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ORIGINAL ARTICLE

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Pharmacokinetic linearity of i.v. vinorelbine from an intra-patient dose escalation study design

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Abstract As pharmacokinetics represents a bridge between pharmacological concentrations and clinical regimens, the pharmacokinetic exploration of the therapeutic dose range is a major outcome. This study was aimed at assessing pharmacokinetic linearity of i.v. vinorelbine through an open design with intra-patient dose escalation (3 doses/group). Three groups of six patients received either 20–25–30 mg/m^2; or 25–30–35 mg/m^2; or 30–35–40 mg/m^2. The inclusion criteria were: histologically confirmed tumour with at least one assessable target lesion, age 25–75 years, WHO PS ≤ 2, normal haematology and biochemistry, life expectancy $\geq$3 months. The pharmacokinetics was evaluated in both whole blood and plasma over 120 h. Twenty-six patients were recruited and 18 were evaluable for pharmacokinetics. The toxicity consisted in grade ≤ 3 leucopenia and neutropenia ($<20\%$ of courses) and two grade 4 constipation with rapid recovery (2/54 courses). Compared to blood, plasma was demonstrated to underestimate the pharmacokinetic parameters. In blood, the drug total clearance was about 0.6 l/h/kg, with minor contribution of renal clearance, steady state volume of distribution close to 13 l/h/kg, and elimination half-life at about 40 h. A pharmacokinetic linearity was demonstrated up to 40 mg/m^2, and even up to 45 mg/m^2 when pooling data from another study. A pharmacokinetic–pharmacodynamic relationship was evidenced on leucopenia and neutropenia when pooling the data from the two studies.

Keywords Vinorelbine · Pharmacokinetics · Phase I study · Linearity · Blood/plasma · PK/PD

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Introduction

Vinca-alkaloids are a class of cytotoxic agents that have demonstrated a wide range of activity over a long period of clinical development [1–4]. The mode of action of these agents depends on their interaction with microtubules during mitosis, which results in a cell division arrest during the prophase. The drug active concentrations are usually based on concentration ranges that have been determined during in vitro pharmacological pre-clinical evaluations [5, 6]. Therefore, pharmacokinetic studies in patients are of critical importance in order to be able to switch from target concentrations to a clinically active amount of drug administered. Significant progress in the use of pharmacokinetics is illustrated through the vinca's history [2, 7–14]. Early studies of vincristine, vinblastine and vindesine used radio-immuno assay (RIA) techniques [14–17] and have demonstrated triphasic or biphasic decay characteristics with the excretion being mainly achieved through the biliary tract [15, 18]. However, because of the methodology used, the ability of these early studies to differentiate the parent molecule from its metabolites was limited [15, 19].

Vinorelbine (VRL) differs from other vinca-alkaloids because its structure involves modifications of the catharanthine ring [3, 20–22]. As a consequence, its binding affinity to axonal microtubules is altered, an

effect that is likely to reduce its clinical neurotoxicity [23, 24]. Previous pharmacokinetic studies of VRL have suggested that there is considerable inter-patient variability, even when allowing for differences in the dose and schedules [3, 14–18, 25]. Although some of these variations might reflect genuine differences in VRL metabolism and clearance, the technical limitations of the RIA methodology may also have contributed to the difficulties in interpreting the results [19]. The improved methodology provided by modern high-pressure liquid chromatography (HPLC) techniques allows to clarify some of the issues that have been raised by these historical studies [25–28].

The clinical phase I study reported by Mathe et al. [29] concluded that VRL dose-limiting toxicity (DLT) was haematological (neutropenia) and that neurological toxicity was less than that associated with other vinca-alkaloids. These investigators recommended a schedule of 30 mg/m^2/week for phase II clinical trials. Subsequent clinical experience confirmed that neutropenia was the major cause of vinorelbine DLT, and drew attention to the effects of autonomic neuropathy resulting in severe constipation [30].

VRL has demonstrated to be active in patients with non-small cell lung cancer (NSCLC) and advanced breast cancer [31]. As single agent, phase II/III studies have evidenced response rates of 12–36% in previously untreated patients with stage III and IV NSCLC [32–36], and 0–20% when given as second line therapy [37–40]. In metastatic breast cancer, response rates were 40–60% in previously untreated patients [41–45], and about 30% in second or third line chemotherapy [46, 47]. The therapeutic recommended i.v. doses of VRL were 30 mg/m^2/week as a single agent, and 20–25 mg/m^2/week or 30 mg/m^2 D1,8 Q 3w in combination chemotherapy [22, 48–52].

Since different dose levels may be used, it is important to control the dose-proportional increase of blood exposure that will allow an easy and flexible therapeutic use of the drug. A non-linear pharmacokinetics would result either in increased toxicity or insufficient efficacy. This was illustrated with taxanes pharmacokinetics which differs between short and long infusion periods where as a consequence, dose-limiting toxicities (DLT) depend on the infusion schedule that is used; neurotoxicity is dose limiting with short infusion while mucositis is dose limiting with long infusion [53–58].

Following i.v. administration, VRL rapidly distributes into tissues and its volume of distribution is large (25–100 l/kg) [59]. Concentration in lung tissues has been evaluated to be up to 300-fold higher than in plasma in NSCLC patients undergoing thoracic surgery [60].

VRL metabolism involves carboxylesterases and isoform CYP3A4 of cytochrome P450 [61, 62]. Most of the administered dose is eliminated through the biliary system as parent compound and phase I metabolites [63]. Only one metabolite (4-0-deacetyl vinorelbine, DVRL) is active [64] but accounts only for a small amount of the administered dose [63]. No conjugates were observed [65].

The aim of this study was to evaluate the pharmacokinetic linearity of i.v. VRL in a larger range of doses (20–40 mg/m^2) than the one used in most therapeutic regimens (25–30 mg/m^2). As a result, the knowledge on VRL safety should be reinforced since this major pharmacokinetic property has never been explored before.

Furthermore, VRL pharmacokinetics is frequently completed in plasma although the drug is highly bound to platelets and blood cells. The current study is the opportunity to assess whether blood or plasma is the most relevant for pharmacokinetic determination.

Patients and methods

Patients' selection

Patients with histologically confirmed advanced solid malignancies refractory to conventional therapy, or for whom no effective therapy existed, were enrolled on this phase I clinical trial.

The main inclusion criteria were the following: a histologically confirmed malignant solid tumour with at least one assessable target lesion in patients of age ≥18 years and ≤ 75 years with an estimated life expectancy of at least 3 months; patients with Performance Status ≤ 2 by WHO criteria; with satisfactory haematological status (granulocytes ≥2,000 per mm^3, platelets ≥100,000 per mm^3, haemoglobin ≥10 g/dl); with satisfactory hepatic and renal function in relation to the upper limit of the normal range (UNL), i.e. SGOT ≤ 1.25 UNL, SGPT ≤ 1.25 UNL, alkaline phosphatase ≤ 1.25 UNL, bilirubin ≤ 1.25 UNL, creatinine ≤ 1.25 UNL. Radiotherapy or hormonotherapy was withdrawn at the time of study entry.

Exclusion criteria were the following: evidence of intracranial or meningeal involvement by tumour, serious inter-current infection or other progressive systemic illness, inability to complete the study period for psychological, family, social or geographical reasons, or evidence of grade 2 or greater neuropathy unless directly due to the malignant disease.

Study design

The principal objective of this phase I pharmacokinetic study was to assess the dose-proportional increase of blood exposure following an i.v. administration of VRL at various dose levels. This was an open design study with an intra-patient dose escalation and a 2-week period between administrations.

The protocol was approved by the Ethic Committee of Hôpital La Pitié Salpétrière, Paris, France and 18 clinical centres were involved in the study. Written informed consent was obtained from all the patients entered in the trial. The clinical and pharmacokinetic parts of the study complied with the standards of good

clinical practices (GCP), and the good laboratory practices (GLP), respectively.

Three cohorts of six patients had to receive one of the following sequences of increasing dose-levels of VRL: either 20, 25, 30 mg/m^2 (Group I) or 25, 30, 35 mg/m^2 (Group II), or 30, 35, 40 mg/m^2 (Group III).

Blood samples were collected over 5 days following each administration and pharmacokinetic linearity was assessed on an intra-patient and inter-patient analysis. Patients were considered evaluable when pharmacokinetics was achieved for one complete sequence of three dose levels.

Drug dosage and administration

IV vinorelbine was supplied as a pyrogen free, sterile parenteral dosage form in glass vials containing 13.85 mg of vinorelbine ditartrate and 1 ml of water for injection. The total dose to be administered to each patient was calculated using the value of their body surface area (BSA) obtained on the day of treatment. The corresponding amount of VRL was drawn from the vial into a syringe and diluted in 50 ml of normal saline solution which was infused throughout a central venous catheter over 20 min using an electrical syringe driver. After administration of VRL, a further 50 ml of *N*-saline were infused to flush the catheter and the vein in order to decrease the risk of phlebitis. After the last administration of VRL defined in the protocol, the patient could be treated with standard chemotherapy including i.v. VRL, according to the physician decision.

Safety

At the inclusion, medical history, full clinical and biochemistry evaluations were carried out. Following each administration, haematology and biochemistry were fully controlled, and all adverse events either related or not with VRL administrations were noted according to WHO classification. Complete blood cell counts were done on days 6, 8, 10 and 12 post-dosing in order to determine the nadir.

Pharmacokinetics

Sampling

Blood samples (5 ml) were collected into heparinised silicon coated tubes from a forearm vein through a Teflon canula at the following times: predose (T0), then 10 min, 20 min, 40 min, 1 h, 2 h, 6 h, 9 h, 11 h, 24 h, 48 h, 72 h and 120 h after the beginning of infusion. One aliquot of blood was kept while the rest was centrifuged (10 min at 3,000 rpm, 10°C) and then the plasma was transferred into silicone-treated glass tubes. All the tubes were then immediately frozen and stored at −20°C until further analysis.

Urines were collected over 11 h post-dosing. The volume was noted and aliquots were stored at −20°C until further analysis.

Drug bioanalysis

The plasma, blood and urinary VRL levels were quantified by a HPLC assay with UV detection [26] derived from Jehl and Debs [66] in order to ensure better specificity and precision. Briefly, VRL was extracted from biological fluids (1 ml) with diethyl ether at alkaline pH together with vinblastine (internal standard), and purified by a pH 3 buffered aqueous solution. This extract was injected on a reversed phase cyano HPLC column, and VRL and its active metabolite, DVRL, were quantified. Bioanalytical variability expressed as coefficient of variation was lower than 12% for all biological media in the concentration range used (limit of quantification set at 2.5 ng/ml). Clinical samples were quantified using a daily calibration curve (2.5–200 ng/ml). When VRL concentrations were greater than 200 ng/ml, samples were diluted with an adequate volume of blank medium, and analysed as described above.

Pharmacokinetic analysis

Vinorelbine pharmacokinetic parameters in blood and plasma were calculated using SIPHAR/WIN (version 1.2 b) software running on a PC compatible computer under Windows 95. Data were fitted to a three compartment open model using a proportional weighting ($1/y^2$). The following parameters were calculated:

- AUC_{last} Area under the curve concentration against time from the first to the last quantifiable concentration, calculated by the linear trapezoidal rule
- AUC_{inf} Area under the curve concentration against time extrapolated to infinite, calculated by $AUC_{inf} = AUC_{last} + C_{last}/\lambda_z$, where C_{last} is the last quantifiable concentration, and λ_z is the slope of the elimination phase
- $T_{(1/2)z}$ Terminal half-life, calculated by $T_{1/2} = \log_e 2/\lambda_z$
- C_{max} Peak concentration observed at the end of infusion
- T_{max} Time to C_{max}
- Cl_{tot} Total body clearance, calculated by: $Cl_{tot} = \text{Total dose}/AUC_{inf}$
- Vd_{ss} Volume of distribution at steady state, calculated by: $Vd_{ss} = MRT \times Cl_{tot}$ where MRT is the mean residence time, calculated by: $MRT = AUMC_{inf}/AUC_{inf}$, $AUMC_{inf} = \int_0^\infty tc\,dt$

Ae_{0-11} Amounts of drug (or metabolite) excreted in urines during the interval 0–11 h after dosing

$Cl_{r\ 0-11}$ Renal clearance of the drug (or metabolite) calculated on the interval 0–11 h and estimated by: $Cl_{r\,0-11} = Ae_{0-11}/AUC_{0-11}$ where AUC_{0-11} is the area under the curve during the interval 0–11 h

Whenever possible, DVRL parameters in blood and urine were calculated. DVRL amounts excreted in the urine were calculated by:

$$\%Ae_{0-11}\mathrm{DVRL} = \left(\frac{1.0571 \times Ae_{0-11(\mathrm{mg})}}{\mathrm{VRL\,total\,dose}}\right) \times 100$$

where 1.0571 is the molecular weight ratio (VRL/DVRL).

Pharmacokinetic/Pharmacodynamic analysis

Non-haematological toxicities. In order to gain preliminary information on the relationships between drug exposure and non-haematological toxicity, the following variables, representative of the major toxicities following each administration were studied: nausea/vomiting; diarrhoea; neuroconstipation; peripheral neurotoxicity. The patients were arbitrarily split into two groups by grade of toxicity. The cut-off value was selected in order to approximately obtain an equal number of patients between the two sub-groups. The main values of C_{max} and AUC_{inf} were compared between the two sub-groups by a Student *t*-test with SAS program (release 6.12).

Haematological toxicities. The relationships between drug exposure and haematological toxicities were studied. At each administration, the percentage of reduction from the initial blood cell count (corresponding pre-dosing value of neutrophil, red cell and platelet counts) to nadir was calculated (% nadir). The relationships between % nadir and C_{max} and AUC_{inf} were investigated with PROC REG procedure using SAS software.

Table 1 Patient characteristics

Parameter	Mean value	Range
Age	56	27–73
Body weight	68	40–84
BSA	1.75	1.35–2.00
Male/female	14/12	
PS[a]		
0	5 (19%)	
1	15 (58%)	
2	6 (23%)	
Primary tumour site		
Breast	5 (19%)	
Lymph-nodes	3 (11%)	
Gastro-enterologic	7 (27%)	
Kidney	2 (8%)	
Others	9 (35%)	
Histological diagnosis		
Squamous	4 (15%)	
Adeno carcinoma	14 (54%)	
Sarcoma	3 (11.5%)	
Hemato sarcoma	3 (11.5%)	
Others	2 (8%)	
Prior oncological treatment		
Surgery	18 (69%)	
Radiotherapy	16 (61%)	
Immunotherapy	2 (8%)	
Hormonotherapy	3 (12%)	
Chemotherapy		
At least one	22 (85%)	
At least one of type neo-adjuvant	5 (19%)	
At least one of type adjuvant	4 (15%)	
At least one of type advanced	17 (65%)	
At least one of type anthracycline	11 (42%)	

[a]Performance status according to WHO criteria

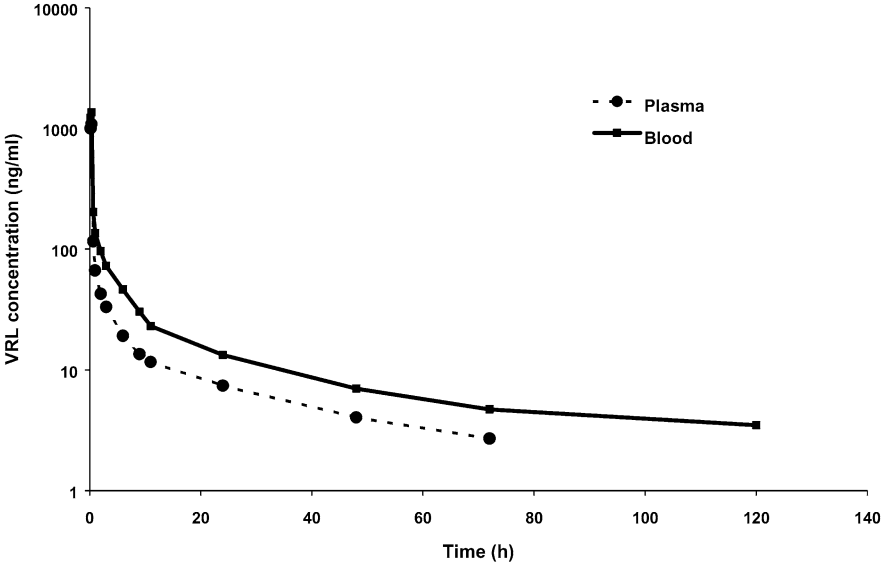

Fig. 1 Mean blood and plasma profiles following i.v. vinorelbine at 40 mg/m^2

Statistical analysis

Linearity of VRL pharmacokinetics was assessed in evaluable patients by comparing the following parameters between dose levels = C_{max}, C_{max}/dose, AUC_{last}, AUC_{last}/dose, AUC_{inf}, AUC_{inf}/dose, Cl, Vd_{ss} and $T_{(1/2)z}$. Comparison was performed using PROC GLM with SAS program (release 6.12) running under Windows 95, patient and level dose being the explored factors. When non-normal distribution was detected by the Shapiro Wilk's test, parameters were log-transformed before analysis. In a second step, an exploratory regression analysis was performed with all data using PROC REG with SAS program. C_{max} and AUC_{inf} vs dose levels were assessed.

Results

Twenty-six patients were enrolled in the study and 18 were evaluable for the pharmacokinetic study objective (six per group of dose level). Eight patients were removed from the study: two for disease progression (one in group I and one in group II), three for venous access problems or in sample collection (two in group II and one in group III), one for refusal to comply with the study protocol (group II), two for treatment toxicity (one in group II for febrile neutropenia and one in group III who developed a grade 4 stomatitis and intestinal obstruction at 30 mg/m^2, recovered but was removed from the study). The main characteristics of enrolled patients are presented in Table 1.

The median age of the patients was 57 years with very few elderly patients ($n = 4$ ≥70 years). However, it was demonstrated that there was no age effect on VRL pharmacokinetics in elderly patients [67, 68]. Body weight and body surface area were in the common clinical range and there was no obese patients (median 1.75 m^2). Both male and female were represented (14 males and 12 females). Most of the patients had a PS = 1, with 77% having a PS of 0 or 1. Different

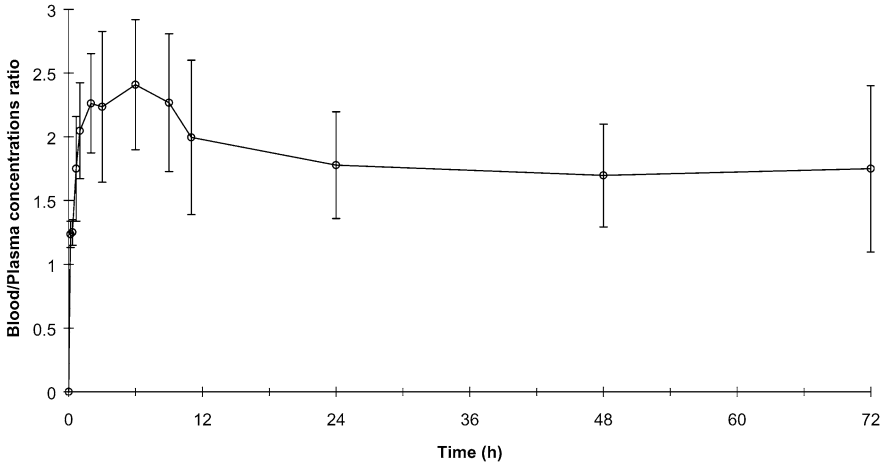

Fig. 2 Blood to plasma distribution ratio at dose level 40 mg/m^2

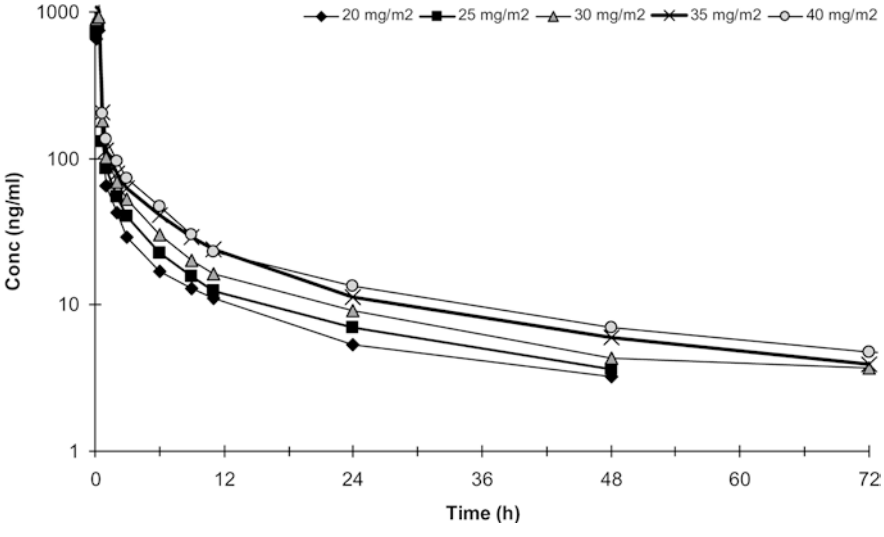

Fig. 3 Mean blood profile for different i.v. vinorelbine dose levels

tumour types existed with no predominant tissue target. Most of them were adeno-carcinoma. Prior treatment mostly consisted in surgery and radiotherapy (60–70%) associated with at least one chemotherapy for advanced disease (65%) including at least one anthracycline (42%).

Safety

Grade 3 haematological toxicity (no grade 4) was limited to leucopenia and neutropenia, and was mostly observed at the highest dose levels (14, 6, 9, 17 and 0% at 20, 25, 30, 35 and 40 mg/m^2, respectively). Two treatment

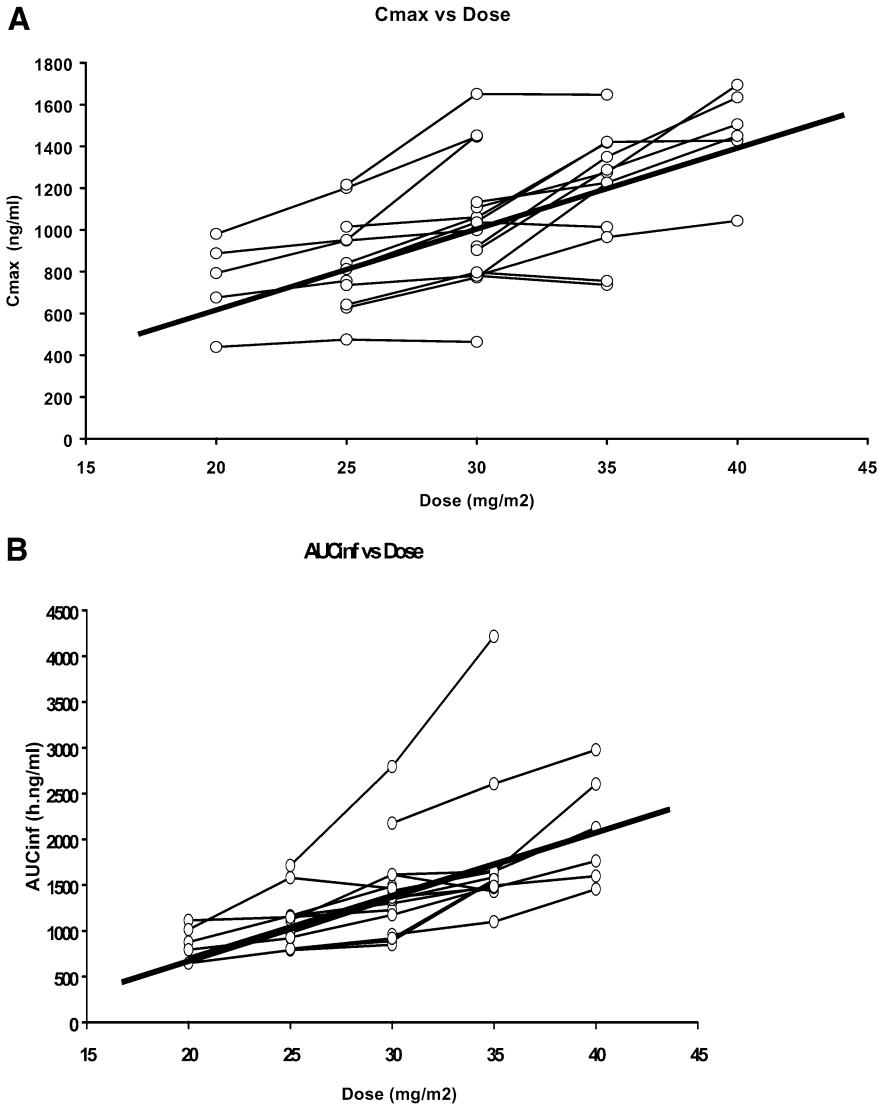

Fig. 4 Blood C_{max} and AUC vs vinorelbine dose

Table 2 Mean (SD) vinorelbine blood and urine pharmacokinetic parameters calculated in evaluable patients receiving i.v. vinorelbine as 20 min infusion

Parameters	20 mg/m^2 $n=6$	25 mg/m^2 $n=12$	30 mg/m^2 $n=18$	35 mg/m^2 $n=12$	40 mg/m^2 $n=6$
T_{max} (h)	0.39 (0.15)	0.29 (0.07)	0.27 (0.08)	0.26 (0.08)	0.32 (0.08)
C_{max} (ng/ml)	647 (326)	852 (226)	1,024 (291)	1,193 (276)	1,459 (229)
AUC_{last} (h ng/ml)	655 (340)	925 (263)	1,255 (454)	1,631 (785)	1,899 (556)
AUC_{inf} (h ng/ml)	890 (183)	1,093 (296)	1,407 (484)	1,816 (833)	2,087 (600)
$T_{(1/2)z}$ (h)	21.0 (5.1)	28.1 (14.1)	32.0 (14.2)	39.4 (11.8)	36.8 (9.0)
Cl_{tot} (l/h/kg)	0.64 (0.17)	0.65 (0.16)	0.62 (0.18)	0.58 (0.14)	0.54 (0.12)
V_{ss} (l/kg)	9.3 (4.8)	12.9 (5.7)	13.1 (4.9)	16.0 (5.8)	13.6 (2.9)
$Cl_{r\ 0-11\ h}$ (l/h/kg)	0.10 (0.05)	0.10 (0.05)	0.09 (0.04)	0.08 (0.04)	0.09 (0.04)
VRL $Ae_{0-11\ h}$ (%)	8.1 (4.1)	8.4 (3.7)	8.1 (3.3)	6.5 (2.8)	9.1 (3.1)
DVRL $Ae_{0-11\ h}$ (%)	0.08 (0.04)	0.04 (0.02)	0.10 (0.14)	0.06 (0.09)	0.16 (0.24)

Table 3 Mean (SD) vinorelbine plasma pharmacokinetic parameters calculated in evaluable patients receiving i.v. vinorelbine as 20 min infusion

Parameters	20 mg/m^2 $n=6$	25 mg/m^2 $n=12$	30 mg/m^2 $n=18$	35 mg/m^2 $n=12$	40 mg/m^2 $n=6$
T_{max} (h)	0.39 (0.14)	0.29 (0.07)	0.27 (0.08)	0.28 (0.08)	0.29 (0.10)
C_{max} (ng/ml)	584 (304)	784 (217)	878 (295)	1,018 (226)	1,170 (162)
AUC_{last} (h ng/ml)	481 (151)	617 (189)	747 (275)	907 (313)	1,048 (111)
AUC_{inf} (h ng/ml)	592 (160)	734 (217)	896 (331)	1,066 (363)	1,192 (136)
$T_{1/2}$ (h)	23.0 (7.7)	24.8 (10.6)	30.8 (14.7)	37.8 (15.8)	31.9 (8.7)
Cl_{tot} (l/h/kg)	0.98 (0.33)	0.99 (0.33)	0.99 (0.33)	0.97 (0.30)	0.91 (0.10)
Vd_{ss} (l/kg)	13.2 (3.9)	15.7 (6.3)	19.1 (7.7)	23.7 (9.1)	19.8 (4.0)
$Cl_{r\ 0-11\ h}$ (l/h/kg)	0.15 (0.09)	0.15 (0.08)	0.15 (0.09)	0.12 (0.06)	0.15 (0.05)

delays occurred in group I, one for haematological toxicity, the other for a non-medical problem; in group II, eight treatment delays were recorded, six for haematological toxicity, one for anaemia due to vascular bleeding requiring transfusion, one for a mistake in the therapy schedule; in group III, three treatment delays were observed, two for haematological toxicity, one for non-medical reason.

Severe non-haematological toxicities were recorded in only two patients: both consisted in grade 4 constipation with rapid recovery, one at the first and one at the last dose of the sequence 30–35–40 mg/m^2. There was no $>$ grade 2 toxicities regarding hepatic or renal functions, diarrhoea, cardiac, pulmonary or cutaneous systems.

Pharmacokinetics

Typical blood and plasma profiles are presented in Fig. 1. A sharp concentration decrease was observed within few minutes following the end of VRL infusion. Concentration vs time-decrease fitted a three exponential decay with an intermediate decrease rate between 1 and 11 h, followed by a slower elimination phase. Concentrations in blood were about twice those observed in plasma. The blood to plasma concentration ratio increased rapidly to 2–2.5 and then decreased slowly to 1.5 over the 72 h time period, suggesting an important distribution phenomena in blood cells (Fig. 2).

Mean blood profile at each dose level is presented in Fig. 3, and illustrated a constant concentration increase from 20 up to 40 mg/m^2 of VRL i.v. administrations. Pharmacokinetic parameters were calculated in both blood and plasma (Tables 2, 3).

The percentage of extrapolated AUC varies from 10 to 18% for dose levels 25–40 mg/m^2. Higher extrapolation was noted at 20 mg/m^2 (36%), which was probably due to an insufficient sensitivity of the bioanalysis method at that dose level because concentrations were below the limit of quantification (2.5 ng/ml) 48–72 h after dosing. Half-life values varied from 21 h (20 mg/m^2) to 39 h (35 mg/m^2). Total drug clearance in blood was high (mean global value 0.6 l/h/kg) and represented about half the value of hepatic blood flow, resulting in an extraction ratio close to 0.5. The volume of distribution at steady state was large ($\approx$13 l/kg) indicating an important tissue diffusion [60]. Although evaluated on a time period of only 11 h, the contribution of renal clearance to total clearance was low ($<20\%$), indicating that non-renal clearance was the major component of VRL elimination.

The amount of unchanged VRL recovered in urine over 11 h was low ($\approx$8% of the dose) and much lower was the amount of DVRL ($<0.2\%$ of the dose). Since each patient received three increasing doses of i.v. VRL, dose-proportional increases of C_{max} and AUCs were evaluated on both individual and global data (Fig. 4).

Individual pharmacokinetic linearity was clearly illustrated on patient plots, especially for AUCs, whereas more variability was observed on C_{max}, partly due to some slight differences on the infusion duration (see T_{max} values on Tables 2, 3). The dose-proportional increase of both C_{max} and AUC was also demonstrated on global datasets from regression analysis ($p \leq 0.0001$). In order to confirm this pharmacokinetic linearity through a different approach, an ANOVA analysis was carried out on the main parameters in blood. C_{max} and AUC were dose-normalised to be comparable. No statistical differences were detected between dose levels on C_{max}/dose, AUC/dose, Cl_T, V_{ss} and $T_{(1/2)z}$.

Of note, one patient presented an outlier profile with high AUC values but, nevertheless, presented a dose-proportional increase of blood and plasma VRL exposures. His medical history included gastrotomy and cholecystectomy. These high exposure values were not associated with severe adverse events during the dose escalation, and the patient was further treated with VRL after study completion.

Pharmacokinetic–pharmacodynamic relationship (PK/PD)

Haematological toxicities. Leucopenia and neutropenia were the dose-limiting toxicities (DLT) of VRL chemotherapy. Therefore PK/PD firstly focused on these biological markers. The study results suggested a relationship between the decrease in blood cell counts

(leucocytes and PMN) and either C_{max} or AUC values (Fig. 5). No significant correlations were observed. No relationships were detected between erythrocytes or thrombocytes levels and pharmacokinetic parameters.

Non-haematological toxicities. No correlation between pharmacokinetic parameters and non-haematological toxicities was observed. This is probably due to the classification scale consisting in four grades (categorical variable), which preclude powerful regression analysis. As a matter of fact, absence of significant correlation was noted between pharmacokinetic parameters and haematological toxicities when grade classification was used instead of nadir blood cell count values. No difference on blood exposure was observed between patients arbitrarily split into two balanced sub-groups for each tissue or organ toxicity.

Discussion

Pharmacokinetic linearity

Vinorelbine is widely used in NSCLC and advanced breast cancer. Doses usually administered are either 30 mg/m^2 i.v. as single agent or 20–25 mg/m^2 in combination with other chemotherapies. Nevertheless, smaller dosing, down to 5 mg/m^2/d over 3 days has been administered in a study using VRL as a radiosensitiser agent [69]. Several papers have been published on VRL pharmacokinetics [14, 15, 17, 18, 25–28, 59] but they usually concerned only the 30 mg/m^2 i.v. dose level. Therefore, the main objective of this study was to assess the dose-proportional increase of blood exposure on a wide range of doses. An intra-patient dose escalation with three dose levels per group of patients offered a powerful design to assess pharmacokinetic linearity, first on intra-patient controls and then on a complete data set. The three groups of dose levels were defined so that they had two common doses between two consecutive groups, and therefore allowing a large groups overlap in order to better assess the intra-patient and inter-patient linearity. As a consequence, this linearity was concluded from both individual dose escalation (graphical observation) and global inter-patient analysis (regression and ANOVA analysis on all data).

In a literature review comparing several studies, Leveque and Jehl [59] concluded also on pharmacokinetic linearity of this drug. Nevertheless, substantial differences on pharmacokinetic parameters were noted between those studies because various methodologies had been used. In a separate study aimed at determining the maximal tolerated dose (MTD) of i.v. VRL, we explored the blood and plasma pharmacokinetics at the three dose levels administered: 30, 40 and 45 mg/m^2 with a methodology similar to the present one [70]. Main results are reported in Table 4.

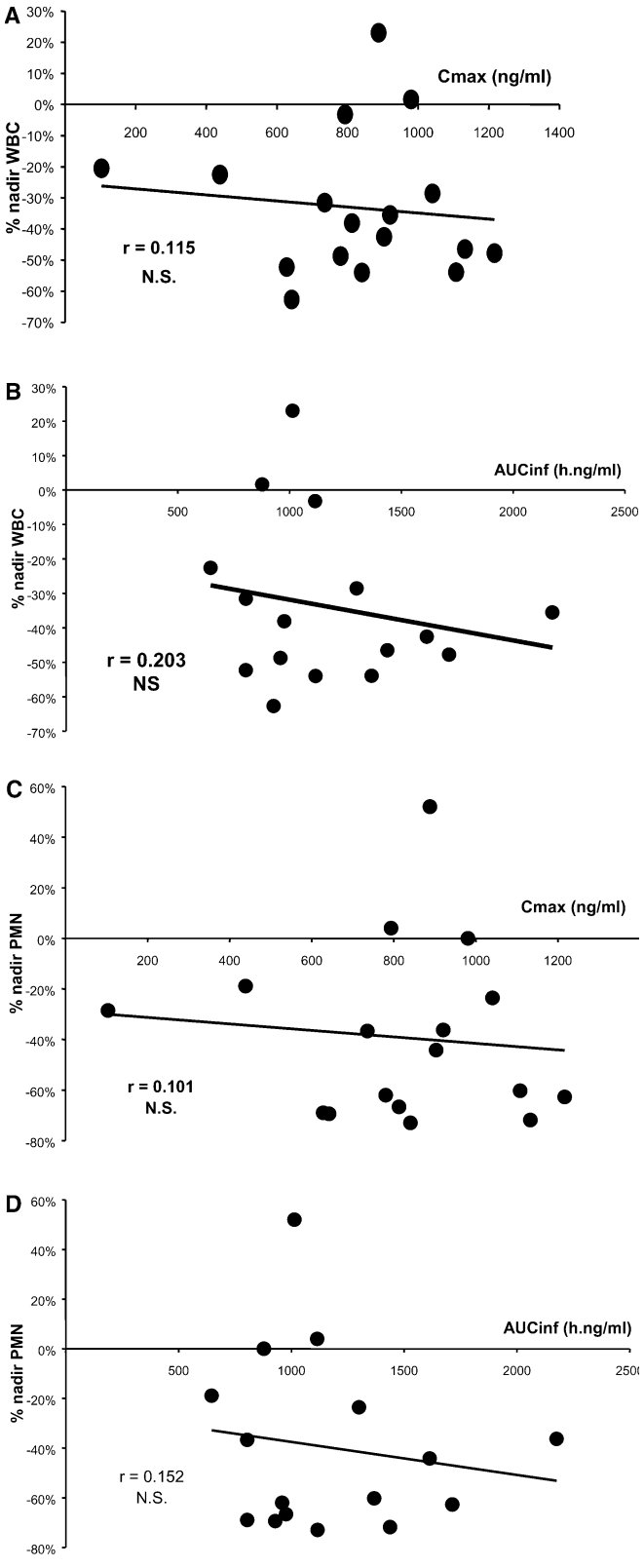

Fig. 5 PK/PD relationship on haematological toxicities. **a** Leucocyte decrease vs C_{max}; **b** leucocyte decrease vs AUC; **c** PMN decrease vs C_{max}; **d** PMN decrease vs AUC

Table 4 Mean value (SD) of main PK parameters from MTD study of i.v. vinorelbine [70]

Parameters	35 mg/m^2 ($n=4$)		40 mg/m^2 ($n=8$)		45 mg/m^2 ($n=4$)	
	Blood	Plasma	Blood	Plasma	Blood	Plasma
T_{max} (h)	0.35 (0.02)	0.35 (0.02)	0.29 (0.08)	0.29 (0.08)	0.33 (0.00)	0.34 (0.02)
C_{max} (ng/ml)	1,245 (218)	1,076 (209)	1,448 (181)	1,338 (231)	1,761 (523)	1,750 (674)
AUC_{last} (h ng/ml)	1,341 (235)	895 (102)	1,720 (409)	1,179 (314)	1,762 (391)	1,344 (343)
AUC_{inf} (h ng/ml)	1,450 (238)	1,014 (131)	1,882 (424)	1,309 (316)	1,894 (414)	1,482 (331)
$T_{(1/2)z}$ (h)	25.2 (2.2)	26.4 (3.5)	25.7 (8.9)	32.0 (13.8)	21.0 (3.1)	28.5 (5.0)
Cl (l/h/kg)	0.66 (0.07)	0.94 (0.07)	0.60 (0.13)	0.86 (0.19)	0.66 (0.16)	0.85 (0.20)
V_{ss} (l/kg)	11.2 (1.5)	16.8 (2.5)	10.7 (2.9)	17.7 (7.3)	9.6 (2.1)	16.9 (9.3)
$Cl_{r\ 0-11\ h}$ (l/h/kg)	0.09 (0.02)	0.13 (0.03)	0.08 (0.03)	0.10 (0.05)	0.08 (0.03)	0.11 (0.04)
VRL $Ae_{0-11\ h}$ (%)	7.7 (1.7)		6.4 (2.3)		7.1 (1.1)	
DVRL $Ae_{0-11\ h}$ (%)	0.07 (0.02)		0.06 (0.06)		0.12 (0.04)	

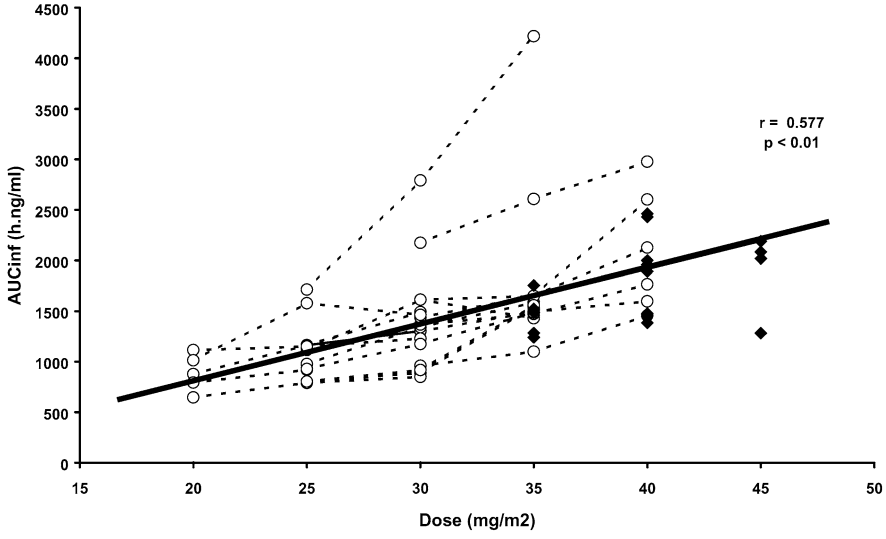

Fig. 6 AUC_{inf} vs dose when pooling data from present study and MTD study [73]

The parameters obtained from the MTD study are close to those achieved in the present study. Therefore, when pooling data from both studies, pharmacokinetic linearity of i.v. VRL is observed up to 45 mg/m^2 (Fig. 6). Furthermore, the PK/PD relationship on haematological toxicity was highly improved when pooling the data from both studies. A significant PK/PD correlation was observed between leucocytes decrease and C_{max} ($r=0.787$; $p<0.001$) or AUC ($r=0.628$; $p<0.001$) and between PMN and C_{max} ($r=0.450$; $p<0.01$) or AUC ($r=0.524$; $p<0.001$) (Fig. 6). Although thrombopenia was not a DLT of VRL ($\leq$ grade 1 at all dose levels in this study), a correlation between platelets decrease and C_{max} was also detected ($r=0.527$; $p<0.001$) or AUC ($r=0.438$; $p<0.01$), whereas no correlation between either red blood cell counts or haemoglobin levels and pharmacokinetic parameters was once more evidenced.

Pharmacokinetic in blood vs plasma

The present study was also a good opportunity to evaluate and compare VRL pharmacokinetics when carried out either in blood or in plasma. In literature, studies were mostly performed in plasma although VRL is largely bound to platelets and blood cells. Therefore, blood was likely to be more adapted.

Altogether, the shape of plasma and blood concentration profiles were much comparable, but the distribution ratio between plasma and blood cells varied over time. In fact, the blood/plasma ratio was close to one at the end of the VRL infusion, then sharply increased up to 2–2.4 over the 6–10 first hours and went down to 1.5–1.8 on day 4 (Fig. 2). It illustrated the high VRL affinity for blood cells and the continuous distribution equilibrium between tissues and blood cells.

Because VRL concentration in platelets is high and because platelets content in plasma is very dependent of its preparation process, whereas blood is not, the large intra-patient and inter-patient variability on individual blood/plasma ratio values advocated for some differences in the centrifugation conditions that have been used to separate plasma from whole blood. Urien et al. [71] demonstrated that 84% of VRL were bound to blood cells and particularly to platelets (78%). Recently, Urien et al. confirmed (unpublished data) that the blood/plasma ratio was highly influenced by the

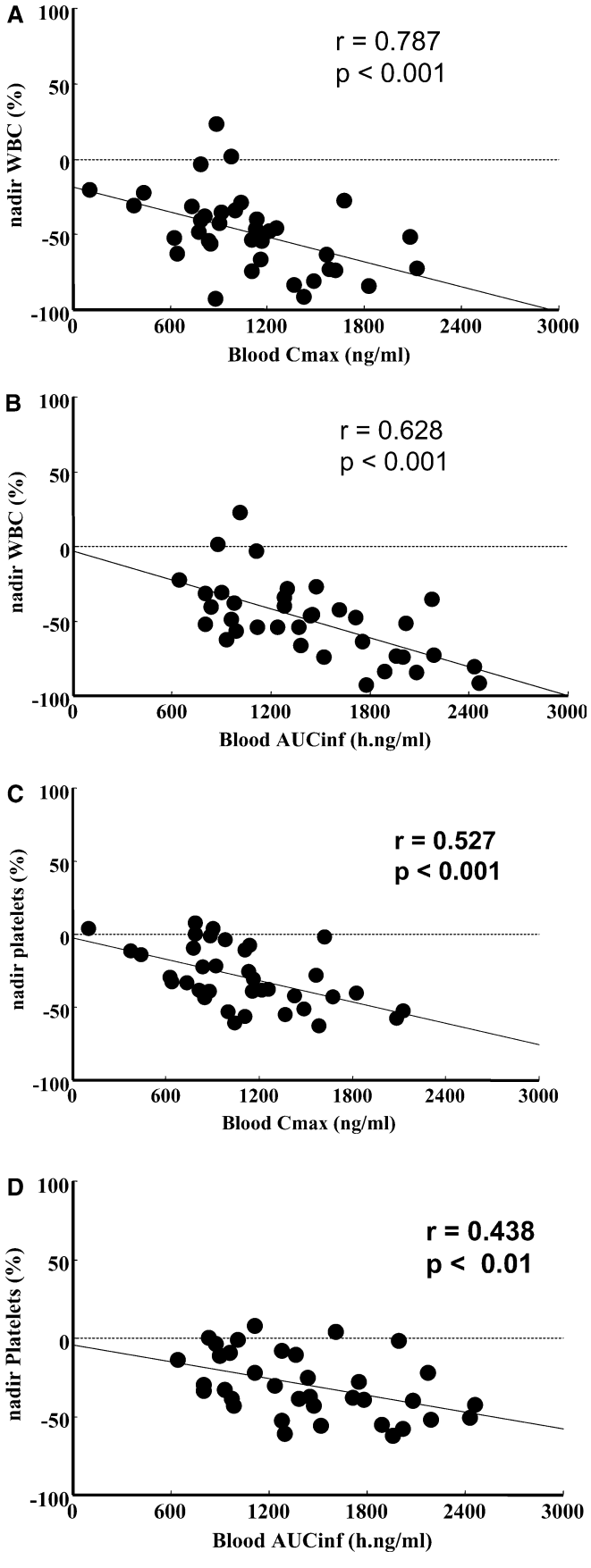

Fig. 7 PK/PD relationship on haematological toxicities when pooling data from present study and MTD study [73]. **a** Leucocyte decrease vs C_{max}; **b** leucocyte decrease vs AUC; **c** platelets decrease vs C_{max}; **d** platelets decrease vs AUC

conditions used to obtain plasmas (anti-coagulant, temperature, etc.), and that binding to platelets was reversible with a rapid re-equilibrium. Consequently, variable residues of platelets in plasma are likely to generate representative values rather than the true plasma concentrations.

As a result, measuring VRL concentration in blood is clinically more relevant and is likely to provide more accurate values than in plasma since concentrations are higher in blood (i.e. better HPLC detection). The limit of quantitation being reached more rapidly in plasma, less concentration values will be available for the regression analysis that is necessary to the elimination of half-life calculation. The bias generated by an insufficient number of data in the elimination phase is illustrated by the pharmacokinetic parameters achieved at the 20 mg/m^2 dose level. The limit of quantitation being reached quicker than at higher doses, the resulting half-life (20–30 h) was in fact a mix between distribution and elimination phases (Table 2).

Another consequence was the over-estimation of VRL clearance when using plasma (Cl_{tot} close to 1.0 l/h/kg) rather than blood (0.6 l/h/kg). Variability may be increased as noted on plasma V_{ss} values (CV = 15–55% in plasma vs 13–27% in blood). Marty et al. [72] evaluated recently the bioavailability of oral VRL on 24 patients in a cross-over study design and using the same HPLC method. At 25 mg/m^2 i.v. dosing, their parameters in whole blood were close to those reported in the present study with only a 5% difference in AUCs, and very similar clearance values (0.72 ± 0.25 l/h/kg vs 0.65 ± 0.16 l/h/kg). It advocates the reliability of pharmacokinetic parameters determined in blood whereas substantial differences between studies from literature were noticed for plasma [59].

Metabolite in blood vs plasma

Concerning VRL metabolism, the 4-O-deacetyl vinorelbine (DVRL) was only detected at the two higher doses (35 and 40 mg/m^2). This metabolite appeared slowly in blood from 2 h post-dosing and presented a low concentration plateau (≈4 ng/ml) during 48 h. DVRL was not detected in plasma. The small amount recovered in urines (≤ 0.12% of the administered dose on 0–11 h time interval), confirmed that bile was the main route of metabolites elimination at all dose levels [63]. The same is certainly true for VRL since renal clearance was a minor component of total clearance (10–20%).

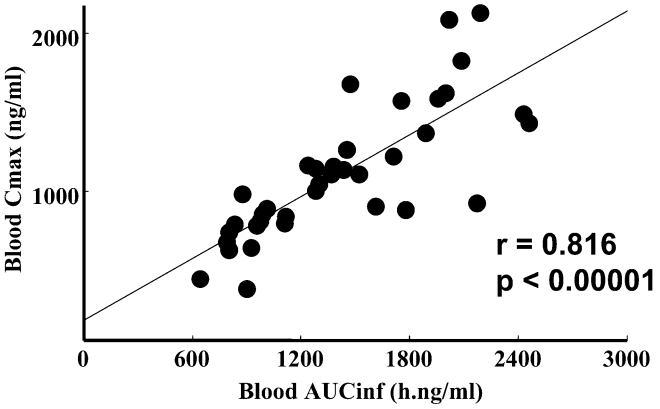

Fig. 8 Relationship between vinorelbine C_{max} and AUC in blood

Safety and PK/PD

Safety data were collected during this trial although the major objective was pharmacokinetics. The intra-patient dose escalation did not allow the real safety assessment of each dose level but rather of a dosing sequence (three increasing dose levels). Therefore only descriptive statistics were carried out.

No relevant PK/PD relationship was noted for non-haematological toxicities. An evaluation scale with a more continuous variable should be necessary instead of a scale limited to few grades. Nevertheless, this relationship is not obvious since the patient who experienced grade 4 constipation at 40 mg/m^2 following 30 and 35 mg/m^2 administrations had the lowest VRL and DVRL AUC out of the six patients dosed at 40 mg/m^2 (half value of the highest AUC). Similar conclusions are drawn for the second patient with grade 4 constipation at 30 mg/m^2 (first dose of group III).

Concerning haematological toxicities, PK/PD relationships were suggested in the present study but correlation coefficients were not significant. Nevertheless, when adding data from the MTD study [70] the relationships between pharmacokinetic parameters (C_{max} and AUC) and leucopenia and neutropenia become significant (Fig. 7), which was consistent with the known DLT of VRL. However, the correlation between C_{max} and haematological toxicities was weaker than that with AUC, probably due to the strong correlation existing between C_{max} and AUC (Fig. 8) ($r = 0.816$, $p < 0.00001$) [73]. As a consequence, AUC is likely to be the major parameter for the assessment of PK/PD.

A correlation was also observed between platelets decrease and pharmacokinetic parameters. However, the decrease was small and not clinically relevant; thrombocytopenia has never been reported as a vinorelbine DLT, and grade 0–1 toxicity was observed in the present study on intent-to-treat (ITT) patients.

In conclusion, dose-proportional increase of blood exposure is a major safety issue in daily therapeutic practice. The results of this study demonstrated the pharmacokinetic linearity of i.v. VRL in the dose range 20–40 mg/m^2 or even 20–45 mg/m^2. Evaluation of pharmacokinetic parameters can be achieved in blood and in plasma, but data in blood are likely to be more reliable. Furthermore, using blood will minimise the sample handling by nurses and will reduce the total sample volume required from patients.

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