Original article

Annals of Oncology 13: 1140–1150, 2002
DOI: 10.1093/annonc/mdf174

Phase I clinical and pharmacokinetic studies of the taxoid derivative RPR 109881A administered as a 1-hour or a 3-hour infusion in patients with advanced solid tumors

C. Sessa[1]*, C. Cuvier[2], S. Caldiera[1], J. Bauer[3], S. Van den Bosch[1], C. Monnerat[3], D. Semiond[4], D. Pérard[4], A. Lebecq[4], M. Besenval[4] & M. Marty[2]

[1]*Oncology Institute of Southern Switzerland, Ospedale San Giovanni, 6500 Bellinzona, Switzerland;* [2]*Saint-Louis Hospital, Paris;* [3]*Centre Pluridisciplinaire d'Oncologie, CHUV, Lausanne, Switzerland;* [4]*Aventis, Antony, France*

Received 17 September 2001; accepted 16 January 2002

Purpose: To define the maximum tolerated dose (MTD), the recommended phase II dose, the optimal infusion duration and pharmacokinetics of the semisynthetic taxoid derivative RPR 109881A, given as a 1-h or 3-h infusion every 3 weeks.

Patients and methods: RPR109881A was administered as a 1-h i.v. infusion to 34 patients (study 1) with oral steroids as pre-medication. In a subsequent study, 29 patients were treated at the recommended dose or at the dose immediately below (study 2); the first 14 patients received RPR 109881A as a 3-h infusion, while the subsequent 15 were randomized to receive the drug as a 1-h or 3-h infusion. The pharmacokinetics of RPR109881A was studied in plasma and urine and for selected patients in some biological fluids (cerebrospinal fluid, pleural effusion, ascitis).

Results: In study 1, the dose was escalated from 15 to 105 mg/m^2, at which dose two of five patients presented dose-limiting toxicities with febrile neutropenia (FN) after the first cycle, thus defining the MTD. The dose of 90 mg/m^2, at which grade 3/4 neutropenia was almost universal with FN in 18%, was recommended for phase II. At 90 mg/m^2 the incidence of diarrhea, fatigue and alopecia were 59, 29 and 70%, respectively. The results of study 2 were comparable to those of study 1, thus recommending the 1-h infusion duration for phase II evaluation. RPR 109881A exhibited a high total body clearance, a large distribution volume and long terminal half-life of 20 h. RPR 109881A was detected in cerebrospinal fluid shortly after the end of 1-h infusion. Three objective responses were observed in non-small-cell lung cancer (NSCLC) patients, including a patient with brain metastases.

Conclusions: The antitumor activity in NSCLC, the reproducible profile of toxicity and above all the ability to cross the blood–brain barrier make RPR 109881A worthy of further disease-oriented clinical development.

Key words: pharmacokinetics, phase I, taxanes, taxoid derivative

Introduction

RPR 109881A (4, 10-β-diacetoxy-2α-benzoyloxy-5β, 20-epoxy-1, 13α-dihydroxy-9-oxo-19-nor-cyclopropa [g] tax-11-ene, 13 ester with (2R, 3S)-*N*-tert-butoxycarbonyl-3-phenylisoserine, dihydrate), a semisynthetic taxoid derivative, prepared as a single diastereoisomer by partial synthesis from 10-deacetyl baccatin III, was identified within a medical chemistry program of discovery of taxoid analogs [1] active in tumors with a high level of MDR1 expression (Figure 1).

In *in vitro* cell lines bearing the multidrug resistance phenotype, RPR 109881A was recognized less than docetaxel by highly resistant (P388/Dox) as well as moderately resistant (P388/TXT, P388/VCR) cell lines. The activity in *mdr*-expressing tumors was confirmed in murine models (P388/VCR and B16/TXT) by using a pre-clinical standard formulation of ethanol: polysorbate (50:50 v/v) with a final concentration after dilution of 5% ethanol, 5% polysorbate.

RPR 109881A showed an antitumor activity comparable to that of docetaxel both in sensitive s.c. tumors (early B16 melanoma, advanced mammary adenocarcinoma MA13/C, colon C38, pancreatic P02) and in poorly sensitive models (Lewis lung carcinoma, mammary MA44/C, colon C26). The antitumor activity was also comparable to that of docetaxel in breast Calc 18, colon HCT, pancreas PaCa-2 and lung PC14 human xenografts.

A schedule dependency of toxicity, with better tolerance after intermittent than daily for five consecutive days adminis-

**Correspondence to:* Dr C. Sessa, Oncology Institute of Southern Switzerland, Ospedale San Giovanni, 6500 Bellinzona, Switzerland.
Tel: +41-91-811-9039; Fax: +41-91-811-9044;
E-mail: csessa@ticino.com

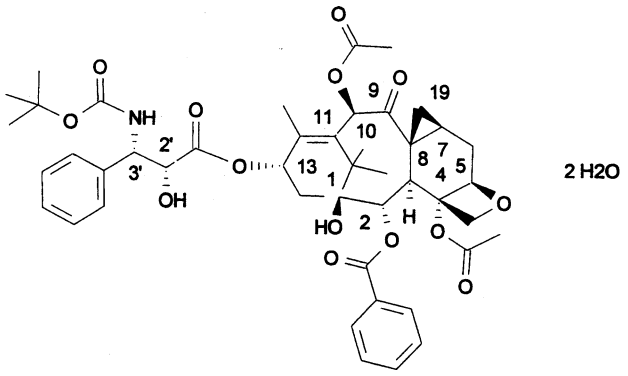


Figure 1. Chemical structure of RPR 109881A.

tration, was observed in mice and was the main rationale to select single dosing for phase I studies. Similar to docetaxel, target organs for toxicity in mice and dogs were bone marrow and gastrointestinal tract, while central neurotoxicity with necrosis of neurones in the brain and peripheral neurotoxicity with lumbar roots degeneration were observed at the highest doses and in mice only.

After single administration, the mice LD_{10} ($MELD_{10}$) was 150–195 mg/m^2 and the toxic dose low (TDL) in dogs was 10–20 mg/m^2.

Pharmacokinetics in mice was consistent with a two-compartment open model. RPR 109881A showed a low plasma clearance (CL) of 0.6 l/h/kg, a large volume of distribution (V_{ss}) of 2.4 l/kg and a terminal half-life ($T_{½}$) of 3.2 h (internal data on file).

Tissue distribution studies in mice showed that drug exposure in brain and tumor was more prolonged than in other tissues and in plasma. RPR 109881A was completely eliminated by metabolism and its metabolites mainly excreted in feces via the bile (83% to 96% of the administered dose).

In 1996 a large phase I program was started in Europe, Japan and North America to define the maximum tolerated dose (MTD), dose limiting toxicities (DLTs) and optimal duration of infusion of single every 3 week RPR 109881A administration given over 1, 3, 6 and 24 h [2, 3]. In addition, a split dosing schedule (day 1 and day 8) was studied [4]. In the present study, the MTD, pharmacokinetic profile and recommended dose (RD) of 1-h infusion were established first in study 1. The optimal duration of infusion was then defined in the subsequent study 2, in which patients received RPR 109881A as a 1-h or 3-h infusion at the RD or at the dose immediately below.

Patients and methods

Patients

Adult patients aged 18 to 75 years old, with histologically/cytologically confirmed diagnoses of solid tumors not amenable to conventional local or systemic treatments, were eligible for this trial. Patients had to have recovered from the toxic effects of prior therapies, with a treatment-free period of at least 4 weeks (6 weeks for those given nitrosoureas, mitomycin C or extensive radiotherapy). Inclusion criteria also included a WHO performance status (PS) of ≤2, a life expectancy of ≥3 months, an adequate bone marrow function [absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l], normal liver (bilirubin within normal limits and ALAT/ASAT/AP ≤2.5× normal) and renal function (creatinine ≤120 µmol/l), and written informed consent. Serious concomitant medical disease, clinically uncontrolled brain metastases, grade 2 or above pre-existent peripheral neuropathy, concomitant steroids at daily doses of >20 mg of methylprednisolone or equivalent, uncontrolled hypertension or arrhythmias, more than three previous chemotherapy regimens for study 1 and more than two for study 2, were criteria for exclusion.

Study design

A starting dose of 15 mg/m^2, corresponding to one-tenth of the $MELD_{10}$, every 3 weeks, was selected.

In study 1, the dose was escalated according to the continual reassessment method modified by Faries (MCRM) [5, 6] up to the definition of the MTD (Table 1). With this method, dose levels were pre-established according to animal toxicology and corresponded to a double of the initial dose at the second dose level and then to 15 mg/m^2 increases; at each dose level, only one patient was treated in case of no toxicity after the first cycle, while three and six were treated in case of no DLTs, or DLTs, respectively. Before including the first patient at the subsequent dose level, the expected MTD has to be recalculated according to the toxicities already occurred in the first cycles, because the next planned dose level should not exceed it.

The MTD was defined as the dose level at which 50% of the patients experienced DLT; the RD for phase II, which corresponded to one dose level below the MTD, had to be confirmed in a set of at least nine patients with a maximum of two previous lines of chemotherapy. DLTs were defined as grade 4 neutropenia of >7 days duration, grade 4 thrombocytopenia, febrile neutropenia defined as grade 2 fever with grade 4 neutropenia, grade 3 or 4 non-hematological toxicity excluding nausea, vomiting and alopecia.

Treatment was repeated every 3 weeks either when ANC were $\geq 1.5 \times 10^9$/l and platelet $\geq 100 \times 10^9$/l, or when severe non-hematological toxicities had recovered to grade 1, whichever occurred first; a maximum delay of 1 week from the day scheduled for retreatment was allowed.

No dose reductions were planned; a dose reduction to a lower dose level could be done only at recommended dose and at the MTD in patients for whom treatment was of significant benefit and only if they had experienced serious DLT.

Chemistry [including electrolytes, creatinine, uric acid, glucose, total protein and albumin, aspartate aminotransferase (ASAT)/alinine aminotransferase (ALAT), total bilirubin, alkaline phosphatase (AP), lactate dehydrogenase (LDH), γ-glutamyltransferase (GGT)], coagulation tests

Table 1. Study design

	Study 1	Study 2
Starting dose (mg/m^2)	15	75
Dose escalation	MCRM	15 mg/m^2 increase
Highest dose tested (mg/m^2)	105	90
Duration of infusion (h)	1	1 versus 3
No. of patients	34	29

and urinalysis were repeated weekly and complete blood counts (CBC) with differential twice a week or more often in case of severe toxicity; ECG and neurological examination were repeated before each cycle.

Toxicity was evaluated according to the NCIC Common Toxicity Criteria. Patients were evaluable for hematological toxicity if at least weekly CBC with differential were available for 3 weeks, and for non-hematological toxicity if they received at least one administration of RPR 109881A.

In patients with measurable or evaluable disease, tumor response was assessed after two cycles and classified according to WHO criteria [7]; patients with stable disease or tumor response continued treatment until tumor showed progression or until toxicity became unacceptable. Responses were confirmed by an external review committee.

In study 2, patients were treated at the RD or the dose immediately below (Table 1). Criteria for dose modifications, retreatment and DLT were similar to those applied in study 1.

Drug administration

RPR 109881A was supplied by Aventis Pharma (Antony cedex, France) in 15 ml brown glass vials containing RPR 109881A at a concentration of 40 mg/ml, i.e. 94.4 mg of product in 2.36 ml of polysorbate 80 (i.e. 80 mg/2 ml). The solvent for RPR 109881A, ethyl alcohol 95%/water (13:87 w/w), was supplied in 15 ml glass vials containing 7.33 ml of solvent (6 ml theoretical volume).

RPR 109881A was administered with a volume pump. Prophylactic pre-medication with steroids (8 mg oral dexamethasone, 25, 13 and 1 h before the infusion) was given to prevent hypersensitivity reactions (HSR). Anti-histamines were added at subsequent cycles if grade 2 HSR had occurred. Prophylactic antiemetics were not administered at the first cycle but could be added at subsequent cycles in case of nausea or vomiting. A prophylactic treatment could be prescribed with oral antibiotics in case of ANC $<0.5 \times 10^9$/l.

Pharmacokinetics

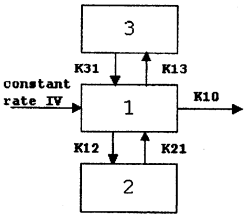
Sampling procedure. Pharmacokinetic studies of RPR 109881A were performed at cycle 1 and, when possible, at cycles 2, 4 and 6. When RPR 109881A was given as a 1-h infusion, 5 ml blood samples were taken before, middle and end infusion, and then 5, 10, 20 30, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24 and 48 h from the end. Blood samples were taken at the same time intervals in case of a 3-h infusion, with an additional sample 10 h from the end leaving out the 20 min, 90 min and 4 h samplings.

Urine was collected at cycle 1. Four (study 1) and five (study 2) cerebrospinal (CSF) samples were collected concomitantly with a 5 ml blood sample when it was possible, to evaluate the passage of RPR 109881A through the blood–brain barrier in humans. CSF samples were collected in a limited number of patients and at different time intervals from the drug administration to have a clear picture of the kinetic of the drug. Ascitis and pleural fluids were also collected in study 2.

All biological specimens were stored at approximately –20°C until analysis.

Analytical assay and pharmacokinetic analyses

RPR 109881A concentrations were measured in various biological fluids (plasma, urine, ascitis and pleural fluids) by high-performance liquid chromatography (HPLC) (O. Pasquier, J. C. Vergniol, N. Ktorza et al., submitted). Briefly, this method involved preparation of the fluid samples by solid phase extraction followed by isocratic reversed-phase liquid chromatography at 40°C and ultraviolet detection at 200 nm. Epidocetaxel was used as the internal standard. The lower limit of quantitation was 5 µg/l. Drug concentrations are expressed as non-hydrated compound. In addition, RPR 109881A was measured in one human brain specimen by a liquid chromatography tandem mass spectrometry method with a lower limit of quantitation of 10 ng/g. A three-compartment open model with first-order elimination using non-linear least-square regression analysis with software WinNonlin® (Figure 2) was fitted the plasma concentration[C(T)]–time profile. Concentration at the end of infusion (C_{max}), AUC, total body CL, V_{ss} (according to the statistical moment method) and half-lives were determined.



$$C(T) = A_1\left(\exp(-ALPHA*TSTAR) - \exp(-ALPHA*T)\right) + B_1\left(\exp(-BETA*TSTAR) - \exp(-BETA*T)\right) + C_1\left(\exp(-GAMMA*TSTAR) - \exp(-GAMMA*T)\right)$$

$$A_1 = \frac{(D/TI)*(K21-ALPHA)*(K31-ALPHA)}{V*ALPHA*(GAMMA-ALPHA)*(BETA-ALPHA)}$$

$$B_1 = \frac{(D/TI)*(K21-BETA)*(K31-BETA)}{V*BETA*(GAMMA-BETA)*(ALPHA-BETA)}$$

$$C_1 = \frac{(D/TI)*(K21-GAMMA)*(K31-GAMMA)}{V*GAMMA*(ALPHA-GAMMA)*(BETA-GAMMA)}$$

where TI = Length of infusion,
TSTAR = T-TI for T>TI,
and TSTAR = 0 for T≤TI

Figure 2. Equation 1 to determine three compartment open model with first-order elimination using non-linear least-square regression analysis with WinNolin® software.

Results

From April 1996 to April 1998, 34 patients entered study 1, and from August 1997 to September 1998, 29 patients entered study 2 (Table 2). In the first 14 patients, RPR 109881A was administered as a 3-h infusion, while the subsequent 15 were randomized to receive treatment as a 1-h (seven patients) or 3-h infusion (eight patients). Patients treated in the two studies were comparable in terms of PS, tumor type, age and prior treatment. Only six of 34 patients in study 1 and two of 29 in study 2 had been pre-treated with taxanes.

Table 3 reports the number of patients and cycles administered per dose level. In study 1, the dose was escalated from 15 up to 105 mg/m^2 with 107 cycles of treatment administered (median per patient 2; range 1–8); 65% of patients were treated at the MTD or at the dose immediately below. In study 2, only

Table 2. Patients' characteristics

Duration of infusion	Study 1 1 h (no. of pts)	Study 2	
		1 h (no. of pts)	3 h (no. of pts)
Total	34	7	22
Female/male	17/17	2/5	9/13
Median age (years) (range)	59 (19–73)	61 (49–68)	57 (31–71)
WHO PS			
0/1	32	7	22
2	2	–	–
Tumor types			
NSCLC	5	–	7
SCLC	2	1	–
Soft tissue sarcoma	5	1	–
Gastric	4	–	4
Renal	4	–	–
Head and neck	–	2	2
Other	14	3	9
Prior therapy			
No	–	1	3
CT	22	2	9
CT + RT	11	4	9
RT	1	–	1
No. of prior CT* regimens			
1	11	6	11
2	14	–	5
≥3	8	–	2
*Including taxanes	6	–	2

pts, patients; CT, chemotherapy; RT, radiotherapy.

Table 3. Number of patients and cycles per dose level

Duration of infusion	Study 1 (n = 34)							Study 2 (n = 29)			
	1 h							1 h		3 h	
Dose (mg/m^2)	15	30	45	60	75	90	105	75	90	75	90
No. of patients	1	1	1	6	3	17	5	2	5	5	17
No. of cycles	2	5	3	21	10	58	8	2	15	12	54
Median	NA	NA	NA	4	1	3	2	NA	2	2	3
Range				1–6	1–8	1–6	1–2	1–1	1–6	1–5	1–8

NA, not applicable.

the doses of 75 and 90 mg/m^2 were investigated with 83 evaluable cycles (median per patient 2; range 1–8).

In study 1, only one patient per dose level was treated at 15, 30 and 45 mg/m^2, because of absence of toxicity, while a total of six patients had to be entered at 60 mg/m^2 because of a grade 3 diarrhea in the first (Table 3). Since DLTs after the first cycle were not reported in the other five patients, the dose could be escalated to 75 mg/m^2 (three patients) and 90 mg/m^2 (eight patients). Two DLTs (infection grade 5 and FN associated with diarrhea grade 3) were reported in the two first patients treated at 90 mg/m^2 (Table 4A). However, because the occurrence of the infection grade 5 was also related to some

Table 4A. Neutropenia and related complications in study 1 (1-h infusion)

Dose (mg/m^2)	Evaluable pts/cycles	Pts with NCIC CTC grade		Median ANC nadir $\times 10^3/\mu l$ (range)	Median time to nadir in days (range)	Pts with neutropenia-related DLT (all cycles)
		3	4			
15	1/2	0	0	–	–	–
30	1/5	0	0	–	–	–
45	1/3	0	0	–	–	–
60	6/21	5	0	0.8 (0.5–6.7)	10 (8–14)	0
75	3/10	1	2	0.3 (0–0.9)	10 (8–13)	0
90	17/58	1	14	0.2 (0–2.2)	11 (6–13)	1 infection grade 5
						2 FN
						1 FN with diarrhea grade 3
						5[a] neutropenia grade 4 >7 days
						2 FN with neutropenia grade 4 >7 days
105	5/8	0	5	0 (0–0.4)	10 (6–11)	1 FN with diarrhea grade 4 and fatigue grade 3

[a]With grade 2 fever in one patient.
pts, patients; FN, febrile neutropenia.

Table 4B. Neutropenia and related complications in study 2 (1-h versus 3-h infusion)

Dose (mg/m^2)	Evaluable pts/cycles	Pts with NCIC CTC grade		Median ANC nadir $\times 10^3/\mu l$ (range)	Median time to nadir in days (range)	Pts with neutropenia-related DLT (all cycles)
		3	4			
75 (1 h)	2/2	–	2	– (0.1–0.1)	– (6–9)	1 infection grade 5
						1 FN
75 (3 h)	5/12	1	2	0.7 (0.1–4.0)	13 (13–15)	1 infection grade 3
90 (1 h)	5/15	1	2	0.6 (0.1–1.1)	11 (8–17)	1 FN with neutropenia grade 4 >7 days
						1 neutropenia grade 4 >7 days
90 (3 h)	17/54	2	12	0.2 (0–3.0)	10 (6–14)	3 FN
						2 neutropenia grade 4 >7 days
						1 infection grade 3

pts, patients; FN, febrile neutropenia.

unfavorable patient characteristics, dose escalation was continued and the level of 105 mg/m^2 was tested in five patients. At this dose, two patients showed DLTs after the first cycle (one case of FN with diarrhea grade 4 and fatigue grade 3, and one FN associated with neutropenia grade 4 for >7 days), thus defining the MTD (Table 4A). Additional patients were entered at 90 mg/m^2 up to a total of 17 patients and 58 cycles. The median number of evaluable cycles per patient at 90 mg/m^2 was three (range one to six).

In study 2, a total of 29 patients were treated, seven at 75 mg/m^2 and 22 at 90 mg/m^2, seven with a 1-h infusion and 22 with a 3-h infusion (Table 3). The median number of cycles per patient was between two and three. Two patients died because of uncontrolled infections while in neutropenia after the first administration at 75 and 90 mg/m^2, respectively.

Hematological toxicity

All 34 patients were evaluable for hematological toxicity in study 1 (Table 4A). Dose-dependent neutropenia was the most frequent toxicity, first observed at 60 mg/m^2, where it was already grade 3, and almost universal at doses ≥75 mg/m^2 (Table 4A). Median time to nadir was 11 days, with neutrophils recovering within 1 week. Neutropenia grade 4 of >7-day duration was first observed at 90 mg/m^2 in almost 30% (five of 17) of patients (12% of cycles). Febrile neutropenia occurred in 15% of patients, with three patients treated at 90 mg/m^2 and two patients treated at 105 mg/m^2, while one toxic death, occurring 2 weeks after treatment due to lung infection in a period of severe neutropenia, was reported for one patient at 90 mg/m^2.

In study 2 (Table 4B), the incidence of grade 3/4 neutropenia at 75 and 90 mg/m^2, given as a 1-h (in two and five patients, respectively) or a 3-h infusion, (in five and 17 patients, respectively) was comparable to that observed in study 1. Notwithstanding the limited number of patients and the possible differences in selection, it seems that the overall incidence of neutropenia-related complications was also comparable, and consisted of FN in 14% of patients (7% of cycles) at 75 mg/m^2 and in 18% of patients (7% of cycles) treated at 90 mg/m^2. Also in study 2, grade 4 neutropenia of >7 days duration occurred in 14% of patients (6% of cycles) treated at 90 mg/m^2. One patient died because of a lung infection with respiratory failure while he experienced a severe neutropenia 17 days after the first cycle at 75 mg/m^2 with a 1-h infusion.

In view of the comparable incidence of grade 3 and 4 neutropenia at 90 mg/m^2 and of the possible differences in duration, the data achieved in study 1 and study 2 were pooled together to evaluate the effect of a prior antitumor treatment on myelotoxicity. In both studies, a median ANC count of 0.2–0.3 $\times$ 10^3/μl was reported in patients with one or less or 2 or more prior chemotherapies. The number of patients with >7-day duration of grade 4 neutropenia was also comparable (five of 17 in study 1 and four of 22 in study 2).

Non-hematological toxicity

Diarrhea was the most important non-hematological toxicity, occurring in ~50% of patients in both studies (Table 5). In study 1, a grade 3 dose-limiting diarrhea was first observed in one patient at 60 mg/m^2; its incidence was dose-related and increased from 59% at 90 mg/m^2 to 80% at 105 mg/m^2. At this dose level, one patient presented grade 4 diarrhea with severe abdominal cramps and concomitant neutropenia 1 week after the first administration cycle. The patterns of appearance and incidence of diarrhea at 75 and 90 mg/m^2 were comparable in study 2. In study 2, diarrhea was also the most frequent gastrointestinal adverse event, being reported in 57% and 45% of the patients at 75 and 90 mg/m^2 dose levels, respectively. Neutropenia grade 3 or 4 was concomitantly reported in almost all patients who experienced diarrhea, but it was complicated by an infection in only two cases. Diarrhea started a few days (5–7 days) after treatment and could be controlled by loperamide. The duration of diarrhea was short, with a median duration of 2 days. The mechanism of these late episodes of diarrhea is not yet elucidated.

The other important non-hematological toxicity was fatigue, which was first observed at 60 mg/m^2 in study 1 and at 75 mg/m^2 in study 2. Fatigue was dose-dependent; in study 1 it was reported in 29% of patients at 90 mg/m^2 and in 80% of patients at 105 mg/m^2. In study 2 at 90 mg/m^2, fatigue was reported more often after a 3-h than after a 1-h infusion (47% versus 40%); it was not cumulative and was mostly of mild to moderate degree. Fatigue was classified in flu like symptoms class according to the NCIC classification and was not related to a potential neurotoxicity of the drug. Alopecia was partial,

Table 5. Non-hematological toxicities

	Study 1				Study 2			
					1 h	3 h	1 h	3 h
Dose (mg/m^2)	60	75	90	105	75		90	
No. of evaluable pts	6	3	17	5	2	5	5	17
Diarrhea								
No. of pts with toxicity	3	1	10	4	2	2	1	9
Grade 3/4	1/0	0/0	2/0	0/1	0/0	0/0	0/0	2/1
Fatigue								
No. of pts with toxicity	1	0	5	4	0	3	2	8
Grade 3/4	0/0		0/0	1/0		0/0	0/0	1/0
Arthralgia								
No. of pts with toxicity	0	0	7	1	0	1	0	5
Grade 3/4			1/0	0/0		0/0		0/0
Neurosensory toxicity								
No. of pts with toxicity	0	1	5	0	0	0	1	2
Grade 3/4		0/0	0/0				0/0	0/0
Alopecia								
No. of pts with toxicity	4	1	12	3	0	3	4	7
Grade 2/3	0/1	0/0	4/4	0/0		0/1	2/0	6/1

pts, patients.

cumulative and dose dependent; it was first observed at 60 mg/m^2 in study 1 and was complete (grade 3) at 90 mg/m^2 in <13% of patients in both studies. The other non-hematological toxicities were arthralgia, appearing 24–48 h after treatment, usually controlled with non-steroidal autoinflammatory drugs, and cumulative neurosensory toxicity. The latter were neither schedule-dependent nor DLT.

Three patients treated at 90 mg/m^2 in study 1 and one treated at 90 mg/m^2 with a 3-h infusion in study 2 presented an acute HSR. In study 1, two of them experienced a grade 3 and 4 HSR during the second infusion, respectively.

Toxic deaths

Three toxic deaths were reported, one in study 1 and two in study 2. In study 1, one patient with a metastatic gastric carcinoma, previously treated with three chemotherapy lines and radiotherapy, died because of septic shock due to *Escherichia coli* 6 days after the first dose of 90 mg/m^2 of RPR 109881A. The infectious death was considered as possibly drug related; the patient had also a baseline leucocytosis and an elevated LDH, suggesting that a pre-existing infection and/or a highly aggressive disease was partly responsible for this unfavorable outcome.

In study 2, a 65-year-old man with squamous cell cancer of the lung, pre-treated with carboplatin/vinblastine and prior mediastinal radiotherapy, completed 4 months before inclusion in the study, died 17 days after the first administration of RPR 109881A at 90 mg/m^2 given as a 3-h infusion. The patient developed a FN with lung infiltrates that was not controlled with i.v. antibiotics. Death was due to progressive respiratory failure. The post-mortem examination showed diffuse interstitial pneumonitis with fibrosis probably related to prior radiation.

The third toxic death was observed in a 67-year-old male head and neck cancer patient with a percutaneous gastrostomy, pre-treated with one neoadjuvant chemotherapy and radiotherapy. The patient developed febrile neutropenia with lung infiltrates and dyspnea 6 days after the first administration of RPR 109881A at 75 mg/m^2. The patient was hospitalized to receive i.v. fluids, antibiotics and granulocyte colony-stimulating factor, but died the same day because of septic shock. The necrotic material isolated from the percutaneous gastrostomy was considered a potential source of infection.

Another case of death was reported in study 2 in one patient with ovarian cancer who died 10 days after the fourth administration of RPR 109881A at 90 mg/m^2 as a 3-h infusion. Post-mortem examination showed brainstem alterations unlikely to be related to the study drug, and consequently this was not considered as a toxic death. The patient had concomitantly developed thrombocytopenia grade 4, stomatitis grade 4 and FN, which were not the primary cause of death.

Antitumor activity

One patient with squamous cell lung cancer pre-treated with carboplatin and VP16 achieved a partial response of 16-week duration after 90 mg/m^2 of RPR 109881A given as a 1-h infusion in study 1. The objective response was observed at the site of primary recurrence, with concomitant decrease of neoplastic pleural thickening and disappearance of pleural effusion. Two objective responses were reported in non-small-cell lung cancer (NSCLC) patients in study 2. One untreated patient, with brain metastases, received first line RPR 109881A at 90 mg/m^2 as a 3-h infusion. A partial response of 14-week duration was achieved in brain and primary tumor. The other response was also achieved at 90 mg/m^2 in a patient with local recurrence and brain metastases of NSCLC pre-treated with cranial irradiation, completed 1 month before, carboplatin and etoposide. A partial response of 15-week duration was achieved in the primary tumor while response in brain was not evaluable because of prior radiotherapy.

Pharmacokinetics

Pharmacokinetic evaluation was performed in study 1 in 28 patients from 45 to 105 mg/m^2. Plasma samples were collected and analyzed in 18 patients after one cycle, in eight patients after two cycles and in two after four out of six cycles. Urine specimens were mainly collected after the first course in all patients.

The plasma elimination profile of RPR 109881A was triphasic and a typical plasma concentration–time profile at the dose of 90 mg/m^2 given as 1-h infusion is shown in Figure 3.

Table 6 reports the main pharmacokinetic parameters of RPR 109881A after the first administration in study 1. The total plasma CL was high (mean 33 l/h/m^2) and was independent of the dose resulting in a proportional dose–exposure relationship. Figure 4 shows the relationship between C_{max} and AUC with the dose, respectively (data from study 1 and study 2).

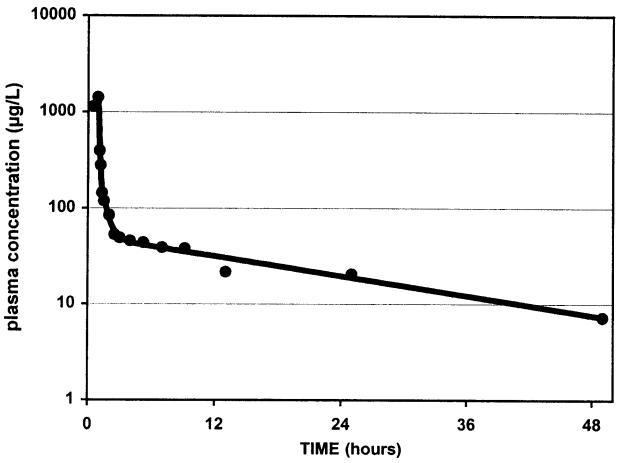


Figure 3. Typical plasma concentration–time profile in one patient treated at 90 mg/m^2.

Table 6. Pharmacokinetic parameters (mean ± SD) of RPR 109881A in study 1

Dose (mg/m^2)	Number of pts		Pharmacokinetic parameters				
	Sampled for PK	Evaluable for PK	C_{max} (µg/l)	AUC (µg·h/l)	CL (l/h/m^2)	V_{ss} (l/m^2)	$T_{½}$ λ 3 (h)[a]
15	1	0	–	–	–	–	–
30	1	0	–	–	–	–	–
45	1	1	376	1141	38.7	577	16.4
60	6	4	1811 ± 589	2668 ± 771	24.5 ± 9	154 ± 129	13 ± 3.1
75	3	3	1033 ± 991	2490 ± 1198	35.6 ± 17	813 ± 645	23.6 ± 6
90	16	15	1536 ± 784	2969 ± 851	32.5 ± 9.1	454 ± 295	20 ± 9.3
105	5	5	1138 ± 789	3069 ± 1295	38.3 ± 12.6	721 ± 327	22.8 ± 6.5
Overall	33	28	–	–	33 ± 10.7	502 ± 364	19.7 ± 8.1

[a]Terminal half-life.
pts, patients; PK, pharmacokinetics.

The drug had a large V_{ss} (mean 502 l/m^2) and a long terminal $T_{½}$ (mean 19.7 h). Urinary excretion accounted for <1.3% of the administered dose. The interpatient variability was moderate, especially for CL, with a coefficient of variation (CV) of 30%. A lower intrapatient variability of the CL was observed in the 10 patients who were sampled during at least two cycles (median variation 13.6%; range 0.8% to 32.7%).

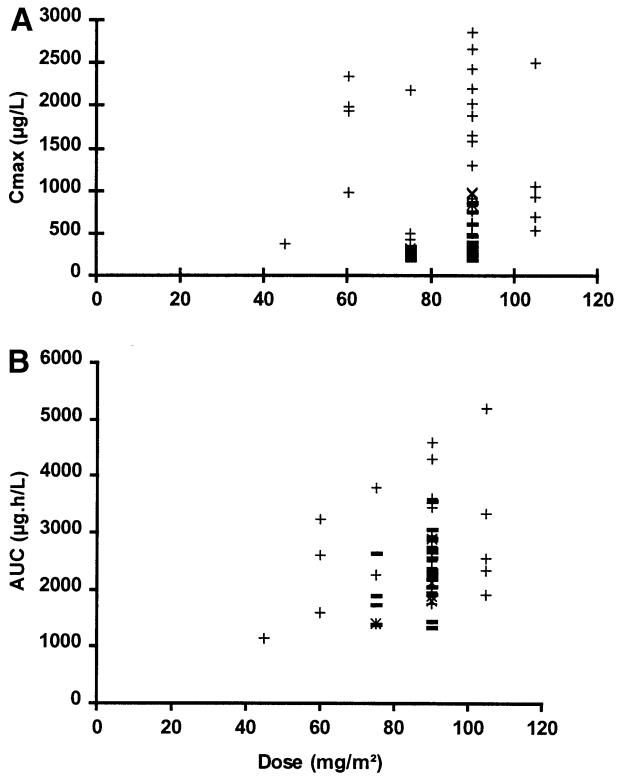


Figure 4. (**A**) Relationship between C_{max} and RPR 109881A dose. (**B**) Relationship between AUC and RPR 109881A dose.

CSF samples were obtained in four patients without brain metastases treated at 90 or 105 mg/m^2, at different times (from 15 min to 8 days) after the end of the infusion (Table 7). The highest concentration (5.27 µg/l) was observed ~15 min from the end of the administration of 105 mg/m^2, with a concomitant plasma level of 267 µg/l. CSF concentrations were below the quantitation limit in the three other samples taken between 77 min and 8 days after treatment.

In study 2, pharmacokinetic evaluation was performed in 26 patients (in 21 cases after 3-h and in five after 1-h i.v. infusion). Plasma samples were collected and analyzed in 22 patients after one cycle, in one patient after two cycles, in two patients after three and in one patient after four out of six cycles administered.

The main pharmacokinetic parameters after 1-h or 3-h infusion at 75 and 90 mg/m^2 were slightly higher that those reported in study 1 (Table 8). RPR 109881A exhibited a total plasma CL of 41.4 l/h/m^2, a V_{ss} of 870 l/m^{2}and a $T_{½}$ of ~26 h. The interpatient variability of CL was moderate with CV of 25.6%. No relevant pharmacokinetic differences were observed between cycles (data not shown). Urinary excretion accounted to <1.2% of the dose.

After the administration of 90 mg/m^2 as a 3-h infusion, RPR concentrations in CSF (three patients), pleural (one patient) and ascitic fluid (one patient) were below the quantitation limit at time intervals ranging from 8 min to 9 days after treatment. In one human brain specimen, collected 11 days after the fourth administration at 90 mg/m^2, the RPR 109881A concentration was 51.2 ng/g.

Discussion

The semisynthetic taxoid derivative RPR 109881A was selected for clinical development because of *in vitro* and *in vivo* activity against *mdr*-expressing murine models, antitumor activity comparable to that of docetaxel in some human xenografts and ability to cross blood–brain barrier in mice.

Table 7. RPR 109881 concentrations in biological fluids

Dose (mg/m^2)	Infusion duration (h)	Time of collection after the end	RPR concentrations (μg/l)			
			Plasma	CSF	Pleural	Ascitis
90	1	2 h	112	ND		
90	1	8 days	ND	ND		
105	1	1 h 17 min	172	ND		
105	1	12 min (plasma)	267	5.27		
		15 min (CSF)				
90	3	10 min (plasma)	169	ND		
		8 min (CSF)				
90	3	2 h 30 min	37.1	ND		
90	3	9 days	ND	ND		
90	3	10 min (pleural)	285		ND	
		15 min (plasma)				
		(before end)				
90	3	4 min (before end)	365			ND

ND, not detectable.

Table 8. Pharmacokinetic parameters (mean ± SD) of RPR 109881A in study 2

Schedules	Dose level (mg/m^2)	Number of pts		Pharmacokinetic parameters				
		Sampled for PK	Evaluable for PK	C_{max} (μg/l)	AUC (μg·h/l)	CL (l/h/m^2)	V_{ss} (l/m^2)	$T_{½}$ λ 3 (h)
3-h i.v. infusion	75	5	5	256 ± 64	1873 ± 465	40.9 ± 9.6	928 ± 253	26.5 ± 7.1
	90	16	16	395 ± 187	2374 ± 591	40.4 ± 11.6	803 ± 423	25.4 ± 7.7
1-h i.v. infusion	75	2	1	312	1399	55	1616	29.5
	90	4	4	764 ± 321	2176 ± 501	42.4 ± 8.2	880 ± 190	25.8 ± 10.4
Overall	75–90	27	26	–	–	41.4 ± 10.6	870 ± 384	25.8 ± 7.5

pts, patients; PK, pharmacokinetics.

A single intermittent schedule was applied in all phase I studies, in which the toxicity profile and tolerability of different duration of infusion, from 1–6 up to 24 h, was assessed, with 140 patients in European [2], US [3], and Canadian [4] studies, and 19 in a Japanese study [8], treated so far. Overall, a reproducible pattern of toxicity has been reported in all trials, with neutropenia and diarrhea as the main DLTs and no evidence of correlation between infusion duration and toxicity.

The pharmacokinetic profile of the parent compound was also consistent in the various studies, and the drug could be detected in CSF shortly after the administration, confirming pre-clinical expectations. This latter result represents the most innovative feature of RPR 109881A as compared with docetaxel, and alone makes further clinical development worthwhile.

In the first part of the present study, which assessed the shortest duration of 1-h infusion (study 1) given every 3 weeks, a MCRM of dose escalation was applied up to the MTD of 105 mg/m^2. This design proved to be successful, considering that the study was performed in two different centers, because 65% of the patients were treated at the MTD or at the level below, with 50% of patients and 54% of cycles evaluable at the RD [9].

The study was completed in 24 months and a further evaluation of the optimal duration of infusion (3-h vs 1-h), only at the RD and at the level immediately below, was performed as well (study 2). The toxicity profiles of a 1-h and 3-h infusions were comparable, with no advantages of the longer infusion; the data from both studies were therefore pooled, thus providing information on toxicity from a large data set of 39 patients and 127 cycles at 90 mg/m^2, which is the RD in pre-treated patients. At this dose, >70% of patients had grade 4 neutropenia, with a median time to nadir of 11 days and recovery within 1 week. Neutropenia grade 4 lasting >7 days was

complicated by FN in 9% of patients after a 1-h infusion. Thrombocytopenia was almost never observed.

Almost all patients were pre-treated with one or more chemotherapy regimens without taxanes in the majority of cases. The study does not therefore provide information on tolerability of RPR 109881A as first-line treatment, but it is very likely that, also when given as initial therapy, the dose of 90 mg/m^2 is associated with grade 4 neutropenia and diarrhea in a significant percentage of patients. On the other hand, the extent of prior chemotherapy did not seem to affect duration of grade 4 neutropenia or the occurrence of neutropenia related complications. Neutropenia-related infection was the main factor in the three cases of toxic deaths; concomitant factors were a rapidly aggressive disease, radiation-induced lung fibrosis and presence of a percutaneous gastrostomy in another patient.

Diarrhea and fatigue were more frequently observed with RPR 109881A than with docetaxel. Diarrhea occurred in ~50% of patients at 90 mg/m^2 given either as 1-h or 3-h infusion, but it was of grade 3/4 in only 13%. It appeared between 5 and 7 days after treatment, was preceeded by abdominal cramps when severe and could be controlled by high dose loperamide if started at the appearance of first symptoms. Fatigue, the other important non-hematological toxicity, was observed in 32% of patients receiving 90 mg/m^2 as a 1-h infusion and 47% as a 3-h infusion; it appeared a few days following treatment and was not related to the potential neurotoxicity of the compound.

The pharmacokinetics of RPR 109881A was investigated in patients treated in both studies. Plasma profile of the parent compound was consistent with a three-compartment open model. The total body CL was stable over 45–105 mg/m^2 dose range, which resulted in a dose-proportional exposure. The main pharmacokinetic features of RPR 109881A given as a 1-h infusion (study 1) are a high CL (mean 33 l/h/m^2), a large V_{ss} (mean 502 l/m^2) and a long terminal $T_{½}$ (mean 19.7 h). Urinary excretion amounted to ~1% of dose, and elimination biliary excretion is likely to be the main excretion pathway based on *in vitro* data and *in vivo* pre-clinical data.

It is unclear why a higher clearance value was observed in study 2. However, there was no effect of the infusion duration on clearance and the patients characteristics (PS, liver function) were similar. Of note, the terminal $T_{½}$ was longer in study 2.

Interpatient variability of CL was limited in both studies, with a CV of 25% to 30%, comparable to those reported in previous studies [4, 8]. The variability of V_{ss} at 90 mg/m^2 between the two studies is difficult to judge because of the limited number of patients sampled in study 2 after a 1-h infusion. No plasma drug accumulation was observed up to six consecutive chemotherapy cycles in both studies.

Compared with the marketed taxoids (docetaxel and paclitaxel), the pharmacokinetic profile of RPR 109881A is quite different. RPR 109881A has the highest CL (21.1 l/h/m^2 for docetaxel and 9.1–17.7 l/h/m^2 for paclitaxel), the highest V_{ss} (72 l/m^2 for docetaxel and 56–75 l/m^2 for paclitaxel), and the longest terminal $T_{½}$ (13.5 l/h/m^2 for docetaxel and 6.5–18.7 h for paclitaxel) [10–14]. More importantly, RPR 109881A was shown to cross the blood–brain barrier in patients also without brain metastases with a plasma/CSF ratio of 2%, corresponding to the plasma-free fraction of 1% to 3% reported in *in vitro* studies. RPR 109881A could be detected in CSF only for a few minutes, possibly due to rapid and wide tissue distribution. Nevertheless, RPR 109881A was still detectable in brain tissues 11 days after a dose of 90 mg/m^2.

Antitumor activity was reported in three patients with NSCLC, in two patients who initially responded to and then relapsed after carboplatin, etoposide and in one chemotherapy-naive patient. Objective responses were observed in both primary and metastatic sites, including brain, at 90 mg/m^2 given as a 1-h (one case) or a 3-h infusion (two cases).

The toxicity results of this study confirm those achieved with the same schedule in the Japanese trial [8], in which neutropenia and, to a lesser extent, fatigue were dose-limiting. Because of a more conservative criteria of 3-day duration to define neutropenia as dose-limiting, the MTD and the RD were fixed at 75 and 60 mg/m^2, respectively. On the other hand, the substantial amount of data collected at 90 mg/m^2 in the present study indicates that 90 mg/m^2 is a universally myelotoxic dose, but is usually well tolerated provided that patients are properly selected and controlled.

The RD for the split dose schedule (days 1 and 8 every 3 weeks) is 45 mg/m^2, corresponding to a dose intensity of 30 mg/m^2/week, comparable to that achieved in the present study. As reported with other taxanes, the use of lower weekly doses might improve tolerability because of lower peak levels with decreased neurosensory toxicity, fatigue and possibly less cumulative effects. The development of a continuous weekly regimen might be worthwile because of the possibility of administering prolonged treatments and combination with other neurotoxic antitumor drugs.

In conclusion, the recommended schedule of treatment with RPR 109881A is 90 mg/m^2 as a 1-h infusion every 3 weeks, with oral steroids as pre-medication. DLTs are selective, short-lasting neutropenia and delayed diarrhea; the other important non hematological toxicity is fatigue, while neurotoxicity—mainly neurosensory disorders—seems to be moderate. More importantly, RPR 109881A could be detected in CSF and was shown to be active in brain metastases from NSCLC. These results provided the rationale for performing a multicenter, disease-oriented phase II study in patients with brain metastases from NSCLC, previously untreated with chemotherapy.

The first promising results of this ongoing study have led to the implementation of a broader disease-oriented clinical development of RPR 109881A.

Acknowledgements

We wish to thank Tania Trisconi for her assistance in preparing the manuscript, as well as the nurses and patients for their participation in the study.

References

1. Rhône-Poulenc Rorer. RPR 109881A: Investigator's brochure, v. 6.0. Rhône-Poulenc Rorer: Antony, France 1999.
2. Barthier S, Dieras V, Kalla S et al. A Phase I and pharmacokinetic (PK) study of RPR 109881A given as a 6-hour IV infusion in patients (pts) with advanced solid tumors. Proc Am Soc Clin Oncol 1998; (Abstr 747).
3. Slaughter M, Pazdur R, Hoff PM et al. Phase I trial of RPR 109881A (RPR), a new taxoid derivative administered as a 24 hour continuous infusion. Proc Am Soc Clin Oncol 1998; (Abstr 748).
4. Gelmon KA, Latreille J, Tolcher A et al. Phase I dose finding study of a new taxane, RPR 109881A, administered as a 1-hour intravenous infusion days 1 and 8 to patients with advanced solid tumors. J Clin Oncol 2000; 18: 4098–4108.
5. O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase I clinical trials in cancer. Biometrics 1990; 46: 33–48.
6. Faries D. Practical modifications of the continual reassessment method for Phase I cancer clinical trials. J Biopharm Stat 1994; 4: 147–164.
7. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207–214.
8. Kurata T, Shimada Y, Tamura T et al. Phase I and pharmacokinetic study of a new taxoid, RPR 109881A, given as a 1-hour intravenous infusion in patients with advanced solid tumors. J Clin Oncol 2000; 18: 3164–3171.
9. Lebecq A, Dieras V, Marty M et al. Preliminary evaluation of the modified continual reassessment method (MCRM) in four Phase I studies of RPR 109881A. Proc Am Soc Clin Oncol 1998; (Abstr 817).
10. Rosing H, Lustig V, van Warmerdam LJC et al. Pharmacokinetics and metabolism of docetaxel administered as a 1-h intravenous infusion. Cancer Chemother Pharmacol 2000; 45: 213–218.
11. Ohtsu T, Sasaki Y, Tamura T et al. Clinical pharmacokinetics and pharmacodynamics of paclitaxel: a 3-hour infusion versus a 24-h infusion. Clin Cancer Res 1995; 1: 599–606.
12. Gianni L, Kearns CM, Giani A et al. Nonlinear pharmacokinetics and metabolism of paclitaxel and its pharmacokinetic/pharmacodynamic relationships in humans. J Clin Oncol 1995; 13: 180–190.
13. Huizing MT, Keung ACF, Rosing H et al. Pharmacokinetics of paclitaxel and metabolites in a randomized comparative study in platinum-pretreated ovarian cancer patients. J Clin Oncol 1993; 11: 2127–2135.
14. Extra M, Rousseau F, Bruno R et al. Phase I and pharmacokinetic study of Taxotere given as a short intravenous infusion. Cancer Res 1993; 53: 1037–1042.