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High Efficacy and Low Toxicity of Weekly Docetaxel Given as First-Line Treatment for Metastatic Breast Cancer

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Key Words
Docetaxel · Breast cancer, metastatic · Chemotherapy

Abstract
Background: Docetaxel is one of the most effective antitumor agents currently available for the treatment of metastatic breast cancer (MBC). This phase II multicenter study prospectively analyzed the efficacy and toxicity of docetaxel given on a weekly schedule as first-line treatment of metastatic breast cancer. ***Patients and Methods:*** All patients received docetaxel, 35 mg/m^2 weekly for 6 weeks, followed by 2 weeks of rest. Subsequent cycles (3 weeks of treatment, 2 weeks of rest) were given until a maximum of 5 cycles or disease progression. Premedication consisted of 8 mg dexamethasone intravenously 30 min prior to the infusion of docetaxel. ***Results:*** Fifty-four patients at a median age of 58 years with previously untreated MBC were included in the study. A median of 10 doses (median cumulative dose 339 mg/m^2) was administered (range: 2–18). The overall response rate was 48.1% (95% CI: 34–61%, intent-to-treat). Median survival was 15.8 months and median time to progression was 5.9 months (intent-to-treat). Hematological toxicity was mild with absence of neutropenia-related complications. Grade 3 neutropenia was observed in 3.7% of patients and grade 3 and 4 anemia was observed in 5.6 and 1.9% of patients, respectively. ***Conclusion:*** The weekly administration of docetaxel is highly efficient and safe as first-line treatment for MBC and may serve as an important treatment option specifically in elderly patients and patients with a reduced performance status.

Introduction

Docetaxel (Taxotere®, Aventis, Bad Soden, Germany) is one of the most effective antitumor agents currently available for the treatment of metastatic breast cancer (MBC). When compared with the gold standard doxorubicin, docetaxel showed a significantly superior response rate (47.8 vs. 33.3%, p = 0.008) and a trend towards a prolonged time to tumor progression (26 vs. 21 weeks) [1]. After failure of anthracycline-containing chemotherapy, single-agent docetaxel has demonstrated superior results when compared with mitomycin/vinblastine [response, time to progression (TTP), survival] or metho-

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trexate/5-fluorouracil (response, TTP) [2, 3], and has shown equivalent efficacy when compared with vinorelbine/5-fluorouracil (response, TTP, survival) [4].

The major rationale of a weekly schedule is the marked reduction of hematological toxicity [5–8]. When docetaxel is administered at a dose of 100 mg/m^2 every 3 weeks, 70–90% of patients develop grade 3/4 neutropenia. In previously reported phase II studies, severe (grade 3/4) hematological toxicity was uncommon at doses less than 40 mg/m^2 given on a weekly basis [5–8]. The response rate achieved in these studies for pretreated patients ranged from 25 up to 41% [5–8].

An additional rationale for weekly docetaxel might be an equivalent dose intensity of treatment compared with the 3-weekly administration of docetaxel at a standard dose of 100 mg/m^2. However, in pretreated and elderly patients, the 3-weekly dose of 100 mg/m^2 frequently needs to be adjusted to 75 mg/m^2 [9, 10]. Given the improved tolerability of the weekly schedule, an increase of dose intensity may be achieved specifically in these patients [5–8].

While numerous studies have evaluated the weekly application of docetaxel in pretreated patients, this is the first report to analyze the efficacy and toxicity of weekly docetaxel in first-line therapy of MBC.

Patients and Methods

Patient Selection

Fifty-four patients with MBC were recruited. None of the patients had received chemotherapy for metastatic disease. The treatment protocol was approved by the local ethics committee and all patients gave written informed consent before treatment was started.

Patients were required to have histologically proven MBC, bidimensionally measurable disease, a WHO performance status of 0–2, be aged between 18 and 70 years, and have an anticipated survival of at least 12 weeks. Cardiac, hepatic, renal and hematological function had to be adequate [leukocyte count $\geq 3.0 \times 10^9$/l; platelets $\geq 100 \times 10^9$/l; hemoglobin ≥ 8 g/dl; bilirubin $\leq 1.25 \times$ normal range; ALT:AST (alanine aminotransferase:aspartate aminotransferase) ratio $\leq 3 \times$ normal range; alkaline phosphatase $\leq 2.5 \times$ normal range]. Patients with only bone metastases were not eligible for the trial. Additional exclusion criteria were radiotherapy of more than 25% of marrow-containing bone, brain metastases, previous neuropathy $\geq$ grade 2, and a history of a second malignancy other than resected basal cell and/or squamous cell carcinoma of the skin.

Treatment Regimen

Patients were treated with a weekly dose of 35 mg/m^2 docetaxel for 6 weeks, followed by 2 weeks of rest. Further treatment cycles were performed with a modified schedule, where docetaxel was administered on days 1, 8 and 15 every 29 days (cycle 2 started on day 50). Docetaxel (35 mg/m^2 in 100 ml 0.9% NaCl) was given by intravenous (i.v.) infusion over 30 min. Premedication consisted of 8 mg dexamethasone given i.v. 30 min before the start of docetaxel infusion.

Treatment was continued until either progression of disease, demonstration of severe side effects, or up to a maximum of 18 single doses of docetaxel (5 cycles).

In case of myelosuppression (leukocyte count $\leq 3{,}000/\mu$l, platelet count $\leq 100{,}000/\mu$l) on the day of planned treatment, further drug administration was postponed for 1 week until bone marrow recovery occurred. A full dose of docetaxel was administered if the blood counts had risen to leukocytes $\geq 3{,}000/\mu$l and platelets $\geq 100{,}000/\mu$l. Dose reductions for toxicity were 30 mg/m^2 (level –1) and 25 mg/m^2 (level –2). The dose was reduced by one level for nonhematological toxicity $\geq$ grade 3 (excluding alopecia and nausea/vomiting) or hematological toxicity grade 3 or 4 complicated by fever or infection or both. There was a maximum of two dose reductions per patient.

Data Collection

Drug administration, performance status and toxicity or adverse events were recorded after every cycle of docetaxel treatment. Weekly blood counts were performed. Febrile neutropenia was defined as fever ($\geq 38°$C) with grade 4 neutropenia requiring i.v. antibiotics and/or hospitalization without documented infection. Fluid retention included peripheral edema and/or pleural and pericardial effusions.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria [11]. Imaging studies using ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) were performed after every two cycles of docetaxel treatment.

Response Evaluation

In all patients, tumors were measured by physical examination, imaging procedures such as CT or MRI within 14 days prior to entry into the study and subsequently after every two cycles of treatment. Standard evaluation by history, physical examination and routine laboratory tests (including complete blood cell count, chemistry profile and electrolyte determination) was performed before each treatment.

Patient response was assessed by standard WHO criteria, as follows complete response (CR) was defined as the disappearance of all known disease, as determined by two observations not less than 4 weeks apart, while partial response (PR) was defined as a decrease by at least 50% of the sum of the products of the largest perpendicular diameters of all measurable lesions, as determined by two observations not less than 4 weeks apart. Stable disease (SD), lasting for at least 6 weeks from the start of study (i.e. first drug administration), was defined as <50% decrease and <25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions. Progressive disease (PD) was a >25% increase in the size of at least one bidimensionally or unidimensionally measurable lesion, or the appearance of a new lesion. The occurrence of pleural effusion was considered to be a sign of progression if it could be substantiated by positive cytology.

Survival and TTP

TTP was determined by the interval between the initiation of therapy and the first date when disease progression was objectively documented. Overall survival was measured from the date of treatment start to the date of death from any cause. All patients were included for the analysis of TTP and survival (intent-to-treat).

Statistical Methods

The primary study end point was response rate. Probability of survival and time to progression were estimated by Kaplan-Meier analysis, and confidence intervals for response rates were calculated using methods for exact binominal confidence intervals [12, 13].

Results

Patient Characteristics

Patient characteristics are presented in table 1.

Efficacy

In an intent-to-treat analysis 6 CR (11.1%), 20 PR (37.0%), 15 SD (27.8%) and 10 PD (18.5%) were observed. Three patients (5.6%) were not evaluable. The overall response rate was 48.1% (95% CI: 34–61%). Among 41 patients who had received adjuvant chemotherapy, there were 5 CR (12.2%), 16 PR (39.0%), 10 SD (24.4%) and 7 PD (17.1%). Three patients (7.3%) were not evaluable. The overall response rate in this subgroup was 51.2% (95% CI: 35–67%). The clinical benefit rate, defined as patients who achieved a CR or PR and patients who achieved a stabilization of the disease (CR + PR + SD), amounts to 75.9% (95% CI: 64–88%).

The response data are presented in detail in table 2.

Survival data were available for all patients with a median follow-up period of 16.2 months. The median TTP was 5.9 months and the median overall survival amounts to 15.8 months (fig. 1, 2).

Table 1. Patient characteristics

Characteristic	Patients
Patients	54
Age, years	
Median	58
Range	37–80
≥65 years	21
WHO performance status	
Median	1
0	18
1	22
2	14
Estrogen receptor status	
Positive	26
Negative	24
Unknown	4
Measurable disease sites	
Lung	10
Liver	28
Lymph nodes	15
Skin	4
Skeletal	16
Number of disease sites per patient	
1	21
2	23
≥3	10
Prior treatment	
Adjuvant chemotherapy	41
Adjuvant chemotherapy (anthracyclines)	26
Adjuvant hormonal therapy	28
Radiation	28
Surgery	49
Biopsy only (initially metastatic disease)	5

Table 2. Efficacy (intent-to-treat; n = 54)

	Total, n	PR, n	SD, n	PD, n	Not evaluable, n	OR	
						%	95% CI
All	54	20	15	10	3	48.1	34–61
Adjuvant chemotherapy[1]	41	16	10	7	3	51.2	35–67
Adjuvant chemotherapy including anthracyclines[1]	26	11	4	6	1	57.7	37–78

[1] Percentage values are calculated relative to size of evaluable patients of subgroup.

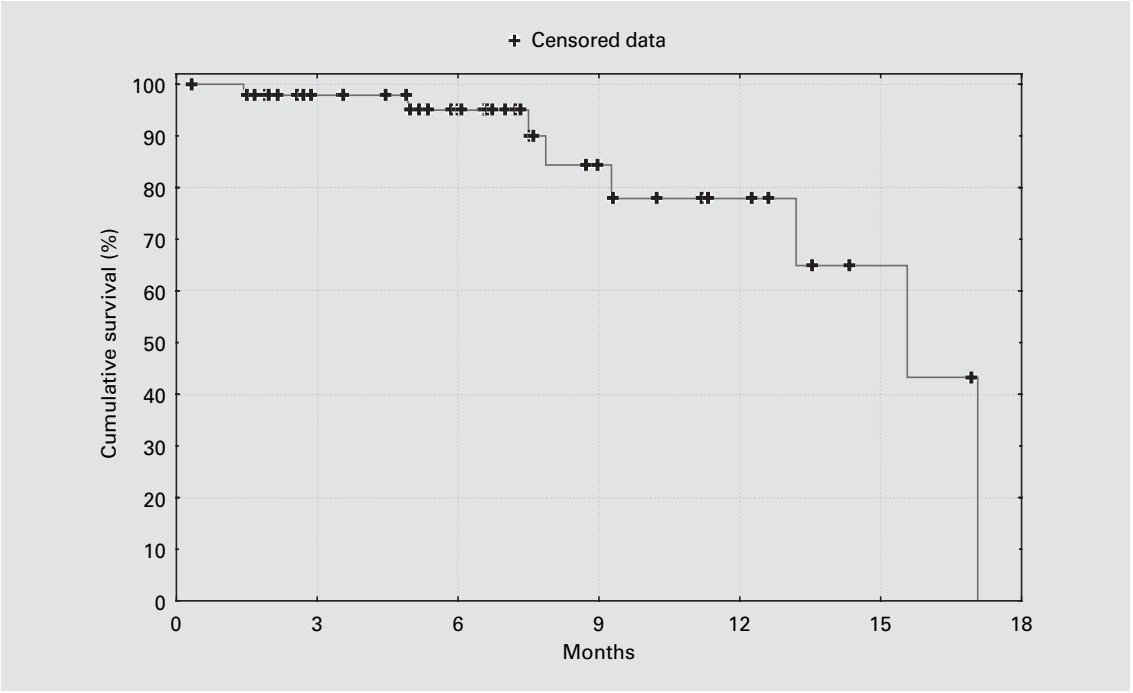

Fig. 1. Survival (intent-to-treat; n = 54), median 15.8 months (range 0.3–17.1 months).

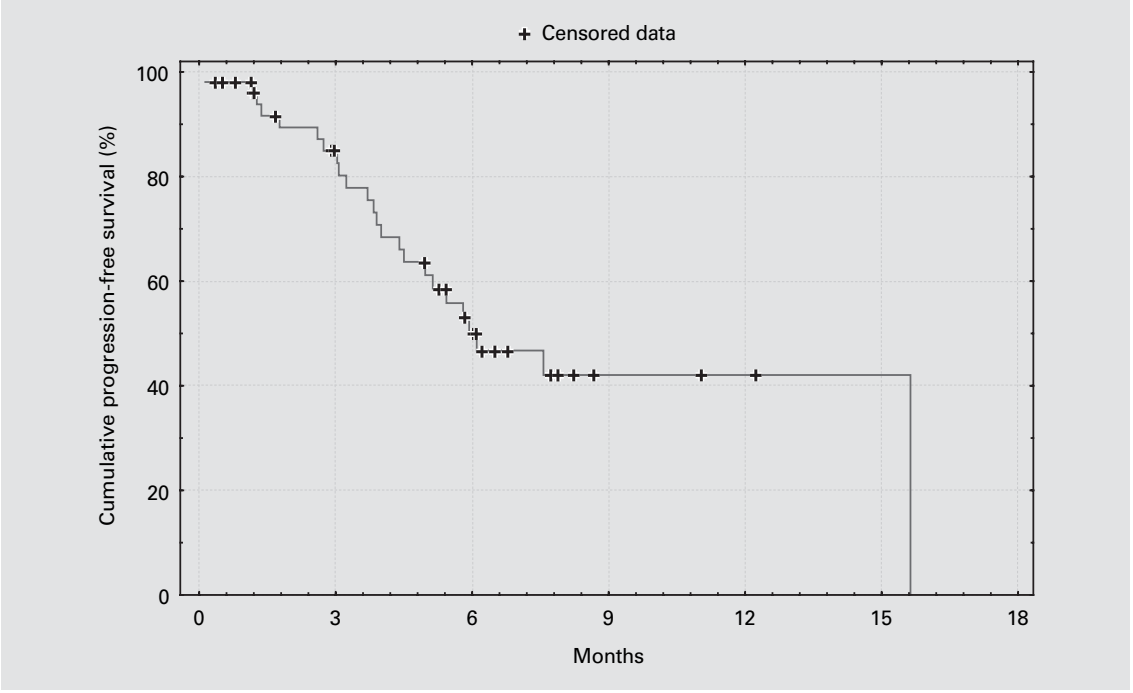

Fig. 2. TTP (intent-to-treat; n = 54), median 5.9 months (range 0.1–15.6 months).

Table 3. Toxicity profile of weekly administered docetaxel (per patient analysis, n = 54)

Toxicity	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %
Hematological toxicity				
Neutropenia	18.5 (12.1 vs. 9.5)	18.5 (12.1 vs. 9.5)	3.7 (6.1 vs. 0)	–
Febrile neutropenia	–	–	–	–
Anemia	25.9 (24.2 vs. 28.6)	13 (12.1 vs. 14.3)	5.6 (6.1 vs. 4.8)	1.9 (3.0 vs. 0)
Thrombocytopenia	5.6 (6.1 vs. 4.8)	3.7 (6.1 vs. 0)	1.9 (3.0 vs. 0)	–
Nonhematological toxicity				
Alopecia (grade 0–2)	16.7 (18.2 vs. 14.3)	40.1 (45.0 vs. 33.3)	–	–
Asthenia	7.4 (6.1 vs. 9.5)	5.6 (3.0 vs. 9.5)	5.6 (9.1 vs. 0)	–
Conjunctivitis/lacrimation	5.6 (3.0 vs. 9.5)	5.6 (6.1 vs. 4.8)	–	–
Diarrhea	9.3 (12.1 vs. 4.8)	3.7 (3.0 vs. 4.8)	3.7 (3.0 vs. 4.8)	–
Fever	3.7 (3.0 vs. 4.8)	1.9 (3.0 vs. 0)	–	–
Fluid retention/edema/effusions	–	13.0 (21.2 vs. 0)[a]	1.9 (3.0 vs. 0)[b]	–
Infection (not neutropenia-related)	5.6 (6.1 vs. 4.8)	–	3.7 (6.1 vs. 0)	–
Mucositis	16.7 (18.2 vs. 14.3)	–	3.7 (0 vs. 9.5)	–
Nail disorders	5.6 (3.0 vs. 9.5)	5.6 (6.1 vs. 4.8)	1.9 (3.0 vs. 0)	–
Nausea/vomiting	18.5 (12.1 vs. 28.6)	3.7 (3.0 vs. 4.8)	3.7 (6.1 vs. 0)	–
Neurotoxicity	14.8 (24.2 vs. 0)	1.9 (3.0 vs. 0)	–	–
Nose bleeding	7.4 (9.1 vs. 4.8)	–	–	–
Constipation	3.7 (3.0 vs. 4.8)	–	–	–
Pain (cancer-related)	16.7 (21.2 vs. 9.5)	7.4 (9.1 vs. 4.8)	7.4 (9.1 vs. 4.8)	–
Taste disturbance	3.7 (6.1 vs. 0)	–	–	–

Values in parentheses represent toxicity profile of younger patients (<65 years; n = 33) vs. elderly patients (≥65 years; n = 21); percentage values are calculated relative to the size of patients of subgroup.

[a] Edema: n = 7.

[b] Cytological positive pleural effusion in 1 patient.

Table 4. Toxicity profile of weekly administered docetaxel (653 single doses)

	Single doses	
	n	%
Dose reduction		
Dose level –1 (30 mg/m^2, weekly)	20	3.1
Dose level –2 (25 mg/m^2, weekly)	7	1.1
Delayed doses		
Total	55	8.4
Due to cytopenia	41	6.3
For other reasons	14	2.1

Toxicity

All investigated hematological and nonhematological toxicities are listed in table 3. Only 3.7% of patients experienced severe neutropenia (grade 3) and no febrile neutropenia was observed. None of the patients required hematological growth factor support. Mild anemia was common (grade 1 and 2: 25.9 and 13% of patients), but severe anemia was rarely noted including grade 3 and 4 anemia in 5.6 and 1.9% of patients. Severe thrombocytopenia was uncommon and was observed in only 1.9% of patients (grade 3).

Except fluid retention symptoms (grade 2) and neurotoxicity (grade 1) there were no significant differences regarding the toxicity profile in younger patients (<65 years) versus elderly patients (age ≥65 years).

A dose reduction of one dose level (30 mg/m^2) was necessary in 3.1% of all administered doses (n = 653), while a second reduction (25 mg/m^2) was required in only 1.1%. Delayed applications of single doses were necessary in 8.4% (table 4).

Discussion

Docetaxel has shown high efficacy in first-line treatment of MBC yielding response rates up to 54% (95% CI: 37–71%) and 67.7% (95% CI: 49–83%) when adminis-

Table 5. Comparative analysis of hematological and nonhematological toxicity

	Grade 3/4 toxicity			
	weekly regimen of docetaxel 35 mg/m^2	3-weekly regimen of docetaxel 100 mg/m^2		
	this trial	Chan et al. [1]	Nabholtz et al. [2]	Sjöström et al. [3]
Median cumulative dose, mg/m^2	339	679	564	570
Hematological, % of patients				
Neutropenia	3.7	93.5	93.1	77[a]
Anemia	7.5	4.4	n.a.	2
Thrombopenia	1.9	1.3	4.1	3
Febrile neutropenia	0	5.7	9	n.a.
Nonhematological, % of patients				
Alopecia (grade 2)	40.1	n.a.	n.a.	74
Asthenia	5.6	14.5	16	12
Conjunctivitis/lacrimation	–	n.a.	n.a.	–
Diarrhea	3.7	10.7	7.5	10
Fluid retention overall	1.9[b]	6.3[b]	n.a.	3
Infection	3.7	2.5	11	26[c]
Mucositis/stomatitis	3.7	5	9	9
Nausea/vomiting	3.7	3.1	4.5/2.5	6
Neurotoxicity	–	8[d]	5[e]	5
Skin/nail	0/1.9	1.9/n.a.	4/2.5	2/5

n.a. = Not available.
[a] Leukopenia; [b] edema and pleural effusion; [c] includes febrile infection; [d] neurosensory plus neuromotor; [e] neurosensory.

tered at a dose of 100 mg/m^2 every 3 weeks [14–16]. In pretreated patients, docetaxel treatment resulted in response rates of 48–55% [1, 9, 10, 17]. When docetaxel was given after anthracycline failure, response rates of 30–42% were achieved in two randomized trials [2, 3].

Although the 3-weekly regimen has proven a high level of antitumor activity, it is accompanied by considerable hematological toxicity. Grades 3–4 neutropenia was observed in up to 97% of patients [1, 9, 10, 17]. Regarding these side effects, a dose reduction of docetaxel was recommended specifically in elderly and unfit patients [9, 10]. When docetaxel doses were reduced to 60–75 mg/m^2 every 3 weeks, overall response rates of 33–35% were reported in pretreated patients with a moderate reduction of hematological side effects [10, 18, 19].

The administration of docetaxel at a weekly dose of 35–40 mg/m^2 combines the advantages of a preserved dose intensity with a markedly reduced hematological toxicity relative to standard 3-weekly regimens [5–8]. The response rate achieved in phase II studies for pretreated patients ranged from 25 up to 41% [5–8]. But until now, there are no data of weekly docetaxel given as first-line treatment for MBC. In this trial of previously untreated patients for metastatic disease, docetaxel induced an overall response rate of 48.1% (95% CI: 34–61%). The clinical benefit rate (CR + PR + SD) amounts to 75.9% (95% CI: 64–88%). A disease control was achieved in a limited time of cytotoxic treatment (median doses/patient = 10), supporting the high efficacy of single-agent weekly docetaxel. In this trial, the median TTP was 5.9 months (range: 0.1–15.6), which was within the range of that reported for every three-week regimen (3–9 months) [14, 16, 17].

The standard regimen is accompanied by severe neutropenia in up to 97% leading to infections (including febrile neutropenia) in up to 26% of the patients. This potentially life-threatening toxicity may, however, be prevented by the application of docetaxel at weekly doses below 40 mg/m^2 [5–8]. In fact, grade 3 and 4 hematological toxicity was reduced to 5% (grade 3) and 1% (grade 4) of patients [5–8]. In the present study, grade 3 and 4 neutropenia was observed in 3.7 and 0% of patients. Neu-

tropenic fever was not observed and none of the patients required G-CSF support. The low number of dose reductions [dose level –1 (30 mg/m^2): 3.1%; dose level –2 (25 mg/m^2): 1.1%] and treatment delays (8.4% of cycles) also reflects the low hematological toxicity of this regimen.

Despite the marked difference in hematological toxicity, nonhematological side effects were not significantly different between the weekly and the 3-weekly schedule (table 5). The incidence of severe nonhematological toxicity was low.

Asthenia and fatigue were reported as the most common reason for dose reduction. In this study, grade 3 asthenia was reported only in 5.6% of patients. The lower weekly dose of 35 mg/m^2 chosen in this study compared to the dose of 40 mg/m^2 used by Burstein et al. [5] may explain the lower incidence of severe asthenia observed in this trial (table 5).

Conjunctivitis and lacrimation are also known sequelae of docetaxel treatment [20]. The incidence of 11.2% (grade 1 and 2 toxicity) in the present study is in good agreement with a previous report stating a 12% overall incidence in the 3-weekly regimen [3]. Also mucositis, stomatitis, and nausea occurred at similar frequencies compared to the 3-weekly regimen.

Due to the low emetogenic potential of weekly docetaxel, 5-HT$_3$ antagonists were not required on a routine basis.

Severe fluid retention symptoms occurred in 1.9% of patients (grade 3), which is in the range reported by other authors [1, 3].

To determine the toxicity profile of weekly docetaxel in younger (<65 years) and elderly patients (≥65 years) the incidence of side effects was presented for the whole study population and for each group separately (table 3). Except fluid retention symptoms and neurotoxicity, there were no significant differences regarding the toxicity profile in younger and elderly patients, which supports the feasibility of weekly docetaxel even in the elderly patients. The significantly increased incidence of fluid retention symptoms (grade 2) and neurotoxicity (grade 1) in the younger patients may be explained by the low number of patients in these subgroups.

This is the first trial that evaluated a weekly administration of docetaxel given as first-line treatment for MBC. The weekly schedule induced a high level of activity and was well tolerated. Compared to a standard 3-weekly regimen, the weekly regimen greatly reduced hematological toxicity. Specifically in elderly patients, where intensive chemotherapy is not feasible, a weekly administration of docetaxel may serve as an important treatment option. The limited duration of cytotoxic treatment in this trial (median 10 weeks) appears to be another argument for this schedule. Moreover, the short duration of drug administration (30 min) clearly supports the use of this regimen on an outpatient basis. Since conclusive data are missing, a randomized phase III study has been started to prospectively evaluate efficacy and safety of a 3-week versus a weekly schedule in elderly patients.

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