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ORIGINAL ARTICLE

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Ifosfamide given by continuous-intravenous infusion in association with vinorelbine in patients with anthracycline-resistant metastatic breast cancer: A phase I–II clinical trial

Abstract *Background*: Vinorelbine (VNR) is highly active in metastatic breast cancer (MBC) and has shown an overall response rate of 40%–50% as first-line treatment. In vitro, a synergy has been observed between this drug and ifosfamide (IFX). In addition, the pharmacokinetics of IFX suggest that it may have greater activity when given by continuous-intravenous infusion (C.I.V.I.). The aim of this study was therefore to assess the antitumor efficacy and toxicity of the combination of bolus VNR and C.I.V.I. IFX as second-line therapy in anthracycline-resistant breast cancer patients. *Patients and methods*: Forty-two patients with MBC who had already received anthracycline-based chemotherapy were treated with a regimen consisting of IFX, by C.I.V.I. for 72 hours and bolus VNR. The courses were repeated every three weeks for a maximum of eight cycles. Four dose intensification steps were planned. IFX, 1.5 g/m^2 on days 1–3 + VNR, 30 mg/m^2 on day 1 (six patients); IFX, 2 g/m^2 on days 1–3 + VNR, 25 mg/m^2 on day 1 (six patients); IFX, 1.8 g/m^2 on days 1–3 + VNR, 25 mg/m^2 on days 1 and 8 (six patients); IFX, 2 g/m^2 on days 1–3 + VNR, 25 mg/m^2 on days 1 and 8 (24 patients). Sodium-2-mercaptoethane sulfonate (mesna) was associated with IFX at an infusion ratio of 1:1 and, once the infusion was completed, per os every four hours for three times. *Results*: All of the 42 patients entered were assessable for toxicity, and 41 of them for response. Neutropenia was the most frequently-occurring toxicity, but only five patients at the highest dose level (11.9%) presented grade 4, and none of those at the first three steps. Other significant toxic effects were mild (only grade I–II). The median relative dose intensity was 95% at the highest dose level and all the treatments were administered on an out-patient basis. The overall response rate was 36.5% with a CR rate of 4.8% (two of 41 patients, all at the highest dose level) and a PR rate of 31.7% (13 of 41 patients). The median response duration was 7.0 months (range 2–13 months). *Conclusions*: The present phase I–II study shows that the IFX and VNR combination is an active and well-tolerated treatment in MBC and provides an alternative to taxanes for patients previously treated with anthracyclines.

Key words Ifosfamide · Metastatic breast cancer · Vinorelbine

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Introduction

Ifosfamide (IFX), a structural isomer of the oxazaphosphorine cyclophosphamide, appears to be active on neoplastic cells at every stage of the mitotic cycle, but more active in phase S. Clinical trials have demonstrated interesting activity of IFX in breast cancer patients, especially since the use of sodium-2 mercaptoethane sulfonate (mesna) has permitted the administration of

higher IFX dosages [1–7]. Employed alone, this agent has shown objective response rates in approximately one-third of the patients with MBC with a tolerable toxicity.

Vinorelbine (VNR), on the other hand, is a semi-synthetic vinca alkaloid that acts as a neoplastic agent through microtubule depolimerization. From a pharmacological point of view, this drug differs from other vinca alkaloids used, in that its MTD is four-fold higher than that of vinblastine, and it causes less neurotoxicity. Neutropenia is the main dose-limiting toxicity. When used as a single agent against MBC, VNR has provided response rates of 40% to 50% in first-line treatment and 20% in second-line. However, its activity in association with other antineoplastic agents for this disease, even though very promising, must still be better defined [8].

Vinorelbine and ifosfamide have different mechanisms of action. In vitro, a synergy of action has been demonstrated, and clinical studies of other solid tumors, such as non-small-cell lung cancer, have documented positive activity [9]. Pharmacokinetic studies have shown that a great amount of IFX is metabolized when given in divided, rather than in single high doses, and the 24-hour infusion of IFX has been shown to be effective administration schedule for solid tumors [10].

On the basis of these considerations, this phase I–II trial was initiated to evaluate the activity and toxicity of the VNR-IFX association as salvage treatment for anthracycline-resistant MBC patients.

Patients and methods

Patients with histologically- or cytologically-proven breast cancer and evidence of progressive metastatic and/or local recurrent disease were admitted to the study. Additional eligiblity criteria included: performance status (PS) ≤2 (ECOG scale), age ≤70 years, evaluable or measurable lesions, no brain or leptomeningeal involvement, normal liver and renal function, leukocyte count $>3{,}000$/ml and platelets $>100 \times 10^9$/l patients had to have had previous anthracycline containing treatment. Prior treatment with anthracyclines in either the adjuvant or metastatic settings was an inclusion criterion. Therapy with cytotoxic drugs or hormones had to have been discontinued six weeks before their entry into the study. Previous therapy with cyclophosphamide was acceptable. In addition, oral informed consent was obtained.

Before starting treatment, the patients underwent a physical examination, and measurements of the study parameters were made. During treatment, patients had weekly hematologic counts. Response to treatment was assessed after every two cycles and four weeks after the last treatment. Toxicity and objective responses were evaluated according to WHO criteria.

Chemotherapy was administered on an out-patient basis. The IFX infusions were given with elastomeric or electronic pumps by means of a permanent central venous system.

Treatment consisted of three different dose levels of IFX given as a C.I.V.I. for 72 hours combined with mesna and i.v. bolus VNR, as shown in Table 1. Oral hydration was performed during C.I.V.I. IFX. Six patients were treated at each dose level. If no dose-limiting toxicity (DLT) was encountered. The dose was escalated for next cohort. For each level, the first treated patient was followed for three weeks before the succeeding patients were allowed to enter the study.

Six patients were included in the first three steps and 24 in the last. The latter group entered the phase II study.

A total of 226 therapeutic cycles were administered, with the dose-limiting toxicity never being reached, considered as grade 4 neutropenia or thrombocytopenia for a period of more than four days, neutropenic fever or the need for platelet infusion, grade 4 emesis/nausea, grade 2 creatinine or any grade 3 non-hematologic toxicity except for alopecia.

Results

Between June 1994 and June 1996, 42 patients were enrolled in this study. Their characteristics are summarized in Table 2. This was a representative population of anthracycline-pretreated patients, six of whom were refractory (progressive disease during anthracycline-containing regimens) and 30 resistant (stable or progressive-disease within six months of metastatic or adjuvant anthracycline-containing regimens, respectively). The majority of the patients had dominant sites of metastasis in the viscera, 11 in the soft tissues and only one in the bones. All of the patients had previously undergone at least one chemotherapy course with anthracyclines: 17 patients (40.4%) in the adjuvant setting and 25 patients (59.5%) for metastatic disease; 11 patients had received more than one chemotherapy course.

Patients received a mean of five cycles (range two to nine) of the study combination. The overall toxicity observed with this combination regimen was acceptable. Hematological toxicity at the first step consisted of grade 2 leucopenia in two patients (33%); at the second step of grade 2 and grade 3 leucopenia in two (33%) and one patients, (16.6%) respectively. At the third step two patients (33%) had grade 3 neutropenia without fever; only five patients, at the fourth step, were classified as having grade 4 neutropenic (11.9%). There were no cases of neutropenia fever, anemia or thrombocytopenia, and none of the patients required hospitalization.

Other non-hematologic toxic effects were mild (only grades 2–3), and consisted mainly of nausea, alopecia and two cases of severe asthenia. Macroscopic hematuria occurred after two courses in two different pa-

Table 1 Study design: planned dose-intensification steps

Dose level	Ifosfamide	Mesna	Vinorelbine
Step I	1.5 g/m^2/day c.i 72 hours	1.5 g/m^2/c.i 72 hours + 300 mg/m^2 p.o. at hour: 72, 76, 80	30 mg/m^2 i.v on day 1
Step II	2.0 g/m^2/day c.i 72 hours	2.0 g/m^2/c.i 72 hours + 400 mg/m^2 p.o. at hour: 72, 76, 80	25 mg/m^2 i.v on day 1
Step III	1.8 g/m^2/day c.i 72 hours	1.8 g/m^2/c.i 72 hours + 360 mg/m^2 p.o. at hour: 72, 76, 80	25 mg/m^2 i.v on days 1, 8
Step IV	2.0 g/m^2/day c.i 72 hours	2.0 g/m^2/c.i 72 hours + 400 mg/m^2 p.o. at hour: 72, 76, 80	25 mg/m^2 i.v on days 1, 8

The courses were repeated every three weeks

Table 2 Patient characteristics

Characteristic	*n*
Total no. of patients	42
Evaluable for toxicity	42
Evaluable for responses	41
Age (years)	
Median	54.5
Range	35–70
Menopausal status	
Pre-	14
Post-	28
Performance status (ECOG)	
0	19
1	23
Previous chemotherapy	
Anthracycline-based	42
One line	31
> one line	11
Dominant metastatic sites	
Viscera	30
Bone	1
Soft tissues	11

tients but recovery was complete and immediate in both instances (four hours). Peripheral neuropathy was not observed.

There were no dose reductions; 10 of 226 cycles (4.4%) were delayed and in eight cycles, the eighth day's dose of VNR was not administered (3.5%).

The median relative dose-intensity of the fourth step was 95% for both drugs.

Of the 42 patients entered, 41 were evaluable for response. One patient was not evaluable having failed to meet the eligibility criteria of the study

The responses obtained with this regimen are summarized in Table 3. No responses were obtained at step one. Overall responses were obtained in 15 of the 41 patients (36.5%) and partial responses in 13 (31.7%). There were two complete responses (CRs) in the last step: in both cases, the metastatic sites involved the liver, lung, bone and lymph nodes.

The median response duration was seven months (range 2–13 months).

Discussion

Despite the progress that has been achieved in recent years in the management of breast cancer, prognosis in patients with metastatic disease is still poor, principally for those who have received second-line therapy and who experience progression or relapse after an anthracycline-based combination. In this last group of patients, the objective response rate in second-line treatment is less than 30% and response duration is usually very short.

The prolonged infusion of IFX increases the exposure of tumor cells to the drug with moderate hematological toxicity, allowing a combination with i.v. bolus VNR, one of the most active drugs in MBC.

The present study shows that IFX plus VNR has an interesting activity, as confirmed by the objective response rates of 36% with a median duration of 7.0 months in a series of patients with a prevalence of visceral metastases who had previously received heavy, anthracycline-based treatment. A direct relationship between dose and response seems to be evident with two complete responses obtained at the highest dose level. Because of the high response rates obtained at steps 2 and 3 of the phase I study in this cohort of patients heavily pretreated with chemotherapy we decided to refrain from further increasing the drug doses to avoid unacceptable toxicity.

Results of this study may suggest that the therapeutic efficacy could be ascribed to the synergism association rather than to an overlapping of the two drugs.

The toxicity observed during the 226 courses of treatment was mild and reversible, but the MTD was not reached. Severe neutropenia was observed in only five patients (12%) with no cases of neutropenic fever. Other side effects were negligible; three and 12 patients had severe and moderate asthenia, respectively and two patients hematuria. The activity of this combination as found in our study was similar to that reported by Bruno [11]. In the latter study a higher incidence of myalgias and peripheral neurotoxicity was observed.

In conclusion, this association of IFX and VNR is well tolerated, and for anthracycline-resistant and heavily pretreated out-patients with MBC, may represent an alternative to taxanes for those previously treated with anthracyclines. In this regard a randomised study of this combination in comparison with taxoids in anthracycline-resistant metastatic breast cancer is needed.

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Table 3 Response to treatment

Dose level	No. of pts	OR (%)	CR (%)	PR (%)	SD (%)	PD (%)
Step I	5	0	–	–	5 (100)	–
Step II	6	2 (33.3)	–	2 (33.3)	3 (50)	1 (16.6)
Step III	6	3 (50)	–	3 (50)	2 (33.3)	1 (16.6)
Step IV	24	10 (41.6)	2 (8.3)	8 (33.3)	8 (33.3)	6 (25)
Total	41	15 (36.5)	2 (4.8)	13 (31.7)	18 (43.9)	8 (19.5)

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