Low-dose capecitabine plus docetaxel as first-line therapy for metastatic breast cancer: phase II results

Vasiliki Michalaki, Spyridon Gennatas and Konstantine Gennatas

The addition of capecitabine to docetaxel significantly improves overall survival in anthracycline-pretreated metastatic breast cancer. We evaluated a low-dose capecitabine–docetaxel regimen as first-line therapy. Patients who had received adjuvant anthracyclines received docetaxel 75 mg/m^2 on day 1 and capecitabine 950 mg/m^2 twice daily, days 1–14, every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint was time to progression. Forty-five patients were evaluable (median age 56 years, range 35–75). The response rate was 42%, including two complete responses. Nine patients (20%) attained stable disease. Median time to progression was 8 months and median overall survival was 23 months. Five patients (11%) experienced grade 3 neutropenia but febrile neutropenia was absent. Three patients (7%) experienced grade 3 hand–foot syndrome; there was no significant gastrointestinal toxicity. This capecitabine–docetaxel regimen is an active first-line therapy and appears better tolerated than regimens using a higher capecitabine dose. Data from the randomized trial comparing the registered versus a lower capecitabine dose, both in combination with docetaxel, should definitively answer whether a lower dose provides a better safety profile while maintaining the considerable efficacy of this combination. *Anti-Cancer Drugs* **20:204–207 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Oncology Clinic Department of Surgery, Areteion Hospital, University of Athens, Athens, Greece

Correspondence to Professor Konstantine Gennatas, Oncology Clinic Department of Surgery, Areteion Hospital, University of Athens, Arnis 5, Athens 115 28, Greece
Tel: +30 210 7244758; fax: +30 210 7246878; e-mail: gennatas@otenet.gr

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Introduction

Metastatic breast cancer (MBC) remains a destructive, largely incurable, and highly heterogeneous disease. Selection of the most appropriate treatment for an individual from the expanding range of available agents is usually driven by tumor biology, symptoms, metastatic pattern, disease-free interval, quality of life, and patient choice. Among the most effective drugs for the treatment of breast cancer are taxanes and anthracyclines, given either in combination or sequentially [1–3]. The use of anthracycline-based regimens in the adjuvant setting is now firmly established, and consequently first-line therapy frequently includes a taxane. The efficacy of taxanes can be improved through combination with other chemotherapeutic or biologic agents, such as the oral fluoropyrimidine capecitabine [4] or the humanized monoclonal antibody, bevacizumab, which targets vascular endothelial growth factor [5,6]. Capecitabine is a logical combination partner for taxanes, as both docetaxel and paclitaxel upregulate the enzyme thymidine phosphorylase, which plays a pivotal role in the conversion of capecitabine to 5-fluorouracil preferentially in tumor tissue [7–9]. Capecitabine has shown synergistic antitumor activity with both docetaxel and paclitaxel in the preclinical setting [8], and these observations were substantiated in the clinical setting. In a large, randomized, phase III trial, the addition of capecitabine to docetaxel significantly improved response rate, time to disease progression (TTP) and overall survival (OS) compared with docetaxel alone in anthracycline-pretreated MBC [4]. However, the regimen investigated was associated with quite frequent toxicity and a substantial proportion of patients required dose reduction. To avoid early discontinuation of an effective treatment, it is important to define the most appropriate starting dose, thus enabling patients to remain on a tolerable treatment for longer and derive maximum benefit. Retrospective comparison of patients requiring dose reduction at the second cycle versus those continuing at the full starting dose suggested improved tolerability at a lower dose without detrimental effect on efficacy [10]. A randomized trial has been conducted to compare the registered dose, as used in the trial reported by O'Shaughnessy *et al.* [4], with a lower dose of capecitabine and docetaxel. However, data are not yet available. Here, we report findings from our single-arm, prospective study evaluating a lower starting dose of capecitabine in combination with docetaxel as first-line therapy for patients with MBC.

Patients and methods

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

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Patients

Eligibility criteria were as follows: histologically confirmed advanced breast cancer, presence of at least one measurable lesion, prior adjuvant anthracycline therapy, no prior therapy for advanced disease, Karnofsky Performance Score ≥ 70, life expectancy more than 3 months, adequate hematologic parameters (white blood cell count $\geq 3500/\mu l$, platelet count $\geq 100\,000/\mu l$, hemoglobin concentration > 9 g/dl), and adequate hepatic and renal function (serum bilirubin < 2.0 mg/dl; serum creatinine < 1.5 mg/dl); HER2 status negative or unknown. Patients were excluded if they had previously received docetaxel or capecitabine.

Treatment plan

All treatments were administered in the outpatient setting. Patients received docetaxel 75 mg/m^2 on day 1, with routine steroid premedication and postmedication, and oral capecitabine 950 mg/m^2 twice daily (b.i.d.), on days 1–14, every 3 weeks until disease progression or unacceptable toxicity. Blood count was carried out on days 1 and 10 of each cycle. If hand–foot syndrome (HFS) or other toxicities with intensity of grade ≥ 2 (World Health Organization criteria) were reported, treatment (capecitabine and/or docetaxel, depending on the type of toxicity) was delayed until toxicity resolved to grade 1 (maximum 1 week). At the second occurrence, a dose reduction to 75% was performed. Dose adjustments of capecitabine were based on the observed toxicity. If nonhematologic toxicity occurred simultaneously with grade > 2 hematologic toxicity, administration of capecitabine was to be interrupted. Doses omitted because of toxicity were not replaced.

Study assessments

Tumors were assessed every 3 months with computed tomography scans of the chest and the abdomen, with additional work-up if indicated according to International Union Against Cancer criteria. Tumors were reassessed when clinical symptoms of disease progression occurred. Complete response (CR) was defined as the disappearance of all measurable lesions for a minimum of 8 weeks. Partial response (PR) was defined as $\geq 50\%$ reduction in sum of the largest diameters of measurable lesions, no increase in lesion size, and no new lesions. Stable disease (SD) was defined as less than 50% decrease and less than 25% increase without the appearance of new lesions. Progressive disease was defined as greater than 25% increase in tumor size or the appearance of new lesions. TTP was defined as the interval from the first day of study treatment until tumor progression. OS was defined as the interval from the first day of treatment until death from any cause. Toxicity was graded according to World Health Organization criteria and the worst episode in each patient was recorded.

Statistical analysis

The primary endpoint was TTP. Secondary endpoints were overall response rate, clinical benefit rate, and OS. TTP and OS were estimated using the Kaplan–Meier product-limit method. All statistics were calculated using SPSS version 12.0 (SPSS Inc., Chicago, Illinois, USA). The sample size was calculated according to Simon's two-step optimal design. The null response rate (P0) below which there would be no further interest in the proposed regimen was set at 5%, and the rate beyond which further studies would be of interest (P1) was set at 20%. Assuming an α error rate of 0.05 and a β error rate of 0.10, 21 patients were to be accrued in the first step. If two or more responses were observed, 20 more patients were to be entered. The regimen was considered of clinical interest if more than five responses were observed among 45 treated patients.

Results

Patient characteristics

Forty-five consecutive patients were enrolled in the study between May 2004 and February 2008. Table 1 lists the baseline characteristics of the study population. All patients received at least one dose of capecitabine and docetaxel and were included in the intent-to-treat analyses of efficacy and safety.

Efficacy

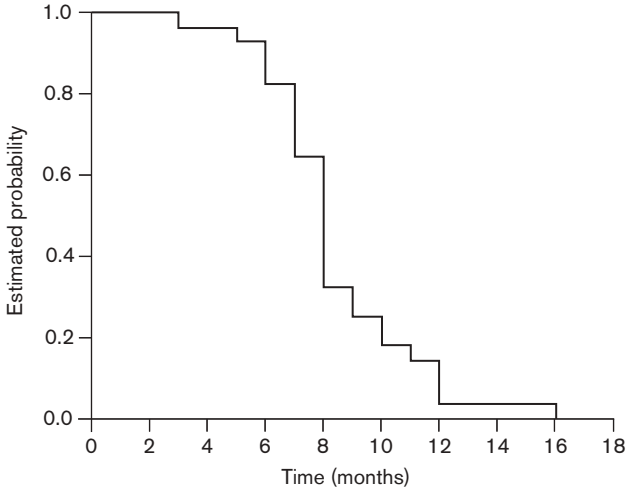
At the time of this analysis (March 2008), median duration of follow-up was 28 months (range 3–42). Median TTP was 8 months (range 3–18; 95% confidence interval: 6.07–9.93; Fig. 1). Median OS was 23 months (range 3–40; 95% confidence interval: 20.23–27.77). Two patients (4%) achieved CR, 17 (38%) achieved PR, and SD lasting ≥ 6 months was observed in nine patients

Table 1 Baseline characteristics ($n = 45$)

Age (years)	
Median	56 (35–75)
Median Karnofsky performance status (%)	90
ER/PgR status (%)	
ER and/or PgR positive	48
ER and PgR negative	43
Unknown	9
HER2 status (%)	
Positive	0
Negative	76
Unknown	24
Metastatic sites (%)	
Visceral	87
Lymph nodes	44
Liver	46
Bone	40
Bone only	13
Lung	32
Skin	23
Adjuvant chemotherapy (%)	100
Paclitaxel	0
CMF	18
CEF	82

CEF, cyclophosphamide, epirubicin and 5-fluorouracil; CMF, cyclophosphamide, methotrexate and 5-fluorouracil; ER, estrogen receptor; PgR, progesterone receptor.

Fig. 1



Time to progression.

Table 2 Treatment-related adverse events

Toxicity	Grade 1/2 (%)	Grade 3/4 (%)
Neutropenia	7 (16)	5 (11)
Nausea/vomiting	6 (13)	0
Hand–foot syndrome	8 (18)	3 (7)
Fatigue	4 (9)	0
Diarrhea	5 (11)	1 (2)
Stomatitis	4 (9)	1 (2)

(20%). Thus, the overall response rate was 42% and the clinical benefit rate (CR, PR, or SD $\geq$ 6 months) was 62%. The median duration of response was 3.2 months and the median duration of SD was 5.1 months.

Safety

In total, 315 cycles were administered. Median duration of combination therapy was 6 months. Mean delivered capecitabine dose was 920 mg/m^2 b.i.d. Treatment was well tolerated, as shown in Table 2. The main toxicity was myelosuppression, with grade 3 neutropenia in five patients (11%), which led to treatment delay for 1 week. No dose modification was implemented for these events. Febrile neutropenia was not encountered. There was no significant gastrointestinal toxicity: grade 3 diarrhea occurred in only one patient (2%) and could be managed with capecitabine dose reduction to 75% of the start ing dose; there were no grade 4 episodes. Grade 3 HFS was observed in three patients (7%) and resolved with dose reduction (to 75%). Side effects were manageable with appropriate medical intervention (e.g. loperamide and rehydration for diarrhea, mouthwash and fluconazole for stomatitis, and oral vitamin B6 preparations and emollients for HFS). There were no treatment-related deaths.

Discussion

In our study, a regimen of capecitabine 950 mg/m^2 b.i.d. and docetaxel 75 mg/m^2 showed high activity and good tolerability, with a median TTP of 8 months and a median OS of 23 months. The median duration of response was 3.2 months and the median duration of SD was 5.1 months. Although cross-trial comparison has limitations because of differences in patient populations and the response criteria used, these data compare favorably with results from randomized trials evaluating capecitabine-docetaxel combination therapy, albeit at different doses. Median TTP was 6.1 months in the pivotal trial in which patients were treated with capecitabine at a dose of 1250 mg/m^2 b.i.d. plus docetaxel 75 mg/m^2, predominantly in the second-line or third-line setting [4]. Two subsequent randomized trials evaluating the same regimen showed median TTP (progression-free survival in the second trial) of 7.7–8.0 months and median OS of 21.5–22 months [11,12]. In both of these trials, all patients were anthracycline pretreated. However, one was conducted exclusively in the first-line setting, whereas approximately one-third of patients had received prior therapy for advanced disease in the second. Preliminary results of a Mexican trial in patients with anthracycline-pretreated MBC treated with capecitabine 825 mg/m^2 plus docetaxel showed corresponding values of 8.1 months and 24+ months [13]. Most recently, final results from a randomized trial in the first-line setting were reported by the Hellenic Oncology Research Group [14]. In this trial, capecitabine was given at a dose of 950 mg/m^2 b.i.d. plus docetaxel 75 mg/m^2. Median TTP was 10.5 months and median OS was 37.5 months. Differences in performance status seem unlikely to explain differences in efficacy between the trials: in this study and two of the three trials evaluating capecitabine 1250 mg/m^2 b.i.d., the median Karnofsky Performance Score was 90%. One possible explanation for the high efficacy in this study and the trial by the Hellenic Oncology Research Group is the lower capecitabine dose – by using a regimen that is more tolerable, treatment can be continued for longer (median duration of therapy 6 months in this study, compared with 3.8 months in the study reported by O'Shaughnessy *et al.* [4]), enabling patients to derive maximum benefit. The efficacy findings from this study are consistent with results from phase II studies in the literature in similar patient populations, in which even lower capecitabine doses in combination with a taxane (either paclitaxel or docetaxel), showed response rates of 44–55%, median TTP of 5.5–10.6 months, and median OS of 17–29.9 months [15–18]. Taken together, these observations suggest that decreasing the dose of capecitabine in combination with a taxane is not detrimental to activity.

The most common grade 3 adverse events were neutropenia and HFS. There were no cases of febrile neutropenia. Side effects were manageable with appropriate medical

intervention and treatment interruption (with subsequent dose reduction if necessary). The safety profile of capecitabine–docetaxel in this study was markedly better than in the original phase III trial reported by O'Shaughnessy *et al.* [4], in which capecitabine was given at 1250 mg/m^2 b.i.d. in the combination arm. This observation is consistent with results of the trials reported by Soto *et al.* and Mavroudis *et al.* [12,14], which tested a lower dose of capecitabine (825 and 950 mg/m^2 b.i.d., respectively). For example, at the registered dose of 1250 mg/m^2, grade 3/4 diarrhea was reported in up to 18% of patients [4,11,12], whereas at the lower doses, grade 3/4 diarrhea was reported in only 4–7% of patients [13,14] (and only 2% in this study). Similarly, grade 3 HFS was reported in 24% of patients in the pivotal trial [4], 18–26% in subsequent trials with capecitabine at 1250 mg/m^2 b.i.d. [11,12], and only 4–13% in our trial and others evaluating lower doses of capecitabine [13,14]. Our results are also consistent with the previously described analysis of tolerability among patients undergoing early dose reduction in the O'Shaughnessy *et al.* trial [4], which suggested that efficacy was not compromised if capecitabine and docetaxel were administered at lower doses [10].

In conclusion, our results suggest that the combination of capecitabine 950 mg/m^2 b.i.d. plus docetaxel 75 mg/m^2 is effective for the management of patients with anthracycline-pretreated MBC. It is easily administered on an outpatient basis, providing there is adequate support and monitoring for leukopenia. Notably, gastrointestinal toxicities and HFS were not problematic. Therefore, this regimen may be regarded as an active combination therapy option for patients with high tumor burden and/or visceral metastases, for whom monotherapy approaches may not be adequate. Our results suggest that a capecitabine starting dose lower than that evaluated by O'Shaughnessy *et al.* [4] provides a better tolerated therapy without compromising activity, supporting results of phase III trials in the literature evaluating similar dosing regimens [13,14]. These data provide reassurance that the lower capecitabine starting dose typically adopted in routine clinical practice is valid. A randomized trial comparing the registered versus a lower capecitabine dose, both in combination with docetaxel, has almost completed recruitment and should definitively answer whether a lower dose provides a better safety profile while maintaining the considerable efficacy of this combination. Finally, as we have entered an era of biological therapies for the management of MBC, agents such as bevacizumab, which significantly improves efficacy when added to a taxane in the first-line setting, must not be neglected. Integration of biologic agents that combine significant efficacy benefits with excellent tolerability into treatment practice must be a priority.

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