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Vindesine in the Treatment of Metastatic Breast Cancer

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Abstract—*Thirty-five patients with advanced metastatic breast cancer refractory to prior chemotherapy were treated with vindesine given at a fixed dose as a continuous 5-day infusion of* 1.5 mg/day *every* 4 weeks. *All patients were considered evaluable, and there were four patients with partial responses for more than* 3 months (11%) *and* 13 *patients with stable disease* (37%). *Two of the four responders had had disease progression on other vinca alkaloids. None of the responders had proven doxorubicin resistance. Side-effects included myelosuppression, neurotoxicity, nausea, stomatitis and fever, but these were seldom dose-limiting. The results—together with the results of other single-agent studies of vindesine summarized in the paper—indicate that the drug is an active agent in advanced breast cancer. However, the optimum way of administering vindesine and its inclusion in first-line therapy needs further study.*

INTRODUCTION

VINDESINE is a semisynthetic vinca alkaloid derived from vinblastine, with a range of activity against experimental tumors wider than that of vinblastine and similar to that of vincristine, but with less neurotoxicity [1]. In phase I and II clinical studies in man vindesine has shown activity in a variety of tumors [2–4]. Only limited information is available on continuous i.v. infusion in breast cancer, but one randomized study [5] suggests an improved therapeutic index of vindesine given as a 5-day infusion compared to bolus injection.

We conducted a phase II investigation of continuous vindesine infusion in patients with breast cancer refractory to conventional chemo- and hormonal therapy.

MATERIALS AND METHODS

Thirty-five patients with histologically proven breast cancer who failed prior therapy entered the study consecutively between July 1980 and December 1982. Patient characteristics are summarized in Table 1 and previous chemotherapy in Table 2. All patients had had previous endocrine therapy.

Vindesine was administered as a continuous i.v. infusion at a fixed dose of 1.5 mg/day for 5 days every 4 weeks. The dose was modified when patients had persistent neurotoxicity or myelosuppression, and in patients with significant liver dysfunction. To maintain a steady rate of drug delivery infusion pumps were used, also on an outpatient basis.

Investigations before and during treatment

Table 1. *Patient characteristics**

Characteristic	
Age (yr)	
Median	57
Range	34–76
Disease-free interval (months)	
Median	16
Range	0–121
Menopausal status	
Premenopausal	15
Postmenopausal	20
Duration of prior chemotherapy (months)	
Median	15
Range	1–68
Performance status†	
0–1	17
≥2	18
Site of disease	
Bone	22
Nodes and/or soft tissue	19
Visceral	26
Liver dysfunction (bilirubin >20.3 μmol/l)	5

*Unless otherwise indicated, values = No. of patients.
†ECOG scale.

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Table 2. Response to vindesine related to prior exposure to other drugs

Drugs						No. of patients		
Cyclophosphamide	5-Fluorouracil	Methotrexate	Doxorubicin	Vincristine	Vinblastine	Total	PR	SD
x	x	x				1	1	0
x	x		x			8	0	1
x	x	x	x			9	1	4
x	x	x	x	x		13	1	7
x	x	x	x	x	x	3	1	1
x	x	x		x	x	1	0	0

included history and physical examination, total hematology survey, blood chemistry, urine analyses and appropriate radiologic and isotopic examinations. Tumor measurements were documented prior to each course of chemotherapy.

Responses were defined as follows [6, 7]. A complete response (CR) was defined as the complete disappearance of measurable disease. A partial response (PR) was defined as a decrease of at least 50% in the sum of the products of the perpendicular diameters of all measurable lesions for at least 3 months, without the appearance of new lesions and with or without recalcification of osteolytic lesions. In the case of liver involvement PR was defined as a 50% reduction in the sum of the vertical dimensions of the liver below the costal margin in both midsternal and midclavicular lines. Stable disease (SD) was defined as a $<50\%$ decrease or $<25\%$ increase in measurable disease without the appearance of new lesions. Progressive disease (PD) was defined as a $>25\%$ increase of measurable disease or appearance of new lesions. All patients who entered the study were considered evaluable. Patients who died early or who received only one course of therapy were defined as having PD. Time to disease progression was calculated from the first day of chemotherapy, and illustrated graphically using the method of Kaplan and Meier, as described by Peto *et al.* [8].

RESULTS

Of the 35 patients who entered the study none had CR and four (11%) had PR (103, 141, 173 and 196 days). These occurred in soft tissue and nodes (two patients) and liver (two patients). Two of the responding patients had received vinca alkaloids in the past (Table 2). Thirteen patients (37%) had SD for a median of 70 days, range 55–225 days. Figure 1 shows the time to disease progression for all patients.

The toxic effects are summarized in Table 3. Myelosuppression was moderate and only one patient had a life-threatening leucopenia-associated infection. Nausea, vomiting and stomatitis rarely occurred, but two patients had severe mucositis. They had significant liver dysfunction, and after dose reduction treatment was well tolerated. Three other patients with liver dysfunction had no toxic effects necessitating dose reduction. Fever during infusion was experienced by ten patients, but was only a major problem in two and never dose-limiting. Alopecia could not be assessed as it pre-existed in most patients due to prior chemotherapy.

Neurotoxicity was modest. Two patients with severe toxicity had PD when symptoms occurred and had no further treatment. In one patient who had received a vinca alkaloid in the past neurotoxicity was dose-limiting.

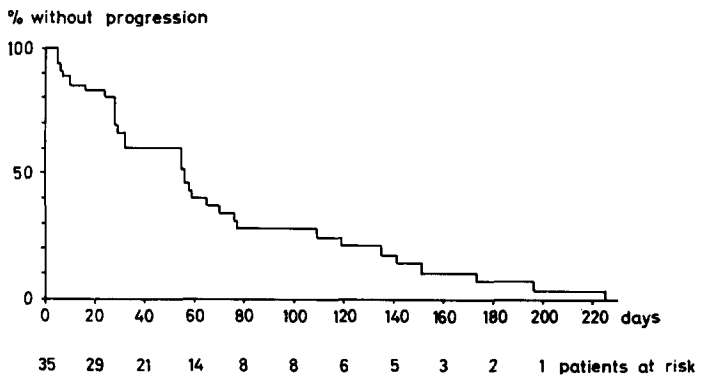

Fig. 1. Time to disease progression in patients receiving vindesine.

*Table 3. Toxicity**

Toxic effect	
WBC count nadir (cells/l × 10^9)	
Median	3.1
Range	0.4–10.7
Absolute platelet count nadir (Cells/l × 10^9)	
Median	100
Range	15–715
Anemia (hemoglobin ≤6.0 mmol/l)	12 (34)
Neurotoxicity	
Paresthesia/loss of deep tendon reflexes	5 (14)
Constipation/muscular weakness	7 (20)
Ileus	1 (3)
Paresis	1 (3)
Nausea/vomiting	4 (11)
Stomatitis	3 (9)
Fever with infusion	10 (29)
Infections	4 (11)

*Unless otherwise indicated, values = No. of patients (%).

DISCUSSION

Theoretically continuous infusion of a phase-specific cytostatic builds up and maintains an effective concentration of the agent while asynchronously proliferating tumor cells proceed to the sensitive cell cycle phase. Experimental studies [9] have indicated that for vincristine and vindesine the concentration was the important determinant of lethal effect, while for vinblastine cell kill increased with the length of exposure time. However, one study indicates that the clinical advantages obtained with prolonged infusions of vinblastine might extend to vindesine but not to vincristine [10].

The therapeutic activity of vindesine in advanced heavily pretreated breast cancer has been tested in studies of more than 300 patients (Table 4). Although CR was obtained in only five of these patients [11, 15, 16], one study of ten previously untreated patients showed CR in two patients [3], suggesting considerable activity of vindesine in untreated breast cancer.

Vindesine has been given either as bolus injection of 3–4 mg/m^2 every 1–2 weeks or as a continuous 5-day infusion of 1.0–1.2 mg/m^2/day every 3 weeks. The toxic effects have been those summarized in Table 3, but at a higher level than we observed. Severe myelosuppression has been observed at a dose level higher than 1.2 mg/m^2/day for continuous 5-day infusions [5], and cumulative neuromuscular toxicity has been a significant problem whatever schedule has been used [5, 13], limiting the ability to deliver the planned dose in a number of patients. When the number of patients (Table 4), assessment of response, definition of response duration (1 vs 3 months) and exclusion criteria (early death and protocol violation excluded vs defined as having PD) [7] are taken into account, the results we report here are in accordance with those obtained at higher dose levels and with a more severe toxicity.

Three of our four responding patients had received vinca alkaloids in the past (Table 2) and had had disease progression with this therapy. Other authors have reported similar findings [3, 4, 10, 13]. Thus, either there is a lack of cross-resistance between the vinca alkaloids—which is fairly unlikely according to experimental data [20]—or, due to differences in individual pharmacology and toxicity, vindesine may have a

Table 4. Phase II trials of vindesine in the treatment of metastatic breast cancer

Investigators (ref. No.)	Method	No. of patients	CR + PR (%)	CL (%)*
Smith *et al.* [3]†	Bolus	11	9	0–41
Miller *et al.* [4]	Bolus	13	23	5–54
	Bolus	26	8	1–25
Yap *et al.* [5]				
	Infusion	25	28	12–49
Yap *et al.* [10]	Infusion	16	31	11–59
	Daily bolus	25	24	9–45
Fleishman *et al.* [11]				
	Infusion	26	31	14–52
DiBella *et al.* [12]	Bolus	26	8	1–25
Cobleigh *et al.* [13]	Bolus	21	29	11–52
Gilby *et al.* [14]	Bolus + infusion	7	29	4–71
Staumbough *et al.* [15]	Bolus + infusion	11	63	31–89
Skelley *et al.* [16]	Bolus	17	18	4–43
ten Bokkel Huinink *et al.* [17]	Bolus	17	12	1–36
Fiorentino *et al.* [18]	Bolus	9	11	0–48
Pooled by Nagel [19]	Bolus	50	10	3–22
Present study	Infusion	35	11	3–27

*Confidence limits at a $P < 0.05$ level.

†Includes only previously treated patients; 2 CR and 3 PR in 10 previously untreated patients.

better therapeutic index when compared to other vinca alkaloids in certain clinical situations.

Cross-resistance between vinca alkaloids and anthracyclines appears to be a widespread phenomenon in experimental tumor systems [20, 21]. However, clinical responses have been reported in doxorubicin-resistant patients [5, 13]. In our study three of the responders (Fig. 1) responded previously to doxorubicin until maximum tolerable dose was reached. Consequently, clinical cross-resistance could not be assessed.

Vindesine is another active antitumor agent in metastatic breast cancer. The inclusion of the drug in first-line combination therapy needs further study and the question of clinical cross-resistance to anthracyclines is of major interest. At present the value of adding vindesine to an anthracycline in metastatic breast cancer is being studied in a randomized way [Skovsgaard, personal communication].

The optimum way of administrating vindesine is not yet established, and though vindesine may yield a more favourable therapeutic index when administered by continuous infusion, further randomized studies are needed to establish these findings. The correlation between plasma concentration of vindesine and clinical activity is unknown. However, the gamma half-life of vindesine is 24 hr [1] and four half-lives are needed to reach steady state when administered by continuous infusion [22]. Giving a priming dose prior to infusion would shorten the interval until plateau concentration is reached without adding the peak dose known from conventional bolus therapy [22]. This procedure might be an object for further investigations.

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