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ORIGINAL ARTICLE

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Ifosfamide and vinorelbine in metastatic breast cancer in patients with prior anthracycline therapy

Abstract *Objective*: A prospective trial to evaluate the efficacy and toxicity of ifosfamide (IFX) and vinorelbine (VNB) in patients with prior anthracycline therapy for metastatic breast cancer (MBC) was conducted. At the same time, the scheduling of VNB in order to minimize toxicity of the combination was also evaluated. *Patients and methods*: Twenty-three patients with MBC who had already received initial chemotherapy with doxorubicin-containing regimens either as adjuvant or as first-line treatment in MBC were entered into the study. IFX 3 g/m^2 and mesna 3 g/m^2 were given in divided doses over 2 days. In 4 patients, VNB was given 25 g/m^2 on days 1 and 3 in 3-h infusion. In 8 patients, VNB was given on days 1 and 8 and in 5 patients VNB was given on days 1 and 15. Thirteen patients had received doxorubicin in adjuvant setting, while 10 patients received doxorubicin as first-line treatment in metastatic disease. Dominant disease sites were soft tissues in 7 patients, visceral in 12 patients, and bone in 4 patients. The median age was 47 years. *Results*: Overall objective response was seen in 12/23 patients (52.2%). Four patients achieved complete remission (CR), 8 patients achieved partial remission (PR). The median duration of response was 9 months in responding patients, and the median overall survival duration was 15 months. The major dose-limiting toxicities were neutropenia grade III and IV in 8/17 patients and asthenia grade III and IV in 4 patients. *Conclusion*: IFX and VNB is an active combination. Neutropenia and asthenia were most significant when VNB was given on days 1 and 3. In the best-tolerated regimen, VNB was given on days 1 and 8.

Key words Metastatic breast cancer · Chemotherapy · Ifosfamide · Vinorelbine

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Introduction

Metastatic breast cancer (MBC) is considered incurable with currently available therapies. The median survival of patients with MBC is less than 2 years [1]. Approximately 50% of patients who have received adequate treatment for early breast cancer with surgery, chemotherapy and radiation will eventually relapse and require further therapy [2]. The results of second-line treatment are disappointing. Cases of complete remission (CR) are rare, and overall response (OR) rates range from 10 to 35% [1]. New drugs and innovative strategies are needed to induce higher and more durable remission in MBC [3].

Anthracyclines are increasingly used as part of adjuvant chemotherapy in the treatment of early breast cancer. In an adjuvant setting, doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 have now become the treatment of choice owing to shorter duration of treatment and less toxicity after the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial (B-15) reported its 3-year results [4]. In MBC, doxorubicin is of limited use owing to increased cardiotoxicity [5] if used as part of adjuvant treatment.

Vinorelbine (VNB) is a unique semisynthetic vinca alkaloid. It binds and induces complete depolarization of microtubules [6]. Significant single-agent activity with VNB is seen in metastatic breast cancer at a weekly dose of 30 mg/m^2 [7, 8]. In combination with anthracyclines, overall response rates of 70% are achieved with a CR

rate of 21% [9]. Ifosfamide (IFX) is a semisynthetic alkylating oxazaphosphorine with a similar therapeutic index as cyclophosphamide. Clinical evidence from studies in soft tissue sarcomas indicates lack of cross-resistance between IFX and cyclophosphamide [10]. In solid tumors including breast cancer, IFX has shown response rates in one-third of patients [11, 12]. The combination of IFX and VNB as first-line therapy in breast cancer has produced CR rates of 14–35% and OR rates of 54–58% [13, 14].

We decided to use the combination of IFX and VNB in MBC in patients who have received prior anthracyclines either in adjuvant setting or in metastatic disease. Secondly, we also wanted to evaluate the scheduling of VNB on days 1 and 3, days 1 and 8 or days 1 and 14 in order to minimize toxicity.

Patients and methods

Patient selection

A phase II trial was conducted on women with histologically confirmed breast cancer and evidence of metastatic disease. Eligibility criteria included a life expectancy of >3 months, a performance status of 2 or less according to Eastern Cooperative Oncology Group (ECOG) performance status and measurable disease sites. Adequate hematological, renal, and hepatic profile were necessary unless tumor involvement was present. Patients with metastasis in skeleton only had to have lytic disease measurable on X-ray. The patients must have received prior chemotherapy with doxorubicin either as adjuvant treatment or for treatment of metastatic disease. A minimum interval of 4 weeks following completion of adjuvant chemotherapy or chemotherapy for metastatic disease was required.

Ineligibility criteria included pleural effusion or ascites as only evidence of disease, prior treatment with IFX or VNB, central nervous system (CNS) metastasis.

Pretreatment and follow-up evaluation

Clinical staging was performed in all patients and included a complete history and physical examination with tumor measurement. Complete blood cell counts with differential and platelet counts were repeated weekly, and a biochemical profile was assessed every 4 weeks. Imaging procedures included chest X-rays, bone scans, and ultrasound. Computed tomography (CT) scans were done if necessary. In areas with abnormal uptake on bone scans, skeletal X-rays were performed. Both X-rays and scans of the abnormal areas were repeated as needed for response assessment with a minimum interval of 3 months.

Treatment plan

Chemotherapy consisted of IFX 3 g/m^2 + mesna 3 g/m^2 in divided doses on days 1 and 2 as a 3-h infusion. VNB 25 mg/m^2 was given on days 1 and 3 in 4 patients. In 13 patients, VNB was given on days 1 and 8, and 6 patients received VNB on days 1 and 15. VNB was given as a 3-h infusion in 500 cc of dextrose saline.

Response criteria

Patients were assessible for response after a minimum of 2 cycles of therapy; however, all patients were assessible for toxicity if they had received treatment. Standard criteria were used. OR included either CR or partial remission (PR). CR was defined as the complete disappearance of all known disease for at least 1 month. CR in bone was defined as recalcification of all lytic osseous lesions and the disappearance of all abnormal uptake areas previously noted in a bone scan, with complete absence of bone pain without analgesics. PR was recorded as a ≥50% reduction in the sum of the product of the two longest perpendicular diameters of all measurable lesions for at least 1 month. PR in bone was considered an improvement or stabilization of radiographic assessment of disease with subjective improvement (a decrease in bone pain and lowering of analgesics by at least 50%) and improvement in performance status by one grade or more that lasted at least 3 weeks. Stable disease (SD) was defined as a less than 50% decrease in tumor size. Progressive disease (PD) was defined as a 25% increase in the sum of the product of the two longest perpendicular diameters of all measurable lesions (even with regression of other lesions) or the appearance of new lesions.

Toxicity and dosage modification guidelines

Toxicity evaluations were based on World Health Organization (WHO) criteria [15]. No dose modification was made for grade I and II hematological toxicity. Treatment was delayed until ANC >1500 and platelets $>100{,}000$. For grade III and IV toxicity, chemotherapy with IFX and VNB was restarted at 50% of the original dose.

Results

Twenty-three women were entered into the study. All patients were evaluable for response, toxicity and survival. Patients' characteristics are shown in Table 1. Age ranges from 31 to 65 years with a median age of 47 years. The majority of the patients was premenopausal. The most frequent metastatic sites involved were soft tissue (69%), bone (52%), followed by lung (43.5%) and liver (39%).

The OR rate was 52.2%, with 34.8% achieving PR. There were 4 (17.4) patients who achieved CR. Stable disease was present in 6 patients, while 5 patients did not respond to treatment. Table 2 depicts response according to patients' characteristics. Most of the responses were seen in patients who had received chemotherapy in adjuvant setting (61.5%) and had had a disease free interval of >3 years.

Dose intensity

A total of 96 courses of chemotherapy was delivered to 23 assessible patients. The median number of courses delivered was 4 (range 2–6). Treatment cycles were delayed in 8 patients (34.8%) owing to hematological toxicities. Dose modifications were made in 5 patients for severe myelosuppression.

Dose intensity was calculated for cycles 1 and 3. The projected DI for IFX was 1.5 g/m^2 per week and for VNB, 12 mg/m^2 per week. The mean dose intensity received was 1.5 g/m^2 per week for cycle I and 1.25 g/m^2 per week for cycle III of IFX, and 11.5 mg/m^2 per week for cycle I and 10.9 mg/m^2 per week for cycle III for VNB. The RDI was 1 and 0.83 for IFX and 0.95 and 0.91 for VNB for cycles I and III.

Table 1 Patients' characteristics

Characteristics	No. of patients (%)
Entered on study	23 (100)
Age (years)	
Range	31–65
Median	47
Performance status	
0, 1	18 (78.3)
2	5 (21.7)
Menopausal status	
Premenopausal	15 (65.2)
Postmenopausal	8 (34.8)
Prior chemotherapy	
Adjuvant	13 (56.5)
Metastatic	10 (43.5)
Metastatic sites	
Liver	9 (39.1)
Lung	10 (43.5)
Other visceral	3 (13.0)
Bone	12 (52.2)
Soft tissue	16 (69.6)
Dominant site of disease	
Visceral	12 (52.2)
Bone	4 (17.4)
Soft tissue	7 (30.4)
No. of metastatic involved organs	
1	6 (26.1)
2	9 (39.1)
≥3	8 (34.7)
Disease-free interval (years)	
<1	6 (26.1)
1–3	7 (30.4)
>3	10 (43.5)

Table 2 Response according to patients' characteristics

Characteristics	No. of patients (%)	Response
Entered on study	23 (100)	12/23 (52.2)
Performance status		
0, 1	18 (78.3)	12/18 (66.7)
2	5 (21.7)	0/5 (0)
Menopausal status		
Premenopausal	15 (65.2)	7/15 (46.7)
Postmenopausal	8 (34.8)	5/8 (62.5)
Prior chemotherapy		
Adjuvant	13 (56.5)	8/13 (61.5)
Metastatic	10 (43.5)	4/10 (40.0)
Metastatic sites		
Liver	9 (39.1)	1/9 (11.1)
Lung	10 (43.5)	6/10 (60.0)
Other visceral	3 (13.0)	2/3 (66.7)
Bone	12 (52.2)	4/12 (33.3)
Soft tissue	16 (69.6)	8/16 (50.0)
Dominant site of disease		
Visceral	12 (52.2)	5/12 (41.7)
Bone	4 (17.4)	1/4 (25.0)
Soft tissue	7 (30.4)	6/7 (85.7)
No. of metastatic involved organs		
1	6 (26.1)	5/6 (83.3)
2	9 (39.1)	5/9 (55.6)
≥3	8 (34.7)	2/8 (25.0)
Disease-free interval (years)		
<1	6 (26.1)	1/6 (16.7)
1–3	7 (30.4)	4/7 (57.1)
>3	10 (43.5)	7/10 (70.0)

Toxicity

Toxicity profile is listed in Table 3. Grade III and IV neutropenia was present in 6 patients. Of these, 3 patients developed febrile neutropenia. Two patients died due to septic shock when they arrived in the hospital. Grade I and II myalgias occurred in 17 patients. They normally started on day 4 or 5 and resolved within 1 week. Only 1 patient developed grade IV myalgias requiring hospitalization.

Table 3 Toxicity profile

Characteristics	Grades 1, 2 *n* (%)	Grades 3, 4 *n* (%)
Granulocytes	13 (56.5)	5 (26.1)
Infection	5 (21.7)	3 (13.0)
Hemoglobin	17 (73.9)	0 (0)
Platelets	18 (78.3)	1 (4.3)
Stomatitis	13 (56.5)	1 (4.3)
Ncuropathy	12 (52.2)	0 (0)
Phlebitis	13 (56.5)	0 (0)
Nausea/vomiting	16 (69.6)	1 (4.3)
Myalgia	17 (73.9)	2 (8.7)
Diarrhea	16 (69.6)	0 (0)
Alopecia	5 (21.7)	18 (78.3)
Asthenia	13 (56.5)	2 (8.7)
Constipation	13 (56.5)	0 (0)

Discussion

MBC has variable natural history. In some patients the disease is very aggressive, causing multiorgan involvement and death in a few months. In others disease progression is more benign, running an indolent course with an overall survival of 10–15 years [16]. There is no standard treatment for MBC. Combination chemotherapy is an effective mode of palliation in stage IV breast cancers which are hormonal refractory. Taxanes and anthracyclines are considered to be the most active drugs in the treatment of breast cancer. With taxanes, single-agent activity of more than 50% has been reported. A 28% response was documented in doxorubicin refractory patients [17, 18]. Taxanes, however, are extremely expensive, and the use of this class of drugs is limited in the developing countries, where resources are limited and the entire cost of treatment is borne by the patient. The role of anthracyclines is also decreasing in MBC with increasing use of these compounds in adjuvant setting.

IFX has shown significant activity both as a single agent [19, 20] and in combination therapy. IFX in combination with mitoxantrone, etoposide or doxorubicin induces high response rates with tolerable side effects [21–23]. In combination with VNB, a 38% response rate has been documented in untreated non-small cell lung cancer [24]. The combination of IFX and VNB is attractive, as these drugs are not part of standard treatment protocols in early and late breast cancer. As previously mentioned, despite structural similarity between IFX and cyclophosphamide the two drugs are not completely cross-resistant. VNB has also shown no cross-resistance with doxorubicin and mitoxantrone [25]. In previously untreated MBC, Leone et al. have reported an OR in 58% of patients, with CR occurring in 14% [13]. In our series in which patients had received prior anthracyclines, the OR was approximately 52.2%. This response is similar in range to that reported with various combinations [26]. In four patients who achieved CR, the median DFS was 10 months. The major dose-limiting toxicity was myelosuppression requiring dose modification or delay in cycle. Two patients with grade IV myelosuppression expired in septic shock. One of the contributing factors was delay in reporting to the hospital after development of the febrile episode. The other significant toxicity was severe asthenia in two patients, which occurred in patients receiving VNB on days 1 and 3. Other side effects including constipation, myalgias, and phlebitis were generally of a milder degree, and the regimen was well tolerated, especially if VNB was given on days 1 and 8 or days 1 and 15. However, when VNB was given on days 1 and 15 there was a delay in the subsequent cycle in three patients.

In conclusion, the combination of IFX and VNB has shown considerable activity in our series of patients with prior anthracycline therapy. The treatment has tolerable side effects and can be administered on an outpatient basis.

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