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A Pilot Study of Vinorelbine Safety and Pharmacokinetics in Patients with Varying Degrees of Liver Dysfunction

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Disclosures of potential conflicts of interest may be found at the end of this article.

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Abstract

Background. Vinorelbine has demonstrated anticancer activity and is primarily metabolized in the liver. This single-institution, phase I pilot study describes the safety and pharmacokinetics of vinorelbine in patients with varying degrees of hepatic impairment.

Materials and Methods. Patients with treatment-refractory solid tumors were enrolled into treatment arms based on vinorelbine dose (weekly infusions of 7.5–30 mg/m^2) and liver function (normal liver function, mild, moderate, or severe liver dysfunction). Vinorelbine pharmacokinetics were evaluated to describe its relationship with liver function. Indocyanine green (ICG) clearance was assessed for correlation with pharmacokinetics.

Results. Forty-seven patients were enrolled, and a total of 108 grade 3–4 treatment-related adverse events (AEs) occurred. Of these, grade 3–4 myelosuppression was the most common (34.3%). Thirty-three (30.6%), 22 (20.4%), and 9 (8.3%) grade 3–4 AEs were observed in the vinorelbine 20 mg/m^2/severe, 15 mg/m^2/moderate, and 7.5 mg/m^2/severe liver dysfunction groups, respectively, with the majority being nonhematologic toxicities. ICG clearance decreased as liver function worsened. Vinorelbine pharmacokinetics were not correlated with ICG elimination or the degree of liver dysfunction.

Conclusion. For patients with severe liver dysfunction (bilirubin >3.0 mg/dL), vinorelbine doses ≥7.5 mg/m^2 are poorly tolerated. The high incidence of grade 3–4 AEs with 15 mg/m^2 vinorelbine in moderate liver dysfunction (bilirubin 1.5–3.0 mg/dL) raises concerns for its safety in this population. Vinorelbine pharmacokinetics are not affected by liver dysfunction; however, levels of the active metabolite 4-O-deacetylvinorelbine were not measured and may be higher in patients with liver dysfunction if its elimination is impacted by liver impairment to a greater degree than the parent drug. ***The Oncologist*** 2019;24:1137–1145

Implications for Practice: Vinorelbine remains widely prescribed in advanced malignancies and is under development in immunotherapy combinations. Given vinorelbine is primarily hepatically metabolized, understanding its safety and pharmacokinetics in liver dysfunction remains paramount. In this phase I pilot study, weekly vinorelbine at doses ≥7.5 mg/m^2 is poorly tolerated in those with severe liver dysfunction. Furthermore, a high incidence of grade 3–4 toxicities was observed with vinorelbine at 15 mg/m^2 in those with moderate liver dysfunction. Vinorelbine pharmacokinetics do not appear affected by degree of liver dysfunction. Further evaluation of levels of the free drug and active metabolites in relationship to liver function are warranted.

Introduction

Vinorelbine tartrate is a semisynthetic vinca alkaloid and an inhibitor of microtubule polymerization with demonstrated antitumor properties across a spectrum of cancers [1]. Vinorelbine, as a single agent or in combination with cisplatin, was first approved by the U.S. Food and Drug Administration (FDA) for the treatment of non-small cell lung cancer (NSCLC) and has

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demonstrated response rates as high as 30% in this population [2, 3]. In advanced or metastatic breast cancer, single-agent vinorelbine has produced response rates of 40%–60% and 15%–20% in first-line and second-line settings, respectively [4]. Furthermore, vinorelbine has demonstrated clinical activity in other tumors including lymphoma, multiple myeloma, small cell lung cancer (SCLC), and esophageal, colorectal, ovarian, and cervical cancer [5, 6].

The metabolism and elimination of vinorelbine occurs primarily in the liver where the majority of the drug is excreted unchanged in bile [7–9]. Two potential metabolites, vinorelbine N-oxide and deacetylvinorelbine, have been isolated in human urine and in low concentrations in plasma [9]. However, renal excretion accounts for <20% of an intravenous (IV) dose with the majority being eliminated through fecal excretion [7, 9]. Investigations attempting to elucidate the precise mechanisms by which vinorelbine is cleared showed that cytochrome P450 3A (CYP3A) likely plays a lesser role as its activity failed to correlate with drug clearance, whereas adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1 or multidrug resistance protein 1 or P-glycoprotein 1) activity has a potential association with vinorelbine clearance [10]. Nevertheless, plasma clearance of vinorelbine is high and has been shown to approach hepatic blood flow in humans, suggesting high liver uptake and that hepatic blood flow is the major determinant of elimination of vinorelbine [9].

Understandably, the pharmacokinetics of vinorelbine may be altered in individuals with liver dysfunction given that hepatic metabolism serves as the predominant route of drug elimination. To the best of our knowledge, there are only two prospective studies that have investigated the relationship between liver function and vinorelbine pharmacokinetics [11, 12]. In one study, five patients with >75% of their liver volume replaced by metastatic breast cancer had a lower vinorelbine clearance rate compared with those with no liver disease or a lesser degree of metastatic invasion [11]. Prothrombin time and bilirubin were found to have a significant correlation to clearance of vinorelbine. However, the dosing guidelines recommended in this study were relatively simplistic and involved a 50% dose reduction in vinorelbine for patients with bilirubin >2 mg/dL whereas the standard 30 mg/m^2 weekly dose of vinorelbine could be administered in those with bilirubin ≤2 mg/dL. A second study evaluated 12 patients with mild and moderate hepatic impairment (no patients with bilirubin >3 × the upper limit of normal [ULN]) and recommended no dosing modifications for vinorelbine in mild-moderate liver dysfunction given that toxicities and pharmacokinetics were similar across cohorts [12]. Dosing recommendations for vinorelbine across more varied settings of hepatic impairment are of significant clinical interest given that myelosuppression, the major dose-limiting toxicity (DLT) of vinorelbine, has been shown to significantly correlate with drug elimination of vinorelbine [6, 10].

Moreover, there is a relative paucity of predictors of vinorelbine pharmacokinetics. Levels of bilirubin, alkaline phosphatase (ALK), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) have traditionally served as markers of overall liver function but may be less predictive when a specific aspect of liver function is in question, that is, the clearance of a drug. Indocyanine green (ICG) is a dye that has been used to measure cardiac output and organ blood flow, has a high extraction ratio, and is rapidly taken up by the liver [13]. ICG is not significantly metabolized by the liver and is secreted largely unchanged in the bile. Its clearance is therefore a good measure of hepatic blood flow. Furthermore, ICG has previously been shown to be a prognostic indicator in the setting of liver transplantation [14]. ICG may thus represent an indirect measure of elimination of drugs that are predominantly dependent on hepatic metabolism such as vinorelbine.

The purpose of this phase I pilot study (NCT00540982) was to describe the pharmacokinetics and safety of vinorelbine in patients with varying degrees of hepatic impairment and inform dosing recommendations in this population. We also aimed to explore the relationship between ICG clearance and vinorelbine pharmacokinetics to determine its potential to predict clearance of vinorelbine.

Materials and Methods

Patient Selection

Patients who were ≥18 years of age with solid tumors of all histologies refractory to standard therapy or for which no standard therapy exists were eligible. In addition, patients with previously untreated and advanced NSCLC were eligible if abnormal liver function was present (defined below). Patients must have had a Karnofsky performance status >60% and estimated survival of ≥2 months with adequate renal function as evidenced by a serum creatinine <1.5 mg/dL or measured creatinine clearance >60 mL/minute. Any prior chemotherapy must have been completed ≥3 weeks prior to study entry and patients must have recovered from toxicities of previous therapy. Patients with measurable disease must have had baseline measurements taken within 4 weeks of study entry. Other eligibility criteria included the following: patients must have recovered from toxicities of prior radiation therapy prior to study entry; the ability to give voluntary informed consent; the ability to comply with study treatment and required tests; female patients must not be pregnant and lactating; patients with obstructive jaundice should have had a drainage procedure prior to study treatment; patients with acute hepatitis from viral or drug etiologies should have recovered to a stable baseline prior to study treatment; and patients with brain metastases must have disease controlled by radiation therapy or surgery, no longer be taking corticosteroids, and demonstrate stable neurologic status.

Patients were excluded if they had any intercurrent illness (e.g., cardiovascular, pulmonary, or central nervous system) that was either poorly controlled or of such severity that per investigator discretion was deemed unsafe. Other exclusion criteria included absolute neutrophil count (ANC) <1,500/mm^3, platelet count <100,000/mL, and hemoglobin <10 g/dL (unless transfused to above this level). This study was approved by the Institution Review Board (protocol 96032) according to the City of Hope National Medical Center (Duarte, CA) ethical and regulatory guidelines and registered under the clinical trials registry number NCT00540982. All patients signed an informed consent prior to participating in this study.

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Study Design and Treatment

This was a single-institution, phase I pilot study investigating the pharmacokinetics and tolerability of vinorelbine in patients with treatment-refractory solid tumors and varying degrees of liver dysfunction. All enrolled patients were administered weekly vinorelbine as a short IV infusion (over 10 minutes maximum). No randomization occurred but enrolled patients were stratified into the following treatment arms based on vinorelbine dose (7.5–30 mg/m^2) and degree of hepatic impairment: normal liver function was defined as bilirubin <1.5 mg/dL, AST/ALT <1.5 × ULN, and ALK <1.5 × ULN; mild liver dysfunction was defined as bilirubin <1.5 mg/dL and ≥1 of the following: AST/ALT 1.5–2.5 × ULN or ALK 1.5–3 × ULN; moderate liver dysfunction was defined as bilirubin 1.5–3.0 mg/dL and/or ≥1 of the following: AST/ALT >2.5 × ULN or ALK >3 × ULN; and severe liver dysfunction was defined as bilirubin >3.0 mg/dL. No distinction was made between hepatic impairment due to metastatic disease or other causes.

Stratification to each group was based on baseline laboratories drawn within 24 hours of study therapy initiation. Vinorelbine at prespecified doses was administered on a weekly basis as allowed by hematologic and nonhematologic toxicities. Full planned doses of vinorelbine were administered for ANC ≥1,500/mm^3, 50% of planned doses were administered for ANC of 1,000–1,499/mm^3, and doses of vinorelbine were held for the week for ANC <1,000/mm^3 or platelet count <100,000/mL. Any worsening of liver function tests (LFTs) by >1 liver dysfunction group from baseline in the normal and mild liver dysfunction groups or a ≥50% worsening of LFTs or bilirubin in the mild, moderate, and severe liver dysfunction groups necessitated restaging and cessation of therapy. If progressive disease was not noted, therapy was withheld until recovery of at least one level or to within 20% of baseline liver function for the moderate and severe liver dysfunction groups. Vinorelbine was held for any other grade 3–4 toxicity that was possibly, probably, or definitely related to vinorelbine as defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) 2.0. Treatment was restarted when toxicities recovered to grade ≤2. Subsequent dosing was reduced by a factor of 50%.

Assessments

Adverse events (AEs) were recorded and graded as defined by NCI CTCAE version 2.0 throughout the study and until 30 days following the last dose of vinorelbine. Patients who received ≥1 weekly cycle of study treatment were considered evaluable for toxicity. Clinical and laboratory examinations were performed at prespecified time intervals as per study protocol. Evaluation of pharmacokinetics was performed in patients receiving the first dose of study treatment in order to determine the interpatient variability in vinorelbine pharmacokinetics and the relationship between pharmacokinetics and liver function. Plasma samples were collected immediately prior to vinorelbine and then at 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after the start of the infusion. Plasma levels of vinorelbine were measured, and plasma concentrations of vinorelbine were determined by high performance liquid chromatography or liquid chromatography tandem-mass spectrometry assay as described previously [15]. Individual pharmacokinetic data were analyzed according to noncompartmental methods using the rule of linear trapezoids, and the area under the curve from 0 to 24 hours after the infusion ($AUC_{0–24}$) was used as the pharmacokinetic endpoint.

To evaluate the relationship between hepatic extraction and vinorelbine pharmacokinetics, ICG clearance was determined on the day prior to the first day of study treatment with vinorelbine. Following a rapid IV push of ICG (0.5 mg/kg), 5 mL of peripheral blood was collected from a site distal to the drug infusion at 1, 3, 7, 15, 30, and 45 minutes after administration of vinorelbine. ICG clearance was assayed using a previously described spectrophotometric assay [13].

Patients were continued on study treatment until any of the following occurred: tumor progression as defined by a 50% increase in the sum products of measurable lesions over the smallest sum observed, reappearance of any lesion that had disappeared, clear worsening of any evaluable disease (unidimensionally measurable lesions, masses with margins not clearly defined, palpable nodal disease not clearly measurable in two dimensions, lesions with two greatest dimensions <0.5 cm, or bone lesions or pleural effusions proved to be malignant), or appearance of any new lesions; unacceptable toxicity requiring discontinuation of treatment per discretion of the investigator; patient request; or any dosing delays >3 weeks. Diagnostic tests for evaluation of tumor response included computed tomography, magnetic resonance imaging, and/or bone scans that were obtained before the study and repeated every 2 months or sooner if otherwise indicated.

Statistical Analysis

Safety assessments were performed in all patients who received ≥1 weekly cycle of vinorelbine and tabulated by dose and liver dysfunction group. Formal statistical comparisons between rates of AEs among the liver dysfunction groups and dose cohorts were not performed because dose-normalization of AEs was not possible and because of small sample sizes. Pharmacokinetics were evaluated in patients with sufficient dosing information and plasma concentration versus time data over 0–24 hours following vinorelbine infusion to allow calculation of $AUC_{0–24}$. Furthermore, dose-normalization of $AUC_{0–24}$ to the standard 30 mg/m^2 dose was performed to allow evaluation of the relationship between liver function and AUC of vinorelbine.

During an interim analysis, 26 patients were accrued initially to this pilot study. Under the working hypothesis that vinorelbine is predominantly cleared by the liver, drug clearance and toxicity rates are likely to correlate with the degree of liver dysfunction. A preliminary safety assessment highlighted a relative tolerability in patients receiving higher doses of vinorelbine 20–30 mg/m^2 with respect to myelosuppression, the major DLT of vinorelbine that has been shown to correlate with vinorelbine clearance. Therefore, it was recognized that accrual of a wider range of liver dysfunction values, particularly in patients receiving vinorelbine at higher dose levels of 30 mg/m^2 and 20 mg/m^2, would be helpful for stable estimates of the relationships between hepatic impairment, toxicity, and vinorelbine pharmacokinetics. Consequently, the protocol was amended in January 2003

to allow the accrual of an additional 21 patients in the study. Results from the final analysis of the preamendment and postamendment cohorts are presented.

Results

Patient Characteristics

From April 1997 to April 2009, a total of 47 patients with treatment-refractory solid tumors were enrolled to the study (Table 1). The median age of the study population was 58 years (range 32–82), and the most common primary tumor type was colorectal (36.2%) followed by breast, lung, and pancreatic with five each (10.6%). Six patients (12.9%) had tumors of unknown primary.

Safety

All 47 patients enrolled received at least one course of weekly vinorelbine and were included in the safety cohort. Overall, there were a total of 368 treatment-related AEs that occurred with incidence ≥2.0% in all groups (Table 2). Myelosuppression (all grades) made up the majority of treatment-related AEs (incidence ≥2.0%) in the study (27.4%). There were a total of 108 grade 3–4 treatment-related AEs that occurred, with myelosuppression accounting for 34.3% of all grade 3–4 events. The most frequent grade 3–4 AEs in the overall cohort were neutropenia (21.3%), abnormal LFTs (10.2%), anemia (7.4%), and hyperglycemia (7.4%). There were 15 grade 4 AEs: 9 events of neutropenia, 3 abnormal LFTs, 2 neutropenic infections, and 1 anemia. There were no treatment-related grade 5 AEs encountered.

Tables 3 and 4 summarize the incidence of treatment-related grade 3–4 AEs by vinorelbine dose and liver dysfunction group in the preamendment cohort of 26 patients and postamendment cohort of 21 patients, respectively. Of the 108 total grade ≥3–4 treatment-related AEs, 33 (30.6%), 22 (20.4%), 21 (19.4%), and 9 (8.3%) grade 3–4 AEs were observed in the vinorelbine 20 mg/m^2/severe, 15 mg/m^2/moderate, 30 mg/m^2/moderate, and 7.5 mg/m^2/severe liver dysfunction groups, respectively, with the majority being nonhematologic toxicities. Preamendment, a total of 45 grade 3–4 AEs occurred, with 16 (35.6%) of these being myelosuppression (Table 3). The majority of preamendment grade 3–4 AEs were observed in the vinorelbine 15 mg/m^2/moderate (48.9%) and 7.5 mg/m^2/severe liver dysfunction groups (20.0%). Postamendment, there were 63 events of grade 3–4 toxicity, with 20 (31.7%) of these being myelosuppression (Table 4). The majority of postamendment grade 3–4 AEs occurred in the vinorelbine 20 mg/m^2/severe (52.4%) and 30 mg/m^2/moderate liver dysfunction groups (33.3%). Notably, all three events of grade 4 abnormal LFTs were seen in patients with severe liver dysfunction, and eight of nine events of grade 4 myelosuppression occurred in patients receiving ≥15 mg/m^2 vinorelbine with moderate liver dysfunction or 20 mg/m^2 vinorelbine with severe liver dysfunction.

Pharmacokinetics

Vinorelbine plasma $AUC_{0–24}$ data were available for a total of 30 subjects, and the data are depicted in Table 5 and Figure 1. For purposes of comparison, results were normalized to a vinorelbine dose of 30 mg/m^2. There were no significant differences in $AUC_{0–24}$ between the three impaired liver function groups (mild, moderate, and severe). As shown in Figure 1, the median vinorelbine AUC was lower in the normal group (271 [111–593] ng/mL × hour) compared with the combined impaired liver function groups (373 [167–1,318] ng/mL × hour), but this was not significant (p = .06).

ICG clearance was also determined in 25 subjects. As expected, ICG clearance was negatively correlated with worsening liver function tests: total bilirubin (p = .0008) and serum glutamic-oxaloacetic transaminase (p = .008; data not shown). However, ICG elimination was not correlated with vinorelbine pharmacokinetics (p = .30; data not shown).

Table 1. Patient characteristics

Characteristic	*n* (%)
No. of patients	47
Age, years, median (range)	58 (32–82)
Sex	
Female	23 (48.9)
Male	24 (51.1)
Ethnicity	
White	23 (48.9)
Hispanic	13 (27.7)
Asian	9 (19.1)
Black	2 (4.3)
ECOG performance status	
0	18 (38.3)
1	29 (61.7)
Prior chemotherapy regimens, median (range)	2 (0–8)
Primary tumor	
Colorectal	17 (36.2)
Breast	5 (10.6)
Lung	5 (10.6)
Pancreas	5 (10.6)
Hepatobiliary	4 (8.5)
Gastric	3 (6.4)
Nasopharyngeal	1 (2.1)
Sarcoma	1 (2.1)
Unknown primary	6 (12.9)
Duration of study treatment, median weekly cycles (range)	
30 mg/m^2 vinorelbine dose	5.5 (0–8)
20 mg/m^2 vinorelbine dose	1.5 (1–28)
15 mg/m^2 vinorelbine dose	3 (0–18)
7.5 mg/m^2 vinorelbine dose	4 (0–16)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Discussion

Evidence from prospective studies to support dosing guidelines for vinorelbine in patients with abnormal liver function has been limited to relatively simple recommendations that include administering the standard 30 mg/m^2 weekly dose of

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Table 2. Treatment-related all grade and grade 3–4 adverse events for the overall cohort

Adverse event	*n* (%)
All grades, *n* = 368[a,b]	
Neutropenia	41 (11.1)
Anemia	33 (8.9)
Fatigue	33 (8.9)
Anorexia/weight loss	25 (6.8)
Hyperglycemia	24 (6.5)
Abnormal LFTs	22 (6.0)
Pain	21 (5.7)
Nausea/vomiting	20 (5.4)
Fever	18 (4.9)
Hypocalcemia	17 (4.6)
Thrombocytopenia	15 (4.1)
Hypokalemia	14 (3.8)
Hypophosphatemia	13 (3.5)
Constipation	12 (3.3)
Dyspnea	12 (3.3)
Edema	12 (3.3)
Hypoalbuminemia	12 (3.3)
Lymphopenia	12 (3.3)
Neuropathy	12 (3.3)
Grade 3–4, *n* = 108[a,b]	
Neutropenia	23 (21.3)
Abnormal LFTs	11 (10.2)
Anemia	8 (7.4)
Hyperglycemia	8 (7.4)
Infection (with febrile neutropenia)	6 (5.6)
Hypokalemia	5 (4.6)
Dehydration	4 (3.7)
Hypotension	4 (3.7)
Fatigue	3 (2.8)
Hypophosphatemia	3 (2.8)
Lymphopenia	3 (2.8)
Pain	3 (2.8)
Thrombocytopenia	3 (2.8)

[a]All grade adverse events with an incidence ≥2.0% in all groups.
[b]Each adverse event included (multiple adverse events can occur in any one patient)
Abbreviations: LFTs, liver function tests.

vinorelbine in patients with bilirubin ≤2 mg/dL while reducing the vinorelbine dose by 50% in those with bilirubin >2 mg/dL [11] or no dose modifications recommended for vinorelbine in patients with impaired liver function (limited to bilirubin up to 3× ULN) [12]. Furthermore, these studies were carried out in relatively small sample sizes with an even smaller number of patients with bilirubin >3 mg/dL evaluated. Current FDA recommendations for vinorelbine dosing in patients with hepatic insufficiency allow for the standard dose of 30 mg/m^2 to be administered in those with a total bilirubin ≤2.0 mg/dL [16]. In patients with bilirubin of 2.1–3.0 mg/dL, it is recommended for the dose of vinorelbine to be reduced to 15 mg/m^2. For a total bilirubin >3.0 mg/dL, the package insert recommends a dose modification to 7.5 mg/m^2 of vinorelbine.

In this phase I pilot study, we sought to evaluate the safety of weekly vinorelbine in a larger cohort of patients with treatment-refractory solid tumors and more varied degrees of hepatic impairment. A total of 108 events of grade 3–4 treatment-related toxicity occurred, with myelosuppression accounting for 34.3% of these. Notably, the majority of grade 3–4 AEs were seen in the vinorelbine 20 mg/m^2/severe (30.6%), 15 mg/m^2/moderate (20.4%), 30 mg/m^2/moderate (19.4%), and 7.5 mg/m^2/severe liver dysfunction groups (8.3%), with the majority being nonhematologic toxicities. There were more grade 3–4 AEs observed postamendment (*n* = 63) than preamendment (*n* = 45), likely owing to a higher incidence of grade 3–4 events occurring in the vinorelbine 20 mg/m^2/severe (33 or 52.4%) and 30 mg/m^2/moderate liver dysfunction groups (21 or 33.3%). Preamendment, the vinorelbine 15 mg/m^2/moderate and 7.5 mg/m^2/severe liver dysfunction groups accounted for 22 (48.9%) and 9 (20.0%) grade 3–4 AEs, respectively.

The relatively high incidence of grade 3–4 AEs observed in our study in patients with bilirubin levels of 1.5–3.0 mg/dL receiving 15 mg/m^2 of vinorelbine raises concerns on the safety of administering the current FDA-recommended vinorelbine dose of 15 mg/m^2 for bilirubin levels of 2.1–3.0 mg/dL [16]. Furthermore, we showed that doses of vinorelbine ≥7.5 mg/m^2 are poorly tolerated in patients with bilirubin >3.0 mg/dL, which similarly raises concerns on the safety of this dose as recommended by the FDA in those with bilirubin >3.0 mg/dL [16]. Our findings contrast with those from a prospective study that did not recommend vinorelbine dose reductions in patients with moderate liver impairment secondary to metastases [11] and another study that did not recommend dose modifications in those with mild-moderate hepatic dysfunction [12]. Notably, our definitions for normal, mild, and moderate liver dysfunction included other parameters of liver function (AST, ALT, and ALK) in addition to bilirubin to allow for safety assessments across more varied settings of hepatic impairment that may be more reflective of current clinical practice. We were also able to enroll a relatively larger number of patients with severe liver dysfunction (bilirubin >3.0 mg/dL). Furthermore, our protocol was in accordance with the NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction, for which normal-mild liver dysfunction has been shown to correlate with Child-Pugh group A liver dysfunction and moderate-severe liver dysfunction has been shown to correlate with Child-Pugh group B and C hepatic dysfunction [17]. The NCI-ODWG index offers a straightforward yet objective method to classify liver dysfunction that can be used for dose modification of chemotherapy in routine practice and clinical trials. Although our findings preclude exact recommendations for vinorelbine dosing in those with moderate-severe liver dysfunction, further studies of prospective design are likely warranted to evaluate dosing ranges of vinorelbine that are safe in those with moderate-severe hepatic impairment; it would also be useful to include the etiology of liver dysfunction in these instances to assess whether drug elimination may be differentially affected in cirrhosis as compared with liver metastases.

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Table 3. Preamendment treatment-related grade 3–4 adverse events by vinorelbine dose and liver dysfunction group

	Adverse event, *n* (%)[a,b]									
Vinorelbine dose and liver dysfunction group (*n* = 26)	**30 mg/m^2 (normal), *n* = 6**		**20 mg/m^2 (mild), *n* = 3**		**15 mg/m^2 (mild), *n* = 2**		**15 mg/m^2 (moderate), *n* = 10**		**7.5 mg/m^2 (severe), *n* = 5**	
Grade	**G3**	**G4**	**G3**	**G4**	**G3**	**G4**	**G3**	**G4**	**G3**	**G4**
Total grade 3–4 adverse events (*n* = 45)	**7**	**1**	**5**	**0**	**1**	**0**	**19**	**3**	**8**	**1**
Anemia			2 (66.7)				2 (20.0)	1 (10.0)		
Lymphopenia	1 (16.7)						1 (10.0)			
Neutropenia	1 (16.7)	1 (16.7)	2 (66.7)		1 (50.0)		3 (30.0)	1 (10.0)		
Thrombocytopenia							1 (10.0)			
Anorexia/weight loss							1 (10.0)			
Cerebrovascular ischemia							1 (10.0)			
Confusion									1 (20.0)	
Constipation							1 (10.0)		1 (20.0)	
Dehydration	1 (16.7)						1 (10.0)			
Diarrhea	1 (16.7)									
Fatigue	1 (16.7)								1 (20.0)	
Infection (including febrile neutropenia)								1 (10.0)		
Hypotension	1 (16.7)								1 (20.0)	
Thromboembolism							2 (20.0)			
Abnormal LFTs							3 (30.0)		2 (40.0)	1 (20.0)
Hypercalcemia							1 (10.0)			
Hyperglycemia	1 (16.7)		1 (33.3)						2 (40.0)	
Hyperkalemia							1 (10.0)			
Hypophosphatemia							1 (10.0)			

Normal liver function: bilirubin <1.5 mg/dL, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) <1.5 × upper limit of normal (ULN), and *alkaline phosphatase (*ALK) <1.5 × ULN.
Mild liver dysfunction: bilirubin <1.5 mg/dL and ≥1 of the following: AST/ALT 1.5–2.5 × ULN or ALK 1.5–3 × ULN.
Moderate liver dysfunction: bilirubin 1.5–3.0 mg/dL and/or ≥1 of the following: AST/ALT >2.5 × ULN or ALK >3 × ULN.
Severe liver dysfunction: bilirubin >3.0 mg/dL.
[a]Each adverse event included (multiple adverse events can occur in any one patient).
[b]Expressed as a percentage of patients affected by adverse event in specific dose/liver dysfunction group.
Abbreviation: LFTs, liver function tests.

The incidence of grade 3–4 AEs involving worsening liver function observed in our study was the second most common grade 3–4 toxicity (10.2%). The FDA currently recognizes that there is a lack of data to support that hepatic toxicity is enhanced in patients with abnormal liver function treated with vinorelbine despite the prominent role of the liver in vinorelbine metabolism [16]. However, most of the events of grade 3–4 abnormal LFTs in our study occurred in patients with moderate and severe liver dysfunction, thus raising the question if hepatic toxicity is worsened in those with more severe liver impairment.

The pharmacokinetics of vinorelbine in patients with normal liver function have been previously and extensively defined [6, 7]. However, data in patients with hepatic impairment are limited and conflicting. One previous study showed an elevated median AUC of vinorelbine in five patients with >75% of their liver volume replaced by metastatic breast cancer (defined as severe liver dysfunction) compared with those with no liver disease (normal liver function) and 25%–75% of their liver volume replaced by metastatic breast cancer (moderate liver dysfunction) [11]. Furthermore, this study demonstrated that patients with severe liver impairment had a lower vinorelbine clearance rate compared with those with no liver disease or a moderate degree of hepatic impairment. A second prospective study by Kitzen et al. [12] reported that the pharmacokinetics of orally and intravenously administered vinorelbine was unaffected by liver dysfunction, and concluded that a priori dose modifications in patients with mild to moderate liver dysfunction were not warranted.

Therefore, we aimed to further describe the pharmacokinetics of vinorelbine in patients with varying degrees of hepatic impairment in recognition that the metabolism of vinorelbine occurs principally in the liver. In general, we observed that the median $AUC_{0–24}$ of vinorelbine decreased as the dose of vinorelbine was reduced. Importantly, when dose-normalization of the $AUC_{0–24}$ to the standard 30 mg/m^2 vinorelbine dose was performed, we observed that the normalized $AUC_{0–24}$ values in patients with worsening liver function were not significantly different compared with patients with normal liver function. Our findings are consistent with those of Kitzen et al., and indicate that hepatic dysfunction does not have a

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Table 4. Postamendment treatment-related grade 3–4 adverse events by vinorelbine dose and liver dysfunction group

Vinorelbine dose and liver dysfunction group (n = 21)	30 mg/m^2 (normal), n = 5		30 mg/m^2 (mild), n = 1		30 mg/m^2 (moderate), n = 8		20 mg/m^2 (severe), n = 7	
Grade	**G3**	**G4**	**G3**	**G4**	**G3**	**G4**	**G3**	**G4**
Total grade 3–4 adverse events (n = 63)	**5**	**1**	**3**	**0**	**17**	**4**	**28**	**5**
Adverse event					n (%)[a,b]			
Anemia	1 (20.0)				1 (12.5)		1 (14.3)	
Lymphopenia							1 (14.3)	
Neutropenia	1 (20.0)	1 (20.0)	1 (100)		3 (37.5)	4 (50.0)	2 (28.6)	2 (28.6)
Thrombocytopenia							2 (28.6)	
Anorexia/weight loss							1 (14.3)	
Ascites							1 (14.3)	
Confusion							1 (14.3)	
Dehydration					2 (25.0)			
Dyspnea							1 (14.3)	
Edema							1 (14.3)	
Fatigue							1 (14.3)	
Generalized weakness							2 (28.6)	
Hallucinations					1 (12.5)			
Hypotension					1 (12.5)		1 (14.3)	
Hypertension					1 (12.5)			
Infection (including febrile neutropenia)					2 (25.0)		2 (28.6)	1 (14.3)
Neuropathy							1 (14.3)	
Pain	1 (20.0)				1 (12.5)		1 (14.3)	
Petechiae/purpura							1 (14.3)	
Pulmonary hemorrhage							1 (14.3)	
Abnormal LFTs			1 (100)		1 (12.5)		1 (14.3)	2 (28.6)
Elevated INR							1 (14.3)	
Hyperglycemia	2 (40.0)		1 (100)				1 (14.3)	
Hypokalemia					3 (37.5)		2 (28.6)	
Hyponatremia							1 (14.3)	
Hypophosphatemia					1 (12.5)		1 (14.3)	

Normal liver function: bilirubin <1.5 mg/dL, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) <1.5 × upper limit of normal (ULN), and *alkaline phosphatase (*ALK) <1.5 × ULN.
Mild liver dysfunction: bilirubin <1.5 mg/dL and ≥1 of the following: AST/ALT 1.5–2.5 × ULN or ALK 1.5–3 × ULN.
Moderate liver dysfunction: bilirubin 1.5–3.0 mg/dL and/or ≥1 of the following: AST/ALT >2.5 × ULN or ALK >3 × ULN.
Severe liver dysfunction: bilirubin >3.0 mg/dL.
[a]Each adverse event included (multiple adverse events can occur in any one patient).
[b]Expressed as a percentage of patients affected by adverse event in specific dose/liver dysfunction group.
Abbreviations: INR, international normalized ratio; LFTs, liver function tests.

significant effect on total clearance of vinorelbine. It is possible that there is a difference in the elimination of non-protein-bound vinorelbine; however, neither we nor Kitzen measured free drug levels. Furthermore, neither we nor Kitzen measured levels of the active metabolite 4-O-deacetylvinorelbine [18], and it is possible that levels of this important metabolite could be higher in patients with hepatic dysfunction if its elimination is impacted by liver impairment to a greater extent than the parent drug.

The ideal and definitive predictor of vinorelbine pharmacokinetics and clearance beyond traditional markers of liver function including bilirubin, AST, ALT, and ALK has yet to be identified. Several potential predictors of vinorelbine pharmacokinetics including monoethylglycinexylidide, albumin, prothrombin time, and hepatic elimination of technetium labeled sestamibi (^{99m}Tc-MIBI) have been previously investigated and described [10, 11]. In our study, we observed that ICG clearance (a surrogate marker of liver blood flow) was negatively correlated with worsening liver function. However, ICG elimination was not correlated with vinorelbine pharmacokinetics. Our findings suggest that ICG clearance alone is not an adequate predictor of vinorelbine elimination. Alternatively, future studies seeking to identify predictors of vinorelbine elimination could focus on the role of pharmacogenomics. For example, single nucleotide polymorphisms in genes encoding for DNA repair enzymes and cell division including *XRCC1*, *XPC*, *STMN1*, and *XPD* have been shown to represent potential biomarkers for

Table 5. Vinorelbine plasma pharmacokinetics

Liver function group	*n*	$AUC_{0–24}$[a] (ng/mL × hour)
Normal	10	271[b] (111–593)
Mild	4	537 (366–812)
Moderate	12	341 (251–1,318)
Severe	4	324 (167–1,090)

[a]Normalized to a vinorelbine dose of 30 mg/m^2.
[b]Medians (ranges).
Abbreviation: $AUC_{0–24}$, area under the curve from 0 to 24 hours after infusion.

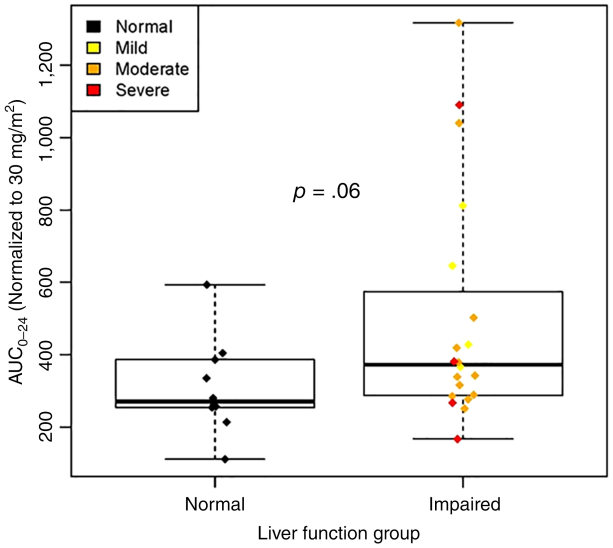

Figure 1. Vinorelbine $AUC_{0–24}$ by liver function group. AUC_{0-24} data were available for a total of 30 subjects. Results were normalized to a vinorelbine dose of 30 mg/m^2. The median vinorelbine AUC was lower in the normal group compared with the combined impaired liver function groups, but this was not significant.
Abbreviation: $AUC_{0–24}$, area under the curve from 0 to 24 hours after infusion.

predicting vinorelbine-based chemotherapy toxicity [19]. Additionally, earlier evidence has suggested that vinorelbine metabolism is mediated by CYP3A enzymes and the ABCB1 transporter, although a recent study failed to confirm such relationships—further investigation may be warranted to clarify these discrepancies [10].

Beyond its FDA approval as a single agent or as part of combination chemotherapy in advanced NSCLC, vinorelbine in combination with cisplatin remains a standard option for neoadjuvant therapy (along with radiation therapy) in locally advanced NSCLC and adjuvant therapy in early-stage NSCLC [6, 16]. Furthermore, vinorelbine represents a viable treatment option in advanced breast cancer and in a number of other malignancies including hematologic malignancies, SCLC, esophageal, colorectal, ovarian, and cervical cancer—particularly in late-line settings when standard therapies have been exhausted [5, 6]. Investigations are ongoing involving the addition of vinorelbine to the following: cetuximab in head and neck cancer (NCT01020864), gemcitabine in myeloma (NCT02791373), lapatinib in metastatic breast cancer (NCT02362958, NCT01730677), the programmed death 1 inhibitor pembrolizumab in advanced solid tumors (NCT02331251), and the programmed death-ligand 1 inhibitor atezolizumab as part of adjuvant therapy in resectable NSCLC (NCT02486718). Therefore, as vinorelbine continues to remain a viable treatment option in refractory settings and continues development as part of novel combination therapeutic strategies including immunotherapy, ongoing investigations of its safety and pharmacokinetics are warranted. Furthermore, given that the liver serves as the primary site of vinorelbine metabolism and remains a common site of metastases for many of these cancers, safety and pharmacokinetic assessments in patients with abnormal liver function are of clinical relevance and underscore the basis of this pilot study.

Conclusion

Findings from this pilot study showed a relatively high incidence of grade 3–4 treatment-related hematologic and nonhematologic toxicities in patients with moderate liver dysfunction receiving vinorelbine 15 mg/m^2 and those with severe liver dysfunction receiving ≥7.5 mg/m^2 of weekly vinorelbine. As previously reported, we confirmed that the pharmacokinetics of vinorelbine are not significantly affected by degree of liver dysfunction, suggesting that a priori dose reductions of vinorelbine may not be warranted in patients with abnormal liver function. Further studies of prospective design are warranted to better elucidate vinorelbine dosing guidelines in patients with abnormal liver function, particularly in those with moderate-severe hepatic impairment.

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Disclosures

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