Eur J Cancer, Vol. 28A, No. 12, pp. 1968–1970, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

A Phase II Study of 5-Fluorouracil and High-Dose Folinic Acid in Combination with Cyclophosphamide and Mitoxantrone for Advanced Breast Cancer

Enrico Aitini, Giovanna Cavazzini, Maurizio Cantore, Carla Rabbi, Anna Rivera, Beatrice Togliani, Adriano Di Marco and Franco Smerieri

38 patients with advanced breast adenocarcinoma were treated in a phase II study with 5-fluorouracil and high-dose folinic acid combined with cyclophosphamide and mitoxantrone. 6 patients had received prior chemotherapy for advanced disease, all with an anthracycline-containing regimen. Treatment was generally well tolerated. The most common side-effect was myelosuppression, with 1 toxic death due to leukopenia-related sepsis. 1 patient developed severe congestive heart failure 12 months from the end of therapy. 36 patients were evaluable for response. The overall response rate was 55%. Median duration of response was 8 months and median survival time was 16 months. This regimen warrants further investigations.
Eur J Cancer, Vol. 28A, No. 12, pp. 1968–1970, 1992.

INTRODUCTION

BIOCHEMICAL STUDIES have demonstrated that an excess of intracellular reduced folates increases the cytotoxic effect of fluorinated pyrimidines through an optimal inhibition of thymidylate synthetase [1–3]. Several clinical trials have shown that folinic acid at high doses increases the effectiveness of 5-fluorouracil (5-FU) given simultaneously in the treatment of advanced colorectal cancer. Only few studies were performed in advanced breast cancer and suggested the efficacy of this combination [4–6].

Mitoxantrone, a new anthraquinone compound, is an active agent in advanced breast cancer [7, 8]; its spectrum of activity is similar to that of doxorubicin, but nausea, vomiting, alopecia, subcutaneous necrosis on extravasation and cardiotoxicity are significantly reduced with mitoxantrone [9]. Some investigations have reported the use of mitoxantrone in combination with cyclophosphamide and 5-FU [10].

We have investigated the value of salvage combination therapy with mitoxantrone, cyclophosphamide, 5-FU and high-dose folinic acid (HDFA) in advanced breast cancer patients using for the latter two drugs the same dose and schedule published by Machover *et al.* [11].

PATIENTS AND METHODS

Patients gave informed consent; all had documented evidence of recurrent or metastatic breast cancer with at least one measurable or evaluable metastatic site. Patients details are shown in Table 1.

Entry requirements also included performance status 0–2 according to Eastern Cooperative Oncology Group (ECOG) criteria, age < 75 years, serum creatinine < 1.4 mg/dl, a white blood cell count (WBC) > 4000/ml, a platelet count > 120000/ml and bilirubin < 2.0 mg/dl, absence of CNS metastases. The patients were required to have no antitumour therapy during the 4 weeks prior to starting treatment. Patients with lytic bone lesions as the only metastatic site were admitted only if oestrogen receptors (ER) were negative, or after failure of hormonal therapy.

Prior to beginning chemotherapy, evaluation included history and physical examination, chest X-ray, radioisotope bone scan, liver ultrasound, electrocardiogram, blood cell count, a serum

Table 1. Patients' characteristics

Entered	38
Evaluable	36
Median age in years (range)	54 (27–74)
Median ECOG performance status (range)	1 (0–2)
Median disease-free interval in months (range)	21 (0–106)
Menopausal status	
Premenopausal	20
Postmenopausal	18
ER status	
Positive	12
Negative	10
Unknown	16
Dominant site of disease	
Soft tissue	8
Bone	9
Visceral	21
Prior systemic therapy:	
Adjuvant chemotherapy (CMF regimen)	18
Anthracycline containing regimen for advanced disease	6
Endocrine therapy (tamoxifen)	13
Prior radiation therapy	14

Correspondence to E.Aitini.
E. Aitini, G. Cavazzini, M. Cantore, C. Rabbi, A. Rivera, B. Togliani and F. Smerieri are at the Department of Medical Oncology, Ospedale Carlo Poma, Viale Albertoni, 1, I-46100 Mantova, Italy; and A. Di Marco is at the Department of Radiation Oncology, Ospedale di Borgo Trento, Verona, Italy.
Revised 18 Mar. 1992; accepted 28 Apr. 1992.

biochemical screening profile including hepatic and renal function tests. Patients with symptomatic congestive heart failure or with a history of myocardial infarction within the previous 6 months were ineligible.

Liver and uterus metastases were assessed by ultrasound, lung localisations by chest X-ray and tomography, lytic bone metastases by X-ray. Metastatic nodes and skin lesions were evaluated by direct clinical measurement.

The chemotherapy regimen consisted of cyclophosphamide 600 mg/m^2 by intravenous bolus injection followed by mitoxantrone 12 mg/m^2 intravenously over 30 min both on day 1 and 5-FU 370 mg/m^2 with HDFA (200 mg/m^2) on days 1–5. Folinic acid was given by intravenous bolus injection and 5-FU was given immediately afterwards by intravenous infusion over 20 min. Cycles were administered every 4 weeks. Treatment courses were repeated until progressive disease developed, to a maximum of 10 cycles or to tolerance. The schedule was modified according to haematological tolerance: treatment was delayed 1 week if pretreatment WBC fell below 4.000/ml and/or platelets were less than 120.000/ml. If the subsequent weekly count was still below these values but WBC > 3.000/ml and/or platelets > 80.000/ml, all drugs were reduced to 75% with the projected dose. If WBC and/or platelets were still below these former values, treatment was delayed another week up to a maximum of 2 weeks.

During the first two courses, haemoglobin, WBC with differential and platelets count were performed weekly. Metoclopramide at a dose of 1–2 mg/kg intravenously and methylprednisolone at a dose of 3–4 mg/kg intravenously were used as routine antiemetic treatment during the first day of therapy. In the last few patients ondansetron at a dose of 8 mg intravenously was used.

Since oral mucositis was remarkable in patients treated with 5-FU and HDFA [11], all patients underwent allopurinol mouthwashes as suggested by Clark *et al.* [12]. Moreover they were recommended to continue mouthwashes with sodium bicarbonate for at least 2 weeks in order to prevent oral mucositis.

Clinical evaluation of each patient was performed every 4 weeks and response evaluation every 8 weeks during chemotherapy and every 3 months thereafter.

A minimum of two courses of therapy were required for response. Response criteria were as follows: complete response (CR)—disappearance of all measurable disease for more than 4 weeks; partial response (PR)—reduction in the sum of the areas of all measurable lesions by at least 50%, in the absence of any new site of malignancy, lasting more than 4 weeks; stable disease (SD)—reduction in the sum of the areas of all measurable lesions by less than 50% or less than 25% increase; progressive disease (PD)—more than 25% increase in the sum of the areas of all measurable lesions and/or the appearance of new lesions.

Duration of response was determined from the start of therapy. Survival and disease-free survival distributions were estimated according to the product-limit method of Kaplan and Meier [13].

Univariate analyses were performed using the $\times 2$ and log–rank tests [14].

RESULTS

Between March 1989 and May 1991, 38 consecutive patients were enrolled in the study. Metastatic sites included liver (n = 13 patients), lung (n = 13), bone (n = 11), lymph nodes (n = 7), skin (n = 4), and uterus (n = 1). 12 patients had more than one site involved.

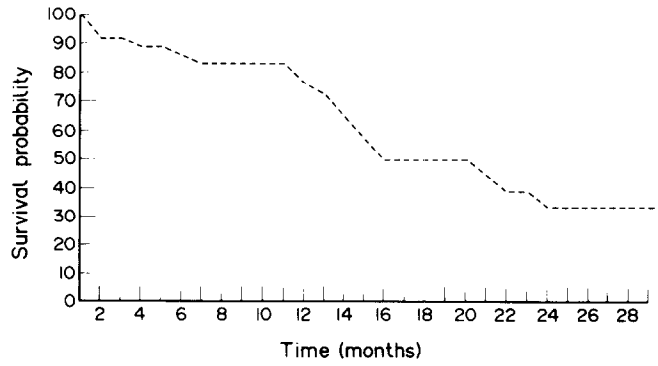

Fig. 1. Overall survival.

The patients received a total of 228 courses (range 2–10, mean 6) and all patients were evaluable for toxicity. 2 patients were not evaluable for response, time to progression and survival. Reasons for nonevaluability were cardiotoxicity after one course (n = 1) and refuse after one course (n = 1).

Toxicity

Median WBC count nadir was 1500/ml (range 200–3100/ml) and median platelet nadir was 115000/ml (range 65000–180000).

There was one toxic death due to leukopenia-related sepsis (200 WBC/ml).

Treatment delay of a week to allow myelotoxicity recovery was necessary in 28% of the courses and dose reductions to 75% of total dose were required in 20% of cycles. The delays were more frequent with the progression of treatment.

Nausea and vomiting were generally mild.

Five episodes of oral mucositis were recorded in 3 patients but were severe (WHO grade 3) only in one course, one episode of diarrhoea was noted in a patient (WHO grade 2).

Moderate alopecia was recorded in only 1 patient.

A 40-year-old woman developed a significant reduction in left ventricular ejection fraction (27% 12 months from chemotherapy discontinuation) followed by development of severe congestive heart failure (total doses: cyclophosphamide = 6.000 mg/m^2, mitoxantrone = 120 mg/m^2, folinic acid 2.000 mg/m^2, 5-FU = 3.700 mg/m^2). She had no prior exposure to anthracyclines, although radiation was delivered after quadrantectomy.

A 50-year-old woman developed a myocardial ischaemia after receiving one treatment course. She had no history of cardiac disease and ECG before the start of therapy was normal. Although serial cardiac enzymes were normal and the ECG returned to normal after 48 h, she was taken off the study.

Response

The overall response rate (CR 25% and PR 30%) was 55%. The overall progression-free survival lasted from 2+ to 29+ months (Median 8+ months). Median overall survival time is 16 months (Fig. 1). Performance status, previous adjuvant CMF chemotherapy and ER status did not influence the likelihood of response.

Response according to metastatic site is described in Table 2. Patients who had involved only one site of disease achieved a better response rate than patients with more than one site of disease (61 vs. 25%, $P < 0.05$).

Among 26 evaluable patients with only one metastatic site we observed 10 CR (liver = 4, node = 4, lung = 2) and 6 PR (liver = 2, lung = 2, skin = 2).

Overall response rate according to metastatic site was 100%

Table 2. Response according to metastatic site

	CR	PR	SD	PD	RR (%)
Liver	5/13	4/13	3/13	1/13	70
Lung	4/13	6/13	1/13	2/13	77
Bone	—	2/11	8/11	1/11	18
Nodes	6/7	1/7	—	—	100
Skin	—	2/4	1/4	1/4	50
Uterus	—	—	—	1/1	0

CR = complete remission, PR = partial remission, SD = stable disease, PD = progressive disease, RR = response rate.

in nodal involvement, 77% in lung involvement, 70, 50 and 18% in liver, skin and bone involvement, respectively.

Among the 6 patients who received an anthracycline-containing regimen for advanced disease we achieved 2 PR, 2 SD and 2 PD.

DISCUSSION

Medical treatment for advanced breast cancer remains a palliative treatment, therefore prolongation of survival and improvement of quality of life are major objectives of chemotherapy in this case.

Despite very high response rates, several trials failed to prolong survival over historical data [15–17].

We have investigated the value of a combination therapy with mitoxantrone, cyclophosphamide, 5-FU and HDFA with the aim to reduce the toxicity usually shown by anthracyclines.

Patients previously treated with an anthracycline-containing regimen were considered eligible because of clinical evidence that mitoxantrone and doxorubicin (or epirubicin) are partially non cross-resistant [8, 18, 19].

Although the treatment was subjectively well tolerated, in some patients myelosuppression was more severe than that expected and 1 patient with widespread bone metastatic disease died because of leukopenia-related sepsis.

An unexpected side-effect was a severe congestive heart failure that a 40-year-old woman developed at 12 months' time from the end of therapy. She had not previously given anthracyclines but underwent radiation after quadrantectomy. This event places an ethical and practical problem: is it possible to prevent this kind of unexpected toxicity?

Serial estimations of the left ventricular ejection fraction did not show impairment of left ventricular ejection in the other patients.

Unlike the study by Zaniboni *et al.* [20], in spite of a total dose of 1850 mg/m^2 for each cycle, we observed a very low degree of oral mucositis and diarrhoea that are typical side-effects of the combination of HDFA and 5-FU: this could probably be due to a prolonged oral cavity protection with sodium bicarbonate and/or the use of mitoxantrone instead of epirubicin.

Alopecia, nausea and vomiting were minimal so that this regimen was psychologically well tolerated by the majority of patients.

In conclusion, our preliminary results suggest that this schedule could be generally an active regimen in the treatment of advanced breast cancer: however further studies with more selected patients are warranted.

1. Buroker TR, Moertel CG, Fleming TR, *et al.* A controlled evaluation of recent approaches to biochemical modulation or enhancement of 5-fluorouracil therapy in colorectal carcinoma. *J Clin Oncol* 1985, **3**, 1624–1631.
2. Moran RG, Keyomarsi K. Biochemical rationale for the synergism of 5-fluorouracil and folinic acid. *NCI Monogr* 1987, **5**, 159–163.
3. Rustum YM, Trave F, Zakrzewski SF, *et al.* Biochemical and pharmacologic basis for potentiation of 5-fluorouracil action by leucovorin. *NCI Monogr* 1987, **5**, 165–170.
4. Allegra CJ, Chabner BA, Sholar PW, Bagley C, Drake JC, Lippman ME. Preliminary results of a phase II trial for the treatment of metastatic breast cancer with 5-fluorouracil and leucovorin. *NCI Monogr* 1987, **5**, 199–202.
5. Marini G, Simoncini E, Zaniboni A, Gorni F, Marpicati P, Zambruni A. 5-Fluorouracil and high-dose folinic acid as salvage treatment of advanced breast cancer: an update. *Oncology* 1987, **44**, 386–340.
6. Doroshow JH, Leong L, Margolin K, *et al.* Refractory metastatic breast cancer: salvage therapy with fluorouracil and high-dose continuous infusion leucovorin calcium. *J Clin Oncol* 1989, **7**, 439–444.
7. Shenkenberg TD, Von Hoff DD. Mitoxantrone: a new anticancer drug with significant activity. *Ann Intern Med* 1986, **105**, 67–81.
8. Smith IE, Stuart-Harris R, Pavlidis N, Bozek T. Mitoxantrone as a single agent and in combination chemotherapy in the treatment of advanced breast cancer. *Cancer Treat Rev* 1987, **10**, 37–40.
9. Allegra JC, Woodcock T, Woolf S. A randomized trial comparing mitoxantrone with doxorubicin in patients with stage IV breast cancer. *Invest New Drugs* 1985, **3**, 153–161.
10. Periti P, Robustelli della Cuna G, Pannuti F, *et al.* Randomized study of 5-fluorouracil, epirubicin and cyclophosphamide vs fluorouracil, mitoxantrone and cyclosphosphamide in advanced breast cancer: preliminary data. *Joint NCI-IST Symposium*, Genoa, Italy, A57, 1989.
11. Machover D, Goldschmidt E, Chollet P, *et al.* Treatment of advanced colorectal and gastric carcinoma with 5-fluorouracil and high-dose folinic acid. *J Clin Oncol* 1986, **4**, 685–696.
12. Clark PI, Slevin ML. Allopurinol mouthwashes and 5-fluorouracil induced oral toxicity. *Eur J Surg Oncol* 1985, **11**, 267–268.
13. Kaplan E, Meier P. Non-parametric estimates from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–458.
14. Cox DR. *The Analysis of Binary Data*. New York, Chapman & Hall, 1970.
15. Tormey DC, Kline JC, Palta M, Davis TE, Love RR, Carbone PP. Short term high density systemic therapy for metastatic breast cancer. *Breast Cancer Res Treat* 1985, **5**, 177–188.
16. Mortimer J, Flournoy N, Livingstone RB, Stephens RL. Aggressive adriamycin-containing regimen (PM-FAC) in estrogen receptor-negative disseminated breast cancer. *Cancer* 1985, **56**, 2376–2380.
17. Cocconi G, Bisagni G, Bacchi M, *et al.* Cisplatin and etoposide as first line chemotherapy for metastatic breast caarcinoma: a prospective randomized trial of Italian Oncology Group for Clinical Research. *J Clin Oncol* 1991, **9**, 664–669.
18. Neidhart TA, Gochnour D, Roach RW. A comparition of mitoxantrone and doxorubicin in breast cancer. *J Clin Oncol* 1986, **4**, 672–677.
19. Cruciani G, Tienghi A, Fiorentini G, *et al.* Mitoxantrone and vinblastine in the treatment of advanced breast cancer. *Tumori* 1990, **76**, 196–198.
20. Zaniboni A, Simoncini E, Marpicati P, *et al.* Cyclofosfamide, epirubicin, high-dose folinic acid and 5-fluorouracil (super-FEC) as first-line chemotherapy for advanced breast cancer: preliminary results. *Eur J Cancer Clin Oncol* 1989, **25**, 1151–1155.