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High-dose ifosfamide and mesna in advanced breast cancer

A phase II study

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Summary. Thirty-two patients with metastatic breast cancer had previously been treated with chemotherapy (including anthracyclines). They were included in a trial to receive 6 g/m^3 ifosfamide, mixed with 6 g/m^2 mesna in 1000 ml saline infusion, infused over 4 h. Therapy was repeated every 21 days; the dose was reduced by 50%. Twenty-eight patients could be evaluated. An average of 4.2 cycles (range 2–8) was applied. One patient (4%) showed complete remission. Ten patients (36%) had a partial response. Ten patients (36%) experienced SD and the remaining patients (25%) PD. We conclude that high-dose ifosfamide shows activity in this group of pretreated patients and merits further investigation.

Combination chemotherapy is the treatment of choice for hormone-resistant breast cancer in phase M1. In fact, 40% to 60% of patients benefit from this mode of therapy, which produces clinical palliation without modifying the natural course of the disease [2, 7]. At present, research on new drugs and strategies for the application of cytostatics is the priority objective of most researchers, with the clear objective of improving the results obtained thus far.

The information that ifosfamide, a structural isomer of the oxazaphosphorine cyclophosphamide, is effective in advanced cancer of the breast goes back more than a decade [1, 5]. However, at that time its considerable urotoxicity rendered this agent inappropiate for further study. With the clinical introduction of the uroprotector mesna [4], this problem became avoidable, resulting in the re-evaluation of ifosfamide in a wide variety of neoplastic processes. This, together with the slight superiority of ifosfamide over cyclophosphamide in different experimental models [6] and its effectiveness, shown to be at least equivalent to that of cyclophosphamide in humans [3], justify its further study.

With the objective of obtaining greater experience with this cytostatic, a phase II study of ifosfamide at high doses was conducted in advanced breast cancer, the results of which are presented.

Patients and methods

A total of 32 patients with histologically confirmed carcinoma of the breast were included in the study; all had bidimensionally measurable metastasic lesions. Only patients with an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 who exhibited normal haematological, hepatic, renal and cardiac functions were included.

Table 1. Patient characteristics

Patients (*n*)	32
Evaluable patients (*n*)	28
Mean age (range)	52 (31–68) years
Premenopausal	14
Postmenopausal	18
Hormonal receptor status:	
Positive	13
Negative	12
Unknown	7
Disease-free period (range)	23.5 (2–86) months
Previous chemotherapy:	
Adjuvant CMF	29
Anthracyclines	14
Hormonotherapy	11
>>2 regimens	21
Sites of metastases:	
Bone	19
Pleura and lung	11
Liver	2
Skin and lymph node	4
>>1 site	2

CMF, cyclophosphamide/methotrexate/5-fluorouracil

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Table 2. Percentage of side effects observed during 118 courses of high-dose ifosfamide

	WHO grade:				
	0	1	2	3	4
Leucopenia	-	7%	39%	54%	-
Thrombocytopenia	7%	7%	86%	-	-
Alopecia	-	36%	36%	28%	-
Nausea and vomiting	-	68%	32%	-	-
Mucositis	75%	25%	-	-	-

At the time of diagnosis, 14 patients were premenopausal and 18, postmenopausal. The oestrogen receptor status was positive in 13 patients, negative in 12, and unknown in 7. The relapse-free interval ranged from 4 to 86 months (average, 23.5 months). All patients had previously been treated with chemotherapy, and 11 had also undergone hormonal treatment. In all, 30 patients showed metastases in one site, and in 2 cases disease had spread in two areas (Table 1).

Ifosfamide was infused at a dose of 6 g/m^2 (diluted in 1,000 ml saline solution) over 4 h; the same dose of mesna (6 g/m^2) was mixed with the infusion. Chemotherapy administration was repeated every 21 days; in patients who had previously undergone intensive chemotherapy, a 50% dose reduction was undertaken. Objective response and toxicity were determined according to WHO criteria. Only patients who completed at least two therapeutic cycles were considered to be evaluable for response. The time to disease progression was calculated from the start of treatment.

Results

In all, 28 patients were evaluable; 4 were non-evaluable due to refusal of treatment after the first cycle. A total of 118 cycles (average, 4; range, 2–8) were given.

One patient (4%) achieved a complete response; ten (36%) showed a partial response; ten cases (36%) were categorized as "no change" and seven patients (25%) had progressive disease. The average time to progression was 7.6 months for the 11 patients on objective response and 3.4 months for the 10 with stable disease.

Toxicity was mild in all 118 courses (Table 2). In general, therapy was tolerable, without WHO grade 4 toxitiy. In patients who had previously received intensive chemotherapy, it was necessary to modify the dose (50% reduction) or to prolong the therapy-free interval. One patient had a urinary infection and another developed a pulmonary infection; in both cases, the use of suitable antibiotics resulted in complete recovery. Urotoxicity, haemorrhagic disorders and treatment-related deaths did not occur.

Discussion

The present results show that ifosfamide produces positive responses in chemotherapeutically pretreated patients with advanced cancer of the breast, including those previously exposed to anthracyclines. Of our patients 40%, showed a response and 4% (1 case) achieved a complete remission. Among patients with pleuropulmonary metastases, one achieved a complete response and the remaining five showed a partial response (54.5%). In three patients with bone disease (15.7%), recalcification of osteolytic lesions continued, and one patient with skin and lymph node lesions showed a partial response (25%). Neither of the two patients with hepatic metastases responded.

Toxicity must be carefully considered in the administration of palliative therapy. In our study, the toxic effects observed during 118 courses of treatment were mild; overall, this therapeutic scheme may be considered to produce acceptable toxicity. As previously stated, grade 4 side effects were not seen, nor were there therapy-related deaths. Dose adjustments due to myelosuppression were necessary only in patients who had previously undergone intensive chemotherapy.

Our results suggest that ifosfamide given at high doses is effective in advanced cancer of the breast. We think that the activity observed justifies further study of this drug, both as a single agent and in combination with other cytotoxic compounds.

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