MTD for irinotecan in patients treated previously to be 50 mg/m$^2$ and in chemotherapy-naive patients, 65 mg/m$^2$; the DLT in both groups was neutropenia (20).

Interestingly, with the addition of amifostine, there was no dose-limiting myelosuppression after administration of the irinotecan/cisplatin combination, although the irinotecan dose was 30% greater than the MTD without amifostine support (Table 3). This result suggests that the addition of amifostine to the combination may allow for further irinotecan dose escalation. This finding is in contrast to the results of a previous pediatric Phase I trial in which higher doses of amifostine ($\leq 2700 \, mg/m^2$) did not allow for dose escalation of melphalan beyond the MTD (12). Thus, the clinical efficacy of amifostine may depend on both the type and dose of chemotherapy. Unfortunately, in this trial, a dose-limiting, amifostine-related toxicity (hypocalcemia) prevented further escalation of the irinotecan dose. However, it is quite possible that a lower amifostine dose or a more aggressive supportive care regimen may ameliorate or prevent some of the amifostine adverse effects. The amifostine dose in this trial (825 mg/m$^2$) is based on our recently completed study of some of the amifostine adverse effects. The amifostine dose in this trial (825 mg/m$^2$) is based on our recently completed study of some of the amifostine adverse effects. The amifostine dose in this trial (825 mg/m$^2$) is based on our recently completed study of some of the amifostine adverse effects. The amifostine dose in this trial (825 mg/m$^2$) is based on our recently completed study of some of the amifostine adverse effects. The amifostine dose in this trial (825 mg/m$^2$) is based on our recently completed study of some of the amifostine adverse effects.

Table 5 Nonprotein-bound (free) and total plasma cisplatin concentrations and amounts of leukocyte DNA-Pt adducts

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>$C_{\text{max}}$ (\mu M)</th>
<th>$t_{1/2}$ (min)</th>
<th>Total plasma cisplatin $C_{\text{max}}$ (\mu M)</th>
<th>Leukocyte DNA-Pt adducts (Pt molecules/10$^6$ nt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.8</td>
<td>27</td>
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<td>78$^d$</td>
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<td>4.5</td>
<td>22</td>
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<td>6</td>
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<td>7</td>
<td>3.1</td>
<td>28</td>
<td>7.3</td>
<td>ND$^e$</td>
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<tr>
<td>8</td>
<td>8.4</td>
<td>20</td>
<td>ND</td>
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</tr>
<tr>
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<td>3.6</td>
<td>30</td>
<td>3</td>
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</tr>
<tr>
<td>10</td>
<td>4.5</td>
<td>21</td>
<td>0.1$^f$</td>
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<td>6.3</td>
<td>21</td>
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<tr>
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<td>2.0</td>
<td>21</td>
<td>5.1</td>
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<tr>
<td>16</td>
<td>5.6</td>
<td>23</td>
<td>6</td>
<td></td>
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<tr>
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<td>5.1</td>
<td>24</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>4.1</td>
<td>33</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
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<td>4.5</td>
<td>25</td>
<td>ND</td>
<td></td>
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<tr>
<td>22</td>
<td>6.6</td>
<td>21</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>1.9$^g$</td>
<td>28</td>
<td>3.2$^g$</td>
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<tr>
<td>24</td>
<td>3.3</td>
<td>24</td>
<td>10</td>
<td></td>
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<tr>
<td>Mean ± SD</td>
<td>4.5 ± 1.6</td>
<td>25.4 ± 5.4</td>
<td>7.0 ± 3.6</td>
<td>10 ± 20</td>
</tr>
</tbody>
</table>

$^a$ Calculation of Pt adducts is based on 1 pg Pt/\mu g DNA = 5.13 femtomoles Pt/\mu g DNA (Pt M.W., 195.078) and 1 femtomole Pt/\mu g DNA = $\sim 0.34$ Pt molecules/10$^6$ nt (average nt M.W., $\sim 343$ g mol$^{-1}$; Ref. 23).

$^b$ Maximum Pt adduct values in the first 4 h after cisplatin infusions.

$^c$ Pt concentrations in the ultrafiltrates at the end of cisplatin infusions.

$^d$ Patient had bilateral hydronephrosis and borderline glomerular filtration rate.

$^e$ ND, non-detected.

$^f$ Lowest limit of detection.

$^g$ 5 min postcisplatin infusion.

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once, briefly and in error. Thus, G-CSF was not required for this regimen.

With amifostine, nonhematologic DLT (hypocalcemia) dominated at an irinotecan dose of 65 mg/m² (Table 3). Nevertheless, grade ≥3 myelosuppression was seen in one (15%) of the seven courses. Frequent calcium monitoring and adequate calcium supplementation are necessary for the prevention and treatment of amifostine-related hypocalcemia, especially in patients receiving cisplatin, because cisplatin may itself induce renal tubular injury.

As shown here (Table 5) and demonstrated in other studies, there is wide variation in the amount of leukocyte DNA-Pt adduct levels among patients (27–33). We reported recently that the rates of adduct formation and repair are rapid, and thus only methods that assure rapid stabilization of the adducts should be used (23).

Data describing the pharmacokinetic disposition of cisplatin administered at conventional doses, e.g., 20–40 mg/m² over 30–60 min, in children are lacking. The pharmacokinetic parameters of cisplatin in this trial (Table 5) are similar to those reported in 7 adult patients who received 40 mg/m² cisplatin over ~30 min (Cₘₐₓ for free plasma cisplatin of ~9 μM and t₁/₂ of 30 ± 3.4 min; Ref. 32).

Neither the cisplatin pharmacokinetics nor the Pt adducts appear to be altered by the amifostine treatment. These findings are consistent with other recent studies (23, 33).

The WR-1065 peaked in the plasma and RBC at the end of amifostine infusion with similar concentrations (Table 6). Free thiol metabolites were rapidly formed from the parent drug and equally distributed between the extra and intracellular compartments. Moreover, the decay rates for WR-1065 in both compartments were similar (t₁/₂ₐ = 6–8 min and t₁/₂ₚ = 20–28 min; Table 6 and Fig. 1). Detectable levels of WR-1065 and its low molecular weight disulfides were present in the plasma and RBC at ~2 h after WR-2721 infusion (Fig. 2). These results are similar to previous reports in patients with Ewing sarcoma who received WR-2721 and mesna (25, 26).

Although we observed no objective responses, 25% of the children enrolled on the trial had evidence of disease stabilization for >4 months. Thus, consideration should be given to evaluate the antitumor activity of the combination in children with refractory malignancies (34).

Table 6. Plasma and RBC levels of amifostine metabolites

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Cₘₐₓ (μM)</th>
<th>t₁/₂ₐ (min)</th>
<th>t₁/₂ₚ (min)</th>
<th>Cₘₐₓ (μM)</th>
<th>t₁/₂ₐ (min)</th>
<th>t₁/₂ₚ (min)</th>
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<tr>
<td>20 plasma</td>
<td>107</td>
<td>8</td>
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<td>22 plasma RBC</td>
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<tr>
<td>22 RBC</td>
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<td>23</td>
<td>135</td>
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<td>23 plasma RBC</td>
<td>82</td>
<td>8</td>
<td>28</td>
<td>90</td>
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