Cancer Chemother Pharmacol (1990) 26 (Suppl): S 63–S 65

Cancer Chemotherapy and Pharmacology

Experience of the Belgian Society of Medical Oncology with single-administration 5 g/m² ifosfamide with mesna as second- or third-line therapy in advanced breast cancer*

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Summary. In an ongoing phase II trial conducted in advanced breast cancer, we tested a therapy schedule consisting of continuous, 24-h infusion of 5 g/m² ifosfamide (IFO) in 3 l dextrose saline with mesna (MSN), repeated every 3 weeks until disease progression. Since September 1988, 16 heavily pretreated patients with advanced disease (11 with visceral lesions) considered refractory to standard chemotherapy (regimens always including cyclophosphamide) have been included. Objective partial remissions were observed in two cases (one in liver and one in soft-tissue and pleural lesions), and disease stabilization for at least 3 months occurred in four cases. No treatment-related death was recorded and tolerance was judged to be excellent (six cases) or acceptable in all instances. The haematological toxicity consisted mainly of transient leucopenia (nadirs evaluated by WHO scale as grade 3 in 43% and grade 4 in 29%), sometimes associated with thrombocytopenia (grade 3 in 7% and grade 4 in 7%). Other side effects included nausea and/or vomiting (grade 3–4 in 33%); worsening of preexisting alopecia (five cases); haemorrhagic cystitis (one case); mild, transient somnolence (two cases); and moderate fluid retention (two cases). We concluded that infusion of 5 g/m² IFO over 24 h with MSN rescue might represent an acceptable second- or third-line salvage regimen. Close monitoring of haematological and renal function parameters is recommended. A larger number of patients will be treated in a continuation of this study to evaluate the true response rate within narrower confidence limits.

Introduction

In spite of considerable efforts aimed at early diagnosis of breast cancer, many patients suffering from this disease sooner or later develop symptomatic metastases, for which only palliation can be offered. The efficacy of available chemotherapeutic drugs is limited; thus, the development of new drugs or more potent analogs is eagerly awaited. Ifosfamide (IFO) is an alkylating agent that differs chemically from cyclophosphamide in the placement of one of its chloroethyl groups. In early clinical studies, activity was demonstrated for IFO, but at the expense of severe urothelial toxicity that prevented its widespread use.

The discovery of a specific antidote, mesna (MSN), has enabled the reintroduction of IFO into clinical practice, with encouraging results [1, 2, 5]. The combination of IFO and MSN was shown to exert significant antitumor efficacy against sarcomas, testicular cancer, germ-cell tumours, ovarian cancer and, probably, digestive and lung carcinomas. In several instances, IFO has even been found to have a wider spectrum of activity than its parent drug, cyclophosphamide [2, 5]. However, there is at present no consensus about the optimal IFO dose and the time over which it should be given or about the MSN dose and duration of administration required to prevent urothelial toxicity. With the combination, high doses of IFO (5 g/m²) can be given with fair clinical safety, although some neurological toxicity (consisting of transient somnolence and confusion) has been reported [6]. In advanced breast cancer, a wide range (0–80%) of responses seems to have been obtained, probably due to major differences in selection of patients, evaluation criteria and therapy schedules [2, 5].

For these reasons, in 1987 the Belgian Society of Medical Oncology (BSMO) initiated a phase II randomized study aimed at comparing the tolerance and efficacy of IFO with MSN in fractionated administration (1.25 g/m² per day × 4) with 5 g/m² IFO given as an i. v. bolus every 3 weeks in patients with advanced breast cancer who failed to respond to conventional first- or second-line chemotherapy. After inclusion of 11 cases (age, 48–75 years; me-

* Presented at the Satellite Symposium "Ifosfamide in Gynecological Tumors" of the 5th European Conference on Clinical Oncology and Cancer Nursing", London, September 3–7, 1989

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Table 1. Pretreatment characteristics of patients

Patients (*n*)	16
Median age (range)	52 (40–62) years
Median WHO performance index (range)	1 (0– 2)
Predominant metastatic site:	
Soft tissue	4
Bone	1
Viscera	11
Prior endocrine therapy:	
Median treatments/patient (range)	1 (0– 4)
Prior chemotherapy:	
Median treatments/patient (range)	2 (1– 3)

Table 2. Response to treatment

Type of response	Number of patients (%)	Response by involved site:		
		Soft tissue	Bone	Viscera
Partial remission	2 (12.5)	1	–	1
Stable disease	4 (25.0)	–	3	4
Failure	10 (62.5)	4	3	6

dian, 63 years), the trial was stopped due to 2 toxic deaths (CNS + renal toxicities) in the i. v. bolus arm. These events occurred in one patient with initial, massive hepatic involvement and in another who had previously experienced transient renal function impairment during cisplatin therapy. Among nine evaluable cases, one partial remission of lung lesions (in the six patients treated by i.lv. bolus) and one disease stabilization were observed.

Therefore, the BSMO decided to test by phase II trial another therapy schedule derived from that successfully used in soft-tissue sarcomas by the EORTC [3], consisting of continuous 24-h infusion of 5 g/m^2 IFO with MSN rescue. This paper reports the preliminary results obtained in the first 16 patients included in this study.

Patients and methods

Patients. Histologically proven progressive, locally advanced or metastatic breast carcinoma was required. The disease had to be considered no longer suitable for surgery or radiation therapy and refractory to conventional systemic treatment with hormones and chemotherapy. All patients had measurable or evaluable lesions, assessable by physical and/or radiological examination. Lymphoedema, hilar enlargement, pleural or peritoneal effusion, bone marrow infiltration or osteoblastic metastases were all considered to be non-evaluable. All prior antineoplastic drugs had been withdawn for at least 4 weeks before the initiation of the present protocol. Patients with uncontrolled neuromeningeal metastases, a second malignancy, or a poor prognosis (performance status of ≥ 3 or massive lung or liver involvement) were excluded. Other eligibility criteria included an age of <75 years, a leucocyte count of $\geq 4{,}000/mm^3$, a platelet count of $\geq 100{,}000/mm^3$, serum albumin levels of ≥ 30 g/l and normal hepatic and renal function (i. e. bilirubin values of <1.2 mg/dl and creatinine clearance of >60 ml/min).

Treatment schedule. All patients were prehydrated with 1 l 5% dextrose 0.5 *N* saline solution (DNS) containing 1.25 g/m^2 MSN, given over 2 h.

Table 3. Toxic effects

Type	Proportion of patients with toxicity of:		
	WHO grade ≥ 1	WHO grade ≥ 3	WHO grade 4
Nausea + vomiting	80%	33%	6%
Diarrhea	12%	0	0
Mucositis	6%	0	0
Myelosuppression	86%	72%	29%
Infection	12%	0	0
Alopecia (worsening)	30%	30%	0
Somnolence	12%	0	0
Renal function impairment	6%	0	0
Haemorrhagic cystitis	6%	0	0
Cardiac	6%	0	0

Table 4. Haematological toxicity recorded during the 2nd week of treatment (nadirs)

WHO grade	0–1	2	3	4
WBC:				
1st cycle	23%	31%	31%	15%
2nd cycle	33%	33%	23%	11%
Next cycles	0	20%	40%	40%
Overall worst	14%	14%	43%	29%
Platelets:				
1st cycle	84%	8%	8%	0
2nd cycle	89%	11%	0	0
Next cycles	83%	0	0	17%
Overall worst	72%	14%	7%	7%

At 1 h prior to IFO administration, 200 ml 20% mannitol solution was added. A 24-h infusion of 3 l DNS with 5 g/m^2 IFO and 2.5 g/m^2 MSN was then given, followed by a 12-h infusion of 2 l DNS containing 1.25 g/m^2 MSN.

Treatment duration and response evaluation. Therapy was repeated every 3 weeks until disease progression. The haematological nadirs (WBC and platelets) were systematically controlled during the 2nd week, and subsequent doses of IFO and MSN were eventually reduced by 25% if a grade 4 toxicity (WHO scale) had occurred. Treatment was delayed by 1 week when incomplete haematological recovery had occurred (i. e. WBC count of $<3{,}000/mm^3$; granulocyte count of $<2{,}000/mm^3$; or platelet count of $<100{,}000/mm^3$) or if major toxic manifestations or metabolic changes had been observed. The response to treatment was assessed according to standard UICC (International Union Against Cancer) criteria [4]. All patients underwent a physical examination every 3 weeks, when superficial lesions were measured and side effects were recorded. All baseline investigations, including chest X-rays, liver echography, bone scintigraphy or skeletal survey, were repeated after 6 weeks and at 3-month intervals thereafter. The treatment was continued until progression of the disease was documented.

Results

Six Belgian institutions contributed to this study by including 16 eligible cases between September 1988 and April 1989. All case-report forms were reviewed by the study coordinators (C.F. and R.P.). The characteristics of patients are summarized in Table 1. Most of them were

considered to have far advanced disease, as indicated by the high proportion of patients (69%) with visceral metastases, and the vast majority had undergone multiple endocrine manipulations. All had experienced disease progression under appropriate therapy with one or more chemotherapy regimens combining the most active agents against breast cancer (i.e. cyclophosphamide, 5-fluorouracil, anthracyclines and vinca alkaloids).

A total of 46 cycles of IFO were given, with a median of 2.5 cycles/patient. The details of responses are given in Table 2. Two patients had a partial remission of good quality in the liver (one case) and in soft-tissue and pleural lesions (one case), lasting for 4+ and 2+ months, respectively. Disease stabilization for a median duration of 4+ months (range, 3+–6+ months) was also seen in four patients with dominant visceral (three cases) or bone (one case) metastases. Overall, the median time to progression was 6 weeks (range, 3–24+ weeks). To date, five patients have died of their disease.

Most of the patients experienced side effects, which are listed in Table 3. However, tolerance was judged to be excellent in six cases and at least acceptable in all others. No treatment-related death was recorded. The haematological toxicity, described in Table 4, consisted mainly of transient, generally short-lived leucopenia, sometimes associated with mild thrombocytopenia; these changes resulted in dose reductions by 25% in three cases or occasional delay of treatment by 1 week in six cases. Other side effects included nausea and/or vomiting (grade 3–4 in 33%); worsening of preexisting alopecia (five cases); mild, transient somnolence (two cases); and moderate fluid retention (two cases). Renal and urothelial toxicity was rare, one patient having short-lived haemorrhagic cystitis and another exhibiting a mild, transient increase in creatinine levels (1.6 mg/dl).

Discussion

The present study demonstrates that infusion of 5 g/m^2 IFO over 24 h with MSN rescue might represent an acceptable second- or third-line salvage regimen in advanced breast cancer. It confirms the results recently published by Steger et al. [7] on a smaller series of patients. The response rate observed (12.5%) was rather low, but it should be emphasized that it might have been underestimated due to hazards of sampling (SE=8%) and the selection of patients with far advanced disease. It should also be recalled that all patients had lesions that had progressed under standard chemotherapy regimens containing cyclophosphamide. Thus, there is probably no absolute cross-resistance between IFO and its parent drug, the former possibly being more active than the latter.

In view of the toxicological data reported in our series and in our previous trial, described in the introducion, we recommend close monitoring of haematological parameters (with nadir determinations during the 2nd week) and of renal function before and during treatment. A larger number of cases will be treated in a continuation of this study to evaluate the true response rate within narrower confidence limits.

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