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ORIGINAL ARTICLE

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Population pharmacokinetics of short intravenous vinorelbine infusions in patients with metastatic breast cancer

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Abstract *Purpose*: To develop a population pharmacokinetic model of vinorelbine administered by short intravenous infusion in metastatic breast cancer patients. *Methods*: Vinorelbine was administered as infusions of 5–10 min at 15, 20 or 25 mg/m^2 to 30 patients. Blood samples were collected over 18 h. Plasma concentrations of vinorelbine were determined by HPLC. Population pharmacokinetic analysis was performed using a nonlinear mixed effects modeling method. *Results*: Vinorelbine concentration-time profiles were best described by a three-compartment open model. Plasma clearance (CL) was high and positively related to lean body weight (LBW) and body surface area (BSA) or to a combination of height and body weight (BW). Elevated serum alkaline phosphatases had a negative effect on CL. Typical population estimates of CL and central distribution volume (V_1) were 74.2 l/h and 7.8 l, respectively. The interindividual population coefficients of variation for CL and V_1 were 17.0% and 32.0%, respectively. The stability and predictive performance of the final population pharmacokinetic model were assessed using 200 bootstrap samples of the original data. *Conclusion*: This study identified combined effects of BSA and serum alkaline phosphatases on clearance. These results partly support the conventional dose adjustment of vinorelbine based on BSA, but suggest dose modification in cases of extreme values of serum alkaline phosphatases.

Keywords Anticancer drugs · Population pharmacokinetics · Vinorelbine

Abbreviations *ALT* Alanine amino transferase · *AST* Aspartate amino transferase · *AUC* Area under the concentration curve · *BSA* Body surface area · *BW* Body weight · *CL* Clearance · *ISV* Intersubject variability · *LBW* Lean body weight · *OFV* Objective function value · *SAP* Serum alkaline phosphatases · *SCr* Serum creatinine · V_1 Distribution volume

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Introduction

Vinorelbine is a semisynthetic vinca alkaloid highly effective in the treatment of non-small-cell lung cancer and metastatic breast cancer. The pharmacokinetic profile of plasma vinorelbine has already been investigated via classical approaches in a limited number of patients [9, 13]. Recently, the pharmacokinetics of vinorelbine based upon blood concentration measurements have been investigated via population approaches in 64 patients and 175 patients with various types of tumor (gynecological, gut, lung, liver metastases, lymphomas, others) in phase I and phase I/II trials [11, 18]. Additionally, the population pharmacokinetics of plasma vinorelbine have been investigated in a group of 27 elderly patients [6].

Since vinorelbine is now included in first-line combinations used in the treatment of metastatic breast cancer, the main objective of this study was to investigate its pharmacokinetics via a population approach in female patients with this specific cancer. Demographic and biological data were collected to assess the influence of patient characteristics on

vinorelbine plasma pharmacokinetics. Two other features differentiated this study from the previous ones: (1) the very short infusion time (5 min instead of 10 or 20 min), and (2) the pharmacokinetic and error model parameterization. Because there were only 30 patients in this study, the stability and predictive performance of the final population pharmacokinetic model were assessed using a bootstrap procedure.

Methods

Patients and treatment

Between February 1998 and May 2000, 30 patients were entered into the multicenter pharmacokinetic prospective study with vinorelbine administered in combination with leucovorin and UFT. Written informed consent from each patient and ethics committee approval were obtained before beginning treatment. Eligibility criteria included: patients with histologically proven metastatic breast cancer, objectively measurable and/or evaluable disease, age ≥18 years, World Health Organization (WHO) performance status of 0–2, and adequate hematological parameters (granulocytes $\geq 2.0\times10^9$/l, platelets $\geq 100\times10^9$/l), hepatic parameters (total bilirubin not more than 1.5 times the upper limit of normal, AST and ALT not more than twice the upper limit of normal), and renal function (SCr not more than 1.25 times the upper limit of normal).

Vinorelbine, 15, 20 or 25 mg/m^2, was given as a 5-min i.v. infusion on days 1, 8 and/or 15. Vinorelbine pharmacokinetics were investigated during cycle 1 in which vinorelbine was given 6 h after the first dose of UFT + leucovorin. The total administered dose of vinorelbine was diluted in 50 ml 0.9% NaCl solution, starting at 15 mg/m^2.

For each patient, the demographics and baseline laboratory values were recorded. BSA and LBW were calculated according to usual formulae from BW in kilograms and height in centimeters. Specifically, equations for BSA and LBW were:

$$\begin{aligned} \mathrm{BSA} &= 0.007184 * \mathrm{BW}^{0.425} * \mathrm{Height}^{0.725} \\ \mathrm{LBW} &= 1.07 * \mathrm{BW} - 148 * (\mathrm{BW}/\mathrm{Height})^2, \text{ for females} \\ &\quad (\text{for males, coefficients should be 1.10 and 128}) \end{aligned} \quad (1)$$

Analytical method

Pharmacokinetics of vinorelbine were examined on day 1 of cycle 1. Blood samples were collected through an indwelling catheter inserted in the arm. Blood samples (5 ml) were collected at the following points: immediately before vinorelbine administration, at 5, 15 and 30 min, and at 1, 2, 4, 7, 11 and 18 h after administration of vinorelbine. All samples were immediately centrifuged at 1000 *g* for 10 min at 4°C and stored at −70°C until analysis.

Vinorelbine plasma concentrations were assessed using high-performance liquid chromatography with UV detection. Vinorelbine and vinblastine used as an internal standard were extracted from plasma with diethyl ether and ammonium acetate buffer, pH 3, and 80 µl injected onto a Spherisorb CN column (3 µm, 100×4.6 mm). Vinorelbine was eluted using an isocratic buffer comprising 0.05 *M* ammonium acetate plus acetonitrile, pH 3 (70:30, vol/vol), and detected at 268 nm. The limit of quantification of the method was 2.5 ng/ml using a 0.5-ml plasma specimen. The precision and accuracy for standard curves and quality control samples were less than 15% in the calibration range 2.5–500 ng/ml.

Population pharmacokinetic modeling

Concentration-time data were analyzed using the non-linear mixed effects modeling approach, implemented in the program MP2 [15]. First, a search was made for the best structural pharmacokinetic model for the vinorelbine data covering compartmental and statistical models. Two- and three-compartment pharmacokinetic models were considered. Intersubject variabilities (ISV) and residual variability were ascribed to proportional and/or additive error models [10, 17].

The procedure for selection of covariates was performed as described previously [10, 17]. The influence of each patient covariate on CL and V_1 was systematically tested via generalized additive modeling. Such covariates included gender, age, BW, height, BSA, LBW, SCr, AST, ALT, bilirubin, platelet count and SAP. Full and reduced models (one parameter less) were compared by the chi-squared test of the difference between their respective objective function values (OFV). The effect of a covariate was considered to have improved the fit if there was a significant decrease in the OFV of at least 4 units ($P < 0.05$, one degree of freedom) compared to the base pharmacokinetic model (with no covariate) and a reduction in the ISV of the associated pharmacokinetic parameter. In order to keep only the covariates with the largest contribution to prediction of vinorelbine pharmacokinetics in a final multivariate model, a change of 7 units ($P < 0.01$, one degree of freedom) of the OFV was required for the retention of a single parameter during backward stepwise multiple regression analysis.

To describe the influence of a covariate on a pharmacokinetic parameter, an allometric model was used. Assuming an influence of BW on clearance, for example, the model would be:

$$\mathrm{CL} = \mathrm{TV(CL)} * (\mathrm{BW}/\mathrm{median(BW)})^{\theta\mathrm{BW}} \quad (2)$$

where CL is the model-predicted value given a BW value. TV(CL) is the population typical value of CL and corresponds to CL when BW = median(BW), i.e., subjects with median covariate values have typical pharmacokinetic parameter values. The exponent θBW (or influential factor) denotes a scale factor quantifying the influence of covariate: $\theta = 0$, no effect, the covariate can be deleted without any deterioration of the fit; $\theta = 1$, direct proportional relationship; $\theta < 1$ or $\theta > 1$, non-linear relationship. The sign of this exponent, + or −, indicates that the pharmacokinetic parameter increases (positive effect) or decreases (negative effect) when the covariate increases.

Bootstrap assessment of the final population model

The accuracy and robustness of the final population model were assessed using a bootstrap method, as previously described in detail [12]. Briefly, this includes the following steps:

1. From the original data set of *n* individuals, B bootstrap sets (usually B = 200) of *n* individuals are drawn with replacement (resampling)
2. For each of the B bootstrap sets, the population pharmacokinetic parameters are estimated
3. With the B estimates of each population pharmacokinetic parameter, the corresponding mean, median and standard deviation are estimated
4. To validate the model, the mean parameters estimated from the bootstrap must be close to estimates obtained from the original population set.

The entire procedure was achieved in an automated fashion using the MP2 program, in which this procedure was implemented.

Results

Demographic data

Available for pharmacokinetic evaluation were 30 female patients (ranging in age from 20 to 68 years). Their characteristics are listed in Table 1.

Table 1 Characteristics of the 30 female patients studied

Characteristic	Mean	Median	Range
Age (years)	52	53.5	20–68
Body weight (kg)	61	59	41–90
Height (cm)	160	160	147–172
Body surface area (m^2)	1.63	1.61	1.38–2.03
Lean body weight	43.1	42.5	34–56
Platelet count ($10^3/mm^3$)	266	252	175–437
Serum Creatinine (μmol/l)	78	79	53–119
Aspartate amino transferase (IU/l)	35.5	33	11–77
Alanine amino transferase (IU/l)	30	28	7–91
Alkaline phosphatase (IU/l)	123	112	42–310
Total bilirubin (μmol/l)	5.7	5.5	2–11

Population pharmacokinetics

For the 30 patients included, 257 time-concentration points were available for the pharmacokinetic modeling, five to nine samples per patient. The median infusion time was 7 min (5 to 9 min). Concentration-time courses are depicted in Fig. 1.

Development of the structural pharmacokinetic model indicated that the three-compartment model best fit the data (the OFV was decreased by 242 units relative to the two-compartment model). ISV and residual variability were both described by proportional error models. At this step, the ISV on peripheral pharmacokinetic parameters approached zero and exclusion of these parameters had no effect on the OFV.

In the screening phase, the covariates that individually reduced the OFV by more than 4 units were BW, LBW, BSA, height, age and SAP. BW, LBW, height and BSA had a positive influence on CL, whereas age and SAP had a negative influence on CL. The substitution of one covariate with another was continuously explored for strongly correlated covariates, e.g., BW, LW and BSA (Table 2). These covariate effects were then combined, BW or LBW or BSA or height, age, SAP. In all cases, the deletion of age did not change the OFV by at least 7 units. The covariate submodel candidate was then:

$$\mathrm{CL} = \mathrm{TV(CL)} * \{\mathrm{B}/\mathrm{median(B)}\}^{\theta \mathrm{B}} * \{\mathrm{SAP}/\mathrm{median(SAP)}\}^{\theta \mathrm{SAP}} \quad (3)$$

where B denotes BW, BSA, LBW or height. Table 2 summarizes these combined covariate effects on OFV and ISV of CL. When both height and BW were taken

Table 2 Summary of covariate effects on plasma vinorelbine clearance. A covariate effect is retained if its deletion from the model results in an increase in objective function value (OFV) of >7, and a significant decrease in intersubject variability (ISV) (*S* significant, *NS* not significant)

No.	Covariate(s)	OFV decrease from base model	ISV on CL (%)	Remark
	Base model	0	26.0	
1	BSA	−16	23.0	
2	Height	−16	19.0	
3	BW	−11	20.5	
4	LBW	−17	19.3	
5	Age	−6	21.0	
6	SAP	−19	21.0	
7	Height + BW + age + SAP	−50	16.2	
8	Height + BW + SAP	−50	16.3	Age deletion from no. 7, NS
9	Height + BW	−16	19.0	SAP deletion from no. 8, S
10	Height + SAP	−43	17.3	BW deletion from no. 8, S
11	BSA + age + SAP	−45	16.8	
12	BSA + SAP	−43	17.0	Age deletion from no. 11, NS; SAP deletion (=no. 1), S
13	LBW + age + SAP	−46	16.8	
14	LBW + SAP	−45	17.0	Age deletion from no. 13, NS; SAP deletion (=no. 4), S

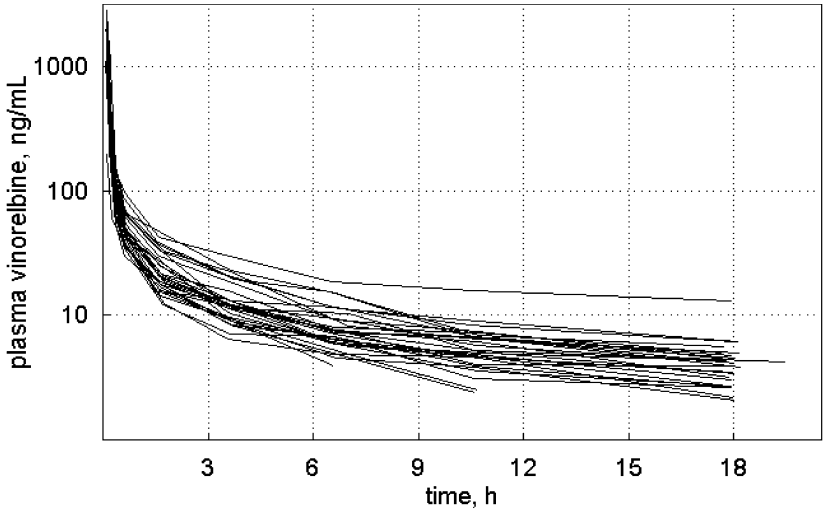

Fig. 1 Observed vinorelbine plasma concentration-time courses on a semilog scale

Table 3 Population pharmacokinetic parameters of vinorelbine and bootstrap validation (*CV* coefficient of variation; *TV(CL)* typical value of clearance; V_1, V_2, V_3 central and peripheral distribution volumes; Q_2, Q_3 intercompartmental clearances; ω intersubject variability; $\theta_{COVARIATE}$ influential factor for covariate; *BSA* body surface area; *SAP* serum alkaline phosphatases)

Parameter	Final model, original dataset		Bootstrap[a]	
	Mean	Precision CV (%)	Mean	Precision CV (%)
Structural model				
V_1 (l)	7.85	8.0	8.01	8.0
TV(CL) (l/h)	74.2	4.5	74.8	4.0
CL, θ_{BSA}	+1.25	35.0	+1.19	37.0
CL, θ_{SAP}	−0.25	35.0	−0.22	40.0
Q_2 (l/h)	32.7	7.0	33.0	8.0
V_2 (l)	19.4	10.0	19.7	13.0
Q_3 (l/h)	47.0	5.0	47.5	7.0
V_3 (l)	388.0	7.5	394.0	7.0
Statistical model				
Residual variability, σ (%)	21.6	17.0	21.2	14.0
ω_{V1} (%)	32.0	74.0	29.4	75.0
ω_{CL} (%)	17.0	58.0	13.4	40.0

[a]Mean of 200 bootstrap analyses

into account (these covariates were not significantly correlated), the height-BW-SAP submodel produced the greatest reduction in OFV, but the ISV improvement of CL was small, <1% versus BSA-SAP or LBW-SAP combinations. Thus, this height-BW-SAP model was not retained, for the ISV improvement of CL was negligible and the precision of θBW was poor (CV = 72%). Then, the best candidates were the BSA-SAP and LBW-SAP combinations. Finally, the BSA-SAP CL model was chosen, for BSA combines BW and height information. Moreover, BSA is more easily obtained than LBW. Table 3 summarizes the parameter estimates and Fig. 2 shows scatterplots that allow the appreciation of the goodness of fit of the final population model.

Bootstrap assessment of the final population model

The final model obtained with the original dataset was subjected to a bootstrap analysis. As shown in Table 3, the mean parameter estimates obtained from the bootstrap process, 200 runs, were statistically identical to the estimates previously obtained with the original dataset.

Discussion

Vinorelbine plasma pharmacokinetics was best described by a three-compartment open model with first-order elimination, as previously reported in studies using classical pharmacokinetic approaches [9, 13]. Several covariates with a potential effect on vinorelbine plasma CL were identified: LBW, height, BSA or BW and SAP.

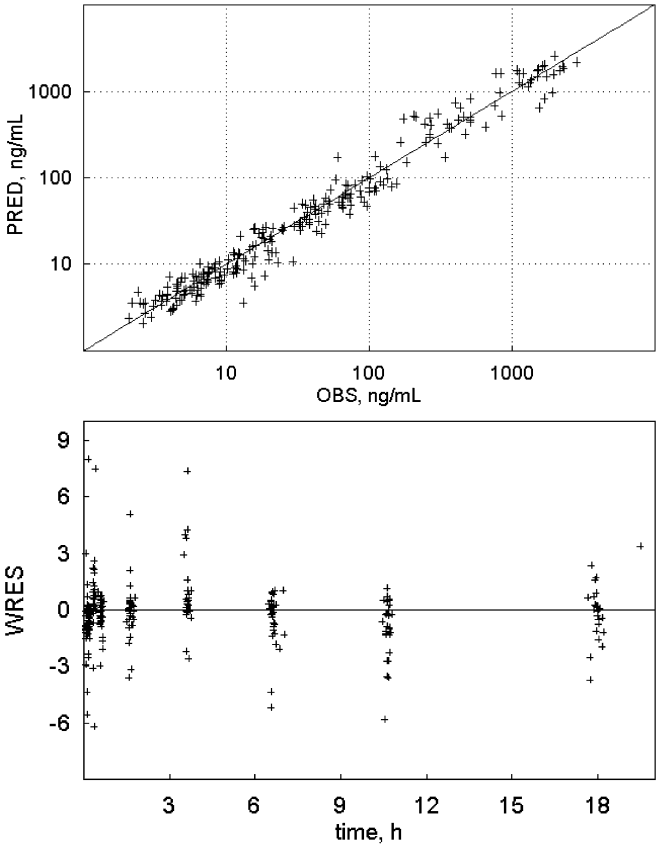

Fig. 2 Predicted (*PRED*) versus observed (*OBS*) plasma vinorelbine concentrations and weighted residuals (*WRES*) versus time from the final pharmacokinetic model (30 patients, 257 concentration-time points). The data are plotted on a log scale for ease of visualization

No other covariate significantly influenced vinorelbine pharmacokinetics, in accordance with our criterion to finally retain a covariate in the model.

Reported values for plasma clearance, including various cancer diseases, range from 0.83 to 1.28 l/h per kg, with two "outlier" values of 0.42 and 0.66 l/h per kg [9, 13]. Our mean CL estimate (1.21 l/h per kg) is in the high range of these values. Vinorelbine plasma population pharmacokinetics has been investigated in 12 and 15 elderly patients (aged 66 to 79 and 71 to 80 years) with advanced metastatic cancer [4, 5]. In these studies, the mean population clearance estimates were 61.2 and 43.8 l/h with an ISV of 28% and 24%, respectively. In a recent study in 27 elderly patients, plasma clearance was estimated as 47.1 l/h (ISV 31.7%), with an age effect on CL [6].

Intravenous vinorelbine population pharmacokinetics has been studied in a larger group of 64 patients (42 males/22 females) [11]. However, the pharmacokinetics was based upon vinorelbine blood concentrations, so that parameter comparisons had to take into account the AUC_{blood}/AUC_{plasma} ratios which averaged 1.7 [5, 14]. Similarly, vinorelbine blood pharmacokinetics was described by a three-compartment model and blood clearance was also related to BSA, with corrections for

Table 4 Final population pharmacokinetic model: covariate effects (minimal and maximal observed values in this population) on plasma vinorelbine clearance and systemic exposure (AUC)

Covariate	Median	Change in covariate (observed value)		Effect on clearance		Effect on AUC	
		Min.	Max.	Min.	Max.	Min.	Max.
SAP	112 IU/l	−63% (42 IU/l)	+280% (310 IU/l)	−28%	+23%	−22%	+29%
BSA	1.61 m^2	−15% (1.38 m^2)	+26% (2.03 m^2)	−18%	+34%	+22%	−25%

the platelet count and the BW-to-SCr ratio. Intersubject variability estimates for V_1 and CL were also of the same order (22% and 21%, respectively). The blood clearance was 39.4 l/h, i.e., the corresponding plasma clearance averaged 67 l/h, which is close to our estimate of 74.2 l/h in this specific group of 30 female patients. The low blood clearance of vinorelbine relative to plasma and the effect of platelets on blood clearance can be explained by high-affinity binding to blood cells and particularly platelets, which accounts for a high degree of blood binding (>98%, whereas plasma binding is only 80–90%) [16].

A covariate submodel for CL including combined height-BW-SAP effects on CL induced the greatest decrease in OFV. However, the population pharmacokinetic model including only BSA and SAP effects on plasma CL was finally chosen on the basis of statistical criteria and the principle of parsimony. Moreover, BSA combines information on BW and height. A significant effect of height-BW combination on clearance has also been reported for topotecan [3]. There was no evidence of influence of liver enzymes on vinorelbine CL, although vinorelbine is mainly cleared via liver metabolism, as previously reported for other anticancer drugs [2, 7]. However, a negative effect of SAP was observed on vinorelbine CL. Increased SAP levels reflect both cholestasis and the presence of bone metastases, i.e., poor physiological conditions. The exponent, −0.25, indicates that the eventual CL decrease will be significant for only very high SAP values. Table 4 summarizes the effects of changes in the significant covariates, BSA and SAP, on vinorelbine CL. As expected, a high increase in SAP (310 IU/l) would cause a 23% reduction in clearance, resulting in a 29% increase in AUC.

For some anticancer drugs, including carboplatin [1], epirubicin [7], doxorubicin, etoposide and ifosfamide [2], no significant relationship has been observed between plasma CL and BSA. In the present study, a relationship was found between a BSA-SAP combination and vinorelbine plasma CL. Also, the population pharmacokinetic study based on blood concentration identified BSA as the main determinant of vinorelbine CL. This supports the conventional vinorelbine dose adjustment calculated on a BSA basis, with possible correction for highly increased values of SAP.

In at least three studies, significant relationships have been observed between vinorelbine plasma AUC and hematotoxicity, particularly absolute neutrophil count depletion [4, 5, 8]. So the potential impact of this

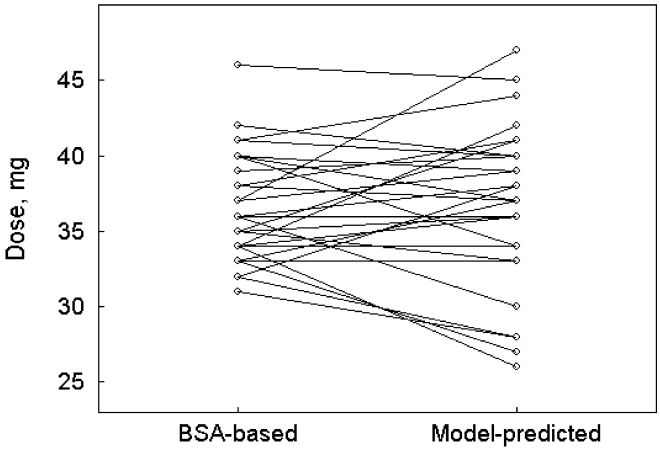

Fig. 3 Model-predicted versus BSA-based vinorelbine dose required to reach a target AUC of 476 ng·h/ml (AUC of typical patient with median covariate values receiving 36 mg/1.61 m^2)

population model on vinorelbine dosage was illustrated using this pharmacokinetic endpoint. Individualized doses were generated using the BSA-SAP clearance model in order to provide a target AUC of 476 ng·h/ml (this is the AUC for a typical patient with median BSA and SAP values and a median dose of 36 mg/1.61 m^2 or 22.5 mg/m^2). Figure 3 illustrates the differences between BSA-based dose and model-predicted dose for each patient. Although most lines were near the identity, five patients were over-dosed by more than 20% (mainly because their SAP levels were between 198 and 310 IU).

In conclusion, this study including 30 female patients with metastatic breast cancer showed that plasma clearance was related to individual characteristics, BSA and SAP. The accuracy and robustness of the model were assessed by a bootstrap method. The bootstrap analysis assessed both the stability and predictive performance of this model. The conventional dose adjustment of vinorelbine based on BSA could be corrected for highly increased values of SAP (dose reduction).

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