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ORIGINAL ARTICLE

Dose-finding study of capecitabine in combination with weekly paclitaxel for patients with anthracycline-pretreated metastatic breast cancer

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Summary

Purpose: *Capecitabine and paclitaxel show high efficacy, non-overlapping toxicity profiles and preclinical synergism, providing the rationale for their combination in metastatic breast cancer (MBC). This dose-escalation study aimed at determining the maximum tolerated dose (MTD) of capecitabine plus paclitaxel in anthracycline-pretreated MBC patients.*

Patients and methods: *Patients with MBC received flat-dose of oral capecitabine (1,000 mg/m^2 twice daily, days 1-14) plus weekly paclitaxel 60, 75, or 90 mg/m^2, i.v., days 1, 8 and 15, every 3 weeks.*

Results: *All 11 patients enrolled onto study were evaluable for toxicity and response. Two patients receiving paclitaxel 75 mg/m^2 experienced grade 3 nail toxicity, with grade 3 hand-foot syndrome (HFS) in one patient and grade 2 dermatitis in the other. Although not life-threatening, these were considered unacceptable and the preceding dose level was selected. Eight of 11 patients achieved objective responses.*

Conclusion: *The recommended regimen is capecitabine 1,000 mg/m^2 twice daily, days 1-14, plus paclitaxel 60 mg/m^2/week. Escalation of the paclitaxel dose above 60 mg/m^2/week is not feasible due to severe skin toxicity.*

Key words: capecitabine, metastatic breast cancer, paclitaxel

Introduction

The goal of chemotherapy in MBC is to reduce tumor burden, resulting in improvement of tumor-related symptoms and delay of disease progression. In anthracycline-naïve patients, anthracycline-containing regimens are often used as first-line chemotherapy for MBC, giving an objective response rate (ORR) of more than 50% and overall survival of approximately 2 years [1,2]. The introduction of taxanes provided an active treatment option after disease progression with anthracyclines [3,4]. First- and second-line monochemotherapy with paclitaxel 175 mg/m^2 given as a 3-hour infusion every 3 weeks is highly effective in MBC [5-7]. Recently reported results of the Cancer and Leukemia Group B (CALGB) 9840 study [8] confirmed the superiority of weekly paclitaxel over a 3-weekly regimen in terms of response rate and time to progression (TTP), although this was accompanied by a significantly higher incidence of severe sensory and motor neuropathy.

Capecitabine (Xeloda®; F. Hoffmann-La Roche, Basel, Switzerland), an oral fluoropyrimidine carbamate, is activated preferentially in tumor tissue through exploitation of the significantly higher activity of thymidine phosphorylase (TP) in tumor cells compared with normal tissue. The standard capecitabine dose of 1,250 mg/m^2 twice daily, days 1-14, followed by a 7-day rest period, has demonstrated high activity in anthracycline and taxane-pretreated MBC [9-13] and as first-line therapy [14]. The most common adverse events are diarrhea, stomatitis and HFS, which are ge-

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nerally manageable with appropriate dose modification. Severe hematologic toxicity is rare and alopecia is absent.

The rationale for combining capecitabine and paclitaxel in breast cancer is based on the high single-agent efficacy of both drugs, non-overlapping toxicity profiles and preclinical data showing synergistic antitumor activity of paclitaxel and capecitabine via up-regulation of TP [15]. In addition, capecitabine plus docetaxel has demonstrated high efficacy in a large randomized phase III trial, extending survival compared with docetaxel alone [16]. Two phase II studies of capecitabine and 3-weekly paclitaxel in MBC demonstrated ORRs of 51-52% and median TTP of 10.6 months and 8.1 months, with acceptable safety profile [17,18]. Most recently, a randomized phase III trial demonstrated a 52% response rate, median progression-free survival of 12.0 months, and median overall survival of 25.6 months in patients receiving first-line capecitabine plus 3-weekly paclitaxel [19]. The combination of capecitabine and weekly paclitaxel was expected to be more efficacious and better tolerated. In a phase I study in patients with advanced solid tumors reported by Elza-Brown et al., capecitabine 1,000 mg/m^2 twice daily, days 1-14, and weekly paclitaxel 60 mg/m^2 showed promising results [20].

The aim of the current study was to determine the maximum tolerated dose (MTD), tolerability, and preliminary antitumor activity of capecitabine plus escalating doses of weekly paclitaxel therapy in patients with MBC previously treated with anthracycline-based regimens.

Patients and methods

Eligibility criteria

Eligible patients were females ≥ 18 years old with histologically proven MBC who had previously received adjuvant or first-line anthracycline-containing therapy, had received no more than one prior line of chemotherapy, and had received the last dose of chemotherapy at least 12 weeks prior to enrollment. Previous capecitabine or taxane therapy was not permitted, but endocrine therapy for metastatic disease was allowed. Other eligibility criteria were: Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, presence of at least one measurable lesion, and normal hematologic (absolute neutrophil count [ANC] ≥ 2.0×10^9/L and platelets ≥ 100×10^9/L), hepatic (total bilirubin < 1.5×upper normal limit [UNL] and/or aspartate aminotransferase [AST] and alanine aminotransferase [ALT] < 2.5×UNL), renal (serum creatinine < 1.5×UNL; if serum creatinine concentration was > 1.25×UNL, creatinine clearance had to be ≥ 60 ml/min) and cardiac function (ejection fraction ≥ 50% measured by MUGA scan or ultrasound).

Study design

This was a prospective, open-label, single-center, dose-finding study. The study was designed during the Workshop on Methods in Clinical Cancer Research, held in Flims (Switzerland), 2000, and was approved by the Institutional Ethics Committee. All patients signed informed consent to participate in the study.

The primary objective was to determine the MTD of weekly paclitaxel when combined with capecitabine 1,000 mg/m^2 twice daily, days 1-14. MTD was defined as one dose level below the one causing a dose-limiting toxicity (DLT) in 2 or more patients.

The National Cancer Institute of Canada Common Toxicity Criteria (NCIC CTC), version 3.0, were used to grade toxicity. The following acute and cumulative adverse events were considered as DLTs: grade 4 neutropenia lasting > 7 days, febrile neutropenia, grade 4 thrombocytopenia, hemorrhagic syndrome due to thrombocytopenia, grade 4 diarrhea, grade 4 nausea, grade 4 vomiting, grade 4 neurotoxicity, grade 4 constipation, or grade 3 stomatitis.

Three patients were to be treated at dose level 1. If 1 of these patients experienced a DLT, 3 further patients were to be treated at the same dose level. If no DLT occurred at dose level 1, or a DLT occurred in only one of 6 patients, 3 patients were to be treated at the next dose level. If a DLT occurred in more than 1 patient receiving dose level 1, the study was to be closed. The first 2 patients included in the first or second dose level had to complete the first 2 cycles of therapy (6 weeks) without DLT before enrolment to the next dose level was allowed. If a DLT occurred during any cycle at any dose level, any patients already being treated at a higher dose level were to be moved down to one level below the one that caused the DLT.

Treatment

Oral capecitabine (1,000 mg/m^2 twice daily, days 1-14) was combined with escalating doses of weekly paclitaxel administered as a 1-hour i.v. infusion on days 1, 8, and 15 (level 1: 60 mg/m^2/week; level 2: 75 mg/m^2/week; level 3: 90 mg/m^2/week). Day 21 was the first day of the next cycle. The following premedication was administered 30 min prior to each paclitaxel dose: dexamethasone 8 mg i.v. during the first

cycle, with de-escalation as appropriate (in the absence of hypersensitivity reaction, 4 mg dexamethasone during the second cycle and no further dexamethasone during subsequent paclitaxel doses); chlorpyramine 20 mg i.v.; ranitidine 50 mg i.v., and ondansetron 8 mg p.o. Patients achieving a complete response (CR) received 2 further cycles after first recording of CR (minimum of 6 cycles). Patients with a partial response (PR) were treated until progression or unacceptable toxicity. Treatment was stopped if patients achieved stable disease (SD) for 18 weeks. Post-study therapy was at the physician's discretion.

Study assessments

Complete medical history and physical examination, laboratory tests (complete blood count [CBC], serum biochemistry), and tumor measurement (chest X-rays, bone scan or X-rays, abdominal ultrasound or computed tomography) were performed up to 3 weeks before starting therapy. Every week patients were evaluated for adverse events and CBC. Biochemistry tests were repeated before each cycle of therapy and tumor measurements were performed every 6 weeks. Tumor response was determined according to Response Evaluation Criteria in Solid Tumors (RECIST) [21].

Safety and dose reduction

Both paclitaxel and capecitabine were delayed for 1 week in case of ANC < 1.5×10^9/L or platelet count < 100×10^9/L on day 1. Paclitaxel was delayed for 1 week and capecitabine was discontinued until recovery in case of ANC < 1.5×10^9/L or platelet count < 100×10^9/L on days 8 and 15. Paclitaxel dose was reduced by 15 mg/m^2 if patients experienced ANC < 0.5×10^9/L for > 7 days, febrile neutropenia, platelet count < 25×10^9/L, or hemorrhagic syndrome due to thrombocytopenia.

The capecitabine dose was reduced by 25% at the second occurrence of a grade 2 event, or after the first occurrence of the following grade 3 events: nausea, vomiting, diarrhea, dermatitis, or HFS. Paclitaxel was reduced by 15 mg/m^2 at the second occurrence of grade 3 constipation or neurotoxicity. Treatment was permanently discontinued if a toxicity that had previously resulted in either dose reduction or treatment delay > 14 days recurred. Treatment was also discontinued if patients experienced symptomatic cardiac arrhythmia, grade 2 or 3 atrioventricular block, symptomatic cardiac insufficiency, > 10% left ventricular ejection fraction (LVEF) decrease between two successive measurements with simultaneous decrease below the lower limit of 50%, or > 20% decrease in LVEF between two successive measurements.

Results

Patient characteristics

Between February 2003 and April 2004 11 patients were enrolled, all of whom were assessable for toxicity and response. Median age was 48 years (range 35-60). Baseline characteristics are shown in Table 1. Ten patients received the combination as first-line therapy and one as second-line therapy. HER2 status was unknown in all patients; none had received prior trastuzumab. Previous anthracycline-based chemotherapy consisted of doxorubicin, cyclophosphamide, and fluorouracil in all patients. Median LVEF at study entry was 57% (range 50-63%).

Treatment administered

A total of 55 cycles of chemotherapy were administered (median 4, range 2-8). The dose escalation scheme and patient distribution are summarized in Table 2. Three patients completed all planned cycles of therapy, 3 discontinued because of disease progression, 2 discontinued because of DLTs and 3 discontinued because of unacceptable toxicities not meeting the criteria for DLTs (repeated grade 2 stomatitis and/or grade 2 dermatitis and/or grade 2 HFS despite capecitabine dose reduction).

Table 1. Patient characteristics

Characteristic	*No. of patients*
Menopausal status	
Premenopausal	2
Postmenopausal	9
ECOG performance status	
0	10
1	1
SR status	
ER-positive and/or PgR-positive	6
ER-negative/PgR-negative	5
Dominant sites of disease	
Visceral	9
Soft tissues and lymph nodes	2
Previous anthracycline chemotherapy	11
Adjuvant	3
Primary systemic therapy for LABC	7
First-line for MBC	1
Previous endocrine therapy	7
Previous radiotherapy	9

ECOG: Eastern Cooperative Oncology Group, LABC: locally advanced breast cancer, MBC: metastatic breast cancer, SR: steroid receptors

Table 2. Dose escalation scheme

Dose level	*Capecitabine (mg/m² twice daily, days 1-14)*	*Paclitaxel (mg/m², days 1, 8,15)*	*No. of patients*	*No. of cycles*
1	1,000	60	3	22
2	1,000	75	6	26
3	1,000	90	2	7

Dose limiting toxicities (DLTs)

After the first 3 patients at dose level 1 had received at least 2 cycles of therapy without DLT, 3 patients were enrolled to dose level 2. The third of these patients experienced severe nonhematologic toxicity (grade 3 nail changes, grade 3 HFS) in cycle 4, leading to treatment discontinuation. At that time 2 patients were already receiving therapy at dose level 3 (one had completed cycle 3 and the other cycle 2). According to the protocol, treatment was de-escalated to dose level 1 in both of these patients, and a further 3 patients were enrolled to dose level 2. One of these 3 patients experienced grade 3 nail toxicity and grade 2 dermatitis during cycle 2. We concluded that the severe skin toxicity seen in this study, although not life-threatening, met the criteria for DLT. There were no hospitalizations for adverse events.

Safety

A. *Nonhematologic toxicity*

The most frequent adverse events not meeting the criteria for DLT are shown in Table 3. Apart from the nail toxicity described above, the most common nonhematologic adverse events were dermatitis consisting primarily of skin redness and dry desquamation limited almost exclusively to skin exposed to sunlight, HFS, and nail toxicity. Grade 2 stomatitis and grade 2 diarrhea were infrequent. However, grade 1 diarrhea (defined as an increase of < 4 stools per day over baseline) was seen in 9 patients throughout the study period. Figure 1 shows the incidence of dermatitis, HFS and nail toxicity by cycle. Mild sensory neuropathy

Table 3. Treatment-related adverse events

Adverse event	*Grade 1-2 (No. of patients)*	*Grade 3-4 (No. of patients)*
Dermatitis	10	0
Hand-foot syndrome	9	1
Nail changes	6	2
Stomatitis	5	0
Diarrhea	11	0
Neutropenia	5	2

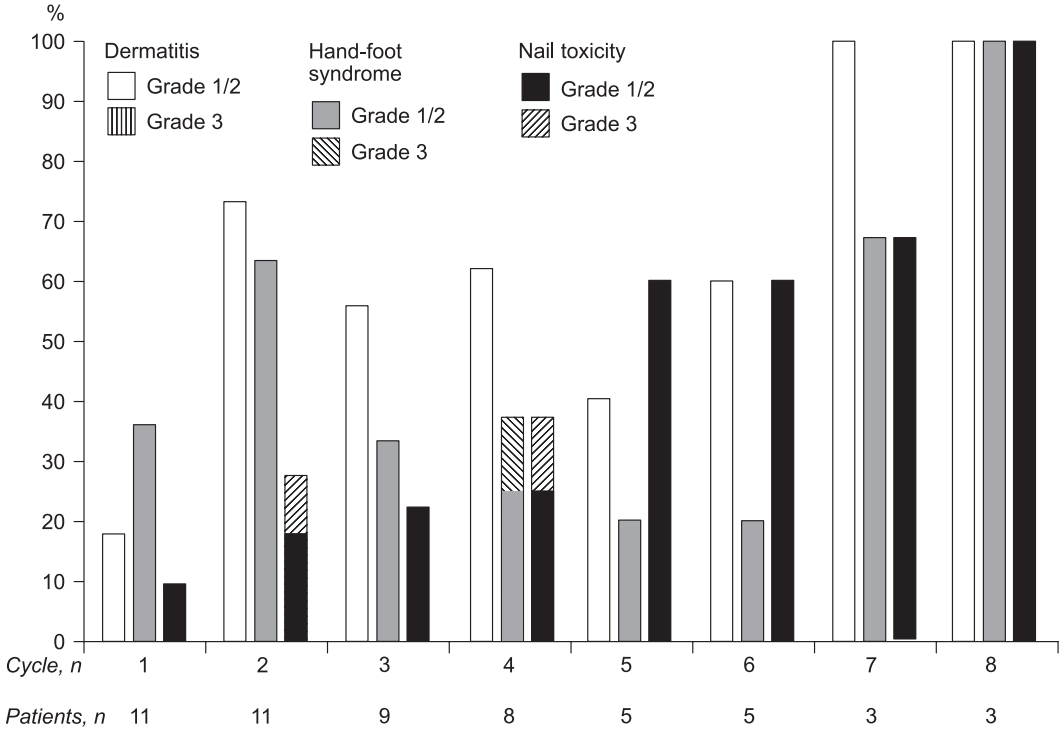

Figure 1. Skin and nail toxicity by chemotherapy cycle.

was observed in 6 patients and 1 patient experienced grade 2 sensory neuropathy.

The reasons for treatment delays, capecitabine dose reductions and paclitaxel dose omissions are shown in Table 4. None of the patients experienced any significant cardiotoxicity according to clinical and cardiac ultrasound assessment. There were no hypersensitivity reactions to paclitaxel.

B. *Hematologic toxicity*

Hematologic toxicity was mild in all patients: grade 2 neutropenia occurred in 5 of 11 patients and grade 3 neutropenia in only 2 patients receiving dose level 3. These adverse events led to a 7-day treatment delay in 6 cycles. In addition, paclitaxel doses were omitted because of grade 2 or 3 neutropenia in 16 (9.7%) of 165 planned paclitaxel doses. One patient started chemotherapy with grade 1 anemia, which did not deteriorate during therapy. Grade 1 anemia developed in 2 patients, and in 1 of them deteriorated to grade 2. Thrombocytopenia was absent throughout the study.

Tumor response

One patient treated at dose level 1 achieved a CR. Seven patients achieved PR, 2 patients had SD lasting for 12 and 4 months, and 1 patient had progressive disease. To date, 10 patients have died from their breast cancer and one is lost to follow up after disease progression.

Discussion

In this phase I dose-finding study we sought to determine the MTD of escalating doses of weekly paclitaxel (days 1, 8, and 15) combined with oral capecitabine 1,000 mg/m^2 twice daily, days 1-14, every 3 weeks. The recommended regimen was identified as capecitabine 1,000 mg/m^2 twice daily, days 1-14, plus paclitaxel 60 mg/m^2/week. Adverse events occurring at dose level 2 (paclitaxel 75 mg/m^2/week) did not meet the predefined criteria for DLT. Nevertheless, severe cumulative skin toxicity in 2 patients (grade 3 nail toxicity occurring with grade 3 HFS in 1 patient and grade 2 dermatitis in another one), although not life-threatening, significantly interfered with patients' daily activities and was considered as unacceptable toxicity.

To date, 2 phase I and 3 phase II studies of capecitabine and weekly paclitaxel in patients with MBC have been reported [22-26]. Uhlmann et al. [22] identified a regimen of capecitabine 1,000 mg/m^2 twice daily, days 1-14, plus paclitaxel 80 mg/m^2/week as most appropriate for phase II evaluation. Further escalation of the capecitabine dose was not recommended due to significant cumulative skin toxicity and the need for dose reduction in all patients included in a higher dose level. The investigators proceeded with a phase II study, but this was closed prematurely, primarily due to an unfavorable balance between efficacy and skin toxicity [23]. Two out of 19 enrolled patients discontinued therapy because of grade 2 nail changes, neurosensory toxicity and HFS, 1 patient discontinued therapy because of grade 3 HFS, and 3 patients went off therapy due to diarrhea, anaphylactic reactions and grade 3 HFS. Overall, the most common treatment-related adverse events were HFS (grade 3: 37%), alopecia (grade 3: 26%), neurotoxicity (grade 3: 16%), and diarrhea (grade 3: 11%). The Gruppo Oncologico Italiano de Ricerca Clinica (GOIRC) and Gruppo Oncologico del Lazio (GOL) [24] found intermittent capecitabine 1,250 mg/m^2 twice daily in combination with weekly paclitaxel 80 mg/m^2 to be well tolerated. DLTs with

Table 4. Adverse events resulting in cycle delays and capecitabine dose reductions

	No. of delayed cycles of therapy			*No. of patients with reduced doses of capecitabine*		
Paclitaxel dose (mg/m^2/wk)	*60 (22 cycles)*	*75 (26 cycles)*	*90 (7cycles)*	*60 (n=3)*	*75 (n=6)*	*90 (n=2)*
Grade 2/3 neutropenia	0	2	4	0	0	0
Grade 2 stomatitis	0	1	0	0	2[a]	0
Grade 2 dermatitis	0	0	0	0	0	1
Grade 2 hand-foot syndrome	0	1	0	0	1[a]	0
Grade 2/3 nail toxicity	1	1	0	0	0	0
Other	0	0	0	0	0	0
Total	1	5	4	0	2	1

[a]One patient had both grade 2 dermatitis and grade 2 hand-foot syndrome

capecitabine 1,250 mg/m^2 twice daily plus weekly paclitaxel 100 mg/m^2 were grade 3 diarrhea associated with grade 2 vomiting and grade 2 HFS. The combination of intermittent capecitabine 1,250 mg/m^2 twice daily with paclitaxel 90 mg/m^2/week resulted in unacceptable cumulative severe neurotoxicity and skin toxicity. Grade 1-2 cumulative onycholysis occurred more frequently at higher dose levels.

In a phase II study of capecitabine 1,000 mg/m^2 twice daily, days 1-14 with paclitaxel 60 mg/m^2/week (like in our phase I study) in heavily pretreated MBC, the most common grade 3/4 adverse events were HFS (21%), neutropenia (12%), mucositis/stomatitis, anemia, nausea/vomiting, nail disorders, anemia (each in 9%), and diarrhea (6%) [25]. Recently, a phase II trial evaluating capecitabine 825 mg/m^2 twice daily in combination with paclitaxel 80 mg/m^2 on days 1 and 8 was reported by Blum et al. [26]. The regimen included only 2 paclitaxel doses, with the third weekly dose of the cycle omitted in an attempt to reduce the frequency of sensory neuropathy. The combination yielded a 55% response rate, median time to progression of 10.1 months and median survival of 17 months. The most common grade 3/4 adverse events were HFS (18%) and neutropenia (13%). Sensory neuropathy was reported in 62% of the patients, although almost all cases were mild to moderate in intensity.

Brittle nails and onycholysis accompanied by complete nail loss, which in our study occurred almost exclusively on the feet, have been observed as typical taxane toxicities, especially with weekly paclitaxel [27, 28]. It was suggested that nail toxicity was a result of vascular abnormalities, direct toxicity of the nail bed or inhibition of angiogenesis. It was also hypothesized that nail changes observed during weekly paclitaxel administered via 1-hour infusion might occur because of higher systemic exposure to Cremophor EL, possibly through neurotoxic damage [28]. In our study the addition of capecitabine to weekly paclitaxel appeared to exacerbate nail toxicity. Although no pharmacokinetic analysis was included in our study, a previous study revealed no major pharmacokinetic interactions between capecitabine and 3-weekly paclitaxel [29].

The majority of patients in our study experienced HFS and dermatitis, side effects typically occurring with capecitabine, which seemed to be cumulative, since in the majority of patients grades 2/3 skin toxicity occurred during later cycles. This observation is in accordance with the results of Gick et al. [23]. Moreover, skin toxicity appeared to be dependent on the cumulative dose of paclitaxel: skin toxicities occurred earlier at higher paclitaxel dose levels. We found that in some patients whose capecitabine treatment was temporarily interrupted due to grade 2 dermatitis and grade 2 HFS, paclitaxel infusion exacerbated these toxicities, which might indicate a negative influence of paclitaxel on capecitabine-induced skin toxicity. There were no cases of severe neuropathy at any dose level, in contrast to studies with higher doses of paclitaxel [8, 30]. In the present study, the cumulative dose of paclitaxel did not exceed 1,260 mg/m^2 and all patients had neither previous exposure to neuropathy-inducing cytotoxic agents, nor pre-existing peripheral neuropathy associated with diabetes or alcohol abuse. Nevertheless, the lack of significant sensory neuropathy is noteworthy and highlights the good tolerability of this capecitabine/weekly paclitaxel regimen.

There are no clear recommendations on the use of dexamethasone in the premedication regimen for weekly administration of paclitaxel. We chose to de-escalate the dexamethasone dose based on the report by Breier et al. [31] of a high incidence of Cushing's syndrome in patients treated with weekly paclitaxel and dexamethasone 8 mg i.v. given before each dose of paclitaxel. This resulted in de-escalation of premedication to 4 mg, then to 2 mg and, finally, to total exclusion of dexamethasone premedication, without compromising the tolerability of chemotherapy. We found a de-escalation scheme of dexamethasone to be effective while reducing the risk of developing complications induced by prolonged corticosteroid treatment.

Our results also confirmed that the combination of intermittent capecitabine and weekly paclitaxel is well tolerated with respect to hematologic toxicity. This is consistent with results of previous studies combining capecitabine and weekly paclitaxel [22-25].

Two out of 11 patients (18%) experienced grade 3 neutropenia, which was not clinically significant. However, the lack of grade 3/4 myelosuppression in our study contrasts with results of the phase II study by Blum et al. [26], in which myelosuppression was one of the most common grade 3/4 toxicities. Compared with published phase II and III studies of capecitabine and 3-weekly paclitaxel [17-19], neutropenia was less frequent in our study, probably due to 1-hour i.v. administration of paclitaxel. It has previously been shown that the most important factor influencing the development of significant neutropenia is the duration of paclitaxel plasma concentration above a threshold of 0.05 or 0.1 mmol/L [32, 33].

Eight of 11 patients in our study achieved objective responses, including all patients treated at dose level 1, suggesting high activity of the combination of capecitabine and weekly paclitaxel. This is consistent with results of the phase II study (capecitabine 1,000

mg/m^2 twice daily plus paclitaxel 60 mg/m^2/week) reported by Bari et al. [25], showing a 45% response rate, median progression-free survival of 9.2 months, and median overall survival of 19.6 months in patients with anthracycline-pretreated HER2-negative MBC, with manageable toxicity. Taking into account the results of the phase II studies and our study, we suggest that the risk of severe skin toxicity may be reduced by administering weekly paclitaxel at doses not exceeding 60 mg/m^2 when given in combination with intermittent capecitabine 1,000 mg/m^2 twice daily in patients with MBC.

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