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Combination of capecitabine and mitomycin C as first-line treatment in patients with metastatic breast cancer

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Optimal first-line chemotherapy for metastatic breast cancer (MBC) is challenging, particularly in patients previously treated with (neo) adjuvant anthracyclines/taxanes. Based on preclinical synergy with mitomycin C (MMC) and capecitabine in human tumor xenografts, we conducted a phase II study of first-line capecitabine and MMC in MBC. Patients received 3-weekly chemotherapy comprising MMC 8 mg/m^2 day 1 and capecitabine 1000 mg/m^2 twice daily, days 1-14. Combination chemotherapy was administered for a maximum six cycles, single-agent capecitabine could be continued until progressive disease or unacceptable toxicity. Thirty patients were included, objective response rate was 65.5%. After a median follow-up of 18.5 months, median time to progression was 8.5 months and median overall survival was 29.8 months. The main adverse events were thrombocytopenia, pneumonitis and hemolytic uremic syndrome. Our data suggest that first-line capecitabine and MMC has good antitumor activity in MBC, but is associated with MMC-specific toxicity.

Keywords metastatic breast cancer; capecitabine; mitomycin C; chemotherapy.

Breast cancer is the most frequent malignant disease in women in the Western world and the second (USA) or third (Europe) most common cause of cancer-related death in women [1,2]. Despite significant progress in the treatment of breast cancer, especially early disease, median overall survival (OS) remains at between 12-30 months, with a 5-year survival rate of 15-30% [1,3]. Based on hormonal and HER2 tumor status, as well as extent of disease, many patients with metastatic breast cancer (MBC) are candidates for first-line chemotherapy.

There is no widely accepted first-line chemotherapy protocol or approach. Sequential monochemotherapy or polychemotherapy upfront are equally used throughout the world. The choice of first-line chemotherapy for MBC is based on numerous tumor and patient characteristics, but the most important factors guiding this choice include prior adjuvant chemotherapy and disease-free interval (DFI). Most patients with MBC have received chemotherapy in the (neo) adjuvant setting, commonly comprising taxanes and/or anthracyclines. Data reporting retreatment with taxanes are sparse and inconsistent [4-7] and the optimal first-line treatment for MBC in (neo) adjuvant taxane-pretreated patients has not been clearly defined. Most commonly, capecitabine, vinorelbine and gemcitabine, either as monotherapy or in combination, have been recommended in this setting, especially for patients with a short DFI. Of these agents, capecitabine has the most widespread and long established approval for the management of patients with taxane-pretreated MBC.

Capecitabine has established activity as a monotherapy and in combination therapy strategies in MBC [8-13] and is associated with a favorable tolerability profile, including minimal myelosuppression and alopecia. Notably, as well as affording a significant survival benefit in MBC as a single agent [13], the combination of capecitabine with docetaxel was the first combination to demonstrate a survival benefit compared with single-agent docetaxel therapy in MBC [8]. An orally available 5-fluorouracil (5-FU) prodrug, capecitabine is transformed into the active metabolite through a three-phase activation process; the final step of this activation process depends on thymidine phosphorylase (TP), an enzyme with increased activity in various solid tumors compared with normal tissue [14,15]. An observed positive correlation between the efficacy of capecitabine and the ratio of TP to dihydropyrimidine dehydrogenase (DPD) activities in human cancer xenografts [16] indicates that increased TP activity may result in an enhanced therapeutic index for capecitabine. Preclinical data from human cancer xenografts have shown that various chemotherapy drugs, most

significantly docetaxel, paclitaxel and mitomycin C (MMC), up regulate tumor TP activity [17,18] and combinations of capecitabine with these agents thus have the potential for clinically significant synergy. In addition, it was suggested that MMC up regulates the TP level and TP/DPD ratio in human rectal cancer tissue [19].

MMC, an antitumor antibiotic with alkylating activity, has demonstrated promising activity in MBC as a single agent, achieving objective response rates (ORRs) of approximately 35% and 25% in patients with chemo-naive and pretreated MBC, respectively [20-23]. MMC has also shown good efficacy in combination strategies for MBC; in a randomized phase III study in first-line MBC, epirubicin and MMC (EM) (± lonidamid) demonstrated at least equivalent efficacy, in terms of ORR, time to progression (TTP), OS, and tolerability compared with standard 5-FU/epirubicin/cyclophosphamide (FEC) [24]. Furthermore, in combination with 5-FU and leucovorin in pretreated patients with MBC, MMC achieved a response rate of 43%, with favorable tolerability [25]. The combination of MMC and capecitabine has previously demonstrated good results in patients with pretreated MBC [26,27].

Based on their demonstrated clinical efficacy in MBC, both as single agents and in combination, and favorable pharmacoeconomic potential, together with the established preclinical rationale for their use in combination, we undertook the current phase II study of first-line combination therapy with capecitabine and MMC in patients with MBC.

Patients and methods

This prospective, open-label, phase II study was conducted at the Department of Oncology, University Hospital Split, Croatia. All patients gave written informed consent in accordance with national legislation. The study adhered to the principles of the Declaration of Helsinki and the protocol was reviewed and approved by the Central Ethics Committee of Republic of Croatia. The study started on 23 March 2006, with Central Ethical Committee approval in 2005; the clinicaltrials.gov registered trial number is NCT01196455.

Study eligibility. The main eligibility criteria were: histologically confirmed MBC, with at least one target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) [28]; age ≥18 years; Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1; life expectancy ≥3 months; and adequate hematological (hemoglobin >8.0 g/dL, absolute neutrophil count [ANC] >1.5x10^9/L, platelet count >100x10^9/L), renal (serum creatinine <1.25 upper limit of normal [ULN], creatinine clearance >50ml/min), and hepatic (total bilirubin <2.0xULN, ASAT and/or ALAT<2.5 [in case of liver metastases < 5] xULN) function. Patients were excluded in case of prior cytotoxic chemotherapy or active/passive immunotherapy for MBC, prior (neo) adjuvant therapy with capecitabine or MMC, concomitant hormonal therapy, HER2-positive tumor status, clinical or radiological evidence of CNS metastases, clinically significant cardiac disease, or malabsorption syndrome.

Treatment plan. Treatment consisted of 3-weekly chemotherapy cycles comprising MMC 8 mg/m^2 i.v. bolus on day 1 and capecitabine 1000 mg/m^2 twice-daily, administered orally on days 1-14. Ondansetron i.v. 8 mg, dexamethason i.v 8 mg and ranitidin i.v. 50 mg were administered as premedication. Combination chemotherapy was administered for a total of six cycles or until disease progression. Treatment with capecitabine alone was continued beyond six cycles until disease progression, unacceptable toxicity, patient refusal, non-compliance to the protocol, physician decision to discontinue treatment or treatment delay >2 weeks (except in the case of perceived patient benefit).

Dose modification. The Common Terminology Criteria for Adverse Events v3.0 (CTCAE) scale was used for toxicity grading [29]. Blood counts were performed on day 10 (±2 days) and day 21 before the next cycle. Decrease by one dose level (to MMC 6 mg/m^2, capecitabine 875 mg/m^2 twice-daily) was applied in case of one of the following adverse events (AEs): ANC <0.5x10^9/L persisting >3 days, ANC <0.1x10^9/L, febrile neutropenia (body temperature >38.5° C and ANC < 0.5 x 10^9/L), platelet count ≤30x10^9/L or repeated cycle prolongation (more than once, more than 7 days) for granulocytopenia and/or thrombocytopenia. Decrease by two dose levels (to MMC 5 mg/m^2, capecitabine 750 mg/m^2 twice-daily) was applied in the case of a second occurrence of these AEs. If patient enrolled in the study despite two dose levels reduction had hematological adverse events of grade 3 or 4, she was excluded from the study. If hematological recovery was not achieved at day 35 the patient was withdrawn from the study (except in the case of perceived patient benefit). Hematopoietic growth factors (i.e., G- or GM-CSF) were used according to the institutional guidelines for treatment of febrile neutropenia, but could not be used as prophylaxis except in case of ANC <0.5 x 109/L persisiting >3 days.

In cases of hemolytic-uremic syndrome (HUS) or interstitial pneumonitis, MMC treatment was to be stopped and grade 2 or 3 renal toxicity required that MMC was immediately interrupted until the event resolved or improved to grade ≤1. In cases of grade 2 or 3 stomatitis, diarrhea, vomiting or hand-foot-syndrome, capecitabine was to be immediately interrupted until the event resolved or improved to grade ≤1 and then resumed at a reduced dose (capecitabine 875 mg/m^2 twice-daily). Second occurrences of the same grade 2 or 3 toxicity required dose reduction to capecitabine 750 mg/m^2 twice-daily and in cases of a third occurrence or the first occurrence of grade 4 toxicity, permanent discontinuation of capecitabine was required.

Baseline and tumor evaluation. Staging assessment included physical examination, complete blood count, serum tumor markers (CA15.3, CEA), electrocardiogram, chest X-ray or/and chest computed tomography (CT) scan, abdominal ultrasound or/and abdominal CT scan and bone scan. Complete clinical and radiological tumor restaging was performed every two cycles and at the end of treatment.

Statistical plan and data analyses. The primary endpoint was the objective response rate (ORR) evaluated according to RECIST [28]. Sample size was planned according to Simon optimal two-stage design for phase II clinical trials [30]. The minimax variant of the method was chosen; the method minimizes the total sample size in cases of a poor response rate, which we defined as ≤30%, and allows for an early termination of a study upon completing the first stage of a trial if the null-hypothesis of a poor response rate is accepted with an alpha error, which we set at the 5% level. The method also ensures, with beta error, which we set at 20%, that the tested drug will not be rejected, if the true response rate equals or surpasses the minimally clinically significant level, which we set at 50%. The method does not permit early acceptance of a drug. With these definitions, the null-hypothesis is tested in the first 19 evaluable patients. If ≤6 responses are observed, the null-hypothesis is accepted and the study terminated, and if >6 responses are observed, an additional 20 patients are recruited. The null-hypothesis is excluded if at least 16/39 patients respond to treatment.

Secondary endpoints included TTP (measured from the date of enrollment to the beginning of disease progression), OS (measured from the date of enrollment to death), incidence and severity of adverse events. The intention-to-treat (ITT) principle was adopted in defining the patient population analyzed. The Kaplan-Meier method was applied to OS and TTP.

Table 1. Patient and tumor characteristics (n=30)

	No. (%)
Median age, years	59.5
(range)	44-77
ECOG PS	
0	21 (70.0)
1	9 (30.0)
Premenopausal	6 (20)
Postmenopausal	24 (80)
ER/PgR status	
ER+/PgR+	16 (53.3)
ER+/ PgR-	7 (23.3)
ER-/ PgR+	1 (3.3)
ER-/ PgR-	5 (16.7)
unknown	1 (3.3)
(Neo) adjuvant chemotherapy	18 (60.0)
Anthraycline	18 (60.0)
Anthracycline+taxane	5 (16.7)
Previous hormonal therapy	
Adjuvant	17 (56.7)
For metastatic disease	5 (16.7)
Median DFI (months)	24.5
Number of metastatic sites	
1	6 (20.0)
2	14 (46.7)
3	6 (20.0)
≥4	4 (13.3)
Visceral metastases	22 (73.3)
Non-visceral metastases only	8 (26.7)

DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, estrogen receptor; PgR, progesterone receptor

Results

Patients' characteristics. From July 2006 to May 2009, 30 patients with MBC were enrolled in this study (Table 1). Median age was 59.5 years (range 44-77), the majority of patients were post-menopausal (80%), and had ER- and/or PgR-positive tumor status (83%), unimpaired performance status (70%; ECOG PS 0) and visceral metastases (73%). Eighteen patients (60%) had received prior chemotherapy in the (neo) adjuvant setting, all received anthracyclines, five of them anthracyclines and taxanes.

Response and survival data. A total of 29 patients were evaluable for response; one patient discontinued treatment after the first cycle as a result of prolonged thrombocytopenia. The ORR was 65.5% (95% confidence interval [CI], 48.2-82.8%; Table 2) and a further 31% of patients experienced disease stabilization. The median TTP was 8.5 months (CI 95%, 6.1-10.9; Figure 1). Subgroup analysis of patients with prior exposure to (neo) adjuvant chemotherapy (n=18) demonstrated an ORR of 61.1% and TTP of 7.3 months. After a median follow up of 18.5 months (range 5.7-47), 14 patients (46.7%) were still alive and the median OS was 29.8 months (CI 95%, 18.3-41.3; Figure 2).

Adverse events. The main adverse events are shown in Table 3. The most frequent hematological events were thrombocytopenia, anemia and granulocytopenia (grade 3 in 23.3%, 3.3%, and 6.7% of patients, respectively). No grade 4 hematological toxicity was observed. Gastrointestinal adverse events were generally mild. HUS and pneumonitis were observed in two and five patients, respectively.

Treatment exposure. Patients received a median of five cycles of capecitabine and MMC combination therapy (range 1-6) and 13 (43.3%) patients received a median of five further cycles (range 2-28) of single-agent capecitabine.

Treatment was delayed due to toxicity in 20 (66.7%) patients and study drugs were dose-reduced in 15 (50%) patients. Treatment discontinuation due to toxicity was required in

Table 2. Tumor response on chemotherapy (N=29)

Response	No. (%)
CR	1 (3.4)
PR	18 (62.1)
OR (CR+PR)	19 (65.5)
SD	9 (31.0)
PD	1 (3.4)

CR, complete response; OR, objective response; PD, progressive disease; PR, partial response; SD, stable disease

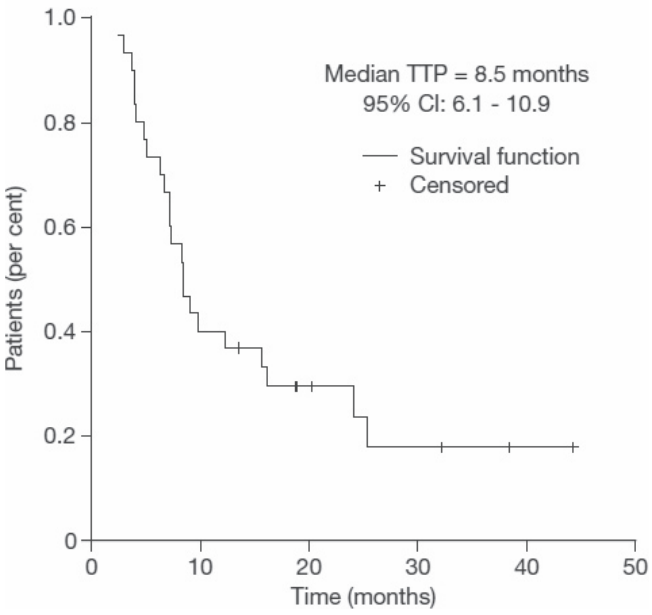

Figure 1. Time to progression in the ITT population

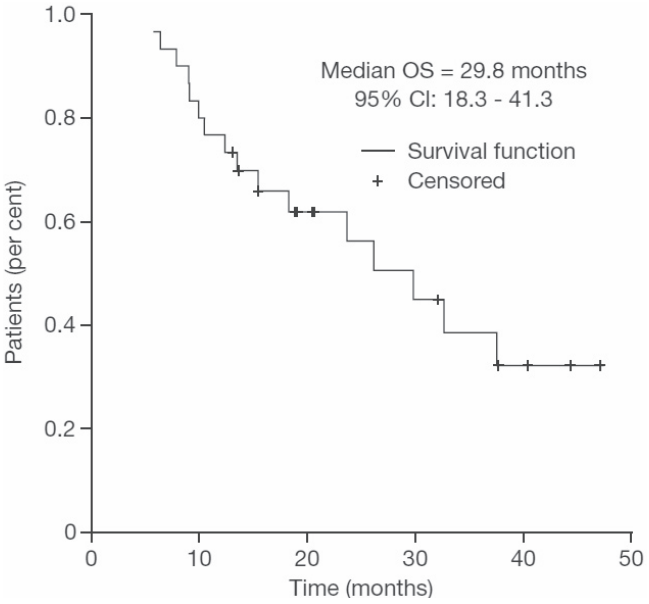

Figure 2. Overall survival in the ITT population

11 (36.7%) patients during capecitabine and MMC combination therapy and seven (23.3%) patients during single-agent capecitabine therapy. The reasons for treatment discontinuation were: thrombocytopenia (n=7), pneumonitis (n=5), HUS (n=2), and CNS hemorrhage, pulmonary embolism, granulocytopenia and vomiting (all n=1). There were no treatment-related deaths.

The majority of patients received further treatment after discontinuation of study therapy, including chemotherapy (50%), hormone therapy (43%) and radiotherapy (30%).

Discussion

In recent years there has been a clear trend for taxanes to be used earlier in the course of breast cancer and with up to 70% of patients with MBC having received (neo) adjuvant therapy, a substantial proportion of patients with MBC will have been previously treated with anthracyclines and/or taxanes. Consequently, there is substantial interest in the optimal chemotherapy for anthracycline- and/or taxane-pretreated patients with MBC. However, in our quest to improve the treatment of MBC, some conventional drugs, including MMC, have been largely ignored, even though they have been shown to be effective and safe in breast cancer treatment.

The combined use of capecitabine and MMC in breast and colorectal tumors is recommended by their different mechanisms of action and non-overlapping toxicities, as well as a strong preclinical rationale, based on MMC-mediated up regulation of TP in tumor tissue. However, while several studies have evaluated and reported satisfactory efficacy and favorable tolerability for the combined use of capecitabine and MMC in patients with metastatic colorectal carcinoma [31-35], the experience in MBC is limited to two phase II studies in patients with heavily pretreated disease [26,27]. An early dose-finding study evaluated the combination of capecitabine and MMC in 21 patients with pretreated MBC and prior exposure to anthracyclines and taxanes [36]. Notably, despite the fact that 81% of patients had received at least two prior regimens for MBC, capecitabine-MMC achieved objective responses in 20% of patients, with dis-

Table 3. Adverse events, n (%) of patients

	Overall incidence	Grade 3	Grade 4
Anemia	16 (53.3)	1 (3.3)	0
Thrombocytopenia	25 (83.3)	7 (23.3)	0
Leucopenia	6 (20.0)	1 (3.3)	0
Granulocytopenia	8 (26.7)	2 (6.7)	0
Nausea	13 (43.3)	1 (3.3)	0
Vomiting	5 (16.7)	1 (3.3)	0
Stomatitis	2 (6.7)	0	0
Diarrhea	5 (16.7)	0	0
Fatigue	10 (33.3)	0	0
Hand-foot syndrome	11 (36.7)	0	0
Pneumonitis	5 (16.7)	0	0
Hemolytic uremic syndrome	2 (6.7)	2 (6.7)	0
CNS hemorrhage	1 (3.3)	1 (3.3)	0
Thrombosis/embolism	2 (6.7)	0	1 (3.3)
Phlebitis	1 (3.3)	0	0
Rash	1 (3.3)	0	0
Keratitis	1 (3.3)	0	0

ease stabilization observed in a further two patients. In the subsequent study by Massacesi and al. [26], conducted in 53 patients with pretreated MBC, all patients had anthracycline- and taxane-resistant disease and 92% of patients had received at least two prior regimens for MBC. However, even in the face of such intensive pretreatment, the combination of capecitabine and MMC achieved objective responses in 37.2% of patients, including two complete responses, and median TTP and OS of 8.1 and 17.4 months, respectively. Furthermore, the combination was generally well tolerated, with treatment discontinuation due to toxicity in 13% of patients. In the study by Maisano et al. [27], 55 patients with MBC, previously treated with anthracyclines and taxanes, including treatment for metastatic disease (1-2 lines of therapy), received chemotherapy with capecitabine and MMC with a response rate, median TTP and median OS of 38%, 8 months and 17.6 months, respectively, with no therapy discontinuation due to toxicity.

The current study represents the first evaluation of the combination of capecitabine and MMC as first-line chemotherapy for patients with MBC. The study demonstrated an ORR of 65.5%, with a further 31% of patients experiencing disease stabilization. Therefore, in this population of patients with chemo-naïve MBC, the combination of capecitabine and MMC afforded clinical benefit to the vast majority (96%) of patients. Furthermore, with a median TTP of 8.5 months, and a median OS of 29.8 months, the clinical efficacy of capecitabine-MMC is comparable to that afforded by combinations of capecitabine with taxanes or vinorelbine in this setting [9,37,38]. It is also notable that the efficacy of capecitabine-MMC was preserved in patients who had received (neo) adjuvant chemotherapy.

All major treatment-related toxicities were MMC-specific and have been described previously [39,40]. Notably, the observed high incidence of prolonged thrombocytopenia, pneumonitis and HUS is in contrast with the previous reports of capecitabine and MMC combination therapy in MBC [26,27]. However, in contrast to the poor outcomes previously reported for such patients [41], both patients with HUS in our study successfully recovered after symptomatic therapy, including prolonged plasmapheresis. Furthermore, symptomatic treatment with corticosteroids achieved complete clinical recovery in all patients with pneumonitis. The increased incidence of MMC-specific toxicities may be attributable, at least in part, to the higher doses of MMC in the current compared with earlier study (8 mg/m^2 versus 6 mg/m^2) [26]. However, in the current study, HUS and pneumonitis were observed after relatively acceptable cumulative dose of MMC (HUS in both patients after a cumulative MMC dose of 42 mg/m^2 and pneumonitis in five patients after a cumulative MMC dose of 28, 32, 38, 40 and 40 mg/m^2, respectively. Another plausible explanation might be that patients with chemo-naïve MBC are immunologically more preserved, and therefore reactive, in comparison to pretreated patients.

In conclusion, our results indicate that the combination of capecitabine and MMC is an effective first-line therapy in patients with MBC. However, further considerations on the use of this combination should be evaluated in the light of the MMC-specific toxicity profile.

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