Safety and efficacy of weekly docetaxel in frail and/or elderly patients with metastatic breast cancer: a phase II study

Randal D'hondt[a], Robert Paridaens[a], Hans Wildiers[a], Karen Pauwelyn[a], Jose Thomas[a], Herlinde Dumez[a] and Allan T. Van Oosterom[a]

This phase II study was designed to evaluate the safety and efficacy of weekly docetaxel (36 mg/m^2) for the treatment of metastatic breast cancer in 47 frail and/or elderly patients who were ineligible for the standard 3-weekly docetaxel (100 mg/m^2) regimen. Reasons for ineligibility to the latter were age $\geq$ 70 years (10 patients), poor hematological reserves (15 patients), impaired liver function (eight patients), intolerance to previous taxanes administered 3-weekly without demonstrated resistance (five patients) or any combination of these reasons (nine patients). There was a median of two prior chemotherapy regimens and more than 60% had a WHO performance score at baseline of 2–3. A total of 408 weekly administrations were given over a period of 525 weeks (78% of the intended dose intensity) and the median cumulative dose of docetaxel per patient was 278 mg/m^2. The incidence of serious adverse events was low. Grade 3 neutropenia occurred in six patients and grade 4 in four patients. Of these 10 patients, eight had pre-existing hematological abnormalities and four developed neutropenic fever. Neurotoxicity was mild and grade 3 paraesthesia occurred in one patient. The overall objective response rate in 37 evaluable patients was 30% and responses were observed in all subgroups of patients. We conclude that weekly docetaxel (36 mg/m^2) is active, safe and well tolerated in heavily pre-treated frail/elderly patients with poor prognostic features, including low performance scores and multiple metastatic sites, who would not be eligible for treatment with the standard 3-weekly regimen. *Anti-Cancer Drugs* 15:341–346 © 2004 Lippincott Williams & Wilkins.

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[a]Department of Oncology, University Hospital Gasthuisberg, Catholic University of Leuven, Leuven, Belgium.

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Correspondence to R. Paridaens, Department of Oncology, University Hospital Gasthuisberg, Herestraat 49, Leuven 3000, Belgium.
Tel: +32 16 346900; fax: +32 16 346901;
e-mail: Robert.Paridaens@uz.kuleuven.ac.be

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Introduction

Chemotherapy plays a central role in the management of metastatic breast cancer. However, tumor response rates and overall survival remain disappointing, and most women die from metastatic disease despite chemotherapy. Therefore, it is important to identify regimens that prolong survival while preserving quality of life. At present, there is no consensus on the choice of chemotherapy for patients with metastatic disease, particularly those with poor performance status.

Docetaxel belongs to the taxane class of chemotherapeutic agents and is one of the most effective single agents for the treatment of breast cancer. In phase II trials of first-line chemotherapy of metastatic breast cancer, monotherapy with docetaxel, 100 mg/m^2 administered once every 3 weeks, produced response rates of 54–68% [1–3]. In patients with previous exposure to anthracyclines, similarly high response rates of 53–58% have been reported, indicating a lack of cross-resistance between docetaxel and this group of drugs [4–6]. Phase III trials conducted in metastatic breast cancer patients who had failed previous therapy yielded response rates of 30 and 42% (two trials in patients failing anthracyclines), and 48% (one trial in patients failing alkylating agents) [7–9]. Furthermore, docetaxel is active even in heavily pre-treated patients with advanced disease [10,11].

In metastatic breast cancer, docetaxel is generally administered at a dose of 100 mg/m^2 given as a 1-h i.v. infusion, repeated every 3 weeks. The main dose-limiting toxicity of docetaxel is myelosuppression, which is dependent on the dose administered rather than the schedule [12,13]. Management of this myelosuppression and of other chemotherapy-associated toxicities [14] in patients who are frail or elderly is particularly challenging; various taxane regimens have therefore been investigated with the aim of increasing the tolerability of these agents in this patient population.

The delivery of lower, more frequent doses of docetaxel appears to alter the toxicity profile of the drug. Several phase I and II studies have shown that weekly docetaxel, administered at a similar dose intensity to the 3-weekly schedule (36–40 mg/m^2/week), may exhibit comparable activity with fewer adverse effects, in particular reduced

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myelotoxicity, but also fewer nail changes and less neurological toxicity than 3-weekly docetaxel regimens [15–21]. Furthermore, the weekly regimen appears to be well tolerated by elderly patients. Docetaxel 36 mg/m^2/week was associated with a low incidence of adverse events in elderly patients with advanced, previously untreated non-small cell lung cancer [22].

In view of the favorable tolerability profile of weekly docetaxel, the present phase II study evaluated the tolerability and activity of docetaxel 36 mg/m^2/week in frail/elderly patients with metastatic breast cancer who were considered unlikely to tolerate the 3-weekly regimen because of advanced age, problems with previous taxane-based therapy, or abnormal hematological or liver function.

Patients and methods

Study design

This was a single-center, prospective, open-label, phase II study evaluating the toxicity and activity of a once-weekly dose of docetaxel (36 mg/m^2) in mostly pre-treated elderly or frail women with metastatic breast cancer. Secondary objectives were the evaluation of time to progression and overall survival. Local ethical committee approval was obtained for the protocol. All patients were required to provide oral or written informed consent before entry into the study.

Patient population

Women with histologically proven metastatic breast cancer, who were considered unlikely to tolerate the standard 3-weekly docetaxel regimen, were recruited into the study. A total of 47 patients were included and 37 patients were evaluable for response including measurable lesions [at least one lesion with a diameter ≥ 1 cm if assessed clinically or ≥ 2 cm if measured using computed tomography (CT) scans]. Ten patients were not evaluable for response, but were included for the toxicity and overall survival evaluation. Two of these patients had switched from the 3-weekly regimen due to toxicity problems and continued with weekly docetaxel immediately afterwards. Response could not be evaluated according to classical criteria in eight other patients either due to the presence of bone lesions that were not measurable or to severe myelophthysis without other measurable disease at baseline.

Tolerance of the standard 3-weekly docetaxel regimen was considered unlikely when patients exhibited at least one of the following features:

(i) Conditions that predisposed to hematological problems, i.e. confirmed bone marrow invasion (with or without myelophthysis), a low neutrophil count ($< 2 \times 10^9$/l) and/or platelet count ($< 100 \times 10^9$/l) at baseline, history of chemotherapy-associated hematological complications (e.g. neutropenic fever) or previous exposure to extensive radiotherapy.
(ii) Liver function abnormalities [serum bilirubin $>$ upper limit of normal (ULN), liver transaminases $> 2.5 \times$ ULN or transaminases $> 1.5 \times$ ULN plus alkaline phosphatases $> 5 \times$ ULN].
(iii) Side-effects after previous exposure to treatment with taxanes (hematological or fluid retention).
(iv) Aadvanced age ≥ 70 years.

Patients were excluded from the study if they were considered eligible for 3-weekly docetaxel therapy, had uncontrolled metastases in the central nervous system or had poor WHO performance status associated with a life expectancy of < 1 month.

Treatment

Docetaxel was given as an i.v. infusion (36 mg/m^2 over 1 h) once weekly for the initial 6 weeks, followed by 1 week of rest. Treatment was then given in cycles that each consisted of 2 or 3 weeks of therapy followed by a 1-week break, depending on the ability of patients to tolerate the regimen and the dose intensity achieved during the first 6 weeks. Treatment continued until either disease progression or the occurrence of unacceptable side-effects, to a maximum of 24 administrations. Oral methylprednisolone 32 mg was administered 12 and 3 h before, and 1 and 12 h after the infusion.

Decisions to interrupt or stop treatment based on hematological parameters were as follows: treatment was delayed for 1 week if the absolute neutrophil count fell to $< 1 \times 10^9$/l. Chemotherapy only recommenced when the neutrophil count was above this level; if there was no recovery after 3 weeks, the patient was withdrawn from the study. In the case of thrombocytopenia (platelet count $< 100 \times 10^9$/l), treatment was interrupted in patients whose platelet count had been normal at baseline. Chemotherapy was recommenced when the platelet levels had recovered; if there was no recovery after 3 weeks, the patient was withdrawn from the study. In patients who had thrombocytopenia at study entry, treatment was continued provided the neutrophil count was satisfactory.

Patient and treatment evaluation

The patients were given a complete medical history and physical examination at the time of enrolment. Hematological and clinical chemistry profiles were also obtained. Blood samples were taken weekly for toxicity monitoring according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC version 2.0).

Tumor responses were evaluated at baseline, after 7 weeks and then every 2 months during the study, either

by measurements (clinically measurable lesions) or by CT scan. Tumor responses were defined according to WHO criteria [23] and evaluated by two independent observers. The time to progression was the period between the start of treatment and the earliest date of documented disease progression. Blood levels of the tumor marker CA 15.3 were measured weekly.

Statistical analysis

Estimates of the time to progression and overall survival were made using the Kaplan–Meier intention-to-treat analysis.

Results

Patient characteristics

A total of 47 women with metastatic breast cancer were enrolled between March 1999 and August 2000, and data were collected up to August 2003. These women were considered unlikely to tolerate 3-weekly docetaxel at 100 mg/m^2 for various reasons detailed in Table 1. Hematological problems were present in 22 patients: baseline hematological abnormalities in 10 patients, past history of severe hematological problems with previous chemotherapy in 10 patients and prior extensive radiotherapy in two patients. Thirteen patients had impaired liver function tests. Eleven patients were aged 70 or older. Previous exposure to 3-weekly taxane treatment, with intolerance, was recorded in 10 patients (six patients exposed to docetaxel and four to paclitaxel). The two patients who received 3-weekly taxanes immediately before switching to weekly docetaxel were excluded from the efficacy data; the other eight patients received taxanes at least 2 months before being included in the study and were included in the efficacy study if they had measurable disease.

The baseline characteristics of the patients are shown in Table 2. The median baseline WHO performance score was 2 (range 0–3). The four patients with a WHO score of 3 specifically requested treatment, despite their bad performance score. Metastases of the primary tumor were present in a median of two organs, with 23 patients having three or more affected organs. The majority of patients had skeletal (35 patients, 74.5%) or visceral (34 patients, 72%) involvement. Subjects had received a median of two prior chemotherapy regimens for the treatment of advanced breast cancer in the palliative setting. Baseline hematological abnormalities were present in 10 patients: two patients had leukopenia (white cell count $< 2 \times 10^9$/l), six patients had thrombocytopenia (platelet count $< 100 \times 10^9$/l) and two patients had leuko-thrombocytopenia due to bone marrow invasion. Liver function abnormalities were detected in 13 patients at baseline (bilirubin $>$ ULN or transaminases $> 1.5 \times$ ULN plus alkaline phosphates $> 5 \times$ ULN), and were all secondary to metastatic involvement of the liver.

Treatment

A total of 408 administrations of docetaxel were received by the 47 patients over a period of 525 weeks, with a median of 8 administrations per patient (range 1–23). The median docetaxel dose intensity administered during the study was 28.0 mg/m^2/week (i.e. 78% of the intended dose intensity) and the median cumulative dose was 278 mg/m^2.

Safety

All 47 patients were evaluated for safety. The incidence of toxicity is shown in Table 3. Of the 10 patients who reported grade 3–4 neutropenia, baseline hematological abnormalities were observed in eight. Three of the patients with baseline hematological abnormalities developed neutropenic fever, whilst a fourth experienced neutropenic sepsis. Grade 3–4 thrombocytopenia not requiring platelet transfusion was detected in three patients, all of whom had a platelet count at baseline $< 50 \times 10^9$/l. Five patients who reported fluid retention and three who reported paraesthesia had previously been treated with taxanes. No patients experienced grade 4 neurological symptoms.

Table 2 Patient characteristics

Characteristic	No. of patients (%)
Patients enrolled	47
Median age [years (range)]	63 (43–82)
WHO scores 0/1/2/3	1 (2)/16 (34)/26 (55)/4 (9)
No. organs involved 1/2/3/4	10 (21)/14 (30)/15 (32)/8 (17)
Disease sites: bone/liver/lung/soft tissue	35 (74.5)/30 (63.8)/19 (40.4)/28 (59.7)
Estrogen receptor status at diagnosis: positive/negative/unknown	29 (62)/14 (30)/4 (9)
Prior radiotherapy: adjuvant/palliative	29 (62)/23 (49)
Prior chemotherapy: adjuvant/palliative	17 (36)/37 (79)
Number of regimens: 0/1/2/3/4/5	10/12/17/3/4/1
Previous hormonal therapy: adjuvant/palliative	15 (32)/38 (81)
Anthracycline resistance: yes/no/unknown	18 (38)/17 (36)/12 (26)
Evaluable for response: yes/no	37 (79)/10 (21)

Table 1 Reason(s) why patients (pts) included in this trial were not candidates to receive 3-weekly taxanes ($n=47$)

Reason	Age (A) ($n=11$ pts)	Hematological (B) ($n=22$ pts)	Liver (C) ($n=13$ pts)	Taxanes (D) ($n=10$ pts)
Single reason (total $n=38$ pts)	A alone ($n=10$ pts)	B alone ($n=15$ pts)	C alone ($n=8$ pts)	D alone ($n=5$ pts)
Combined reasons (total $n=9$ pts)	A + other ($n=1$ pt	B + other ($n=7$ pts)	C + other ($n=5$ pts)	D + other ($n=5$ pts)
Detail of combined reasons	A + B = 1 pt	B + A = 1 pt	C + B = 3 pts	D + B = 3 pts
		B + C = 3 pts	C + D = 2 pts	D + C = 2 pts
		B + D = 3 pts		

Table 3 Incidence of hematological and non-hematological toxicities ($n=47$)

Adverse event	No. of patients (%) with toxicity (NCI-CTC)		
	Overall (grade 1–4)	Grade 3	Grade 4
Hematological			
neutropenia	18 (38)	6 (13)	4 (9)
thrombocytopenia	7 (15)	1 (2)	2 (4)
anemia	15 (32)	0	0
Non-hematological			
fluid retention	14 (30)	1 (2)	0
paraesthesia	11 (23)	1 (2)	0
nail disorder	12 (26)	1 (2)	0
conjunctivitis	9 (19)	0	0
fatigue	27 (57)	0	0

Table 4 Incidence of toxicity in 11 patients aged >70 years

Adverse event	No. of patients (%) with toxicity (NCI-CTC)		
	Grade 1	Grade 2	Grade 4[a]
Neutropenia	0	0	1[b] (9)
Thrombocytopenia	0	0	0
Fluid retention	2 (18)	2 (18)	0
Nail changes	2 (18)	1 (9)	0
Conjunctivitis	3 (27)	0	0
Fatigue	6 (55)	2 (18)	0

[a]No grade 3 adverse events were recorded.
[b]This patient had hematological abnormalities at baseline.

Treatment interruptions or terminations encountered by nine patients were due to fatigue (three patients), and neurotoxicity, fluid retention and nail disorder (each in two patients). There were no toxic deaths.

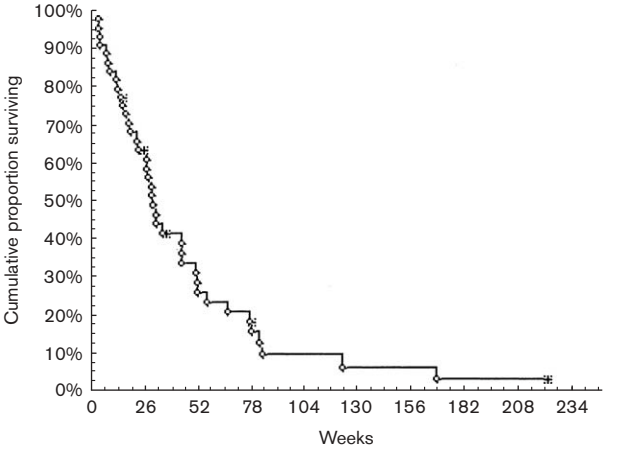
The incidence of toxicity recorded in the subgroup of patients aged >70 years ($n=11$) is shown in Table 4.

Efficacy

After 7 weeks, patients were evaluated and responses were confirmed after 4 weeks. In the 37 evaluable patients, no complete responses (CR) were observed; however, partial responses (PR) were observed in 11 patients giving an overall response rate of 30% in the intent-to-treat population ($n=37$). Ten patients (27%) had stable disease (SD), 16 (43%) had progressive disease (PD). The clinical activity rate (CR + PR + SD) of the weekly docetaxel regimen was 57% (21 of 37 patients).

Responses were observed in all subgroups of patients, whatever the reason(s) precluding the administration of 3-weekly docetaxel. Among the 10 (on 11) evaluable patients aged ≥ 70 years without any other risk factor, there were four PRs and one SD. For the 16 (on 22) evaluable patients whose hematological problems were one of the reasons they did not receive the 3-weekly regimen, there were seven PRs and four SDs. Among the 13 patients with impaired liver function tests (all evaluable), there were four PRs and three SDs, whereas response rates were slightly lower in the seven (on 10) evaluable patients previously exposed to 3-weekly taxanes (one PR and two SDs).

Fig. 1



Actuarial survival curve for 44 patients. Median survival was 28 weeks. Six- and 12-month survival rates were 61% and 29%, respectively. A circle indicates non-censored data ($n=39$) and a 'plus' indicates censored data ($n=5$).

The median time to progression for 44 evaluable patients enrolled in this study was 14 weeks (range 1–99). Their median overall survival was 28 weeks, with 6- and 12-month survival rates of 61 and 29%, respectively (see Fig. 1).

In all responders, the blood concentration of the tumor marker CA 15.3 increased approximately 20% during the first 2–3 weeks of treatment and subsequently fell to levels lower than those at baseline. There was a similar initial rise in CA 15.3 levels in non-responders.

Performance status

The WHO performance score remained unaltered in most patients for the duration of the study. Improvement in performance by a single grade was detected in five patients. Only two patients had a one-grade decrease in the performance index. Treatment with docetaxel did not adversely affect the performance of the 16 patients who experienced disease progression.

Discussion

This study demonstrates that the administration of weekly docetaxel (36 mg/m^2) is feasible in elderly or frail subjects, most of whom have been heavily pre-treated. The weekly regimen shows good hematological tolerability, with grade 3 neutropenia being observed in six (13%) patients and grade 4 neutropenia in four (9%) patients, mostly observed in patients with baseline

hematological abnormalities. The overall response rate was 30%.

Previous phase II studies of weekly docetaxel in advanced breast cancer have reported toxicity lower than observed in this study, with grade 3 neutropenia ranging from 2 to 14% and grade 4 neutropenia absent or occurring in only 2% of patients [15,19,24–26]. The higher rate observed in the current study may reflect the poor condition of the patients enrolled, more than 60% of whom had a WHO performance score of 2 or 3. Nonetheless, the incidence of major toxicities was low in our study, with only four patients experiencing neutropenia complicated by fever or infection; all of these patients already had hematological abnormalities at baseline. Paraesthesia was the most common non-hematological toxicity, but this was only severe (grade 3) in one patient (2.9%) and no other neurological side-effects were observed. There was a high incidence of fatigue, but only at grades 1 and 2. This contrasts with the study of Hainsworth [26] in elderly breast cancer patients treated with weekly docetaxel, where grade 3/4 fatigue occured in 20% of patients. This difference might be based on the fact that after an initial 6-weekly administration (identical in both studies), the duration of consequent docetaxel administrations was tailored in our study depending on tolerance, while in the study of Hainsworth, docetaxel continued to be given once weekly for 6 weeks. In a study involving elderly patients with advanced non-small cell lung cancer [22], weekly docetaxel was equally well tolerated.

Previous studies of weekly docetaxel have reported PR values between 35 and 41%, and occasionally CR [19,24–26]. The lower—but nevertheless clinically relevant—efficacy observed in the present study is attributable to differences in patient populations. Our patients were selected for their inability to tolerate 3-weekly taxane-based therapy and in most cases would not be eligible for any form of chemotherapy. Furthermore, it is well established that patients with visceral metastases have a poorer prognosis than those with advanced disease confined to the skeleton and/or soft tissues [27]. With the high prevalence of visceral disease among women in the present study (64% had liver metastases; 40% had lung involvement), the observed overall response rate of 30% with limited toxicity is encouraging. The 36% objective response rate (CR + PR) reported in a study of Hainsworth involving 41 elderly breast cancer patients treated with weekly docetaxel [26], of whom 51% were chemotherapy-naive, is similar to that observed in our present series.

Of particular note is the finding that patients with impaired liver function and/or hematological problems precluding the use of the more classical 3-weekly regimen responded to weekly docetaxel. Similarly, older patients aged ≥ 70 years, who were less pre-treated than the remainder, showed an encouraging number of PR while hematological tolerability was surprisingly good: there was only one case of grade 4 neutropenia in a patient with hematological abnormalities at baseline.

We examined the levels of CA 15.3 at weekly intervals in order to determine whether changes in the levels could be used to predict treatment outcome. Although of interest, the pattern of early changes in CA 15.3 levels observed within the first 3 weeks of treatment cannot be used to predict whether or not a patient will respond. The initial peak in CA 15.3 concentrations is observed in both responders and non-responders. In responders, it is likely to be related to tumor lysis which—combined with the subsequent fall in levels—may indicate a biochemical response to treatment.

This study shows that docetaxel (36 mg/m^2) administered on a weekly basis is active and well tolerated in heavily pre-treated patients not suitable for hormone therapy, and with poor prognostic features including low performance scores and multiple metastatic sites. The activity and tolerability of weekly docetaxel observed are encouraging in such a frail patient population, for whom the only therapeutic alternative may be supportive care. The weekly docetaxel regimen, therefore, represents a useful alternative for heavily pre-treated patients who would not be eligible for treatment with the standard 3-weekly regimen. Furthermore, the low incidence of myelotoxicity associated with weekly docetaxel suggests that this regimen might be used in combination with other chemotherapeutic agents in the treatment of advanced breast cancer.

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