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ORIGINAL ARTICLE

A phase I and pharmacokinetic study of paclitaxel poliglumex and cisplatin in patients with advanced solid tumors

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Abstract
Purpose Determine the toxicity, maximum tolerated dose (MTD), and pharmacokinetics of paclitaxel poliglumex (PPX; CT-2103) in combination with cisplatin administered every 3 weeks.
Patients and methods Forty-three patients with advanced solid tumors were treated at escalating doses of PPX with a fixed dose of cisplatin at 75 mg/m^2. Conjugated and unconjugated paclitaxel were measured in plasma and urine. Cisplatin, as total platinum content in urine, was also assayed.
Results Dose-limiting toxicities included neutropenia and neuropathy with a cycle 1 MTD of 210 mg/m^2. Conjugated taxanes had a prolonged half-life of >100 h. Nine patients had partial responses, and 19 had stable disease.
Conclusions PPX is a water-soluble paclitaxel-polymer conjugate with a prolonged half-life and a limited volume of distribution. PPX/cisplatin showed good activity in a refractory patient population; however, cumulative neuropathy was a significant issue at high doses, suggesting that a lower dose may be appropriate for prolonged therapy.

Keywords Paclitaxel poliglumex · PPX · Cisplatin · Chemotherapy · Conjugated taxanes · Neuropathy

The authors who are not employed by Cell Therapeutics do not have disclosure to make.

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Introduction

The antimicrotubule paclitaxel is poorly water-soluble and is formulated for clinical use in Cremophor-EL, which is associated with acute hypersensitivity reactions [1]. Modified formulations of paclitaxel have been investigated [2–5], including a nanoparticulate formulation (Abraxane), a polymeric micellar formulation (Genexol-PM), and a liposomal formulation. In paclitaxel poliglumex (PPX), paclitaxel is covalently linked at the 2′-hydroxyl group by an ester bond to poly-L-glutamate, a highly hydrophilic macromolecular carrier (Fig. 1). The hyperpermeable angiogenic tumor vasculature and the suppressed lymphatic clearance in tumor tissue may facilitate the retention of macromolecules within the interstitial tumor space, resulting in higher intratumoral concentrations for a prolonged period of time [6, 7]. Such polymers are stable in the systemic circulation but can be broken down by intracellular lysosomal enzymes to release free drug after entering cells by endocytosis [8, 9]. PPX has shown antitumor activity in preclinical studies with human tumor xenografts and in early phase I trials [10–12]. The maximum tolerated dose (MTD) of PPX as a single agent, based on the first cycle toxicity, was 235 mg/m^2. The most common side effect has been grade 3 neutropenia, seen at doses at or above 175 mg/m^2. Dose-dependent and cumulative neuropathy has been observed, and the

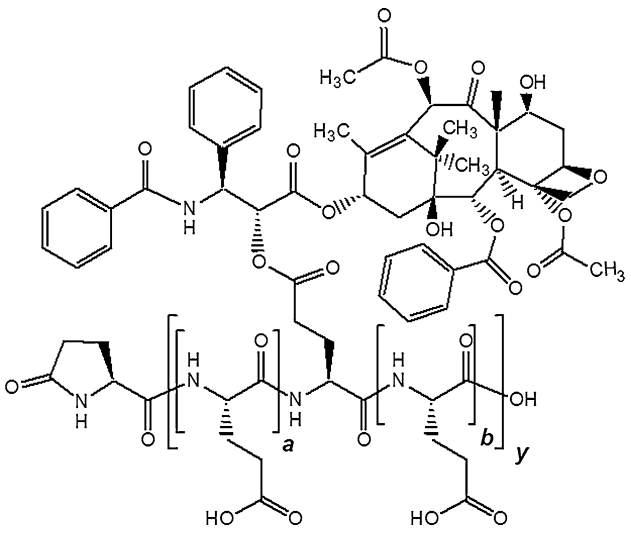

Fig. 1 Chemical structure of PPX

incidence may be increased in patients with preexisting exposure to neurotoxic agents [12, 13]. Without premedication, hypersensitivity reactions have occurred infrequently and resolved with appropriate treatment. Alopecia is infrequent. The objectives of this phase I study were to determine the MTD, toxicity profile, pharmacokinetics (PK), and preliminary efficacy of PPX when it is administered with cisplatin every 3 weeks to patients with advanced solid tumors.

Patients and methods

The study was approved by the local research ethics committees.

Patients

All patients gave written informed consent. Inclusion criteria included a histologically proven solid tumor refractory to treatment or for which no conventional treatment was available; performance status of 0 to 2; >18 years of age; life expectancy $\geq$12 weeks; hemoglobin $\geq$10 g/dL; ANC $\geq 1.5 \times 10^9$/L; platelets $\geq 100 \times 10^9$/L; bilirubin $\leq$1.5 × upper limit of normal (ULN); alkaline phosphatase $\leq$2.5 × ULN; alanine aminotransferase/aspartate aminotransferase $\leq$2.5 × ULN if no liver metastases (or 5 × ULN in the presence of liver metastases); and plasma creatinine $\leq$1.5 × ULN. Patients were excluded if they had received radiotherapy, endocrine therapy, immunotherapy, or chemotherapy <4 weeks before treatment. Exclusion criteria used were typical of any phase I clinical trial. Patients with preexisting drug-related neuropathy were also excluded.

Baseline assessment included a history, physical examination, chest X-ray, and electrocardiogram. Laboratory evaluations included a full blood count, blood biochemistry, and coagulation panel before treatment and weekly during the study. Disease status was documented by radiologic imaging before treatment and every two cycles.

Treatment

PPX was supplied by Cell Therapeutics, Inc. (Seattle, WA, USA). All administered doses are expressed as paclitaxel equivalents. On day 1 of each 21-day treatment cycle, patients received the assigned doses of PPX by a 10-min infusion at doses of 175, 210, 225, 250, or 270 mg/m^2, followed by cisplatin 75 mg/m^2 as 3-h infusions. PPX could be administered until disease progression or intolerable toxicity. After cycle 4, cisplatin administration could be discontinued based on investigator discretion. Premedications consisted of an antiemetic regimen that included a 5-HT-3 antagonist (e.g. ondansetron or granisetron), and an antiinflammatory steroid such as dexamethasone, as per institutional practice. Dose reductions were required for febrile neutropenia or platelet count (<20,000 cells/dL or bleeding associated with platelet count <50,000 cells/dL) at any time and if at the time of dosing there was a grade 2 or higher neuropathy or drug-related grade 3/4 nonhematologic toxicity. Patients were retreated when toxicities resolved to grade 1 or lower, but delay could not exceed 2 weeks. Treatment was discontinued after the second dose reduction and for grade 3 or 4 hypersensitivity.

Dose-limiting toxicity (DLT) definition

A phase I 3 + 3 design was followed with an extension cohort at the MTD to further analyze the PK of this combination. Adverse events were assessed using the National Cancer Institute Common Toxicity Criteria, version 2. DLT was defined as grade 4 hematologic toxicity >7 days, grade 4 febrile neutropenia, or drug-related grade 3/4 nonhematologic toxicity. The MTD was defined as the dose level below which two of three to six patients experienced DLT in cycle 1.

Pharmacokinetics (PK)

The concentrations of conjugated and unconjugated paclitaxel in plasma and urine were measured with liquid chromatography and mass spectrometry [12]. Plasma was collected from three patients at 175 mg/m^2, four at 210 mg/m^2, two at 225 mg/m^2, and two at 250 mg/m^2 before treatment; 20, 40, and 90 min after treatment; and then 3, 4, 6, 8, 10, 12, 16, 24, 32, 40, 48, 168, and 336 h after the first cycle. Plasma was collected from all other patients before

treatment, 1 min before the end of infusion, 30 min after treatment, and 2, 6, 10, 24, 48, 72, 96, 168, and 336 h after administration during cycle 1. Additional samples were collected before and at the end of infusion during subsequent cycles. No plasma samples were collected from patients treated at 270 mg/m^2. Urine was collected from one patient treated at 175 mg/m^2 up to 12 h, one patient treated at 175 mg/m^2, one at 225 mg/m^2, and two at 250 mg/m^2 up to 24 h. Urine was collected from nine patients treated at 210 mg/m^2 up to 72 h and eight treated at the same dose up to 108 h.

PK analysis was performed for conjugated and unconjugated taxanes using a noncompartmental model and WinNonlin Enterprise 4.1 (Pharsight Corp., Mountain View, CA, USA). Area under the curve from time 0 to t (AUC_{0-t}), and AUC were calculated using the linear/log trapezoidal rule. Peak and trough concentrations on successive treatments were analyzed to determine any accumulation effect. Renal clearance, calculated as the ratio between the urinary excretion to the last quantifiable time point (Ae_{0-t}), and AUC_{0-t}, was estimated. Cisplatin was evaluated in the urine of six patients treated with 210 mg/m^2 PPX in combination with 75 mg/m^2 cisplatin. Cisplatin content was assayed by inductively coupled plasma mass spectrometry and expressed as total platinum content.

Results

Patient characteristics

Forty-four patients were enrolled. One patient was ineligible and was not treated. A summary of patient characteristics is shown in Table 1.

Table 1 Patient characteristics

Characteristic	*N*
No. of patients enrolled	44
No. of patients assessed	
For toxicity	43
For response	43
For pharmacokinetics	21
Median age, years (range)	51 (24–73)
Gender	
Male	20
Female	23
Karnofsky performance status	
100	16
90	18
80	7
70	2
Race/ethnicity	
White	38
Hispanic	3
Asian	1
Black	1
Primary tumor type	
Sarcoma	14
Ovarian	7
Lung	7
Mesothelioma	3
Thyroid	3
Breast	2
Salivary	2
Endometrial	1
Thymoma	1
Bladder	1
Melanoma	1
Neuroendocrine	1

Treatments

Drug exposure is summarized in Table 2. The median number of cycles was three (range 1–12 cycles). At the MTD (210 mg/m^2), 24 patients received a median of four cycles (range 1–10 cycles).

Adverse events

Twenty-five patients were treated in the dose-escalation portion of the study. The dose was escalated to 270 mg/m^2. Table 3 shows the escalation cohorts and the adverse events observed during the first course. The most common were neutropenia with or without associated infections, anemia, fatigue, and nausea, vomiting, or diarrhea with or without associated dehydration. None of the three patients treated at 175 mg/m^2 experienced a DLT in cycle 1. One patient treated at 210 mg/m^2 experienced grade 3 dehydration with peripheral edema, thrombosis, syncope, and grade 4 neutropenia during cycle 1, which necessitated cohort expansion to include 6 patients. At 225 mg/m^2, one of the first three patients experienced a DLT with grade 3 fatigue and peripheral sensory neuropathy. These events were not deemed directly related to PPX. However, the cohort was subsequently expanded to include a total of seven patients; one additional patient experienced grade 3 dehydration and febrile neutropenia during the first treatment cycle. At 250 mg/m^2, one of the first three patients experienced drug-related grade 3 diarrhea and grade 4 febrile neutropenia. Another patient had grade 3 fatigue, deemed not related to the drug. The cohort was subsequently expanded to include a total of six patients. At 270 mg/m^2, one of the three patients experienced grade 3 febrile neutropenia. Dose-

Table 2 Cohort dosing

	Cohorts, mg/m^2				
	175 (n = 3)	210 (n = 24)	225 (n = 7)	250 (n = 6)	270 (n = 3)
Median no. of cycles (range)	6 (3–12)	4 (1–10)	4 (1–12)	1 (1–6)	2 (1–3)
Median cumulative dose of cisplatin, mg/m^2 (range)	436 (224–870)	283 (73–523)	217 (76–509)	76 (72–296)	150 (76–224)
Median cumulative dose of PPX, mg/m^2 (range)	174 (173–178)	207 (136–212)	225 (202–227)	248 (239–256)	271 (263–273)
Best response					
Partial response	1	6	2	0	0
Stable disease	2	11	3	2	1
Progressive disease	0	7	2	4	2

PPX paclitaxel poliglumex

escalation was terminated after three patients were treated at this dose. At that point of the study, neuropathy, although not appreciated immediately in the first cycle, was clearly cumulative after the fourth cycle. Because of this cumulative side effect, the 210-mg/m^2 cohort was chosen as the phase II dose and expanded to a total of 24 patients.

All adverse events

The most frequent adverse events for all patients and all cycles are summarized in Table 4. Twenty-six patients (60%) experienced at least one neuropathy event (including Medical Dictionary for Regulatory Activities terms peripheral neuropathy NOS, peripheral sensory neuropathy, neuropathy not otherwise specified (NOS), balance impaired NOS, gait abnormal, hypoesthesia, paresthesia, peripheral motor neuropathy, or peripheral sensorimotor neuropathy). Neuropathy affected all sensations (prick, point discrimination, vibration, position, and reflexes). In 24 patients, the neuropathy was ongoing at the final visit. Five patients experienced hypersensitivity reactions (HSRs) within 1 day of drug infusion. All had been pretreated with steroids. All of the HSRs were less than grade 2 in intensity and were considered to be related to the study drug. Seven patients experienced serious, drug-related febrile neutropenia; all resolved within 1 week of onset. Three episodes were seen at the MTD and four in higher cohorts. Clinical laboratory data suggested a mild (grade 1) cumulative effect on the neutrophil counts and transaminase serum levels that may persist at the end of treatment and an asymptomatic interaction with warfarin. Hypokalemia, probably related to cisplatin administration, was seen in six patients.

Maximum tolerated dosing (MTD)

Twenty-four patients were treated at 210 mg/m^2. The most common grade 3/4 side effect was neutropenia (83%). Neuropathy (46%) was the next most frequent adverse event and was cumulative. There were no major differences in the panel of side effects experienced by this cohort vs. all cohorts.

Withdrawal, dose reductions, and delays

The most common reason for withdrawal was disease progression (60%). Thirteen patients (30%) discontinued due to adverse events: at a median of four cycles (range 2–12) for neuropathy (10 patients, all cohorts), at cycle 1 for febrile neutropenia (two patients treated at 210 and 270 mg/m^2), and for dyspnea (1 patient). Withdrawal for neuropathy was related to nonresolution to grade 1 or less after 2 weeks of delay. The withdrawal occurred between days 56 and 260 after treatment start (mean, day 116 [or after an average of four courses]). Two patients withdrew consents, and two patients died on days 10 and 11 after drug administration, one of progressive disease and one of intercurrent infection with Klebsiella bacteremia considered unrelated to treatment. Delays of more than 7 days without dose reductions were caused by treatment in 10 cases (seven neuropathies between cycles 4 and 11 and three neutropenias in cycles 2 and 7). Dose reductions occurred in five patients (three due to neuropathies in cycles 4 or 5 and one to emesis and one to febrile neutropenia both in cycle 2). Cisplatin was discontinued in seven patients after cycle 4 because of cumulative neuropathy or grade 4 neutropenia. Neuropathy was also observed in several patients who received five or more cycles at 225 mg/m^2 PPX and cisplatin, and this dose was therefore considered too high for chronic dosing.

Response

PPX/cisplatin demonstrated activity in a variety of refractory tumors that in many cases did not respond to previous therapy. Nine patients had a partial response (PR), and 19 patients had stable disease (SD). PRs were achieved in

Table 3 All adverse events per cohort during cycle 1

Adverse event	Worst NCI grade	Dose groups, mg/m^2				
		175 (n = 3)	210 (n = 6)	225 (n = 7)	250 (n = 6)	270 (n = 3)
Neutropenia	1	0	0	1	0	1
	3	0	2	2	1	0
	4	0	2	1	3	1
Anemia	1	0	0	0	0	1
	2	0	0	1	3	1
Nausea	1	1	1	0	1	1
	2	1	1	4	3	0
	3	0	2	1	0	1
Vomiting	1	0	1	0	1	0
	2	1	0	2	1	0
	3	0	2	1	0	1
Diarrhea	1	0	1	0	1	0
	2	0	1	3	2	0
	3	0	0	0	1	0
Weight loss	2	0	0	1	1	0
Fatigue	1	0	2	0	0	0
	2	1	1	1	1	1
	3	0	0	2	2	0
Febrile neutropenia	3	0	0	1[a]	0	1[a]
	4	0	0	0	1[a]	0
Dehydration	2	0	1	0	1	0
	3	0	1[a]	1[a]	1	0
Anorexia	2	0	1	0	0	0
	3	0	0	0	1	0
Tinnitus	1	0	1	0	0	0
	2	1	0	1	0	0
Muscle weakness/myalgia	1	0	0	0	0	0
	2	1	0	1	1	0
	3	0	0	1	1	0
Neuropathy[b]	1	0	0	0	1	0
	2	0	0	0	1	0
	3	0	0	1	0	0
Mucositis	1	1	0	0	0	0
Rash	1	1	2	0	0	0
Alopecia	2	0	1	1	1	0
Dyspnea NOS	1	0	0	1	0	0
	2	0	0	0	1	0
Infusion reaction	1	2	1	1	0	0
	2	0	0	0	0	1

NCI National Cancer Institute, *NOS* not otherwise specified

[a] Dose-limiting toxicity related to paclitaxel poliglumex

[b] Includes medical dictionary for regulatory activities terms:peripheral neuropathy NOS, peripheral sensory neuropathy, neuropathy NOS, balance impaired NOS, gait abnormal, hypoesthesia, paresthesia, peripheral motor neuropathy, and peripheral sensorimotor neuropathy

ovarian or primary peritoneal cancer [3], non-small-cell lung cancer (NSCLC), breast cancer, liposarcoma, mesothelioma, schwannoma, and thymoma (one each). Of the 16 assessable patients who had received prior taxanes, four had a PR, six had SD, and five had progressive disease. Interestingly, PRs were observed only in the three lowest dose cohorts. Median time to disease progression (TTP) was 5 months (range 1 month [270 mg/m^2] to 10 months [175 mg/m^2]). Of seven patients with ovarian or primary peritoneal cancer, three had a PR and 3 SD, with a time to progression of 10 months (range 3–63 months). Except for one patient with stable disease who was previously untreated, all but one had relapsed within 6 months of the last platinum containing regimen.

Table 4 Most common drug-related adverse events for the recommended phase II dose cohort

Adverse event	Cohort 210 mg/m^2 ($N = 24$) grades 3 and 4 N (%)
Neutropenia	20 (83)
Nausea	4 (17)
Vomiting	4 (17)
Diarrhea	3 (12)
Fatigue	2 (8)
Febrile neutropenia	2 (8)
Dehydration	2 (8)
Neuropathy[a]	11 (46)

NCI National Cancer Institute, *NOS* not otherwise specified

[a] Includes medical dictionary for regulatory activities terms: peripheral neuropathy NOS, peripheral sensory neuropathy, neuropathy NOS, balance impaired NOS, gait abnormal, hypoesthesia, paresthesia, peripheral motor neuropathy, and peripheral sensorimotor neuropathy

Pharmacokinetics

Figure 2 shows the plasma vs. time profiles of conjugated taxanes and unconjugated paclitaxel after the first administration of PPX in the dose range of 175 to 250 mg/m^2. A linear relationship was observed between conjugated taxane exposure (AUC) and administered doses ($r^2 = 0.9266$). Table 5 shows the mean PK parameters for conjugated taxanes and unconjugated paclitaxel at the recommended dose of 210 mg/m^2. No or modest accumulation of conjugated taxanes and unconjugated paclitaxel in the systemic circulation occurred on repeated treatment every 3 weeks (data not shown).

Due to the complexity of cisplatin biotransformation, only cisplatin urinary excretion was assessed to determine whether PPX administration altered cisplatin disposition. Most of the platinum excretion (approximately 26% of dose), occurred 8 h post-PPX administration (approximately 6 h postcisplatin infusion). The overall urinary excretion during a 108-hour time interval (106-hour time interval from cisplatin infusion) accounted for approximately 42% of the dose, in keeping with the reported renal elimination of cisplatin [14].

Discussion

Neuropathy observed with multiple dosing led to the conclusion that PPX at a dose of 210 mg/m^2 with cisplatin 75 mg/m^2 was the MTD. The most common adverse events were neuropathies and neutropenia. Peripheral neuropathies were frequently observed (60% of patients), were cumulative, and were not always completely resolved at the last visit. This was the most chronic adverse event, which led to discontinuation of cisplatin after four cycles. Given that neurotoxicity is associated with both PPX and cisplatin, the contribution of each agent to this toxicity could not be readily assessed. However, due to demonstrated activity of this

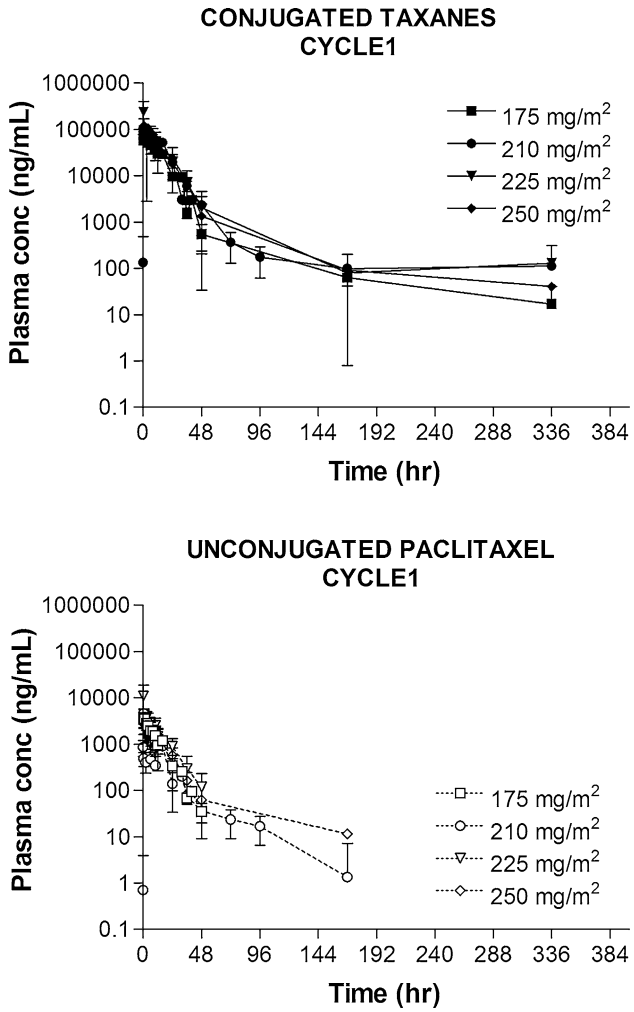

Fig. 2 Average plasma concentration (±SD) vs. time profiles of conjugated taxanes and unconjugated paclitaxel in patients who received 175, 210, 225, and 250 mg/m^2 PPX doses in cycle 1

Table 5 Mean ± SD for pharmacokinetic parameters of conjugated taxanes (210-mg/m^2 dose cohort [$n = 21$])

Parameters	Conjugated taxanes	Unconjugated paclitaxel
$t_{1/2,\,z}$ (h)	132.5 ± 85.6	42.4 ± 31.3
C_{max} (ng/mL)	111,857 ± 19,519	879 ± 320
AUC (mg h/L)	1,655.4 ± 443.9	10 ± 4.49
V_{ss} (L/m^2)	3.2 ± 2.3	–
CL (mL/h/m^2)	137.5 ± 44.1	–
Renal clearance (mL/h/m^2)	9.8 ± 5.5	713 ± 400

SD standard deviation, *AUC* areas under the curve, V_{ss} volume of distribution at steady state, *CL* systemic plasma clearance

combination at a PPX dose of 175 mg/m^2, it is likely that this dose or lower would both be effective and produce a lower level of neuropathy. Serious febrile neutropenia that was related to treatment was observed in seven patients but was quickly reversible. HSRs were mild and did not require dose modification, but evaluation is confounded by the common use of routine corticosteroids. Transient myelosuppression and transaminase elevations were noted during study treatment.

PPX and cisplatin demonstrated activity in a variety of refractory tumors. Nine of 44 patients (23%) achieved a PR, and an additional 19 patients (43%) had SD at the cycle 2 assessment. Responses were most common in patients with ovarian cancer, even when they had been previously treated with paclitaxel and/or cisplatin. Of interest, all major responses were observed at doses $\leq$225 mg/m^2, suggesting that a dose $\leq$210 mg/m^2 may be effective given the lack of a clear-cut dose-response relationship for paclitaxel [15, 16]. It is also possible that the reduced dose intensity of cisplatin in the higher cohort of PPX (Table 2) was responsible for the lack of response seen in these cohorts. However the small number of patients makes any conclusion difficult.

The PK of unconjugated paclitaxel when PPX is given in combination with cisplatin does not substantially differ from the PK of standard PPX as a single agent, nor was the cisplatin disposition affected by PPX [14, 17, 18]. After PPX administration, the conjugated drug was stable in the systemic circulation and there was not a significant release of free paclitaxel in the plasma compartment (<1%), which remained fairly constant during the whole treatment period and entire collection time interval. The elimination half-life of conjugated taxanes was long, and the volume of distribution at steady state suggested a restricted polymer distribution to plasma and part of the extravascular fluids, a finding consistent with the PK characteristics of a macromolecule and the enhanced permeability and retention effect. For the same reason, the volume of distribution of conjugated taxanes increased during the terminal disposition phase. The systemic plasma clearance of the conjugated taxanes was much lower than liver and kidney plasma flows, indicating low drug elimination efficiency and supporting a prolonged residence time in the body. Conjugated taxanes and unconjugated paclitaxel were excreted via the renal route with a limited efficiency. This is consistent with both the physicochemical properties of the macromolecule and the PK features of paclitaxel. Based on its PK features, PPX could be considered a targeted, slow-release prodrug of paclitaxel.

Two phase I studies of single agent PPX have been published. In one, PPX was administered as a short intravenous infusion every 3 weeks. In the other study, PPX was administered every 2 weeks. In the 3-week schedule, the DLT was neutropenia encountered at 266 mg/m^2 and the MTD was defined as 233 mg/m^2. In the 2-week schedule, neuropathy was the DLT and the MTD was 177 mg/m^2. PK parameters were similar to those reported in this study [12].

Because most responses to PPX were observed in patients with ovarian cancer, a phase I study was conducted in 99 patients at 175 mg/m^2 administered over 10 min every 3 weeks without routine premedications. Platinum-sensitive (n = 42), and platinum-refractory or platinum-resistant patients (n = 57) were enrolled. The response rate (RR) for all patients was 10%, with median TTP of 2 months. In patients with only one or two prior regimens, the RR in platinum-sensitive and platinum-resistant patients was 28% (5/18), and 10% (2/21), with a median TTP of 4 and 2 months, respectively. Grades 2 and 3 neuropathy was reported in 15 patients each (30%). Eight percent and 1% of grade 2 and 3 hypersensitivity were observed, respectively [15].

Twenty-eight untreated patients with advanced-stage NSCLC (age $\geq$70 years and Karnofsky scale >70) received PPX at 175 mg/m^2. The overall RR was 7% (PR in two patients), and 57% (16 patients) experienced SD. Median duration of response in patients with SD or better was 9 weeks. Overall median survival was 6 months. Three patients experienced grade 3 neuropathy. Hematologic toxicity was moderate. Based on these results, three phase III trials in NSCLC have been completed and demonstrated equivalent efficacy to standard agents with enhanced safety when used as a single agent compared with gemcitabine or vinorelbine in a first-line setting or with docetaxel in second-line patients [19–21].

The combination of PPX with carboplatin has been studied in a phase I study. Twenty-two adult patients with advanced solid tumors were treated every 21 days with PPX followed by carboplatin (AUC = 6). The MTD was determined to be 225 mg/m^2 with DLTs observed at 250 mg/m^2 of neutropenia and thrombocytopenia [22].

In conclusion, the combination of PPX with cisplatin is an active regimen, but neuropathy, which was severe and persistent, was a concerning side effect causing discontinuation of cisplatin. It may be worthwhile to use carboplatin instead, or to study this combination with a lower dose of PPX (135–175 mg/m^2) as well as to test the ability of amifostine to act as a neuroprotective agent with this combination [23].

Conflict of interest statement Amy Eisenfeld, Jack Singer, and Fred Oldham are employees of Cell Therapeutics, Inc.

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