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ORIGINAL ARTICLE

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Inability to escalate vinorelbine dose intensity using a daily ×3 schedule with and without filgrastim in patients with metastatic breast cancer

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Abstract *Purpose*: Vinorelbine (Navelbine) is a semisynthetic vinca alkaloid with documented activity in breast cancer. The major dose-limiting toxicity (DLT) when given weekly is myelosuppression with minimal neurologic toxicity. This phase I study attempted to define the maximally tolerated dose (MTD) and the DLT of vinorelbine on a daily ×3 schedule with and without filgrastim support. *Methods*: A total of 19 patients with stage IV breast cancer were enrolled in separate studies at Duke University Medical Center (DUMC) and the Dana-Farber Cancer Institute (DFCI). Eligible patients could have received up to two prior chemotherapy regimens in the metastatic setting and had to have an ANC $>1500/mm^2$, PLT $>100\,000$ m^3, creatinine <2.0 mg/dl, bilirubin <2.0 mg/dL, SGOT not more than three times normal, and performance status 0–1. Vinorelbine was administered using a daily ×3 schedule every 3 weeks. The protocols were designed to study dose escalation with and without growth factor support. At DUMC, in the initial phase of the study, the starting dose was 15 mg/m^2 per day and dose escalations of 5 mg/m^2 were planned until DLT developed and the MTD was defined. DLT was defined as granulocytopenia $<500/mm^3$ for >7 days, grade IV thrombocytopenia, febrile neutropenia, or grade III or greater nonhematologic toxicity. In the second phase of the study, growth factor support was given with vinorelbine at the MTD. Filgrastim at a dose of 5 μg/kg was started on day 4 of the 21-day cycle and was continued until the neutrophil count exceeded 10 000 cells/mm^3. At DFCI, all patients received growth factor starting on day 4 and the starting dose of vinorelbine was 25 mg/m^2. *Results*: At DUMC, DLT was seen at 20 mg/m^2 in three of three patients and included febrile neutropenia, grade IV neutropenia >7 days, grade III neurotoxicity, and grade III vomiting. Despite the addition of filgrastim, DLT was again seen at 20 mg/m^2 and included grade III neurotoxicity (jaw pain, abdominal pain, constipation, ileus) and grade IV mucositis. Three patients at DFCI were treated with vinorelbine at a dose of 25 mg/m^2 with growth factor support, and two developed DLT including febrile neutropenia, neutropenia >7 days, and grade III stomatitis. *Conclusions*: Our effort to escalate the dose intensity of vinorelbine on this schedule was not successful and was complicated by hematologic and nonhematologic toxicity. A daily ×3 schedule of vinorelbine should not be pursued as an alternative treatment regimen in patients with previously treated metastatic breast cancer.

Key words Vinorelbine · Breast cancer · Phase I · Dose intensity · Growth factor

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Introduction

Chemotherapy and hormonal therapy provide palliation and may prolong life in patients with metastatic breast cancer [7]. The investigations of new drugs, alternative treatment schedules, and more effective combinations continue to be important areas of clinical research in this disease. Vinorelbine is a novel vinca alkaloid which is active in patients with metastatic breast cancer and may

become an integral part of future breast cancer regimens. Clinical trials with vinorelbine have demonstrated efficacy in the metastatic setting in both first- and second-line therapy [2–4, 8–13]. In most studies vinorelbine has been well tolerated, but reversible, noncumulative granulocytopenia has limited the delivered dose to between 20 and 30 mg/m^2 when given on a weekly schedule [6]. Although the optimal dose and schedule of vinorelbine has yet to be determined, there is preliminary evidence of an important relationship between dose intensity and response rates [12].

One approach to overcoming the dose-limiting hematologic toxicity may be to provide hematopoietic support through the use of colony-stimulating factors. While weekly schedules have been administered in conjunction with G-CSF support, an every 3-week dosing schedule may be more amenable to growth factor support. For this reason, we conducted a dose escalation study of single-agent vinorelbine given on a daily ×3 schedule every 3 weeks in patients with breast cancer. The objective was to define the maximally tolerated dose (MTD) and dose-limiting toxicities (DLT) of vinorelbine when given on this schedule with and without filgrastim support. This report describes results obtained from two institutions that enrolled patients on comparable phase I vinorelbine protocols.

Table 1 Patient characteristics

Characteristic		No. of patients (%)
Entered on study		19
Age (years)		
Median	54	
Range	33–83	
Prior treatment		
Adjuvant chemotherapy		15 (79)
Chemotherapy for metastases		14 (74)
1 regimen		5 (26)
≥2 regimens		9 (47)
Hormonal therapy		
Adjuvant		11 (58)
Metastatic		10 (53)
Radiation therapy		
Adjuvant		8 (42)
Metastatic		7 (37)
Site of disease		
Viscera		13 (68)
Bone		5 (26)
Soft tissue		12 (63)
No. of metastatic sites		
1		9 (47)
2		1 (5)
≥3		9 (47)

Patients and methods

Patient selection

The two trials reported here together were conducted in patients with histologically confirmed breast cancer and evidence of metastatic disease. Patients were enrolled in separate studies at Duke University Medical Center (DUMC) and the Dana-Farber Cancer Institute (DFCI). Because the studies and results were similar, we combined them in the same report. In the DUMC study, patients could receive up to two prior chemotherapy regimens in the metastatic setting, but no chemotherapy was permissible within 4 weeks of study entry (see Table 1). Hormonal therapy had to be discontinued 4 weeks prior to study entry unless there was definite evidence of disease progression on therapy. Radiation therapy must have been completed 2 weeks prior to entry, and patients could not have received radiation to >25% of the bone marrow. Other eligibility criteria were as follows: ECOG performance status 0–1, expected survival ≥12 weeks, adequate bone marrow reserve (ANC >1500 mm^3, PLT >100 000/mm^3), adequate renal (serum creatinine <2.0 mg/dl) and hepatic function (bilirubin <2.0 mg/dl, SGOT less than three times normal), and measurable or evaluable disease.

Exclusion criteria included the following: age less than 18 years, metastatic CNS disease, previous high-dose therapy with autologous bone marrow rescue, and preexisting grade III peripheral neuropathy, except for abnormalities related to cancer. Patients with a history of any other malignancy within the past 5 years other than superficial nonmelanomatous skin cancer and in situ carcinoma of the cervix were also excluded.

With the exception of several minor differences, eligibility and exclusion criteria were comparable at DFCI. At DFCI, patients were required to have metastatic breast carcinoma refractory to one or more prior chemotherapy regimens and an ECOG performance status of 2 or better. Measurable or evaluable disease was not required, and there was no stipulation regarding prior hormonal therapy. Other eligibility criteria included a total WBC ≥3000/mm^3, PLT ≥100 000/mm^3, and hemoglobin ≥8 g/dl. The creatinine and total bilirubin were required to be ≤2.0 mg/dl, and the SGOT and alkaline phosphatase not more than four times the upper limits of normal. Patients were not to have received radiotherapy or chemotherapy for 3 weeks prior to entering the study. Exclusion criteria were as in the DUMC protocol. Written informed consent was obtained from all patients, and the protocols and consents were approved by the Institutional Review Boards of DUMC and DFCI.

Pretreatment and follow-up evaluation

The pretreatment evaluations included a complete history and physical, documentation of measurable and/or evaluable disease, and recording of signs and symptoms of the patient's illness. Laboratory studies included a complete blood count, differential, creatinine, serum electrolytes, calcium, albumin, AST, ALT, alkaline phosphatase, and bilirubin. Radiographic studies to be used for tumor measurement were carried out within 2 weeks of the study. Physical examinations and appropriate laboratory studies were obtained prior to each cycle of chemotherapy. Complete blood counts were obtained at least twice per week, and radiographic studies to assess measurable disease were carried out after every two cycles of therapy.

Treatment plan

The DUMC protocol consisted of two parts and was designed to study dose escalation with and without growth factor support. In the initial phase of the study, vinorelbine was administered using a daily ×3 schedule every 3 weeks. The starting dose in the first cohort was 15 mg/m^2 per day administered over 6–10 min. Dose escalations of 5 mg/m^2 per day in subsequent cohorts were planned until DLT developed. A minimum of three patients were to be treated at each dose level. If DLT developed in two out of three patients, then the dose level was considered excessively toxic and the next lower dose was considered the MTD. If one out of three patients developed DLT, then three additional patients were added at the same dose level. If three out of six patients developed DLT, the MTD

was defined as the next lower dose level. DLT was defined as granulocytopenia $< 500/mm^3$ for > 7 days, grade IV thrombocytopenia at any assessment, febrile neutropenia (fever > 101 °F with neutrophil count $< 500/mm^3$), or grade III or greater nonhematologic toxicity. In the second phase of the study, growth factor support was given with vinorelbine at the MTD (the dose below which DLT had been reached). Filgrastim at a dose of 5 μg/kg was started on day 4 of the 21-day cycle and continued daily until the total neutrophil count exceeded 10 000 cells/mm^3. The same criteria were used to define DLT as described above.

The DFCI protocol was comparable, with the starting dose of vinorelbine 25 mg/m^2 ×3 days. At the time the trial was initiated, this starting dose was considered reasonable, as long as all patients received G-CSF support. Vinorelbine was given over 6–10 min on days 1, 2, and 3 on an every 21-day schedule, and filgrastim at 5 μg/kg on days 4–11 or until ANC $\geq$10 000/μl. Dose escalations of 5 mg/m^2 were planned until DLT developed. Three patients were to be entered at each level and their toxicities assessed. DLT was defined as grade IV toxicity, as per NCI Common Toxicity Criteria, except for neutropenia. The DLT for neutropenia was defined as an ANC $< 500/\mu l$ for > 7 days or any episode of febrile neutropenia. The MTD was defined as one level below that at which one of three patients had grade IV toxicity.

Toxicity and dose modifications

The Cancer and Leucemia Group B expanded toxicity criteria were used for the assessment of toxicity. At DUMC, patients experiencing toxicity must have recovered to grade I or less prior to continuing therapy, and those requiring a delay in treatment of > 3 weeks were taken off study. Patients who developed DLT during either the initial or second part of the study were eligible for retreatment in the absence of progressive disease, but the dose was decreased by one dose level.

At DFCI, patients requiring a delay in treatment of > 2 weeks were taken off study. No dose modifications were made.

Response criteria

Standard criteria for response were used. Complete response was defined as the disappearance of all clinically and radiographically evident disease for a minimum of 4 weeks. Partial response was defined as a reduction of $> 50\%$ in the product of the two greatest perpendicular diameters of all measurable disease for a minimum of 4 weeks. Patients who had an increase of $> 25\%$ in the product of the two greatest perpendicular diameters of any measurable disease had progressive disease. A lesion within a previously irradiated field had to progress after radiation to be considered evaluable. Any disease not meeting the definition of progression or response was classified as stable.

Criteria for removal from study

Patients were removed from study if progressive disease developed after any course of therapy. Patients were also removed if they requested to withdraw from study or if general or specific changes in the patient's condition or toxicity rendered the patient unacceptable for further treatment in the judgment of the investigator.

Results

A total of 19 patients (16 at DUMC and 3 at DFCI) were enrolled at the two institutions from February 1994 to February 1996. All patients were evaluable for toxicity. The median patient age was 54 years. Of the 19 patients, 14 had received prior chemotherapy in the metastatic setting, and 9 had received two or more prior chemotherapy regimens for metastatic disease. The median number of prior chemotherapy regimens (adjuvant + metastatic) was 2.6. The median performance status was < 1. Additional patient characteristics are detailed in Table 1.

Dose escalation without filgrastim support

In the first phase of the study, we conducted dose escalation without filgrastim support. Six patients were

Table 2 Toxicity of vinorelbine daily × 3

Dose level	No. of patients	Grade III or IV toxicity	No. of patients
15 mg/m^2 without Filgrastim	6	Neutropenia	4
		Stomatitis	1
		DLT	2
20 mg/m^2 without Filgrastim	3	Neutropenia	3
		Febrile neutropenia	2
		Abdominal pain	1
		Peripheral neuropathy	1
		Vomiting	1
		Thrombocytopenia	1
		DLT	3
15 mg/m^2 with Filgrastim	3	DLT	0
20 mg/m^2 with Filgrastim	4	Neutropenia	2
		Abdominal pain/ileus	2
		Jaw pain	1
		Stomatitis	1
		Thrombocytopenia	1
		Hyponatremia	1
		DLT	3
25 mg/m^2 with Filgrastim	3	Neutropenia	3
		Febrile neutropenia	1
		Stomatitis	2
		DLT	2

treated at the 15 mg/m^2 × 3 days dose level. In the first cycle of therapy, four patients experienced grade IV neutropenia and one patient had DLT as defined as ANC $< 500/mm^3$ for > 7 days (Table 2). There was no grade III/IV neurotoxicity, but one patient had grade III stomatitis. A total of 14 cycles were administered at this dose level. In total, five of the six patients experienced grade IV neutropenia at some point during the treatment course. Seven of 14 cycles were complicated by transient grade IV neutropenia and 2 cycles were associated with neutropenia of > 7 days duration.

At 20 mg/m^2 without filgrastim, DLT was experienced by three of three patients on cycle I. All three patients experienced grade IV neutropenia. Two patients had febrile neutropenia, and two patients had grade IV neutropenia of > 7 days duration. In addition, a range of other grade III and IV toxicities was observed, including severe constipation, ileus, vomiting, jaw pain, and peripheral neuropathy. Without filgrastim support, it was concluded that the MTD was 15 mg/m^2 ×3 days.

Dose escalation with filgrastim support

Three patients were treated with vinorelbine 15 mg/m^2 × 3 days with filgrastim support. No patients developed DLT. A total of six cycles were administered at this dose level. One patient developed grade IV neutropenia with cycle III, but this was of short duration and was not associated with fever. No other grade III or IV toxicity was observed.

At a dose of 20 mg/m^2 ×3 days with filgrastim support, four patients were treated and DLT was experienced by three. DLT in two patients manifested as grade III abdominal pain and ileus, and in a third patient as grade IV stomatitis. Other grade III or IV toxicities included jaw pain, hyponatremia, and thrombocytopenia. Three patients experienced transient grade IV neutropenia, but there was no dose-limiting neutropenia.

Three patients at DFCI were treated at a dose of 25 mg/m^2. Two of the three patients experienced DLT. Two patients developed neutropenia for > 7 days, and one of these developed febrile neutropenia. Additionally, both patients experienced severe, dose-limiting stomatitis.

Responses

Of the 19 patients enrolled in the study, 12 were evaluable for response to therapy. Two responses were seen, including one partial response and one complete response. Additionally, two patients had stable disease. Both responses occurred in disease on the chest wall. No responses in visceral disease were seen. Of interest, two patients who had both chest wall and visceral disease had improvement in their chest wall disease concurrently with disease progression at the visceral site.

Discussion

The effort to improve therapy for patients with breast cancer continues to include investigations of novel drugs and alternative treatment schedules. Vinorelbine is active and well tolerated in patients with breast cancer, but the optimum dose and treatment schedule has yet to be determined. The primary objectives of this phase I study were to determine the DLT of vinorelbine given intravenously daily ×3 on an every 21-day schedule and to define the MTD of this regimen with and without filgrastim support in patients with breast cancer. In this cohort of heavily pretreated patients with metastatic disease, the MTD of vinorelbine daily ×3 was 15 mg/m^2. Growth factor support did not allow dose escalation or an increase in dose intensity on this schedule. DLT included neurotoxicity, neutropenia, and stomatitis. Symptoms of neurotoxicity included jaw pain, ileus, abdominal pain, constipation, and peripheral neuropathy. Although the duration of myelosuppression was shortened with the addition of filgrastim, neutropenia tended to be cumulative in patients receiving more than two cycles, and nonhematologic toxicities were prohibitive at greater than 15 mg/m^2 ×3.

It is interesting to compare and contrast the results of our study with other investigations of vinorelbine which have attempted dose escalation with granulocyte colony stimulating factor support. Livingston and colleagues used continuous G-CSF support in a group of patients with refractory breast cancer and achieved a dose intensity of 35 mg/m^2 per week with acceptable toxicity [9]. Of note, an encouraging response rate of 25% was seen, despite the fact that the patient population was heavily pretreated. The principal hematologic toxicity was neutropenia, which occurred in 58% of patients; however, febrile neutropenia requiring hospitalization occurred in only 3 of 40 patients. Importantly, nonhematologic toxicities were seldom severe and only two patients experienced grade III or IV constipation and ileus. Peripheral neuropathy was not severe and only two patients experienced mild mucositis. The results of this study suggest that a weekly schedule with continuous G-CSF support may offer the greatest potential for dose escalation of vinorelbine.

In an attempt to develop a schedule that could be better integrated with growth factor support, Hoffman et al. combined ifosfamide 1.6 g/m^2 and vinorelbine 30 mg/m^2 daily ×3 every 21 days (30 mg/m^2 per week) with G-CSF on days 5–11 [5]. A total of 42 patients with previously untreated non-small-cell lung cancer were treated with this regimen. Despite the use of concurrent ifosfamide, considerably higher doses of vinorelbine were tolerated in this group of patients than in our trial. Moreover, the principal toxicity was neutropenia, and clinically significant neurologic toxicity and mucositis were not seen. It is unclear why patients in the study by Hoffman et al. were able to tolerate substantially higher doses of vinorelbine in combination with ifosfamide and

mesna than patients in our trial. In all likelihood, the major difference between the two studies was the very different patient populations and the extensive prior treatment in our patients with breast cancer. On the other hand, the possibility of a pharmacodynamic interaction of vinorelbine and ifosfamide (leading to better tolerance of vinorelbine) cannot be excluded.

With a half-life of 28–44 h [6], it is likely that daily ×3 drug administration leads to progressive increases in vinorelbine levels. A combination of higher drug levels (than one would see with the same dose administered weekly) and longer duration of exposure may have resulted in the high degree of toxicity seen in our study. On the other hand, the fact that Hoffman et al. were able to administer 30 mg/m^2 ×3 suggests the daily ×3 schedule is not associated with unacceptable toxicity in all settings. Even at this dose, however, it is not clear that the daily ×3 regimen would result in greater dose intensity than a weekly schedule, particularly if one considers the dose modifications and delays that accompany almost any regimen. Of interest, attempts to escalate the dose of other vinca alkaloids, particularly vincristine, have often been unsuccessful as well [1].

Our study did not address whether the scheduling or dose intensity of vinorelbine are important determinants of clinical efficacy. Data from a phase I/II trial of continuous infusion vinorelbine for advanced breast cancer by Toussaint et al. do suggest a correlation between dose intensity and clinical response [12]. Patients receiving 8–10 mg/m^2 per week had a response rate of 13.3%, those receiving 10–12 mg/m^2 per week had a response rate of 35.4%, and those receiving 12–14.5 mg/m^2 per week had a response rate of 55.5%. Other studies in pretreated patients with advanced breast cancer have found response rates with a weekly administration of vinorelbine of 30–35 mg/m^2 per week in the range of 25–30% [3, 4, 8, 11, 13]. While the MTD was only 15 mg/m^2 per week in our trial, there were two responses and two patients with stable disease in the 12 patients who were evaluable for response. Interestingly, both responses were seen in patients with recurrent chest wall disease.

Our effort to escalate the dose intensity of vinorelbine on this schedule was not successful. Both with and without G-CSF support, 20 mg/m^2 per day ×3 was excessively toxic in patients with metastatic breast cancer. Without G-CSF, hematologic and nonhematologic toxicity were dose limiting. With G-CSF, nonhematologic toxicities precluded dose escalation. We conclude that a daily ×3 schedule of vinorelbine should not be further pursued as an alternative treatment regimen in patients with previously treated, metastatic breast cancer.

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