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ORIGINAL ARTICLE

Phase I study of paclitaxel poliglumex administered weekly for patients with advanced solid malignancies

Monica Mita · Alain Mita · John Sarantopoulos · Chris H. Takimoto · Eric K. Rowinsky · Ofelia Romero · Patrizia Angiuli · Cecilia Allievi · Amy Eisenfeld · Claire F. Verschraegen

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Abstract
Background Paclitaxel poliglumex (PPX, also called Xyotax® or CT-2103) is a water soluble macromolecular drug conjugate that links paclitaxel with a biodegradable polymer, poly-L-glutamic acid. The recommended phase II dose of PPX every 3 week is 235 mg/m^2 administered over a 10-min infusion without premedication. This study was designed to determine the MTD and pharmacology of PPX administered weekly to patients with solid malignancies.
Methods The starting dose of weekly PPX was 20 mg/m^2. Each cycle consists of 6 weekly treatments with pharmacokinetics of PPX (the conjugated paclitaxel) and unconjugated paclitaxel obtained after the first and sixth dose. Three to six patients were enrolled at each dose level. Toxicity and response were assessed by the NCI Common Toxicity criteria version 2 and RECIST criteria, respectively.
Results Twenty-six patients were treated with PPX at the following dose levels: 20 mg/m^2 (five patients), 40 mg/m^2 (four patients), 60 mg/m^2 (four patients), 70 mg/m^2 (eight patients) and 80 mg/m^2 (five patients). Dose-limiting toxicities, consisting of grade 3 neutropenia, occurred in the 80 mg/m^2 cohort during cycle 1. Therefore, the dose recommended for phase II studies was 70 mg/m^2. In this cohort, a single dose-limiting event, consisting of diarrhea, was seen. Neuropathy and fatigue were the most common toxicities. No objective responses were noted. Pharmacokinetics was dose-proportional, and the degree of neutropenia related to drug exposure, but not to peak plasma concentration. There was no significant accumulation of conjugated or unconjugated paclitaxel with this dosing schedule.
Conclusions The recommended dose of PPX for subsequent disease-directed studies is 70 mg/m^2 weekly.

Keywords Paclitaxel poliglumex · Phase I · Solid tumors · Clinical trials · Pharmacokinetics · Pharmacodynamics · Paclitaxel · PPX

Introduction

The antimicrotubule agent paclitaxel is a poorly water-soluble drug formulated for clinical use (brand name, Taxol®) in polyoxyethylated castor oil (Cremophor-EL; BASF Corp, Ludwigshafen, Germany), which is associated with acute hypersensitivity reactions. The pharmacokinetics of paclitaxel have been extensively studied [1]. Various formulations of paclitaxel have been investigated and none have consistently demonstrated major improvements over paclitaxel formulated in polyoxyethylated castor oil [2–5]. Paclitaxel poliglumex (PPX) is a novel formulation, in which paclitaxel is covalently linked by an ester bond at the 2′-hydroxyl group to poly-L-glutamate, a highly hydrophilic macromolecular carrier [6]. The rationale for evaluating PPX includes: (1) the stability of this complex in the systemic

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C. F. Verschraegen (✉)
The University of New Mexico Cancer Research and Treatment Center, 900 Camino de Salud, Albuquerque, NM 87131, USA
e-mail: cverschraegen@salud.unm.edu

M. Mita · A. Mita · J. Sarantopoulos · C. H. Takimoto · E. K. Rowinsky · O. Romero
Cancer Therapy and Research Center, San Antonio, TX, USA

P. Angiuli
Cell Therapeutics, Inc., Sede Secondaria, Via Ariosto, 23, 20091 Bresso, Italy

P. Angiuli · C. Allievi · A. Eisenfeld
Cell Therapeutics, Inc., Seattle, WA, USA

circulation (2) the retention of this polymer in the hyperpermeable neoplastic tumor neovasculature and the interstitial tumor space, and (3) the degradation of this macromolecular complex by intracellular lysosomal enzymes, which release free drug in the tumor cells through endocytosis [6, 7]. These three characteristics result in prolonged intratumor exposure to biologically relevant paclitaxel concentrations [8, 9]. PPX has shown antitumor activity against various human tumor xenografts as well as in early phase 1 trials [6, 10]. The maximum tolerated dose (MTD) of PPX administered as an every 3 week intravenous infusion is 235 mg/m^2. The most common adverse event is neutropenia. A known effect of PPX is a non-clinically significant prolongation of the partial thromboplastin time (PTT), which values returned to baseline within 24–48 h. The most clinically significant adverse event is cumulative neuropathy, with an unacceptable incidence rate seen at doses above 175 mg/m^2, which causes patients to discontinue therapy after a median of four courses. The incidence of neurotoxicity may be increased in patients who have received prior treatment with neurotoxic agents [11, 12]. Neutropenia and neuropathy induced by paclitaxel seem to be related to the duration of exposure to plasma paclitaxel concentrations exceeding 0.05 μmol/l, but not to peak concentration, the area under the curve (AUC), or the dose [13, 14]. The weekly schedule of paclitaxel administration was studied in a breast cancer trial. This schedule provides less neutropenia than with the every 3 week dosing schedule, with similar efficacy [15]. Because PPX is a drug that slowly releases unconjugated paclitaxel, we hypothesized that the weekly administration of PPX may decrease the patient exposure below this 0.05 μM threshold, and further reduce the occurrence of toxic effects. Minimal toxicity would eliminate the need for recovery time, so no break was designed in this weekly regimen. This also fit the concept of "metronomic" dosing of chemotherapy that was proposed by many investigators in the field of antiangiogenic therapy.

The objectives of this phase I study were to determine the MTD, toxicity profile, pharmacokinetics and pharmacodynamics of weekly PPX in patients with refractory solid tumors.

Patients and methods

This was an open label dose escalating phase I study of PPX. The study was approved by the local research ethics committees.

Patients

Inclusion criteria included a histologically proven diagnosis of solid malignancy refractory to treatment, or for which no conventional therapy was available; an Eastern Cooperative Oncology Group performance status of 0–1; at least 18 years of age; a life expectancy greater than 16 weeks; a hemoglobin level equal or greater than 9 g/dl, an absolute neutrophil count equal or greater than 1.5 × 10^9/l, a platelet count equal or greater than 100 × 10^9/l, a bilirubin less than 1.5 times the upper limit of normal (ULN); alanine or aspartate aminotransferases less than 2.5 times the ULN in the absence of liver metastases, (or up to 5 times the ULN in the presence of liver metastases), and a serum creatinine less than 1.5 times the ULN. Patients had to sign a written informed consent. Patients were excluded if they had received radiotherapy, endocrine therapy, immunotherapy, or chemotherapy within 4 weeks before starting PPX. Exclusion criteria included cancer treatment within 4 weeks of enrollment, treatment with more than two alkylating regimens or a stem cell transplant, persistent neuropathy grade 2 or higher, and comorbid conditions precluding safe PPX administration.

Pre-treatment assessment included a history, physical examination, chest radiograph and electrocardiogram. Every 6 weeks, a simple neuropathy assessment questionnaire and a focused neurological examination were performed to assess strength, reflexes, point discrimination, vibration recognition, and toe position. Laboratory evaluations included a complete blood count every week and a blood biochemistry plus a coagulation panel every 6 weeks. Patients were assessed for disease response in the sixth week of every second cycle of study treatment by RECIST criteria. Patients with stable disease or better could continue on the study until the documentation of disease progression, documentation of complete response, or until occurrence of unacceptable toxicity. All patients were then to be followed until documentation of disease progression.

Treatment

PPX was supplied by Cell Therapeutics, Inc. (Seattle, WA). All administered doses are expressed as paclitaxel equivalents. The standard phase I 3 + 3 design (three to six patients per cohort) was used to establish the MTD. PPX was administered weekly for a 6-week cycle by a 20-min infusion at a starting dose of 20 mg/m^2/week. Between cycles 1 and 2, no treatment was given for 2 weeks to allow characterization of the complete pharmacokinetic profile of PPX. Beginning with cycle 2, cycles were repeated without interruption unless a delay was warranted for toxicity. Dose escalation was based on toxicities from the first cycle for each cohort of patients. At least three patients were initially enrolled at each dose level. Additional patients were accrued to a cohort as needed in the event that an initial patient did not receive all planned cycle 1 doses. If none of the three patients experienced

dose-limiting toxicity (DLT), the dose was escalated. If one of the initial three patients developed DLT, at least three additional patients were enrolled at the same dose level. If one-third or more patients developed DLT at a given dose level, the dose was decreased to the previous dose level. The provisional MTD was defined as the dose level immediately below that at which one-third or more patients experienced DLT. Dose reductions of 10 mg/m^2 were required for febrile neutropenia or grade 4 thrombocytopenia at any time, grade 3 neutropenia before dosing, and if at the time of dosing there was a drug-related grade 3 or 4 non-hematologic toxicity (excluding fatigue, nausea and vomiting of all grades and grade 3 hypersensitivity). In case of grades 1 to 3 hypersensitivity, prophylaxis was given before subsequent doses, but dose reduction was not required. Patients were re-treated when toxicities resolved to grade 1 or less but delay could not exceed 2 weeks. Treatment delay due to drug-related toxicity also caused a dose reduction. Once the dose had been reduced, it was not re-escalated. Treatment was discontinued for grade 2 neuropathy after the second dose reduction and for grade 4 hypersensitivity at any time.

Dose-limiting toxicity definition

Adverse events were assessed using the NCI Common Toxicity criteria, version 2. DLT was defined as a grade 3 neutropenia on retreatment day, a grade 4 febrile neutropenia, a drug-related grade 3 or 4 non-hematologic toxicity (except fatigue, nausea, vomiting or grade 3 hypersensitivity reaction) or a grade 2 or greater motor or sensory neuropathy, which could preclude safe retreatment. Treatment delay longer than 2 weeks due to drug-related toxicity and death were also considered DLTs. The MTD was defined as the dose level below which two of three to six patients experienced DLT in cycle 1.

Pharmacology

The concentrations of conjugated and unconjugated paclitaxel in plasma were measured with liquid chromatography and mass spectrometry as described [11]. Blood samples were collected into Vacutainer tubes containing sodium heparin at the following time points: during cycle 1 on days 1 and 36: at pre-dose, 30 min, and 1, 2, 4, 6, 8, 12, 24, 48, and 72 h after the start of the infusion; at pre-dose on days 8, 15, 22, and 29; and on days 43 and 50. During cycle 2 day 1: at pre-dose, 30 min, 4, 24, and 72 h after the start of the infusion; and at pre-dose on days 8, 15, and 22. During the first cycle, additional blood samples were drawn to assess the following coagulation parameters: prothrombin time and partial thromboplastin time (PTT) at the following times: on day 1 at predose, 30 min, and 2, 6 12, 24 and 72 h after the start of the infusion and at pre-dose on days 8, 15, 22, 29 and on days 36 and 50.

The conjugated and unconjugated taxane pharmacokinetic parameters determined for each patient were: the absorption profile parameters of maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the plasma concentration-time curve (AUC) from time zero to infinity (AUC), terminal half-life, systemic plasma clearance, and volume of distribution at steady state. Pharmacokinetic values were estimated by non-compartmental methods using WinNonlin® [Enterprise version 4.1 (Pharsight Corporation, Mountain View, CA, USA]. The effects of plasma concentrations of conjugated and/or unconjugated paclitaxel on the relative neutropenia and thrombocytopenia nadirs, and on the coagulation parameters were investigated during cycle 1.

Statistics

Demographic data were reported, and summary statistics used to describe the study population (i.e., means and range of age, weight, height, race, numbers of males and females, descriptions of baseline performance status characteristics, and tabulation of tumor types and histologies). The pharmacokinetic/pharmacodynamic relationship between plasma concentrations and myelosuppression was investigated during cycle 1 and fitted using *WinNonlin Enterprise 4.1* with the simple maximum response (E_{max}) model, described by the following equation: $E = (E_{max} \times C)/(C + EC_{50})$ where E represents the effect (i.e., the percent reduction of ANC or platelets), E_{max} corresponds to the maximum effect, C is the concentration ($AUC_{0-t(last)}$ and/or C_{max}), and EC_{50} is the concentration ($AUC_{0-t(last)}$ or the C_{max}) associated to 50% of the effect. The $AUC_{0-t(last)}$ was used since AUC was missing for some patients.

Results

The study was open for accrual from August 2002 to September 2005.

Patient characteristics

Twenty-six patients were enrolled and treated in this study. Patient characteristics are listed in Table 1. Twenty-four patients had received at least two prior treatment regimens of chemotherapy. Five patients were treated at 20 mg/m^2, four at 40 mg/m^2, four at 60 mg/m^2, eight at 70 mg/m^2, and five at 80 mg/m^2. All patients enrolled received at least one dose of PPX and a median of six doses were administered (range, 1–23 doses). All patients were included in the safety and pharmacology

Table 1 Patient characteristics

Number of patients enrolled	26
Number of patients assessed	
For toxicity	26
For response (completed two cycles)	10
Median age (range), years	64 (32–83)
Gender	
Male	12
Female	14
ECOG performance status	
0	5
1	20
2	1
Race/ethnicity	
Caucasian	19
Hispanic	7
Primary tumor types	
Colon	5
Breast	3
Prostate	3
Lung NSCLC, unknown, ovarian, esophagus	2 Each
Lung SCLC, pancreas, carcinoid, hepatocellular, renal, melanoma, head and neck	1 Each
Number of prior chemotherapy regimens	
1	2
2	1
3	5
4	7
>4	11

analysis. Only ten patients were assessable for disease assessment by RECIST criteria. The number of cycles administered and the DLTs are shown in Table 2. Reasons for withdrawal included disease progression (22 patients), deterioration in medical condition not related to study treatment (2 patients), and neuropathy (2 patients).

Determination of the MTD

In cohorts 1–3, only three patients completed cycle 1 and none of these patients experienced a DLT. At 80 mg/m^2, five patients were enrolled and four completed cycle 1. Two patients experienced a DLT of grade 3 neutropenia with an absolute neutrophil count below 1,000 cells per mm^3 at the dosing time, preventing re-dosing. Therefore, the next cohort enrolled patients at 70 mg/m^2. Eight patients were treated and seven completed cycle 1, but one of them had rapidly progressive disease in the liver which prevented an objective assessment of DLT. Of the six assessable patients, one had a DLT of grade 3 diarrhea. No more patients were enrolled because it was determined that the goals of the study had been met, and the MTD was determined to be 70 mg/m^2/week.

Ten patients, one in the 40 mg/m^2 cohort, one in the 60 mg/m^2 cohort, three in the 70 mg/m^2 cohort, and five in the 80 mg/m^2 cohort experienced dose delays and/or dose reductions due to neutropenia (five patients), patient related reasons (four patients), and grade 2 hypotension (one patient). No patients experienced more than one dose reduction. At the MTD, the main reason for dose delay and reduction was neutropenia (two of three patients, the third delay was for patient personal reason and was not accompanied by a dose reduction).

Safety and tolerability

Most patients (69%) experienced at least one drug-related adverse event during the study (Table 3), with the majority of events being grade 1 to 2. Drug-related grade 3 neutropenia and grade 3 anemia were reported in three and two patients, respectively. Grade 3 diarrhea and grade 3 neuropathy were reported in one patient each. The grade 3 and 4 hemorrhagic adverse events were not related to PPX. Neutropenia usually occurred after the third dose. Although severe neutropenia limited further dose escalation above

Table 2 Number of courses of PPX per dose level

Dose level (mg/m^2)	*n*	No. of patients assessable	Median number of PPX courses (range)	DLTs (*n*)	Reasons for treatment discontinuation			
					Disease progression	Peripheral neuropathy	Pneumonia	Renal failure
20	5	3	1 (1–3)	None	5			
40	4	3	1 (1–2)	None	4			
60	4	3	1 (1–2)	None	2		1[a,b]	1[b]
70	8	6	1 (1–2)	Grade 3 diarrhea (1)	7	1[a]		
80	5	4	2 (1–4)	Grade 3 neutropenia (2)	4	1		

n number of patients per cohort

[a] Both patients also withdrew consent

[b] Not PPX related

Table 3 Adverse events related to PPX administration for all cohorts and at 70 mg/m^2

	Grade 1	Grade 2	Grade 3	Total
Adverse event—70 mg/m^2				
Neutropenia		1 (13%)	1 (13%)	2 (25%)
Anemia	1 (13%)	1 (13%)		2 (25%)
Peripheral neuropathy	2 (25%)	2 (25%)		2 (50%)
Anorexia	1 (13%)			1 (13%)
Diarrhea			1 (13%)	1 (13%)
Nausea	1 (13%)			1 (13%)
Pain in limb	1 (13%)			1 (13%)
Fatigue		1 (13%)		1 (13%)
Adverse event—all cohorts				
Neutropenia		2 (8%)	3 (12%)	5 (19%)
Anemia	1 (4%)	1 (4%)	2 (8%)	4 (15%)
Peripheral neuropathy	5 (16%)	4 (8%)	1 (4%)	10 (38%)
Anorexia	1 (4%)	1 (4%)		2 (8%)
Diarrhea	3 (12%)	1 (4%)	1 (4%)	5 (19%)
Nausea	3 (12%)	1 (4%)		4 (15%)
Rash	1 (4%)	2 (8%)		3 (12%)
Myalgia	3 (12%)	2 (8%)		5 (19%)
Pain in limb	1 (4%)	1 (4%)		2 (8%)
Fatigue	4 (15%)	3 (12%)		7 (27%)
Hypersensitivity	1 (4%)	1 (4%)		2 (8%)

the 70 mg/m^2, it was infrequent at the lower doses. Neuropathy was seen in ten patients (38%), fatigue in seven (27%), diarrhea in five (19%), and anemia and nausea in four each (15%). Mild hypersensitivity reactions, consisting of dyspnea and flushing, were seen in two patients. Most patients did not require premedication. The only serious adverse events related to PPX occurred in three patients at the 80 mg/m^2 dose and were grade 1 epistaxis and hematuria, grade 2 anemia, and grade 3 peripheral neuropathy unresolved at the end of the study.

Ten patients (38%) had at least one incidence of neuropathy (which included peripheral sensory neuropathy, peripheral motor neuropathy, hypoesthesia, impaired balance, or paresthesia). Seven of the ten patients with neuropathy had received prior therapy with at least one neurotoxic chemotherapy agent, and five of the ten had at least one risk factor for neuropathy noted at the baseline assessment (i.e., prior neuropathy, diabetes mellitus, hyperglycemia, or hypothyroidism). Neuropathy was most frequent at the highest doses, occurring in 4/8 patients (50%) at the 70 mg/m^2 dose and 4/5 patients (80%) at the 80 mg/m^2 dose. The worse grade of neuropathy was 1 in five patients, 2 in four, and one patient had a grade 3 event. No grade 4 neuropathy was reported. The neuropathy usually occurred at the fifth dose. Two patients discontinued the study due to grade 2 and 3 neuropathy.

The inter-patient variability of the coagulation parameters was low (data not shown). Seven patients who were taking warfarin and 14 who were not experienced an asymptomatic grade 1–3 prolongation of the PTT. There were no differences in the frequency or nature of hemorrhagic events between patients who were and who were not receiving warfarin during treatment with PPX. Ten hemorrhagic events occurred in seven patients, mostly grade 1 epistaxis or hematuria. Two serious hemorrhagic events of grade 3 hemoptysis occurred in a patient with renal cell cancer and lung metastases, and grade 4 cardiac tamponade occurred in a patient with small cell lung cancer, but neither was attributed to PPX.

Antitumor activity

The best response was stable disease which lasted at least 12 weeks in eight patients (range 84–213$^+$ days). The median time to progression was 62 days for all patients.

Pharmacology

Conjugated taxane pharmacokinetics

After the administration of PPX at 70 mg/m^2, the mean maximal concentration (C_{max}) ± standard deviation (SD) was 41.2 ± 8.60 μg/ml and was reached just after the end of the infusion, then declined with a mean terminal half-life of 15.7 ± 3.17 h. The mean AUC at the MTD was 455 ± 112 μg h/ml and the mean average systemic plasma clearance was 0.16 ± 0.04 l/h/m^2. At the MTD, the mean volume of distribution at steady state and during the terminal phase were 1.41 ± 0.28 l/m^2 and 3.62 ± 1.13 l/m^2, which is lower than the volume of extracellular body fluids and total body water (10 and 23 l/m^2, respectively [16, 17]), indicating the distribution of the conjugated polymer was mostly restricted to plasma. The low doses administered in the current study prevented the evaluation of the longer terminal half-life and the larger volume of distribution during the terminal phase (V_z) observed in previous trials, in which patients received higher doses of PPX (175–270 mg/m^2) [11].

The mean AUC ± SD (μg h/ml) per dose level was as follows; 20 mg/m^2, 76.9 ± 32.3; 40 mg/m^2, 81.8 ± 23.5; 60 mg/m^2, 306 ± 152; and 80 mg/m^2, 651 ± 195. These values are depicted in Fig. 1. Plasma concentrations of conjugated taxane in the range tested appeared dose proportional (Fig. 1).

Unconjugated paclitaxel pharmacokinetics

At the MTD, the mean C_{max} (±SD) of unconjugated paclitaxel was 0.21 ± 0.07 μg/ml, the mean T_{max} 0.56 ± 0.18 h,

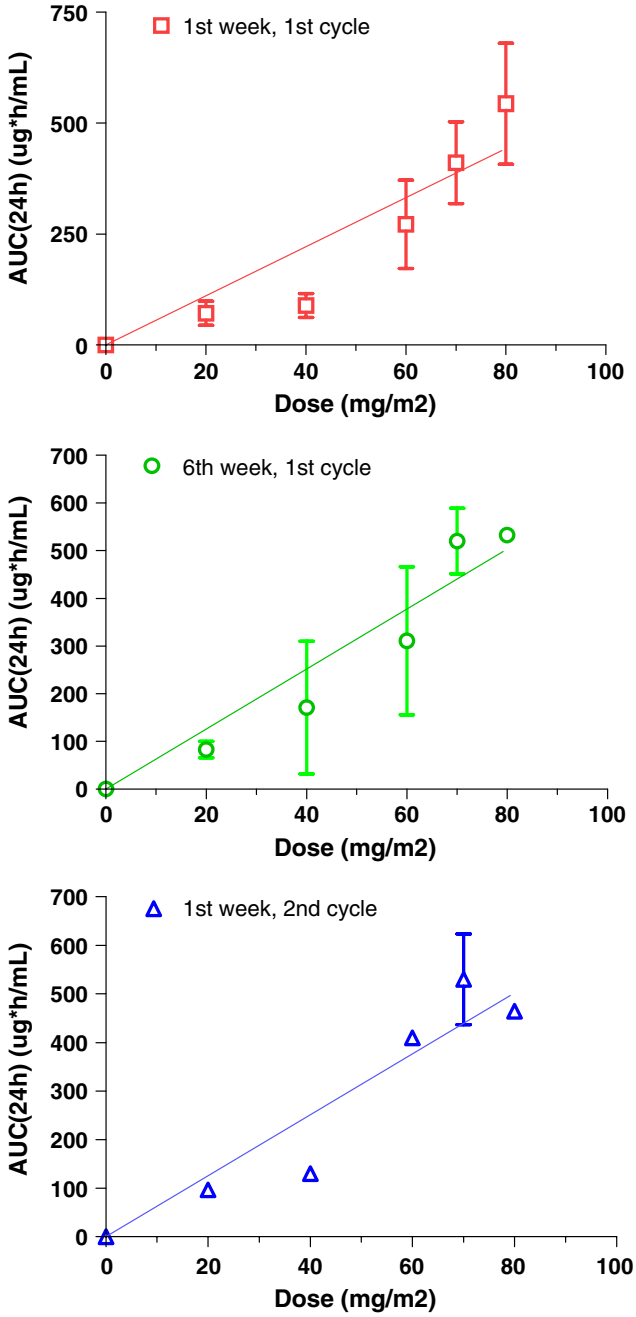

Fig. 1 *Linear plot* of conjugated AUC (0–24 h) and PPX dose. The *regression line*, passing through the *origin*, indicates the increase of plasma levels in direct proportion with the dose

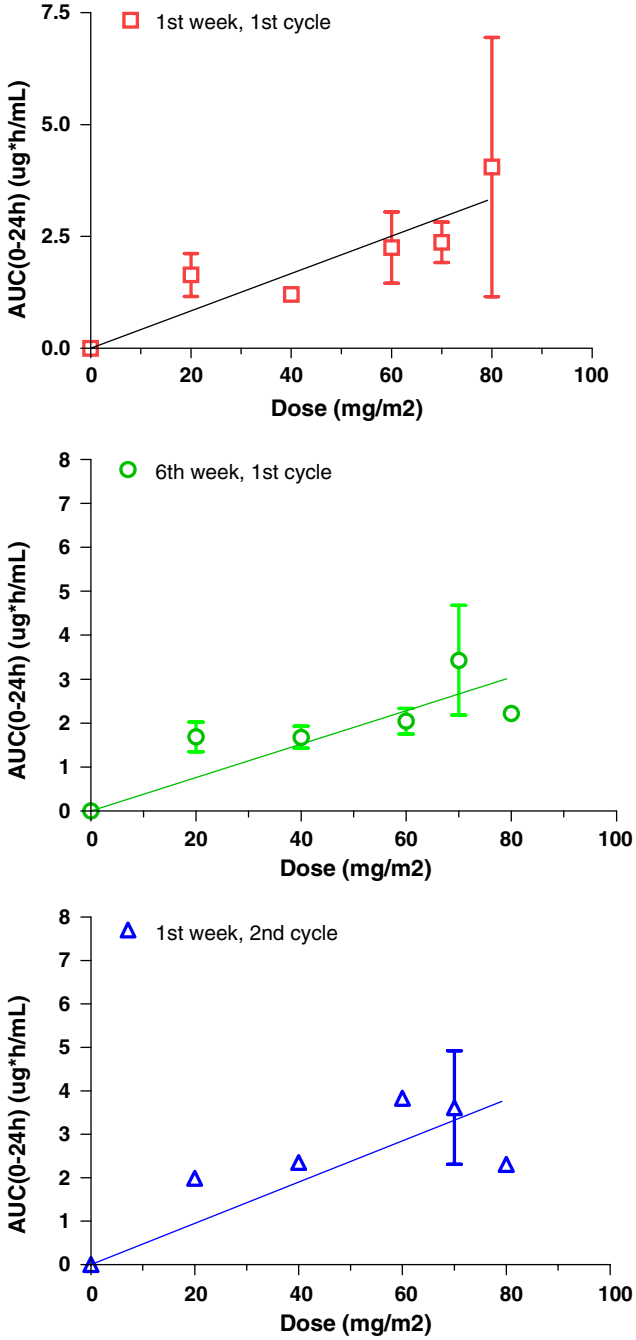

Fig. 2 *Linear plot* of unconjugated AUC (0–24 h) and PPX dose. The *regression line*, passing through the *origin*, indicates the increase of plasma levels in direct proportion with the dose

the mean terminal half life 16.6 ± 7.85 h, and the mean AUC 3.15 ± 1.16 μg h/ml. The ratio of the unconjugated paclitaxel AUC over the conjugated paclitaxel AUC was 0.7%. As with conjugated taxane, the plasma concentration of the unconjugated form increased largely in direct proportion with the dose (Fig. 2) and remained similar after repeated administration.

Pharmacodynamics

The relationship between the plasma concentration and the decrease of neutrophils is shown in Fig. 3. The reduction of ANC seemed to correlate with unconjugated paclitaxel AUC [Fig. 3a, E_{max} (%ANC reduction): 105 ± 49, (mean ± SEM) (CV 47%) and EC_{50} (μg h/ml): 4.12 ± 3.63 (mean ± SEM)

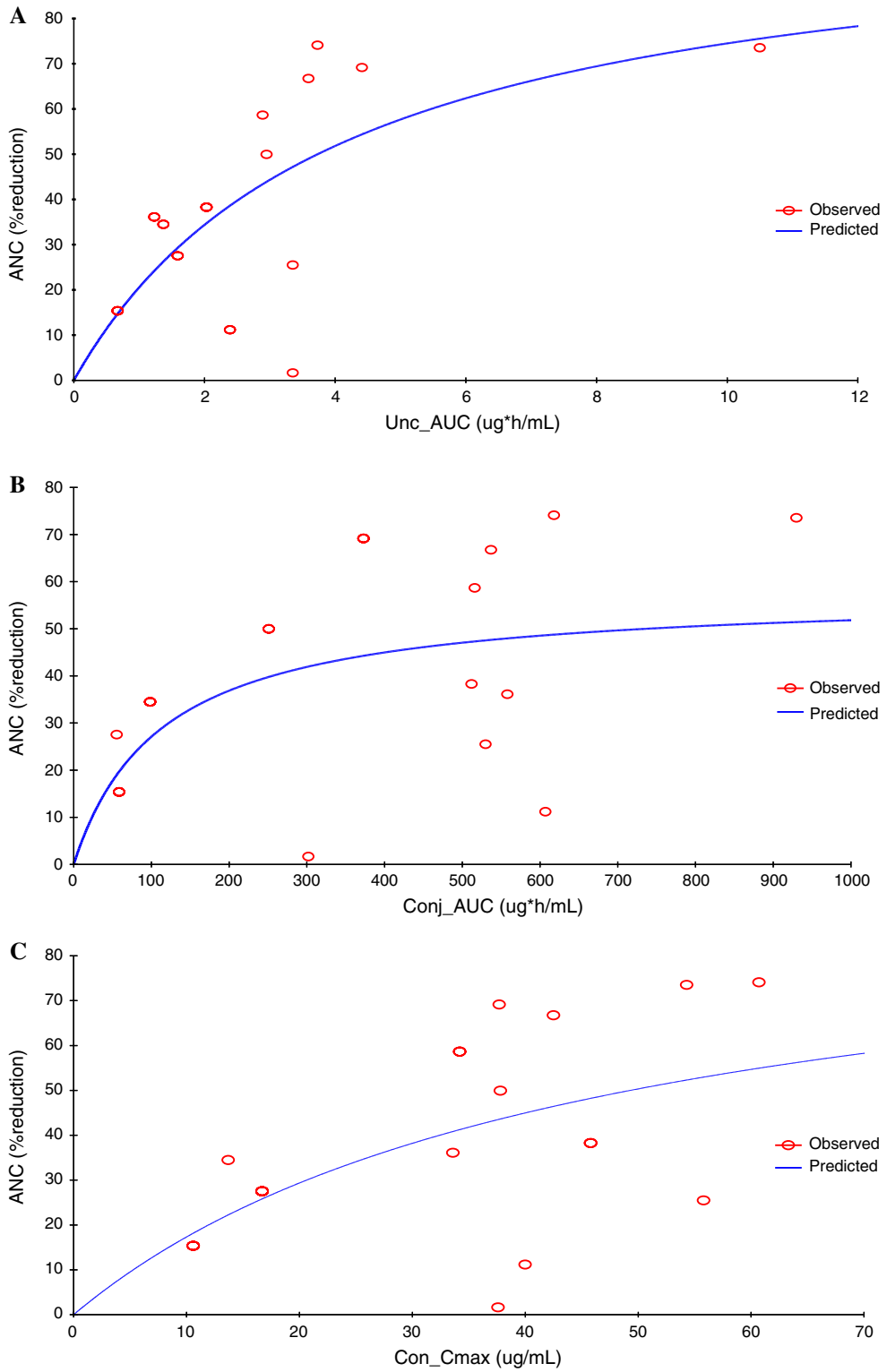

Fig. 3 Correlation between decrease of ANC and conjugated and unconjugated paclitaxel AUC 0-t(last) and C_{max} during first cycle. See text for details

(CV 88%)]; with conjugated taxane AUC [Fig. 3b, E_{max} 58 ± 18 (mean ± SEM) (CV 31%) and EC_{50} (μg h/ml): 113 ± 146 (mean ± SEM) (CV 130%)]; and with conjugated taxane C_{max} [Fig. 3c, E_{max} 96 ± 92 (mean ± SEM) (CV 96%) and EC_{50} (μg h/ml): 46 ± 83 (mean ± SEM) (CV 183%)]. The reduction in platelets appeared to relate to conjugated taxane C_{max} through a simple E_{max} model, but not with unconjugated paclitaxel (data not shown).

Discussion

The recommended phase II dose of PPX on a weekly schedule is 70 mg/m^2. The DLT is neutropenia, occurring in the third week of treatment. This dose corresponds to the MTD of PPX administered every 3 weeks and is the same as the MTD established in a study of weekly PPX and concurrent radiotherapy [18]. The most common side effects were peripheral neuropathy and fatigue seen in about a third of the patients. Other side effects included myalgia, gastrointestinal effects mainly diarrhea, and anemia (Table 3). Most side effects were grade 1, and the weekly schedule was therefore well tolerated.

The reduction of ANC seemed to correlate with unconjugated paclitaxel AUC and conjugated taxane AUC and C_{max} through a simple E_{max} model. Thrombocytopenia appeared to correlate with conjugated taxane C_{max} through a simple E_{max} model. The above results appeared different from those observed in a previous trial of doses varying between 175 and 270 mg/m^2 where the relationship between the neutropenia and the plasma concentrations was described by a sigmoidal E_{max} model and no relationship was found between plasma concentrations and thrombocytopenia. With doses of 175–270 mg/m^2, neutropenia nadir occurred when the values of unconjugated and conjugated paclitaxel AUC and unconjugated and conjugated paclitaxel C_{max} were higher than approximately 10 and 1,000 μg h/ml and 1 and 100 μg/ml, respectively. In this weekly study, the low C_{max} of unconjugated taxane did not correlate with neutropenia. Exposure reached values seen with the administration of paclitaxel, potentially accounting for the correlation represented by an E_{max} model curve. However, this curve depended on one outlier (patient 16 treated at 80 mg/m^2 whose AUC was three times that of the other patients treated at the same dose; Fig. 3), and was probably not real.

The PPX formulation does not protect against the development of side effects. While neutropenia was not profound at the MTD (no grade 4 and only 12% grade 3), re-treatment is not possible on a weekly basis with these low neutrophil counts. Dose delays will happen in about 20% of patients at the MTD (Table 3). Neuropathy, usually grade 1 or 2, was the most common side effect (Table 3), and has also been related to a paclitaxel exposure threshold of 0.05 μM [14]. The occurrence of neuropathy was not frequent enough for a complete statistical analysis, but the mean AUC for patients without neuropathy was about 25% lower than for patients with neuropathy. Mean AUCs on day 1, 36, and 56 were 4.04, 5.74, and 4.73 μg h/ml for patients with neuropathy, and 3.45, 4.35, and 3.73 μg h/ml for patients without neuropathy. Because the population of patients in this study was heavily pretreated with neurotoxic chemotherapies, it is not clear whether this schedule of PPX administration helps prevent neuropathy. The 38% rate of neuropathy observed at the MTD in this heavily pretreated population compares favorably to the 50–60% observed for weekly paclitaxel [19–21].

In the majority of patients, PTT values increased just after the administration and returned to baseline about 24 h post-dosing without major hemorrhagic side effects. Preliminary preclinical data suggest that PPX is a non-competitive inhibitor of Factor Xa and thrombin. However, the exact mechanism of this abnormality is not yet fully characterized. This observation may not be of great clinical significance, since hemorrhagic events are similar whether the PTT increases or not after PPX administration. This effect would be better ascertained in a larger population of patients.

In conclusion, weekly PPX is well tolerated at a dose of 70 mg/m^2. The side effects are moderate, mainly grade 2 or lower neutropenia, fatigue, and peripheral neurotoxicity. The pharmacokinetics is dose proportional. There was a reversible metabolic effect on the PTT without clinical significance. No major anticancer activity was seen in this refractory patient population. Despite the lack of efficacy in this phase I study, the weekly dosage compares favorably in terms of side effects to the every 3 week administration [11]. The weekly administration of PPX, as a single agent or in combination with other cancer drugs, is worthy of further testing in a minimally pretreated cancer population.

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