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Clinical report

A limited-sampling strategy to estimate individual pharmacokinetic parameters of vinorelbine in elderly patients with advanced metastatic cancer

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The aim of this study was to characterize the population pharmacokinetic of vinorelbine in elderly patients and to propose a limited-sampling strategy to estimate individual pharmacokinetic parameters. Vinorelbine was administered by a 10-min continuous infusion at a dose of 20–30 mg/m^2. The population parameters were computed, using a three-compartment model, from an initial group of 27 patients. Twelve additional courses were used for model validation and evaluation of eight different limited-sampling strategies. The inter-individual variability of CL was explained by a linear dependency with age. The population average parameters and the interindividual variabilities (CV%) were: CL=47.1 l/h (31.7%), V=16.6 l (64%), k_{21}=0.776 h^{-1} (20%), k_{31}=0.0346 h^{-1} (15.2%), α=0.431 h^{-1} (6.84%) and β=0.0167 h^{-1} (25%). Bayesian estimation with three measured levels (end of infusion, and 6 and 48 h) can be selected, because it allows adequate estimation of CL, elimination half-life and vinorelbine concentrations with a non-significant bias. Moreover, the choice of these three sampling times presents practicality advantages for the patient's comfort. Vinorelbine clearance decreasing with age and AUC being a good predictor of several toxicity end points during vinorelbine treatment, the limited-sampling strategy developed in this paper may be clinically relevant. [© 2002 Lippincott Williams & Wilkins.]

Key words: Limited-sampling strategy, population pharmacokinetics, vinorelbine.

Introduction

Vinorelbine (5′-noranhydrovinblastine), a semi-synthetic anticancer drug which belongs to the *Catharanthus* alkaloid family, displayed activity against a wide variety of neoplasms. Today, this drug is registered in some European countries including France in the treatment of (i) advanced metastatic breast cancer and (ii) non-small cell lung cancer, and in USA in the treatment of non-small cell lung cancer. Like other vinca alkaloids, vinorelbine induces cytotoxicity by inhibiting microtubule assembly; however, this drug appears to be more specific in that it preferentially binds to the mitotic spindle and affects microtubules in neural structures to a lesser degree.[1] Vinorelbine shows reduced neurotoxicity compared with other vinca alkaloids, but a dose-limiting neutropenia was reported to be relatively frequent.[2] The pharmacokinetic profile of vinorelbine after i.v. bolus injection is characterized by a high plasma clearance (approaching the rate of hepatic blood flow), a large volume of distribution and a long terminal half-life.[3] Elimination via biliary excretion represents 70–80% of the administered dose.[4] However, some discrepancies appear in the determination of the elimination half-life and of the steady-state volume of distribution. According to the study, the volume of distribution ranged from 23 to 76 l/kg and elimination half-life values were 18–48 h.[2–16] However, higher elimination half-lives of 56.5 and 79.8 h have been reported.[8,16] In a recent paper, Sabot *et al.*[13] developed a population pharmacokinetic of vinorelbine in a group of eight non-small cell lung male cancer patients (mean age 61 years) using a Bayesian estimation to compute individual pharmacokinetic parameters from few blood samples. These authors concluded that the best blood sampling protocol consisted of two samples (6 and 24 h after the start of infusion).

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Due to its favorable toxic profile, vinorelbine is an attractive candidate for chemotherapy in elderly patients. In a recent study, Vogel *et al.*[17] reported that vinorelbine appears to have meaningful clinical activity in such a population of patients. Moreover, in aging patients with advanced non-small cell lung carcinoma, it has been shown that vinorelbine was well tolerated and capable of ensuring relatively long survival.[18,19] However, the aging process may be the cause of alteration in hepatic metabolism, but vinorelbine pharmacokinetics data collected in elderly patients are limited.[12,15] Moreover, a relationship between systemic exposure and hematological toxicity (neutropenia) has been reported after vinorelbine administration of 35, 40 and 45 mg/m^2.[3,14] These results were confirmed recently by Gauvin *et al.*[15] in a population of 12 elderly patients. As reported for other anticancer drugs, AUC-guided dosing of vinorelbine should be clinically relevant, particularly in this population of patients.

The aim of this study was to validate a limited-sampling strategy to estimate individual pharmacokinetic parameters in elderly patients, compatible with clinical practice and patient's comfort, based on population approach. This study was undertaken in a group of 30 patients older than 66 years with metastatic cancer in progression who received vinorelbine. Successive courses were repeated every week and the total number of courses was 39.

Patients and methods

Patients and eligibility criteria

This study was initiated in September 1999 and was closed in February 2001. Thirty patients older than 66 years entered in the study. Patients were eligible to participate in this trial if they had: metastatic cancer in progression, histologically or cytologically proven solid tumors (of known or unknown primary site), a performance status $\leqslant 3$ (Eastern Cooperative Oncology Group scale), adequate bone marrow function (neutrophil count $\geqslant 1500/mm^3$, platelet count $\geqslant 100\,000/mm^3$), hemoglobin levels > 10 g/dl, adequate hepatic function (serum bilirubin $\leqslant 1.5 \times$ the upper normal limit, ALAT and ASAT $\leqslant 3 \times$ the upper normal limit) and adequate renal function (creatinine clearance > 50 ml/min).

The primary tumor types were ovarian carcinoma (three patients), non-small cell lung cancer (eight patients), breast cancer (seven patients), prostate cancer (three patients), kidney cancer (two patients), bladder cancer (one patient), and head and neck cancer (one patient). Five patients had adenocarcinoma of unknown primary. Among the patients, 10 received prior chemotherapy, nine received prior hormone therapy and 13 had prior radiotherapy. Twelve patients had prior surgery. WHO performance status levels were 0 (two patients), 1 (13 patients), 2 (10 patients) and 3 (five patients).

The study protocol was reviewed and approved by the institutional review board. It was performed in accordance with the legal requirements and the Declaration of Helsinki, and with current European Community and US Food and Drug Administration guidelines for good clinical practice. The patients were fully informed about the procedure and the purpose of the experiment, and gave written consent.

Treatment regimen and blood sampling

All patients were undergoing single-agent vinorelbine therapy. The drug was given as a short (10 min) peripheral i.v. infusion in 100 ml normal saline solution. The administered dose was 20–30 mg/m^2. Eleven patients were entered onto the study at the 20 mg/m^2 dose level, three at the 22.5 mg/m^2 dose level, six at the 25 mg/m^2 dose level and 10 at the 30 mg/m^2 dose level. Premedications consisted of dexamethasone, methylprednisolone, metoclopramide and alizapride.

Vinorelbine was administered on a weekly basis and continued until progression of disease, severe toxicity or patient refusal. For each patient, the administered dose remained constant during the treatment period. For most of the patients only the samples collected at the first course were included; for nine patients, samples were collected after the first and the fifth courses.

Serial venous samples for drug assay were drawn in heparinized glass tubes through an indwelling catheter at the end of infusion, and 20 min, 1, 6, 12, 18, 24, 48 and 72 h after the start of infusion. However, for four patients, due to venous problems, all blood samples were not available. Each sample was immediately centrifuged (1500 *g* for 10 min) at 4°C to separate plasma, which was transferred into pre-labeled polypropylene tubes and promptly frozen at −20°C until analysis.

Analytical method

The vinorelbine concentration in plasma was assayed using a previously published high-performance

liquid chromatography method with spectrofluorimetric detection.[20] The detection was performed at 280 nm for excitation and at 360 nm for emission. The assay was sensitive and specific. The limit of quantitation was 1 μg/l. Precision was in the range 3.9–16%. Accuracy was in the range 92–120%.

Population pharmacokinetic analysis

The subjects included were allocated into a model building set (population group: 27 patients, first course) and a test-data set (validation group: three patients, first course and nine patients, fifth course). Potential explanatory covariables such as patients' age, weight, height, body area and gender were included in the original data files.

Pharmacokinetic analysis was performed using the non-linear mixed-effect modeling approach as implemented in the NONMEM computer program (version 5.1)[21] through the Visual-NM graphical interface.[22] The population characteristics of the pharmacokinetic parameters (fixed and random effects) were estimated using the FO method using the subroutines ADVAN-5 and TRANS-1 from the library of programs provided with the NONMEM-PREDPP package.

Pharmacostatistical model. As previously published,[15] an open three-compartment pharmacokinetic model with zero-order input rate was used to describe the kinetics of vinorelbine. The basic parameters (θ) considered in the population analysis were total body clearance (CL), initial volume of distribution (V), transfer rate constants (k_{21} and k_{31}), distribution rate (α) and elimination rate (β).

Secondary pharmacokinetic parameters were calculated from the individual (Bayesian estimates) primary pharmacokinetic parameters. The area under concentration–time curves was computed as AUC=dose/CL, the elimination half-life ($t_{1/2\text{elim}}$) was computed as $t_{1/2\text{elim}}=0.693/\beta$ and the volume at the end of the distributive phase ($V_{d\beta}$) was calculated as $V_{d\beta}=\text{CL}/\beta$.

The interpatient variability of pharmacokinetic parameters was assessed according to a proportional error model associated with each fixed effect parameter. The error of the concentration measurements of each individual was modeled by a combined additive and proportional model.

The predicted concentrations (IPRED) were computed, for each individual, using the empirical Bayes estimate of the pharmacokinetic parameters using the POSTHOC option in the NONMEM program.

Estimation of population parameters. Data analysis was performed using a three-step approach. In step 1, the population parameters (fixed and random effects) together with the individual posterior estimates were computed assuming that no dependency existed between the pharmacokinetic parameters and the covariates. In step 2, the influence of covariates was first assessed by plotting individual empirical Bayesian pharmacokinetic estimates against all the preselected potential covariates, i.e. gender, age, weight, height and body area. Then, each selected covariate was added to the model and tested for statistical significance [χ^2-test on the change in the objective function (OF)]. In step 3, accepted covariates were added to the model and the population pharmacokinetic parameters were estimated.

Model acceptance. The adequacy of the model to the data was evaluated by using graphics and descriptive statistics. Individual predicted concentrations (IPRED) were plotted versus observed concentrations (DV), and results were compared to the reference line of slope=1 and intercept=0.

Performance of Bayesian individual parameter estimates

Twelve courses not included in the calculation of population parameters were used to evaluate the performance of the Bayesian estimation. In all of these patients, nine blood samples were drawn. Individual pharmacokinetic parameters were computed using Bayesian estimation procedure. From the resulting individualized parameter values, AUC, $t_{1/2\text{elim}}$, $V_{d\beta}$ and vinorelbine concentrations in plasma at each sampling time (IPRED) were calculated for each patient.

Computing of a limited-sampling strategy

Two sampling times are usually required to estimate CL and V.[23] The first sample should be taken as early as possible after the end of the infusion and the other as late as possible.[24] On the other hand, patients being outpatients, it is very interesting to limit the duration of hospitalization to maximum of 2 days and the number of blood samples to two or three. All these sampling times were chosen because they could be integrated in clinical practice and in order to preserve the quality of life of the patient. Consequently, the following four sampling strategies were: (i) three sampling times with an observation

time up to 24 h after the start of infusion (10 min, 6 or 12 and 24 h); (ii) three sampling times with an observation time up to 48 h after the start of infusion (10 min, 6 or 12 and 48 h); (iii) two sampling times with an observation time up to 24 h after the start of infusion (10 min and 24 h); (iv) two sampling times with an observation time up to 48 h after the start of infusion (10 min and 48 h). In this assessment, the limited-sampling protocol published by Sabot *et al.*[13] was also tested (i.e. 1–6–24 h; 6–24 h). Thus, in the validation group eight files were generated from the original data file (nine blood samplings): end of infusion–6–48 h, end of infusion–12–48 h, end of infusion–6–24 h, end of infusion–12–24 h, end of infusion–24 h, end of infusion–48 h, 6–24 h and 1–6–24 h. Individual pharmacokinetic parameters were estimated based on Bayesian estimation and limited number of samplings.

Statistical analysis

The performance of Bayesian estimation was assessed in the validation group (12 patients with nine blood samplings) by comparing the observed concentrations (DV) to the ones estimated using the Bayesian approach (IPRED) using bias and precision.[25,26] Confidence interval for bias was computed and the *t*-test was used to compare the bias to 0.

To evaluate the reliability of the parameter estimates using a limited-sampling protocol, for each combination, individual pharmacokinetic parameters estimated using a Bayesian methodology and a limited-sampling strategy were compared to the ones estimated using a Bayesian methodology and the entire set of data. The CL and $t_{1/2elim}$ were only considered for this purpose due to their clinical interest. Moreover, predicted concentrations were compared to the observed concentrations. These comparisons were performed by computing the bias and the precision.

Results

Population pharmacokinetic parameters

The population included 27 patients and the pharmacokinetic database consisted of 232 vinorelbine concentrations. The basic pharmacokinetic parameters (before inclusion of covariates) are shown in Table 1. From the population characteristics computed in step 1, it can be seen that α is the parameter that exhibited the lowest coefficient of variation (CV ~ 10%) and *V* the highest (CV ~ 62%). In step 2, a linear correlation was found between patient age's and CL ($r=-0.66$, $p=0.000233$) (Figure 1). In step 3, final population parameters are computed accounting for the relationship between age and CL. The inclusion of this second stage model significantly improved the fit of the basic model and provided a substantial decrease in unexplained clearance interindividual variability (Table 1). The difference in objective function between the full model and the basic model was: OF=38.1, $p<0.001$. The error of estimate ranged from 5.2 to 29.7%.

Secondary pharmacokinetic parameters such as AUC (normalized to a 30 mg/m^2 dose), $t_{1/2elim}$ and

Table 1. Population pharmacokinetic parameters of vinorelbine

Parameters	Population parameters computed from 27 patients (27 courses) (population group)				Population parameters computed from all chemotherapy courses ($n=39$)	
	Without covariate (step 1)		With covariate (step 3)		With covariate (step 3)	
	Population mean	Interindividual variability, (CV%)	Population mean	Interindividual variability, (CV%)	Population mean	Interindividual variability, (CV%)
V (l)	18.2	61.8	16.6 (16.7%)	64.0	20.9 (11.1%)	69.6
CL (l/h)	45.5	40.6	47.1 (6.6%)	31.7	42.1 (5.9%)	35.1
			3.36 (29.7%)		2.10 (36%)	
α (h^{-1})	0.444	9.9	0.431 (5.2%)	6.84	0.441 (4.8%)	11.9
β (h^{-1})	0.0162	31.6	0.0167 (8.7%)	25.0	0.0175 (6.2%)	35.4
k_{21} (h^{-1})	0.865	29.4	0.776 (7.2%)	20.0	0.767 (7.2%)	22.7
k_{31} (h^{-1})	0.0352	20.0	0.0346 (7.7%)	15.2	0.0384 (6.3%)	25.1
Residual variability	σ_{ε_1}: 14.1%; σ_{ε_2}: 33.9%		σ_{ε_1}: 14.9%; σ_{ε_2}: 34.9%		σ_{ε_1}: 11.2%; σ_{ε_2}: 24.4%	
Objective function	984.3		946.2		1443	

Values in parentheses are the error of estimates expressed as coefficient of variation.

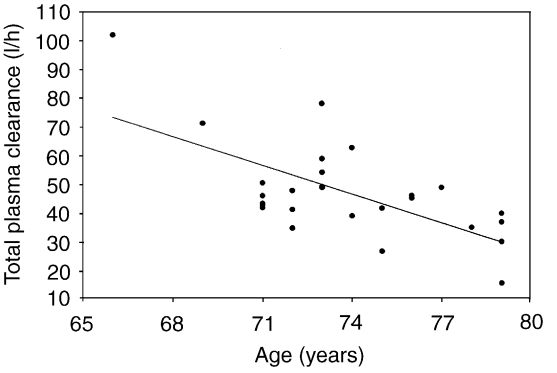

Figure 1. Linear dependency between clearance and age.

$V_{d\beta}$ were calculated from the primary pharmacokinetic parameters (CL, V, k_{21}, k_{31}, α and β). Mean values of these secondary parameters calculated by Bayesian estimation were 1215.5 ± 514.9 μg h/l (469–3378 μg h/l), 41.6 ± 7.95 h (32.8–64.7 h) and 44.4 ± 16.3 l/kg (21.4–102.5 l/kg), respectively.

The goodness of fit has been evaluated (i) by comparing the regression line estimated on the individual predicted versus observed concentration values (slope=1.01, SE=0.0053; intercept=2.18 ng/ml, SE=1.79) to the reference line of slope=1 and intercept=0; no significant difference occurred (Figure 2); (ii) by comparing the bias (−3.18 with 95% confidence interval of −7.09, 0.725) to zero; a *t*-test showed that this value was not statistically different from zero; and (iii) by studying the frequency distribution histogram of the normalized residuals which reveals a distribution very close to the expected one (normal with zero mean and unitary variance).

Evaluation of the Bayesian pharmacokinetic parameter prediction

Individual pharmacokinetic parameters for the patients in the validation group were estimated using the population characteristics. The regression line between empirical Bayes predicted values and individual observed vinorelbine concentration values (108 data) did not differ significantly from the reference line of slope=1 and intercept=0. A typical posterior individual fitting is displayed in Figure 3. Bias (−4.99 ng/ml) was not statistically different from zero (*t*-test) and the 95% confidence interval included the zero value (−11.0/1.05). We can also note that the precision on the concentration prediction (32.3 ng/ml) remains lower than the interindividual standard deviation (398.2 ng/ml).

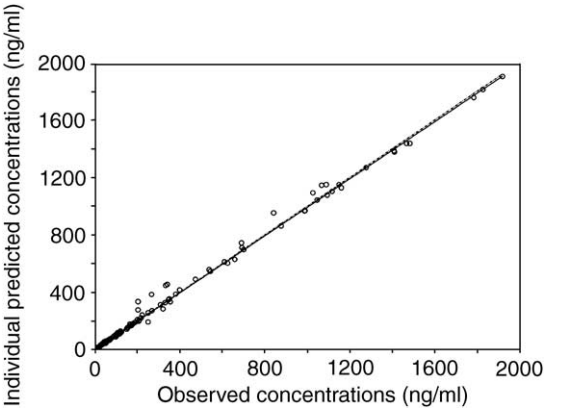

Figure 2. Relationship between individual predicted and observed plasma concentrations. The solid line represents the line of identity and the dotted line the linear regression line.

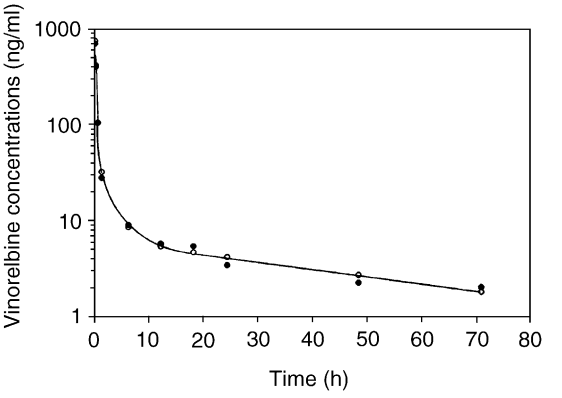

Figure 3. Plasma concentration–time profile of vinorelbine in a representative patient (validation group). Solid circles: observed plasma concentrations; open circles: individual predicted plasma concentrations.

Validation of limited-sampling strategies

Validation consisted of comparing CL and $t_{1/2elim}$ assessed by Bayesian estimation using complete plasma concentration–time data (considered as the reference) and CL and $t_{1/2elim}$ determined by Bayesian estimation with limited-sampling strategies (two or three observed sampling times.). Results are given in Table 2.

None of the limited strategies was biased except for CL estimated using samples collected at 1–6–24 h, (bias of −3.18 l/h with the confidence interval, which does not include zero). From all the other strategies, CL was well estimated (37–42 l/h) with the same degree of variability between subjects (37–41%) than the reference value (39.2 l/h, CV: 36%). Concerning

Table 2. Predictive performance of Bayesian estimation of CL, $t_{1/2elim}$, and vinorelbine concentrations with the different sampling strategies

Sampling times (h)	CL (l/h)			$t_{1/2\,elim}$ (h)			Concentrations (ng/ml)		
	Mean (CV%)	Bias	Precision	Mean (CV%)	Bias	Precision	Mean (CV%)	Bias	Precision
0.166–6–48	39.9 (39.3)	−0.685 (−3.35/1.98)	4.08	42.1 (25.0)	−1.96 (−4.75/0.82)	4.63	352.8 (163.4)	1.51 (−5.03/8.05)	19.8
0.166–12–48	36.6 (38.3)	2.61 (−0.52/5.73)	5.38	39.0 (23.9)	1.14 (−1.05/3.32)	3.49	351.9 (164.7)	0.39 (−6.12/6.90)	19.6
0.166–6–24	39.9 (38.2)	−0.659 (−3.47/2.15)	4.28	40.5 (16.7)	−0.322 (−4.45/3.80)	6.22	344.1 (165.8)	1.58 (−4.97/8.13)	20.1
0.166–12–24	37.4 (38.2)	1.79 (−1.40/4.98)	5.12	37.8 (13.0)	2.30 (−2.27/6.88)	7.26	352.9 (166.3)	0.785 (−5.88/7.45)	20.1
0.166–24	39.0 (38.2)	0.18 (−2.58/2.94)	4.16	38.8 (11.6)	1.36 (−4.39/7.12)	8.78	522.2 (123.2)	2.96 (−7.29/13.2)	23.9
0.166–48	39.3 (40.6)	−0.106 (−3.65/3.44)	5.35	39.7 (16.5)	0.44 (−4.27/5.14)	7.11	520.7 (123.7)	3.45 (−6.42/13.3)	23.2
6–24	41.7 (37.3)	−2.53 (−5.59/0.52)	5.25	41.4 (12.8)	−1.27 (−6.01/3.46)	7.25	10.4 (60.1)	−0.114 (−0.45/0.23)	0.816
1–6–24	39.0 (35.9)	−3.18 (−6.14/−0.22)	5.48	42.3 (12.2)	−2.14 (−7.26/2.98)	8.01	37.1 (172.2)	−0.881 (−1.75/−0.01)	2.78

Reference values: CL, 39.2 $l\,h^{-1}$ (CV: 35.9%); $t_{1/2\,elim}$, 40.1 h (CV: 28.5%).

the elimination half-life, the use of three sampling times with an observation time up to 48 h after the start of infusion give the better results. The other sampling strategies decreased the interindividual variability of this parameter. Precision was quite good for all the strategies, ranging from 4.1 to 5.5 l/h for CL and from 3.5 to 8.8 h for $t_{1/2elim}$.

Furthermore, vinorelbine plasma concentrations were computed at each sampling time for each patient using the individual parameter estimates. In general, the estimation of vinorelbine concentrations was not biased except when the following samples, 1–6–24 h, were considered (Table 2).

The schedules with three sampling times (end of infusion, 6 and 48 h or end of infusion, 12 and 48 h) had very good performances. However, when the chemotherapy started at the end of the morning or at the beginning of the afternoon, a sampling time 12 h after the start of infusion was not acceptable for the patient. Thus, Bayesian estimation with three measured levels (at the end of infusion, and at 6 and 48 h after the start of infusion) can be selected, because it allows adequate estimation of clearance, elimination half-life and vinorelbine concentrations with non-significant bias.

Final population pharmacokinetic parameters

In a last step, population pharmacokinetic parameters (including the error on each population parameter estimate) were re-estimated using all individuals (30 patients and 39 kinetics) (Table 1). Mean values of the secondary parameters calculated by Bayesian estimation were AUC (normalized to a 30 mg/m^2 dose) = 1285 ± 580 μg h/l (476–3282 μg h/l), $t_{1/2elim}$ = 39.7 ± 10.8 h (21.3–71.3 h) and $V_{d\beta}$ = 42.1 ± 17.1 l/kg (21.4–102.5 l/kg).

Discussion

Although an oral formulation of navelbine was recently approved (February 2001) for the treatment of non-small cell lung cancer in France, Portugal, Finland and Switzerland, this anticancer drug is widely administered i.v. Thus, the primary objective of the present study was to assess the population pharmacokinetics of vinorelbine in elderly patients after i.v. administration. Then, using these estimates, a limited-sampling strategy to estimate vinorelbine plasma clearance and vinorelbine elimination half-life was developed.

Today, the effective treatment of cancer in the elderly is becoming an important issue. Indeed,

according to Hutchins *et al.*,[17] by 2030, the number of persons over the age of 65 years will have doubled and the number of persons over the age of 85 years will have quadrupled. Because of the relatively high risk of cancer in these populations, a high prevalence of cases of cancer will occur in the future. However, for a lot of drugs, no practical guidelines are available to insure an appropriate treatment policy for this population of cancer patients.

Since hepatic function might be altered in aging patients, the pharmacokinetic parameters of vinorelbine, a drug for which the elimination via biliary excretion represents 70–80% of the administered dose,[4] could be modified. Consequently, the assessment of interpatient pharmacokinetic variability is thought to be of central importance to establish optimal and safe dosage recommendations for the clinician. In a recent paper,[15] we have studied the pharmacokinetic properties of vinorelbine in patients older than 65 years. Despite the limited number of patients included, we have found a correlation between patient ages and vinorelbine total clearance. Moreover, a reduction in vinorelbine clearance by 35–40% was observed in patients aged 70 years and older when compared to average clearance values in previous published studies carried out in patients under 65 years.[2,9,10,13]

Thus, in the present paper, vinorelbine population characteristics were estimated from 27 elderly patients (first chemotherapy course) according to an open three-compartment model using NONMEM. Covariate model building was performed using NONMEM and exploratory regression analyses based on individual estimates. Both analyses led to very similar findings, vinorelbine total clearance was shown to be statistically correlated with age. However, from the results reported in Figure 1, a great part of the variation of CL is explained by the variation of age between 66 and 70 years. The other covariates did not explain statistically part of the interindividual variability on pharmacokinetic parameters. The performance of the Bayesian estimation was evaluated using the complete plasma concentration–time data from nine patients (fifth course) and three patients (first course) not included in the calculation of population parameters. The low values of the bias (−4.99 ng/ml with the confidence interval, which included zero) and of the precision (32.3 ng/ml, lower than the interindividual standard deviation, 398.2 ng/ml) on the concentration prediction showed that the population characteristics allowed a good prediction of individual pharmacokinetic parameters in very different subjects belonging to the same population. Indeed, in this group of 12 patients CL ranged from 15.4 to 63.6 l/h and $t_{1/2\text{elim}}$ from 26.7 to 64.7 h.

In this paper different sampling strategies were investigated for the estimation of vinorelbine CL and $t_{1/2\text{elim}}$ using a Bayesian approach. Indeed, CL (from which AUC can be computed) is a good predictor of several toxicity end points during vinorelbine treatment (particularly neutropenia[13]) and $t_{1/2\text{elim}}$ is a good predictor of the drug accumulation process since this drug is administered on a weekly basis. Eight different protocols were tested, among them those published by Sabot *et al.*[13] (6–24 h and 1–6–24 h). For all of the limited-sampling strategies tested, except when the following three samples, 1–6–24 h, were taken, CL has been found well estimated, with the same degree of variability between subject, when compared with the reference value. Concerning $t_{1/2\text{elim}}$, the use of three sampling times with an observation time up to 48 h after the start of infusion gives the better results. In the other cases, $t_{1/2\text{elim}}$ was overestimated for low $t_{1/2\text{elim}}$ values and underestimated for high $t_{1/2\text{elim}}$ values.

A three sampling times strategy (end of infusion, and 6 and 48 h after the start of infusion) was finally retained as the optimal one. The last blood sample can be drawn at the patient's home. This choice not only enables precise and unbiased CL and $t_{1/2\text{elim}}$ estimates, but also present practicality advantages for the patient's comfort.

In a last step, vinorelbine pharmacokinetic parameters were estimated using all kinetics (39 kinetics from 30 patients). The computed population parameters were of the same order of magnitude than those computed from the 27 patients.

Conclusion

Vinorelbine clearance decreasing by 35–40% in patients aged 70 years old and older compared to younger patients, and with AUC being a good predictor of several toxicity end points during vinorelbine treatment,[3,15] the limited-sampling strategy proposed in this paper to estimate individual vinorelbine pharmacokinetic parameters may be clinically relevant.

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