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Report

Weekly schedule of vinorelbine in pretreated breast cancer patients

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Summary

Purpose: In this phase II study, we explored tolerability and activity of vinorelbine administered according to a dose-dense weekly schedule with hematopoietic growth factor support in pretreated, advanced breast cancer patients.

Patients and Methods: From January 1994 to March 1996, 40 patients with metastatic breast cancer, pretreated with at least one prior anthracycline-containing regimen, were entered into the study. Patient characteristics: median age 53 years (range 32–70); ECOG performance status 0-1: 34 patients, 2: 6 patients; dominant visceral metastatic disease: 15 patients, dominant non-visceral: 25; anthracycline-refractory/resistant: 2 patients, sensitive: 38 patients. Six patients were treated as first-line therapy for metastatic disease and 34 in second- or subsequent lines.

All patients received vinorelbine at the dose of 25 mg/m^2/week as a short intravenous infusion, together with routine antiemetic medication. Granulocyte-colony stimulating factor (Lenograstim) at the dose of 150 μg/m^2 subcutaneously on day 3 was included in the treatment schedule.

Results: The median number of treatment weeks was 23 (range: 4–24), with a delivered dose-intensity (DDI) of 23.8 mg/m^2/week (range: 18.7–25, 95.2% of projected dose-intensity).

Toxicity was mild, with non-complicated neutropenia being the main toxicity observed (grade 3–4 in 25% of the patients but only 2% of treatment weeks). Overall response rate was 52.5%, with complete responses in 12.5% of patients. Median duration of the response and median time to progression were 10 and 9 months, respectively. Median overall survival was 19 months.

Conclusion: Dose-dense weekly vinorelbine is safe and effective with minimal toxicity in pretreated advanced breast cancer patients.

Introduction

Breast cancer is the most frequent neoplasm in women in European countries, with estimated incidence of 135,000 new cases per year (24% of all cancer cases) and 58,000 recorded deaths per year (18% of all cancer deaths) [1]. Notwithstanding the increasingly widespread use of adjuvant chemotherapy, about 60% of the patients will ultimately develop distant metastases.

Metastatic breast cancer is considered an incurable disease, but currently available treatments (chemo-or hormone therapy) can produce substantial palliative benefits and appear to prolong the average survival by approximately 9–10 months [2–3]. The main objective of treatment is therefore to make patients' lives symptom free for as a long as possible with the fewest adverse effects.

Anthracyclines (doxorubicin and epirubicin) are among the most active agents for the treatment

of metastatic breast cancer. Although anthracycline-containing regimens obtain objective responses in the majority of patients (50–70% in first-line), with a high rate of complete responses [4], the response rate in pretreated patients is much lower (about 30%) [5]. Therefore, the discovery of new active drugs, as well as the exploration of new combinations and schedules of drugs with proven efficacy, is clearly needed.

Vinorelbine and the taxanes are promising new agents with demonstrated efficacy against advanced breast cancer both as single agents and in combination. Vinorelbine is a semisynthetic vinca alkaloid and it is the first analogue of this family to bear a chemical substitution in the catharanthine ring, rather than in the vindoline portion of the molecule [6]. The reaction of vinorelbine with tubulin is similar to that of other vinca alkaloids, and causes microtubule depolymerization while blocking their formation [7]. Among all vinca alkaloids, vinorelbine has the weakest affinity for axonal microtubules, while maintaining a very strong affinity for spindle tubulin [8]. Used as single agent at the dose of 20–30 mg/m^2 on a weekly basis, or on days 1–8 every three weeks it has been proven active in advanced breast cancer as both first-line (response rate 41%–50%) [9–13] and second-line (response rate 30%–42%) [14, 18] treatment.

Hematological toxicity is dose-limiting. Myelosuppression is usually not cumulative and is mainly characterized by neutropenia [19]. This effect often limits the possibility of maintaining a planned weekly interval between administrations. The other common toxicity of vinorelbine is mild peripheral neuropathy, characterized by paraesthesias and hyperesthesias [20] and autonomic neuropathy causing constipation.

In this phase II study we have explored the activity and tolerability of vinorelbine plus G-CSF in a weekly schedule in pretreated patients with metastatic breast cancer.

Patients and methods

From January 1994 to March 1996, 40 patients with metastatic breast cancer were entered into the study. All patients provided informed consent. Eligibility criteria included the following: histologic or cytologic proof of breast cancer with at least one bidimensionally measurable or evaluable metastatic lesion, life expectancy $\geq$3 months, age between 18 and 75 years, performance status (PS, Eastern Cooperative Oncology Group [ECOG] scale) 0–2. Other requirements were adequate bone marrow function (absolute neutrophil count >2,000/μl; platelet count >100,000/μl; haemoglobin >9 g/dl); adequate liver function (total bilirubin $<$ 1 $\times$ upper normal limit (UNL); ASAT and/or ALAT $<$ 3.5 $\times$ UNL except in the presence of concomitant bone metastases and normal liver function); adequate renal (serum creatinine $<$ 1.5 $\times$ UNL; BUN <45 mg/dl) and cardiac function.

All patients had to have received prior chemotherapy with at least one anthracycline-containing regimen, in either the adjuvant or the metastatic setting, completed at least 4 weeks before beginning the new treatment. Prior hormone therapy was allowed, as well as prior radiotherapy provided that at least 4 weeks had elapsed since the last treatment and no more than 20% of the bone marrow reserve had been irradiated. Irradiated lesions were not used for response assessment, unless clearly progressive.

Patients with brain metastases, pulmonary carcinomatous lymphangitis, neoplastic ascites, and/or pleural effusion as the only site of disease were considered not eligible. Other exclusion criteria included inadequate bone marrow reserve and renal or cardiac insufficiency.

The baseline evaluation of each patient consisted of complete medical history and physical examination, neurological evaluation, including electromyography (EMG) and PS assessment. All patients had baseline chest radiograms, bone scan, and abdomen ultrasonography as well as other appropriate imaging techniques to document the extent of disease.

Laboratory studies at presentation included determination of complete blood cell and platelet counts, biochemical profile, and serum tumor markers (CEA and CA 15-3). Complete blood cell and platelet counts were repeated once a week during treatment. Patients underwent complete physical examination and biochemical profile before each treatment, while neurological examinations by EMG were repeated after 12 and 24 weeks of treatment, and at 3 and 6 months during follow-up.

Treatment

Vinorelbine was administered weekly at the dose of 25 mg/m^2 as a 20 min i.v. infusion in 100 ml of normal saline through a peripheral venous access. A total of 24 weeks of treatment were planned in the absence of unacceptable toxicity or disease progression.

In order to avoid unplanned treatment delays, G-CSF (Lenograstim) at the dose of 150 μg/m^2 s.c. on

day 3 was included in the treatment schedule. Emesis was prevented with 8 mg of ondansetron given i.v. before chemotherapy plus 8 mg of dexamethasone given i.v. after the vinorelbine infusion.

Toxicity and dose modifications

Toxicity was graded by WHO criteria [21]. Asthenia was graded as absent, mild (asymptomatic or minor symptoms, no treatment required), moderate (moderately symptomatic, minor treatment required), or severe (symptomatic and interfering with function, major treatment required). No dose reductions were planned for toxicity. In the presence of hematological toxicity of $\geq$ grade 2, treatment was suspended until WBC recovered to 2.5×10^9/l and the neutrophil count recovered to a minimum of 1.5×10^9/l. In the presence of non-hematological toxicity $>$ grade 2, treatment was suspended until recovery to $\leq$ grade 1.

Response criteria

WHO criteria were used to evaluate responses [21]. Criteria used to define a complete response of bone metastates were the disappearance of all osteolytic lesions, normalization of bone scans for at least four weeks, and no need for pain medication. A partial response was defined as improvement or stability of X-ray images with reduced intensity and number of high-uptake areas in scintiscans, alleviation of bone pain allowing at least 50% reduction of analgesic dosages, and an improvement in performance status by at least one score for at least four weeks.

Responses were assessed at 12 and 24 weeks of treatment, by repeating the same investigations performed at entry. Response duration was defined as the interval between the first day of treatment and the time of PD. Survival was calculated from the first day of treatment to the day of death or the last available follow-up.

Statistical analysis

The dose intensity (DI, mg/m^2/week) was calculated as previously described by Hryniuk et al. [22]. Continuous data were summarised as the median and the range 95% confidence intervals (CI) were calculated, where appropriate. Response duration, progression-free and overall survival were calculated according to the Kaplan–Meier method [23].

Results

All 40 patients were evaluable for toxicity and activity. Patient characteristics are given in Table 1. Patients who had progressed during treatment with anthracyclines were defined as anthracycline-refractory. Patients who had progressed within 6 months from the completion of an anthracycline-containing adjuvant regimen or had SD as the best response to anthracycline-containing regimens for metastatic disease were defined as resistant. The

Table 1. Patient characteristics

Median age (range)	53 (32–70)
Performance status (ECOG)	
0–1	34 (85%)
2	6 (15%)
Menopausal status	
Premenopausal	10 (25%)
Postmenopausal	30 (75%)
Hormone receptor status	
ER +	17 (42.5%)
ER −	8 (20%)
Unknown	15 (37.5%)
Metastatic sites	
Dominant visceral	15 (37.5%)
Dominant non-visceral	25 (62.5%)
Lung	4
Pleura	2
Pericardium	1
Liver	13
Bone	26
Soft tissues	17
Ovarian	1
Number of metastatic sites	
1	15 (37.5%)
2	23 (57.5%)
≥ 3	2 (5%)
Treatment strategy	
First-line	6 (15%)
Second-line	25 (62.5%)
$\geq$ Third-line	9 (22.5%)
Anthracycline status	
Refractory/resistant	2 (5%)
Sensitive	38 (95%)
DFS	
<24	19 (47.5%)
>24	21 (52.5%)

Table 2. Hematological toxicity

Toxicity	Maximum toxicity per patient (no = 40) (%)				Toxicity per week (no = 803) (%)			
	G1	G2	G3	G4	G1	G2	G3	G4
Neutropenia	25.0	32.5	20	5	10.8	6	2	0.2
Anemia	42.5	22.5	10.0	–	28	9	1	–
Thrombocytopenia	5.0	2.5	–	–	0.9	0.1	–	–

Table 3. Non-hematological toxicity

Toxicity	Maximum toxicity per patient (no = 40) (%)				Toxicity per week (no = 803) (%)			
	G1	G2	G3	G4	G1	G2	G3	G4
Nausea/vomiting	22.5	7.5	–	–	2.1	0.9	–	–
Mucositis	10.0	–	–	–	0.5	–	–	–
Neuropathy	15.0	7.5	–	–	1.7	0.3		
Phlebitis	27.5	17.5	15.0	–	4.0	1.0	1.0	–
Constipation	32.5	7.5	–	–	2.5	0.5	–	–
Alopecia	20.0	22.5	12.5	–				
Asthenia								
Mild	12.5				7			
Moderate	47.5				5			
Severe	17.5				1			

remaining patients were considered anthracycline-sensitive.

All patients received at least 4 weeks of treatment (median 23, range 4–24). Projected dose intensity (DI) was 25 mg/m^2/week; median delivered DI was 23.8 mg/m^2/week (range 18.7–25.0 mg/m^2/week, 95.2% of projected DI)

Table 4. Response to treatment

Response	
Overall response rate (95% CI)	52.5% (37–68)
CR	5/40
PR	16/40
NC	14/40
PD	5/40

Toxicity

A total of 40 patients and 803 weeks were assessable for toxicity. Haematological toxicity, particularly neutropenia, was the main toxicity observed (Table 2). Grade 3 and 4 neutropenia occurred in 10/40 (25%) patients, despite the use of prophylactic G-CSF, but in only 17/803 (2%) weeks. Neither febrile neutropenia nor documented infections were observed. Four out of 40 (10%) patients developed grade 3 anemia in 9/803 (1%) weeks. Median delay was one week. Thrombocytopenia was negligible.

Non-haematological toxicity was mild (Table 3). Peripheral neurosensory toxicity did not exceed grade 2 and was always reversible. Mild constipation ($\leq$ grade 2) occurred in 16/40 (40%) patients and in 23/803 (3%) weeks, respectively. Gastrointestinal tolerability was excellent. Grade 3 local phlebitis and pain at the injection site was observed in 6/40 (15%) patients and 8/803 (1%) weeks. Grade 2 alopecia was seen in 9/40 (22.5%) and grade 3 in 5/40 (12.5%). Severe asthenia occurred in 7/40 (17.5%) patients and 8/803 (1%) weeks.

Response to treatment

Overall response rate was 52.5% (95% CI 41.3–67.7), with 5 CRs (12.5%) and 16 PRs (40%). Disease stabil-

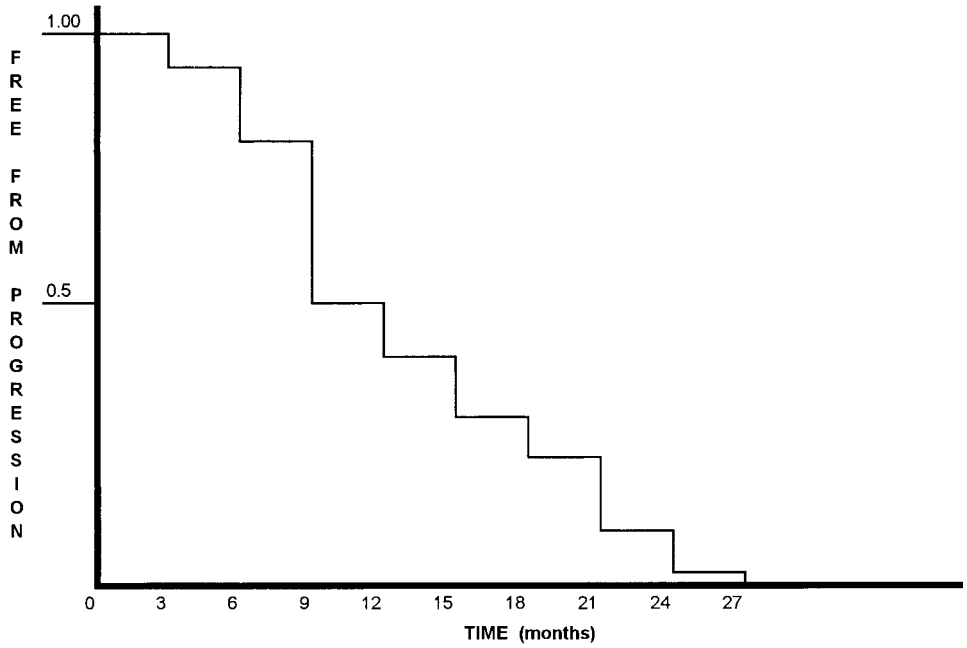

Figure 1. Progression-free survival.

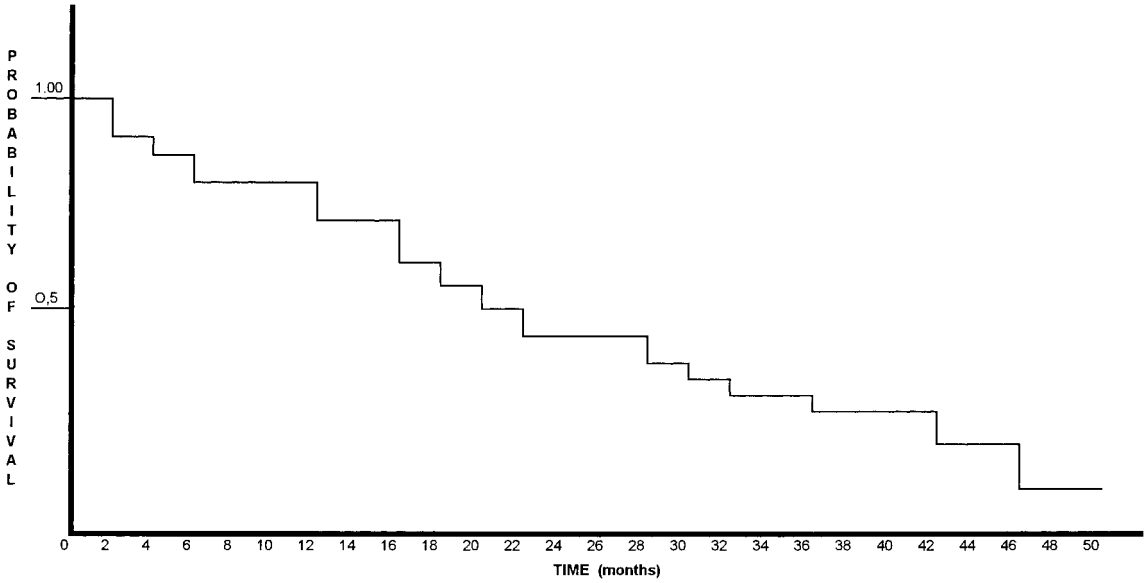

Figure 2. Overall survival.

ization (NC) was achieved in 14 patients (35%), and 5 patients (12.5%) had PD. Objective responses on liver metastases were observed in 8/13 (61.5%, 1 CR, 7 PRs) patients.

Median duration of the response was 10 months (range 5–21). Median time to progression was 9 months (range 1–27) Figure 1. At a median follow-up of 45 months, estimated overall survival was 19 months (range 2–54+) Figure 2.

Discussion

The clinical results of vinorelbine are impressive and suggest that this agent is an important vinca alkaloid

for the treatment of several solid tumors, including breast cancer. Although activity is higher in breast cancer patients treated with vinorelbine as first-line chemotherapy for stage IV disease [9–13], significant anti-tumor activity has also been reported in women who had received and failed prior chemotherapy for metastatic disease [14–18].

An important attempt at increasing the therapeutic efficacy of vinorelbine is the use of prolonged infusion schedules. The results of a phase I/II trial by Toussaint et al. employing continuous infusion vinorelbine indicate a good clinical activity (response rate at the highest dose-level 55.5%) and suggest the existence of a relationship between objective responses and actually delivered DI [24].

Another approach aimed at increasing the delivered dose-intensity is that of using weekly administration schedules, which represents the clinical application of the dose-density theory [25]. The availability of hematopoietic growth factors has, indeed, recently allowed myelotoxic agents to be given more frequently. A dose-dense weekly schedule assures that more drug is given per unit of time, resulting in the death of more cancer cells; in addition, the theoretical superiority of dose-density may relate to the temporal limits imposed on regrowth between cycles [26]. Besides, the use of G-CSF is important not only to avert severe hematological toxicity but to maintain the frequency of weekly administration.

In fact Livingston et al. [27] tested a weekly intravenous vinorelbine schedule employing doses ranging from 30 to 35 mg/m^2/week in pretreated metastatic breast cancer patients. This study demonstrated that vinorelbine can be given on a weekly basis safely with concurrent hematopoietic growth factor support. This permitted a DDI of 27.7 mg/m^2/week, versus 15.7 mg/m^2/week for Gasparini et al. [28] and 19.3 mg/m^2 in the series reported by Jones et al. [29].

Dose intensity may be important as a determinant of response to the vinca-compounds. A report by Toussaint et al., in which vinorelbine was given as a continuous infusion over five days, indicated a direct relationship of response rate to dose-intensity.

In the present study, we employed a weekly vinorelbine schedule with a planned DI of 25 mg/m^2/week, which represents a 50% dose-intensity increase as compared with the standard schedule of 25 mg/m^2 on days 1 and 8 every three-week (planned DI 16.6 mg/m^2/week). By using G-CSF this schedule has been proven feasible (DDI 23.8 mg/m^2/week, 95.2%) with acceptable toxicity, even in our cohort of heavily pretreated patients. The present dose-dense weekly schedule did not increase the incidence of either clinical and electrophysiological neurotoxicity, as compared with the classical schedule [30]. Both the high response rate (52.5%, 95% CI 37-68) and the overall survival (19 months, range 2–54 and above) observed in this subgroup of patients mainly treated as $\geq$ second-line strategy (85%) favourably compare with those reported with single-agent vinorelbine administered according to the standard schedule [9–18]. In addition, a high activity on visceral sites of disease, particularly liver metastases (response rate 61.5%, 95% CI 35–88), has been observed, which also favourably compares with that reported for standard-scheduled vinorelbine (response rate on liver metastases of about 30%).

In conclusion, weekly vinorelbine administered with G-CSF support is an active and well-tolerated treatment for advanced breast cancer. Further exploration of this schedule is warranted also in a first-line setting.

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