A Phase I and Pharmacokinetic Study of Paclitaxel Poliglumex (XYOTAX), Investigating Both 3-Weekly and 2-Weekly Schedules

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Abstract

Purpose: To determine the safety, maximum tolerated dose, pharmacokinetics, and toxicities associated with administration of paclitaxel poliglumex (PPX, XYOTAX, Cell Therapeutics, Inc., Bresso, Italy) given on either 3-weekly or 2-weekly schedule.

Experimental Design: Nineteen patients were investigated on the 3-weekly phase Ia study and 11 patients on the 2-weekly phase Ib study. Dose escalation starting with 100% increments and one patient per dose level was modulated in accordance with the observed toxicities. Conjugated and unconjugated paclitaxel were measured in plasma.

Results: Dose-limiting toxicity of neutropenia was encountered at 266 mg/m^2 (paclitaxel equivalents) in phase Ia and the maximum tolerated dose was 233 mg/m^2. Neuropathy was dose-limiting in phase Ib with a maximum tolerated dose of 177 mg/m^2. Pharmacokinetic investigations indicated a prolonged half-life of >100 hours for conjugated taxanes. Plasma concentrations of unconjugated paclitaxel were similar to those following administration of an equivalent dose of Taxol. Two partial responses were observed, one in a patient with mesothelioma at 177 mg/m^2 in phase Ia and one in a patient with gastric carcinoma at 175 mg/m^2 in phase Ib.

Conclusion: PPX is a water-soluble paclitaxel-polymer conjugate with a prolonged half-life and limited volume of distribution. Dose-limiting toxicities were neutropenia and neuropathy. PPX showed activity in this patient population.

Taxanes are antimicrotubule agents widely used in cancer treatment. Paclitaxel, first described in 1971, binds to the β subunit of tubulin, promoting the formation of abnormal microtubules and inhibiting depolymerization. Subsequently, mitotic cell division is inhibited, followed by apoptosis (1). Paclitaxel has a wide spectrum of antitumor activity including breast, ovarian, head and neck, prostate, and non–small-cell lung cancers (2). Paclitaxel is poorly water-soluble and is formulated for clinical use in Cremaphor-EL. Cremaphor-EL is a biologically and pharmacologically active compound and its use is associated with acute hypersensitivity reactions (3). Modified formulations and more water-soluble analogues of paclitaxel have been investigated (4–6), including a nanoparticulate formulation (ABI-007), a polymeric micellar formulation (Genexol-PM), and a liposomal formulation. However, these have yet to show improved antitumor activity over paclitaxel (7, 8).

To enhance aqueous solubility, drugs can be conjugated to highly hydrophilic macromolecular carriers such as polyglutamate (9). Macromolecular drug conjugates may also increase tumor exposure through the enhanced permeability and retention effect. 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 (10, 11). Polymer-drug conjugates are presumed to enter the cell by endocytosis and to release the active drug intracellularly by lysosomal enzymatic cleavage (9, 12).

Paclitaxel poliglumex (PPX, XYOTAX, Cell Therapeutics, Inc., Bresso, Italy) is a macromolecular drug conjugate that links paclitaxel with a biodegradable polymer, poly-L-glutamic acid (Fig. 1). PPX showed antitumor activity in preclinical studies with human tumor xenografts (13). Biodistribution studies in mice bearing OCa-1 tumor treated with i.v. injections of tritium-labeled PPX showed a five times greater distribution of paclitaxel to tumor tissue than those treated with standard paclitaxel (14). The exposure [area under the curve (AUC)] of B16 melanoma tumor to total taxanes was 12 times greater in animals treated with [^{3}H]PPX than in those treated with [^{3}H]paclitaxel. Although PPX itself has no biological activity, overall tumor exposure to unconjugated paclitaxel was also higher after [^{3}H]PPX administration (15).

This article reports the results of a phase I study of PPX under the auspices of the phase I/II committee of Cancer Research

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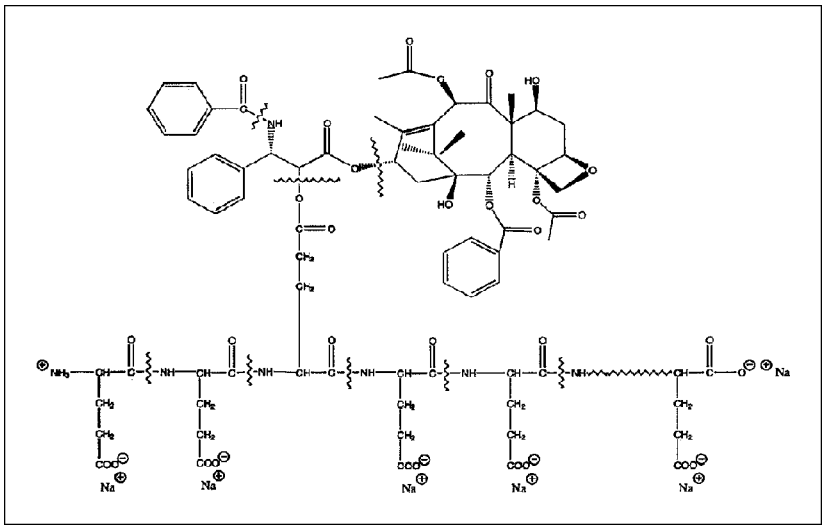

Fig. 1. Schematic representation of PPX. The structure shown is illustrative of a fragment of the molecule; conjugated taxanes (*top*) represent ~37%, by weight, of the conjugate, equivalent to about one paclitaxel ester linkage per 11 glutamic acid residues of the polymer.

UK. The study is composed of two stages. Phase Ia had a primary objective to determine the safety profile and cumulative toxicity and to investigate the pharmacokinetic profile of PPX when administered as a 30 minute i.v. infusion every 21 days. Phase Ib commenced after the maximum tolerated dose was established in phase Ia and investigated a 2-weekly schedule.

Patients and Methods

Patient selection

This dose escalation study was undertaken at the Northern Centre for Cancer Treatment, Newcastle Upon Tyne, and at Aberdeen Royal Infirmary, United Kingdom. The study was approved by Cancer Research UK and local research ethics committees. All patients gave written informed consent.

Inclusion criteria. All patients had a histologically proven solid tumor, which was refractory to treatment or for which no conventional treatment was available. Patients had WHO performance status of 0 to 2, >18 years of age, had life expectancy of at least 12 weeks, and had adequate bone marrow (hemoglobin $\geq$10 g/dL, ANC $\geq 2 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L), liver (alanine aminotransferase/aspartate aminotransferase no more than 2.5 times the upper limit of normal if no liver metastases, or five times upper limit of normal in the presence of liver metastases), and renal function (plasma creatinine $\leq$ 1.36 mg/dL or 120 μmol/L). Patients were eligible if they had not received radiotherapy, endocrine therapy, immunotherapy, or chemotherapy for 4 weeks (6 weeks for mitomycin C) before treatment.

Exclusion criteria. Common phase I clinical trial exclusion criteria were used. Additionally patients previously treated with a taxane or with preexisting drug-related neuropathy were excluded.

Patient monitoring. Before commencing on the trial, patients had a complete history taken and a full physical examination. A full blood count and blood biochemistry (electrolytes and liver and renal function) were done before treatment and weekly throughout the study. Although this was a phase I study, disease status was documented by radiological investigation or clinical assessment before treatment and after every two cycles.

Materials

PPX was supplied by Cell Therapeutics, Inc. (Seattle, WA) in 20 mL glass vials containing 250 mg PPX as the sodium salt. When reconstituted in 10 mL water for injection and diluted with 5% dextrose, the reconstituted solution was stable for 24 hours at room temperature. Acetonitrile, ethyl acetate, and ammonium hydroxide solution were purchased from Fisher Chemicals (Loughborough, United Kingdom); potassium dihydrogen phosphate, sodium hydroxide, formic acid, hydrochloric acid, and glacial acetic acid were from

Table 1. Patient characteristics

Characteristic	Phase Ia	Phase Ib
Total no. patients	19	11*
Sex		
Male	12	7
Female	7	4
Age, y		
Median	58	56
Range	29-71	29-71
WHO performance status		
0	1	2
1	12	7
2	6	2
Disease type		
Lung	5	1
Colorectal	5	3
Unknown primary	3	0
Mesothelioma	2	1
Kidney	2	1
Soft tissue sarcoma	1	
Salivary gland	1	
Esophagus		1
Cervix		1
Adrenal		1
Stomach		2
Prior treatment		
Surgery	17	11
Radiotherapy	9	5
Hormonal/biologic therapy	0	2
Chemotherapy	17	11

*One patient was recruited but never received treatment with PPX due to clinical deterioration.

Table 2. Dose escalation summary

Dose level (mg/m^2)	Dose increment (%)	No. patients	Total no. cycles	No. patients with DLTs
11		1	2	
22	100	1	20	
44	100	1	6	
88	100	2	4	
177	100	1	7	
266	50	6	14	3*
233	−12.5	7	16 (+1 at 25% dose reduction)	2†
Phase Ib (2-weekly)				
177/175		7	13 (+3 at 20% dose reduction)	
210	19	4	8 (+2 at 20% dose reduction)	2‡

*Grade 4 neutropenia; grade 3 febrile neutropenia and grade 3 stomatitis; grade 3 febrile neutropenia, grade 3 stomatitis, and grade 3 neuropathy.
†Grade 4 neutropenia; grade 4 neutropenia.
‡Grade 4 febrile neutropenia; grade 4 diarrhea, cardiac ischemia, and death.

BDH Ltd. (Poole, Dorset, United Kingdom); and paclitaxel and sodium formate were from Sigma Chemical Co. (Poole, Dorset, United Kingdom). Cephalomannine was obtained from Hauser, Inc. (Boulder, CO). All chemicals were of the highest grade available. Water was deionized and further purified by Elgastat (USF Elga, Bucks, United Kingdom).

Methods

Drug administration and dose escalation. PPX was administered as a 30-minute i.v. infusion on day 1, with cycles repeated every 21 days in phase Ia and every 14 days in phase Ib. The starting dose for PPX on phase Ia was 11 mg/m^2. All administered doses were expressed as paclitaxel equivalents. Dose escalation began by doubling the dose with one patient at each dose level until grade 2 toxicity was seen in the first cycle. That dose level was expanded to three patients and, subsequently, three patients were recruited at each dose level.

During the single-patient cohort stage, patients were recruited every 21 days. Once the cohorts had been expanded to three patients, the first patient must have completed at least 2 weeks on study before the second and third patients could be enrolled. Dose escalation could not take place until all patients at the preceding dose level had completed 21 days on study.

At any dose level, if one of three patients experienced a first course dose-limiting toxicity (DLT), a further three patients were enrolled at that dose level. DLT was defined as Common Toxicity Criteria grade 4 hematologic toxicity lasting ≥5 days or grade 4 febrile neutropenia. Common Toxicity Criteria grade 3/4 nonhematologic toxicity that was deemed drug-induced was also classified as DLT. The maximum tolerated dose was defined as the dose level below that at which two of three to six patients experienced DLT.

Pharmacokinetic sampling. Plasma samples were taken for pharmacokinetic analysis before drug administration and at 30 minutes (end of infusion), 1, 2, 4, 6, 8, 24, 36 and 48 hours, then at days 8, 15, and 22, before the next course of treatment during cycle 1, then at the end of infusion and at 24 and 48 hours during cycle 2. Sampling for phase Ib was identical except that day 15 was the sample before cycle 2.

Conjugated taxanes assay. Concentrations of conjugated taxanes in plasma were analyzed by liquid chromatography-tandem mass spectrometry. Plasma samples (100 μL) were buffered (pH 6.5) and washed thrice with 1 mL acetonitrile. The internal standard (cephalomannine 0.05 μg/mL in 0.1 mL acetonitrile) was added before addition of 1 mL of 3 N HCl acid and digestion at 85°C for 2 hours. Following neutralization (0.85 mL of 5 mol/L sodium formate), the samples were extracted into 5 mL ethyl acetate and the organic layer was separated and evaporated to dryness under N_2. The samples were reconstituted in 200 μL of 1:4 acetonitrile/dH_2O and 25 μL were transferred to a vial for analysis by liquid chromatography-tandem mass spectrometry. Chromatography was conducted using a Prodigy ODS-3, 5 μm, 100 × 2 mm column (Phenomenex, Macclesfield, Cheshire, United Kingdom) fitted with a guard column of the same material. The column was maintained at 35°C. The mobile phase was 0.1% formic acid and acetonitrile with a combined flow rate of 300 μL/min at 35°C. Samples were eluted using a gradient of 20% acetonitrile increasing to 50% acetonitrile by 6.3 minutes, to 80% acetonitrile by 6.4 minutes, and decreasing back to 20% acetonitrile by 7.3 minutes with a total run time of 10 minutes. The chromatography system consisted of Series 200 Micro pumps, autosampler, and a column oven (all Perkin-Elmer, Bucks, United Kingdom) and an API 2000 MS/MS (Applied Biosystems, Foster City, CA). Masses detected in ESI+ mode were 286.2/105 (for conjugated taxane) and 264.2/83 (for internal standard cephalomannine). Data acquisition and processing was controlled by Analyst software (Applied Biosystems). The method was linear between 25 and 2,000 ng/mL conjugated taxanes. Plasma samples in which the concentration of conjugated taxanes exceeded this range were diluted in blank plasma as appropriate.

Unconjugated paclitaxel assay. Plasma paclitaxel was measured by a previously published high-performance liquid chromatography method (16).

Pharmacokinetics. Pharmacokinetic analysis was done by noncompartmental methods using WinNonlin version 3.1 (Pharsight Corporation, Cary, NC). The areas under the drug concentration-time curves $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ were calculated using the linear/log trapezoidal rule.

Results

Patient characteristics. Nineteen patients were recruited to the phase Ia study and 11 patients to the phase Ib. A summary of patient demographics, tumor type, and previous treatment is shown in Table 1. The two phases of the study were comparable in terms of sex ratio, median age of patients, and extent of previous treatment. A preponderance of lung and gastrointestinal carcinomas was recruited to both parts of the study. There were more patients with performance status of 2 recruited to the 3-weekly schedule (32% versus 18%) but this trend towards a lower performance status was not reflected in the toxicity observed.

Dose escalation. Details of patients treated at each dose level and the number of cycles administered are given in Table 2. In phase Ia, the starting dose was 11 mg/m^2 and was increased by 100% for each of the next four dose levels. The first three dose levels were well tolerated with no drug-related toxicity. The first patient treated at 88 mg/m^2 became agitated during the drug administration; the infusion was stopped although the full dose was subsequently given. A second patient was recruited at this dose level and tolerated the first infusion without an adverse event. During cycle 2, this second patient developed grade 3 neutropenia and leucopenia. A more cautious approach to dose escalation was adopted although no toxicity had been seen in the patient already treated at 177 mg/m^2. First cycle DLT was observed in the first patient treated at 266 mg/m^2; the dose level was expanded and DLTs were seen in two of six patients. The dose was reduced to 233 mg/m^2 based on experience in an ongoing parallel study. This dose level was generally well tolerated and was defined as the maximum tolerated dose on the 3-weekly schedule although pharmacokinetic data indicated little difference between the two higher dose levels. One patient at 233 mg/m^2 required a 25% dose reduction and treatment delay, as per the protocol, for grade 2 peripheral neuropathy and neutropenia on the third cycle. All other treatment delays were due to administrative reasons, patient choice, or concomitant illness.

The starting dose for the phase Ib (2-weekly) study was 177 mg/m^2. This dose was generally well tolerated and a second dose level of 210 mg/m^2 was initiated. Dose-limiting toxicity was seen in two of four patients. Further patients were then recruited to the 177 mg/m^2 dose level. One patient at 177 mg/m^2 and two patients at 210 mg/m^2 required a 20% dose reduction, as per protocol, for grade 2 peripheral neuropathy after the first or second cycle. One patient at 210 mg/m^2 had a treatment delay of 1 week due to neutropenia.

Toxicity. The major toxicities of PPX were myelosuppression and peripheral neuropathy although only one patient had treatment delayed on each of the schedules investigated due to prolonged myelosupression. Four patients in the phase Ia part of the study had grade 2 or 3 hypersensitivity reactions (at 177-266 mg/m^2); in one patient, this prevented re-treatment. Reactions occurred on cycle 2 or later and symptoms included dyspnea, rash, and facial flushing. All but one rash resolved within 1 hour although most required treatment with steroids. There was one drug-related toxic death in a patient treated on the 2-weekly schedule at the maximum dose. This patient developed grade 4 diarrhea, cardiac ischemia, and died 7 days after the first administration of PPX.

Hematologic toxicities are summarized in Table 3. Myelosuppression was expected given that this is the dose-limiting toxicity of paclitaxel. Common Toxicity Criteria Version 2.0 grade 3 or 4 leucopenia and neutropenia were seen at doses >88 mg/m^2. No significant myelosuppression was observed at lower doses despite some patients receiving two or more cycles. Two patients developed grade 3 drug-related anemia at the maximum dose given on the 2-weekly schedule. Significant drug-related thrombocytopenia was not seen. Neutropenia was the DLT, one patient developing prolonged grade 4 neutropenia and two patients developing grade 3 febrile neutropenia at 266 mg/m^2 on the 3-weekly schedule. The overall incidence of febrile neutropenia was low; there was only one additional patient at 210 mg/m^2 on the 2-weekly schedule having this complication of treatment. At the maximum tolerated dose on phase Ia (233 mg/m^2), two patients developed first-cycle grade 4 neutropenia but this was uncomplicated and the patients recovered. Both these patients had received prior treatment with mitomycin C and it was felt that this had contributed to the degree of myelosuppression observed. Prior treatment with mitomycin C was excluded for further patients and significant myelosuppression was not documented.

Table 3 also summarizes all drug-related nonhematologic toxicities, including grade 2 neuropathy and hypersensitivity. Patients were not premedicated with steroids or antihistamines. Peripheral neuropathy did occur; grade 1 neuropathy was reported in one patient at each of the dose levels 44 to 266 mg/m^2 on the 3-weekly schedule. This progressed to grade 2 in only one patient at 266 mg/m^2. At this dose level, another patient

Table 3. Hematologic and nonhematologic toxicities showing number of courses complicated by each toxicity grade

Dose (mg/m^2)	No. cycles	WBC		Neutrophils		Hypersensitivity	Neuropathy	Stomatitis	Diarrhea	Liver dysfunction
		Grade 3	Grade 4	Grade 3	Grade 4					
Phase Ia										
88	7	1		1						
175*	1				1					
177	7					Grade 3 (1)				
266	14	1	3		4	Grade 2 (1)	Grade 3 motor (1)	Grade 3 (2)		Grade 3 (1)
						Grade 3 (1)	Grade 2 sensory (1)	Grade 2 (2)		Grade 2 (3)
233	16	1	1		2	Grade 2 (1)				Grade 2 (1)
Phase Ib										
177	13	1	1	2			Grade 3 sensory (2)		Grade 2 (1)	Grade 3 (1)
210	8	2	1	2	2		Grade 3 sensory (2)	Grade 2 (1)	Grade 4 (1)	
							Grade 3 motor (1)		Grade 2 (1)	
							Grade 2 sensory (1)			

*Patient with dose reduction from 233 mg/m^2.

Table 4. Pharmacokinetic parameters for conjugated taxanes and for unconjugated paclitaxel in plasma after administration of PPX

Patient number(s)	Conjugated taxanes						Unconjugated paclitaxel		
	Dose level (mg/m^2)	AUC ($\mu g/mL\ h$)	Clearance (mL/h)	V_z (L)	Half-life (h)	V_{ss} (L)	AUC ($\mu g/mL\ h$)	Half-life (h)	C_{24} ($\mu g/mL$)
1	11	18	1,105	6.38	4.0	4.2	0.2	1.2	
2	22	77	601	5.29	6.1	4.3	1.5	4.8	
3	44	189	384	4.31	7.8	2.7	5.0	24.9	
4	88	394	449	16.1	24.9	6.7			
5	88	184	937	100.0	74.0	12.3	10.7	13.5	
6	177	898	406	84.9	145	11.2	7.1	14.2	
Phase Ia									
13-18	233 ($n = 4$)	1,583 ± 572	276 ± 63	48.0 ± 15.4	120 ± 28	6.2 ± 2.1	27.8 ± 14.3	10.6 - 103	0.30 ± 0.18
7-12	266 ($n = 4$)	1,986 ± 1,078	347 ± 231	62.9 ± 28.7	119 ± 15	13.2 ± 8.2	25.0 ± 7.5	8.3 - 62.2	0.30 ± 0.19
Phase Ib									
21, 22, 28-30	177 ($n = 5$)	800 ± 366	462 ± 163	91.6 ± 67.5	128 ± 72	9.2 ± 4.7	15.0 ± 7.0	8.6 - 37.4	0.13 ± 0.10
23, 24, 26	210 ($n = 3$)	1,118 ± 160	349 ± 95	31.1 ±13.0	69 ± 47	5.2 ± 0.8	18.7 ± 5.3	9.6 - 30.3	0.18 ± 0.03

NOTE: V_z, volume of distribution estimated from clearance and log-linear slope of terminal phase of disposition. C_{24}, plasma concentration of unconjugated paclitaxel at 24 hours after the dose of PPX. Estimates of V_z and half-life at doses less than 133 mg/m^2 are based on data from the first 48 hours after dosing. Drug was not detectable in samples taken after this time. Patients 12, 16, 25, and 27 were omitted from the calculation of summary pharmacokinetic parameters as there were insufficient data to estimate individual parameters. Patients 9, 17, and 20 were omitted from the calculation of summary pharmacokinetic parameters as spuriously high values for conjugated taxanes were found in samples obtained just before the second cycle of treatment.

developed grade 3 motor neuropathy in the distal extremities after course 3. Neuropathy was more significant on the 2-weekly schedule. Three patients at either 210 or 175 mg/m^2 developed sensory neuropathy that affected activities of daily living. One patient with gastric carcinoma, treated with seven cycles in total, developed grade 3 sensory and motor neuropathy 1 week after his final dose. Up to this point, he had mild sensory neuropathy only.

Other toxicities were mild. Grade 1 to 2 nausea and vomiting occurred in 21% of patients and only three patients developed grade 2 alopecia. Grade 3 fatigue was reported in one patient at the 44 mg/m^2 dose, which was felt to be drug-related.

Response. Response to treatment was reassessed every two cycles. Two partial responses were observed, one in a patient with mesothelioma at 177 mg/m^2 on the 3-weekly schedule and one in a patient with gastric carcinoma treated at the same dose on the 2-weekly schedule. Two patients had stable disease over six cycles of treatment, one with non–small-cell lung carcinoma treated at 44 mg/m^2 and one with renal carcinoma treated at 233 mg/m^2. Another patient with renal cell carcinoma received 20 cycles of PPX at the second dose level (22 mg/m^2); however, the lack of progression may reflect the natural history of his disease given the low treatment dose. He remained well and received no further treatment up to 1 year later. An additional nine patients (eight in phase Ia) were regarded as having stable disease, seven (four in phase Ia) had progressive disease, and nine (six in phase Ia) were not evaluable.

Pharmacokinetics. After administration of PPX, concentrations of conjugated and unconjugated paclitaxel were measured in plasma. The analytic methods were designed and validated to ensure no cross-contamination between the two measurements. Plasma samples were stored at −80°C due to limited drug stability during storage at −20°C. During the dose escalation in phase Ia (11-177 mg/m^2), peak concentrations of conjugated taxanes increased from 6.3 to 88.6 μg/mL. Over the same dose range, peak concentrations of unconjugated paclitaxel rose from 0.08 to 1.44 μg/mL. At the 266 mg/m^2 dose level, in which significant toxicities were observed, plasma concentrations were highly variable among the six patients studied. For conjugated taxanes, the C_{max} varied from 100 to 277 μg/mL with a similar degree of variation in AUC (Table 4).

At 266 mg/m^2, peak concentrations of unconjugated paclitaxel varied from 1.08 to 2.89 μg/mL. Although less toxicity was observed at 233 mg/m^2, the range of unconjugated paclitaxel concentrations was similar (0.93-3.25 μg/mL). Figure 2 shows mean plasma concentration data for the 266 and 233 mg/m^2 dose levels in phase Ia and corresponding data for the 177 and 210 mg/m^2 dose levels in phase Ib. A summary of pharmacokinetic variables for conjugated paclitaxel and unconjugated paclitaxel is given in Table 4 for both phase Ia and Ib. For conjugated taxanes, the half-life was over 100 hours in most patients at ≥233 mg/m^2, indicating the prolonged stability of the polymer in plasma. Clearance of conjugated taxanes was low (<10 mL/min; Table 4). The steady-state volume of distribution (V_{ss}) was low, indicating a distribution of the conjugated polymer mostly restricted to plasma and extracellular fluids. The estimate of the volume of distribution associated with the terminal phase, V_z, was larger than V_{ss}, probably because the conjugated taxanes eventually distribute to some tissue compartments. The long half-life resulted in detectable levels of conjugated taxanes in plasma before the second dose in phase Ib, but only rarely in phase Ia.

Pharmacokinetic variables for unconjugated paclitaxel suggest a slow release of drug from the polymer, which may be

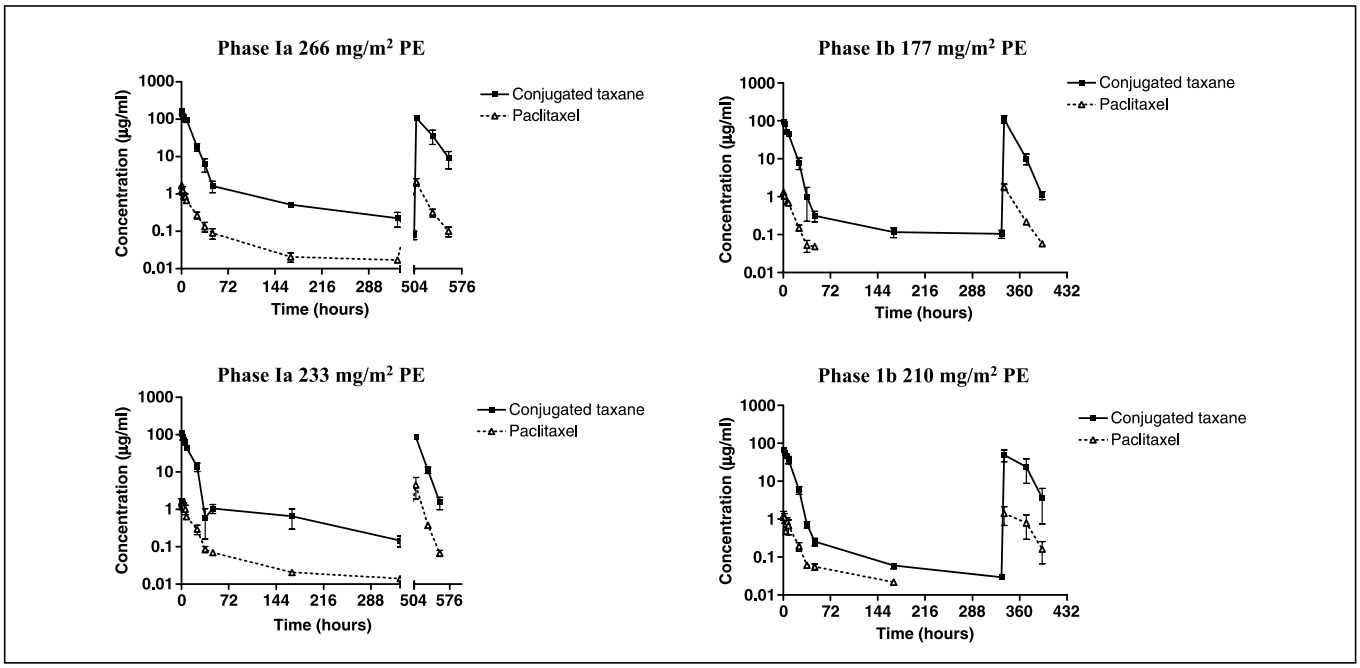

Fig. 2. Mean plasma concentration data for the 266 and 233 mg/m^2 dose levels in phase Ia and mean plasma concentration data for the 177 and 210 mg/m^2 dose levels in phase Ib.

sustained beyond the time when unconjugated drug is detectable in plasma. However, the apparent half-life of the unconjugated drug was less than that of the conjugated taxanes in every patient. Such an anomaly may reflect limitations in the analytic methods. Area under the concentration-time curves of unconjugated paclitaxel for patients treated at the highest dose levels were comparable with those seen at equivalent doses of Taxol. For instance, 175 mg/m^2 of Taxol given as a 3-hour infusion results in an AUC of 14.3 $\pm$ 4.2 μg/mL h (16) compared with an AUC of 15.0 $\pm$ 7.0 μg/mL h for 177 mg/m^2 PPX. These results should be treated with caution due to the possibility of hydrolysis of PPX during the assay. After PPX administration, high paclitaxel peak concentrations (C_{max}) are avoided, which may have some therapeutic advantage. At a dose of 177 mg/m^2, administration of PPX results in a paclitaxel C_{max} of 1.14 $\pm$ 0.54 μg/mL compared with a C_{max} of 3.92 $\pm$ 0.23 μg/mL following a 3-hour infusion of 175 mg/m^2 Taxol (17). At doses >175 mg/m^2, plasma concentrations of unconjugated paclitaxel remained above the previously identified threshold for activity of 1 μmol/L for at least 24 hours after administration but were undetectable (<0.02 μg/mL) before the second cycle of treatment in both phases.

Discussion

This trial reports the results of a phase I pharmacokinetic trial of PPX investigating two dosing schedules. The maximum tolerated dose was identified as 233 mg/m^2 on a 3-weekly schedule and 177 mg/m^2 on a 2-weekly schedule. The latter gave a higher dose intensity at the expense of greater neurotoxicity.

The observed toxicities of PPX are similar to those expected with standard paclitaxel but hematologic toxicity seems to be less frequent and milder. Neutropenia associated with standard paclitaxel is dose limiting and related to infusion time; febrile neutropenia rates of 16% to 36% are reported for a 24-hour infusion of 250 mg/m^2 every 3 weeks (18); however, <5% of patients are affected if the same dose is administered over 1 or 3 hours (19–21). In the current study, the maximum tolerated dose of PPX on a 3-weekly schedule is 233 mg/m^2. Febrile neutropenia was not reported at the maximum tolerated dose and grade 4 neutropenia was seen in only 13% patients. Paclitaxel is known to cause cumulative peripheral neuropathy. Initially, this presents as a "glove and stocking" sensory loss, progressing to motor loss in severe cases (22). Shorter infusion times are associated with a higher reported incidence of neuropathy. In addition, dose intensity and cumulative dose increase the likelihood of neuropathy. Dosing with 175 mg/m^2 over 3 hours every 3 weeks results in myalgia and neuropathy in 6% of patients treated with standard paclitaxel (23). Grade 2/3 neuropathy was reported in 50% of patients receiving the same dose on a weekly schedule (24). PPX did cause peripheral neuropathy as a dose-limiting side effect. However, incidence of grade 2 and 3 peripheral neuropathy on the 3-weekly schedule (14%) compares favorably with 31% reported for a similar dose (210 mg/m^2) of standard paclitaxel infused over 3 hours every 3 weeks (25). Neuropathy was a more significant problem on the 2-weekly schedule even at a lower dose intensity of 177 mg/m^2 every 2 weeks. The occurrence of hypersensitivity reactions in a Cremophor-free formulation is noteworthy and unlikely to be related to paclitaxel itself.

The pharmacokinetic data on conjugated taxanes in plasma suggest that the distribution of conjugated taxanes is mostly restricted to plasma and, in part, to extracellular body fluids. This is consistent with the assumption, based on preclinical data (15), that PPX distributes into those tissues characterized by enhanced permeability and retention, like the tumor, or by the presence of the reticuloendothelial system, like the liver and spleen. As suggested by the large difference between V_{ss}

and V_z, we can speculate that after an initial limited distribution, conjugated taxanes may enter slowly and progressively into the cells with subsequent release of active paclitaxel. The long half-life is consistent with the stability of the polymer in plasma. The persistence of detectable polymer at the end of the 2-weekly cycle may underlie the increased risk of neuropathy although unconjugated paclitaxel was not detectable in plasma at this time. Plasma concentrations of conjugated taxanes were 10- to 100-fold higher than those of unconjugated paclitaxel. Compared with the plasma concentration-time profiles seen following equivalent doses of Taxol, concentrations of unconjugated paclitaxel were lower but persisted for longer. Peak concentration-time profiles of unconjugated paclitaxel coincided with those of the conjugated taxanes and, subsequently, concentrations of the two species declined in parallel. Paclitaxel was present at active concentrations (>1 μmol/L) for at least 24 hours in all patients at the highest dose levels in phase Ia and phase Ib. These data must be interpreted with caution because it is possible that some of the unconjugated paclitaxel measured in the plasma may have dissociated from the polymer *ex vivo*. Intensive analytic validation was not able to exclude this possibility but all possible steps were taken to minimize such artifactual measurements.

Macromolecular polymer-drug conjugates can enhance the antitumor efficacy of cytotoxic compounds by increasing the amount of drug distributed to tumor tissue and by prolonging exposure while decreasing systemic exposure to the active drug (9). The available preclinical and clinical data are consistent with a volume of distribution of PPX limited to the vascular space with slow distribution to tumor and reticuloendothelial tissues (15). PPX provides a method of administering clinically relevant doses of paclitaxel to patients with cancer. Hypersensitivity reactions were mild, required no premedication, and there were no other formulation-related problems. Neutropenia was relatively mild, but neuropathy, although similar to that associated with comparable schedules of Taxol, was more of a problem on the 2-weekly schedule. Notably, alopecia was almost absent in patients treated with PPX compared with an incidence of over 50% following Taxol as a 3- or 24-hour infusion (21). The recommended phase II dose for the 3-weekly schedule is 235 mg/m^2. Clinically significant responses were observed in this phase I study. A phase II study in ovarian cancer (26), using a dose of 175 mg/m^2, reported a response rate of 28% in platinum-sensitive patients and 10% in platinum-resistant patients. However, the degree of neurotoxicity was higher than expected. Phase II studies in other cancers are ongoing.

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