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Treatment of metastatic breast cancer with the combination of ifosfamide, epirubicin and 5-fluorouracil*

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Summary. An ongoing trial of combination chemotherapy using ifosfamide (Holoxan), epirubicin and 5-fluorouracil was started in 1987. A total of 30 patients with metastatic cancer of the breast received 1.5 g/m^2 i.v. ifosfamide over 60 min on days 1–3, 50 mg/m^2 i.v. epirubicin on day 1 and 500 mg/m^2 i.v. 5-fluorouracil on day 1, followed by mesna (Uromitexan) given at 20% of the ifosfamide dose at 0, 4 and 8 h. The courses were repeated every 4 weeks. In all, 198 courses were given, ranging from 3 to 13 (median, 7) cycles/patient. The mean age of the 30 patients was 48 years (range, 35–66 years); 5 had not previously received chemotherapy and the others had failed prior cytotoxic and endocrine therapy. Overall, 28 patients were evaluable, 7 (25%) showed a complete response and 15 (54%) had a partial response, for an overall response rate of 22/28 (79%). Three patients showed stable disease with improved symptoms, and in three cases disease progression occurred. The median duration of response was 9 months (range, 3–20 months). Median survival was 11 months for all patients, 15 months for CRs, 10 months for PRs, 6 months for stable disease and 12 months for progressive disease (PD). Survival for the 22 responding patients was 12 months. Toxicity was acceptable and included alopecia, mucositis, nausea, vomiting, diarrhoea, mild cystitis and myelosuppression. Epirubicin did not appear to produce cardiac toxicity, and ifosfamide with mesna did not seem to result in severe urotoxicity. Chemotherapy with ifosfamide, epirubicin and 5-fluorouracil proved to be effective for treatment of advanced breast cancer and should be further studied in large, controlled trials.

Introduction

Ifosfamide (Holoxan) has a wide range of antitumour activity [2]. Its mechanism of action is not completely clear because of the complex pharmacology of the drug, requiring activation by liver microsomal enzymes. In metastatic breast cancer, ifosfamide given as a single agent has shown modest activity, with minimal subjective and objective toxicity [2]. Thus, it appeared reasonable to attempt combination therapy substituting ifosfamide for cyclophosphamide and epirubicin for doxorubicin [1, 3, 4]. A major factor leading to the decision to test this new combination was the well-documented late cardiomyopathy noted with doxorubicin and cyclophosphamide [4]. A lesser consideration was the hope that epirubicin, ifosfamide and 5-fluorouracil might be symptomatically better tolerated by patients with advanced breast cancer.

Patients and methods

Between June 1987 and February 1989, 30 consecutive patients with widely metastatic cancer of the breast were entered into a study of combination chemotherapy consisting of 1.5 g/m^2 i.v. ifosfamide given over 60 min on days 1–3, 50 mg/m^2 i.v. epirubicin given on day 1 and 500 mg/m^2 i.v. 5-fluorouracil given on day 1, followed by mesna (Uromitexan) given at 20% of the ifosfamide dose at 0, 4 and 8 h. The courses were repeated every 4 weeks. Assessment parameters included toxicity, patient acceptance, response, duration of response and survival.

To be eligible for this trial, patients were required to have metastatic disease and to have failed endocrine, radiation and surgical therapy as well as prior adjuvant chemotherapy with cyclophosphamide/methotrexate/5-fluorouracil (CMF) or cyclophosphamide/doxorubicin/5-fluorouracil (CAF). No treatment had been received within 3 months of entry into the study. None of the patients was excluded because of age, severity of disease or site of disease involvement. The mean age of the patients was 48 years (range, 35–66 years). All patients had intraductal carcinoma except one, who had medullary carcinoma. An adequate trial consisted of at least two chemotherapy courses.

No early death was noted among 30 patients. All measurable sites of disease involvement, including bone, were assessed for objective response by the same examiner. For bone metastases, evidence of healing in radiographs and bone scans and improved symptoms were necessary for accurate assessment of overall improvement. The usual criteria for

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Table 1. Patient characteristics

Patients entered in the trial (*n*)	30
Non-evaluable cases:	
Lost to follow-up	1
Refused treatment	1
Prior chemotherapy	25
Progression of disease	3
Prior hormone manipulation	28
Estrogen receptor unknown	30
Pre-/post-menopausal	17/13
Prior radiotherapy	13

Table 2. Results of treatment with ifosfamide, epirubicin and 5-fluorouracil in 30 patients with advanced breast cancer

Total number of patients	Evaluable	CR	PR	Improved / stable disease
30	28 (93%)	7 (25%)	15 (54%)	3 (10.7%)

CR, complete response; PR, partial response

complete and partial responses were used for assessments; these were correlated with improved performance status. Improved or stable disease was recorded but not included in the assessment of response. Disease in two or more sites was observed in 70% of patients.

Results

All patients were assessed for response. In all, 28 (93%) were evaluable for response, having received 3 or more courses of treatment. Nine patients received more than 3 courses, two completed seven courses and refused further therapy for reasons unrelated to treatment and one patient died of advanced liver metastases after six courses. A complete response was noted in 7 of the 28 evaluable patients and a partial response, in 15, for an overall response rate of 79% (22/28) (Table 2). Three patients showed stable disease with improved symptoms, and in three cases disease progression occurred. One patient refused treatment and another was lost to follow-up.

Table 3. Response according to lesion site in 28 patients

Lesion	Responses (*n*)
Soft-tissue	11
Bone	8
Pleural effusion	9
Lung	2
Liver	2
Peripheral nerve	2

Response was most rapid in soft-tissue disease, generally after one course of treatment, followed by liver and pulmonary lesions, which showed a measurable response after two or more courses (Table 3). Response in bone was generally observed after three or more courses; evidence of this was provided by new calcification on radiographs and by a reduction in the size and number of lesions on isotope scans. One patient experienced hypercalcemia as a consequence of bone metastases, but blood calcium levels promptly returned to normal during therapy. All surviving patients with bone metastases had improved symptoms; no mixed responses were seen. None of the surviving patients relapsed after an average of six courses, with three patients having received nine courses.

Median survival at 20 months for all patients in the study was 11 months: 15 months for complete response (CR), 10 months for partial response (PR), 6 months for stable disease and 12 months for progressive disease (PD). Survival for the 22 responding patients was 12 months (Fig. 1). The median duration of remission was 9 months (range, 3–20 months) (Fig. 2).

The toxicity observed with this combination of agents was acceptable (Table 4). The haematological toxicity observed was mild granulocytopenia, but dose adjustments were not required and no life-threatening infections were experienced. Thrombocytopenia was noted in two patients.

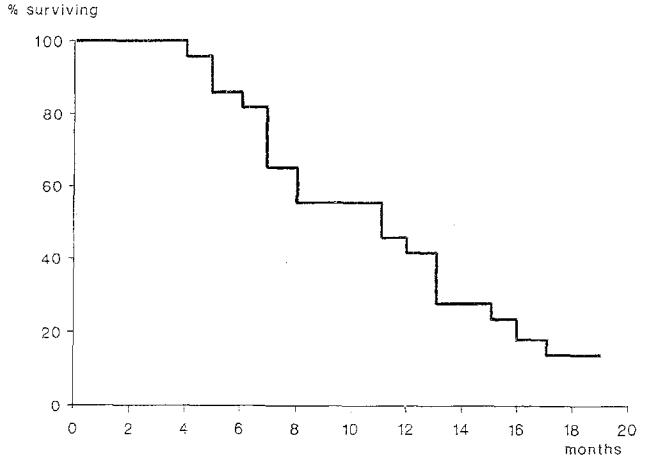

Fig. 1. Duration of survival in 22 patients with advanced breast cancer treated with ifosfamide, epirubicin and 5-fluorouracil

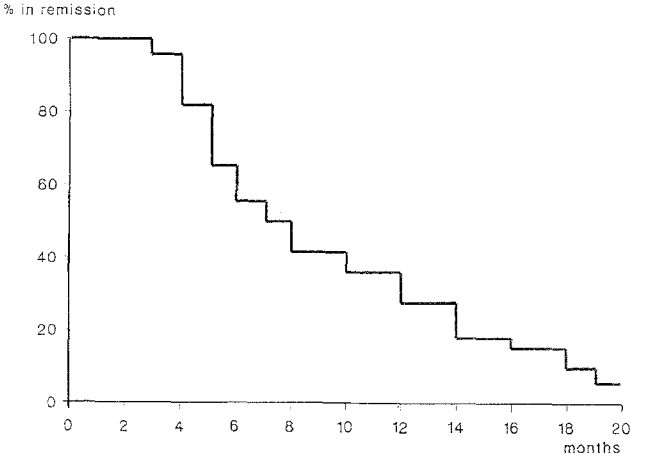

Fig. 2. Remission duration in 22 patients with advanced breast cancer

Table 4. Toxicity of 198 evaluable courses of ifosfamide, epirubicin and 5-fluorouracil in 30 patients with metastatic breast carcinoma

Type	Patients (*n*)
Vomiting	22
Alopecia	26
Mucositis	5
Diarrhoea	1
WBC depression	4
Platelet depression	2
Haemorrhagic cystitis	1

Moderate to complete alopecia occurred in 85% of patients; however this effect was reversible, and most patients showed regrowth of hair either before or soon after completion of treatment. Moderate to severe nausea and vomiting were observed, but no dose modifications were required; antiemetics given at home by injection were very helpful. Haemorrhagic cystitis due to ifosfamide occurred in one patient, and diarrhoea due to 5-fluorouracil was observed in another. No clinically or electrocardiographically demonstrable arrythmias were noted in any of the patients immediately after epirubicin.

Discussion

In this pilot study, ifosfamide/epirubicin/5-fluorouracil proved to be a safe and effective chemotherapy combination in advanced metastatic breast cancer. In this small but unselected group of patients, response rates equal to or better than those achieved with CAF were obtained, with no demonstrable cardiac toxicity. When ifosfamide is given with mesna , the bladder and renal toxicity of the former are minimal and no longer dose-limiting. Combinations of ifosfamide, epirubicin and 5-fluorouracil are of considerable interest, considering the relatively mild myelosuppression observed in this study. Although nausea and vomiting occurred more often with ifosfamide than with cyclophosphamide, these side effects rarely limit the use of a cytotoxic agent and are largely alleviated by antiemetic regimens.

Rapid disappearance of soft-tissue and lymph node involvement in breast cancer as a result of chemotherapy is not uncommon, but disappearance of all inflammatory changes in the non-operable primary breast tumour, with softening of the breast to its former state after only two courses of treatment, is unusual. Immediate relief of bone pain and weight gain were noted in all patients, which suggests unusually early efficacy for this combination.

Our results suggest that the combination of ifosfamide/epirubicin/5-fluorouracil (IEF) is at least as effective as the CAF regimen, resulting in better patient acceptance, no demonstrable cardiac toxicity and extremely mild urothelial toxicity. The patients in this study had not been heavily pre-treated, unless adjuvant chemotherapy is considered to be heavy treatment. We conclude that IEF is an effective chemotherapeutic combination with minimal toxicity that should be studied further in large, controlled trials.

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