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Improvement of Safety Profile of Docetaxel by Weekly Administration in Patients with Metastatic Breast Cancer

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Key Words
Breast cancer, metastatic · Docetaxel: weekly administration; safety profile

Summary
Background: This is a retrospective cohort study on the safety and efficacy profiles of weekly docetaxel at varying doses in patients with pretreated metastatic breast cancer. **Patients and Methods:** Twenty-five anthracycline-pretreated patients received docetaxel administered on a weekly basis, as a one-hour infusion, at various dosage levels (25, 30, 35, 40 mg/m^2) depending on their baseline Karnofsky index. Each 8-week cycle consisted of 6 weeks of drug infusion, followed by a 2-week rest period. **Results:** Of the 25 patients investigated, none achieved complete response (CR), while 9 patients showed partial response (PR), which corresponds to an overall response rate of 36%. Five patients (20%) maintained stable disease (SD), whereas 11 patients (44%) suffered tumor progression (PD) during treatment. Clinical response (defined as PR+SD) was achieved in 14 patients (56%). Median time to progression was 231 days (95% CI, 187–275). The baseline Karnofsky index was 87% ± 9% (range: 70–100). Patients pretreated with anthracyclines only tended to have a better response than anthracycline/paclitaxel-pretreated patients (n = 6, p = 0.054). Higher dosages were associated with neurotoxicity, skin/nail toxicity, leukopenia, nausea/vomiting, fatigue/asthenia, peripheral edema, but not with diarrhea and alopecia. The cumulative dose per patient was largest for a weekly docetaxel dosage of 35 mg/m^2 and almost as large for 30 mg/m^2. **Conclusion:** Balancing toxicity vs. efficacy/cumulative dosage delivered, our results support weekly administration of docetaxel at dosages of 30–35 mg/m^2 in metastatic breast cancer. Response in patients pretreated with anthracyclines and taxanes may be poorer than in those pretreated with anthracyclines only.

Schlüsselwörter
Mammakarzinom, metastasiertes · Docetaxel: wöchentliche Gabe; Nebenwirkungsprofil

Zusammenfassung
Hintergrund: Bei der vorliegenden Studie handelt es sich um eine retrospektive Kohortenstudie zu Wirksamkeit und Nebenwirkungsprofil von wöchentlichem Docetaxel in Abhängigkeit von der Dosierung bei Patientinnen mit vorbehandeltem metastasiertem Mammakarzinom. **Patientinnen und Methoden:** 25 mit Anthrazyklinen vorbehandelte Patientinnen erhielten wöchentlich Docetaxel als einstündige Infusion in unterschiedlichen Dosierungen (25, 30, 35, 40 mg/m^2), die ihrem anfänglichen Karnofsky-Index gemäß zugeordnet wurden. Jeder 8-wöchige Zyklus setzte sich aus 6 Wochen Chemotherapieinfusion und anschließend 2 Wochen Pause zusammen. **Ergebnisse:** Bei keiner der 25 untersuchten Patientinnen wurde eine Vollremission (CR) erreicht, während es bei 9 Patientinnen zu einer partiellen Remission (PR) kam, was einer Gesamtansprechrate von 36% entspricht. Während der Behandlung zeigten 5 Patientinnen (20%) einen stabilen Verlauf (SD), 11 Patientinnen (44%) erlitten eine Progression (PD). Damit konnte bei 14 Patientinnen (56%) ein klinisches Ansprechen (definiert als PR+SD) erreicht werden. Die mediane progressionsfreie Zeit betrug 231 Tage (95%-KI, 187–275). Der anfängliche Karnofsky-Index betrug 87% ± 9% (Bereich: 70–100). In der Gruppe der mit Anthrazyklinen bzw. Paclitaxel vorbehandelten Patientinnen (n = 6) wurde keine PR festgestellt, das Ansprechen war schlechter (p = 0,054) als in der nur mit Anthrazyklinen vorbehandelten Gruppe. Bei Erhöhung der Dosierung nahmen Neurotoxizität, Haut- und Nagelreaktionen, Leukopenie, Übelkeit/Erbrechen, Fatigue/Asthenie und peripheres Ödem zu, jedoch nicht Diarrhö bzw. Haarverlust. Im Durchschnitt war die kumulative Dosis pro Patientin bei einer wöchentlichen Docetaxeldosis von 35 mg/m^2 am höchsten, und fast so hoch bei 30 mg/m^2 Docetaxel. **Schlussfolgerung:** Unter Abwägung der Toxizität gegenüber der Wirksamkeit bzw. der kumulativen Dosis sprechen die Ergebnisse für eine wöchentliche Chemotherapie mit Docetaxel in der Dosierung von 30–35 mg/m^2 beim metastasierten Mammakarzinom. Bei Patientinnen, die nur mit Anthrazyklinen behandelt wurden, ist ein besseres Ansprechen zu erwarten als in der Gruppe der mit Taxanen und Anthrazyklinen vorbehandelten Patientinnen.

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Introduction

Despite advances in systemic therapy, metastatic breast cancer (MBC) is still regarded as an incurable disease with a median survival time of approximately two years after confirmed metastases [1]. The situation is especially difficult for patients with progressive disease despite prior treatment with anthracycline-containing chemotherapy.

Among the recently developed new agents for adjuvant therapy, the taxanes seem to represent the most active drugs in this setting. Docetaxel (Taxotere®, Sanofi-Aventis, Berlin, Germany) was introduced in 1996 and is most often given at a standard dose of 75 to 100 mg/m^2 as a one-hour intravenous infusion every 21 days. It has proven to be highly active even in MBC patients classified as anthracycline-resistant. Phase II studies of docetaxel in anthracycline-pretreated patients yielded response rates of 53–57% [2–5]. Median time to progression (TTP) was 4.3 months and median survival time 10.6 months [6, 7].

However, the high activity of docetaxel is associated with substantial myelosuppression, which is dose- but not schedule-dependent [8]. In most published studies, the incidence of grade 3 or 4 neutropenia ranged from 90% to 95% with docetaxel administered at the standard dose of 100 mg/m^2 every 3 weeks [5, 9]. Other frequently observed nonhematologic side effects include fatigue, skin toxicity, and peripheral edema [10, 11].

Various phase I studies have suggested that a weekly dosage schedule ranging from 30 to 45 mg/m^2/week might improve the toxicity profile of docetaxel while maintaining its clinical activity [12]. Phase II studies indicated a dose of 36 mg/m^2 weekly for 6 consecutive weeks followed by a 2-week rest [12–15]. The goal of the present study was to test the hypothesis of improved toxicity profile and verify efficacy when docetaxel is administered on a weekly schedule in the range of 25–40 mg/m^2/week in women with progressing MBC after previous chemotherapy. As it turned out, it was also possible to observe and quantify the relationship between dosage and severity of side effects.

Material and Methods

Patients

In the present observational study, 25 consecutive women with histologically confirmed MBC treated between 1999 and 2002 are retrospectively evaluated. The selection and eligibility criteria were as follows: anthracycline-based prior treatment, age 18–75 years, World Health Organization (WHO) performance status (PS) of 0–2, estimated life expectancy of at least 3 months, bidimensionally measurable lesions, adequate bone marrow (leukocyte count ≥ 4,000/µl, granulocyte count ≥ 1,500/µl, platelet count ≥ 100,000/µl), hepatic (serum bilirubin ≤ 1.25 mg/dl and aspartate aminotransferase, AST ≤ two times the upper limit of normal values), and renal (serum creatinine < 1.5 mg/dl) functions, as well as normal cardiac function. Treatment was administered in accordance with hospital and national guidelines in effect at the time: Indication for docetaxel chemotherapy was proven progression. Pregnant patients and those with symptomatic peripheral neuropathy of any origin (WHO grade ≥ 2) or evidence of brain metastases were excluded.

Table 1. Patient characteristics

	n
Total number of patients	25
Median age, years (range: 46–74)	61.4
Estrogen receptor status	
Negative	11
Positive	14
Baseline Karnofsky index, %	
70	2
80	9
90	8
100	6
Number of metastatic sites involved	
1	9
2	7
3	7
≥4	2
Location of metastases	
Bone	16
Lymph node	6
Liver	14
Lung/pleura	10
Chest wall/breast	4
Skin	3
Number of prior chemotherapy regimens	
0	0
1	16
2	7
3	1
≥4	1
Previous paclitaxel treatment	6

Evaluation

Prior to receiving docetaxel, each patient was evaluated by a complete blood cell count with differential serum chemistry for hepatic and renal function. In addition, the patient's complete medical history was recorded and a physical examination, chest x-ray, abdominal computed tomographic scan or ultrasound, as well as a bone scan were performed. The Karnofsky index was determined.

Weekly examinations included complete blood counts, serum chemistries, and physical examinations. At a leukocyte count ≥ 2,000/µl and a platelet count of ≥ 75,000/µl, a full dose of docetaxel related to the Karnofsky index (see 'Treatment') was administered. If any count was below these limits, docetaxel treatment was interrupted and the blood counts were reevaluated the following week. Treatment proceeded as scheduled if the blood counts increased (leukocytes ≥ 2,000/µl and platelets ≥ 100,000/µl). A 20% dose reduction of the previous dose was intended for patients who experienced grade 4 leukopenia and/or grade 4 thrombocytopenia, which either lasted for more than 7 days or was accompanied by fever (>38.5 °C) and thus required intravenous antibiotics. Dose reescalation after dose reduction was not permitted.

Sites of measurable breast cancer metastases were assessed after 6 infusions by appropriate imaging techniques (MRI, CT). Response to treatment was evaluated according to WHO criteria (Miller 1981). Complete response (CR) required the total disappearance of clinically and radiologically detectable disease for at least 4 weeks. Partial response (PR) was defined as at least a 50% reduction in the size of all measurable lesions, assessed by multiplying greatest length and maximum width, with no new

Table 2. Dependence of hematologic toxicity (WHO grade 2/3/4) and response on docetaxel dosage

Docetaxel dose, mg/m²/week	n	Number of infusions	Total medication per patient, mg/m²	Leukopenia grade			Response					
				2	3	4	PR		SD		PD	
							n	%	n	%	n	%
25	6	61	254	4	0	0	1	17	1	17	4	67
30	8	80	300	2	0	0	4	50	1	13	3	38
35	5	46	322	2	1	0	2	40	1	20	2	40
40	6	31	207	1	4	0	2	33	2	33	2	33
Cohort	25	218	271	9	5	0	9	36	5	20	11	44

Table 3. Dependence of nonhematologic toxicity (WHO grade 2/3) on docetaxel dosage.

	Docetaxel dosage, mg/m²							
	25		30		35		40	
Toxicity grade:	2	3	2	3	2	3	2	3
Nausea/vomiting	2	0	2	0	2	1	3	2
Fatigue/asthenia	1	0	1	1	2	1	2	2
Skin/nail toxicity	0	0	0	0	1	1	1	4
Peripheral edema	0	0	0	0	1	1	1	2
Diarrhea	0	0	0	1	1	0	1	1
Neurotoxicity	0	0	0	0	1	1	1	2
Alopecia	0		1		1		2	

lesions appearing. Stable disease (SD) was defined as a reduction of less than 50% or an increase of less than 25% in the size of lesions, with no new lesions appearing. Patients were considered having progressive disease (PD) if any new lesions appeared or if the size of existing ones increased by 25% or more. Response was evaluated regularly at 3-month intervals.

Treatment

Docetaxel was administered weekly as a one-hour infusion. Each 8-week cycle consisted of 6 weekly infusions, followed by a 2-week treatment break. Of the 25 patients, 6 received 25 mg/m², 8 received 30 mg/m², 5 received 35 mg/m², and 6 received 40 mg/m² docetaxel. The weekly dose of docetaxel was calculated according to the Karnofsky index at baseline (≥ 70% < 90%: 25–30 mg/m², ≥ 90%: 35–40 mg/m²). No patient received more than 18 docetaxel doses (3 cycles of 8 weeks). Patients were premedicated with dexamethasone 8 mg as a short infusion given one hour prior to docetaxel. Antiemetics, such as ondansetrone were prescribed as required by the patients. Hematologic and nonhematologic toxicity were evaluated weekly, too, and classified according to WHO criteria. Patients were to be taken off protocol for any grade 4 nonhematologic toxicity. In order to assess the efficacy of this treatment, a reevaluation of the metastatic status was performed during the 2 weeks of rest period. Patients with PD were scheduled for a different chemotherapy or hormone therapy regimen. Patients with CR and PR or SD continued treatment as many cycles as possible to completion unless toxicity was no longer tolerable. If necessary, patients received granulocyte colony-stimulating factor.

Statistical Analysis

Response duration was evaluated for all patients achieving objective response (CR or PR). Median response duration was estimated by the Kaplan-Meier (product limit) method. TTP was defined as the time interval between initial docetaxel administration and relapse, documented by growth of lesions. Overall survival (OS) was defined as the time span from treatment start until death by any cause, calculated by the Kaplan-Meier method.

The p values for associations, such as those between dosages and toxicities, were computed according to Fisher's exact test unless otherwise stated. Statistical analysis was performed using the SPSS statistical package (SPSS Inc., Chicago, IL, USA) and by Microsoft Excel.

Results

Patients and Treatment

All 25 patients in this study were included in evaluation of toxicity and response. The entire patient population was pretreated with anthracyclines in the metastatic setting. None of the patients received trastuzumab. Patient characteristics are shown in table 1. Most patients had disease with multiple metastatic sites and visceral involvement. As a consequence of the inclusion criteria, the baseline Karnofsky index ranged from 70 to 100% (mean 87, standard deviation 9).

The relation between initial dosage category, number of docetaxel infusions, and cumulative dose is shown in table 2 (total of 218 infusions given on a weekly schedule). A median of 9 infusions in the range of 2 to 18 over a median time of 68.8 days (range: 14–158) were administered according to the protocol. There was no evidence of significant age-related differences in response within each dosage level. The median cumulative dose administered was 271 mg/m² (range: 75–540). A total of 3 patients received a dose reduction from 40 mg/m² to 30 mg/m². Two patients required a dose adaptation due to

Table 4. Significant dosage-dependent toxicities (one-sided p values according to Fisher's exact test)

Effect	Dosage categories[1]	Classification of toxicity[2]	p value
Nausea/vomiting	25–30 vs. 35–40	present vs. absent	0.047
Fatigue/asthenia	25–30 vs. 35–40	present vs. absent	0.049
Skin/nail toxicity	25, 30, 35, 40	present vs. absent	0.006
Skin/nail toxicity	25, 30, 35, 40	present (3) present (2) absent	0.001
Peripheral edema	25–30 vs. 35–40	present vs. absent	0.009
Diarrhea	25–30 vs. 35–40	present vs. absent	n.s.
Neurotoxicity	25–30 vs. 35–40	present vs. absent	0.009
Alopecia	25–30 vs. 35–40	present vs. absent	n.s.
Leukopenia	25, 30, 35, 40	present (3) present (2) absent	0.042
Leukopenia	25–30 vs. 35–40	present (3) vs. 2 or absent	0.009

[1]Docetaxel in mg/m^2.
[2]Toxicity grade in parentheses.

fatigue, and one patient needed a dose reduction due to neurotoxicity.

Toxicity

Weekly docetaxel was generally well tolerated. There was no grade 4 toxicity of any type at any of the scheduled dosage levels. Myelosuppression was mild. Only 5 (14%) patients suffered grade 3 leukopenia (4 patients at 40 mg/m^2 docetaxel, one at 35 mg/m^2). One patient in the 40 mg/m^2 group required growth factor support because of leukopenia (< 1.5 × 10^9/l) (table 2).

Skin and nail changes as well as nausea, vomiting, and alopecia were the most common nonhematologic treatment-related toxicities, occurring mainly at the highest dosage level (table 3). In addition, peripheral neuropathy, fatigue, and asthenia, occurred most frequently after treatment with docetaxel at 40 mg/m^2. Two patients (14%) developed peripheral edema grade 3, while one patient (4%) had grade 3 diarrhea. Other nonhematologic side effects did not exceed grade 2.

Table 4 shows the results of different tests of trends toward increased toxicity with increased dosage: In 2 × 2 tables obtained by grouping toxicity by 'presence vs. absence' and classifying patients by high (35–40 mg/m^2 docetaxel) vs. low (25–30 mg/m^2 docetaxel), significant increases in toxicity were significantly associated with higher dosages in the cases of nausea/vomiting, fatigue/asthenia, peripheral edema, and neurotoxicity according to Fisher's exact test. Diarrhea and alopecia were not significantly associated with dosage. Considering all WHO grades and dosages as separate classifications, an association of dosage with severity was seen for skin/nail toxicity and for leukopenia. Grouping leukopenia as grade 3 vs. grade 2 or absent also led to a significant association with higher dosage.

Efficacy

The overall response rate (OR) was 36% (fig. 1). No CR was reported. Nine of 25 patients achieved a PR (50% in the 30 mg/m^2/week dosage group). Treatment outcome according to dosage is given in table 2. Five of 22 patients (18%) showed SD, and 9 patients (41%) had PD during treatment. The median time until response was 8 weeks (range: 3–18). Clinical benefit (PR+SD) was observed in 14 of 25 patients (56%). The median TTP in the responder group was 231 days (95% CI: 187–275). The median survival time for PR was calculated to 397 days (95% CI: 284–510). Survival is significantly correlated with treatment response.

The response characteristics of the various dosage groups are shown in table 2. The apparently poorer response in the group with 25 mg/m^2 docetaxel is not significant according to the Mann-Whitney test and Fisher's exact test, nor is the dependence of response on total medication per patient.

Table 5 summarizes the relationship between pretreatment and response. In the subgroup of anthracycline- and paclitaxel-pretreated patients (n = 6), no PR was observed, while SD was seen in 16% of patients (1/6) and PD in 84% (5/6). A better response was associated with anthracycline pretreatment compared to pretreatment by both anthracycline and taxane (p = 0.054, Fisher's exact test). Among the 6 patients pretreated with paclitaxel, the median time to progression was 23 days (95% CI: 0–59).

Discussion

In the present study, 25 anthracycline-pretreated women with MBC received docetaxel in doses ranging from 25 mg/m^2 to 40 mg/m^2 depending on the patient's baseline Karnofsky index. None of the patients achieved a CR. The overall response rate for the entire cohort was 36%, with responses distributed among all dosage categories. This rate is consistent with observed response rates of 36% [23], 30% [24], and 33.4% [16–19] to weekly docetaxel.

The standard schedule of docetaxel of 75–100 mg/m^2 once every 3 weeks in patients with MBC is associated with a high

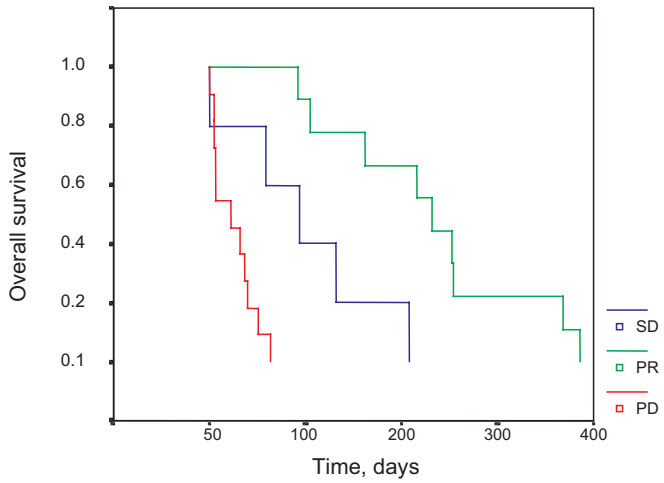

Fig. 1. Overall survival. SD = Stable disease; PR = partial response; PD = progressive disease.

Table 5. Relationship between pretreatment and response (p = 0.054 by Fisher's exact test)

Response	Anthracyclines only	Taxane and anthracyclines	Total
Partial response	9	0	9
Stable disease	4	1	5
Progressive disease	6	5	11
Total	19	6	25

incidence of grade 3/4 neutropenia. Various phase I studies have suggested that lower doses of docetaxel administered weekly may be better tolerated [16–19]. In the present study, no severe (grade 4) hematologic toxicity occurred during treatment, but grade 3 leukopenia was significantly associated with higher (35–40 mg/m^2) dosages. Higher dosages were also significantly associated with nonhematologic events, i.e., neurotoxicity, skin/nail toxicity, leukopenia, nausea/vomiting, fatigue/asthenia, and peripheral edema, but not with diarrhea and alopecia. There was no grade 4 toxicity of any type at any of the scheduled dosage levels.

Although the data give the impression of poorer response in the group with 25 mg/m^2 docetaxel, the apparent relationship is not statistically significant, nor is the dependence of response on total medication per patient. The same is true for 'clinical benefit' (PR or SD). However, as discussed above, there is already strong evidence from previous studies that the dosage of 35 mg/m^2 for weekly docetaxel comes close to the optimal dose-response relationship. In our study, the total medication that could be delivered was also maximized for this group.

In the context of MBC, with clearly limited survival, the safety profile plays a key role in clinical decision support. Our results support the existing evidence that grade 4 toxicity is substantially decreased for weekly docetaxel dosage in the range up to 40 mg/m^2 compared to administration of 100 mg/m^2 every 3 weeks.

This paper also sheds some light on the risks and benefits of reducing the weekly dosage from the previously reported optimum of 36 mg/m^2 to 30 mg/m^2 or even 25 mg/m^2 in the more frail patients (as characterized by a lower Karnofsky index). Our results illustrate in detail that the toxicity profile (both hematologic and nonhematologic) does indeed become significantly less severe as dosage is decreased from 40 mg/m^2 down to 25 mg/m^2. However, compared to the decrease in grade 4 toxicity resulting from weekly administration compared to triweekly administration, the additional improvement of the safety profile attributable to the dosage reduction to 25 mg/m^2 would not appear to justify decreased response at this level as expected from previous studies. It is noteworthy that this relationship persists in spite of stratification by the Karnofsky index, which would have been expected to elevate the side effects at lower dosages (patients with more disability).

The cumulative dose per patient was largest for a docetaxel dosage of 35 mg/m^2 and almost as large for 30 mg/m^2. Considering the influence of dosage on toxicity, cumulative dose, and response, and taken together with the existing evidence, our study suggests that dosages of 30 mg/m^2 or 35 mg/m^2 would appear to offer the most favorable tolerability profile that does not compromise clinical activity, and that these dosages might be justified even in patients with a lower Karnofsky index.

Our findings can be compared with the recommendations from phase II studies that administration of docetaxel on a weekly basis at dosages from 30 to 40 mg/m^2 is a safe and feasible treatment option for pretreated patients with MBC (96.4%; 42.9% had prior anthracycline therapy) [10, 13, 20, 21].

In a study conducted by Burstein et al. [12], no grade 4 toxicity was observed at a docetaxel dose of 40 mg/m^2 weekly given to mostly pretreated MBC patients. The overall incidence of grade 3 toxicities was 28%, with neutropenia and fatigue being most common. Hainsworth et al. [17] reported the dose-limiting toxicities of fatigue and asthenia at a maximum tolerated dose of 43 mg/m^2/week and a 50% response rate with docetaxel 35–40 mg/m^2/week in patients with MBC.

As summarized in table 2, the cumulative dosages achieved in our study were about 300 mg/m^2. This level was well below the threshold cumulative dose for neurological toxicity previously estimated at 720 mg/m^2 by Kaplan-Meier analysis [22].

A more recent study showed that the rate of grade 3 neutropenia with 35 mg/m^2 weekly docetaxel, given as a 6-week cycle, was 3.7% and the overall response rate was 48.1% [10]. These findings are consistent with those of our study, where 4% of patients had grade 3 hematological toxicity at 35 mg/m^2.

Hainsworth et al. [23] showed that in elderly patients with advanced breast cancer, weekly docetaxel 36 mg/m^2 for 6 consecutive weeks followed by a 2-week rest was well tolerated and active, with an objective response rate of 36%. Similarly, D'hondt et al. [24] showed that 36 mg/m^2 of weekly docetaxel led to an overall response of 30%. Severe neutropenia occurred in only 0.4% of cycles, and no other hematologic adverse events were observed. Shin et al. [25] found that at the maximum tolerated dose of 55 mg/m^2 bi-weekly docetaxel, 50% of patients developed severe grade 3/4 neutropenia. Massacesi et al. [26] showed that there were no differences in toxicity among weekly, 2-weekly, and 3-weekly docetaxel regimens.

Based on the high level of clinical activity and minimal myelosuppression, weekly docetaxel appears to be an attractive option for use in combination with other agents, such as doxorubicin, gemcitabine, or vinorelbine [27–29]. Weekly docetaxel and trastuzumab may be synergistic in MBC patients overexpressing Her/2 neu [30]. In a recent study, Marty et al. [31] found an overall response rate of 61% versus 43% with docetaxel alone, but a significantly higher incidence of grade 3 and 4 neutropenia for the combination (32% vs. 22%) of trastuzumab with docetaxel.

Summarizing, our study confirms that weekly administration of docetaxel of about 30–35 mg/m^2 is well tolerated and effective in patients with MBC, particularly those pretreated with anthracycline but not taxanes.

The authors declare no conflict of interest.

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