Eur J Cancer, Vol. 29A, No. 13, pp. 1814–1816, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

Mitoxantrone, Folinic Acid, 5-Fluorouracil and Prednisone as First-line Chemotherapy for Advanced Breast Carcinoma. A Phase II Study

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The purpose of this prospective clinical trial was an attempt to find an effective and relatively non-toxic schedule for patients with metastatic breast cancer who decline to receive aggressive cytotoxic chemotherapy. A total of 36 patients with disseminated breast cancer were treated with mitoxantrone 8 mg/m² intravenously (iv) day 1, folinic acid 400 mg/m² in a 2-h iv infusion with 5-fluorouracil 500 mg/m² as an iv bolus 1 h later, days 1 and 8 at 3-week intervals plus prednisone 20 mg/m² orally daily with diminishing doses over several weeks. Objective regressions were observed in 24/36 (67%) patients, 9 being complete (25%). Responses were seen at all disease sites, mainly pleural/lung, bone and liver. The median duration of response was 8 months (range 4–25+) and the median survival 12 months (range 3–26+). Myelosuppression, mainly leucopenia and thrombocytopenia, was the major toxicity but without complications. Other toxicities included mild or moderate nausea and/or vomiting (50%), stomatitis (33%) and diarrhoea (11%). Alopecia was minimal. No cases of cardiotoxicity were detected. The substantial response rate obtained with this relatively well tolerated regimen against advanced breast cancer warrants its assessment in a larger number of patients.
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INTRODUCTION

IN THE LAST 20 years, different drugs, used either alone or in combination, have been used in the palliative treatment of disseminated breast carcinoma but this disease remains incurable. The optimal regimen is as yet undefined and the evaluation of new schedules is of considerable importance. Until now, the objective response rates obtained with first-line chemotherapy range between 50 and 80%, but only in about 20% of patients is complete response achieved. Based on the results obtained in our previous studies using mitoxantrone [1, 2] to attempt to maximise the response and reduce toxicity of chemotherapy, a new prospective clinical trial has been carried out with a combination comprising mitoxantrone, folinic acid, 5-fluorouracil and prednisone. Mitoxantrone, a new anthracenedione which has been used as an alternative to doxorubicin, has demonstrated considerable antitumour activity in these patients. It causes relatively little severe vomiting, cardiotoxicity and alopecia in comparison with doxorubicin. The combination of folinic acid and 5-fluorouracil, used as second-line cytotoxic chemotherapy in metastatic breast cancer, has also been shown to be active [3–6]. We have, therefore, studied the efficacy of mitoxantrone in combination with 5-fluorouracil modulated by high-dose folinic acid. The addition of prednisone to this schedule was intended to enhance the well-being of the patients. There is also evidence that such an approach can reduce the myelotoxicity of cytotoxic chemotherapy [7–9].

The aim of the present phase II prospective clinical trial, used as first-line chemotherapy in disseminated breast cancer, was to evaluate the effectiveness and toxicity of this new regimen and the results of this study are reported here.

PATIENTS AND METHODS

36 evaluable women with progressive disseminated breast cancer, resistant to endocrine treatment or those with oestrogen receptor-negative tumours and previously untreated with chemotherapy (except postoperative adjuvant treatment not including anthracyclines) were eligible for this study and accrued from August 1989 until November 1990 (last follow-up 30 November 1991). Other eligibility criteria included age $\leq$ 70 years, performance status $>$ 60% (Karnofsky scale), the presence of measurable or evaluable disease, a total white blood count $\geq$ 4000 cells/μl, a platelet count $\geq$ 100 000/μl, and normal hepatic and renal functions. Informed consent was obtained from all patients before entering the study. Patients with symptoms or signs of brain metastases, active infection, congestive heart failure or ischaemic heart disease were excluded. Patients with osteoblastic skeletal lesions or pleural effusions as the sole manifestation of metastatic disease were also ineligible for the study. The regimen of chemotherapy used included mitoxantrone 8 mg/m² intravenous (iv) bolus day 1 and folinic acid 400 mg/m² in a 2-h infusion with 5-fluorouracil 500 mg/m² 1 h later on days 1 and 8 at 3-week interval, plus prednisone 20 mg/m² orally daily for 2 weeks with subsequent reduction of the dose, but maintaining a daily dose for 4 more weeks and then continuing with 10 mg on alternate days.

Before each course of cytotoxic chemotherapy a full physical examination was carried out including a full blood and platelet count and a biochemical screening. All palpable or superficial lesions were measured in two perpendicular diameters and visible lesions photographed. Skeletal and visceral disease was evaluated every 3 months by radiographs, bone scans and ultrasonograms. Cardiac function was reassessed every 3 months

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Revised and accepted 7 April 1993.

by repeated electrocardiogram (ECG) and determinations of left ventricular ejection fraction (LVEF).

Dose modifications were adopted in the presence of myelosuppression. With a white blood count, on day 21, less than 4000 cells/μl, or a platelet count < 100 000/μl, the administration of treatment was delayed for 1 week or 2 weeks, when the level of leucocytes reached in all the cases ≥ 3000 cells/μl or platelet count was ≥ 100 000/μl. With a white blood count < 3000 cells/μl or a platelet count < 100 000, the administration of chemotherapy at day 8 was not given. The courses of therapy were administered on an out-patient basis, with at least two cycles of chemotherapy to be administered before the regimen was deemed ineffective. Patients in progression were removed from the study and all others remained until progression occurred.

Response rate, median duration of response, median time of survival and toxicity were evaluated. Criteria for response were adopted according to those recommended by the UICC [10]. Complete response (CR) is total disappearance of all evidence of tumour, with no appearance of new lesions. Partial response (PR) is a 50% or more decrease in the sum of the products of the longest perpendicular diameters of all measurable lesions without detection of new ones. No change (NC) is a less than 50% decrease or less than a 25% increase in the sum of the product of the longest perpendicular diameters of measurable lesions. Progressive disease (PD) is an increase of 25% or more in the product of the longest perpendicular diameters of all measurable lesions and/or appearance of new ones. When some regress while others progress or new lesions appear (mixed response) this is considered to represent progressive disease.

The response to treatment was evaluated by at least two sequential observations, 4 weeks apart. The patients with stationary disease were considered and included in the non-responders group (PD).

The duration of response was measured from the beginning of cytotoxic chemotherapy until objective evidence of progression. Survival was calculated from the date of the last follow-up (30 November 1991), for the patients still alive. Both parameters were analysed by the Kaplan–Meier method and the toxicity assessment was defined according to the World Health Organization (WHO) criteria [11].

RESULTS

All 36 patients selected for this study were eligible for assessment of response and toxicity. The clinical characteristics of the patients are summarised in Table 1. The number of courses given varied from two to 18 (median seven) and the median cumulative dose of mitoxantrone was 56 mg/m^2 (range 16–144 mg/m^2).

The overall response rate was 67% (24/36) (95% confidence interval 50–80%), with 9 CR (25%) and 15 PR (42%). In 12 patients (33%) NC or PD was observed. The median duration of response was 8 months (range 4–25+ months) and the median duration of survival was 12 months (3–26+ months) (last follow-up 30 November 1991) (Fig. 1). From the 36 patients selected to this trial, 13 are still alive, 9 being in remission.

In considering prognostic grouping according to the site of dominant disease, there were no apparent differences in response frequencies. There were 8/12 responders in patients with only soft tissue disease, 7/11 in patients with dominant osseous disease with or without soft tissue lesions but without visceral metastases, and 9/13 in patients with dominant visceral disease. Responses were seen at all disease sites, breast, skin, lymph nodes, bone, pleural and/or lung and liver (Table 2). In 2 out of 9 complete responders we observed a complete recalcification of the lytic lesions on both plain radiography and bone computed tomography scanning. In other cases, we registered complete regression of pleural and/or lung metastases and in 1 patient with liver dissemination there was a total disappearance of the hepatic lesions. In patients with bone metastases complaining of severe osseous pains there was a complete improvement of that symptom, before the administration of the second cycle of chemotherapy.

Table 1. Characteristics of patients

Number of patients	36
Age (years)	
Median	54
Range	32–68
Interval from diagnosis to chemotherapy (months)	
Median	37.5
Range	3–233
Oestrogen receptor status	
Positive	11
Negative	11
Unknown	14
Menstrual status	
Premenopause	10
Postmenopause	26
Previous systemic treatment	
None	11
Adjuvant chemotherapy	1
Endocrine treatment	24

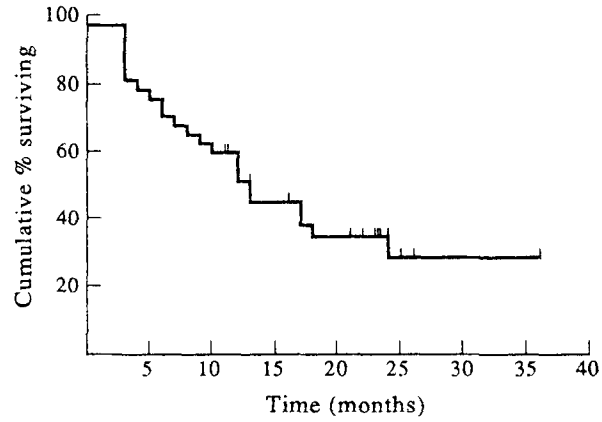

Fig. 1. Kaplan–Meier plot of survival.

Table 2. Number of sites involved and response

	Number involved	Response
Breast	9	4 (CR=0,PR=4)
Skin	7	4 (CR=2,PR=2)
Lymph nodes	13	10 (CR=2,PR=8)
Pleura and/or lung	9	7 (CR=6,PR=1)
Bone	14	9 (CR=2,PR=7)
Liver	4	2 (CR=1,PR=1)

Table 3. Toxicity

	Number of patients
Total no. of patients	36
Haematological	
Leucocyte nadir (per μl)*	
3999–3000 (WHO grade 1)	5
2999–2000 (WHO grade 2)	11
1999–1000 (WHO grade 3)	9
< 1000 (WHO grade 4)	1
Platelet nadir (per μl)†	
99 000–75 000 (grade 1)	4
74 000–50 000 (grade 2)	2
49 000–25 000 (grade 3)	1
< 25 000 (grade 4)	4
Nausea and/or vomiting (grades 1–3)	18
Diarrhoea (grade 1)	4
Mucositis/stomatitis (grades 1–2)	12
Alopecia	2
Cardiotoxicity	0
Sepsis	4

* Leucocyte nadir = 0.8 μl. † Platelet nadir = 10 000 μl.

The haematological toxicity is shown in Table 3. Myelosuppression, based on the nadir at day 21 of the cycle and consisting of mainly leukopenia and/or thrombocytopenia was observed in 26 patients (72%), 0.8/μl being the lowest leucocyte count recorded. In 11 patients (31%), the median nadir registered was 10 000 platelets/μl. Delays in treatment of 1 or 2 weeks were necessary for haematological toxicity in 26 patients (72%), but no more than four cycles were delayed in any patient. There were no cases of persistent leukopenia and/or thrombocytopenia.

Mild or moderate nausea and/or vomiting, always less than grade 4, were registered in 18 patients, but was well controlled with prophylatic use of metoclopramide and dexamethasone. Stomatitis, oral ulceration and mucositis, never surpassing grade 2, were observed in 12 cases. Diarrhoea, grade 1, was reported by 4 patients, and alopecia requiring a wig in 2 patients. 4 patients developed neutropenic sepsis, but all of them responded successfully to antibiotics.

No cases of clinical congestive heart failure were registered, serial determinations of LVEF being normal. No cases of drug-related deaths occurred.

DISCUSSION

The purpose of this phase II clinical trial was to attempt to find an effective and relatively non-toxic schedule for patients with metastatic breast carcinoma. The response rate obtained in this study was 67%. This regimen caused low gastrointestinal toxicity, moderate vomiting and minimal mucositis. No cases of cardiotoxicity were observed and alopecia was minimal. Myelosuppression (leukopenia and thrombocytopenia) were the main side-effects. Good palliation of bone pain was achieved with the regimen.

The substantial response rate obtained with this relatively well-tolerated regimen against advanced breast cancer warrants its assessment in more patients. Recent publications [5,6] of this type of combination when used as second-line treatment in disseminated breast cancer have confirmed the efficacy and good tolerance of this approach. Further innovative strategies are needed to improve therapy. Therefore, another study has been initiated using higher doses of mitoxantrone, folinic acid and 5-fluorouracil in combination with granulocyte colony-stimulating factor [12] to protect bone marrow. This should reduce both the intervals between cycles of chemotherapy and the infectious complications of treatment.

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Acknowledgements—We thank Dr P. Pimentel, University Hospital of Santa Maria, Bone Marrow Transplantation Unit, Lisbon for external review of patients in this study, and Professor R. D. Rubens, Clinical Oncology Unit, Guy's Hospital, London for revising the manuscript.