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ORIGINAL ARTICLE

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Folinic acid, 5-fluorouracil and mitomycin C in metastatic breast cancer patients previously treated with at least two chemotherapy regimens

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Abstract *Purpose:* To assess the activity and safety of combined folinic acid (FA), 5-fluorouracil (5-FU) and mitomycin C (MMC) in metastatic breast cancer patients previously treated with at least two chemotherapy regimens. *Patients and methods:* A total of 104 consecutive patients were enrolled for treatment with FA 100 mg/m^2 plus 5-FU 400 mg/m^2 i.v. on days 1–5, and MMC 3 mg/m^2 on days 3–5 (FFM). The cycles were repeated every 21 days until progression, severe toxicity or patient refusal. *Results:* Of the 104 patients, 96 were evaluable for response and toxicity. The overall response rate was 43% (95% confidence interval 32.8–53.2%); 40 patients achieved stable disease (42%) and 15 progressed (15%). In a retrospectively defined subgroup of patients with clinical resistance to taxanes (12 patients) or anthracyclines (14 patients), the response rate was 42%. The median time to progression was 8 months (3–18 months), and the median overall survival was 10.5+ months (2–36 months). The most common treatment-related adverse events were stomatitis, neutropenia, nausea/vomiting and diarrhea. Stomatitis, neutropenia and thrombocytopenia were the only grade 4 treatment-related adverse events, and occurred in no more than 3% of patients. *Conclusion:* The tested FFM regimen seems to offer a valid option for patients with metastatic breast cancer who have been pretreated with two or more chemotherapeutic lines or who have failed on regimens containing anthracyclines or taxanes.

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Introduction

First-line anthracycline-containing chemotherapy regimens lead to high objective response percentages in patients with metastatic breast cancer, but the results are often disappointing when they are used as second-line therapy [6, 10, 19, 24]. The therapeutic prospects for patients progressing after a second-line treatment become even more limited as the disease gets worse [13]. Many cytotoxic drugs are used for salvage chemotherapy but, in addition to unsatisfactory objective results, they may lead to severe side effects [15, 28, 31].

Mitomycin C (MMC) and 5-fluorouracil (5-FU) are often used singly or in combinations with other drugs to treat metastatic breast cancer [5, 11, 21]. MMC is an antitumoral antibiotic that mainly acts by alkylating DNA, and is effective in various gastrointestinal, pulmonary, genitourinary, squamous cell and breast cancers. The single-agent response rates in previously treated advanced breast cancer patients are 15–20%. The main side effect is bone marrow suppression, which is clearly dose-related [11]. 5-FU is an antimetabolite that has significant antitumor activity as a single agent and as a component of the FAC regimen (5-FU, doxorubicin, cyclophosphamide), one of the most active combination regimens currently used for metastatic breast cancer [10]. 5-FU is not affected by multidrug resistance mechanisms in breast cancer, and its moderate bone marrow toxicity means it can be combined with other myelotoxic agents. The most frequent toxicities are stomatitis and diarrhea [5]. Theoretically, combining MMC with 5-FU should lead to advantages because they have different mechanisms of cytotoxicity and resistance, and their toxicities overlap very little [20, 27, 32]. Furthermore, 5-FU combined with folinic acid (FA) has proved to be more

active than 5-FU alone against many chemoresistant tumors [22, 23].

In a previous study, we have found that combination chemotherapy with FA, 5-FU and MMC (FFM) is satisfactorily effective in a small group of women with advanced breast cancer who had failed first-and second-line chemotherapy [8]. In the light of these encouraging results, an extended study was performed in order to characterize more fully the activity and safety of the FFM regimen in patients with metastatic breast cancer who had already been treated with two or three lines of chemotherapy. Further objectives were to determine the time to progression, overall survival and the quality of life.

Patients and methods

Eligibility criteria

In order to be eligible, the patients had to be female, aged 18 years or more, and have an ECOG performance status (PS) of 0–3 and bidimensionally measurable or assessable metastatic breast cancer. They also had to have received at least two chemotherapeutic regimens as treatment for metastatic disease. Hormone therapy was permitted in the adjuvant setting or for advanced disease. They were not allowed to have received chemotherapy or hormonal therapy in the 3 weeks preceding study entry. All of the patients stopped hormone therapy before starting chemotherapy. Radiation therapy could have been given to treat bone lesions at risk of fracture or sites other than those used to assess response. The following hematological values were required: an absolute neutrophil count of $\geq 1.5\times10^9$/l, a platelet count of $>100{,}000$/μl and hemoglobin levels of >11 g/dl. Patients were also considered eligible if they had widespread bone metastases and a platelet count of 50,000–100,000/mm^3 linked to tumor invasion of the bone marrow. Creatinine and total bilirubin levels had to be less than 1.5 times and transaminases less than 2.5 times the upper normal limit. Life expectancy had to be at least 3 months. Patients with bone metastases as their only site of assessable disease were not eligible if bisphosphonate therapy had been initiated less than 2 months before enrollment. Any patients with osteoblastic bone lesions as the only site of metastases or with central nervous system metastatic disease at the time of enrollment were excluded. All of the patients gave their written informed consent. The trial was approved by the University Ethics Committee.

In accordance with Simon's two-stage phase II designs, a sample size of 83 patients was calculated assuming a response rate of approximately 20% for other third-line treatments, and a target activity of interest of 35%, with an α value of 0.05 and a β value of 0.90. Given the advanced disease stage and poor PS of the patients, it was planned to enroll an additional 20 patients in the expectation that at least 10–15% of the patients would be inevaluable.

Assessment of response, toxicity and quality of life

After their medical history had been recorded, the patients underwent a complete physical examination, complete blood cell count, serum chemistry and liver function tests, ECG and echocardiography. Before each treatment cycle, any adverse events were recorded and a complete blood cell count was done, including the WBC differential formula and platelet count, and physical examination and serum chemistry tests were repeated at the same time. Tumor response was assessed by means of a physical examination, ultrasonography and radiography every three cycles in accordance with World Health Organization (WHO) criteria [17]. When appropriate, CT, MRI and bone scans were also performed every three cycles.

A complete response was defined as complete disappearance of all clinical, radiographic and biochemical evidence of disease for a minimum of 1 month. A partial response required a 50% or greater reduction in the sum of the product of the longest diameter and its perpendicular. Stable disease was defined as a decrease of less than 50% or an increase of less than 25% in the product of the longest perpendicular diameters of measurable lesions lasting 3 months. Progressive disease was defined as the appearance of new lesions or an increase of ≥25% in the sum of the products of the longest diameter and its perpendicular, as compared with the lowest value recorded. The responses in the group of patients with predominant bone metastases were assessed on the basis of the complete or partial radiological recalcification of osteolytic lesions.

Toxicity was assessed using a five-point rating scale based on WHO criteria. At the first occurrence of grade 2 toxicity, the treatment was interrupted and only started again at the same dose when the toxicity regressed to grade 1 or less, with prophylaxis where possible. In the case of grade 3 or 4 toxicity, the treatment was interrupted and the patients were allowed a maximum of 3 weeks to recover before being withdrawn from the study. No dose reductions were scheduled. Hematopoietic growth factors were not routinely used, but only given when neutrophil counts fell below 1000/mm^3 and continued until complete hematological recovery. Anemia was treated as clinically indicated. Diarrhea, and nausea and vomiting were treated symptomatically. On the first day of each cycle, the patients' ECOG PS was assessed and their mean analgesic consumption was recorded in morphine-equivalent milligrams. Quality of life (QL) was rated using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (EORTC QLQ-C30), which consists of nine domains and six single items, a 13-item breast cancer-specific questionnaire, and five questions evaluating changes [1].

Treatment plan

The treatment consisted of FA 100 mg/m^2 plus 5-FU 400 mg/m^2 i.v. on days 1–5, with MMC 3 mg/m^2 i.v. on days 3–5. The cycles were repeated every 21 days for a maximum of six cycles, or until progression or severe toxicity. Initially, the patients with an ECOG PS of 3 received chemotherapy in hospital; if their PS improved during treatment, chemotherapy was administered on an outpatient basis.

Relative dose intensity was defined as the actual weekly doses of FA, 5-FU and MMC at the end of treatment, divided by the planned weekly doses. Mild antiemetic drugs, such as metoclopramide and dexamethasone, were administered.

Results

A total of 104 consecutive patients were enrolled between January 1995 and May 2001. Their main characteristics are shown in Table 1. All had received two lines of chemotherapy, at least one containing an anthracycline. Within 6 months of completing adjuvant anthracycline chemotherapy, 13 patients (12%) had relapsed, and 68 (65%) had received one anthracycline-containing regimen as first-line treatment for advanced disease. Second-line chemotherapy had consisted of CMF (cyclophosphamide, methotrexate, 5-FU) in 35 patients, taxanes alone in 26, vinorelbine alone in 22, and anthracycline-containing regimens in 21. As third-line therapy, 18 patients had received taxanes, and 14 vinorelbine. All of the patients with a positive or unknown hormone receptor status had received adjuvant

Table 1. Main characteristics of 104 pretreated patients with metastatic breast cancer

Number of patients	
Entered	104
Evaluable	96
Age (years)	
Median	59
Range	36–74
Menopausal status	
Premenopausal	38
Postmenopausal	66
PgR status	
Positive	56
Negative	36
Unknown	12
ER status	
Positive	54
Negative	38
Unknown	12
Performance status (ECOG)	
1–2	72
3	32
Disease-free interval (months)	
0–12	16
13–24	34
>24	54
Predominant metastatic site	
Bone	56
Viscera	32
Soft tissue	16
Metastatic sites	
1	11
2	72
≥3	21
Prior hormonal therapy	
Adjuvant	66
Metastatic disease	42
Adjuvant chemotherapy	69
Previous chemotherapy lines for metastatic disease	
One	104
Two	104
Three	32

hormonal therapy, including 42 who had also received second-line hormonal therapy for metastatic disease. Most of the patients had more than one metastatic site and a PS of 2 or more. Bone lesions were predominant in 56 patients (54%), visceral sites in 32 (30%) and soft tissue sites in 16 (16%).

Response to treatment

Of the 104 patients, 96 were evaluable for response and toxicity; the remaining 8 were lost to follow-up after one or two treatment cycles. All were evaluable for survival. Of the 96 evaluable patients, 41 (43%; 95% confidence interval 32.8–53.2%) were confirmed as partial responders during treatment, 40 (42%) experienced stable disease and 15 (15%) progressive disease. In a retrospectively defined subgroup of patients with clinical resistance to taxanes (12 patients) or anthracyclines (14 patients) (disease progression while receiving anthracyclines or taxanes), the response rate was 42%. Responses were obtained at all metastatic sites, the highest (48%) being in patients with predominant bone disease (Table 2). Of the 11 patients with widespread bone metastases, anemia and platelet counts of 50,000–100,000/mm^3, 6 showed a gradual improvement in their hematological picture after one or two treatment cycles. An objective response was obtained in 31 (46%) of 68 evaluable patients who had received two lines of chemotherapy, and in 10 (36%) of 28 who had received three lines.

Table 2. Response to treatment by predominant metastatic sites in 96 evaluable patients

Response	All patients	Bone	Viscera	Soft tissue
Partial remission	41 (43%)	25 (48%)	12 (39%)	4 (31%)
Stable disease	40 (42%)	23 (44%)	12 (39%)	5 (38%)
Progressive disease	15 (15%)	4 (8%)	7 (22%)	4 (31%)

The median time to progression was 8 months (range 3 to 18 months). After a median follow-up of 12 months (range 2 to 37 months), 68 patients had died. Median survival was 10.5+ months (range 2 to 36 months). PS gradually and constantly improved during the first three cycles in responders (from 2.58 ± 0.79 to 1.17 ± 0.83, $P < 0.01$). PS improved in many patients with an initial ECOG PS of 3, and so the subsequent cycles could be administered on an outpatient basis. A total of 79% of all cycles were administered in this manner. Mean daily analgesic consumption (in morphine-equivalent milligrams) gradually decreased during the first three cycles in responders (from 42.4 ± 35.2 mg to 15.5 ± 19.2 mg; $P < 0.001$), and dropped after six treatment cycles in 68% of cases who had reported pain at enrollment.

The QL questionnaire was completed by 74 of the 96 patients who received at least three chemotherapy cycles, and 59 of the 76 who received six cycles. The mean global QL scores significantly improved after three ($P < 0.05$) and six ($P < 0.01$) treatment cycles. In the responding patients, there were significant differences between baseline and cycle 3 in pain, and emotional, social and functional wellbeing ($P < 0.001$, $P < 0.005$, $P < 0.005$, $P < 0.01$). In all of these patients, the mean scores were higher at the time of the third cycle. In the nonresponding patients, there were significant differences between baseline and cycle 3 only for functional wellbeing ($P < 0.05$). In all of these patients, the mean scores were higher at baseline.

Toxicity

A total of 516 cycles were administered, with a median of five cycles per patient (range one to six cycles). The chemotherapy was well tolerated and there were no treatment-related deaths. Stomatitis, neutropenia and nausea/vomiting were the most frequent side effects, but

Table 3. Toxicity after three and six cycles of chemotherapy in 96 evaluable patients

Toxicity	WHO grade					
	Third cycle			Sixth cycle		
	≤ 2	3	4	≤ 2	3	4
Stomatitis	73%	13%	0	81%	18%	1%
Neutropenia	76%	15%	0	84%	21%	2%
Nausea/vomiting	68%	8%	0	71%	13%	0
Diarrhea	32%	11%	0	38%	15%	0
Anemia	56%	2%	0	61%	1%	0
Thrombocytopenia	62%	26%	0	68%	31%	2%

were grade 1 and 2 in most cases. The main toxicities after three and six cycles are shown in Table 3. The treatment was delayed for at least 1 week in 44 patients, the reasons for the delays being hematological in 36 patients (82%) and nonhematological (stomatitis, diarrhea, nausea) in 8 patients (18%). Toxicity was slightly greater after the sixth cycle than after the third, but the differences were not significant. One patient had grade 4 stomatitis with grade 3 diarrhea after five cycles, and the therapy had to be discontinued. Two patients presented grade 4 neutropenia and thrombocytopenia with grade 3 anemia after five and six cycles, respectively; the treatment was stopped and one patient had to be admitted to hospital. Most of the patients rapidly recovered from the side effects with appropriate support therapy (intravenous electrolytes, antifungal drugs, hematopoietic growth factors, and transfusion of platelet concentrates). There was no severe cardiac or pulmonary toxicity, and no hemolytic-uremic syndrome was observed. The median delivered dose intensity was 146 mg/m^2 per week for FA, 586 mg/m^2 per week for 5-FU, and 2.6 mg/m^2 per week for MMC.

Discussion

Metastatic breast cancer is still essentially incurable and inevitably progresses during or after therapy. At this stage of disease, an ideal cytotoxic drug should offer a reasonable chance of a response, be possible to administer without the need for hospitalization, and carry no substantial risk of life-threatening toxicity.

The most widely used drugs for salvage therapy in patients with metastatic breast cancer are the taxanes, vinorelbine, MMC and 5-FU [28, 31]. Taxanes and vinorelbine lead to excellent results when combined with other antitumoral agents as first-line therapy, but the results are often unsatisfactory and only short-lasting as third-line treatment, and side effects such as peripheral neurotoxicity and constipation may be particularly bothersome to these heavily pretreated patients [14, 18, 19]. MMC used with anthracyclines, and 5-FU in combination with other cytotoxic drugs, both lead to high objective response rates in first- and second-line regimens, but are less satisfactory as a third-line approach [2, 11].

The results of our trial of FFM show that the regimen is active in metastatic breast cancer, leading to a 43% response rate in 96 evaluable patients previously treated with at least two chemotherapy lines, all of whom had characteristics predictive of a poor outcome. This is one of the highest overall response rates reported in this setting. The best response rate (48%) concerned bone metastases. Although bone lesions are usually predictive of a better prognosis than other metastases, and bone was the predominant metastatic site in 54% of our patients, it is worth pointing out that most of our patients had more than one metastatic site and a poor PS, and all had received more than two lines of chemotherapy [3]. It is unlikely that MMC alone was responsible for these results because its response rate in anthracycline-pretreated patients does not exceed 20% [11, 21]. Similarly, the response rates with 5-FU plus FA as second- or third-line therapy in metastatic breast cancer are between 20% and 30% [33]. The high response rate observed in the present study was therefore probably due to in vivo synergism between the two antitumoral agents rather than to an overlapping effect.

As expected, the overall response rate was higher in the patients previously treated with two lines of chemotherapy as adjuvant treatment or for advanced disease than in those pretreated with three lines (46% vs 36%), but the results in the latter are still worth underlining because they are much better than usually reported in such heavily pretreated patients. It is also interesting to note that FFM salvage treatment was active in 42% of the patients who had progressed while receiving anthracyclines or taxanes. The response rates to most regimens are usually less than 15% in patients with anthracycline-resistant metastatic breast cancer, and only 20–40% with single-agent taxanes [7, 12]. Thus our results seem to suggest that the FFM regimen is not cross-resistant with anthracyclines or taxanes and therefore may represent a valid option in patients with progressive disease receiving anthracycline or taxane-based chemotherapy. However, interesting results can be expected from some ongoing studies, such as the randomized trial by the Anglo-Celtic Co-operative Oncology Group now under way in the UK comparing 3-weekly vs weekly paclitaxel in patients with metastatic breast cancer.

The median time to progression was 8 months, and the median survival was 10.5 months. These are encouraging findings given the poor prognosis of our heavily pretreated patients. Before the introduction of the taxanes, the median survival after second- or third-line chemotherapy in patients who had received anthracyclines was less than 6 months, and that achieved with taxanes in anthracycline-resistant breast cancer patients is 9–10 months [12, 13, 18, 30]. During the first three chemotherapy cycles, the responders showed a rapid and progressive improvement in PS, and their daily analgesic consumption gradually decreased. Moreover, the improvement in performance status during treatment of many patients with an initial ECOG PS of 3 led to them being treated on an outpatient basis

after one or two cycles received as inpatients. Despite the ethical uncertainty of the benefit of third-line chemotherapy and breast cancer as a general issue, quality of life was also maintained relatively well in the nonresponding patients, as is reflected by the fact that only functional wellbeing was significantly different between baseline and the third cycle of treatment [26, 28].

As this was not a randomized trial, it is not possible to be sure that these improvements were solely related to the study treatment, but it is known that placebo effects on chronic pain are typically brief and diminish rapidly over time [29]. It is therefore more likely that the sustained improvements observed in this trial indicate a true effect of the chemotherapy on tumor-associated symptoms, as we suspected may have been the case in a previous study involving a smaller number of patients [8].

The adverse events associated with the FFM regimen were predictable and controllable, the clinically important toxicities being those expected when using a fluoropyrimidine and MMC. The only grade 4 treatment-related adverse events were stomatitis, neutropenia and thrombocytopenia, which occurred in only 3% of the patients. The hematological picture of 11 patients with widespread bone metastases, anemia and a platelet count of less than 100,000/mm^3 improved after one or two treatment cycles, which may reflect a chemotherapy-induced improvement in bone marrow reserve and/or the protective effect of FA on myelopoiesis [9, 16]. No hemolytic-uremic syndrome was observed. This may have been due to the combination of MMC and 5-FU, the administration of frequent low doses of MMC (3 mg/m^2 for three consecutive days) and the infusion time (30 min). The concomitance of these three factors could have caused an increase in total body clearance and a reduction in the AUC of MMC, leading to a reduction in the risk of hemolytic-uremic syndrome [4, 25]. The safety profile of the FFM regimen was confirmed by the high dose intensity of the individual drugs, which was close to the planned dose intensity (88%. range 79–100%).

In conclusion, the FFM regimen used in this trial seems to be a valid option for patients with metastatic breast cancer who have been previously treated with two or more chemotherapeutic lines or have failed to respond to regimens containing anthracyclines or taxanes. Furthermore, at this advanced stage of disease, the treatment had a positive effect on tumor-related pain and the quality of life. Finally, the FFM regimen is particularly effective in patients with predominant bone disease, can be administered on an outpatient basis with no substantial risk of life-threatening toxicity, and at a low cost.

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