Weekly docetaxel in patients with pretreated metastatic breast cancer: a phase II trial

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Docetaxel has consistently demonstrated its high activity as an antineoplastic agent in the treatment of metastatic breast cancer. However, 90% of patients receiving the recommended dose of 100 mg/m^2 every 3 weeks will develop grade 3 or 4 neutropenia. Recent data suggest that the safety profile of a weekly docetaxel regimen compared favorably with the standard 3-week schedule. Thus, we initiated a phase II study to assess the efficacy and toxicity of weekly docetaxel in pretreated patients with metastatic breast cancer. Twenty patients with advanced, anthracycline-refractory breast cancer were included in this phase II trial. Docetaxel was administered at a starting dose of 40 mg/m^2, repeated once a week for 3 consecutive weeks followed by a 1-week rest period (1 cycle). Patients were evaluated for tumor response every 8 weeks (after every other cycle). Therapy was continued for a maximum of six courses in patients showing tumor response or stable disease. Twenty patients received a total of 204 weekly infusions of docetaxel. The mean number of treatments was 10.2 (range 1–18). Eighteen patients were assessable for response. Five patients achieved a partial response and six patients showed either stable disease or a minor response. Seven patients had disease progression. The median survival was 7.8 months. Grade 3/4 leukopenia occurred in two patients. No other grade 3 or 4 hematologic toxicities were observed. The following grade 3/4 non-hematologic toxicities were seen: nausea/vomiting (one patient), infection (one patient), mucositis (two patients) and diarrhea (one patient). Three patients withdrew from the study due to dose-limiting toxicities (one due to severe neutropenia and two due to mucositis). We conclude that administration of docetaxel at a dose of 40 mg/m^2 was effective and well tolerated even in heavily pretreated patients with metastatic breast cancer. This regimen is associated with only mild myelosuppression. *Anti-Cancer Drugs* 14:233–238 © 2003 Lippincott Williams & Wilkins.

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Introduction

Docetaxel is widely accepted as one of the most active agents in the treatment of metastatic breast cancer. It demonstrates significant activity in both first- and second-line therapy, even in anthracycline-pretreated patients [1–7]. During its clinical development, the standard dose of docetaxel for the treatment of metastatic breast cancer was 75–100 mg/m^2, administered as a 1-h i.v. infusion every 21 days. The apparent dose-limiting toxicity associated with this schedule was myelosuppression [8]. Most studies have reported an incidence of grade 3 or 4 neutropenia of 90–95% with docetaxel given as an every-3-weeks regimen [6,9]. Other toxicities included asthenia/fatigue, alopecia, skin reactions, stomatitis and hypersensitivity reactions, and a fluid retention syndrome characterized by pedal edema and/or serious effusions. The fluid retention syndrome associated with the cumulative dose of docetaxel is usually reversible after discontinuation of treatment and is well managed by co-administration of corticosteroids [10].

The results gained from the experience with paclitaxel indicated that weekly administration of docetaxel might be as efficacious, but with an improved toxicity profile [11,12]. The delivery of paclitaxel at lower, more frequent doses reduced the hematological toxicity compared with schedules using higher doses at less frequent intervals. Myelosuppression was mild to moderate in intensity. Sensory neuropathy proved to be the dose-limiting toxicity [11,13,14]. Based on these observations, it was assumed that the same might be true for docetaxel.

Initial trials with weekly docetaxel involved patients with a variety of advanced malignancies and produced encouraging evidence of reduced hematologic toxicity [15,16]. The recommended dose for the following phase

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II study was 36–40 mg/m^2/week. The objective of this phase II study was to evaluate the efficacy and safety profile of a weekly docetaxel regimen in patients with pretreated advanced metastatic breast cancer.

Patients and methods

Eligibility

Between May 1997 and June 2001, 20 patients were enrolled in this phase II study. All patients were required to meet the following eligibility criteria: histologically confirmed metastatic breast cancer, age between 18 and 70 years, and assumed life expectancy of at least 12 weeks. Patients had to have received at least 1 prior systemic chemotherapy regimen for metastatic disease. Prior systemic adjuvant therapy (chemotherapy and/or hormonal therapy and/or local radiation therapy) was allowed. Radiation or other chemotherapy had to be terminated at least 3 weeks prior to entering the study. Previous treatment with either paclitaxel or docetaxel was not allowed. Patients were required to have two-dimensionally measurable disease. Indicator lesions had to be located outside of previously radiated areas. Patients with brain metastases were not eligible. Adequate general health status (WHO performance status ≥ 2; absence of active co-morbid illness such as uncontrolled infection, cardiopulmonary disease, uncontrolled diabetes mellitus) and laboratory parameters [absolute neutrophil count (ANC) $\geq 2000/\mu$l, platelet count $\geq 100\,000/\mu$l, hemoglobin level ≥ 10 g/dl, bilirubin level ≤ 1.5 mg/dl, creatinine concentration $\leq 1.5\times$ upper limit of normal) were required. Patients with pre-existing neuropathy of grade 1 or more were excluded. The study was approved by the Ethical Committee of our hospital and all patients gave written informed consent for their participation in the study.

Treatment plan

Docetaxel was administered at a dose of 40 mg/m^2 as an i.v. infusion for 30 min. Each 4-week cycle consisted of 3 weeks of treatment followed by a 1-week rest period. Patients were re-evaluated for response every 8 weeks. A maximum of 18 treatments was administered. Patients continued treatment until development of unacceptable toxicity or disease progression. All patients received standard premedication with oral dexamethasone 8 mg twice daily 1 day prior to application of docetaxel and 16 mg i.v. 30 min prior to infusion of the chemotherapeutic agent. At the physician's discretion, antiemetics such as metoclopramide or alizaprid were prescribed as needed.

Based on the WHO toxicity scale, patients underwent a weekly toxicity assessment. A complete blood count was performed weekly, whereas other laboratory parameters like creatinine and bilirubin levels, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were evaluated every other week. Treatment was postponed for 1–2 weeks on occurrence of an ANC $< 2000/\mu$l or a platelet count $< 80\,000/\mu$l or with any WHO toxicity grade ≥ 1 (with the exception of alopecia). In case of a treatment interruption during any given 3-week cycle, the dose of docetaxel was reduced to 35 mg/m^2 (dose level 1) or 30 mg/m^2 (dose level 2) in the subsequent 3-week cycle. Patients who were ineligible for treatment for 3 consecutive weeks were taken off protocol. For patients who developed severe neutropenia (absolute neutrophil count $\leq 500/\mu$l for more than 7 days) and/or febrile neutropenia and/or severe thrombocytopenia (platelet count $< 25\,000/\mu$l) necessitated further dose reduction in the next 3-week cycle. Dose re-escalation after dose reduction was not permitted.

Data collection

Drug administration, performance status, toxicity profile and adverse events were recorded after each administration of docetaxel. Toxicity was graded according to WHO criteria. Patients were evaluated for response every 8 weeks.

Response evaluation

All patients who received at least one dose of docetaxel were included in the toxicity analysis. All patients who received at least three doses of docetaxel were evaluable for response. Response was determined according to standard definitions. A complete response required the disappearance of all radiologically detectable disease for at least 4 weeks. A partial response required at least a 50% reduction in size of all measurable lesions, defined by the product of greatest length and maximum width, with no new lesions appearing. Stable disease was defined as a reduction of less than 50% or an increase of less than 25% in the size of existing lesions, with no new lesions appearing. Patients had progressive disease if any new lesion appeared or if any existing lesion increased in size by 25% or more. Duration of survival and time to progression were counted from the first day of docetaxel therapy. The overall survival curve was determined according to the Kaplan–Meier method.

Results

This single-institution, university-based phase II study was conducted between April 1997 and June 2001, and included a total of 20 patients.

Patient characteristics

The clinical characteristics of all patients are listed in Table 1. The median age was 57 years (range 28–80). One 80-year-old woman was treated, contrary to the inclusion criteria which allowed only patients ≤ 70 years. This patient was included in the intention-to-treat-analysis. The WHO performance status per the number of patients was 0 for six, 1 for 10 and 2 for four. All patients

Table 1 Patient characteristics

Characteristics	No. patients	Percent
No. of patients	20	
Age (years)		
median	57	
range	28–80	
Menopausal status		
premenopausal	6	36
postmenopausal	13	65
WHO performance status		
0	6	30
1	10	50
2	4	20
Measurable disease sites		
lung	5	25
liver	13	65
lymph nodes	5	25
skin	3	15
bone	14	70
No. disease sites		
1	3	15
2	11	55
>2	6	30
No. previous chemotherapies		
1	7	35
2	7	35
>2	6	30
Prior treatment		
chemotherapy	20	100
surgery	20	100
radiation	15	75
hormonal therapy	17	85
previous treatment with chemotherapy	20	100
previously treated with an anthracycline-containing regimen	18	90
Response to prior anthracyclines		
sensitive	10	55
resistant	5	28
unknown/adjuvant	3	17

received prior chemotherapy and most patients had previously received anthracycline-containing regimens in either an adjuvant or metastatic setting (90%). Thirteen patients (65%) were treated with at least two regimens prior to study entry (range 2–5). Seventeen patients (85%) had at least two or more metastatic sites. Sixteen patients (80%) had visceral metastases. Bone, lymph node and chest wall/breast were other common sites of metastatic disease.

A total of 204 docetaxel infusions were administered. The average number of treatments was 10.2 (median 9.5 cycles; range 1–18). The median dose was 40 mg/m^2/week for all patients. Three patients received a reduced dose in the first cycle (35, 30 and 20 mg/m^2) that was not reduced further during the treatment period. In three patients who started with the planned dose of 40 mg/m^2, a dose reduction to 35 mg/m^2 was necessary. In one patient this was due to prolonged neutropenia, and in the other two patients due to grade 2 and 3 diarrhea, respectively. Therefore, the mean dose administered for all patients was 37.5 mg/m^2. The median cumulative dose administered was 380 mg/m^2 (mean 400 mg/m^2). Three patients discontinued the study due to treatment-related toxicities (one patient due to severe neutropenia and two patients due to mucositis).

Efficacy

Of the 20 patients enrolled in this trial, 18 were assessed for response. Two patients were withdrawn from the protocol due to adverse events prior to the first evaluation for response: one patient developed severe grade 4 mucositis after having received four treatments and the other experienced severe grade 4 neutropenia after only one dose.

At the time of analysis, 17 patients (85%) had died and none remained on protocol. The clinical response data are summarized in Table 2 (intention-to-treat). Although no patients achieved complete response, five patients (25%) showed partial response and another six (30%) showed stable disease. Seven patients progressed during therapy (35%). Clinical response was seen at all measurable metastatic sites, including the lung and liver. Four of five patients reported partial response within the initial two courses of therapy (after 8 weeks) and one patient showed clinical response after the restaging at 16 weeks. All patients responding to docetaxel had previously received only one treatment regimen for metastatic disease.

The median response duration in patients with objective response was 4.3 months. The median time to progression was 8.8 months. One- and 2-year survival rates were 40 and 10%, respectively. The survival curve for all patients is shown in Figure 1.

Toxicity

All 20 patients were assessable for toxicity. Treatment was generally well tolerated. Table 3 lists the toxicities observed in patients enrolled in the study. Grade 3/4 toxicities were observed in five patients (25%). Myelosuppression was mild and occurred in only two patients. One patient each had grade 3 and grade 4 neutropenia. No other hematologic grade 3 or 4 toxicity was observed. Eight patients showed grade 1 or 2 anemia. Four patients suffered from mild thrombocytopenia and no cumulative hematological toxicity was seen.

Gastrointestinal side effects were relatively common but usually mild. One patient experienced grade 3 nausea and

Table 2 Efficacy of weekly docetaxel (intention-to treat)

	Patients ($n=20$)	
Response category	No.	%
Complete response	0	0
Partial response	5	25
Stable disease	6	30
Progressive disease	7	35
Not assessable	2	10

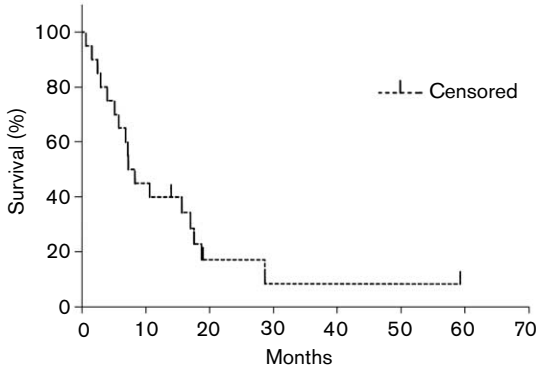
vomiting despite the use of antiemetics. The same patient experienced grade 3 diarrhea after the 12th dose of docetaxel. One patient developed severe mucositis after four doses of docetaxel and required parenteral nutrition. This patient was withdrawn from the study.

As most patients were pretreated with different chemotherapeutic drugs, most entered the study with severe pre-existing alopecia and it was not reasonable to evaluate the impact of docetaxel on this side effect.

Fluid retention was not common, occurring in only five patients. Grade 2 fluid retention (requiring administration of diuretics) developed in two patients (10%), one of whom suffered from pleural effusion. Fluid retention occurred after a median dose of 480 mg/m^2, but did not lead to discontinuation of treatment.

Six patients experienced mild skin or nail changes. All patients received pre-medication with dexamethasone and no hypersensitivity reactions were observed. One patient developed grade 3 infection requiring i.v. antibiotics and hospitalization. No major neurological toxicities were reported. Three patients experienced mild taste disturbances. No treatment-related deaths occurred.

Fig. 1



Kaplan–Meier curve of overall survival (n=20).

Discussion

This phase II trial showed the efficacy and manageable toxicity of weekly docetaxel at a dose of 40 mg/m^2 in 20 heavily treated patients with advanced, anthracycline-refractory breast cancer. The response rate of 25% achieved in this study was slightly lower than that observed in other similar studies and may be due to the substantial disease burden of the patients in this trial. Hainsworth *et al.* [17] observed an objective response in 13 of 41 elderly patients (36%) treated on a weekly basis. Burstein *et al.* [18] treated 29 women with docetaxel 40 mg/m^2 administered weekly for 6 out of 8 weeks and observed a 41% overall response rate (59% clinical activity rate considering patients with stable disease) with modest toxicity. It is important to remember that docetaxel was used as first-line metastatic therapy for 80% of the patient population in the latter trial, whereas in the present trial all patients had prior chemotherapy. In another recently published study by Stemmler *et al.* [19], an overall response rate of 34% in 35 patients was achieved with a weekly regimen of 35 mg/m^2. Aihara *et al.* [20] reported a 38% objective response rate using the same schedule as in our trial. Because of the considerably different subpopulations of patients selected in the different trials and due to the small number of patients included in our trial, a comparison of the efficacy with other regimens is difficult. The substantial disease burden and associated poor prognosis of the patients has to be considered when interpreting the lower response rates in the present trial. The entire study population had received prior chemotherapy, with 90%

Table 3 Highest degree of treatment-related toxicity observed

	Grade 2		Grade 3		Grade 4	
	n	%	*n*	%	*n*	%
Hematological						
neutropenia	4	20	1	5	1	5
thrombocytopenia	2	10	–	–	–	–
anemia	3	15	–	–	–	–
Non-hematological						
nausea/emesis	4	20	1	5	–	–
diarrhea	5	25	1	5	–	–
skin/nail changes	5	25	–	–	–	–
neurosensory	2	10	–	–	–	–
taste disturbance	2	10	–	–	–	–
edema/fluid retention	2	10	–	–	–	–
asthenia	2	10	–	–	–	–
infection	2	10	1	5	–	–
stomatitis/mucositis	–	–	1	5	1	5
hypersensitivity reaction	–	–	–	–	–	–

having received anthracycline-containing regimens. Two-thirds of the patients had been treated with at least two regimens prior to study entry and 80% of the women had visceral metastases.

In accordance with the results gained from other studies with weekly docetaxel, the efficacy observed in the present trial extended to all sites of metastatic disease, including the liver. Altogether, the reported response rates of weekly regimens are comparable to those obtained by every-3-weeks single-agent docetaxel with objective response rates ranging from 23 to 68% [21–23].

The major advantage of the weekly regimen was marked reduction of hematological toxicity, compared to the standard every-3-weeks regimen. Between 90 and 95% of the patients with advanced breast cancer developed grade 3 or 4 leukopenia and considerable non-hematologic grade 3/4 toxicities (sensory neuropathy 5–14%, nail changes 3–5%, stomatitis 5–20%) with a docetaxel regimen of 75–100 mg/m^2 every 3 weeks. Upto 27% of the patients developed grade 3 or 4 treatment-related infections [1,2,4–7,21,24–28]. Compared to the toxicities observed in these trials, previous phase I/II studies have indicated that the incidence of severe neutropenia (grade 3 and 4) was much lower with weekly docetaxel administration [18–20,29,30]. In the present study, only one case each of grade 3 and 4 neutropenia was observed.

The incidence of grade 3/4 non-hematologic toxicities compared favorably with the reported observations from other phase I/II studies with weekly docetaxel. Overall, grade 3/4 non-hematologic toxicity was observed in up to 18% of patients, including alopecia (10%), fatigue and asthenia (1%), skin and nail toxicity (1%), and mucositis (2%) [17,18,29,31]. In the present study, non-hematologic toxicities included skin and nail toxicity (25% grade 2), mild neurotoxicity (10% grade 2) as well as mild asthenia (10% grade 2). Gastrointestinal side effects were common, but usually mild. The incidence of alopecia was not assessed in this study, because of existing hair loss due to extensive pretreatment in a large proportion of patients at study entry. Reversible taste disturbances occurred in two patients (10%) and were also described by Aihara *et al.* [20] who reported a 22% incidence of grade 1 and 2 toxicities of that kind. Weekly docetaxel had a low emetogenic potential, usually not requiring prophylactic administration of 5-HT$_3$ antagonists.

Dexamethasone was administered at a dose of 2 × 8 mg the day before and another 16 mg at 30 min prior to the administration of docetaxel. This schedule was chosen to prevent or reduce docetaxel-related fluid retention and to avoid hypersensitivity reactions. Although conclusive data are still lacking, various recommendations for dexamethasone dosing range from 3 × 8 to 1 × 4 mg [18,30,32,33] and lower dosages may be adequate compared to those used in the present study. Despite the co-administration of dexamethasone, docetaxel-induced fluid retention was observed in five patients (20%), of whom only two required intervention with diuretics. No patient required toxicity-related treatment discontinuation.

In the present study treatment-related fatigue was only seen in two patients (10%). In contrast, fatigue resulted in premature withdrawal in nine out of 41 patients in a phase II trial for the treatment of elderly patients (mean age 74 years) in the Hainsworth study [17]. This may have been due to the younger age of our study population, because this toxicity is generally more common in elderly patients with advanced breast cancer. On the other hand, the once-a-week administration for 3 consecutive weeks followed by a 1-week rest period may account for the lower incidence of this toxicity in the present study compared to the 6-week regimen followed by 2 weeks without treatment used by Hainsworth [17].

Experiences in the treatment of metastatic breast cancer have also been gained with the weekly administration of paclitaxel. The activity observed in these studies seemed to be at least comparable to a 3-weekly schedule of paclitaxel. In 30 women receiving either first- or second-line therapy for metastatic breast cancer, Seidman *et al.* [11] reported a response rate of 53%. With a median weekly paclitaxel dose of 91 mg/m^2/week actually delivered, myelosuppression was uncommon and dose reductions were rarely required. Severe non-hematologic toxicity was also uncommon when weekly doses were kept below 100 mg/m^2. However, in contrast to the application of docetaxel, grade 1/2 peripheral neuropathy developed in 59% of patients and grade 1/2 arthralgia/myalgia was reported in 52%. Perez *et al.* [34] reported a response rate of 21.5% with an additional 41.8% of patients showing stable disease in a large phase II trial including 212 patients with metastatic breast cancer. Paclitaxel was administered on a weekly basis at a dose of 80 mg/m^2. Therapy was generally well tolerated, but a 9% incidence of grade 3 neurotoxicity was observed. It is difficult to compare the efficacy of weekly paclitaxel versus weekly docetaxel. However, high levels of efficacy have been reported with both drugs. Weekly paclitaxel seems to produce more peripheral neuropathy, arthralgias and myalgias than does weekly docetaxel. Fatigue appears to be more common with weekly docetaxel.

In conclusion, the weekly administration of docetaxel is an active regimen in metastatic breast cancer, associated with only mild to moderate toxicity, especially with respect to hematologic toxicity. Therefore, in elderly and/or heavily pretreated patients, where intensive chemotherapy, due to a reduction in bone marrow reserve, is no longer feasible, the weekly administration of

docetaxel offers advantages over the conventional commonly used every-3-weeks regimen. To determine whether weekly docetaxel demonstrates superiority in terms of response rate, survival or quality-of-life over the conventional every-3-weeks regimen, a randomized phase III trial is required. Furthermore, the high level of activity, associated with only minimal myelosuppression, seen with weekly docetaxel also provides attractive possibilities for the investigation of combination chemotherapy regimens with other cytotoxic drugs or novel biological agents. Preliminary data indicate that gemcitabine or vinorelbine may be safely used in combination with docetaxel and it is likely that keeping up the dose intensity of docetaxel is facilitated easier with weekly scheduling than with combination regimens incorporating the every-3-weeks schedule [35]. Recently reported weekly administration of docetaxel in combination with trastuzumab in patients with *Her2*-overexpressing metastatic breast cancer constitutes another highly interesting therapeutic approach warranting further evaluation [36].

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