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Ifosfamide, methotrexate, and 5-fluorouracil: effective combination in resistant breast cancer*

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Summary. Ifosfamide has definite efficacy in many malignant tumours, including breast cancer. In the present study we substituted cyclophosphamide with ifosfamide in the combination CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) regimen in 25 patients with breast cancer whose disease was refractory to CMF or who had relapsed after previous response. Ifosfamide was given in an i.v. infusion at a dose of 1.2 g/m^2 daily for 5 days, together with mesna as a uroprotector (at 20% of the ifosfamide dose). Methotrexate was given at a dose of 40 mg/m^2 and 5-fluorouracil was given at 600 mg/m^2, both by i.v. push. Courses were repeated every 21 days. The 24 evaluable patients received 3–12 courses (average, 5 courses); results included a complete remission in 3 patients (12.5%) and a partial remission in 3 (12.5%). Among the remaining patients, improvement was seen in 4 (16.6%); stable disease, in 7; and progressive disease, in 7 (29.2%). The complete responses lasted for 11+, 13+, and 15+ months, and partial remissions, for 2, 6, and 9 months. The responses were detected in soft-tissue as well as visceral lesions, but not in bony lesions. The responders remain under follow-up. This study shows the efficacy of ifosfamide-containing chemotherapy in breast cancer. As toxicities were tolerable, higher doses of ifosfamide could safely be used in these patients. Use of this combination as first-line therapy in breast cancer could be considered for a future study.

Introduction

Patients with advanced or recurrent breast cancer can be palliated by hormonal manipulation or combination chemotherapy, and those who achieve good response may enjoy prolonged control of their disease. Unfortunately, >50% either relapse or do not respond to conventional therapy. It is well known that second-line therapy in this situation is much less likely to produce responses [1].

In the present study we used ifosfamide instead of cyclophosphamide in the well-known combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) as second-line chemotherapy in breast cancer patients.

Patients and methods

A total of 25 women with advanced or recurrent breast cancer who had received prior CMF chemotherapy and either were refractory to it or relapsed after initial response were eligible for this study. Their age ranged from 23 to 60 years (average, 46 years); 11 were postmenopausal and 14 were premenopausal. The duration of disease was between 2 months and 7 years. A total of 22 patients had recurrent disease after radical mastectomy, whereas the rest had advanced disease at the time of presentation. The sites of the lesions are shown in Table 1.

All patients were evaluated clinically and radiologically. Measurable lesions were evaluated and measured in two perpendicular diameters. Before entry, patients were required to have a total leucocyte count of $\geq$ 4,000/mm^3, a platelet count of $\geq$ 100,000/mm^3, a serum creatinine value of <1.5 mg%, and serum bilirubin levels of <2 mg%. Ifosfamide/methotrexate/5-fluorouracil (IMF) chemotherapy was given as follows: 1.2 g/m^2 ifosfamide in an i.v. infusion given daily for 5 days; 40 mg/m^2 methotrexate by i.v. push on day 1; 600 mg/m^2 5-fluorouracil by i.v. push on day 1. As a uroprotector, mesna was given at 20% of the ifosfamide dose by i.v. push at 0, 4, and 8 h after initiation of the daily ifosfamide infusion. Courses were repeated every 3 weeks, for at least three courses.

The criteria for response were: complete response (CR), complete disappearance of all measurable lesions for $\geq$ 4 weeks; partial response

Table 1. Sites of lesions

Local recurrence, chest-wall lesions	16
Lymph nodes	16
Contralateral breast	10
Liver	9
Lung	6
Bone	3

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Table 2. Response to IMF chemotherapy

	Number of patients
CR	3 (12.5%)
PR	3 (12.5%)
MR	4 (16.6%)
SD	7 (29.2%)
PD	7 (29.2%)

Table 3. Toxicities of IMF chemotherapy

Type	Grade 1	Grade 2
Gastrointestinal	7	17
Alopecia	0	12
Haematological	3	3
Haematuria	3	0

(PR), a reduction of >50% in the size of measurable lesions for ≥ 4 weeks, with no new lesions; stable disease (SD), no change in measurable lesions for ≥ 4 weeks, with no new lesions; and progressive disease (PD), an increase of >25% in the size of existing lesions or the appearance of new lesions.

Results

All patients had a Karnofsky score of 60–80 and received an average of 5 courses (range, 3–12). In all, 1 patient was lost to follow-up and 24 were fully evaluable (Table 2): a CR was achieved in 3 patients (12.5%); a PR, in 3 (12.5%); SD, in 7; and PD, in 7. In the remaining 4 patients, there was minimal reduction (MR) in the size of lesions (25%–50%). Thus, an overall response of 25% was reached; 41%, if MR is included. The duration of CR was 11+, 13+, and 15+ months, and that of PR was 2, 6, and 9 months; responses were observed in soft-tissue and visceral lesions, but not in bony lesions.

There were no severe toxicities. The main side effects were gastrointestinal (mucositis, nausea, and vomiting): grade 1 in 7 patients and grade 2 in 17 [Eastern Cooperative Oncology Group (ECOG)]. Grade 2 alopecia occurred in 12 cases. Haematological toxicities involved leucopenia: grade 1 in three patients and grade 2 in three. Microscopic haematuria was detected in three patients but was reversible in all cases (Table 3).

Discussion

Ifosfamide is a cytotoxic drug that , like other oxazaphosphorines, is inactive in vitro but highly active in vivo. In animal experiments it is characterized by efficacy against tumours resistant to other forms of therapy [1]. In clinical practice there is some evidence that ifosfamide is more effective than cyclophosphamide in sarcomas, testicular tumours, lung cancer, pancreatic cancer, non-Hodgkin's lymphoma, and cervical cancer [7].

Trials of ifosfamide in breast cancer started as early as 1975. In the cooperative study of Schnitker et al. [5], a total of 45 cases with breast cancer after prior chemotherapy were treated with ifosfamide as a single agent; 7 achieved a CR and 24, a PR. Hoefer-Janker et al. [3] observed 12 CRs among 56 patients with mammary carcinoma who received ifosfamide. However, the criteria of response in these studies were not clearly defined. Ifosfamide was also used in combination with vincristine in patients with breast cancer who had not previously undergone chemotherapy; responses were detected in 3 of 12 patients [2]. Treske [6] also used a combination of ifosfamide, vincristine, and tetrahydrofuryl fluorouracil; he achieved PRs in 8 of 24 patients with mammary carcinoma.

The present study was conducted in patients previously treated with CMF. In spite of the pretreatment, they responded to the IMF combination with an overall response (CR+PR) of 25%, with some improvement (MR) in another 16.6%. The complete responders remain in remission. Although the number of cases was small, the results achieved enable the conclusion that ifosfamide plays a role in the management of breast cancer. This encourages us to use higher doses of this drug either as a single agent or in combinations, as toxicities were mild and treatment was quite well tolerated by all patients. For future study, first-line IMF therapy could be tried.

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