Cancer Chemother Pharmacol (2005) 56: 578–584
DOI 10.1007/s00280-005-1025-0

ORIGINAL ARTICLE

**Richard M. Lush · Jeannine S. McCune · Leticia Tetteh
John A. Thompson · J. J. Mahany · Linda Garland
A. Benjamin. Suttle · Daniel M. Sullivan**

The absolute bioavailability of oral vinorelbine in patients with solid tumors

Received: 7 December 2004 / Accepted: 20 December 2004 / Published online: 7 July 2005

Abstract Due to advances in the methods used to quantitate vinorelbine, this study was conducted to characterize fully the bioavailability of an oral dosage form of vinorelbine. Twenty-seven eligible patients with solid tumors were enrolled onto this study and were treated in a randomized crossover design to receive either 70 mg/m^2 orally or 30 mg/m^2 intravenously followed by the alternative treatment one week later. Vinorelbine was administered orally as a soft-gelatin capsule. Pharmacokinetic sampling was carried out for 7 days following each dose. Whole blood vinorelbine concentrations were measured using a sensitive LC/MS/MS method. The data from patients were excluded if they vomited within 3 h after the oral dose. *Results*: Three subjects were removed from study following the first dose due to safety reasons. Of the remaining 24 subjects, five experienced vomiting within 3 h of oral dosing. Total body clearance calculated from the intravenous dose was 43.65 L/h (±10.9) and the terminal half-life was estimated to be 49 h. Using complete data from the remaining 19 subjects, the mean absolute bioavailability of the oral dosage formulation of vinorelbine was calculated to be 33% (±18%). In conclusion we have characterized the pharmacokinetics of both orally administered and intravenous vinorelbine over 7 days after administration and have determined the mean oral bioavailability of this oral formulation to be 33%.

Keywords Pharmacokinetics · Vinorelbine · Bioavailability · Elderly

R. M. Lush (✉) · L. Tetteh · J. J. Mahany · L. Garland
D. M. Sullivan
Experimental Therapeutics Program,
H. Lee Moffitt Cancer Center and Research Institute,
and the Department of Interdisciplinary Oncology,
University of South Florida, 12902 Magnolia Drive,
Tampa, FL, 33612
E-mail: lushrm@moffitt.usf.edu

J. S. McCune · J. A. Thompson
University of Washington, Box 357630, Seattle, WA, 98195

Present address: L. Garland
University of Arizona Cancer Center, 1515 N. Campbell Ave.,
P.O. Box 245024, Tucson, AZ, 85724

A. B. Suttle
Clinical Pharmacology, GlaxoSmithKline,
Research Triangle Park, NC

Introduction

Navelbine (vinorelbine tartate) is a semi-synthetic vinca alkaloid with a modified catharanthine moiety, which causes dissolution of the mitotic spindle apparatus and thus, metaphase arrest in dividing cells. Navelbine was approved by the US Food and Drug Administration as an intravenous formulation in 1994 for the treatment of non-small-cell lung cancer (NSCLC). Trials evaluating single agent vinorelbine have been completed in ovarian, esophageal, head and neck, and breast cancer with reported response rates of 11–30% [1, 2, 4, 5, 17]. In addition, vinorelbine has been shown to have activity following oral administration [10, 21, 22, 24]. The chemical structure for vinorelbine tartrate is shown in Fig. 1.

The soft gelatin capsules used in the present study are the third oral formulation of vinorelbine. The first oral dosage form was a powder-filled, hard gelatin capsule [7, 15, 19]. A liquid-filled, soft gelatin capsule formulation was developed in 1990 and clinical trials with this formulation indicated that oral vinorelbine had safety and efficacy profiles similar to the intravenous formulation [21] with a mean absolute bioavailability of 27±12% [16]. A third oral dosage form was developed in 1994 by Pierre Fabre Medicament (Paris, France). This new formulation of soft gelatin capsules includes the same ingredients as the earlier 1990 formulation, with the exception of the ratio of excipients.

The oral bioavailability of the 1994 formulation was originally reported to be approximately 43 ± 14% [13]. Unfortunately, the terminal elimination phase was not characterized adequately after oral administration, thus requiring the calculation of bioavailability to be made

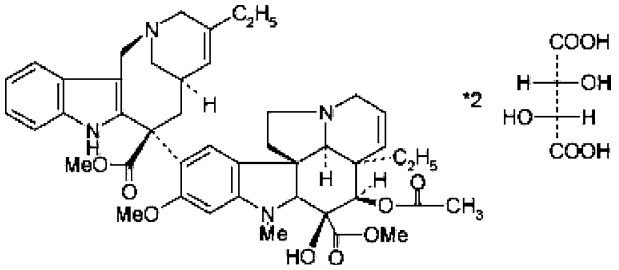

Fig. 1 Chemical structure of vinorelbine tartrate

solely on AUC_{last}(area under the curve calculated to the last measurable time point). Since completion of this study, a new LC/MS/MS assay has been established, with an approximately 4 to 10-fold increase in sensitivity over previous HPLC methods [20]. This assay provides the ability to quantitate pharmacokinetic samples for an extended period, thus allowing the adequate characterization of the terminal phase of the vinorelbine concentration–time profile following oral and intravenous administration.

It is of particular interest to characterize adequately the exposure of oral vinorelbine compared to that of the intravenous formulation. Like other cytotoxic chemotherapeutic agents, vinorelbine has a relatively narrow therapeutic window. An intravenous dose of 25–30 mg/m^2 per week is currently used as single-agent therapy for the treatment of NSCLC, breast cancer, and other solid tumors [4, 5, 8, 10, 17, 22, 24]. An oral dose of 80 mg/m^2 per week has been shown to be the Phase II recommended dose in some studies [3]. However, subsequent studies found this dose to cause neutropenia in a large portion of patients during the first three cycles and have recommended administration of 60 mg/m^2 weekly for the first 3 weeks followed by 80 mg/m^2 weekly [6, 7].

A strong correlation between hematologic toxicity, as assessed by the percent change between baseline white blood count (WBC) and WBC nadir, and AUC_{last} has been demonstrated for both IV and oral dosage forms [3, 13]. Similar relationships for granulocytes and platelets also have been demonstrated. These pharmacokinetic/pharmacodynamic analyses suggest that for a given vinorelbine exposure, comparable hematologic toxicity will be observed, regardless of the route of administration. Conversely, peak concentration (C_{max}) appears to be a poor predictor for the occurrence of hematologic toxicity.

Therefore, this study was undertaken to evaluate more thoroughly the pharmacokinetic profiles of vinorelbine after administration of an intravenous dose of 30 mg/m^2 and an oral dose of 70 mg/m^2, in order to calculate the absolute bioavailability of the oral form.

Additional endpoints were to evaluate the intersubject variability in the pharmacokinetics of oral vinorelbine, to describe the pharmacokinetics of the active metabolite deacetylvinorelbine after oral and intravenous administration of vinorelbine, and to characterize the pharmacodynamic relationship between vinorelbine and toxicity.

Study design

This was an open label, randomized, two-center, single-dose crossover, pharmacokinetic study. Prior to study initiation, this protocol was approved by the Institutional Review Board at both the H. Lee Moffitt Cancer Center & Research Institute and the University of Washington. Written informed consent was obtained from each subject prior to study participation. Subjects were randomized to receive the first dose (day 1) either as the IV (30 mg/m^2) or as the oral (70 mg/m^2) formulation. The second dose (day 8) was administered as the opposite formulation after a 1-week washout. Intravenous vinorelbine was supplied in either 10 or 50 mg vials. Each vial contains vinorelbine tartrate equivalent to 10 mg (1-mL vial) or 50 mg (5-mL vial) vinorelbine in water for injection. No preservatives or other additives are present. Intravenous vinorelbine was administered over 20 min. Vinorelbine for oral administration was supplied as either 30 mg or 40 mg soft gelatin capsules by Glaxo Wellcome, Inc. Blood and urine samples for drug concentration analysis were collected before and throughout the 1-week period after dosing on days 1 and 8. Samples were collected predose (0), 10, 20, 40 min and 1, 3, 6, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hr after the start of the infusion. To characterize the pharmacokinetics of vinorelbine after oral dosing samples were obtained predose (0), 15, 30, 45 min and 1, 1.5, 2, 3, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168 hr after oral dosing. Urine samples were collected for 24 h after each dose on days 1 and 8.

Safety of oral and intravenous vinorelbine was evaluated after each of the two administrations. Subjects had an option to continue vinorelbine therapy with either formulation after the 2-week bioavailability study was completed.

Subjects (18–75 years of age) were eligible for this study if they had pathologically confirmed metastatic or advanced disease that might benefit from single agent vinorelbine therapy, were not pregnant and were practicing an accepted method of birth control, and had normal kidney, liver and bone marrow function (as determined by serum chemistry analysis). Subjects were ineligible if they had a disorder that altered gastrointestinal motility. Subjects requiring therapy with agents known to be metabolized by or interaction with cytochrome P450 3A were excluded from participating in this study. Patients with central nervous system metastases or baseline peripheral neuropathy (> grade 1, NCI CTC, version 2) were also excluded.

Blood and urine vinorelbine and deacetylvinorelbine concentrations were determined using a validated LC/MS/MS method described previously [20]. Briefly, blood samples were deproteinized with methanol and acetonitrile. After dilution with 40 mM ammonium acetate buffer (pH = 3), an aliquot of the final solution was injected onto an HPLC column. Urine samples were prepared by dilution prior to injection onto the HPLC

column. Separation was performed by a reversed phase Spherisorb CN 3 μm column (100×4.6 mm) for both blood and urine. The MS–MS detection was performed in multiple reaction monitoring mode with an electrospray interface in positive mode. The lower limit of quantitation of the assay in blood was 0.25 ng/mL for vinorelbine and deacetylvinorelbine. The coefficient of variation of this assay in blood at 0.25 ng/mL was less than 20% for both analytes. The coefficient of variation for quality control samples in blood was less than 10% with a bias of less than 10% at all concentrations for vinorelbine and deacetylvinorelbine. The coefficient of variation and bias for vinorelbine and deacetylvinorelbine quality control samples in urine were less than 6% at all concentrations.

Pharmacokinetic parameter estimates were calculated using noncompartmental methods [23]. Area under the curve was calculated using the log-linear trapezoidal method and extrapolated to infinity by dividing the last measured blood concentration by the terminal slope. Total body clearance was estimated by dividing the dose by the AUC after intravenous administration. The terminal elimination rate was estimated using log-linear regression of the terminal portion of the concentration–time profiles. Terminal half-life was calculated as the quotient of 0.693 and the terminal slope. The absolute bioavailability (F) was calculated as the dose-normalized ratio of $AUC_{0-\infty}$ observed after oral administration and the $AUC_{0-\infty}$observed after intravenous administration.

Results

A total of 27 patients were enrolled onto this study. Three patients failed to receive both routes of administration due to either unrelated adverse events or disease progression. One subject had a recurrence of a supraventicular tachycardia 2 days after receiving the oral formulation and was subsequently removed from the study. The second subject withdrew consent due to the frequent visit schedule of this study. The third subject developed severe intractable nausea and vomiting secondary to constipation 1 week after the first treatment. The investigator assessed this event as consistent with the subject's previous history of constipation and was not related to study therapy. Of the 24 patients who completed both phases of the study, five experienced vomiting within 3 h of oral dosing and were therefore excluded from the estimation of bioavailability. The demographic information of the 27 subjects who were enrolled in this study is presented in Table 1.

Table 1 Baseline patient characteristics

Characteristics	Mean ± SD (range)
Age (years)	56.9 ± 9.9 (40–74)
Height (cm)	170.7 ± 9.5 (150–193)
Weight (kg)	78.39 ± 11.54 (56.6–99)
KPS	91.5 ± 7.7 (80–100)
Sex (M:F)	13:14
Race/ethnicity	White 26 (96%)
	Hispanic 1 (4%)

Pharmacokinetics

Mean (arithmetic) blood vinorelbine and deacetylvinorelbine concentration–time profiles are displayed in Fig. 2. Similar concentrations of vinorelbine (circles) were achieved after the two different dosage forms and doses. As demonstrated in Fig. 2, a greater amount of the dose is converted to deacetylvinorelbine after oral administration (open squares), which is likely due to the first pass metabolism of the absorbed vinorelbine through the intestine and liver.

Mean (±SD) blood vinorelbine and deacetylvinorelbine pharmacokinetic parameters are summarized in Tables 2 and 3. The mean absolute bioavailability of oral vinorelbine calculated with data from subjects who did not vomit within 3 h of oral administration was 33 ± 18% (Table 2). Pharmacokinetic parameters for vinorelbine

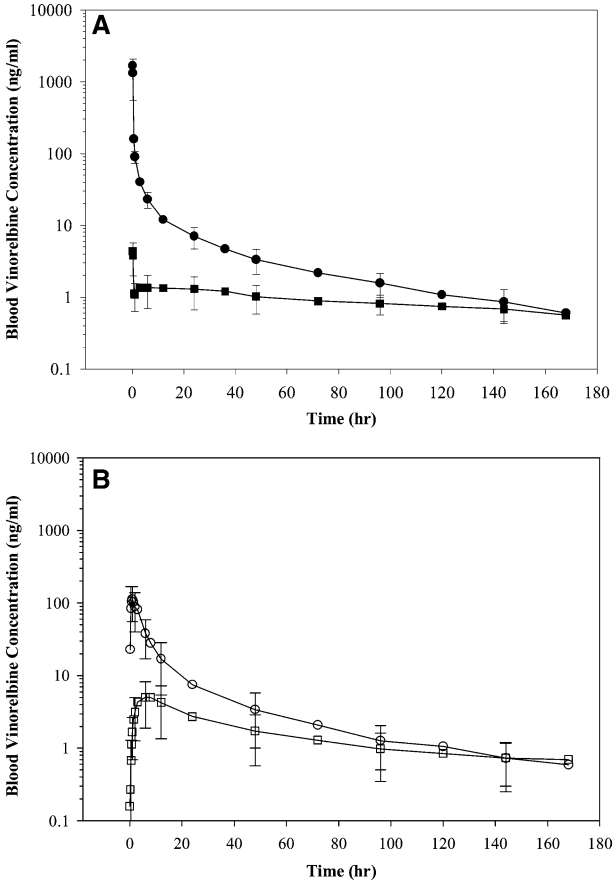

Fig. 2 Mean of (±SD) blood vinorelbine and deacetylvinorelbine concentrations over time. Panel A represents the data after the subjects were dosed with intravenous injection (30 mg/m^2, vinorelbine = *filled circle*, deacetylvinorelbine = *filled square*). Panel B represents the data after oral administration (70 mg/m^2, vinorelbine = *open circle*, deacetylvinorelbine = *open square*)

Table 2 Pharmacokinetic parameter estimates for vinorelbine*

Parameter	Intravenous	Oral
AUC $_{0-\infty}$(ng*h/mL)	1396.8 ± 380.0 (922.8–2137.2)	1061.2 ± 583.1 (273.3–2582.1)
C_{max} (ng/mL)	1877.4 ± 882.2 (547.0–4045.4)	137.9 ± 66.1 (37.8–329.3)
**T_{max} (h)	0.33 (0.17–0.42)	0.75 (0.50–3.00)
Clearance (L/h)	43.65 ± 10.86 (27.30–65.02)	NC
$T_{1/2}$ (h)	49.13 ± 10.04 (36.07–73.38)	51.06 ± 12.07 (35.66–87.23)
F (%)	NC	33 ± 18 (13–83)
Ae $_{(0-24)}$ (mg)	7.75 ± 3.51 (3.95–15.88)	4.40 ± 2.64 (2.07–11.50)
fe $_{(0-24)}$	0.19 ± 0.09 (0.10–0.43)	0.05 ± 0.03 (0.02–0.14)
Renal clearance (L/h)	8.55 ± 5.24 (3.09–21.26)	7.35 ± 4.29 (3.08–16.84)

*Data presented as arithmetic mean ± SD (range); **Median; NC = Not calculated; $AUC_{0-\infty}$ = area under the curve calculation from time 0 to infinity; C_{max} is the maximum observed concentration; T_{max} is the time of the observed maximum concentration; $T_{1/2}$ is the terminal half-life; F is the absolute bioavailability; $Ae_{(0-24)}$ is the amount of drug excreted in the urine within 24 h; $fe_{(0-24)}$ is the estimated fraction of administered dose excreted in the urine within 24 h

Table 3 Pharmacokinetic parameter estimates for deacetylvinorelbine*

Parameter	Intravenous	Oral
AUC_{0-t} (ng*h/mL)	152.1 ± 57.48 (64.3–273.3)	262 ± 163.27 (56.3–670.1)
C_{max} (ng/mL)	4.8 ± 2.4 (1.1–12.0)	5.8 ± 3.0 (1.8–12.5)
**T_{max} (h)	0.33 (0.17–24.02)	6.03 (3.00–12.00)
$T_{1/2}$ (h)	171.70 ± 64.42 (64.83–350.67)	109.09 ± 29.87 (67.90–175.98)

*Data presented as mean ± SD (range); **Median

calculated using data derived from the analysis of urine are also summarized in Table 2. Renal clearance was a minor route of elimination for vinorelbine. Approximately 20% and 5% of the dose was recovered unchanged in the urine after IV and oral administration.

The pharmacokinetic parameter estimates comparing the data obtained from subjects who were 65 years of age or older to those subjects younger than 65 are presented in Table 4. When compared using a student's *t*-test, no differences in the pharmacokinetic parameter estimates were detected between the younger and older subjects.

A significant correlation was found between the vinorelbine exposure and the percent decrease in neutrophil count. As shown in Fig. 3, vinorelbine AUC predicts the percentage decrease in neutrophils over the range of AUCs observed in this study. Significant correlations between measures of exposure (C_{max} or AUC) and reduction in the total WBC count or platelets were not found in this study.

Effect of emesis on oral absorption

Of the 24 subjects that received both oral and IV vinorelbine, five experienced emesis within the first 3 h after oral administration. Of the five subjects that experienced emesis, four subjects vomited between 2 and 3 h after oral vinorelbine administration. The shortest interval between dosing time and time of emesis was approximately 1.5 h. The range of individual bioavailability estimates in subjects who did vomit within 3 h of vinorelbine administration (0.23–0.94) was similar to the range of bioavailability values in subjects who did not vomit within 3 h of oral vinorelbine administration (0.13–0.83). These results suggest that emesis that occurred between 1.5 and 3 h after oral administration had little, if any, effect on the extent of vinorelbine oral absorption in these patients. The mean absolute bioavailability of vinorelbine calculated with data from all 24 subjects (including the five who experienced emesis within 3 h of oral administration), was 36 ± 20%.

Toxicity

Three subjects had their second course of therapy delayed. Each of these subjects had been treated with the intravenous formulation in the first week. The delays were due to granulocytopenia in two subjects and protocol noncompliance in the third subject. A summary of treatment-related adverse events (any grade) experienced by the subjects is presented in Table 5. This table presents the ten most frequent toxicities noted in the subjects. Predictably there was more gastrointestinal

Table 4 Summary of vinorelbine pharmacokinetic parameter estimates after intravenous administration based on age

	C_{max} (ng/ml)	$T_{1/2}$ (h)	$AUC_{0-\infty}$ (ng*h/mL)	Clearance (L/h)
< 65 years [n = 6]	1733.0 ± 888.2	49.89 ± 13.1	1283.15 ± 290.5	45.89 ± 8.4
≥65 years [n = 14]	2183.6 ± 803.7	52.92 ± 8.0	1672.18 ± 487.9	38.10 ± 15.3
P value	0.3231	0.5524	0.1527	0.3289

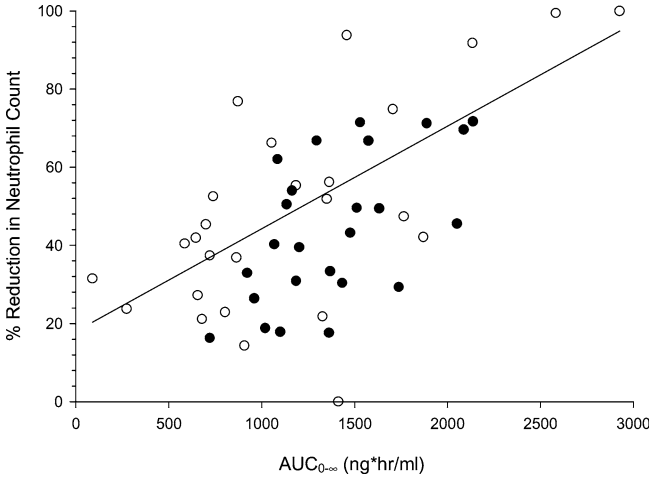

Fig. 3 Relationship between vinorelbine exposure and neutropenia. *Open circles* represent data obtained from oral administration. *Closed circles* represent data obtained after intravenous administration. Regression equation $y = 0.026x + 17.97$; $r^2 = 0.428$

toxicity (nausea, vomiting , and diarrhea) noted in the subjects after oral administration. Two subjects reported shortness of breath (grade 3) after receiving the intravenous formulation. These occurred in a subject with NSCLC and another subject with lung metastases. Both subjects were treated with oxygen and recovered to baseline. One subject reported each of the following treatment-related adverse events after intravenous injection of vinorelbine: tachycardia (grade 2), pruritis (grade 1), hypoesthesia (grade 1), fever (grade 2), jaw pain (grade 3), anorexia (grade 1), injection reaction (grade 2), sore throat (grade 1), and burning at injection site (grade 1). The following treatment-related adverse events were each reported in only one subject following oral administration: fever (grade 2), sore throat (grade 1), alopecia (grade 1), cough (grade 1), dizziness (grade 1), hypoesthesia (grade 1), disturbance in taste (grade 1), stomatitis (grade 1), oral infection thrush (grade 2), and hypokalemia (grade 2).

Discussion

In an effort to make treatment options more patient friendly, oral dosage forms are being developed. The effort to develop an oral dosing formulation for vinorelbine has been ongoing since 1990. Several different formulations have been developed and undergone testing in humans. The first oral dosage form was a powder-filled, hard gelatin capsule that was withdrawn from development due to concerns regarding airborne vinorelbine exposure during the manufacturing process. A second soft gelatin formulation was created and underwent clinical testing. Unfortunately stability problems with this formulation halted its development. Subsequently the oral dosage form was reformulated with a change in the ratio of excipients in 1994 to create the third formulation that continues through the development process.

Our study of the pharmacokinetic behavior of vinorelbine is consistent with some previously published results, but differ on several important aspects. The differences in the reported pharmacokinetic values for that of Marty or Rowinsky and colleagues could have been influenced by the limit of sensitivity of the assay methodology used, the matrix from which the concentration was determined (whole blood versus plasma) and/or the study design. Marty et al. utilized a less sensitive assay (i.e., lower limit of quantitation in whole blood of 2 ng/mL) than the one used in the current study, and collected blood samples for 72 h after administration [13]. Rowinsky et al. [16] measured the vinorelbine plasma concentrations in samples collected for upto 96 h after the administration. We were able to measure the whole blood concentration of vinorelbine in subjects upto 168 h after administration. Therefore we were able to characterize the terminal eliminate rate which resulted in a mean half-life of approximately 50 h compared to the estimate of 30–38 h reported by Marty et al. [13] and 18 h reported by Rowinsky [16]. Our clearance values are also slightly lower than those (0.80 and 0.72 L/h/kg) reported by Rowinsky and Marty [13, 16]. Gauvin et al. provided estimates for vinorelbine plasma pharmacokinetics of a terminal half-life of 38 hrs and clearance of 0.93 L/h/kg using Bayesian estimation [9]. Recently, Khayat reported parameter estimates for a clearance of 0.6 L/h/kg and terminal half-life between 21 and 39 h over five different doses [11].

Since the AUC is extrapolated to infinity using the terminal eliminate rate, slight differences in these estimates can produce significant differences in the estimates for $AUC_{0-\infty}$ and ultimately the calculation of clearance. In our data, the average percentage of the extrapolated AUC to $AUC_{0-\infty}$ was only 3.5%. When we recalculated the pharmacokinetic parameter estimates using data

Table 5 Toxicities

	Diarrhea Grade				Nausea Grade				Vomiting Grade				Headache Grade				Myalgia Grade				Fatigue Grade				Neutropenia Grade				Leukopenia Grade				Thrombocytopenia Grade				Anemia Grade			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Oral	6	10	5	0	6	4	2	0	5	6	1	0	2	0	0	0	2	0	0	0	7	3	0	0	2	1	2	3	5	3	3	2	9	3	0	0	13	7	0	0
I.V.	2	1	0	0	2	0	1	0	3	0	0	0	3	0	0	0	3	0	0	0	5	4	0	0	1	0	2	0	4	2	2	0	6	1	0	1	11	6	1	0

collected only within 72 h of administration the estimates for clearance and terminal elimination rate were 25–30% different compared to our estimates using the entire data set. Different doses of vinorelbine were used in each study, which might affect the calculation of pharmacokinetic parameters of vinorelbine if exhibited non-linear pharmacokinetics. However, vinorelbine AUC has been shown to increase in a dose-proportional fashion after oral doses of 60 mg/m^2 to 100 mg/m^2 [3], suggesting that the pharmacokinetics of vinorelbine are linear at the doses used in the above mentioned studies.

It is also possible that the matrix used to measure the vinorelbine concentration might significantly influence the pharmacokinetic parameter estimates reported by different authors. Khayat et al. [11] reported the pharmacokinetics of intravenous vinorelbine in both plasma and whole blood. The $AUC_{0-\infty}$ estimated in blood was at least 1.5-fold higher than the $AUC_{0-\infty}$ estimated in the same subjects using the plasma concentrations. The resulting estimates in clearance were similarly different. As illustrated by Khayat, studying the pharmacokinetic behavior of the same drug in plasma and whole blood may lead to different estimates in pharmacokinetic parameters for vinorelbine. Therefore some of the differences noted between this current study and previously published reports may be due to the measurement of plasma compared to whole blood vinorelbine concentration [9, 11, 12, 13, 14, 16, 18].

We evaluated the pharmacokinetics of vinorelbine in the subset of subjects 65 years of age and older and compared the results to those of younger subjects enrolled. We did not find any apparent differences between the pharmacokinetic parameters from younger and older patients. However, it should be noted that our study was not powered to evaluate the effect of age on the pharmacokinetics of vinorelbine. The mean total body clearance in the present study is similar to the value reported by Puozzo et al. [14] although the average bioavailability and half-life in the elderly are somewhat different from our findings. Regardless of these differences between studies, our data support the study by Puozzo et al. suggesting that there are no age-dependant differences in vinorelbine pharmacokinetics. Previous reports also compared the pharmacokinetics of vinorelbine between older and younger cancer patients. Gauvin et al. [9] reported an inverse correlation between age and vinorelbine clearance ($P = 0.0017$) in 12 older patients when vinorelbine was administered intravenously. However, no subjects under the age of 65 were included in that study, and the study used plasma concentrations collected only upto 72 h after administration. Sorio et al. [18] studied the pharmacokinetics of vinorelbine after intravenous administration in patients aged 66 years and older. Results indicated a large apparent volume of distribution (mean 23.4 L/kg), a mean terminal half-life of 26.2 h, and a mean total body clearance rate of 1.2 L/hr/kg [18]. These parameter estimates are within the range of those published for younger subjects. Again these investigators were measuring vinorelbine concentration in plasma collected only up to 96 h [18]. Since they did not include a sample of younger subjects with which to compare their estimates within the study, it is impossible to determine if these pharmacokinetic parameter estimates are different from those published for younger subjects.

The oral bioavailability of vinorelbine has been reported in previous studies using the latest two formulations (both soft gelatin capsules). Rowinsky et al. [16] reported a mean (± SD) bioavailability of 27% (±12) for the previous soft gelatin formulation of vinorelbine. The study included 17 patients who were treated with both intravenous vinorelbine (30 mg/m^2) and oral vinorelbine (100 mg/m^2). The investigators sampled blood out to 96 h and also employed an HPLC method with fluorescence detection to quantitate the plasma concentrations of vinorelbine. Marty et al. [13] conducted a bioavailability study using the same formulation tested in this current study (1994 oral soft gelatin formulation) and compared 80 mg/m^2 orally to 25 mg/m^2 intravenously administered. Oral vinorelbine was rapidly absorbed at 80 mg/m^2 (T_{max} 1.4 ± 0.7 h) with a reported absolute bioavailability of 43 ± 14%. Puozzo et al. [14] studied the pharmacokinetics of vinorelbine using the same formulation administered to subjects over the age of 70. They reported an average bioavailability of 37.9% (coefficient of variation (CV) = 24%), a total body clearance of 44.6 L/h (CV = 14%), and a terminal half-life of 36.4 h (CV = 9%). Results of the current study suggest that the absolute bioavailability of this formulation is 33 ± 18%, somewhat lower than the value reported by Marty et al. and Puozzo et al. Although our estimate is 10% lower than that of Marty et al., it is not clear that this would lead to clinically significant differences due to the other factors that might alter the absorption in humans.

We found a weak relationship between $AUC_{0-\infty}$ and the percent reduction in neutrophil count. No relationships were found using either $AUC_{0-\infty}$ or C_{max} and reductions in either total WBC or platelet count. While the strength of the relationship is modest, it is consistent with the previously published correlations noted in other papers [3, 9, 13]. Relationships for these hematologic toxicities may have been obscured by carry-over effects, the presence of the metabolite or confounded by other influences (e.g., infection) that can alter the amount of these circulating cells. Several other investigators have also reported pharmacodynamic relationships with vinorelbine. Gauvin et al. [9] reported that AUC was a strong predictor of the percentage decrease in hemoglobin and neutrophil count. Marty et al. [13] also found a linear correlation between AUC and the percent reduction in both white blood cells and polymorphonuclear cells. Bonneterre et al. [3] reported that vinorelbine AUC and concentration measured 24 hours after drug intake were significantly correlated with percentage reduction of neutrophils.

In conclusion, we have determined that the mean absolute bioavailability of this oral formulation of

vinorelbine is 33%. The reported adverse events for the two dosing formulations are similar except for the higher incidence of gastrointestinal events following oral administration. The oral formulation appears to have a safety profile similar to the intravenous formulation.

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