Mitomycin C plus Capecitabine (MiXe) in Anthracycline- and Taxane-pretreated Metastatic Breast Cancer. A Multicenter Phase II Study

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Abstract. *Background: Capecitabine is considered the treatment of choice for anthracycline- and taxane-pretreated metastatic breast cancer. Mitomycin C seems to improve the activity of capecitabine by up-regulation of thymidine phosphorylase. Patients and Methods: Fifty-five women with metastatic breast cancer previously treated with anthracycline-taxane were treated with mitomycin C 10 mg/m^2 on day 1 every six weeks and capecitabine 1000 mg/m^2 on days 2-15 every three weeks. Results: An overall response rate of 38% was found, consisting of 3 (5%) complete responses (CR) and 18 (33%) partial responses (PR); 8 patients (14%) had a stable disease (SD) for more than 4 months. The combination was well-tolerated, with the main toxicities being neutropenia, diarrhea and fatigue; other toxicities were of mild to moderate intensity without impairment in the quality of life of the patients. Conclusion: Capecitabine is confirmed as the drug of choice in the treatment of anthracycline- and taxane-pretreated metastatic breast cancer and its combination with mitomycin appears to improve its efficacy.*

Anthracyclines and taxanes are the most effective agents against breast cancer, but their increasing use earlier in the disease course means that clinicians are now more frequently faced with the challenge of treating patients with a disease resistant to these highly active agents. In this context, an ideal cytotoxic treatment should offer a reasonable activity, in terms of improvement in time to progression and overall survival, without impairment of a normal lifestyle and, ultimately, easy administration in an outpatient environment. Several drugs, alone or in combination, have been tested in this stage of disease in small phase II studies or in retrospective analyses with response rates ranging from 0% to 62% (1). Capecitabine has considerable activity against breast cancer refractory to anthracyclines and taxanes, yielding 15% to 29% overall response, 31% to 46% disease stabilization and median overall survival duration of 10.1 to 15.2 months in phase II studies (2-6). Capecitabine is an oral third-generation fluoropyrimidine carbamate. It is a prodrug that is converted to 5-fluorouracil (FU) by three enzymatic reactions (7). The rate-limiting step is the final reaction, catalyzed by thymidine phosphorylase (dThdPase). Given the prominent role of dThdPase in the therapeutic index of capecitabine-based treatment, it follows that maximizing dThdPase activity would result in an enhanced therapeutic index (8). Treatment of malignant tumors with various cytokines, such as tumor necrosis factor alpha, interleukin-1, and interferon gamma has been observed to produce increases in intratumoral dThdPase activity and to enhance tumor sensitivity to 5-deoxy-5-fluorouridine (5'-DFUR) *in vitro* and *in vivo* (9). In addition, paclitaxel (100 mg/kg), docetaxel (15 mg/kg) and mitomycin C (5 mg/kg) have also been shown to increase the levels of dThdPase in human colon cancer xenograft studies by 8-, 6.1- and 7.7-fold, respectively (10). These cytotoxic agents are thought to up-regulate dThdPase through increases in tumor necrosis factor alpha levels. Recent data confirm the ability of mitomycin C (MMC) to up-regulate the dThdPase level and the dThdPase/dihydropyrimidine dehydrogenase (DPD) ratio in rectal cancer tissues (11). MMC has been a treatment option for metastatic breast cancer (MBC) since the early 1980s (12). It belongs to the family of antitumor antibiotics and also works against hypoxic tumor cells (13). Its toxicity is comparable with that of other cytotoxic agents and consists of neutropenia and thrombocytopenia. Chronic toxicities, such as renal failure due to the development of haemolytic uremic syndrome (HUS) or pulmonary toxicity, are infrequent but

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Key Words: Mitomycin C, capecitabine, metastatic breast cancer.

may be severe, and therefore an upfront use of MMC should be avoided. A combination of MMC with 5-FU and folinic acid was studied in MBC with interesting results (14). Based on the mechanisms of action, the preclinical data and the lack of overlapping toxicities between MMC and capecitabine, we have previously conducted a dose-finding study of this combination in heavily pretreated MBC (15). Here, we report the results of a phase II study with the combination of MMC 10 mg/m^2 day 1 every six weeks and capecitabine 1000 mg/m^2 *bid* on days 2 to 15 every three weeks.

Patients and Methods

Patient eligibility. Women with histologically or cytologically confirmed MBC were eligible if they had received prior therapy with both an anthracycline and a taxane, and at least one, but no more than two, prior chemotherapy regimens for metastatic disease. If relapse occurred within 12 months of completing adjuvant anthracycline and taxane therapy, patients were eligible without intervening chemotherapy. Patients with HER2-positive disease (3+ protein expression by immunohistochemistry or gene amplification by fluorescence *in situ* hybridization) must have progressed following treatment with trastuzumab. Additional inclusion criteria were bidimensionally measurable disease with at least one lesion measuring ≥1 cm; Eastern Cooperative Oncology Group performance status 0-2; adequate renal, hepatic and hematological function.

Patients were excluded if they had any history or radiographic evidence of CNS disease; screening head computed tomography or brain magnetic resonance image was required. Patients were excluded if they had any other primary malignancy except basal cell carcinoma of the skin or *in situ* cervical cancer within 5 years, major surgery within 4 weeks, other antitumor therapy within 21 days, or clinically significant cardiovascular disease. Concurrent administration of bisphosphonates was allowed if initiated at least 21 days before study entry. Women of reproductive potential were required to use effective contraception. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0 (16). Upon informed consent, all patients gave their written permission in conformity with regulations governing good clinical practice.

Treatment plan. Capecitabine was administered at the dose of 2000 mg/m^2/day in two equally divided oral doses of 1000 mg/m^2 for 14 days starting on days 2 through 15 every 21 days. MMC was administered at the dose of 10 mg/m^2 on day 1 every 42 days by *i.v.* infusion. When the total cumulative dose of MMC reached 40 mg/m^2, 60 mg/m^2 and 80 mg/m^2, a check of peripheral blood for red blood cell fragmentation was performed to detect a subclinical HUS. When 80 mg/m^2 cumulative dose of MMC was reached, investigators were allowed to suspend it and to continue with capecitabine monochemotherapy at the same dose.

Dosage modifications. A new course of treatment was to begin only when the granulocyte count was ≥1,500/mm^3 and the platelet count was ≥100,000/mm^3, and any other treatment-related toxicities were ≤ grade 1; otherwise, treatment was withheld for up to 1 week. If the hematological toxicity had not resolved to grade ≤1 at the end of this period, the patient was withdrawn from the study unless clinical benefit had been documented, in which case a treatment delay of up to 1 additional week to allow recovery was permitted. Planned treatment with capecitabine within a cycle of therapy was withheld in the presence of grade ≥2 non-hematological (except isolated hyperbilirubinemia or alopecia) or grade ≥3 hematological toxicity. Treatment was resumed when hematologic or nonhematologic toxicity, except hand-foot syndrome (HFS), resolved to grade ≤1. In such cases, capecitabine and MMC were resumed at either the original dose level for grade 2 nonhematological and grade 3 hematological toxicity, or with a 25% of reduction for grade ≥3 nonhematological or grade 4 hematological toxicity. For grade 2 or 3 HFS, capecitabine treatment was withheld until resolution to ≤ grade 1 and then restarted at the same dose (for grade 2 HFS) or at the reduced dose level for grade 3 HFS.

Baseline and treatment evaluations. Histories, physical examinations and routine laboratory studies were performed before the start of treatment and before every cycle. Routine laboratory studies included serum electrolytes, chemistries, complete blood cell counts with differential WBC counts, blood clotting times and urinalysis. Tumor assessment was made by TC and bone scan. Lesions were measured after every 2 courses and treatment was continued in the absence of progressive disease or intolerable toxicity. A complete response was defined as the disappearance of all disease on two measurements separated by a minimum of 4 weeks. A partial response required more than 50% reduction in the sum of the products of the bidimensional measurements of all measurable lesions documented by two measurements separated by at least 4 weeks, and progressive disease required an increase of 25% in the sum of the products of the bidimensional measurements of all measurable lesions or the appearance of new lesions.

Statistical plan and analysis. The primary endpoint was the analysis of tumor response. A two-staged minimax Simon accrual design was adopted for this phase II study (17), with error probability limits fixed at $\alpha=0.05$ and $\beta=0.20$. A response rate (partial or complete) of at least 35%, p (1), was considered of interest in this study. In the null hypothesis, p (0), a response rate of <20% was tested in the first 31 evaluable patients. If no more than six responses were observed, the null hypothesis could be accepted with 95% confidence and no further patients would be recruited. If more than six responses were observed, an additional 22 patients would be recruited. At least 15/53 patients were required to have a response in order to exclude the null hypothesis. Secondary endpoints included time to disease progression and overall survival. Time to progression (TTP) and overall survival (OS) were measured from the date of enrollment to the first evidence of disease progression or to death, respectively, and were both determined by the Kaplan-Meier product-limit method (18) . All analyses were performed following an intention-to-treat analysis.

Results

From September 2003 to December 2005, 55 patients were enrolled, all of whom were evaluable for response and toxicity. Patients characteristics are shown in Table I. Median age was 62 years, range 37-76 years, most patients had PS 1 (49%). Thirty-seven patients received anthracycline as

Table I. *Patient characteristics.*

Characteristics	No. of patients	%
Total	55	
Median age (years)	66	
Range	42-77	
ECOG Performance Status		
0	13	24
1	27	49
2	15	27
Hormone receptor status		
Positive	37	67
Negative	18	33
HER2 status		
Positive	6	11
Negative	40	73
Unknown	9	16
Number of metastatic sites		
>3	8	14.5
3	17	31
2	21	38
1	9	16.5
Metastatic sites		
Visceral only	27	49
Visceral and nonvisceral	19	34.5
Non-visceral only	9	16.5
Previous therapy for metastatic disease		
0 line	4	7
1 line	21	38
2 lines	30	55
Previous chemotherapy		
Anthracycline and taxane	55	
CMF-like	12	
Vinorelbine	7	
Gemcitabine	7	
5-Fluorouracil	6	
Trastuzumab plus chemotherapy	6	

Table II. *Tumor response to mitomycin and capecitabine (55 patients).*

Response	No. of patients	%
Complete response	3	5
Partial response	18	33
Overall response	21	28
Stable disease	8	14
Tumor growth control	29	52
Progressive disease	26	48

Table III. *Treatment-related toxicities according to NCI-CTC (total no. of patients, 55).*

Toxicity	Grade					
	1/2		3		4	
	No.	%	No.	%	No.	%
Hematological						
Anemia	10	18	2	3.5		
Granulocytopenia	17	30	5	9	6	10
Thrombocytopenia	5	9				
Gastrointestinal						
Diarrhea	5	9	6	10	5	9
Anorexia	11	20				
Stomatitis	6	10				
Nausea	6	10				
Hepatic						
AST	7	12	3	5		
ALT	4	7	4	7		
GGT	4	7	5	9		
Alkaline phosphatase	9	16	3	5		
Hand and foot syndrome	8	14				
Fatigue	16	29	6	10		

adjuvant therapy and 7 patients received anthracycline and taxane as adjuvant chemotherapy. Six patients were pretreated with trastuzumab as front-line therapy for metastatic disease, 21 patients received mitomycin and capecitabine as second-line chemotherapy, while 15 patients received two chemotherapeutic regimens for metastatic disease. At the time of analysis, in December 2006, after a median follow-up of 18 months (range 8-27 months), seven patients were alive, two in complete response and five in progression of disease. Twenty-one patients (38%, C.I.95% ±12%) achieved a response (Table II), consisting of 3 (5%) complete responses (CR) and 18 (33%) partial responses (PR). Moreover, 8 patients (14%) had a stable disease (SD) for more than 4 months. In total, 29 patients (52%) obtained tumor growth control (TGC). In particular, all CRs were obtained in patients treated as second-line chemotherapy, conversely PRs were observed in a heterogeneous group of patients. None of the 6 patients with HER2-positive tumors achieved a response. The chemotherapy regimen was well tolerated, with no toxic death and no therapy discontinuation for toxicity or patient refusal. The main toxicities are reported in Table III. A total of 338 cycles of MMC and capecitabine were administered, of which 66 as capecitabine mono-chemotherapy. The median number of cycles delivered was six (range 1-18). Dose modifications were necessary in 13 patients (24%), 11 in the capecitabine dose and 2 in the MMC dose. The dose modifications occurred mainly between cycles 2 and 9, primarily due to neutropenia G4, diarrhea G3 and moderate to severe fatigue. Twenty-one cycles were delayed for toxicity; HFS was a rare event and of mild extent; no evidence of MMC-induced HUS was documented. Median TTP was 8 months (Figure 1) with a median overall survival of 17.6

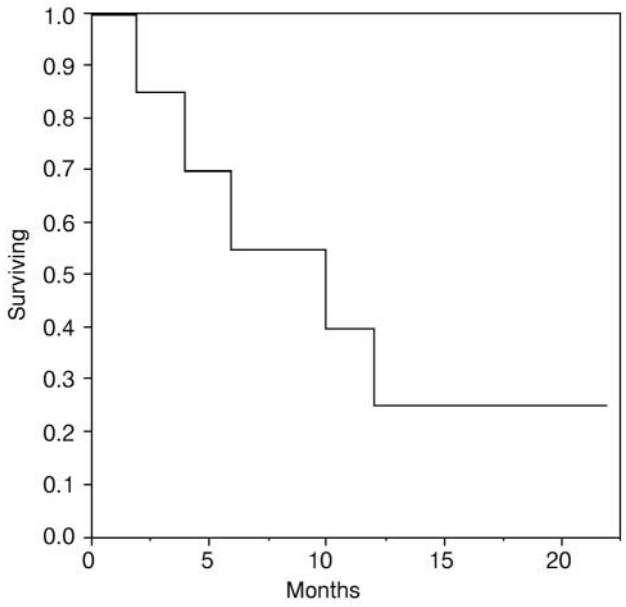

Figure 1. *Time to progression.*

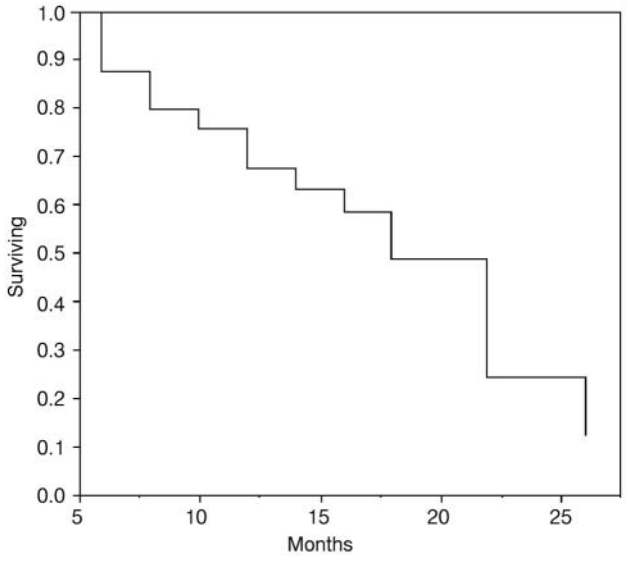

Figure 2. *Overall survival.*

months (Figure 2). Twenty-one patients received further treatment (9 vinorelbine and 12 aromatase inhibitors or fulvestrant) after progression of disease.

Discussion

Currently, effective treatments are available for the management of breast cancer, anthracycline and taxane being the most active agents. A disease that is resistant to both drugs is a challenge for the oncologist. Capecitabine as a single agent has been shown to be effective and well-tolerated in this phase of disease (2-6). Several combination studies have been conducted to improve capecitabine activity in pretreated patients, with disappointing results (19, 20). A MMC and capecitabine combination has been tested in gastrointestinal tumors with positive results and good toxicity profile (21-26). The doses used in this trial derived from the data of a previous dose-finding study conducted by us (15). The results presented are similar to those reported by Massacesi *et al.* (27). Even in our study, the addition of MMC appears to improve the activity of capecitabine without toxicity increase. The best results, 3 CRs and 7 PRs (47.5%) out of 21 patients, were achieved when the combination was used as second-line therapy for metastatic disease after taxane chemotherapy. TGC was achieved regardless of hormone receptor status, 12 patients being negative and 17 positive, or sites of metastases; conversely the six patients with HER-2 positive tumors progressed early during therapy. Specifically, in this subset of patients recent data show that capecitabine combined with lapatinib is superior to capecitabine alone in terms of both TTP and overall response rate (28). The TTP (8 months) and the OS (17.6 months) obtained in our study are noteworthy; these results could be linked to the characteristics of the enrolled patients. Indeed, most of them had ECOG PS 0-1, only six patients (11%) had HER-2 positive status and, finally, 11 out of 21 patients receiving further treatment after disease progression, obtained a disease stabilization. As regards toxicity, the combination was well-tolerated with no toxic deaths and no grade 4 adverse events other than neutropenia. Neutropenia, diarrhea and fatigue were the main side-effects, others toxicities were of mild to moderate intensity without impairment of the quality of life of the patients. Our results confirm capecitabine as the drug of reference in the treatment of anthracycline- and taxane-pretreated metastatic breast cancer; its efficacy appears to be improved by the combination with mitomycin.

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Received March 2, 2007
Revised May 5, 2007
Accepted May 8, 2007