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ORIGINAL ARTICLE

A phase I trial of oral metronomic vinorelbine plus capecitabine in patients with metastatic breast cancer

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Abstract
Purpose To determine the dose-limiting toxicities (DLTs) and the maximum tolerated doses (MTD) of oral metronomic vinorelbine with capecitabine in patients with metastatic breast cancer (MBC).
Patients and methods Escalated doses of oral metronomic vinorelbine (starting dose 30 mg) every other day continuously and capecitabine (starting dose 800 mg/m^2 bid) on days 1–14 every 21 days were administered. DLTs were evaluated during the first cycle.
Results Thirty-six women were enrolled at eight escalating dose levels. For twenty-four patients, treatment was first line, for eight second line, and for four third line. The DLT level was reached at oral metronomic vinorelbine 70 mg and capecitabine 1,250 mg/m^2, and the recommended MTD doses are vinorelbine 60 mg and capecitabine 1,250 mg/m^2. DLTs were febrile neutropenia grade 3 and 4, diarrhea grade 4, and treatment delays due to unresolved neutropenia. There was no treatment-related death. The main toxicities were grade 2–3 neutropenia in 16.6% of patients each, grade 2–3 anemia 16.5%, grade 2–4 fatigue 27.5%, grade 2–3 nausea/vomiting 11%, and grade 3–4 diarrhea 8.2%. Two complete and 10 partial responses were documented.
Conclusion Oral metronomic vinorelbine with capecitabine is a well-tolerated and feasible regimen that merits further evaluation in MBC.

Keywords Metronomic vinorelbine · Capecitabine · Phase I · Metastatic breast cancer

Introduction

The introduction of maximum tolerated dose (MTD) in traditional treatment protocols, typically administered in cycles, aims at a potential maximization of the therapeutic outcome [1]. The concomitant toxicity, however, imposes rest periods between cycles, leaving time and space for the growth of resistant to therapy selected clones and the regrowth of tumor cells in general [2].

A new modality of drug administration called metronomic chemotherapy (MCT) has been proposed to overcome the above-mentioned problems [2–4]. It refers to dense, non-stop, equally spaced administration of generally low, subtoxic doses of various chemotherapeutic drugs over protracted periods of time, without extended rest intervals [4, 5]. The novelty of this concept does not only lie in the change in drug administration's dose and schedule. It also consists of a cell target switch, aiming at the tumor vascular endothelial cells, and thus tumor angiogenesis, exploiting the high turnover rate and remarkable sensitivity of these cells to cytotoxic agents [5, 6].

As with every experimental therapy, MCT built its foundation on laboratory discoveries. With the pioneer experimental work in Judah Folkman's and Robert Kerbel's laboratories, it was for the first time demonstrated that some of the most widely used chemotherapeutic drugs if administered chronically at low doses manifest antitumour efficacy

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as anti-angiogenic agents [7]. Despite robust preclinical data though, early clinical development of MCT has been empirical [8, 9], and only recently the identification of optimal dosing of suitable agents has been elaborated in a rationally designed phase I study [3]. Antimitotic cytotoxic drugs, such as vinorelbine, a third-generation semisynthetic vinca alkaloid, are thought to be ideal for metronomic administration since they interfere with endothelial cell functionality even at low concentrations and suppress microtubule dynamics by inhibiting the tubulin polymerization [10]. Furthermore, the existence of an oral formulation for the drug makes it an even more appropriate candidate for metronomic use [11].

For patients with metastatic breast cancer (MBC) pretreated and/or resistant to anthracyclines and taxanes, effective treatment options are limited [12]. In this setting, it has been shown that vinorelbine and capecitabine are two effective and well-tolerated drugs [13]. While in asymptomatic or mildly symptomatic patients, monotherapy is usually the preferred therapeutic option, for patients with symptomatic and/or rapidly progressing and life-threatening disease the challenge lays in the development of efficient combination regimens that can control the disease without impairing the patients' quality of life.

As a single agent, intravenous vinorelbine administration has been shown to be effective without compromising the quality of life in anthracycline-pretreated MBC patients [14]. Oral vinorelbine, which belongs to the new generation of oral agents, achieves reliable blood exposure and shows bioavailability of 40% (80 mg/m^2 orally corresponds to 30 mg/m^2 intravenously) that is actually not influenced by age, food, interpatient variability and has linear pharmacokinetics [11, 15]. As a single agent, oral vinorelbine was shown to be effective and well tolerated in the first-line treatment of MBC achieving response rates of 30% in phase II studies [16]. The metronomic administration of oral vinorelbine was shown to be feasible and associated with sustainable antitumour activity without overt toxicity [3, 17].

Capecitabine is an oral fluoropyrimidine carbamate, rationally designed to generate 5-FU preferentially at the tumor bed [18]. The conversion of the prodrug to 5-FU requires a three-step enzymatic sequence. The final rate-limiting step that actually produces the active drug (5′-FUDR to 5-FU) is catalyzed by thymidine phosphorylase (TP) that is found at higher levels and with significantly higher activity in tumors, thus resulting in preferential intratumoral cytotoxic drug generation [19]. In MBC, capecitabine as salvage treatment has been shown to induce 20–30% objective responses with a median survival >12 months [20], whereas, as first-line therapy, its antitumor activity is far more impressive [21].

Preclinical data suggest that the vinorelbine/capecitabine combination confers a synergistic and not simply an additive antitumor activity [22]. A number of phase I and II studies have elaborated the intravenous vinorelbine and capecitabine combination as salvage treatment in MBC patients, producing response rates in the range of 30–50% [15, 23], whereas, in the first-line setting, the same combination yielded response rates of 70% [24]. In a phase I study, the oral vinorelbine and capecitabine combination showed a good safety profile with no pharmacokinetic interactions [25]. In two subsequent phase II studies, in the first- and second-line settings, the combination was well tolerated and effective in MBC with response rates of approximately 40% [26]. Furthermore, in resistant/refractory to anthracycline/taxane MBC patients, the efficacy of the combination was comparable with other available combination regimens with the additional advantage of the convenient oral administration [13].

The vinorelbine and capecitabine co-administration constitutes an engaging combination with a theoretical, preclinical, and clinical supportive background. Furthermore, the oral formulations of both drugs make them suitable for metronomic administration. Given that the optimal metronomic dose and the MTD for oral vinorelbine and capecitabine, respectively, when the drugs are administered together, have not yet been established, this phase I study was designed to evaluate the safety and tolerance of the combination (NCT00705375).

Patients and methods

Patient selection

Patients with HER2-negative, histologically confirmed MBC were eligible for the study. It was recommended that women should have been pretreated with an anthracycline and a taxane in the neo-adjuvant, adjuvant, or metastatic settings. However, women who had a contraindication for these drugs or wished to receive an all-oral therapy were eligible for this study. Other eligibility criteria were as follows: age >18 years, performance status (ECOG) 0–2; adequate bone marrow (absolute neutrophil count $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L), renal (creatinine $\leq$1.25 times the upper limit of normal and creatinine clearance >50 ml/min) and liver (total bilirubin $\leq$1.25 times and aspartate and alanine aminotransferases $\leq$3.0 times the upper limit of normal, respectively) function; absence of active infection and malnutrition (loss of more than 20% of the body weight). Patients with brain metastases, severe cardiac dysfunction, chronic diarrhea, incomplete obstruction of the gastrointestinal tract, total colectomy, and patients unable to receive and/or comply with oral medications were excluded from the study. All patients gave their written informed consent prior to enrollment. The study was

approved by the Ethics and Scientific Committees of our institution.

Treatment

Oral vinorelbine was administered every other day, because, as previously evaluated [3, 27], this schedule yields steady-state levels without drug accumulation in chronic use. The drug was received before lunch, thrice a week on Mondays, Wednesdays, and Fridays continuously. Due to the fact that the somatometrically adjusting dose approach is considered insignificant in low-dose therapeutic strategies, a flat-fixed dosing was adopted [28]. The starting dose of oral vinorelbine was chosen to be 30 mg with increments of 10 mg in successive cohorts of patients. Capecitabine was given at escalated doses starting from 800 mg/m^2 given twice a day (bid) on days 1–14 with increments of 150 mg/m^2/day in successive cohorts of patients. Routine antiemetic prophylaxis with a 5-hydroxytryptamine-3-receptor antagonist was used. Each cycle was repeated every 3 weeks, and treatment was administered until maximum response, disease progression, unacceptable toxicity, or until the patient declined further treatment.

Dose escalation

The following 8 dose escalation levels for oral metronomic vinorelbine/capecitabine have been evaluated: 30(mg)/800(mg/m^2 bid); 30(mg)/950(mg/m^2 bid); 40(mg)/950(mg/m^2 bid); 40(mg)/1,100(mg/m^2 bid); 50(mg)/1,100(mg/m^2 bid); 50(mg)/1,250(mg/m^2 bid); 60(mg)/1,250(mg/m^2 bid); and 70(mg)/1,250(mg/m^2 bid). No intrapatient dose escalation was allowed. Initially, 3 patients were enrolled at each dose level. If a DLT was observed in one of the first 3 patients, then 3 additional patients were enrolled at the same dose level.

The DLTs were assessed during the first cycle of chemotherapy. A DLT was defined as the occurrence of any of the following: (1) grade 4 hematologic toxicity, (2) febrile neutropenia, (3) any grade 3–4 non-hematologic toxicity, and (4) any adverse event causing delay of treatment on day 21. The DLT level was reached when at least 50% of the patients treated at that dose level developed a DLT (i.e., at least two of three or three of six patients). The dose level of the maximum tolerated doses (MTD), which will be the doses recommended for further phase II/III trials, was defined as the first level below the DLT dose level.

Dose adjustments

Patients were assessed for toxicity before each cycle using the National Cancer Institute Common Toxicity Criteria version 3.0 [29]. Chemotherapy was delayed until recovery if neutrophils were less than 1.5×10^9/L or platelets less than 100×10^9/L or for significant persisting non-hematologic toxicity. Patients who developed grade 4 neutropenia, grade 4 thrombocytopenia, or febrile neutropenia were subsequently treated with the doses of the previous dose level. No prophylactic administration of granulocyte colony-stimulating factor was allowed. G-CSF was used for the treatment of febrile neutropenia. Doses of capecitabine were reduced by 15% in subsequent cycles in case of grade 3–4 diarrhea, ≥grade 2 mucositis, or ≥grade 2 hand-foot syndrome or dermatitis.

Pretreatment evaluation and follow-up

Pretreatment evaluation included a detailed medical history and physical examination, a complete blood cell count (CBC) with differential and platelet count, whole blood chemistry, electrocardiograph (ECG) and computed tomography scans (CT) of the chest and abdomen, and a whole body bone scan. Pretreatment evaluation had to be performed within 2 weeks prior to study entry.

During treatment, a CBC had to be performed weekly and in cases of grade 3–4 neutropenia, thrombocytopenia or febrile neutropenia, daily until hematologic recovery. In addition, before each treatment cycle, routine biochemical tests and clinical assessment of the patients were performed. Response to treatment was evaluated after 3 cycles or sooner if there was clinical evidence of disease progression.

Although patients were not required to have bidimensionally measurable disease to enter the study, tumor response was assessed using the RECIST criteria every 3 chemotherapy cycles [30]. The time to tumor progression (TTP) was the interval between the initiation of treatment and the date when disease progression was first documented. The duration of response was measured from the first documentation of response until disease progression. Survival was measured from the beginning of treatment in the study until the date of death. The follow-up time was measured from the day of first treatment administration to the last contact or death.

Results

Patients' characteristics

From June 2007 to September 2009, thirty-six women with MBC were enrolled in the study. The median age was 58.5 years (range 39–78), fifteen (41.7%) of the patients had PS 0, nineteen (52.8%) PS 1 and two (5.5%) PS 2. Twenty-four patients received the study treatment as first

Table 1 Patients' characteristics

	No. of patients	%
Number of patients enrolled	36	
Age		
Median (range)	58.5 (39–78)	
Stage		
IIIB	1	2.8
IV	35	97.2
Performance status (ECOG)		
0	15	41.7
1	19	52.8
2	2	5.5
Menopausal status		
Premenopausal	22	61.1
Postmenopausal	14	38.9
Histologic subtype		
Ductal	30	83.3
Lobular	4	11.1
Mixed	2	5.6
Hormone receptors		
ER+ PR+	18	50.0
ER+ PR−	7	19.4
ER− PR+	3	8.3
ER− PR−	6	16.7
Unknown	2	5.6
Line of therapy		
First line	24	66.7
Second line	8	22.2
≥Third line	4	11.1
Type of previous chemotherapy for metastatic disease (n = 12)		
Taxane	2	
Anthracycline	2	
Both	8	
Overview of prior treatments		
Surgery	30	83.3
Neoadjuvant chemotherapy	1	2.8
Adjuvant chemotherapy	26	72.2
Hormonotherapy	27	75
First-line chemotherapy	10	27.8
Second-line chemotherapy	1	2.8
Third-line chemotherapy	1	2.8
Radiotherapy	21	58.3
None	2	5.5
Organs involved		
Local disease	4	11.1
Lung	15	41.7
Nodes	16	44.4
Liver	7	19.4
Pleura	3	8.3
Brain	2	5.6
Skin	1	2.8
Bones	21	58.3
Other	3	8.3

line, 8 as second line, and 4 as ≥third line. Further patients' demographics and clinical characteristics are presented in Table 1. All patients were evaluable for toxicity.

Dose-limiting toxicities

Table 2 shows the dose escalation levels, the number of patients enrolled at each dose level, and the observed DLTs during the first chemotherapy cycle. Febrile neutropenia and grade 2/3 neutropenia resulting in treatment delay were the most common DLTs occurring in three patients each, whereas grade 3 and 4 diarrhea was observed in two patients. The DLT dose level was reached at oral metronomic vinorelbine 70 mg and capecitabine 1,250 mg/m^2 bid since two out of three patients developed DLT events. Therefore, the recommended doses for future phase II/III studies are vinorelbine 60 mg thrice a week continuously and capecitabine 1,250 mg/m^2 bid for 14 consecutive days in cycles of 21 days.

Toxicity

Hematologic and non-hematologic toxicity is summarized in Table 3. Neutropenia was the most common adverse event of the combination. Grade 2 and 3 neutropenia was observed in six (16.6%) patients each and grade 4 in four (11%); none of them required hospitalization. Grade 3 and 4 febrile neutropenia was observed in two (5.5%) patients each. Fatigue was a common adverse event reaching grade 2 in five (13.8%) patients, grade 3 in four (11%), and grade 4 in one (2.7%) patient. Grade 2 and 3 diarrhea was observed in three (8.3%) and two (5.5%) patients, respectively, whereas grade 4 was observed in only one (2.7%) patient. Other hematologic and non-hematologic toxicities were mild. There was no treatment-related death. No treatment-related hospitalizations were reported.

Treatment administration

A total of 186 chemotherapy cycles were administered with a median of 4 cycles per patient (range 1–17). Discontinuation of treatment occurred due to disease progression (n = 13 patients), adverse event related to treatment (n = 3 patients), patients refusal (n = 1 patient), and other reasons

Table 2 Dose escalation levels, number of patients enrolled, and dose-limiting toxicities

Level	Vinorelbine metronomic (mg) trice a week	Capecitabine (mg/m^2 bid) d1–d14	No of patients (no of first-line patients)	DLT (no of patients)
1	30	800	3 (3)	–
2	30	950	3 (1)	–
3	40	950	3 (2)	–
4	40	1,100	6 (4)	Febrile neutropenia grade 3 (n = 1) and treatment delay due to grade 2 neutropenia (n = 1)
5	50	1,100	6 (5)	Febrile neutropenia grade 4 (n = 1)
6	50	1,250	6 (4)	Febrile neutropenia and anemia grade 3 (n = 1)
7	60	1,250	6 (2)	Treatment delay due to grade 2 neutropenia (n = 1) and grade 3 diarrhea (n = 1)
8	70	1,250	3 (3)	Treatment delay due to grade 3 neutropenia (n = 1) and grade 4 diarrhea (n = 1)

Table 3 Worst toxicity per patient in all cycles with the oral metronomic vinorelbine/capecitabine combination (n = number of patients)

	NCI-CTC grade					
	2		3		4	
	n	%	n	%	n	%
Neutropenia	6	16.6	6	16.6	4	11
Anemia	5	13.8	1	2.7	–	–
Thrombocytopenia	1	2.7	–	–	–	–
Febrile neutropenia	–	–	2	5.5	2	5.5
Fatigue	5	13.8	4	11	1	2.7
Nausea/vomiting	4	11	4	11	–	–
Neurotoxicity	–	–	2	5.5	–	–
Diarrhea	3	8.3	2	5.5	1	2.7
Constipation	1	2.7				
Hand/foot syndrome	1	2.7	1	2.7	–	–

not related to disease or treatment (n = 2 patients). For the 3 patients where treatment discontinuation was due to adverse events, one had grade 4 neutropenia after the 2nd cycle, the other had grade 3 febrile neutropenia and anemia after the 1st cycle, and the 3rd had grade 3 diarrhea and vomiting after the 1st cycle. Dose reduction was required in 28 (15.1%) cycles because of hematologic (n = 10 cycles), non-hematologic (n = 12 cycles), or both (n = 6 cycles) toxicities. Treatment delay was observed in 35 (18.8%) cycles due to hematologic (n = 5 cycles), non-hematologic (n = 4 cycles), or both (n = 2) toxicities and other reasons not related to disease or treatment (n = 24 cycles, i.e., pending imaging studies for response evaluation). The median time of treatment delay was 13 days (range 5–49 days).

Efficacy

In an intention to treat analysis, all patients were included for evaluation of response. Four of the thirty-six patients were not evaluable for response due to early discontinuation of treatment, and they were considered as having disease progression. Two patients (5.6%) achieved a complete response, one treated in the 2nd, and one in the 7th dose level. Both patients received the study treatment as front-line treatment. Partial response was recorded in 10 (27.8%) patients and stable disease in another 11 (30.6%) patients. Partial responses were observed in dose levels 3–8. The median response duration was 4.1 (range, 1.0–21.0) months. Disease progression was documented in 13 (36.1%) patients. The median time to tumor progression was 5.6 months (95% CI: 2.8–8.4). After a median follow-up of 16.7 (range, 2.2–34.2) months, the estimated median survival for the entire group was 25.9 months (95% CI: 24.0–27.9) while the probability of 1-year survival was 88.7% (95% CI: 78.4–99.0).

Discussion

Since anthracycline and taxane combination regimens have entered the adjuvant treatment of early stage breast cancer, there is an urgent need for finding effective treatment options for MBC patients pretreated with these active drugs [13]. Furthermore, in the MBC palliative setting, there is increasing interest for oral medications and outpatient regimens both for convenience and to reduce the cost of care, provided that the efficacy and toxicity of the oral therapy is comparable or more favorable to the intravenous one [31].

Although adjuvant combination polychemotherapy has an established survival benefit as documented by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [32], this is not the case for metastatic disease, where the question of using a combination regimen versus a sequential monotherapy approach remains to date largely unsettled. The Cochrane breast cancer group and the large meta-analyses studies have shown an improved response

rate and time to tumor progression, as well as a slight improvement in overall survival with combination versus single-agent chemotherapy at the expense of greater treatment-related toxicity [33–35]. Nevertheless, outdated chemotherapy regimens, methodological flaws, and non-mandatory crossover strategies in the analyzed trials make definitive conclusions difficult to be drawn [36]. Based on the available data and in the absence of solid evidence, the European School of Oncology Metastatic Breast Cancer Task Force recommends sequential single-agent therapy for most MBC patients; however, when rapid clinical progression, life-threatening visceral metastases and disease or rapid symptom control are needed, combination polychemotherapy should be preferred [36].

In our study, the majority of patients were either symptomatic and/or had high-risk visceral or extensive disease. Fourteen of the 36 patients enrolled had more than one organs involved. Of the 24 patients receiving the regimen as first line, 21 had previously received adjuvant therapy, and 18 of them had been exposed to an anthracycline and/or a taxane in the adjuvant setting with a median disease-free interval of 41.3 (12.5–146) months. All patients who received the study treatment as >1st line ($n = 12$) had previously received anthracycline and/or taxane in the first-line setting and had disease progression. Moreover, most patients who enrolled on this study despite having a symptomatic and/or threatening disease also expressed their strong preference for having an oral, outpatient regimen that would prevent them from having frequent hospital visits.

In the era of targeted cancer therapy, MCT has emerged as a novel therapeutic approach. Preliminary evidence of disease control in patients with different types of tumors combined with the associated low toxicity supports its use in the metastatic clinical setting with anticipating results of improved quality of life and even overall survival [2, 3]. Moreover, metronomic administration of vinorelbine as a single agent [3, 17] as well as other drug combinations [8] in breast cancer and other neoplasms provide clinical proof of efficacy and support the antiangiogenic basis of MCT beyond vascular endothelial growth inhibition. The present study is the first one evaluating the combination of capecitabine with oral metronomic vinorelbine. Given that the optimal metronomic dose could theoretically be anywhere within a safe dose range [37], our study explored dose escalation for vinorelbine based on the previous work published by Briasoulis et al. [3]. Our results demonstrate that this two-drug combination in patients with MBC is feasible and well tolerated. The MTD of the combination according to the study design was vinorelbine 60 mg administered thrice a week and capecitabine 1,250 mg/m^2 twice a day for 14 consecutive days in cycles of 21 days. These doses are equal or exceed the monotherapy doses recommended for the individual drugs. Nevertheless, since most patients received the study treatment as first line and considering that a dose decrease in either or both drugs was required in 28 out of the 186 cycles administered (15.1%), we feel that possibly lower doses of the drug combination might be more suitable for heavily pretreated MBC patients or those at high risk for toxicity.

In general, this regimen demonstrated a favorable toxicity profile since the majority of adverse events were mild to moderate in severity and the observed dose-limiting events were mainly hematological. Nevertheless, febrile neutropenia and neutropenia were documented in levels 4–6 and 7–8, respectively. It should be noted that only one of the two drugs, vinorelbine, was administered metronomically; the other drug, capecitabine, was conventionally dosed, and dose escalation was implemented with both agents, which is not usually the case with other studies in the literature evaluating metronomic chemotherapy. This could possibly explain our observed toxicity profile, which differs from that of other published reports with metronomic chemotherapy. For example, in the Briasoulis et al. [3] study where escalating doses of oral vinorelbine were administered as monotherapy, a more favorable toxicity profile was observed with leucopenia grade 4 and 2 occurring at the 60 and 70 mg drug dose, respectively. In our study, only in two cases, DLTs were non-hematological, i.e., grade 2 and 3 diarrhea. The overall good tolerance of the regimen is especially important in view of the fact that the regimen is an all-oral, outpatient one, and the primary therapeutic aim in this patient population is palliation and maintenance of good quality of life. It is indeed unfortunate that our study had not included quality of life evaluations for all patients and therefore these data are lacking.

Although response to treatment was not the primary endpoint of this phase I trial, the objective response rate was 33.4% including 5.6% complete responses, whereas the disease control rate was 64%. Clinical responses were primarily observed at the higher dose levels, as already also reported by Briasoulis et al. [3]. Nevertheless, one complete response was observed in a patient treated at the 2nd level, and partial responses were also observed at the 3rd or higher levels, implying that probably, even in a partially metronomic regimen, the dose level might not be critically relevant to its activity. With a median follow-up time of 16.7 months, the estimated median overall survival was 25.9 months and the 1-year survival 88.7%. These results show encouraging activity for this all-oral, outpatient combination. This level of observed activity is in accordance with published phase II studies in the first- and second-line settings in MBC patients previously treated with anthracyclines and taxanes [13, 26]. Furthermore, in a recent abstract publication of a phase II trial in MBC, the oral metronomic combination regimen of capecitabine and

cyclophosphamide presented comparable with our results mild toxicity and efficacy. The response rate was 36% and the progression-free and overall survival 5.9 and 19.6 months, respectively [38].

The present study is the first one evaluating an all-oral combination with vinorelbine administered metronomically and indeed shows encouraging results. However, it should be stressed that the activity of the regimen cannot be judged from this phase I trial. In order to do so, a formal phase II study, which is underway in our department, should be performed. When considering the promising results reported for metronomic vinorelbine monotherapy in the Briassoulis's et al. study [3], as well as, the increasing demand for oral regimens in the treatment of MBC, we believe that our study further improves our knowledge on oral chemotherapy in this patients' setting.

In conclusion, the results of this phase I study indicate that oral vinorelbine administered metronomically thrice a week continuously, in combination with capecitabine, given for 14 consecutive days in 21-day cycles is a feasible, outpatient regimen with favorable toxicity profile. This regimen showed promising activity and merits further evaluation as front-line or salvage treatment in patients with MBC.

Conflict of interest None.

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