Bayesian Estimate of Vinorelbine Pharmacokinetic Parameters in Elderly Patients with Advanced Metastatic Cancer

Amélie Gauvin, Frédéric Pinguet, Stéphane Culin, Cécile Astre, Roberto Gomeni, and Françoise Bressolle

Oncopharmacology Department, Pharmacy Service [A. G., F. P., C. A., F. B.] and Department of Medicine [S. C.], Anticancer Center, 34298 Montpellier, France, and Clinical Pharmacokinetic Laboratory, Faculty of Pharmacy, University Montpellier I, 34060 Montpellier, France [R. G., F. B.]

ABSTRACT

The objective of the present study was to determine the pharmacokinetic profile of vinorelbine in patients 65 years or older with metastatic cancer in progression. Twelve patients were enrolled in this study. Vinorelbine was administered by a 10-min continuous infusion at a dose of 20–30 mg/m² through a central venous catheter. Chemotherapy was repeated weekly. A total of 46 courses of vinorelbine was studied. Each patient underwent pharmacokinetic evaluation during the first cycle of treatment. Toxicity evaluation was carried out before each course of chemotherapy. Plasma vinorelbine determinations were performed by high-performance liquid chromatography with spectrofluorometric detection. A Bayesian estimation of individual pharmacokinetic parameters was carried out using the nonlinear mixed-effect modeling approach as implemented in the NONMEM computer program. An open three-compartment pharmacokinetic model with a zero order input rate was used to describe the kinetics of vinorelbine. Area under the plasma-concentration time curve (AUC) normalized to a 30 mg/m² administered dose averaged 0.89 mg/liter × h (coefficient of variation = 23.7%). The total plasma clearance averaged 0.93 liter/h/kg (0.61–1.83 liter/h/kg; coefficient of variation = 38.6%). The elimination half-life was 38.1 ± 5.8 h. A high correlation was found between patient age and total clearance (r = −0.8; P < 0.001). The main hematological toxicity observed was anemia in 11 patients. Neutropenia occurred in 50% of patients. Significant correlations were found between AUC and the decrease in the hemoglobin level (r = 0.60) and between AUC and the decrease in the neutrophil count (r = 0.66). Thrombocytopenia was observed in only one patient. In conclusion, the age-related decrease in clearance found in this study supports the design of a Phase I study of vinorelbine in patients older than 65 years or perhaps 70 years.

INTRODUCTION

Vinorelbine is a semisynthetic alkaloid that differs chemically from vinblastine by a modification on the catharanthine moiety of the molecule. Elimination via biliary excretion represents 70–80% of the administered dose (1). Vinorelbine is cytotoxic because it inhibits the polymerization of tubulin into microtubules and therefore prevents the formation of the mitotic spindle (2). Vinorelbine has antitumor activity against a wide spectrum of murine and human cell lines in vitro and in vivo, particularly against non-small cell lung cancer lines (3). In clinical trials of single-agent vinorelbine as a first-line therapy, vinorelbine was generally well tolerated, and response rates of 40–60% were observed in patients with metastatic breast cancer (4, 5). As a second- or third-line chemotherapy, this drug produced objective response rates of about 20–30% (4–6). Vinorelbine does not produce the subjective toxicities associated with many chemotherapeutic agents, the cardiotoxicity associated with anthracyclines, or the myalgia or neurotoxicity associated with paclitaxel. This drug is an attractive candidate for chemotherapy in elderly patients. In a recent study, Vogel et al. (7) reported that vinorelbine appears to offer a promising alternative for the management of advanced breast cancer in elderly patients. Indeed, response rates, tolerability, and dose intensity approximated that reported for women who were not age-restricted. The dose-limiting toxicity was neutropenia; hematological toxicity was minimal.

Several studies have examined the pharmacokinetic profile of vinorelbine in patients with various types of cancer (8–18). The first studies were performed in humans using radioactive assays (8–10) or a radioimmunoassay (10). A wide interpatient variability in pharmacokinetic parameters was found. The total clearance was 0.8–1.5 liters/h/kg. Some discrepancies appear in the determination of the elimination half-life and the steady-state value of distribution. According to the study, the volume of distribution ranged from 23–75.6 liters/kg, and the elimination half-life values ranged from 18–48 h (8, 9, 11–18). However, higher elimination half-life values of 56.5 and 79.8 h have been reported (10, 12). Few studies have examined the pharmacokinetic profile of vinorelbine in elderly patients because the hepatic metabolism of antineoplastic drugs might be altered in this patient population. Only Sorio et al. (17) performed a pharmacokinetic study in patients older than 65 years. These authors reported an elimination half-life of 26 h for the drug and a total clearance of 1.2 liters/h/kg. The volume of distribution averaged 23.4 liters/kg. A Bayesian pharmacokinetic estimation of vinorelbine pharmacokinetic parameters in eight patients with non-small cell lung cancer has been published recently (18).

The aim of this study was to determine the pharmacoki-
nentic profile of vinorelbine in patients age 65 years or older with metastatic cancer in progression. Individual pharmacokinetic parameters were estimated using a Bayesian methodology.

PATIENTS AND METHODS

Requirements for Patient Enrollment. Twelve elderly patients (age, 65 years or older) admitted to the Medical Oncology Service of Anticancer Center (Montpellier, France) with metastatic cancer in progression were included in this study. Patients were eligible if they had histologically or cytologically proven solid tumors (of known or unknown primary site). Eligibility criteria were as follows: 

(a) a performance status of 0–3 on the WHO3 gradation scale; 
(b) adequate bone marrow function (neutrophil count $\geq 1,500$/mm$^3$, platelet count $\geq 100,000$/mm$^3$); 
(c) hemoglobin levels $> 10$ g/dl; 
(d) adequate hepatic function (serum bilirubin $\leq 1.5 \times$ the upper normal limit, alanine aminotransferase and aspartate aminotransferase $\leq 3 \times$ the upper normal limit); and 
(e) adequate renal function (creatinine clearance $> 50$ ml/min).

Pretreatment evaluation consisted of a complete history and physical examination, routine chest X-ray, complete blood cell count, serum chemistry analysis, and neurological assessment.

The study protocol was reviewed and approved by the institutional review board. It was performed in accordance with the Declaration of Helsinki and with current European Community and United States 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. Vinorelbine was administered by a 10-min continuous infusion at a dose of 20–30 mg/m$^2$ through a central venous catheter. Chemotherapy was administered by a 10-min continuous infusion at a dose of written consent.

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Treatment Regimen and Blood Sampling. Vinorelbine was administered by a 10-min continuous infusion at a dose of 20–30 mg/m$^2$ through a central venous catheter. Chemotherapy was repeated weekly. During the first cycle of treatment, each patient underwent pharmacokinetic evaluation. Premedications consisted of dexamethasone (one patient), methylprednisolone (two patients), morphine sulphate (two patients), metoclopramide (two patients), and alizapride (four patients). Serial blood samples (5 ml) were collected from a peripheral vein in heparinized glass tubes before drug administration, at the end of infusion, and 20 min and 1, 6, 12, 18, 24, 48, and 72 h after the start of infusion. Immediately after collection, blood samples were centrifuged (1500 $\times$ g for 10 min) at 4°C; the plasma was placed in two polypropylene tubes and frozen immediately ($-20$°C) until assay.

Toxicity Evaluation. Adverse experiences, serum chemistries, and complete blood cell counting including WBC count differentially and platelet count were determined before each treatment. Physical examination, vital signs, and performance status were reevaluated every 4 weeks. Toxicity was defined according to the Cancer Therapy Evaluation Program Common Toxicity Criteria and graded 1–4.

Analytical Method. Vinorelbine concentrations in plasma were assayed by HPLC with spectrofluorometric detection using the method described by Robieux et al. (19). The detection was performed at 280 nm for excitation and at 360 nm for emission. After adding an internal standard (vinblastine) to the samples to be analyzed, the extraction procedure involved sample clean-up by liquid-liquid extraction with diethyl ether. Two calibration standards were prepared: (a) 1–50 ng/ml; (b) 10–250 ng/ml. Precision ranged from 93–105%. The limit of quantitation was 1 ng/ml; at this level, the analytical error averaged 20%.

Population Pharmacokinetic Analysis. Individual pharmacokinetic parameters were estimated using a Bayesian methodology. Such an approach avoids a possible bias in the estimation of the elimination half-life; indeed, due to venous problems, a blood sample was not drawn from four patients 72 h after drug administration.

Pharmacokinetic analyses were performed using the nonlinear mixed-effect modeling approach as implemented in the NONMEM computer program (Version 5.0; Ref. 20) through the Visual-NM graphical interface (21). The population characteristics of the pharmacokinetic parameters (fixed and random effects) were estimated using the First order conditional estimation method.

As reported previously (22), an open three-compartment pharmacokinetic model with a zero order input rate was used to describe the kinetics of vinorelbine. The six-dimensional vector $\theta$ of kinetic parameters considered in the population analysis consists of total body clearance ($C_1$), initial volume of distribution ($V_1$), the transfer rate constants ($k_{21}$ and $k_{31}$), the distribution rate ($\alpha$), and the elimination rate ($\beta$).

The elimination half-life ($t_{1/2}$ elimination), the total AUC, and the volume at the end of the distribution phase ($V_{40h}$) were calculated as follows:

$$t_{1/2} \text{elimination} = 0.693/\beta$$

(A)
Vinorelbine Pharmacokinetics in the Elderly

interindividual variability was assessed according to a proportional error model associated to each fixed effect parameter; thus, for example, the clearance (Cl) of the subject j was described by the relationship:

$$\text{Cl}_j = \text{Cl}_{mean} \cdot \exp(\eta_{\text{Cl}})$$

where Cl\text{mean} is the population mean, and \eta_{\text{Cl}} is the difference between the population Cl\text{mean} and the Cl value in subject j. \eta_{\text{Cl}} is assumed to be a Gaussian random variable with mean zero and variance \sigma_{\text{Cl}}^2. The error on the concentration measurements at the time of initiation of treatment. Six different tumoral histologies were represented. Among them, one patient had

The predicted serum concentrations (C_{\text{EST}}) were computed for each individual using the empirical Bayes estimate of the pharmacokinetic parameters using the POSTHOC option in the NONMEM program.

Statistical Analysis. To compare observed concentrations (C_{\text{OBS}}) to the ones estimated using the Bayesian approach (C_{\text{EST}}), the bias or mean predictor error was computed as follows:

$$\text{Bias} = \frac{1}{N} \sum_{i=1}^{N} [C_{\text{OBS}}(i) - C_{\text{EST}}(i)]$$

In this expression, the index i refers to the concentration number, and N is the sample size. The confidence interval for bias was also computed. The t test was used to compare the bias to 0.

A regression analysis was carried out to determine the relationship between age and total plasma clearance. Moreover, the intensities of anemia and neutropenia were correlated with the distribution phase.

RESULTS

Patient Characteristics. The main clinical characteristics of the 12 patients entering this study are listed in Table 1. Mean age was 74 years. All patients had advanced-stage disease at the time of initiation of treatment. Six different tumoral histologies were represented. Among them, one patient had

Table 3 Population pharmacokinetic parameters of vinorelbine

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Population mean</th>
<th>Interindividual variability (CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 (liters)</td>
<td>30.3</td>
<td>59.6</td>
</tr>
<tr>
<td>Cl (liters/h)</td>
<td>61.2</td>
<td>27.8</td>
</tr>
<tr>
<td>\alpha (h^{-1})</td>
<td>0.426</td>
<td>12.8</td>
</tr>
<tr>
<td>\beta (h^{-1})</td>
<td>0.0182</td>
<td>18.1</td>
</tr>
<tr>
<td>\kappa_2 (h^{-1})</td>
<td>0.853</td>
<td>24.4</td>
</tr>
<tr>
<td>\kappa_3 (h^{-1})</td>
<td>0.0362</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Residual interindivdual CV: (\sigma_{V1}; 12.7%; \sigma_{Cl}; 0.05%).

V1, initial volume of distribution; Cl, total body clearance; \kappa_2 and \kappa_3, transfer rate constants; \alpha, distribution rate; \beta, elimination rate.

AUC = dose/Cl

$$V_{\text{dih}} = \frac{\text{Cl}}{\beta}$$

Interindividual variability was assessed according to a proportional error model associated to each fixed effect parameter; thus, for example, the clearance (Cl) of the subject j was described by the relationship:

$$\text{Cl}_j = \text{Cl}_{mean} \cdot \exp(\eta_{\text{Cl}})$$

where \text{Cl}_{mean} is the population mean, and \eta_{\text{Cl}} is the difference between the population Cl_{mean} and the Cl value in subject j. \eta_{\text{Cl}} is assumed to be a Gaussian random variable with mean zero and variance \sigma_{\text{Cl}}^2. The error on the concentration measurements at the time of initiation of treatment. Six different tumoral histologies were represented. Among them, one patient had

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RESULTS

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Table 2 Hematological toxicity

<table>
<thead>
<tr>
<th>No. of</th>
<th>Anemia grade</th>
<th>Neutropenia grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/m^2)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>30</td>
<td>9</td>
<td>34</td>
</tr>
</tbody>
</table>

* Values in parentheses are the toxicity during course 1.

Table 4 Individual pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yrs)</th>
<th>Cl (liters/h/kg)</th>
<th>t_{1/2} elimination (h)</th>
<th>Normalized AUC (\mu g/liters x h)</th>
<th>V_{dih} (liters/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>0.835</td>
<td>36.7</td>
<td>819.7</td>
<td>44.3</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
<td>0.609</td>
<td>49.7</td>
<td>1075.6</td>
<td>43.7</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>1.077</td>
<td>32.7</td>
<td>661.2</td>
<td>50.3</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>0.734</td>
<td>39.6</td>
<td>1001.9</td>
<td>42.0</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>0.948</td>
<td>36.1</td>
<td>906.1</td>
<td>49.4</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>1.833</td>
<td>40.3</td>
<td>431.5</td>
<td>106.2</td>
</tr>
<tr>
<td>7</td>
<td>79</td>
<td>0.833</td>
<td>40.5</td>
<td>911.9</td>
<td>48.7</td>
</tr>
<tr>
<td>8</td>
<td>76</td>
<td>0.670</td>
<td>32.5</td>
<td>1134.5</td>
<td>31.4</td>
</tr>
<tr>
<td>9</td>
<td>74</td>
<td>0.714</td>
<td>32.6</td>
<td>973.8</td>
<td>33.6</td>
</tr>
<tr>
<td>10</td>
<td>75</td>
<td>1.483</td>
<td>42.0</td>
<td>676.7</td>
<td>89.6</td>
</tr>
<tr>
<td>11</td>
<td>79</td>
<td>0.748</td>
<td>30.0</td>
<td>1113.9</td>
<td>32.4</td>
</tr>
<tr>
<td>12</td>
<td>78</td>
<td>0.757</td>
<td>44.8</td>
<td>1018.8</td>
<td>48.9</td>
</tr>
</tbody>
</table>
breast cancer, two patients had ovarian cancer, two patients had bladder cancer, one patient had kidney cancer, one patient had prostatic carcinoma, and three patients had non-small cell lung cancer. Two patients received prior chemotherapy, and five patients received prior radiotherapy. Performance status was 0, 1, 2, or 3 according to the patients. A total of 46 courses of chemotherapy were studied (Table 2). No patient received autologous bone marrow support or peripheral blood progenitor cells, and no granulocyte colony-stimulating factors were used during the trial.

Toxicity. All patients were evaluable for toxicity (two patients received only one course, three patients received two courses, one patient received 3 courses, two patients received 4 courses, two patients received 5 courses, one patient received 7 courses, and one patient received 10 courses). The total number of hematological toxicities encountered during this study is reported Table 2. Anemia was the main hematological toxicity, and it was observed in 11 patients (grade 4 in one patient, grade 3 in two patients, grade 2 in three patients, and grade 1 in eight patients). Neutropenia was observed in 50% of patients (grade 4 in five patients, grade 3 in two patients, grade 2 in two patients, and grade 1 in one patient). The median times to anemia and neutrophil nadirs have been computed from 11 patients (patient 5 was an outpatient for whom these data were not available). It occurred at 8.1 days (range, 2–17 days) for anemia and at 8.6 days (range, 1–14 days) for neutropenia. The median times to recovery to pretreatment values were 7.2 days (range, 4–7 days) and 7.3 days (range, 1–14 days), respectively. Episodes of fever were reported in two patients with grade 4 neutropenia; one of them developed sepsis related to vinorelbine.

Thrombocytopenia was observed only in one patient (patient 12, who had received three courses). Grade 3 occurred 13

Table 5  Pharmacokinetic parameters of vinorelbine reported in the literature

<table>
<thead>
<tr>
<th>Dose (mg/m^2)</th>
<th>Route</th>
<th>Analytical method</th>
<th>Clearance (liters/h/kg)</th>
<th>Vss (liters/kg)</th>
<th>t_1/2 elimination (h)</th>
<th>Reference no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>12–40</td>
<td>Infusion</td>
<td>Radioactive</td>
<td>0.95</td>
<td>61.9</td>
<td>32.7</td>
<td>8</td>
</tr>
<tr>
<td>15</td>
<td>Infusion</td>
<td>Radioimmunoassay</td>
<td>0.83</td>
<td>28.6</td>
<td>37.3</td>
<td>9</td>
</tr>
<tr>
<td>30</td>
<td>Infusion</td>
<td>Radioactive and radioimmunoassay</td>
<td>0.42</td>
<td>ND*</td>
<td>79.8</td>
<td>10</td>
</tr>
<tr>
<td>30</td>
<td>Infusion</td>
<td>Radioimmunoassay</td>
<td>1.26</td>
<td>75.6</td>
<td>42.1</td>
<td>11</td>
</tr>
<tr>
<td>30</td>
<td>Infusion</td>
<td>HPLC</td>
<td>0.43–1.45</td>
<td>27.4–45.9</td>
<td>24.2–56.5</td>
<td>12</td>
</tr>
<tr>
<td>30 (50–180 mg)</td>
<td>Oral</td>
<td>Radioimmunoassay</td>
<td>1.28</td>
<td>47.6</td>
<td>44.7</td>
<td>13</td>
</tr>
<tr>
<td>30</td>
<td>Infusion</td>
<td>HPLC</td>
<td>1.21</td>
<td>19</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>30 (130 mg)</td>
<td>Oral</td>
<td>Radioimmunoassay</td>
<td>ND</td>
<td>ND</td>
<td>48.5</td>
<td>15</td>
</tr>
<tr>
<td>30</td>
<td>Infusion</td>
<td>Radioimmunoassay</td>
<td>1.24</td>
<td>26</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>30</td>
<td>Infusion</td>
<td>HPLC</td>
<td>1.20</td>
<td>23.4</td>
<td>26.2</td>
<td>17</td>
</tr>
<tr>
<td>30</td>
<td>Infusion</td>
<td>HPLC</td>
<td>0.98</td>
<td>38.4</td>
<td>42.8</td>
<td>18</td>
</tr>
<tr>
<td>20–30</td>
<td>Infusion</td>
<td>HPLC</td>
<td>0.95</td>
<td>51.7^a</td>
<td>38.1</td>
<td></td>
</tr>
</tbody>
</table>

* ND, not determined.
^a Computed from CL/l.

Fig. 1 Scatter plot of individual C1 values (Bayesian estimates) versus age.
days after the second course, and grade 2 occurred 3 days after the third course.

Nonhematological toxicity was uncommon and consisted of asthenia (five patients), nausea and vomiting (three patients), diarrhea (two patients), mucitis (one patient), and hepatocytotoxicity (one patient). Seven patients had no extramedullary toxicity.

There was no evidence of cumulative toxicity, and one patient had no side effects at all.

Six patients died within 14–60 days of treatment. Five died from progression of cancer. The sixth death was the only death considered to be drug related; the patient developed sepsis and succumbed to cardiac failure.

Pharmacokinetic Characteristics of Vinorelbine.

The population database consisted of 107 vinorelbine concentrations. The population parameters [fixed effect, C1, V1, α, β, k21, and k32; random effect, σ(C1), σ(V1), σ(α), σ(β), σ(k21), and σ(k32)] are given in Table 3. The goodness of fit has been evaluated by (a) comparing the regression line estimated on the predicted versus observed concentration values (slope = 0.993, SE = 0.0049; intercept = 2.82 ng/ml, SE = 1.52) to the reference line of slope = 1 and intercept = 0 (no significant difference occurred); (b) comparing the bias (−1.69 with 95% confidence interval of −4.48−1.11) to zero using the t test (this value was not statistically different from zero).

The main individual pharmacokinetic parameters are reported in Table 4; interpatient variability was important for all these parameters. AUC normalized to a 30 mg/m² administered dose averaged 0.89 mg/liter × h (CV = 23.7%). The total plasma clearance averaged 0.93 liter/h/kg (CV = 38.6%), and the volume of distribution at the end of the distribution phase (Vdab) was 51.7 liters/kg (CV = 44%). The half-life of the terminal observed phase was 38.1 ± 5.8 h. A high correlation was found between patient age and the total clearance (r = −0.8, P = 0.0017; Fig. 1); excluding one patient with an age of 66 years and a higher clearance value of 120 liters/h resulted in a lower correlation (r = 0.76, P = 0.0068). In patients with an age of ≥70 years, the mean clearance was 0.82 liter/h/kg.

Significant correlations were found between AUC and the decrease in hemoglobin level (r = 0.60, P = 0.0479) and between AUC and the decrease in neutrophil count (r = 0.66, P = 0.0256). No relationship was found between vinorelbine concentration at the end of infusion and side effects.

DISCUSSION

Little is known about the pharmacokinetics of vinorelbine in elderly patients. Only Sorio et al. (17) studied the pharmacokinetics of this drug in patients older than 65 years. In the present study, an empirical Bayes methodology was used to estimate individual pharmacokinetic parameters. Such an approach avoided a possible bias in the estimation of the elimination half-life (i.e., underestimation). Indeed, in four patients, samples could not be obtained at the last sampling time (i.e., 72 h) because of venous problems. Table 5 compares the results of the present study with those reported previously by others (8–18). In the present study, the elimination half-life (38 h) is very close to the values reported by Rhamani et al. (9), Jehl et al. (11), Marquet et al. (13), and Sabot et al. (18). In spite of the small number of patients included, a correlation was found between patient age and vinorelbine total clearance. A reduction in vinorelbine clearance by 35–40% was noted in patients ≥70 years old when compared with average clearance values in the previous studies listed in Table 5 (13, 14, 16, 17). This observation supports the design of a Phase I study of vinorelbine in patients older than 65 years or perhaps 70 years.

The main hematological toxicity was anemia, which was observed in 11 patients. Leukopenia occurred in 50% of patients. The AUC correlated with hematological toxicity. These results were in good agreement with those of Khayat et al. (25); indeed, these authors found that a higher systemic exposure results in a higher risk for severe hematological toxicity. As reported for other anticancer drugs, AUC-guided dosing of vinorelbine has a prominent role, particularly in this population of patients.

REFERENCES

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