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Phase I Study of Paclitaxel with Standard Dose Ifosfamide in Children with Refractory Solid Tumors: A Pediatric Oncology Group Study (POG 9376)

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Abstract

PURPOSE—A dose-escalation Phase I study of taxol (paclitaxel) administered in combination with standard dose ifosfamide was conducted in children with relapsed or refractory solid tumors. Primary objectives were to estimate the maximum-tolerated dose (MTD) and to describe the dose-limiting toxicities (DLTs).

PATIENTS AND METHODS—Paclitaxel was administered as a 6-hour continuous infusion (hr 0–6), followed by intravenous ifosfamide (2 gm/m^2 /day × 3days) over 1 hr at hours 6–7, 24–25, and 48–49. Patients at dose level 1 received 250 mg/m^2 paclitaxel. Subsequent dose escalation proceeded using a standard 3×3 Phase I design.

RESULTS—Fifteen patients received a combined 46 courses of therapy. The median age was 14.5 years (range, 2 to 19 years), and diagnoses included sarcoma (7), neuroblastoma (3), and other (5). Three patients received paclitaxel at 250 mg/m^2 (10 courses), six at 325 mg/m^2 (19 courses), three at 425 mg/m^2 (8 courses), and three at 550 mg/m^2 (9 courses). DLTs occurred in 2/3 patients at 550 mg/m^2 paclitaxel during cycle 1, including grade 3 hypotension and grade 4 anaphylaxis in 1 patient each. Common non-dose limiting toxicities included bone marrow suppression and peripheral neuropathy. Response was evaluable in 14 patients and included mixed response (3), stable disease (5) and progressive disease (6).

CONCLUSION—Paclitaxel hypersensitivity reactions were dose limiting when the drug was administered as a 6-hour infusion. The MTD and recommended Phase II dose of paclitaxel administered as a six-hour continuous intravenous infusion followed by standard dose intravenous ifosfamide is 425 mg/m^2 paclitaxel.

Keywords

taxol; ifosfamide; Phase I; Pediatric; Solid Tumor

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Introduction

Paclitaxel (Taxol; NSC 125973) is a taxane derived from the bark of the western yew, *Taxus brevifolia* (1,2). The taxanes inhibit G2 and M-phases of the cell cycle via disruption of cell division and interphase processes by inducing polymerization of intracellular tubulin (promoting microtubule assembly) and stabilizing microtubules from depolymerization (inhibiting tubulin disassembly) (2). Paclitaxel was approved by the United States Food and Drug Administration in 1992 for the treatment of ovarian carcinoma, and subsequently was also approved for the treatment of breast cancer, Kaposi sarcoma associated with AIDS, and for non-small cell lung cancer in combination with cisplatin (3).

Phase I trials of paclitaxel administered most commonly as a 24-hour continuous infusion in adult patients with solid tumors have identified neutropenia as dose limiting (4), and 250 mg/m^2 as the maximum tolerated dose. Additional toxicities encountered included hypersensitivity reactions and neuropathies, which became dose limiting in trials employing shorter infusion times (4). Multiple schedules of paclitaxel administration with antitumor activity against adult tumors have been described; however, some studies suggest that longer infusions result in increased response rates versus shorter infusions (5,6). In prior Phase I trials in pediatric cancer patients, paclitaxel was delivered as either short infusions over three hours once per cycle (7) or twice per week (8); or continuously over 24 hours once per cycle (9–11), weekly (CCG-0903), or daily for six weeks with concurrent radiotherapy (12). As in adult studies, short infusions of one to three hours induced less hematopoeitic toxicity but were complicated by more hypersensitivity reactions (7,13) and neurotoxicity (7).

Ifosfamide is an oxazophosphorine chosen for this combination study because of its broad range of activity in pediatric solid tumors and non-overlapping non-hematological toxicities. In adult studies, combination regimens of paclitaxel with ifosfamide have been developed with favorable toxicity profiles, and activity in patients with non-small cell lung cancer, head and neck cancer, breast, uterine and ovarian cancer (14–24). The current study was undertaken to determine dose limiting toxicities (DLTs) and the maximum tolerated dose (MTD) of 6-hour infusion paclitaxel therapy combined with standard high-dose ifosfamide therapy in pediatric patients with refractory solid tumors.

Patients and Methods

Patient eligibility

Eligible patients were ≤ 21 years of age with a histological diagnosis of cancer (solid tumor or leukemia) refractory to conventional therapy or for which no effective therapy was known. Patients were to be stratified as 1) leukemia or 2) solid tumor. Other eligibility criteria included: (a) Karnofsky performance score of ≥ 50 (ECOG 0–2), (b) adequate nutritional status (> 3rd percentile for weight with respect to height, normal total serum protein and albumin/globulin ratio), (c) recovery from the acute toxic effects of prior chemotherapy, radiotherapy, or immunotherapy, (d) at least 3 months since stem cell transplants with limited or no radiation, (e) at least 6 months since transplants employing total body irradiation, and (f) at least 6 weeks since the administration of a nitrosourea. Study exclusion criteria included: severe or uncontrolled infection, active graft versus host disease, or a history of craniospinal or extensive pelvic, abdominal, or mantle and Y port radiation. Patients were required to have adequate renal function (serum creatinine below the upper limits of normal for age or a creatinine clearance or radioisotope glomerular filtration rate ≥70 mL/min/1.73 m^2 and no history of renal disease); adequate liver function (serum bilirubin ≤1.5 mg/dL, and alanine aminotransferase ≤ 2 times the institutional upper limit of normal for age). Patients without malignant infiltration of the bone marrow were required to have an absolute neutrophil count ≥ 1,500/μL and a platelet count ≥ 100,000/μL. Additional

anti-cancer therapies and enrollment on any other study were prohibited while patients were taking part in this investigation. Informed consent from the patient or their parent(s) and assent, as appropriate, were obtained in accordance with the U.S. National Cancer Institute, Children's Oncology Group, and individual institutional review board policies prior to study entry.

Dosage and drug administration

Paclitaxel, ifosfamide, MESNA and G-CSF were all commercially available. Paclitaxel was formulated in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP 50%. Pre-medication for paclitaxel included dexamethasone at a dose of 0.25 mg/kg/dose (maximum 20 mg) at -14 and -7 hours and diphenhydramine 1mg/kg/dose (maximum 50 mg) at -0.5 hours. Paclitaxel was infused intravenously over 6 hours at a concentration of 1 mg/ml. Diphenhydramine was administered every 6 hours as needed for mild allergic reactions. For severe allergic reactions such as hypotension, alterations in level of consciousness, or respiratory distress, infusions were stopped.

After paclitaxel, MESNA 400 mg/m^2 was administered by intravenous push followed 15 minutes later by ifosfamide at a dose of 2 gm/m^2 administered over 1 hour. MESNA was given every 3 hours for four additional doses. Ifosfamide and MESNA were repeated on days 2 and 3, with intravenous fluids of 3000 ml/m^2/day. G-CSF, 5 μg/kg, was administered daily beginning 24 hours after the final dose of ifosfamide and continued until the absolute neutrophil count was > 5,000/uL on one measurement or > 1,500/uL on two consecutive daily measurements. Treatment cycles were repeated at a frequency of every 21 to 28 days if there was no evidence of progressive disease or significant toxicities, the platelet count was ≥ 100,000/μL, and the absolute neutrophil count had recovered to ≥ 1,000/μL measured at least 48 hours after the discontinuation of GCSF.

Trial design

The starting dose of paclitaxel was 250 mg/m^2 with planned dose escalation levels to 325 mg/m^2, 425 mg/m^2, and 550 mg/m^2. A minimum of three patients were entered at each dose level and the dose level was expanded to up to six patients if one patient experienced dose-limiting toxicity during the first cycle of therapy. When dose-limiting toxicity was observed in two patients of a cohort of three to six patients receiving the same dose of drug, the maximum tolerated dose was exceeded. The maximum tolerated dose of paclitaxel in this combination regimen was defined as the dose level immediately below the level at which at least two patients experienced dose-limiting toxicity in the first cycle of therapy.

Toxicities were graded according to the Pediatric Oncology Group entitled ‘Toxicities and Complications Criteria’ which is similar to National Cancer Institute Common Terminology Criteria for Adverse Events (version 2.0). Dose-limiting nonhematologic toxicity was defined as grade 3 renal, pulmonary, cardiovascular or CNS toxicity, any grade 4 non-hematopoeitic toxicity, grade 4 neutropenia (ANC < 500/μL) lasting > 14 days for those without marrow involvement and marrow aplasia ≥ 4 weeks for those with marrow involvement, and platelet count < 25,000/μL for more than seven days or clinically significant bleeding for those without marrow involvement.

Criteria for assessment of response

Imaging studies to assess response were performed prior to the 2nd and 3rd courses and every other course thereafter. Response assessments were based on the sum of the products of the maximum perpendicular diameters of all lesions on imaging. Response was defined as: complete response (CR) - no evidence of disease; partial response (PR) - ≥ 50% decrease in the sum of the products of the maximum perpendicular diameters of all measurable

disease without evidence of progression in any lesion or the presence of any new lesions; minor response (MR), >25% but < 50% response; stable disease (SD) - < 25% decrease or increase; and progressive disease (PD), ≥ 25% increase and/or the appearance of new lesions.

Results

A total of 18 patients were enrolled. Two patients did not receive study drug and were therefore not evaluable for response or toxicity: one patient with leukemia died before initiation of protocol therapy and one solid tumor patient refused protocol therapy. One patient at dose level 2 received paclitaxel during cycle 1 at an incorrect dose of 325 mg total, and cycles 2 and 3 at the correct dose of 325 mg/m^2. For the purposes of cycle 1 toxicity and therefore MTD/DLT assessments, as well as for response, this patient was not assessable and replaced. Thus, 15 evaluable solid tumor patients received a combined 46 courses of combination paclitaxel/ifosfamide chemotherapy. Five patients were previously treated with both ifosfamide and cyclophosphamide: 1 patient with ifosfamide and 8 patients with cyclophosphamide. In total, 14/15 (93.3%) of patients were pre-treated with oxazophosphorine therapy. Patient demographics are summarized in Table I.

Toxicities

During the first course of therapy, three patients [one at dose level 2 (250 mg/m^2) and two at dose level 4 (550 mg/m^2)] experienced dose limiting grade 3 or 4 acute hypersensitivity reactions (Table II). During the second course of therapy, a third patient treated at dose level 4 experienced dose limiting grade 4 infusion-related loss of consciousness thought to be secondary to intoxication from the ethanol included in the paclitaxel formulation. Two patients at dose level 4 who developed dose limiting infusion reactions (1 grade 3 hypersensitivity reaction and 1 grade 4 loss of consciousness) each tolerated paclitaxel dose level 3 (375 mg/m^2) administered over 24 hours rather than 6 hours, with one patient tolerating re-challenge at dose level 4 for two courses. Paclitaxel infusion-related fevers (all grade 1) occurred in 3/15 (20%) of evaluable patients independent of dose level, and one episode accompanied by grade 1 hypotension. Two patients with paclitaxel infusion-related fever went on to tolerate subsequent courses of paclitaxel without reaction. All reactions in all patients were transient and reversed with appropriate supportive care.

Bone marrow suppression was common at all dose levels with grade 3/4 neutropenia (n=7), thrombocytopenia (n=4), and anemia (n=4) occurring during course 1 (Table III). Grade 4 neutropenia and thrombocytopenia were typically short lived, lasting less than five days in most cases, although one patient at dose level 2 (pre-treated with 6 different chemotherapeutic regimens) experienced grade 4 thrombocytopenia lasting 10 days. There were no significant bleeding episodes.

Infection appeared to be independent of dose level and independent of number and intensity of prior chemotherapy regimens. Four patients experienced febrile neutropenia (26.7%) accounting for 9 episodes of febrile neutropenia in 46 courses administered (19.6%). Associated features included an infected ear-piercing site and mucositis (1) and E coli bacteremia (1). One patient treated at dose level 2, subsequent to course 4 of therapy, developed fatal (grade 5) candidemia associated with acute renal failure. Two patients developed non-neutropenic viral infections including one episode of grade 2 herpes zoster and one episode of grade 3 herpes simplex virus infection.

Neurotoxicity commonly occurred in the form of a mild peripheral sensory neuropathy, and rarely in the form of central nervous system toxicity. Grade 1 peripheral sensory neuropathies occurred within one week of the paclitaxel infusion and manifested as a mild

transient paresthesia of the hands and/or feet. One patient's neuropathy progressed during subsequent courses (dose level 4) to a lower extremity slightly painful grade 2 neuropathy with subsequent long-term decreased sensation in the lower extremity with foot drop. The single patient with grade 2 sensory neuropathy during course 1 (dose level 2) went on to develop grade 3 painful lower extremity sensory neuropathy during subsequent courses concomitant with a decrease in Karnofsky performance status from 100 to 70. Central nervous system toxicity occurred in two patients, with one patient at dose level 2 experiencing grade 2 cortical depression, thought to be attributable to the ifosfamide infusion. A second patient at dose level 4 experienced loss of consciousness during hour five of the second (course 2) paclitaxel infusion as previously discussed. The patient was alert and oriented within one hour following infusion cessation and intravenous dexamethasone.

Additional toxicities were uncommon and included grade 2 hyperbilirubinemia (1; dose level 1), grade 2 hypoalbuminemia and AST/ALT elevation (1; dose level 3), and grade 2 mucositis (1; dose level 1). Mild (grade 1/2) electrolyte disturbances were relatively common and likely attributable to ifosfamide therapy.

Response

Fourteen patients were evaluable for response and eight patients derived clinical benefit [stable disease (5); mixed response (3)]. All three patients with neuroblastoma experienced either transient response or disease stabilization, and received 3, 5, and 4 courses of therapy at dose levels 2, 3 and 4, respectively. Five additional patients who had at least stable disease or mixed response had alveolar soft part sarcoma (6 courses; dose level 1), osteosarcoma (1 course; dose level 2), neurofibrosarcoma (6 courses; dose level 2), Ewing sarcoma (4 courses; dose levels 3 and 4), and omental mesothelioma (4 courses; dose level 2). With the exception of this latter patient who succumbed to a fatal candidal infection, and the three patients for whom follow-up data is unavailable, all patients died from tumor progression.

Discussion

Paclitaxel, administered alone or in combination regimens with ifosfamide, has shown promising activity in a variety of adult malignancies (14–24). This study describes the maximum tolerated dose and toxicity profile of the combination of paclitaxel and ifosfamide in pediatric patients. Overall, the combination regimen was well tolerated with a paclitaxel MTD of 425 mg/m^2 administered as a six-hour continuous intravenous infusion on day 1 followed by standard dose 2 gm/m^2 intravenous ifosfamide on days 1–3. This paclitaxel MTD in children was higher than in adult combination studies employing different paclitaxel infusion durations. In adults, when paclitaxel was administered over either 24 hours or 3 hours on day 1 in combination with ifosfamide on days 1–3, the paclitaxel MTD was 250 mg/m^2 (14,15). Lower dose paclitaxel (135 mg/m^2) was chosen for combination study with ifosfamide in the Gynecologic Oncology Group Phase III trial in patients with advanced uterine carcinosarcoma (20).

Severe hypersensitivity reactions occurred in three patients and defined the DLT for the regimen, despite dexamethasone and diphenhydramine pre-treatment. Two patients successfully tolerated subsequent re-administration of paclitaxel, one re-challenged at dose level 4 with the only change being prolongation of paclitaxel infusion time to 24 hours. Mild reactions on study were relatively uncommon and two patients with febrile reactions went on to tolerate additional courses of paclitaxel without reaction. These findings suggest that minor reactions do not necessarily portend risk for major reactions (4), and as in adult studies (25), pediatric patients with significant paclitaxel infusion-related reactions, despite adequate steroid pre-treatment, can be considered for re-challenge with paclitaxel by

employing a longer infusion time. Lastly, the frequency of severe adverse hypersensitivity reactions in the current study at or below the MTD (1/12; 8.3%) is equivalent to that seen in chemotherapy-naive pediatric neuroblastoma patients (4/33; 12.1%; 26) and more frequent than previously treated pediatric solid tumor patients (1/186; 0.54%; 15) when treated with 325 mg/m^2 given over 24 hours, suggesting that a shortening of the infusion rate to 6 hours imparts a slightly higher rate of acute hypersensitivity reactions in previously treated pediatric solid tumor patients.

Neutropenia has been dose-limiting in adult Phase I single agent paclitaxel trials (4) and common in pediatric Phase I and Phase II single agent paclitaxel trials (7–9,13,26,27). Neutropenia was not considered dose-limiting in three of six adult Phase I trials employing paclitaxel in combination with ifosfamide due to the definition of DLT rather than the absence of significant myelosuppression (15,17,22–24,28). In the current study, myelosuppression, thrombocytopenia, and anemia were common; however, the frequency of bone marrow suppression was similar to that seen in 33 chemotherapy-naive pediatric neuroblastoma patients treated with single agent paclitaxel via a 24-hour infusion at the MTD of 350 mg/m^2 (26). As with other pediatric paclitaxel studies, grade 4 neutropenia in the current study was typically short lived, lasting less than five days, occurred within 1 week of treatment, and associated with febrile neutropenia in < 20% of courses [7, 9, 25, 26 (Michael Harris, personal communication)] (29).

Central and peripheral neuropathic effects encountered in the current study, despite the addition of ifosfamide, were significantly less common and less intense than that experienced in pediatric patients treated with 3-hour paclitaxel infusions (3 of 17 patients; reference 7), and similar in frequency and intensity than that experienced in pediatric patients treated with 24-hour paclitaxel infusions (1 of 12 patients; reference 9). No paclitaxel-associated central nervous system toxicity occurred in patients treated at paclitaxel dose level 3 (425 mg/m^2) or lower. The data suggest that, in children, CNS toxicity occurs less frequently from both 6 and 24-hour higher-dose paclitaxel infusions as compared to 3-hour infusions. Peripheral neuropathy in the form of parasthesias or dysasthesias were relatively common in the current study with a frequency (6/15; 40%), comparable to that seen by Doz et al (5/14; 35.7%; 7), and by Hurwitz et al (10/31; 32%; 9). In the current study, as well as in the study by Doz et al, no dose-peripheral neurotoxicity relationship can be identified. Further investigations into the mechanisms of and protection from taxane-induced neurotoxicity are needed (30–32).

Clinical benefit from this paclitaxel/ifosfamide regimen was noted in all three heavily pre-treated patients with neuroblastoma. However, the clinical effect was not sustained in any of these patients who had not previously received ifosfamide therapy, raising question as to the role of paclitaxel in the response seen in these patients. Two phase II studies conducted by the Pediatric Oncology Group (POG 9340 and POG 9262), have demonstrated activity of paclitaxel (350 mg/m^2 administered intravenously over 24 hours) in chemotherapy naive and pre-treated patients with metastatic or recurrent neuroblastoma respectively (27,29). While paclitaxel's single agent activity remains unsatisfactory for upfront and relapsed neuroblastoma therapy, combination studies employing paclitaxel with ifosfamide or platinum therapy (33) in neuroblastoma patients may be of interest.

In conclusion, the dose limiting toxicity of this paclitaxel/ifosfamide regimen is acute hypersensitivity. Myelosuppression and neurotoxicity are prevalent, but manageable and reversible. While the optimal method of administering paclitaxel continues to be debated (34), paclitaxel administered as a 6-hour infusion at a dose of 425 mg/m^2 followed by standard dose ifosfamide (2g/m^2/day × 3) is the recommended dose for further development of this two-drug combination in pediatric solid tumor patients. The COG is pursuing a

paclitaxel, ifosfamide, carboplatin combination regimen (TIC) for the treatment of pediatric patients with recurrent or resistant malignant germ cell tumors (AGCT0521).

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Table I

Patient Characteristics

Characteristic	No. of Patients
Age (years)	
Range	2 – 18.8
Median	14.8
Gender	
Male	7
Female	8
Performance Status (Lansky/Karnofsky)	
Range	70–100
Median	90
Histology	
Neuroblastoma	3
Ewing Sarcoma	3
Synovial Cell Sarcoma	1
Alveolar Soft Part Sarcoma	1
Osteosarcoma	1
Neurofibrosarcoma	1
Adrenocortical Carcinoma	1
Anaplastic Ependymoma	1
Mesothelioma (omental)	1
Hepatoblastoma	1
Wilm's Tumor	1
No. of Prior Chemotherapy Regimens	
1 – 2	11
3 – 4	3
5 – 6	1
Radiotherapy	10 (66.7%)
Surgery	13 (86.7%)

Table II

DLTs During the First Course of Each Dose Level

Level	Dose (mg/m^2)	No. of Patients Assessable	No. of Patients With DLT During Course 1	DLT
1	250	3	0	
2	325	6	1	ADR - Grade 4 hypotension
3	425	3	0	
4	550	3	2	ADR - Grade 3 hypotension with abdominal cramping, emesis and diarrhea; ADR - Grade 4 anaphylaxis after 1ml of paclitaxel infused

DLT = Dose Limiting Toxicity; ADR = Adverse Drug Reaction

Table III

Non-Dose Limiting Toxicities During the First Course Observed in More Than 10% of the Assessable Patients

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophils (ANC)	0	2	1	6
Platelets	1	3	0	4
Hemoglobin	2	5	4	0
Sensory Neuropathy	5	1	0	0
Infusion-Related Fever	3	0	0	0
Febrile Neutropenia	N/A	N/A	4	0