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Weekly docetaxel in metastatic breast cancer patients: No superior benefits compared to three-weekly docetaxel ☆

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ABSTRACT

Background: In anthracycline-pretreated metastatic breast cancer (MBC) patients, it is unknown whether weekly single-agent docetaxel is preferable to 3-weekly docetaxel regarding its toxicity and efficacy profile.

Patients and methods: In this multicenter, randomised, open-label phase III trial, 162 patients were randomised to weekly docetaxel (group A) or 3-weekly docetaxel (group B). The primary end-point was tolerability; secondary end-points were efficacy and quality of life (QoL).

Results: Group A (weekly docetaxel, $n = 79$) experienced less haematological toxicity, with just 1.3% versus 16.9% febrile neutropenia in group B (3-weekly docetaxel, $n = 77$) ($p = 0.001$). Not this difference, but fatigue and general malaise foremost led to more patient withdrawals in group A (24 versus 12 patients, $p = 0.032$), less patients completing treatment (29 versus 43 patients, $p = 0.014$) and reduced dose-intensity (15.6 versus 26 mg/m^2/week, 58% versus 70% of projected dose, $p = 0.017$). As a result, 3-weekly docetaxel was related to better overall survival in multivariate analysis (hazard ratio 0.70, $p = 0.036$), although in univariate analysis efficacy was similar in both groups. Reported QoL was similar in both groups, but less effective treatment with more general toxicity led to less completed QoL forms in group A (65.4% versus 50%, p=0.049).

Conclusion: Weekly docetaxel is less well tolerated than a 3-weekly schedule, due to more non-haematological toxicity, despite less febrile neutropenia. Also, no efficacy benefits can be demonstrated for weekly docetaxel, which may even be inferior based on

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multivariate analysis. Therefore, a 3-weekly schedule should be preferred in the setting of MBC.

1. Introduction

Breast cancer is the most common cause of cancer death among women worldwide.[1] One of the mainstays in palliative treatment of metastatic breast cancer (MBC) is docetaxel. This was originally registered for 3-weekly intravenous (iv) administration in doses of 60–100 mg/m^2. Reported acute adverse effects include myelosuppression (predominantly with neutropenia), while non-haematological toxicity consists of neuropathy, myalgias, fatigue, and skin- and nail changes.[2,3] Weekly docetaxel administration induced dose-limiting fatigue and asthenia in phase I–II studies.[4–8] At the time of initiation of the present study, it became clear that weekly paclitaxel administration showed reduced toxicity compared to 3-weekly administration,[9] while maintaining efficacy. The hypothesis was that a similar pattern would occur for docetaxel. This randomised study was therefore conducted comparing the toxicity profile (primarily), efficacy- and quality of life (QoL) data (secondarily) of a weekly versus 3-weekly docetaxel treatment regimen in MBC patients.

2. Patients and methods

2.1. Patients

This prospective, open label randomised phase III study was performed in 33 centres in the Netherlands from February 2001 until April 2006. Randomisation was performed centrally and was stratified for patients with bone metastases only. The study was approved by the independent ethics committee at each of the participating centres. All patients gave written informed consent before participating in the trial.

Women aged 18 years or older, with confirmed progressive measurable (RECIST criteria[10]) or evaluable (bone disease) MBC were eligible. Prior treatment for MBC could consist of one line of non-taxane containing chemotherapy, hormonal therapy (not concurrent) and radiotherapy. HER2 status was no standard assessment at the time when this trial was conceived. Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leqslant 2$ was required (additional in- and exclusion criteria in Supplementary text 1).

2.2. Treatment

In group A, patients received docetaxel 36 mg/m^2 per infusion on days 1, 8, 15, 22, 29, 36 of each course of 8 weeks.[4] Treatment duration was 3 courses (24 weeks); a maximum of 4 courses could be administered if it was considered to be in the best interest of the patient. In group B, patients received docetaxel 100 mg/m^2 on day 1 of each course of 3 weeks. Treatment duration was 6 courses (18 weeks); a maximum of 8 courses could be administered. (Infusion schedule, premedication and dose modifications are described in Supplementary text 2).

2.3. Treatment outcome assessment

The primary objective of this study was to assess docetaxel toxicity when administered either weekly or 3-weekly, with regard to febrile neutropenia (FN) and dose reduction or -delay. Toxicity was evaluated according to CTCAE version 2.0.[11] The secondary objective was to assess efficacy of the treatment regarding overall response rate (ORR), progression free survival (PFS) and overall survival (OS). For response evaluation, tumour lesions were categorised at baseline as measurable or non-measurable. The effect of treatment on the target lesions was evaluated according to RECIST criteria.[10] Treatment response was measured every 8 weeks (1 course) in group A, every 6 weeks (2 courses) in group B or at signs of progression (treatment evaluation is described in detail in supplementary text 3). Duration of stable disease was 12 weeks minimum and clinical benefit was measured from first date of partial response, complete response or stable disease until tumour progression or death. PFS was measured from the start of treatment until the moment of documented tumour progression or death. OS was measured from the start of treatment to death of the patient. Time to treatment failure (TTF) was measured from the start of treatment until progression, death due to progression or last chemotherapy before treatment withdrawal due to toxicity. QoL was assessed by means of European Organization for Research and Treatment of Cancer (EORTC) QLQ C30 and QLQ BR23 questionnaires,[12,13] at baseline, after 12 and 24 weeks (end of study).

2.4. Statistical analysis

A total of 155 patients was required to detect a difference in primary end-points of 10% in FN, or a difference of 15% of patients requiring dose reduction or delay (the latter considered as the direct clinical consequence of FN), using a one sided α of 0.05 and a power of 80%. Toxicity profiles were compared using chi-squared tests. Kaplan–Meier curves were used to describe duration of clinical benefit, PFS, OS and TTF. Cox proportional hazard modelling was used to relate treatment group to efficacy criteria, corrected for PS, prior anthracyclines, prior chemotherapy for MBC, bone metastasis only, metastatic sites number and relative dose intensity. The statistical significance level was set at a p-value < 0.05. Analyses were performed using STATA, version 10.1 (Stata Corporation LP, College Station, TX, USA).

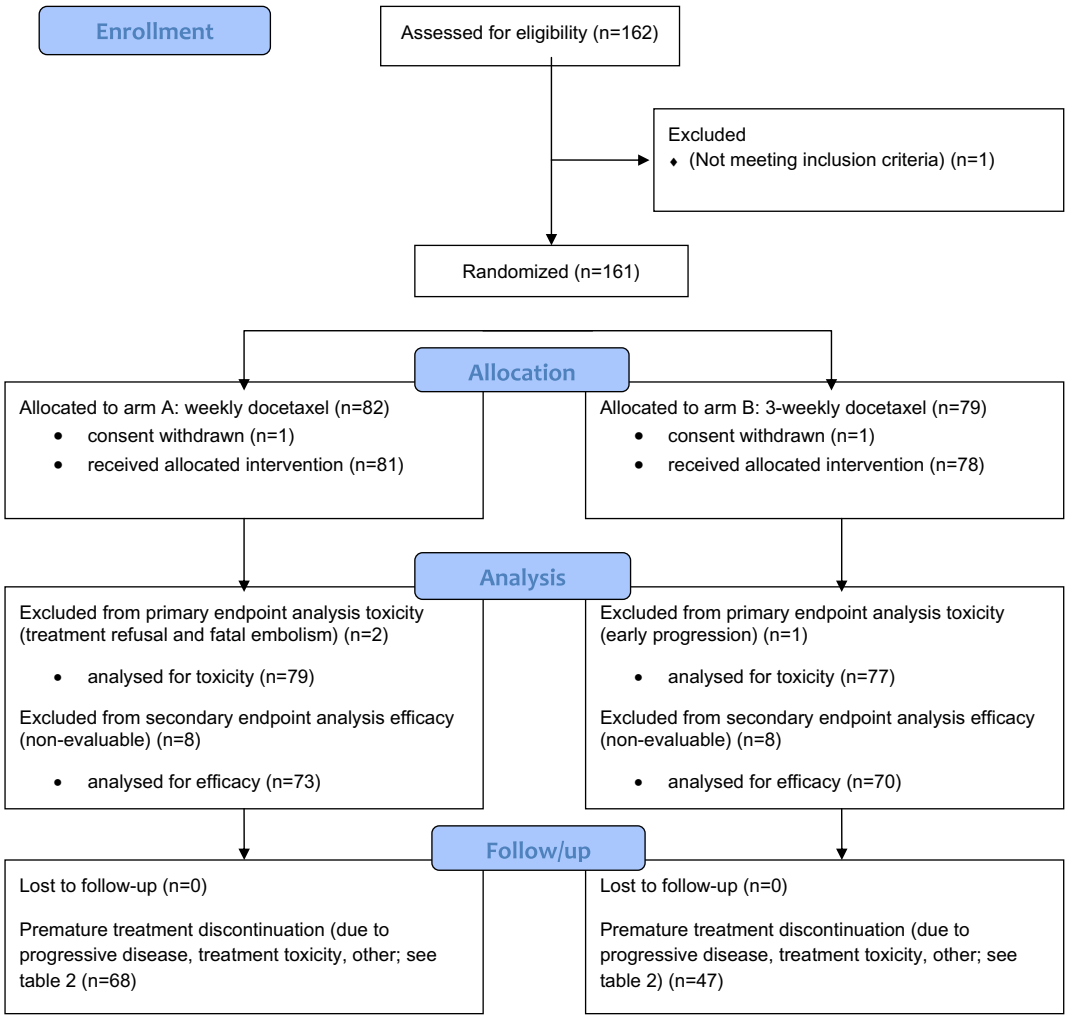
3. Results

3.1. Treatment

A total of 162 patients were enrolled in the study (flow diagram). One patient was found to be ineligible and was subsequently excluded from the study. Eighty-two patients were randomised to receive weekly docetaxel (in group A).

Seventy-nine patients were randomised to receive 3-weekly docetaxel (in group B). Two patients (one in each group) withdrew consent, leaving a total of 159 patients in this study (81 and 78 in group A and B, respectively). At this analysis median follow-up was 8.9 months. Patient characteristics were well balanced between groups (Table 1).

Premature treatment discontinuation was mostly due to (fatal) tumour progression (group A: 24 patients, 29.6% versus group B: 22 patients, 28.2%, p = NS; Table 2).



Patients in group A received a total number of 170 courses including 904 weekly infusions, with median treatment duration 12.8 weeks (range 0–29.9). Patients in group B received a total number of 372 courses of three-weekly infusions with median treatment duration 14.9 weeks (range 0–29.6). Median cumulative dose was 60.2% versus 73.9% of total projected dose (group A: 375 mg/m^2 (range 33–908 mg/m^2) versus B: 488 mg/m^2 (range 95–1100 mg/m^2); p = 0.013). Received dose intensity was 58% versus 70% of projected dose/week (group A: 15.6 mg/m^2/week (range 1.4–28.4 mg/m^2/week) versus B: 26.0 mg/m^2/week (range 5.3–33.9 mg/m^2/week; p = 0.017). In group A, 29 patients completed treatment (36%) versus 43 (55%) in B (p = 0.014). Dose reduction was indicated at the start of treatment for baseline impaired liver function in 5 patients from group A and 4 patients from group B. Dosage was reduced during treatment in one patient from group B, due to treatment related liver function impairment (grade 2), from course 2 onwards.

3.2. *Toxicity*

Seventy-nine patients (of 81) in group A and 77 (of 78) in group B were evaluable for toxicity. Significantly more grade 3–4 haematological toxicities were reported in group B (FN 1.3% in group A versus 16.9% in group B, p = 0.001, Table 3). However, more dose reductions and treatment delays occurred in group A (87.7% versus 73.1% of patients in group B, p = 0.02), leading to reduced dose-intensity (administered/projected dose/week 58.2% = 26 mg/m^2/week versus 69.8% = 15.6 mg/m^2/week, p = 0.017) and significantly more patients withdrew from treatment due to toxicity in group A (24 versus 12 patients in group B, p = 0.032, Table 2).

3.3. *Response*

Seventy-three patients in group A and 70 in group B were evaluable for response. Median follow up time in these pa-

Table 1 – Patient characteristics.

	Weekly docetaxel, Arm A ($n = 81$)		3-weekly docetaxel, Arm B ($n = 78$)		p-Value
	N	%	N	%	
Age (years)					
Median	56		53		0.602
Range	29–74		30–79		
Performance status					
0	28	34.6	22	28.2	0.688
1	38	46.9	40	51.3	
2	15	18.5	16	20.5	
Metastatic sites					
Site of primary or recurrence	9	11.1	8	10.3	0.862
Visceral	57	70.4	53	68.0	0.741
Bone	45	55.6	52	66.7	0.151
Soft tissue[a]	26	32.1	25	32.1	0.995
Other[b]	18	22.2	22	28.2	0.385
Bone metastasis only					
Yes	12	14.8	11	14.1	0.898
No	69	85.2	67	85.9	
No. of metastatic sites					
1	28	34.6	20	25.6	0.738
2	23	28.4	24	30.8	
3	18	22.2	22	28.2	
4+	12	14.8	12	15.4	
Prior anthracycline containing regime					0.688
Yes	77	95.1	73	93.6	
No	4	4.9	5	6.4	
Chemotherapy for metastatic disease					0.610
Yes	53	65.4	54	69.2	
No	28	34.6	24	30.8	

[a] Including skin and lymph nodes.
[b] Including ascites and pleural effusion.

tients was 14.2 months. ORR (partial and complete response) was 24.7% in group A and 25.6% in group B. Clinical benefit (stable disease, partial response or complete response) was 54.3% in group A and 57.7% in group B (overall response according to intention to treat analysis is summarised in Table 4). In univariate analysis, median duration of clinical benefit, PFS and OS were similar in both groups (Fig. 1A–C). Median TTF was 13.8 weeks (95% confidence interval (CI): 10.3–16.9 weeks) in group A and 17.1 weeks (95% CI: 12.7–21.9 weeks) in group B (log rank test $p = 0.015$) (Fig. 1D). In multivariate analysis, dose intensity < 90% of the projected dose, was related to significantly worse outcome (Table 5), with a hazard ratio of 2.83 (1.97–4.07) for TTF. Furthermore, treatment in group B was related to better OS (hazard ratio 0.70 (0.5–0.98), $p = 0.036$, Table 5), even though the statistical design of this study was not primarily aimed at detecting this difference.

3.4. *Quality of life*

Overall QoL scores were not different between groups at treatment start, with 38% versus 45% of patients reporting good

Table 2 – Reasons for premature treatment discontinuation.

	Weekly docetaxel, Arm A ($n = 81$)		Docetaxel 3-weekly, Arm B ($n = 78$)		p-Value (chi-squared)
	N	%	N	%	
Tumour progression	21	26	21	27	
Fatal tumour progression	3	3.7	1[b]	1.3	
Toxicity of treatment	24	29.6	12	15.4	0.032
Treatment refusal	1[b]	1.2	–	–	
Other[a]	1[b]	1.2	–	–	

[a] Patient died of pulmonary embolism.
[b] Not evaluable for primary end-point: treatment toxicity.

Table 3 – Treatment related toxicity (CTCAE version 2.0) and toxicity causing patient withdrawals (maximal toxicity per patient).

	Weekly docetaxel, Arm A ($n = 79$)		Docetaxel 3-weekly, Arm B ($n = 77$)		p-Value (chi-squared)
	N	%	N	%	
Grade 3–4 toxicity					
Total neutropenia	5	6.3	24[a]	31.2	<0.001
Febrile neutropenia	1	1.3	13[b]	16.9	0.001
Neutropenia without fever	4	5.1	13	16.9	0.018
Infection without neutropenia	4	5.1	4	5.2	
Thrombocytopenia	–	–	1	1.3	
Anorexia	2	2.5	3	3.9	
Fatigue/asthenia	9	11.4	8	10.4	
Mucositis/diarrhoea	3	3.8	8	10.4	
Nausea/vomiting	2	2.6	6	7.8	
Skin/hand-foot	5	6.3	2	2.6	
Neurosensory/-motor	1	1.3	5	6.5	
Hypersensitivity reaction	1	1.3	1	1.3	
Fluid retention	4	5.1	1	1.3	
Pulmonary	8[c]	10.1	2[d]	2.6	
Grade 2 toxicity					
Lacrimation	1	1.3	3	3.9	
Onycholysis	11	13.9	3	3.9	0.035
Toxicity causing patient withdrawals					
Total	24		12		0.032
Febrile neutropenia	–	–	2[b]	2.6	
Neutropenia without fever	1	1.3	–	–	
Infection without neutropenia	2	2.5	1	1.3	
Fatigue/asthenia	9	11.3	5	6.5	
Mucositis/diarrhoea	2	2.5	1	1.3	
Skin/hand-foot/nail	4	5.1	–	–	
Neurosensory/-motor	–	–	2	2.6	
Hypersensitivity reaction	2	2.5	1	1.3	
Fluid retention	4	5.1	–	–	

[a] Two patients experienced febrile neutropenia after the 2nd course, and subsequently grade 4 neutropenia without fever with G-CSF after courses 3 + 4 and 6, respectively.

[b] One case of fatal neutropenic sepsis.

[c] Six cases of pleural fluid with dyspnoea, 1 COPD, 1 pneumothorax.

[d] One case of pleural fluid with dyspnoea, one pulmonary embolism, one respiratory insufficiency.

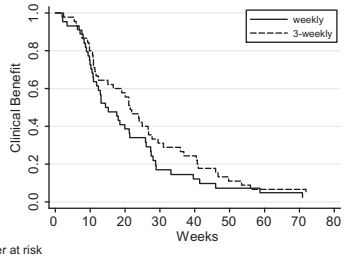
QoL (score 5–7) in group A versus B (p = NS). Scores were also similar at 12 or 24 weeks and deteriorated at the same rate in both groups. However, in group A, 65.4% of forms was returned incompletely (<3 forms from 3 assessment points), versus 50% in group B ($p = 0.049$). Poor PS at study entry was related to return of QoL forms, as 74.2% of forms were returned incompletely by patients with PS = 2 versus 44% by patients with PS = 0 ($p = 0.023$).

Table 4 – Response to treatment (intention to treat analysis).

	Weekly docetaxel, Arm A ($n = 81$)		Docetaxel 3-weekly, Arm B ($n = 78$)		p-value (chi-squared)
	N	%	N	%	
Evaluable	73	90.1	70	89.7	0.937
Overall response	20	24.7	20	25.6	0.890
Complete response	3	3.7	–		
Partial response	17	21.0	20	25.6	0.488
Stable disease[a]	24	29.6	25	32.1	0.741
Progressive disease	26	32.1	23	29.5	0.721
Early death	3	3.7	2	2.6	
Not evaluable	8	9.9	8	10.3	0.937

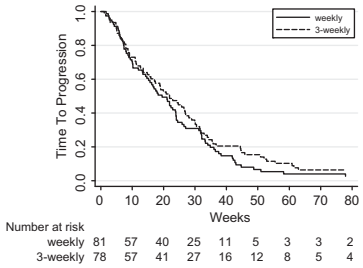
[a] Stable disease was defined as a minimum duration of 12 weeks.

A: Duration of clinical benefit



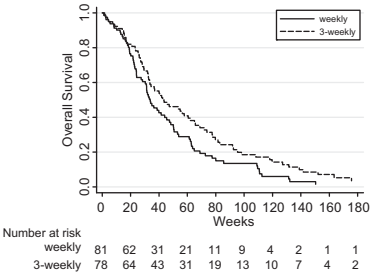
Clinical benefit: stable disease, partial response or complete response. Median duration of clinical benefit: group A (weekly): 14.4 weeks (95% CI: 10.8-21.4 weeks), group B (3-weekly): 21.5 weeks (95% CI: 12.4-26.8 weeks; log rank test: $p = 0.196$). Hazard ratio: Group A: 1, Group B: 0.76 (p=0.198).

B: Progression free survival



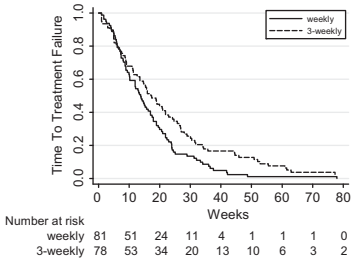
Median progression free survival: group A (weekly) 19.5 weeks (95% CI: 14.7-23.9 weeks), group B (3-weekly): 21.9 weeks (95% CI: 15.4-27.1 weeks; log-rank test p=0.190). Hazard ratio: Group A: 1, group B: 0.81 (p=0.191).

C: Overall survival



Median overall survival time: group A (weekly) 33.7 weeks (95% CI: 28.3-45.4 weeks), group B (3-weekly): 42.6 weeks (95% CI 32.6-62.1 weeks; log rank test p=0.061). Hazard ratio: Group A: 1, Group B: 0.73 (p=0.062).

D: Time to treatment failure



Median time to treatment failure: group A (weekly) 13.8 weeks (95% CI: 10.3-16.9 weeks), group B (3-weekly) 17.1 weeks (95% CI: 12.7-21.9 weeks; log rank test p=0.015). Hazard ratio: Group A: 1, group B: 0.67 (p=0.016)

Fig. 1 – Treatment efficacy.

4. Discussion

In the setting of MBC, it has so far been unclear whether weekly docetaxel is preferable over 3-weekly administration. The present study is the largest randomised study so far comparing toxicity profile, efficacy- and QoL of weekly (group A) versus 3-weekly (group B) docetaxel administration in MBC. Previously, there were only limited data available with regard to toxicity and efficacy in the two treatment schedules. Two smaller randomised trials were published so far in MBC.[14,15] No difference in progression-free survival was shown, in contrast to the adjuvant setting, where an inferior disease free survival was demonstrated with weekly docetaxel.[16] Although in a recent meta-analysis of weekly versus 3-weekly administration of taxanes, a clear benefit for weekly paclitaxel was shown, this was not the case for docetaxel.[17] Therefore, until now it has been unclear which of the docetaxel administration schedules is preferable in the setting of MBC.[18,19] The present study supports the 3-weekly schedule as the preferred regime, based on both toxicity- and efficacy outcome.

With regard to toxicity, we found more haematological toxicity with 3-weekly docetaxel, and our study was designed to detect a significant difference. Initially it was thought that weekly docetaxel would therefore be preferable, in line with other studies.[3,15,20] However, despite its favourable haematological toxicity profile, we found that weekly docetaxel induced a pattern of chronic and poorly tolerated astenia and fatigue (not necessarily grade 3–4) resulting in more dose reductions and treatment delays or premature termination. This is in line with the study by Rivera et al.,[14] in which the dose was reduced in 25% of the weekly regimen compared to 12% in the 3-weekly group. In that study, 3 weekly doses of docetaxel in a 4-weekly regimen was used, while 6 weekly doses in an 8-weekly regimen was used in the present study. The longer treatment duration may have contributed to more dose reductions in our study. Tabernero et al.[15] also found an increased rate of FN during 3-weekly versus weekly docetaxel in respectively 19.5% versus 4.9% of patients. Similarly, more patients withdrew from weekly treatment due to chronic toxicity compared to the 3-weekly arm (46.3% versus 36.6% of patients). In our study, we found that the difference in dose reduction and treatment discontinuation moreover led to reduced dose intensity with the weekly schedule. More opportunities or requests for dose adjustments in the weekly schedule may have contributed to this finding.

With regard to outcome measures, we found no superior benefit of the weekly schedule. While efficacy was similar in both groups in univariate analysis, in multivariate analysis the treatment schedule and dose intensity did affect OS negatively. It should be mentioned that treatment beyond progression could have influenced survival. However, the relation between poorer outcome and lower dose intensity in the weekly schedule suggests a genuine effect of the pres-

Table 5 – Multivariate Cox regression analysis of factors affecting treatment response.

Factors[a]	Duration of clinical benefit			Progression free survival			Overall survival			Time to treatment failure		
	HR	95%-CI	*p*-Value	HR	95%-CI	*p*-Value	HR	95%-CI	*p*-Value	HR	95%-CI	*p*-Value
Arm												
A (weekly)	1			1			1			1		
B (3-weekly)	0.67	0.42–1.06	0.088	0.81	0.58–1.12	0.203	0.70	0.50–0.98	0.036	0.63	0.45–0.89	0.008
Performance status at entry												
0	1		*0.159*	1		*0.082*	1		*0.003*	1		*0.011*
1	0.98	0.58–1.66	0.935	1.03	0.69–1.53	0.893	1.11	0.73–1.69	0.613	1.42	0.91–2.20	0.122
2	1.96	0.89–4.31	0.096	1.66	1.00–2.74	0.049	2.32	1.38–3.91	0.002	2.24	1.32–3.79	0.003
Prior anthracycline containing regime												
Yes	1			1			1			1		
No	1.14	0.47–2.76	0.771	1.11	0.55–2.24	0.772	0.99	0.47–2.06	0.968	1.29	0.64–2.62	0.474
Prior chemotherapy for metastatic disease												
Yes	1			1			1			1		
No	0.56	0.34–0.94	0.028	0.68	0.47–0.96	0.030	0.63	0.44–0.91	0.014	0.85	0.60–1.23	0.407
Bone metastases only												
Yes	1			1			1			1		
No	0.92	0.44–1.92	0.816	0.98	0.54–1.77	0.952	1.00	0.53–1.90	0.998	1.41	0.78–2.56	0.260
No. of metastatic sites												
1	1		*0.308*	1		*0.635*	1		*0.087*	1		*0.494*
2	0.70	0.36–1.37	0.295	1.13	0.69–1.87	0.620	0.91	0.53–1.54	0.717	1.02	0.60–1.72	0.950
3	1.23	0.59–2.54	0.585	1.39	0.81–2.36	0.229	1.43	0.83–2.48	0.199	1.41	0.80–2.48	0.239
4+	0.76	0.31–1.85	0.546	1.33	0.72–2.46	0.359	1.66	0.88–3.10	0.115	1.13	0.60–2.15	0.705
Relative dose intensity												
⩾90% of projected dose/week	1			1			1			1		
<90% of projected dose/week	1.42	0.89–2.28	0.142	1.94	1.35–2.78	<0.001	1.85	1.27–2.68	0.001	2.83	1.97–4.07	<0.001

p-Value [italic] = overall *p*-value.
[a] All factors are included simultaneously in the multivariate model.

ent treatments. This finding is the more striking, as the study was designed primarily to detect differences in toxicity (while efficacy was a secondary end-point). Thus, contrary to what was previously thought, less grade 3–4 toxicity did not translate in improved tolerability or higher efficacy of the weekly schedule. Based on these data, the weekly docetaxel schedule should not be considered as standard treatment. It is not likely a beneficial schedule for the elderly and frail patient population,[9] for which it was previously advocated.[21–23] For selected cases with limited bone marrow reserve or impaired liver function, the potential for dose adjustments at the start may present an advantage over a 3-weekly schedule.

QoL was not different in both treatment groups in the present study, which is remarkable in view of the difference in overall toxicity. However, it was clear that the complete return (e.g. on all three time points) of QoL forms was lower in group A and that poor PS negatively affected the return of QoL forms. Also, the timing of QoL assessments and time-points of maximal toxicity did not necessarily coincide. These factors are likely to have had an impact on the outcome of QoL assessment. This may underline the need for refinement of timing and frequency of the QoL assessments, as was already expressed for the adjuvant setting by others.[24,25]

In conclusion, in view of impaired tolerability and no efficacy benefits of weekly docetaxel, 3-weekly docetaxel should be preferred in the setting of MBC.

Clinical trial number

NTR1506 (ICMJE certified Dutch Primary Registry).

Conflict of interest statement

W.V. is employee of Sanofi-Aventis Netherlands B.V., Gouda.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.12.018.

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