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Phase II study of ifosfamide plus vinorelbine in metastatic breast cancer patients previously treated with combination chemotherapy

Abstract Forty-six patients were included in a phase II study to evaluate the response rate and toxicity of a combination of ifosfamide and vinorelbine in metastatic breast cancer patients previously treated with one or more regimens of chemotherapy. Treatment consisted of ifosfamide 1.6 g/m^2 IV days 1–3 (with mesna) and vinorelbine 25 mg/m^2 IV days 1 and 8, every 3 weeks up to 6 cycles. The median age was 55 years (range 40–76), the World Health Organization (WHO) performance status was 0–1 in 93% of the patients and 2 in the remaining 7%. In all, 43% had received two or more previous lines of chemotherapy, and 91% had been treated with anthracyclines. Forty-four patients were evaluable for response, and all patients for toxicity. The overall response rate was 36.4% [95% confidence interval (CI) 22.4–52.2]. Stabilization was observed in 20.4% and progression in 43.2%. The median time to progression was 25 weeks (95% CI 14–36). Median relative dose intensity (= actual received dose intensity/planned dose intensity) was 0.99 for ifosfamide and 0.80 for vinorelbine. The main toxicity was hematological, with 63% of the patients experiencing grade 3–4 neutropenia. With a moderate toxicity, this is an active regimen that may be taken into consideration in pretreated metastatic breast cancer patients when further chemotherapy is indicated.

Key words Metastatic breast cancer · Vinorelbine · Ifosfamide

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Introduction

Breast cancer is sensitive to a variety of pharmacological treatments, but metastatic disease is not curable with conventional therapy. The median survival from the manifestation of metastases is about 3 years, but occasional patients survive for many years with a good quality of life. Some of these patients have received adjuvant chemotherapy and one, two, or even more lines of chemotherapy for metastatic disease. After having used combination chemotherapy with anthracyclines and with taxanes, the choice of an active chemotherapy regimen, when indicated, is not an easy decision. The chance of response decreases by about half with each subsequent treatment, and there is no effective way of identifying patients with disease sensitive to further chemotherapy [1, 2].

Vinorelbine and ifosfamide are two interesting drugs for the treatment of metastatic breast cancer. Ifosfamide, an alkylator agent, is an oxazaphosphorine analogue of cyclophosphamide with a more effective DNA cross-linking activity [3, 4]. Vinorelbine, a vinca alkaloid, is a very active agent for the treatment of

breast cancer, with responses similar to those observed with anthracyclines [5–7]. The combination of these two drugs deserves evaluation. Different spectra of toxicity allow the use of adequate doses of each drug, and since ifosfamide causes a G2 phase arrest of the cell cycle [8], there is a theoretical advantage for using a phase-specific agent such as vinorelbine after ifosfamide. The activity of this combination in breast cancer patients has already been reported in at least three studies [9–11].

Patients and methods

A total of 46 patients from nine Spanish institutions were entered in the trial. All patients had histologically proven metastatic breast cancer, measurable or evaluable disease, performance status (WHO) 0–2, were over 18 years of age, had normal hepatic and renal function and adequate hematological parameters (granulocytes $>2\times10^3/\mu l$, hemoglobin >10 g/dl, platelets $>100\times10^3/\mu l$). Abnormalities of liver enzymes owing to metastatic disease were permitted, but bilirubin was always in the normal range. There was no restriction for the number of previous lines of chemotherapy, but no prior exposure to ifosfamide or vinorelbine was allowed. Informed consent was obtained according to institutional guidelines in all cases.

Chemotherapy consisted of ifosfamide 1.6 g/m^2 per day IV in a 1-h infusion for 3 consecutive days (days 1–3) and vinorelbine 25 mg/m^2 per day IV on days 1 and 8 (days 1, 8). Mesna was given at a dose of 960 mg/m^2 per day IV divided into 3 doses of 320 mg/m^2 IV administered at the time of ifosfamide infusion, 4, and 8 h later. All patients received prophylactic anti-emetics at the clinician's discretion. Cycles were repeated every 3 weeks for a maximum of 6 cycles unless there was disease progression. For vinorelbine on day 8, the following dose modifications were applied: 100% of the dose if the level of neutrophils was $>1.5\times10^3/\mu l$ and that of platelets $>100\times10^3/\mu l$; 75% of the dose if the level of neutrophils was $1.0–1.5\times10^3/\mu l$ and that of platelets $>100\times10^3/\mu l$; 50% of the dose if the level of neutrophils was $1.0–1.5\times10^3/\mu l$ and that of platelets $75–100\times10^3/\mu l$; 0% of the dose if the level of neutrophils was $<1.0\times10^3/\mu l$ or that of platelets $<75\times10^3/\mu l$. In the case of hematological toxicity on day 21, the following cycle was delayed until recovery. In the case of febrile neutropenia or severe toxicity, the following cycles were given at 75% of the planned dose. After 6 cycles, patients discontinued chemotherapy and were observed at regular intervals until relapse occurred. Relapsing or non-responsive patients were treated at the clinician's discretion.

Patients' performance status, response to treatment, and toxicity were assessed by standard WHO criteria [12]. Relative dose intensity was obtained for each patient by dividing the received dose intensity of ifosfamide and vinorelbine in mg/m^2 per week by the planned dose intensity (mg/m^2 per week) according to the protocol (100% of the dose at 3-week intervals). The time to progression (all patients) and the duration of response (responding patients) were measured from the start of chemotherapy, and the curves were calculated using the Kaplan-Meier method [13].

Results

Between January 1997 and March 1998, 46 patients were entered into the trial. Patients' details are listed in Table 1. The median age was 55 years (range 40–76). The WHO performance status was 0–1 in 93% of the cases and 2 in the remaining 7%. Forty-nine percent of the patients were premenopausal. Two or more sites of metastases were detected in 59% of the cases, and the disease was measurable in the majority of patients (87%). Twenty-six patients had received only one line of chemotherapy before entry into the study protocol, but only in 12 of them had this chemotherapy been given in the adjuvant setting. Two patients could not be evaluated for tumor response: one progressed with brain metastases early during the 1st cycle, and the other patient declined the treatment after the 2nd cycle. All patients were evaluated for toxicity and for dose intensity calculations.

Table 1 Patients' details

	Patients (*n*)
Age (years)	
40–49	11
50–59	18
60–69	14
≥70	3
Menopausal status	
Premenopausal	22
Postmenopausal	23
Unknown	1
Sites of disease	
Lymph nodes	12
Soft tissue	8
Breast/local recurrence	15
Lung	16
Bone	21
Liver	16
Mediastinum	1
Pleura	1
Bone marrow	1
Number of disease sites	
1	19
2	14
≥3	13
Indicator lesion	
Measurable	40
Evaluable	6
Number of previous chemotherapy regimens	
1	26[a]
2	16
≥3	4
Previous anthracyclines	
No	4
Yes	42
Previous hormonal manipulation	
No	14
Yes	32

[a] 12 patients had received only adjuvant chemotherapy

The response data are listed in Table 2. Overall response rate was 36.4% (95% CI 22.4–52.2). One patient achieved complete response of local cutaneous relapse with a duration of response of 28 weeks and 15 partial responses. Stabilization was observed in 20.4% and progression in 43.2%. Menopausal status, presence of liver metastases, number of disease sites, number of previous chemotherapy regimens, previous exposure to anthracyclines, or previous hormonal manipulation did not influence the response in our series of patients. Median time to progression was 25 weeks (95% CI

Table 2 Response to treatment

Response	Patients (*n*)	%	95% CI
Complete response (CR)	1	2.3	0–12
Partial response (PR)	15	34.1	20.5–49.9
Overall response (CR + PR)	16	36.4	22.4–52.2
Stable disease	9	20.4	9.8–35.3
Progression	19	43.2	28.3–58.9

14–36) (Fig. 1). The median duration of response was 39 weeks (95% CI 29–49).

A total of 203 courses of chemotherapy were given. The median number of cycles was 5 (range 1–6). The median relative dose intensity for ifosfamide was 0.99, and for vinorelbine, 0.80 (Fig. 2). The dose of chemotherapy on day 1 was administered on time in 130 cycles, delayed in 48 cycles, reduced in 15 cycles, and delayed and reduced in 10 cycles. The dose of vinorelbine on day 8 was given as planned in 100 cycles, reduced in 15 cycles, and omitted in 88 cycles.

Toxicity was moderate, and no treatment-related deaths occurred. All cycles were administered on an outpatient basis, and no hospitalization was required except for some episodes of febrile neutropenia. Main toxicity is shown in Table 3. Grade 3–4 toxicity was observed with neutropenia (29 patients), anemia (8 patients), thrombocytopenia (4 patients), mucositis (1 patient), and alopecia (10 patients). Notably, 10 patients developed 16 episodes of fever and neutropenia. These episodes resolved completely with intravenous antibiotics and standard supportive measures. Other toxicity not mentioned in Table 3 included local reaction in the site of vinorelbine administration in 5 patients and moderate asthenia in 5 patients.

Discussion

The search for active combination chemotherapy regimens for the treatment of metastatic breast cancer is an area of active clinical investigation. The activity of the combination of ifosfamide and vinorelbine has been reported. Leone et al. [9] treated 35 patients as first-line therapy for metastatic disease. The chemotherapy included ifosfamide 2 g/m^2 IV (days 1–3) with mesna, and vinorelbine 35 mg/m^2 (days 1, 15) every 21 days. The response rate was 57% (95% CI 39–75). The median time to treatment failure was 9 months. Pronzato et al. [10] treated 25 anthracycline-resistant patients. Ifosfamide (with mesna) was given at a dose of 1 g/m^2 (days 1–5), and vinorelbine at 25 mg/m^2 (days 1, 8). Objective responses were seen in 28% (95% CI 12–49.3), and 40% experienced stabilization of the disease. The median time to progression was 4 months. Bruno [11] treated 54 patients in second line. It was a phase I-II study with a dose of ifosfamide (with mesna) ranging between 2 and 3 g/m^2 (days 1–3) and a dose of vinorelbine of 25 mg/m^2 (days 1, 8). The overall response was 50% (95% CI 35–68), and the median duration of response was 15 months. Seven patients achieved a complete response.

The response rate obtained in the present study (36%, 95% CI 22–52) is in the range previously reported. Our series of patients was not homogeneous since patients with one, two, three or even more previous chemotherapy lines were included. This fact makes our patients an unfavorable prognostic group, and the response rate achieved is encouraging. It is well known that the chance of response to chemotherapy in metastatic breast cancer decreases with each subsequent line of treatment [1, 2, 14]. After the most effective agents (anthracyclines and taxanes) have been used, the remaining agents offer very little benefit.

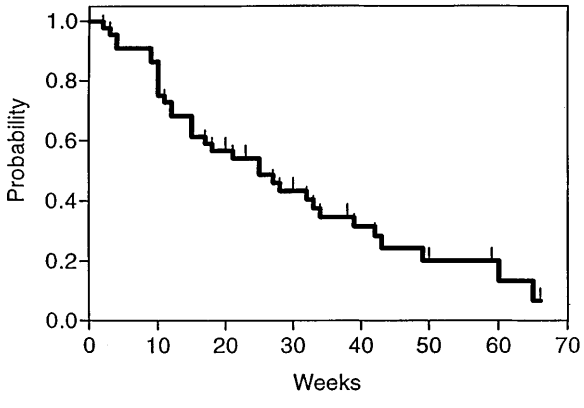

Fig. 1 Time to progression

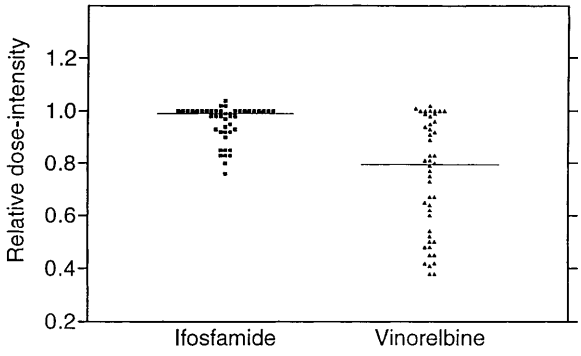

Fig. 2 Relative dose intensity (= actual received dose intensity/planned dose intensity)

Table 3 Worst toxicity ever observed (WHO criteria)

	0	1	2	3	4
Neutropenia	8	1	8	17	12
Anemia	22	7	9	7	1
Thrombocytopenia	35	6	1	4	–
Nausea/vomiting	24	12	10	–	–
Peripheral neuropathy	40	3	3	–	–
Mucositis	36	3	6	1	–
Hematuria	44	2	–	–	–
Hepatic toxicity	44	1	1	–	–
Alopecia	28	3	5	9	1

Toxicity observed in the study, although manageable, was more severe than previously reported, perhaps owing to previous exposure to chemotherapy. The episodes of febrile neutropenia developed by ten patients resolved with standard measures, and many of them could be treated in the outpatient setting.

The delivered dose intensity for vinorelbine was not optimal. The dose on day 8 was omitted or reduced in 50% of the cycles owing to hematological toxicity. This fact may have contributed to a lower activity of the regimen, since vinorelbine is a very active drug in breast cancer.

With a moderate toxicity, the combination of ifosfamide and vinorelbine in this study produces a significant response in a pretreated patient population. It may be taken into consideration in pretreated metastatic breast cancer patients in whom further chemotherapy is indicated. The response rate observed in this unfavorable prognostic group justifies further evaluation of this combination in better prognostic situations.

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