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Phase II study of divided-dose vinblastine in advanced breast cancer patients

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Summary. The pharmacokinetics of a 5-day, continuous infusion of vinblastine have been reproduced by an i.v. divided bolus at 0 and 48 h [10]; this schedule can be easily applied to outpatients. We treated 26 evaluable patients with refractory, advanced breast cancer with 3.5–4 mg/m^2 vinblastine given i.v. by a divided bolus at 0 and 48 h of 21-day cycles. Neurotoxicity and myelosuppression were the main side effects: severe constipation and peripheral neurotoxicity developed in 14% and 3% of the patients, respectively; severe leukopenia and thrombocytopenia occurred in 24% and 10% of the patients, respectively. One partial response, 14 no changes, and 11 progressions were obtained. Our results do not support the use of vinblastine in divided doses in treating this disease.

Introduction

Front-line combination chemotherapy achieves a 50%–80% response rate in patients with advanced breast carcinoma. Vinblastine alone (VBL) has been reported to obtain an overall 20% response rate when given as an intermittent i.v. bolus injection [1–3]. The use of a 5-day, continuous infusion has yielded a 40% response rate despite heavy chemotherapeutic pretreatment [8]. Similarly, improvement of the therapeutic index over that obtained with the intermittent i.v. bolus has also been demonstrated by 5-day, continuous infusion of vindesine in a randomized trial [9]. Pharmacokinetics studies have recently shown comparable blood concentration curves of VBL for both the 5-day, continuous infusion schedule and the divided-dose schema with bolus at 0 and 48 h [10]. In order to reproduce the good results obtained with continuous infusion and provide a more suitable schedule for outpatient treatment, we tested the divided-dose schema with bolus at 0 and 48 h in refractory, advanced breast cancer patients.

Materials and methods

Patients with histologically confirmed, metastatic breast cancer were entered in the study. The requirements for participation were: an Eastern Cooperative Oncology Group (E.C.O.P.) performance status ≤ 3; good hepatic (bilirubin $<.03$ mg/ml), renal (creatinine $<.02$ mg/ml), and cardiac functions; and adequate bone marrow reserve (WBC $\geq 4{,}000/\text{mm}^3$ and platelets $\geq 100{,}000/\text{mm}^3$). Patients with second tumors radically treated for more than 5 years were admitted to the study, and a life expectancy of at least 2 months was required. There was no age limit, and informed consent was obtained from all patients. At least 4 weeks without therapy were also required (6 weeks for mitomycin C and nitrosoureas). Prior exposure to VBL excluded patients from the study.

VBL was given as an i.v. bolus via a peripheral vein at 0 and 48 h of 21-day cycles. Blood cell counts and 12-channel profiles were checked before starting treatment, together with the study of marker lesions made by radiograms and ultrasound or computerized axial tomography (CAT) scans. These studies were repeated as frequently as clinically indicated in order to assess response to treatment. Blood cell counts were repeated weekly during the first two cycles, and the dose was either increased or decreased by 0.5 mg/m^2 in the subsequent cycle if leukocyte and platelet counts were either $\geq 3{,}000/\text{mm}^3$ and $\geq 1000{,}000/\text{mm}^3$, or $<1{,}500$ and $<75{,}000$, respectively. The starting dose of VBL was 3.5 mg/m^2 in patients previously exposed to more than two different chemotherapy regimens or to one chemotherapy regimen plus radiotherapy (e.g., postoperative radiation); in less extensively pretreated patients, the starting dose was 4 mg/m^2. Drug administration was delayed 1 week if leukocytes numbered $<3{,}000/\text{mm}^3$ and/or platelets, $<100{,}000/\text{m}^3$, on the day of retreatment. Criteria for toxicity and response assessment were those recommended by WHO [6]. Response assessment was performed after two full cycles of chemotherapy; however, rapid progression of marker lesions within only one cycle was considered as treatment failure.

Results

Between August 1985 and August 1986, 29 eligible women were admitted to the study. The patients' characteristics are summarized in Table 1. All were of menopausal status, either natural or artificially induced. Of these patients, 7 had already been treated with more than two different chemotherapy regimens, 24 had received anthracyclines (doxorubicin or 4'-epi-doxorubicin), and 8 had been exposed to vincristine.

A total of 118 cycles of VBL were given (mean per patient, 4; range, 1–12); the starting doses were 4 mg/m^2 in 9 patients and 3.5 mg/m^2 in 20. The dose could be incre-

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Table 1. Patients' characteristics and toxicity

Total number of entered/evaluable patients			29/26
Median age (range):			55 (28–72)
Performance status (e.c.o.g.):		0–1	13
		2–3	16
Weight loss:		≤10%	22
		>10%	2
		unknown	5
Metastatic sites: bone	17	skin	9
lung	9	lymph nodes	6
liver	5	pleura	2
contralateral breast			1
Prior treatment: surgery			29
radiotherapy			21
hormone therapy			24
chemotherapy			29
Median number of different regimens (range)			2 (1–4)
Median number of different drugs (range)			5 (1–7)

Toxicity	Number of patients
Nausea and vomiting	7
Mucositis	5
Diarrhea	2
Constipation	9
Peripheral neurotoxicity	13
Hair loss	10
Infection	2
Phlebitis	10
Leukopenia	23
Thrombocytopenia	5
Anemia	8

Nadir counts	Mean value (range)	Mean day (range)
Leukocyte ($\times 10^3$/mm^3)	3.5 (0.3–11.1)	12.3 (6–18)
Platelet ($\times 10^3$/mm^3)	229.7 (2–529)	10.4 (6–21)

mented at least once during the second and third cycles in 13 patients, and reduction was required in 6.

The main side effects were myelosuppression and neurotoxicity (Table 1). Leukopenia (<2,000/mm^3) and thrombocytopenia (<50,000/mm^3) occurred in 7 and 3 patients, respectively; mild anemia was also common. Constipation occurred in 9 patients, which evolved into frank ileus in 4 and resolved within a week; peripheral neurotoxicity developed in 13. The VBL dose had to be reduced by 50% in 2 patients due to neurotoxicity. Significant hair loss was observed in 7 patients; phlebitis was encountered in 10 patients but was severe in only 1; drug extravasation never required skin grafting.

Response was evaluable in 26 patients (after one cycle, 1 stable patient received only the first dose of the second cycle due to severe phlebitis; early death and rapid deterioration of general conditions prevented chemotherapy continuation in 2 other patients). We obtained 1 partial response in lymph nodes and skin deposits, which lasted 332 days; 14 no changes (median duration, 93 days); and 11 progressions. The overall median survival time was 294 days.

Discussion

Continuous infusion of vinca alkaloids has been attempted in order to obtain optimal drug exposure, as these agents are rapidly cleared from the blood after i.v. bolus injection. When given as a 5-day, continuous infusion, VBL has been shown to be one of the most active drugs in advanced breast carcinoma refractory to prior chemotherapy (including doxorubicin), obtaining a response rate in excess of 35% [4, 8]. In this study, 5 of 7 patients already exposed to VBL, given either singly or in combination, responded to the 5-day, continuous infusion of 1.4–2.0 mg/m^2 per day, in a wide series of 106 evaluable patients. Furthermore, doses above 1.7 mg/m^2 have demonstrated higher efficacy than lower doses, with an evident dose-response effect [4]. The continuous infusion of vindesine has also been shown to obtain better results than the bolus injection [9]. Although VBL is active, its continuous infusion usually requires a central venous catheter, careful supervision, and expensive pumping devices, and many patients require hospitalization for treatment. This has been the major reason for limited application of continuous infusion schedules for advanced breast cancer.

However, it has recently been shown that the pharmacokinetics of VBL given as an i.v. bolus of 4.5 mg/m^2 in two divided doses 48 h apart are comparable to those of a 5-day, continuous infusion of 1.75 mg/m^2 per 24 h [10].

We used the divided-dose schedule in our study and obtained only 1 response out of 26 evaluable patients (95% confidence limits: 0–11.1%), despite the fact that more than half of the patients had dose increments that led to an administered dose within the range considered most active (4–5 mg/m^2 ×2). Furthermore, neurotoxicity has been remarkable, with occurrence of ileus in 4 cases, and myelosuppression has also been significant.

In conclusion, our results are as negative as those reported by other authors, who have used a 5-day, continuous infusion of VBL and observed no responses in a total of 32 patients [5, 7]. Our findings do not support the use of VBL given in two divided doses at 0 and 48 h in advanced breast carcinoma patients.

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