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

Carolien P. Schröder [a,], Linda de Munck [b], Anneke M. Westermann [c], Willem M. Smit [d], Geert-Jan M. Creemers [e], Hiltje de Graaf [f], Jacqueline M. Stouthard [g], Gert van Deijk [h], Zoran Erjavec [i], Aart van Bochove [j], Willemijn Vader [k], Pax H. Willemse [a]*

[a] *Dept. of Medical Oncology, University of Groningen and University Medical Centre Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands*
[b] *Dept. of Research, Comprehensive Cancer Centre North East, Groningen, P.O. Box 330, 9700 AH Groningen, The Netherlands*
[c] *Dept. of Medical Oncology, AMC, Amsterdam, P.O. Box 22.660, 1100 DD Amsterdam, The Netherlands*
[d] *Dept. of Medical Oncology, Medisch Spectrum Twente, P.O. Box 50.000, 7500 KA Enschede, The Netherlands*
[e] *Dept. of Medical Oncology, Catharina Ziekenhuis, P.O. Box 1350, 5602 ZA Eindhoven, The Netherlands*
[f] *Dept. of Medical Oncology, MCL Zuid, P.O. Box 888, 8901 BR Leeuwarden, The Netherlands*
[g] *Dept. of Medical Oncology, Maasstad Ziekenhuis, P.O. Box 9100, 3007 AC Rotterdam, The Netherlands*
[h] *Dept. of Medical Oncology, HAGA Ziekenhuis-Rode Kruis, Leyweg 275, 2545 CH Den Haag, The Netherlands*
[i] *Dept. of Medical Oncology, Ommelander Ziekenhuis Groep, P.O. Box 30.000, 9930 RA Delfzijl, The Netherlands*
[j] *Dept. of Medical Oncology, ZaansMC, P.O. Box 210, 1500 EE Zaandam, The Netherlands*
[k] *Dept. of Medical Research, Sanofi-Aventis Netherlands B.V., P.O. Box 2043, 2800 BD Gouda, The Netherlands*

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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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* *Corresponding author*: Tel.: +31 50 361 2821; fax: +31 50 361 4862.
E-mail address: c.p.schroder@int.umcg.nl (C.P. Schröder).

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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).