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Folinic Acid, 5-Fluorouracil Bolus and Infusion and Mitoxantrone with or without Cyclophosphamide in Metastatic Breast Cancer

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60 patients with metastatic breast cancer were entered in a phase II study using folinic acid, 5-fluorouracil bolus and infusion and mitoxantrone with or without cyclophosphamide. 47 had measurable visceral metastases and 13 had exclusively bone metastases. 36 had received previous adjuvant or metastatic treatment (33/36 with anthracycline-based regimens). Overall response rate in visceral metastatic patients was 57.1% [95% confidence interval (CI) 35.4–78.8%]; 45.5% and 70% in previously and non-previously treated patients, respectively; duration of response was 9 and 13 months, respectively. 10 out 13 patients with exclusive bone metastases improved for a median time of 18 months. Median survival was 22 months for the 60 patients; 18 and 31 months for previously and non-previously treated patients, respectively. Cyclophosphamide was scheduled only in the absence of nadir grade 4 neutropenia. However, this toxicity occurred in the first 7 patients. For this reason, we chose to avoid cyclophosphamide in patients over 60 years, or with a performance status of 1–2, or who had received previous chemotherapy. Overall, cyclophosphamide was stopped due to nadir grade 4 neutropenia in 17/24 patients for whom this drug was planned. When mitoxantrone, 5-fluorouracil and folinic acid were used at the doses scheduled, the addition of cyclophosphamide appeared feasible in only about 25% of the patients. Furthermore, survival was identical for patients receiving or not receiving cyclophosphamide. Therefore, cyclophosphamide does not contribute substantially to this regimen. This study confirms the value of folinic acid, 5-fluorouracil and mitoxantrone in metastatic breast cancer.
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INTRODUCTION

METASTATIC BREAST cancer remains a frequently chemosensitive non-curable disease. First-line regimens can provide up to 50 to 70% objective response rates, with 10–20% complete responses [1]. For most patients, duration of response is relatively brief. Cyclophosphamide is commonly used in advanced breast carcinoma with a 34% objective response rate when used as a single agent [2]. Mitoxantrone is an active antineoplastic agent, considered as a substitute for doxorubicin with less non-haematological toxicity in advanced breast cancer [3], resulting in up to 35% response rate in non-pretreated patients [4]. 5-fluorouracil (5FU) bolus modulated with folinic acid bolus (FUFOL) or other 5FU–folinic acid combinations have been studied in gastrointestinal malignancies with increased response rates compared to 5FU alone [5]. We previously reported that high-dose folinic acid, 5FU bolus and infusion provided a greater

5FU dose intensity than FUFOL, was a well tolerated regimen and resulted in high response rates in advanced colorectal adenocarcinoma [6]. 5FU–folinic acid regimens are active in advanced breast cancer patients producing 26.5% response rate in 245 previously treated patients [7] and 40% in 70 first-line patients [8, 9]. A combination of mitoxantrone and 5FU modulated with folinic acid was recently reported as an active and well-tolerated association in metastatic breast cancer [10, 11]. We report here a phase II study of folinic acid, 5FU bolus and infusion and mitoxantrone with or without cyclophosphamide in metastatic breast cancer.

PATIENTS AND METHODS

From November 1988 to December 1991, 60 women with metastatic breast cancer entered this phase II study. Eligibility criteria were metastatic disease at diagnosis or after adjuvant chemotherapy, or progression after previous treatment for metastatic disease. However, patients who previously received mitoxantrone or 5FU modulated with folinic acid were ineligible. Patients who previously received anthracyclines were eligible only if they had not received these drugs within 6 months and if cardiac ultrasonography did not show left ventricular function alteration. Patients should have had a performance status of ≤ 2 (WHO definition) and an expected survival of > 3 months. Apart from patients with only bone metastases, all patients had measurable lesions (physical examination, ultrasonography, computed tomography scan). Non-haematological toxicity was evaluated before each course and blood counts were routinely performed at nadir and before each course. Informed consent was required from all patients.

The regimen consisted of folinic acid 200 mg/m^2 in a 2-h infusion, followed by 5 FU 400 mg/m^2 bolus and 600 mg/m^2 in a 22-h infusion days 1 and 2, mitoxantrone 12 mg/m^2 and cyclophosphamide 500 mg/m^2 day 3 every 3 weeks (FFMC regimen). Due to haematological toxicity observed in the first 7 patients included between November 1988 and February 1989, cyclophosphamide was then given only to patients under 60 years, with a performance status of 0 (WHO definition), and who had never received previous chemotherapy. If white blood cell and/or platelet counts at the time of treatment were < 3000/mm^3 and/or $< 100\,000$/mm^3, respectively, treatment was delayed for 1 week. Cyclophosphamide was stopped in the case of grade 4 haematological toxicity, while mitoxantrone dose was decreased by 25% in the case of a new toxic grade 4 episode. The same mitoxantrone dose reduction was applied in patients not receiving cyclophosphamide. If severe ($\geq$ grade 3) 5FU-related non-haematological toxicity occurred, 5FU dose was given as a 300 mg/m^2 bolus and 300 mg/m^2 22-h infusion.

Patients were evaluated for response every three courses. Treatment was stopped in patients with documented progressive disease. The number of cycles administered was six for stable patients, and six to nine for responders (nine if disease improved between the third and the sixth course). At the time of progression, patients were treated with another combination chemotherapy, mainly vinorelbine–mitomycin-C.

Response criteria were used according to the WHO definition: complete response as the disappearance of all physical, biological and radiographic evidence of tumour lasting at least 4 weeks; partial response as the decrease in the product of diameters of measurable lesions by more than 50% and no new lesions; stable disease as the decrease in the product of diameters of measurable lesions by less than 50% or increase by less than 25%; progressive disease as the appearance of new lesions or an increase of the measurable lesion by more than 25%. Patients with only bone metastases were not considered as evaluable for response. For these patients, improvement was defined as disappearance of bone pain, decrease in CA15-3 level when increased at diagnosis and improvement of bone scan. Response durations were measured from the time the response was observed until progression.

Survival was calculated by the Kaplan–Meier method. Comparison of survival was performed using the log-rank test. The received dose intensity for each patient was calculated and was expressed as a percentage of that intended [12]. Median follow-up time in December 1992 was 32 months.

RESULTS

13 patients had only bone metastases, and 47 had at least one measurable visceral localisation. 33 patients had one metastatic localisation, 21 had two and 6 had three or more. 38 patients had metastatic relapse: 28 after adjuvant chemotherapy, including 25 with an anthracycline-based combination (doxorubicin or epirubicin), and 10 after adjuvant radiotherapy alone. 14 had metastatic disease at diagnosis and 8 relapsed after previous anthracycline-based treatment for metastatic disease. 24 patients received the FFMC regimen, while 36 did not receive cyclophosphamide (FFM). Table 1 summarises clinical data for the 60 patients.

Table 1. Patients' characteristics

	No. of patients
Total no. of patients	60
Age in years (range)	53.8 ± 10.8 (31.76)
Premenopausal	20
Postmenopausal	40
Performance status	
0	18
1	24
2	18
Site of metastasis	
Bone exclusive	13
Visceral	47
Bone	20
Liver	15
Pleural	12
Cutaneous	12
Lung	10
Lymph node	5
Bone marrow	2
Other	5
One site	20
Two sites	21
≥ three sites	6
Previous treatment	
Adjuvant chemotherapy	28 (25 with anthracycline)
Metastatic chemotherapy	8 (8 with anthracycline)
No previous chemotherapy	24
Adjuvant radiotherapy	10
Metastatic disease at diagnosis	14

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Toxicity

324 courses were administered (mean 5.4, range 1–9). Haematological toxicity observed in the first 7 patients (seven nadir grade 4 neutropenia including two febrile episodes) led us to give cyclophosphamide only to patients under 60 years, with a performance status of 0 and without previous chemotherapy. 2 FFM patients died after leaving the hospital within the first 2 weeks (1 without severe leukopenia and 1 before nadir blood count), but were included in the survival analysis. Toxicity was analysed in the 58 remaining patients. A grade 4 neutropenia at nadir was observed in 17/24 FFMC patients, including nine febrile episodes in 7 patients; this toxicity occurred before the third cycle in 11/17 patients. Cyclophosphamide was only given for the all planned courses in 7/24 patients. 24/34 FFM patients presented a grade 4 neutropenia at nadir, including six febrile episodes in 6 patients. Overall, at least one episode of grade 4 neutropenia at nadir occurred in 41/58 patients (37% of courses). 4 patients (2.7% of courses) presented a grade 3 or 4 thrombocytopenia, but none with bleeding complications. Haematological toxicity led to dose reduction or delay of treatment in 49/58 patients (24/24 FFMC and 25/34 FFM). Other toxicities were mild with grade 2 (11 patients) and 3 (3 patients) nausea-vomiting, grade 2 (19 patients) or 3 (10 patients) alopecia, grade 2 (6 patients) and grade 3 (1 patient) mucositis. Only 3 patients presented a grade 2 diarrhoea. These side-effects never required rehospitalisation. One previously doxorubicin (450 mg/m^2)-treated patient presented a reversible cardiac failure after the second course and was withdrawn from the study. Toxicity is summarised in Table 2.

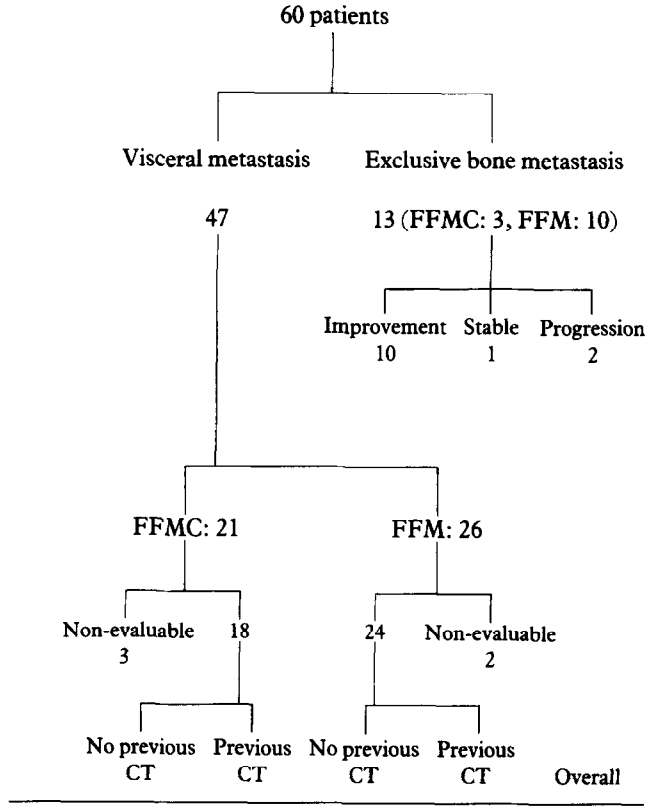
Response

47 patients presented measurable visceral disease at entry. 5 were not evaluable for response (2 early deaths within the first 2 weeks, 1 refusal of reevaluation, 1 lost to follow-up after the first course, and 1 withdrawn from the study because of cardiac failure). 22 patients (5 FFMC, 17 FFM) had received previous chemotherapy and 20 (13 FFMC, 7 FFM) were in first-line treatment. Seven complete responses, 17 partial responses, 11 stable diseases and seven progressions were obtained for an objective response rate of 57.1% [95% confidence interval (CI) 35.4–78.8%]. Objective response rates in previously and non-previously treated patients were 45.5% (95% CI 24.3–66.7%) and 70% (95% CI 49.5–90.5%), respectively. Median durations of response were 9 and 13 months, respectively. Median interval between completion of FFMC/FFM and progression was 7 months (range 0–21) for 34 responders or improved patients.

Table 2. Treatment-related toxicity (WHO grade) for n = 58 evaluable patients, FFMC + FFM

	WHO grade				
	0	1	2	3	4
WBC	1	0	3	13	41
(% courses)			12%	22%	37%
Platelets	37	8	9	3	1
(% courses)			7%	2%	0.7%
Anaemia	48	2	6	2	0
Nausea/vomiting	29	15	11	3	0
(% courses)			7%	2%	
Alopecia	18	13	19	10	0
Mucositis	51	0	6	1	0
Diarrhoea	55	0	3	0	0

Table 3. Responses



Total	13	5	7	17	42
CR	2	1	1	3	7 (16.7%)
PR	9	2	2	4	17 (40.4%)
SD	2	2	1	6	11 (26.2%)
PD	—	—	3	4	7 (16.7%)

13 patients presented exclusive bone metastases (3 FFMC, 10 FFM). 10 out of these 13 patients (76.9%) were improved, 1 remained stable and 2 worsened. Median duration of improvement was 18 months (range 5–29). Responses are summarised in Table 3.

Survival

Median survival for the 60 patients was 22 months, 20 months for patients with visceral localisations and 29 months for patients with exclusive bone metastases (Fig. 1). As shown in Table 4, age (< or > 50 years), number of metastatic sites (1 or ≥ 2),

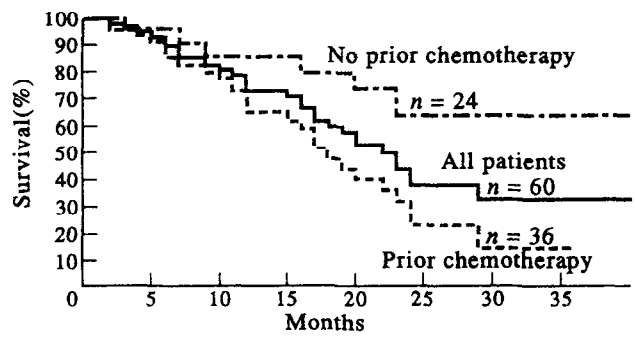


Fig. 1. Survival curve of the 60 patients (Kaplan–Meier).

Table 4. Prognostic factors

		n	Median survival (months)	χ^2	P
Age (years)	< 50	20	23		
	≥ 50	40	20	0.85	NS
Number of metastatic sites	1	33	23		
	≥ 2	27	22	0.09	NS
Performance status	0–1	42	23		
	2	18	19	0.24	NS
5FU theoretic D-I*	< 75%	11	16		
	≥ 75%	48	24	2.22	NS
Cyclophosphamide	Yes	24	23		
	No	36	22	0.06	NS
Liver metastases	Yes	15	15		
	No	45	24	3.01	0.07
Mitoxantrone theoretic D-I*	< 75%	31	17		
	≥ 75%	28	23	3.52	0.06
Previous chemotherapy	Yes	36	18		
	No	24	31	4.23	< 0.05
CA 15-3 level (N = normal value)	< 2 × N	25	30		
	≥ 2 × N	32	17	7.32	< 0.01

* Theoretic D-I = % of theoretic dose-intensity administered. NS: not significant.

dose intensity of 5FU (< or ≥ 75%), initial performance status (0–1 or 2) and cyclophosphamide (FFMC or FFM) were not found to be prognostic factors in this study. Presence of liver metastases and dose intensity of mitoxantrone (< or ≥ 75%) approached significance ($P = 0.07$ and $P = 0.06$, respectively). Absence of previous chemotherapy (median survival 31 months, $P < 0.05$) and initial CA15-3 level < 2 × normal value (median survival 30 months, $P < .01$) resulted in a better survival.

DISCUSSION

Myelosuppression was the most frequent side-effect and led to dose reduction or delay of treatment in the majority of patients. Due to this haematological toxicity, cyclophosphamide was stopped in 17/24 patients, mainly during the first three courses. Even if cyclophosphamide was not given in the FFM group, neutropenia remained the major toxicity. This neutropenia seemed more severe than that reported by Hainsworth [10] and Jones [11] using the same drugs. However, haematological toxicity was recorded at nadir in our study. As in colorectal cancer, neutropenia observed after folinic acid–5FU regimen differs according to 5FU administration in metastatic breast cancer: 45–69% grade 3–4 if 5FU bolus, 0–14% if 5FU infusion [13]. In our experience in colorectal cancer, folinic acid, 5FU bolus and infusion do not induce haematological toxicity [6]. Neutropenia is the dose-limiting toxicity of mitoxantrone. In the study reported by Hainsworth [10], mitoxantrone was given on day 1 at 12 or 9 mg/m^2 in patients older than 65 years or with a performance status of 2, and 5FU at 350 mg/m^2 bolus days 1 to 3. In the study reported by Jones [11], mitoxantrone dose was 10 mg/m^2 day 1 and 5FU 1 g/m^2 infusion days 1 to 3. Overall, the higher haematological toxicity observed in our study could be due either to higher doses of mitoxantrone or to blood counts routinely performed at nadir. However, although 37% of overall courses (FFMC + FFM) led to a nadir grade 4 neutropenia, only 4.6% required hospitalisation for febrile episode and none was fatal. Other side-effects were mild.

It is difficult to assess the role of cyclophosphamide: the response rate was higher in the FFMC group (Table 3), but most patients (13/18) had never received previous chemotherapy and survival of FFMC patients was identical to that of FFM patients. Furthermore, cyclophosphamide was stopped due to haematological toxcicity before the first evaluation in the majority of patients.

The median duration of response was 13 months in non-pretreated patients. The 9-month median duration of response observed in pretreated patients seems slightly higher than that reported by Hainsworth (6 months) or Jones (6 months). The interval between completion of treatment and progression was about 7 months for responders or improved patients. This long treatment-free interval resulted in a higher quality of life for metastatic patients.

Metastatic breast cancer remains non-curable. In such a situation, quality of life and lack of severe toxicity is a major objective, and we cannot recommend the addition of cyclophosphamide to folinic acid, 5FU and mitoxantrone according to this schedule. Our experience and the two previously reported studies [10, 11] suggest a comparison of a mitoxantrone–5FU–folinic acid combination with standard metastatic breast cancer regimens.

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