Phase I and Pharmacokinetic Study of XRP6258 (RPR 116258A), a Novel Taxane, Administered as a 1-Hour Infusion Every 3 Weeks in Patients with Advanced Solid Tumors

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Abstract

Purpose: To assess the feasibility of administering XRP6258, a new taxane with a low affinity for the multidrug resistance 1 protein, as a 1-hour i.v. infusion every 3 weeks. The study also sought to determine the maximum tolerated dose and the recommended dose, to describe the pharmacokinetic (PK) behavior of the compound, and to seek preliminary evidence of anticancer activity.

Experimental Design: Twenty-five patients with advanced solid malignancies were treated with 102 courses of XRP6258 at four dose levels ranging from 10 to 25 mg/m^2. Dose escalation was based on the occurrence of dose-limiting toxicity (DLT) at each dose level, provided that PK variables were favorable. The maximum tolerated dose was defined as the dose at which at least two patients developed a DLT at the first course.

Results: Neutropenia was the principal DLT, with one patient experiencing febrile neutropenia and two others showing prolonged grade 4 neutropenia at the 25 mg/m^2 dose level. Nonhematologic toxicities, including nausea, vomiting, diarrhea, neurotoxicity, and fatigue, were generally mild to moderate in severity. XRP6258 exhibited dose-proportional PK, a triphasic elimination profile, a long terminal half-life (77.3 hours), a high clearance (mean CL, 53.5 L/h), and a large volume of distribution (mean V_{ss}, 2,034 L/m^2). Objective antitumor activity included partial responses in two patients with metastatic prostate carcinoma, one unconfirmed partial response, and two minor responses.

Conclusion: The recommended phase II dose of XRP6258 on this schedule is 20 mg/m^2. The general tolerability and encouraging antitumor activity in taxane-refractory patients warrant further evaluations of XRP6258.

The taxanes have emerged as a major class of chemotherapy agents over the last 2 decades as shown by their extensive use as single agents and in multiagent regimens to treat a wide variety of solid malignancies (1, 2). However, one potential limitation of the taxanes is their high substrate affinity for the multidrug resistance (MDR) proteins, which confer both constitutive and acquired resistance (3, 4). For this reason, efforts have been made to synthesize new taxanes that are not avid substrates for MDR proteins to ultimately broaden their antitumor spectra. The new taxane XRP6258 was selected for clinical development due to its poor affinity for the ATP-dependent drug efflux pump, P-glycoprotein 1 (ATP-binding cassette, subfamily B, member 1 encoded by the *ABCB1* gene and referred to hereinafter as P-gp), and its greater penetration of the blood-brain barrier compared with docetaxel and paclitaxel (5). XRP6258 (formula $C_{45}H_{57}NO_{14}$) is partially synthesized as a single diastereoisomer from 10-deacetyl baccatin III, the major natural taxoid derived from the needles of various *Taxus* species. XRP6258 promotes the assembly of tubulin and stabilizes microtubules against cold-induced depolymerization *in vitro* as potently as docetaxel (5).

The cytotoxicity of XRP6258 was compared with docetaxel in several murine and human cell lines (5). In docetaxel-sensitive cell lines, including P388 (murine leukemia), HL60 (human leukemia) KB (human epidermoid carcinoma), and Calc18 (human breast carcinoma), XRP6258 showed potent antitumor activity comparable with docetaxel, with 50% tumor inhibitory concentrations (IC_{50}) ranging from 0.003 to 0.029 μmol/L. However, XRP6258 was more potent than docetaxel in a broad array of cancer cell lines with acquired resistance to docetaxel due to P-gp overexpression, including P388/DOX, P388/TXT, P388/VCR, HL60/TAX, Calc18/TXT, and KBV1 (5). Resistance

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Translational Relevance

The selective action of conventional cytotoxic agents depends on the relative sensitivity of proliferating tumor over critical normal cells to the effects of exposure to these drugs. One factor limiting the clinical utility of such compounds is the innate or acquired drug resistance of the tumor. Resistance may be mediated by tumor cell overexpression of efflux pumps, such as the ATP-binding cassette, subfamily B, member 1 (MDR1). Although the development of rationally targeted highly specific biological agents represents an exciting new approach to anticancer drug discovery, it is anticipated that there will be a continuing requirement to include broadly active cytotoxic agents in treatment strategies. The complementary approach of improving on the spectrum of activity or tolerability of such cytotoxic compounds therefore remains as an important therapeutic objective. The novel taxoid, XRP6258, was selected for clinical development based on encouraging cytotoxic antitumor activity in cancer cell lines expressing a multidrug resistance phenotype. This agent also showed effective penetration of the blood-brain barrier. The current phase I study was designed primarily to determine the maximum tolerated dose and the dose-limiting toxicity of XRP6258 given as a 1-hour i.v. infusion. As such, this analysis is of direct and immediate clinical relevance.

factor ratios ranged from 1.8 to 10 for XRP6258, whereas comparable values were 4.8 to 50.7 for docetaxel. Furthermore, XRP6258 showed greater cytotoxicity compared with docetaxel in a CaCo-2 human colon adenocarcinoma cell line, which exhibits primary resistance to the taxanes, due to MDR (6).

XRP6258 has also shown a broad spectrum of antitumor activity in mice bearing s.c. implanted human xenografts. For example, a high complete regression rate was observed in eight of nine human tumor cell lines evaluated in human tumor xenograft models, with long-term survivors observed in hosts bearing HCT116 colon, A549 lung, MIA PaCa-2 pancreatic, SR475 squamous cell, and Du-145 prostate cancers (5). Prominent antitumor activity was also documented in SF295 and U251 glioblastoma orthotopic models. XRP6258 retained activity against docetaxel-resistant P-gp–expressing B16/TXT melanoma xenograft models, but not against Calc18/TXT and P388/VCR, which express higher levels of *ABCB1* mRNA. Interestingly, XRP6258 was found to penetrate the blood-brain barrier, which may be due to its low affinity for the P-gp (7), and studies in mice have shown that P-gp–mediated transport at this barrier can be saturated at circulating concentrations of the drug that are likely to be therapeutically useful (8). Schedule-dependent antitumor activity and toxicity was suggested by the results of preclinical studies. Both toxicity and antitumor activity profiles seemed optimal on an intermittent day 1 and 5 dosing schedule compared with daily × 5 or split (three times daily for 5 days) dosing (5).

The encouraging spectrum of antitumor activity of XRP6258 in experimental tumor models, particularly its notable activity against docetaxel-resistant, P-gp–expressing malignancies, served as a rationale to clinical evaluations. The principal objectives of this phase I and pharmacokinetic (PK) study of XRP6258 administered as a 1-hour i.v. infusion every 3 weeks in patients with advanced solid malignancies were to (*a*) characterize the toxicities of XRP6258 administered without premedication on this schedule, (*b*) determine the maximum tolerated dose (MTD) and the recommended dose for phase II studies, (*c*) characterize the PK profile of the compound and its metabolic species, and (*d*) document preliminary evidence of antitumor activity.

Materials and Methods

Eligibility. Patients with histologically documented advanced solid malignancies refractory to conventional treatment were candidates for this study. Only patients who had received less than two prior chemotherapy regimens for metastatic disease and/or radiotherapy affecting <25% of their hematopoietic reserve were eligible. Patients who had been treated with intensive chemotherapy involving autologous stem cell rescue were not eligible. Prior anticancer therapy had to be completed at least 28 d before study enrollment (42 d for nitrosoureas and mitomycin C). Other eligibility criteria included the following: age ≥18 y; a life expectancy ≥12 wk; an Eastern Cooperative Oncology Group performance status of 0 to 2; recovery from the toxic effects of prior treatment to grade ≤1, except for alopecia; adequate organ function, including hematopoietic [absolute neutrophil count (ANC) >2.0 × 10^9/L; platelets >100 × 10^9/L], renal (creatinine <1.5 mg/dL), and hepatic (total bilirubin within normal limits, transaminases, and alkaline phosphatase ≤2.5 times the upper normal limits) functions; and a normal neurologic examination. Prior therapy with taxanes was permitted. Patients with brain metastasis, coexisting medical problems of sufficient severity to limit compliance with the study, as well as patients with a prior history of severe hypersensitivity to docetaxel or paclitaxel were considered ineligible for this study. Routine use of corticosteroids or erythrocyte-stimulating factors as well as prophylactic use of colony-stimulating factors were not permitted. Pregnant or lactating women were not eligible for this trial. Before entering the study, patients gave written informed consent according to federal and institutional guidelines.

Drug administration. XRP6258 was supplied by Sanofi aventis in single-dose vials containing 94.4 mg of active product in 2.36 mL of polysorbate 80 at the concentration of 40 mg/mL XRP6258. The XRP6258 solvent vial contained 7.33 mL of a solution of 95% ethyl alcohol/water (13/87, w/w). XRP6258 was administered as 1-h i.v. infusion every 3 wk using a polyvinyl chloride–free infusion bag and administration set. No prophylactic treatment to prevent hypersensitivity reaction or emesis was administered during the first course. These treatments were provided for subsequent courses, if clinically indicated. Corticosteroids were not permitted as prophylactic treatment for nausea and/or vomiting.

Dose escalation. The starting dose was 10 mg/m^2, which corresponds to approximately one tenth of the severe toxic dose (STD_{10}) in mice and to the single highest nonseverely toxic dose in dogs, with subsequent incremental increase to 15, 20, and 25 mg/m^2 dose levels. A minimum of three patients was treated at each dose level, and a 2-wk interval was required at each dose level from the treatment of the first patient until treatment of subsequent patients. PK variables were monitored during the first course in each patient and dose escalation was to be stopped if total area under the concentration versus time curve (AUC) for plasma was ≥10.8 μg.h/mL (a level that would have exposed the patient to concentrations corresponding to severe toxic effect level in mice). If one of three patients exhibited a dose-limiting toxicity (DLT) during the first course, three more patients were to be treated at this dose level and dose escalation was considered only if no further DLTs occurred in this group. If two or three of the first three treated patients at a dose level experienced DLT during the first course, the MTD had been reached and no further escalation was to be considered. If none of three patients exhibited a DLT, then dose

escalation could be considered without including additional patients. DLT was defined as either grade 4 neutropenia lasting longer than 5 d or associated with fever (>38.5°C); platelets <25,000/mL; or any grade 3 to 4 nonhematologic toxicity excluding nausea, vomiting, hypersensitivity reactions, or alopecia. No intrapatient dose escalation was permitted. Due to the anticipated distribution in tissues and lipophilicity of the drug, the body surface area (BSA) for dose calculation was capped at 2.1 m^2. Treatment cycles were every 3 wk. Before retreatment, patients were required to have recovered from any toxic to no more than a grade 1 severity level, and platelets, total bilirubin, and creatinine values had to meet initial protocol eligibility requirements. If recovery did not occur within 35 d from the administration of XRP6258, the patient was withdrawn from the study. Dose reduction to the previous lower dose level was to be made only in the case of DLT.

The MTD was defined as the dose at which at least two of six patients experienced DLT during the first course. The recommended dose for phase II studies was defined as one dose level below the MTD. Initially, both heavily pretreated (HP) and minimally pretreated (MP) patients were to be accrued together at the same dose level. If hematologic DLT was consistently and preferentially observed in HP patients, then the accrual to the study was to diverge into HP and MP patients to define the principal phase I end points, and the MTD was to be defined for each group. HP patients were defined as patients who had received more than six courses of an alkylating agent (except low-dose cisplatin), more than four courses of carboplatin-containing chemotherapy regimens, or greater than two courses of nitrosoureas or mitomycin C.

Pretreatment and follow-up studies. History and physical examination (including a detailed neurologic examination) were done before study entry and repeated before each course. Pretreatment evaluation included complete blood cell count, full chemistry profile, including electrolytes, transaminases, alkaline phosphatase, and total bilirubin, and electrocardiogram and urine analysis. Thereafter, complete blood cell counts were done twice a week, electrocardiogram and urine analysis were repeated before each course, and the other laboratory screens were repeated weekly. Pretreatment studies also included a routine chest radiograph and relevant radiologic studies to evaluate all sites of disease and these studies were repeated every other course. Toxicities were evaluated according to the National Cancer Institute common toxicity criteria version 1.0. Tumor responses were assessed by standard WHO response criteria.

Plasma sampling and assay. To evaluate the PK variables of XRP6258, blood samples (3 mL) were collected immediately before infusion (time 0), 30 min after the beginning of infusion, 5 min before the end of infusion, and then 5, 15, 30, and 60 min and 2, 4, 6, 10, 24, and 48 h after completion of infusion in patients treated at 10 and 15 mg/m^2. In the subsequent cohorts, patients were sampled up to 120 h (at 25 mg/m^2) and 240 h (at 20 mg/m^2) after infusion. Blood specimens were collected in heparinized tubes (lithium heparinate). The blood samples were centrifuged within 30 min at 3,000 rpm × 15 min, and the plasma was removed and placed into polypropylene tubes, labeled, frozen, and stored at -20°C until analysis. No more than 1 h was allowed between blood collection and plasma sample freezing to avoid degradation of XRP6258.

Drug concentrations of XRP6258 were measured in plasma using a validated liquid chromatography-tandem mass spectrometry method. The quantitative determination was done with RPR 109881 as an internal standard. The limit of quantitation was 1 μg/L for a 200 μL sample size. The assay accuracy, defined as the percent difference between the nominal and the mean measured concentrations of quality controls, ranged from 0.01% to 4.6% (n = 67) XRP6258 in plasma over the analysis period. The accuracy of the dilution controls (1:2 or 1:4) was 1.2% (n = 23). The precision of the assay, established by the coefficients of variation (CV) of the quality controls, ranged from 9.5% to 12% for XRP6258 in plasma over the analysis period.

PK and pharmacodynamic analyses. The PK analyses were done using WinNonlin software, version 2.1 (Scientific Consulting, Inc.). Pertinent PK variables were calculated using a three-compartment open model with a first-order elimination rate, which best fits the data. A weighting factor of $1/\hat{y}^2$ was applied to the concentration data. AUC from 0 to infinity ($AUC_{0-\infty}$), half-life of the first, second, and third phases ($t_{1/2\lambda1}$, $t_{1/2\lambda2}$, and $t_{1/2\lambda3}$, respectively, where $t_{1/2\lambda3}$ was considered the elimination half-life), total body clearance (CL), and volume of distribution at steady state (V_{ss}) were determined by modeling. The plasma concentration measured 5 min before the end of infusion (C_{max} observed) was reported and a noncompartmental analysis (trapezoidal method) was also used to estimate the AUC from 0 to 48 h [$AUC_{(0\text{-}48\ h)}$] to compare the exposure over the whole dose range. The dose proportionality of the exposure was assessed on $AUC_{(0\text{-}48\ h)}$ data after dose normalization using the Proc GLM procedure of SAS (SAS Institute) software version 8.2 followed by a test of linearity applied on $AUC_{(0\text{-}48\ h)}$ against the dose expressed in mg/m^2. The interpatient and intrapatient variability of $AUC_{(0\text{-}48\ h)}$ was estimated using the Proc MIXED procedure of SAS after normalization to the dose and log transformation with patient taken as random effect and course of treatment as fixed effect. In addition, as the drug dosing is based on BSA, the relationship between the total plasma clearance expressed in L/h and the BSA was investigated using a Proc REG procedure of SAS software. All test results with $P < 0.05$ were considered statistically significant. The relative reduction in variability was calculated according to the formula [CV for CL (L/h) - CV for CL (L/h/m^2)]/[CV for CL (L/h)] × 100 and was considered to reach statistical significance when 15 (9).

The relationships between the C_{max} and $AUC_{(0\text{-}48\ h)}$ values and hematologic effect were described using the sigmoidal maximal effect model (E_{max}), which was fitted to the data by nonlinear least-square regression (9). The coefficient of determination (R^2), the SEs for the estimated variables, and visual inspection of the fitted plots were used to gauge goodness of fit of this pharmacodynamic model.

Table 1. Patient characteristics

Characteristic	No. patients
Total patients (evaluable)	25 (25)
Sex: male/female	17/8
Age, median (range), y	60 (32-80)
ECOG performance status	
Median	1
0	12
1	12
2	1
Race	
Caucasian	18 (72%)
Oriental	1 (4%)
Hispanic	6 (24%)
Previous therapy	
Chemotherapy	22 (88%)
Prior taxane-based therapy	8 (32%)
Radiotherapy	12 (48%)
Immunotherapy	2 (8%)
Hormonal therapy	8 (32%)
Tumor type	
Prostate	8
Colon	6
Rectum	2
Unknown primary	2
Other*	7
Median number of courses/patient (range)	4 (1-9)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Includes one of each of the following: head and neck squamous cell carcinoma, malignant melanoma, non–small cell lung cancer, osteosarcoma, pancreatic carcinoma, renal cell carcinoma, and urothelial carcinoma.

Table 2. Dose-escalation scheme

XRP6258 dose level (mg/m^2)	New patients at this dose level (courses)	Patients reduced to this dose level (courses)	Total patients (courses)	New patients with DLT
10	3 (10)	0	3 (10)	0
15	6 (24)	1 (1)	7 (25)	1
20	9 (29)	4 (19)	13 (48)	0
25	7 (19)	0 (0)	7 (19)	3

Results

General. Between June 1, 1999 and July 12, 2001, 25 patients were treated with 102 courses of XRP6258 across four dose levels. The pertinent demographics of the patients are presented in Table 1. The median number of courses administered per patient was 4 (range, 1-9). All 25 patients (100%) were evaluable for safety and 24 patients (96%) were evaluable for efficacy. One patient treated at the 15 mg/m^2 dose level was found to be ineligible for dose level determination due to an elevated alkaline phosphatase value; the patient's toxicities are reported. Twenty-two (88%) patients had previously received chemotherapy, with eight patients having received prior taxane-based therapy. According to the criteria defined in this study, 16 and 9 patients were considered MP and HP, respectively. The numbers of patients treated at each dose, as well as the number of patients experiencing DLT at each dose level, are depicted in Table 2. Dose reduction due to hematologic toxicity was done in four patients; one patient required two dose reductions. The initiation of eight (8%) courses involving four patients were delayed due to unresolved nonhematologic toxicities, specifically fatigue and fever in two patients, or at the patient's request (two patients).

Because drug-related toxicities that exceeded grade 1 were not encountered at the first dose level, dose escalation proceeded to 15 mg/m^2. At this dose level, one patient experienced grade 3 diarrhea during course 1, and the cohort was expanded to a total of six patients, with no additional DLT. At the next higher dose level, 20 mg/m^2, DLT was not observed in the initial three patients enrolled. However, three of seven subjects experienced DLT, including febrile neutropenia in one MP patient and protracted (>5 days) grade 4 neutropenia in two HP patients at 25 mg/m^2. Therefore, the rate of DLT exceeded the predefined limits of tolerability at the 25 mg/m^2 dose level, and because no DLT was observed in six additional MP and HP patients treated at the previous dose level, 20 mg/m^2, it was considered the recommended phase II dose for both MP and HP patients.

Hematologic toxicity. The effects of XRP6258 on ANCs and platelets, as well as toxicity grade, as a function of dose level are shown in Table 3. Neutropenia was the principal toxicity encountered with XRP6258. Severe neutropenia was noted only at the 25 mg/m^2 dose level, with grade 4 events occurring in 8 of 19 (42%) evaluable courses, including the three aforementioned DLTs. The median time to ANC nadir was 12 days (range, 4-17 days). Because ANC recovery to a grade $\leq$1 occurred in all patients by day 22 ($\pm$3 days), treatment delays for unresolved hematologic toxicity were not necessary. The rate of severe toxicities did not seem greater in HP patients compared with MP patients. Neither granulocyte colony-stimulating factor (G-CSF) nor granulocyte macrophage colony-stimulating factor (GM-CSF) was given as prophylactic treatments. Four patients received G-CSF/GM-CSF support during a total of five courses following the occurrence of grade 4 neutropenia (as DLTs in two patients, at cycle 1 and cycles 1 and 2, and at cycle 5 in two others). Thrombocytopenia occurred in only two patients (two courses, one grade 3 in course 5 and one grade 1 in course 1). Except for a single episode of grade 3 anemic relevant, effects on RBCs were either mild or moderate in severity.

Nonhematologic toxicities. The most common nonhematologic toxicities are summarized in Table 4. The most common nonhematologic toxicities were gastrointestinal in nature, principally consisting of diarrhea (52% of patients), nausea (40% of patients), and vomiting (16% of patients). These toxicities were generally grade 1 to 2 in severity, except for a single patient who experienced grade 3 diarrhea in the first course at 15 mg/m^2. The event was short-lived and loperamide was administered for symptomatic management. At the 20 and

Table 3. Hematologic toxicity

Dose level (mg/m^2)	No. evaluable courses	No. courses (first course) with toxicity							
		Neutropenia						Thrombocytopenia	
		Median nadir ANC (range; μL)*	Grade 1-2	Grade 3	Grade 4	Grade 4 >5 d	Grade 3-4 + fever	PLTs (/μL) 25,000-50,000	PLTs (/μL) <25,000
10	10	4,760 (2,980-7,790)	0	0	0	0	0	0	0
15	25	2,480 (880-8,500)	9 (3)	0	0	0	0	0	0
20	48	2,280 (260-4,270)	6 (3)	0 (0)	0	0	0	0	0
25	19	990 (30-5,090)	15 (3)	4 (1)	8 (3)	2 (2)	1 (1)	1 (0)	0

Abbreviation: PLTs, platelets.
*Median values (ranges) for first course.

Table 4. Nonhematologic toxicity occurring at any grade in three or more patients (>10%)

Adverse event, no. patients (cycles)	Dose level (mg/m²)										
	10 (3 patients, 10 cycles)		15 (6 patients, 25 cycles)		20 (9 patients, 48 cycles)		25 (7 patients, 19 cycles)		All (25 patients, 102 cycles)		
	Grade 1-2	Grade 3	Grade 1-2	Grade 3	Grade 1-2	Grade 3	Grade 1-2	Grade 3	Grade 1-2	Grade 3	All
Diarrhea	1 (1)	—	4 (7)	1 (1)	4 (13)	—	4 (7)	—	13 (28)	1 (1)	14 = 56% (29 = 28%)
Fatigue	1 (5)	—	1 (4)	—	3 (15)	—	4 (5)	—	9 (29)	—	9 = 36% (29 = 28%)
Nausea	1 (2)	—	1 (1)	—	3 (13)	—	5 (3)	—	10 (19)	—	10 = 40% (19 = 19%)
Neuropathy (sensory)	1 (1)	—	1 (6)	—	3 (8)	—	4 (4)	—	9 (19)	—	9 = 36% (19 = 19%)
Vomiting	1 (1)	—	—	—	2 (8)	—	1 (1)	—	4 (10)	—	4 = 16% (10 = 10%)
Anorexia	—	—	—	—	—	—	4 (6)	—	4 (6)	—	4 = 16% (6 = 6%)
Arthralgia	—	—	0	—	2 (3)	—	1 (1)	—	3 (4)	—	3 = 12% (4 = 4%)
Stomatitis/pharyngitis	—	—	1 (1)	—	1 (3)	—	1 (1)	—	3 (5)	—	3 = 12% (5 = 5%)

25 mg/m^2 dose levels, grade 1 to 2 fatigue and grade 1 neurosensory symptoms were common. Neurosensory manifestations consisted principally of acral paresthesia and diminished deep tendon reflexes and discrimination of vibratory sensation. Cumulative neurotoxicity was not apparent in nine patients who received more than three courses at the two higher dose levels. Two patients experienced grade 1 hypersensitivity reactions, characterized by flushing, dizziness, and chest tightness, which did not reoccur on retreatment in the absence of premedication. Alopecia was noted in two patients treated at 25 mg/m^2, one each experiencing grade 1 and 2. Neither onychodystrophy nor fluid retention was observed.

Anticancer activity. Evidence of anticancer activity due to XRP6258 was noted in two patients. An 80-year-old male with prostate cancer metastatic to liver and bones whose disease had progressed through surgical castration, bicalutamide, diethyl stilbestrol, and mitoxantrone and prednisone experienced a reduction in prostate-specific antigen from 62 to 21 ng/mL, decreased disease-related bone pain, and reduction in his target lesion, a lymph node metastasis, which qualified as confirmed partial response after four courses at the 15 mg/m^2 dose level. The patient declined further treatment after his sixth course, at which time his response persisted. A 50-year-old male with hormone- and docetaxel-refractory prostate cancer metastatic to bone and iliac lymph nodes also experienced a partial response after treatment with XRP6258 at the 25 mg/m^2 dose level of XRP6258. His prostate-specific antigen decreased from 415 to 44 ng/mL, and his measurable disease showed a confirmed partial response. Progressive disease was noted after eight courses. In addition, a patient with transitional cell carcinoma of the bladder experienced an unconfirmed partial response, and minor responses (tumor size reduction not meeting criteria for partial response) were observed in one patient each with osteosarcoma and prostate cancer. Twelve (48%) patients had stable disease as their best response for greater than 4 months.

PK and pharmacodynamic evaluation. Blood sampling for PK studies was done in 25 patients, and C_{max} and $AUC_{(0\text{-}48\ h)}$ values were estimated in 23 evaluable subjects. Compartmental PK modeling was done in 23 patients, with 9 and 2 patients having PK data from two and three consecutive courses, respectively. A scatter plot of individual $AUC_{(0\text{-}48\ h)}$ data as a function of XRP6258 dose is shown in Fig. 1A. The relationship between XRP6258 dose and $AUC_{0\text{-}48\ h}$ and C_{max} was proportional. The decrease in plasma concentrations of XRP6258 was best described by a triphasic model. Plasma concentration data and superimposed model fit for a typical individual are depicted in Fig. 1B. Pertinent PK variables, as determined by this model, as a function of dose level are listed in Table 5. The PK behavior in plasma was characterized by a rapid initial phase with a $t_{1/2\lambda1}$ averaging 2.6 ± 1.4 minutes, followed by an intermediate phase with a mean $t_{1/2\lambda2}$ of 1.3 ± 0.6 hours, and a prolonged terminal phase (mean $t_{1/2\lambda3}$, 77.3 ± 45.5 hours). V_{ss} values for XRP6258 were very large (mean, 2,034 ± 1,495 L/m^2), and CL rates were high, averaging 53.5 ± 20.3 L/h (27.3 ± 9.7 L/h/m^2), which represented 61% of hepatic blood flow (87 L/h; ref. 10). The interpatient variability was moderate and estimated at 40.7% of $AUC_{(0\text{-}48\ h)}$ (95% confidence interval, 28.9-69.8). The intrapatient variability for $AUC_{(0\text{-}48\ h)}$ was also relatively low (27.3%; 95% confidence interval, 20.6-40.6%) in 18 patients with at least two courses evaluable for PK. Based on CVs, the total variability in CL values expressed in L/h/m^2 was also moderate (CV, 35%), whereas the variability of terminal half-life and V_{ss} values was higher (CV, 59% and 74%, respectively). CL, expressed in L/h, did not relate well to BSA (R^2 = 0.303; P = 0.0065). However, after correction for the BSA of each individual patient (11), the total variability in the CL of XRP6258 was slightly lower (35.4% versus 38.8%). Indeed, the value for relative reduction in PK variability was 8.8%.

An analysis of PK data from individuals in whom plasma sampling was done during multiple courses showed no apparent changes in CL or $AUC_{(0\text{-}48\ h)}$ with repetitive treatment.

Relationships between PK variables reflecting XRP6258 exposure, such as $AUC_{(0\text{-}48\ h)}$ and C_{max} values, from course 1 and the percent decrements in ANCs were assessed, and scatter plots depicting percentage decrements in ANC as functions of both $AUC_{(0\text{-}48\ h)}$ and C_{max} are depicted in Fig. 1C. Although decrements in the ANC seem to loosely relate to these variables, neither linear nor nonlinear models could be derived to adequately fit these relationships.

Discussion

Primary and acquired tumor resistance limits the effectiveness and spectrum of activity of the taxanes in preclinical and

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