Cancer Chemother Pharmacol (1993) 32: 359–364

Cancer Chemotherapy and Pharmacology

Advanced breast cancer treatment with folinic acid, 5-fluorouracil, and mitomycin C

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Received 11 May 1992/Accepted 16 March 1993

Abstract. A total of 44 women with advanced breast cancer who had failed first- and second-line chemotherapy were given combination chemotherapy consisting of folinic acid (FA), 5-fluorouracil (5-FU) and mitomycin C (MMC). The treatment schedule was: 200 mg/m^2 FA and 400 mg/m^2 5-FU given i.v. over 2 h for 5 days plus 5 mg/m^2 MMC given i.v. on days 3–5; in 19 patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 3–4 and bone marrow depression, the MMC dose was 3 mg/m^2 given i.v. on days 3–5. In all, 41 patients were evaluable for response; 15 had a partial remission (PR), 18 had stable disease (SD), and 8 showed progressive disease (PD). The median response duration was 6 months and the median survival was 10 months. Toxicity was mild and consisted mainly of stomatitis, diarrhea, and leukopenia. A rapid improvement in performance status was noted in responding patients. A striking result was the reduction of analgesics in most cases and their complete withdrawal in responding patients. This combination chemotherapy achieved satisfactory effectiveness and improved the quality of life of patients.

Introduction

Advanced breast cancer that has failed first- or second-line chemotherapy does not usually respond to subsequent cytotoxic treatment due to the hormone and chemotherapy resistance that develops in the neoplastic cell population [2, 19, 20]. In these patients, the performance status is poor and bone marrow depression can be very severe because of widespread invasion of bone marrow tissue by the disease and/or toxicity caused by previous treatments [9, 24].

This study was supported in part by grant 92.02170.PF/39 from the Italian National Research Council (CNR) – Clinical Applications of Oncologic Research (ACRO)

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In this stage of the disease, chemotherapy usually produces side effects before bringing about any possible therapeutic benefit. Many cytotoxic drugs have been used alone or in combination, but in all cases, their modest antiproliferative activity has been outweighed by the drawbacks of considerable side effects [8, 36]. Mitomycin C (MMC) is an active drug in advanced breast cancer [12, 30]; moreover, 5-fluorouracil (5-FU) associated with folinic acid (FA) has been proven active against notoriously chemoresistant tumors [16, 27]. 5-FU and MMC seem to produce low levels of cumulative toxicity, and they are often used in combination to treat chemoresistant metastatic tumors [7, 26, 28].

The aim of the present study was to evaluate the palliative effect and toxicity of the combination chemotherapy FA + 5-FU + MMC (FFM) in patients with advanced breast cancer refractory to first- and second-line chemotherapy.

Patients and methods

Patients' characteristics. A total of 44 patients with advanced breast cancer who had failed first- and second-line chemotherapy were given FFM combination chemotherapy. Table 1 illustrates the principal characteristics of the patients. In all 31 patients had failed prior hormonal treatment, and all patients had failed cyclophosphamide/ methotrexate/fluorouracil (CMF) as first-line treatment and then fluorouracil/Adriamycin/cyclophosphamide (FAC) as second-line chemotherapy [5, 21, 33]. This group of patients had achieved a response rate of 67% and 38% to first- and second-line cytotoxic treatment, respectively.

All patients had measurable and evaluable lesions that were assessable by physical and radiological examination. Each patient had at least one measurable lesion. Only patients with osteolytic bone metastases were included. All prior cytotoxic drugs had been discontinued for at least 6 weeks prior to the start of the new protocol. The present study was approved by the ethical committee of our institute, and informed oral consent was obtained from each patient or family.

Treatment. The treatment schedule consisted of 200 mg/m^2 FA given i.v. on days 1–5, 400 mg/m^2 5-FU given i.v. on days 1–5, and 5 mg/m^2 MMC given i.v. on days 3–5. In 19 patients with a performance status (PS) of 3–4 according to Eastern Cooperative Oncology Group (ECOG) criteria [29], a leukocyte count of 2,500–3.500/mm^3, and a platelet count

Table 1. Main characteristics of evaluable patients

Total entered	44
Total evaluable	41
Median age (range)	60 (35–71) years
Menopausal status:	
Premenopausal	12
Postmenopausal	29
ER status:	
Positive	18
Negative	14
Unknown	9
PgR status:	
Positive	19
Negative	12
Unknown	10
Performance status (ECOG):	
1–2	23
3–4	18
Disease-free interval:	
0–6 months	0
7–12 months	1
13–18 months	3
19–24 months	21
>24 months	16
Predominant metastatic site:	
Bone	21
Viscera	13
Soft tissue	7
Previous treatment:	
Hormonal therapy	31
Chemotherapy:	
CMF	41
FAC	41

ER, Estrogen receptor; PgR, progesterone receptor; ECOG, Eastern Cooperative Oncology Group; CMF, cyclophosphamide/ methotrexate/fluorouracil; FAC, fluorouracil/Adriamycin/cyclophosphamide

of 100,000–150,000/mm^3, the dose of MMC was reduced from 5 to 3 mg/m^2 on days 3–5. Patients with a PS of 1–2 began treatment as outpatients, and those with a PS of 3–4 began therapy as inpatients.

Treatment was delayed by 1 week when a leukocyte count of <2,500/mm^3 and a platelet count of <100,000/mm^3 had occurred or if major toxic effects had been observed. A maximal delay of 2 weeks was allowed. In the case of sustained low values, the patient was excluded from the study. No dose reduction was made. Treatment was repeated every 21 days until progression of the disease or serious side effects appeared. Patients who achieved a complete remission underwent three further "consolidation" cycles of chemotherapy.

Response assessment. A physical examination as well as blood counts and chemistry were repeated at each cycle. Baseline investigations, including chest X-rays, liver ultrasonography, bone scans, and skeletal surveys, were repeated at 2-month intervals.

The response to treatment was assessed according to standard UICC (International Union Against Cancer) criteria [23]. A complete response (CR) was defined as the disappearance of all measurable lesions for at least 2 months. A partial response (PR) was defined as a reduction of ≤50% in tumor size and the absence of new lesions for at least 2 months. Stable disease (SD) was defined as stabilization of disease or a reduction of <50% in tumor parameters with no progression of other lesions for at least 3 months. Progression of disease (PD) was defined as an increase of >25% in any of the metastatic lesions. In the case of bone metastases, evidence of healing on radiographs and bone scans and improved symptoms were necessary for the assessment of overall improvement. All osteoblastic metastases were considered to be nonevaluable.

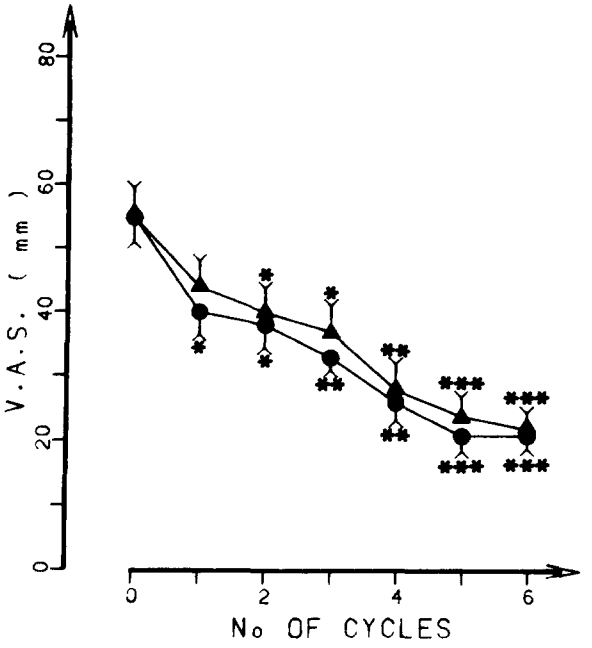

Fig. 1. Sequential changes in millimeters on the visual analogue scale (mean ± SEM) observed in 31 of 38 patients who had painful symptomatology. ▲, scoring by the patients; ●, scoring by the nurse. *P ≤0.05, **P ≤0.005, ***P ≤0.001

For early monitoring of disease, we measured the following tissue and bone markers on a monthly basis: carcinoembryogenic antigen (CEA), tissue polypeptide antigen (TPA), breast carcinoma antigen (CA 15/3), alkaline phosphatase (Alk. Ph.), bone Gla-protein (BGP), the urinary hydroxyproline/creatinine ratio (HOP/Cr), and the 24-h whole-body retention (WBR%) of [^{99m}Tc]-methylene diphosphonate. These measurements were performed by previously described methods [17, 18]. A histological analysis of bone metastases, performed using transiliac bone-biopsy specimens, was made in patients who achieved radiological healing of bone lesions [15].

Patients were considered to be evaluable only after they had undergone three cycles of chemotherapy. Response duration and survival were evaluated from the start of chemotherapy until the end of a follow-up period of at least 1 year.

Toxicity and quality of life. Toxicity was assessed during each cycle on a five-point scale based on World Health Organization (WHO) criteria [38]. As most patients had a low-ranging normal cardiac performance, cardiotoxicity was evaluated by means of the preejection period/left ventricular ejection time (PEP/LVET) according to Hassan and Turner [22].

To evaluate the impact of the treatment on the quality of life, we used the linear analogue self-assessment (LASA) [31]. An interviewer asked the patients questions regarding physical symptoms, functional activity, family and emotional well-being, satisfaction with the treatment, sexuality, and occupational functioning on a weekly basis. The patients were asked to mark a 10-cm line at a point most appropriate to their feeling at that moment. In all, 38 patients reported pain, which was evaluated by means of the Scott-Huskisson visual analogue scale. One scale was filled in by the patient and another, by the nurse [34]. Statistical analyses between posttreatment and pretreatment values were made using Student's t-test.

Results

A median of 8 cycles were given per patient (range, 2–13). The median delivered-dose intensity was 236.4 mg/m^2 per

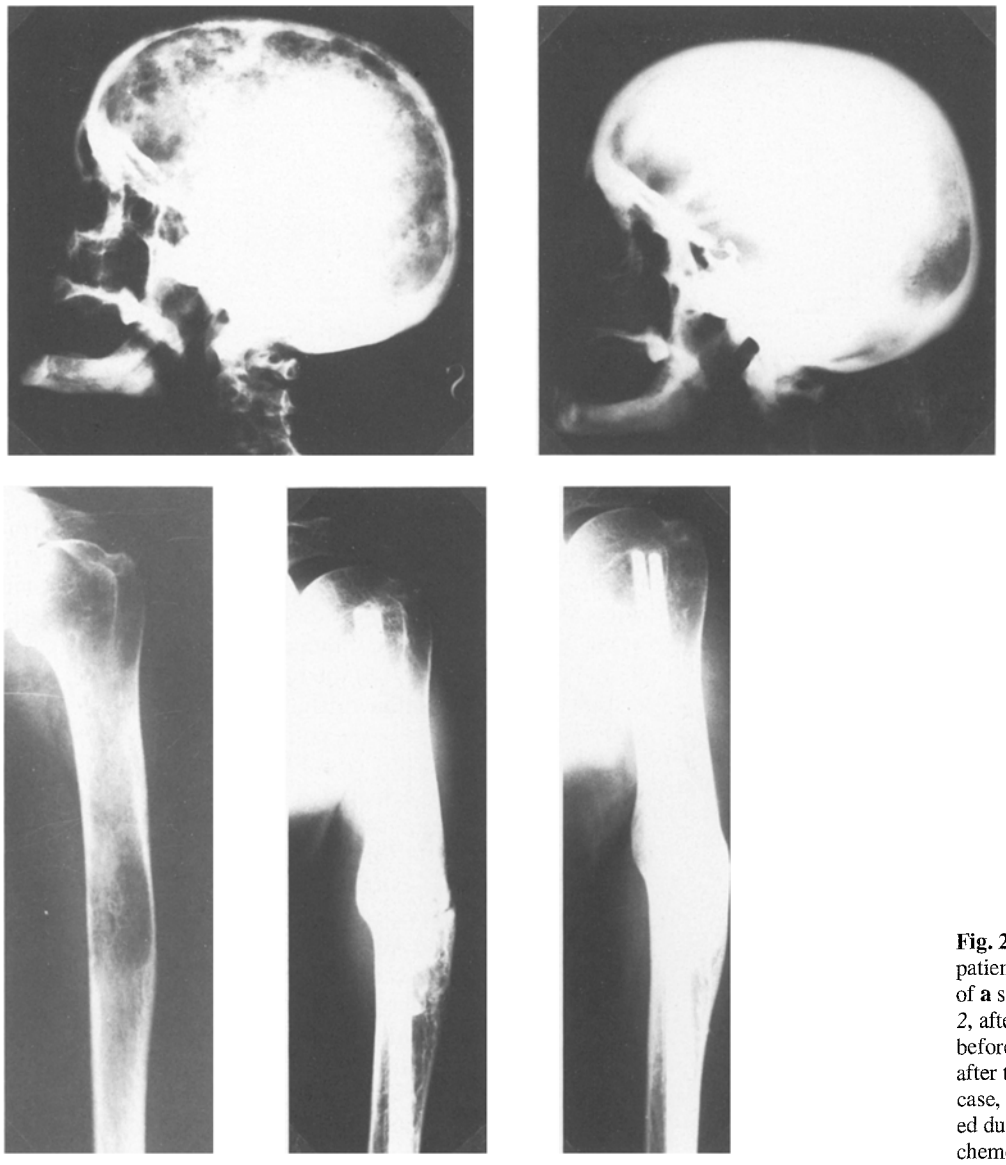

Fig. 2 a, b. X-rays obtained in two patients, showing complete recalcification of **a** skull metastases (*1*, before treatment; *2*, after therapy) and **b** humerus lesions (*1*, before treatment; *2*, during treatment; *3*, after therapy), respectively. In the latter case, fixation of the humerus was performed due to a pathological fracture before the chemotherapy was started

week for FA, 472.8 mg/m^2 per week for 5-FU, and 3.4 mg/m^2 per week for MMC. A total of 41 patients were evaluable for response and toxicity. All patients were evaluated for survival. An overall objective response was verified in 15 of 41 evaluable patients (36.6%; 95% confidence limit, 21%–50%), with 15 PRs, 18 SDs, and 8 PDs being recorded.

After a median of 3 cycles, 31 patients showed a significant improvement in performance status (mean ± SD: from 2.8±0.6 to 1.5±0.4; P <0.01) and a rapid decrease in pain (Fig. 1), resulting in a reduction of analgesics in most cases and their complete withdrawal in responding patients. Data on the quality of life showed a notable improvement in other physical symptoms such as weakness and anorexia and in functional conditions such as the capacity to work and enjoy one's free time. Most of the treated patients showed satisfaction with the treatment and an improvement in emotional well-being. The 15 patients who achieved an objective response showed a significant improvement in their LASA scores during treatment (P <0.05). Seven responding patients were free of all cancer symptoms for a median of 3 months. Most of the patients with an initial PS of 1–2 completed the treatment as outpatients. Most of the patients with an initial PS of 3–4 became capable of receiving the treatment as outpatients.

In terms of the dominant metastatic lesions, objective responses were obtained in bone (9/21, 42.8%), viscera (4/13, 30.8%) and soft tissue (2/7, 28.6%), respectively. The 15 PRs were observed in 9 bone metastases, 2 soft-tissue lesions, 3 lung metastases, and 1 liver lesion. All metastatic lesions were evaluated for response by physical examination and imaging modalities. In the patients with bone metastases that were considered to be responding, X-rays showed a complete (in two cases) or partial (in seven cases) recalcification of the osteolytic lesions (Fig. 2), and a significant improvement was noted in bone scans, bone pain, and bone markers. Bone histological examinations revealed no evidence of tumor cells in two patients following radiological healing of bone lesions.

Palpation documented a reduction of >50% in the lesions in two patients with soft-tissue metastases. Chest

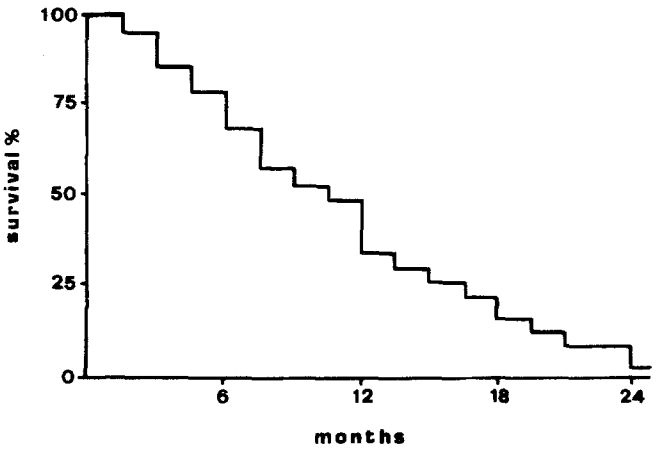

Fig. 3. Survival of 44 patients with advanced breast cancer who were treated with FA + 5-FU + MMC

X-rays and ultrasonography demonstrated a reduction of >50% in the cross-sectional area of lung and liver metastases in four patiens.

The response observed in the nine patients with predominant metastases of bone was also preceded by a rapid and progressive reduction in bone markers (Alk.Ph., BGP, HOP/Cr, WBR%), whereas these markers increased when bone lesions evidenced progression. Specific tissue markers (CEA, TPA, CA 15/3) showed a reduction of $\geq 50\%$ after 3 cycles of treatment in most of the responding patients, whereas these markers showed an increase in nonresponding patients.

The median time to response was 2.5 months, the median response duration was 6 months (range, 2–12 months), and the median survival was 10 months (range, 2–24 months; Fig. 3), with an advantage being noted for responding versus nonresponding patients (13 months vs 6 months).

The toxicity was well tolerated by patients, and no treatment-related death occurred. The main side effects consisted of stomatitis, diarrhea, and leukopenia (Table 2). Grade 2–3 side effects occurred after a median of three cycles. Treatment was delayed by 1 week in five patients and was discontinued in two patients because of persistent leukopenia. No case of severe cardiotoxicity was observed; the PEP/LVET ratio increased slightly in six patients after a median of four cycles but did not require discontinuation of or a delay in the treatment. The best supportive care was given to all of these patients. Other side effects were mild and short-lasting. No treatment-related infection or septicemia was observed.

Table 2. Number of patients showing toxicity

	WHO grade			
	1	2	3	4
Stomatitis	27	9	5	0
Diarrhea	5	7	5	0
Leukopenia	26	10	4	1
Alopecia	24	9	6	2
Nausea	34	4	3	0
Vomiting	10	3	1	0

The toxicity scale indicates the worst grade experienced per patient

Discussion

Advanced breast cancer that has failed first- and second-line chemotherapy is certainly a challenge for the oncologist; indeed, in such patients it becomes difficult to begin a treatment that will guarantee a response without further compromising the quality of life. However, this also implies the treatment of patients with a low performance status to attenuate the symptomatology [2, 20].

Salvage chemotherapy in advanced breast cancer usually comprises cytotoxic drugs that have not been used in previously applied schedules, most frequently MMC and vinca alkaloids [1, 12, 20]. It should be noted that 5-FU and MMC or FA and 5-FU combinations have been evaluated in this clinical setting, but the results obtained in terms of response rates are often difficult to interpret due to the heterogeneity of most of the patients studied [13, 28].

The combination of FA, 5-FU, and MMC investigated in the present study achieved a response rate of 36.6%, a median response duration of 6 months, and a median survival of 10 months (13 months for responding patients vs 6 months for nonresponding patients). These results are similar to those reported for second-line chemotherapy containing MMC or Adriamycin given either alone or in combination but have rarely been described in patients undergoing salvage chemotherapy [1, 2, 6, 14, 30, 37].

Therefore, the results of our study seem encouraging, even if the patients' characteristics would indicate that the present group of patients were somewhat better candidates than one would normally expect to see for second- or third-line chemotherapy of breast cancer. In fact, it would appear that there was a preponderance of patients with bone as the predominant site of metastases, and it is not rare for advanced breast cancer to remain confined to the bone for a long time and to progress slowly [9, 35]. These patients usually achieve prolonged survival but present more often with major complications of their skeletal disease as compared with patients who have metastases to other sites [4, 25]. It would also appear that a significant proportion of our patients (39%) had a disease-free interval of >24 months. Nevertheless, it must be recognized that this treatment achieved a marked palliative effect, even in 18 patients, with a low initial performance status (Table 1). Moreover, the significant improvement in pain and performance status obtained in all patients showing an objective response and in most patients who developed stable disease was an interesting result inasmuch as palliation and an improvement in the quality of life is more important than prolongation of survival in these individuals. Indeed, most patients were free to carry out their daily habits for some time. This improvement in the day-to-day performance of the patients seemed to be correlated with the effectiveness of the combination chemotherapy.

The response rate of 42.8% observed in bone metastases was higher than the rates previously reported for second- or third-line chemotherapy [9, 30]. These results were confirmed by the bone markers [Alk.Ph., BGP, HOP/Cr, WBR%), which showed more sensitivity in monitoring bone lesions relative to specific tissue markers for breast cancer (CEA, TPA, CA 15-3), in accordance with previous studies [10, 17]. The difference in the behavior of these two groups of markers might indicate the greater efficacy of the treatment in bone lesions relative to soft-tissue and visceral metastases. On the other hand, this discrepancy may simply be due to the better prognosis for bone metastases, which can be considered an indolent disease [35].

Nevertheless, bone metastases may progress within a short time because of the neoplastic cells that persist in the bone marrow despite radiological healing [11, 32]. Moreover, as most clinicians affirm, the quantification and definition of a response in bone disease is very difficult. According to UICC (International Union Against Cancer) criteria, a complete response to antineoplastic therapy of a bone metastasis indeed requires the reversal of abnormal radiographic findings and a partial response requires some evidence of sclerosis within previously lytic lesions without any evidence of new osteolytic lesions [23].

The assessment of response in bone metastases may be based on X-rays, bone scans, bone pain, and bone markers, but each of these has its own sources of inaccuracy. The radiological evidence of recalcification of lytic metastases may be considered as the golden standard reflecting the healing of osteolytic lesions. Changes in the number of hot spots on a bone scan, bone pain, and the levels of bone markers seem to be less accurate in response evaluation [3, 25]. Therefore, the complete recalcification of osteolytic lesions observed in two patients with bone metastases is unlikely to represent a true complete response. A certain amount of caution must be applied in considering these two responses as being truly complete; however, it must be stressed that of these two patients, one continued to show extensive recalcification of the osteolytic lesion at 12 months after the end of the treatment, whereas the other progressed 6 months after achieving a remission.

The toxicity of the treatment was acceptable, considering that all patients had been heavily pretreated with anthracyclines and that many of them had suffered from bone marrow depression before starting the treatment. No infection or septicemia was observed, but it must be emphasized that a delay in the chemotherapy was introduced every time a reduction of <2500 leukocytes/mm^3 occurred and that the best supportive care was given to all of these patients.

It may be concluded that FA + 5-FU + MMC seems to be a non-cross-resistant combination that can be given as a means of palliation to patients with advanced breast cancer who have been heavily pretreated with conventional chemotherapy. Furthermore, these findings may justify the use of this regimen as second-line cytotoxic treatment in patients who have never responded to previous chemotherapy and, above all, in patients with predominant metastatic bone lesions.

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