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First-line Combination Chemotherapy with Mitoxantrone, Methotrexate, Vincristine and Carboplatin (MIMOC) in Advanced Breast Cancer

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51 patients with stage IIIB and IV breast cancer entered a prospective phase II study of combination chemotherapy that consisted of mitoxantrone (8 mg/m²) day 1, methotrexate (25 mg/m²) day 1, vincristine (1 mg/m²) day 2 and carboplatin (250 mg/m²) day 2 (MIMOC) given in a 3-weekly schedule. None had received prior chemotherapy for metastatic disease, although 16 patients were given adjuvant chemotherapy. Objective response to treatment was seen in 29 of 48 patients analysed for response (60%) with 8 complete responses (CR). 7 out of 8 patients with stage IIIB disease responded, 2 of them completely. Responses were seen in all sites but the best results were achieved in lung metastases with 50% CR. The median duration of response was 8 months and the median time to disease progression was 12 months. The main toxicity was nausea and vomiting which was severe in 20% of the patients. Other toxicities were mild. MIMOC was administered on an out-patient basis and appears to be effective as first-line treatment in advanced breast cancer.
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INTRODUCTION

BREAST CANCER was one of the first solid tumours to be treated with chemotherapy more than 20 years ago, and also one of the first tumours treated with polychemotherapy [1]. The treatment of advanced breast cancer has undergone many developments, with variable degrees of success and response rates. Unfortunately, it has been several years since the results of cytotoxic therapy have shown any improvement and, to date, this disease remains incurable [1]. Under such circumstances, the chemotherapy of breast cancer continues to be strictly a clinical research issue, and the introduction of new effective drugs or new effective combinations should be the basis for future treatment.

Mitroxantrone an anthracenedione intercalating agent, methotrexate an antimetabolite and vincristine a vinca alcaloid, have each been shown to be active in human breast cancer when administered both as single agents and/or in combinations with other active drugs [1]. Cisplatin has been shown to be active as a first-line chemotherapeutic agent in the treatment of advanced breast cancer and has been shown to induce response rates of 47–54% [2,3]. Carboplatin has shown antitumoral activity in a phase II study of advanced breast cancer with a response rate of 32% and in combination with the aforementioned drugs has shown synergistic efficacy in other diseases such as bladder cancer [4,5].

The objective of this study was to evaluate the efficacy and the toxicity of the combination of mitoxantrone, methotrexate, vincristine and carboplatin (MIMOC) as first-line chemotherapy in advanced breast cancer.

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PATIENTS AND METHODS

Eligibility

A total of 51 women with metastatic or locally advanced breast cancer and with an estimated life expectancy of at least 3 months, who were not given prior chemotherapy except as adjuvant, were entered into the study. Other entry criteria included an upper age limit of 75 years, performance status (WHO) grade 2 or less, normal haematological values (white blood cells $\geq 3 \times 10^3$, platelets $\geq 0.1 \times 10^6$), creatinine < 1.5 mg% (133 μmol/l) and normal liver function tests. Other exclusion criteria included the presence of central nervous system metastases, other concomitant invasive malignant disease, congestive heart failure and severe infections.

Pretreatment and follow-up investigations

Pretreatment investigations included history, complete physical examination, chest radiograph, blood count and chemistry test, tumour markers (carcinoembryonic antigen and CA 15-3), bone scintigraphy, ultrasound of the liver and/or computerised tomography of the abdomen and electrocardiogram. Physical examination, blood count, chemistry tests, tumour markers and evaluation of side-effects, were repeated every 3 weeks. Evaluation of the patients was done every second cycle of chemotherapy.

Therapeutic regimen and duration

The scheme was mitoxantrone 8 mg/m² intravenously (i.v.) and methotrexate 25 mg/m² i.v. on day 1, and vincristine 1 mg/m² i.v. and carboplatin 250 mg/m² in 250 ml (N/S infusion) over 30 min on day 2. Courses were repeated every 3 weeks for a total of six courses. A minimum of two cycles of treatment was required for evaluation. Patients were removed from the study at any sign of progressive disease.

Definition of response and toxicity

Standard UICC criteria were used to define complete response (CR), partial response (PR), no change (NC) or progression

of disease (PD). Toxicity and side-effects were classified as recommended by the WHO criteria [6,7].

RESULTS

From August 1989 to November 1990 a total of 51 patients entered the study. 42 received two or more cycles of treatment and were considered eligible for analysis. Prior adjuvant chemotherapy consisted of cyclophosphamide/methotrexate/5-fluorouracil or anthracycline-based regimens. 6 patients received only one cycle of chemotherapy due to early death ($n = 1$) and loss to follow-up ($n = 5$) and were included in the response analysis as non-evaluable. 3 other patients refused chemotherapy, without receiving any treatment and were not included in the analysis of the study. Characteristics of patients are shown in Table 1.

A total of 8 CR [17%, 95% confidence interval (C.I.) 6–27%] were registered, 2 of which were noted in patients with stage IIIB disease, 4 with lung metastases and pleural effusion and 2 with metastases in only the lymph nodes. 21 patients (48%, 95% C.I. 29–58%) achieved PR, 11 (23%) had PD, whereas 2 showed a stabilisation of the disease until progression (NC). The overall response rate (CR + PR) was 60% (95% C.I. 46–74%). When we exclude from the results the patients with stage IIIB, the response rate (CR + PR) for the remaining cases was 53% (Table 2). 7 out of 8 patients with stage IIIB disease responded with 2 CR and 5 PR. The response according to the metastatic site is listed in Table 3. The best results were achieved in patients with pulmonary and pleural site metastases with 4 out of 8 and 3 out of 11 CR, respectively. The response according to the number of metastatic sites is listed in the Table 4.

The correlation of many variables to the treatment response was examined. Only the number of metastatic sites and the performance status of the patients was associated significantly ($P = 0.001$ and 0.003, respectively) with the response to chemotherapy. The median duration of CR was 10 months and of PR was 6.5 months. The median time to PD in responding patients was 12 months. It is too early to draw final conclusions on overall survival, but the current mean overall survival from the beginning of the treatment is 20+ months for the responders (2 deaths) and 5 months for the non-responders (11 deaths).

The myelotoxicity of MIMOC was mild; grade 4 toxicity for leukocytes, haemoglobin or platelets was observed only in 1 case with massive liver metastases, who died from cerebral bleeding. Nausea and vomiting were severe in 20% of patients and moderate in the remaining 80%. The frequency of diarrhoea, stomatitis and alopecia were acceptable. No toxic or allergic

Table 1. Characteristics of patients treated with MIMOC

	No. of patients
Analysed	48
Evaluable patients	42
Age (years)	
Median	60
Range	35–71
Performance status (WHO)	
0	24
1	15
2	9
Premenopausal	8
Postmenopausal	40
ER(+), PR(+)	20
ER,PR status unknown	19
Disease-free interval	
Median	24 months
Range	0–120
Stage	
IIIB	8
IV	40
No. of involved sites	
1	12
2	17
3	11
Sites of metastases	
Bone	16
Liver	13
Lung	8
Pleura	11
Soft tissue	20
Prior therapy	
Adjuvant chemotherapy	19
Adjuvant tamoxifen	27
Palliative endocrine therapy	18

ER = Oestrogen receptor; PR = Progesterone receptor.

Table 2. Response to MIMOC treatment

		No. of patients				
Group	No.	CR	PR	NC	PD	NE
Total	48	8(17)	21(44)	2(4)	11(23)	6
Stage IIIB	8	2		1	—	—
Stage IV	40	6(15)	16(40)	1(3)	11(27)	6

NE = Non-evaluable.

Table 3. Response to MIMOC according to site of metastases

		No of patients			
Site	Total no. involved	CR	PR	PD	CR + PR
Soft tissue	20	2	11	4	13
Bone	16	0	2	11	2
Liver	13	0	4	7	4
Lung	8	4	1	3	5
Pleura	11	3	4	3	7

Table 4. Response to MIMOC according to number of metastatic sites

	No. of patients				
No. of metastatic sites	CR	PR	NC	PD	CR+PR
1($n = 12$)	3	4	—	1	7
2($n = 17$)	3	8	1	4	11
≥3($n = 11$)	0	4	—	6	4

Table 5. Toxicity of MIMOC

Toxicity	Grade (WHO)				
	0	1	2	3	4
Nausea/vomiting	0	0	8	26	8
Diarrhoea	39	3	0	0	0
Stomatitis	40	1	1	0	0
Alopecia	17	10	3	12	0
Infection	32	4	4	0	2
Toxic/allergic reactions	42	0	0	0	0
Congestive heart failure	42	0	0	0	0
Blood cells					
Haemoglobin	18	12	8	3	1
Leukocytes	10	10	15	5	2
Platelets	14	17	7	3	1
Deaths	1				

No. of patients = 48.

reactions, or congestive heart failure, have been registered. Toxicity is summarised in Table 5.

DISCUSSION

The objective of this study was to investigate the antitumour activity and toxicity of a new combination regimen in patients with advanced breast cancer, as first-line chemotherapy. Cisplatin was proven to be very active in patients with metastatic breast cancer who had not received previous chemotherapy, with an overall response rate of 50% but with remarkable toxicity (nausea, vomiting, neurotoxicity) [2,8]. The cisplatin derivative, carboplatin, has been shown to be less active than cisplatin in breast cancer patients with an overall response rate of 24% in previously untreated patients, although it is currently being used as part of intensive combination chemotherapy regimens with autologous bone marrow rescue with high response rate [8].

In our study, objective remissions were observed in 60% of patients, with 17% CR. 9 patients were not evaluable. 1 patient died from cerebral haemorrage owing to severe thrombocytopenia during the first cycle of treatment. (At that time we had observed a regression of her measurable disease). 5 patients received only one cycle of chemotherapy and were lost to follow-up for unknown reasons. These 6 patients are included in the response and toxicity analysis of the study. The remaining 3 patients refused chemotherapy before receiving any treatment and are, therefore, not eligible for the study. MIMOC induced a response rate of 60% (95% CI = 46–74%). Other mitoxantrone-based combination regimens like the mitoxantrone + methotrexate + mitomycin-C (MMM) combination, the mitoxantrone + prednimustine (NOSTE), the CNF and the mitoxantrone + methotrexate + fluorouracil (NMF) combination, have induced responses between 37 and 57% in previously untreated patients [9–11]. The MIMOC combination has also been used in different dosage schedules with remarkable activity in bladder cancer [5, 12]. Thus, these results promoted us to study whether the addition of carboplatin to a combination of active drugs, including mitoxantrone, methotrexate and vincristine, had any synergistic effect. However, carboplatin-based combination regimens have, thus far, had a limited use in advanced breast cancer, and the encouraging results of the present trial should stimulate us to use new combinations in metastatic disease in an attempt to improve the response rate and possibly the survival of these patients.

The main toxicity of this combination was nausea and vomiting which was severe in 20% of the patients and moderate in most others. With the use of $5HT_3$ antagonists as antiemetic treatment, during the last 3 months of the study, tolerance to the therapy was substantially improved. The myelotoxicity was mild and alopecia was observed in 30% of the patients. The treatment was administered on an out-patient basis.

We conclude that MIMOC is an effective combination regimen as first-line combination therapy in either stage IIIB or IV disease with acceptable toxicity.

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