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Prospective Multicenter Randomized Phase III Study of Weekly versus Standard Docetaxel (D2) for First-Line Treatment of Metastatic Breast Cancer

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Key Words
Docetaxel · Weekly application · Metastatic breast cancer · Combination chemotherapy

Abstract
Purpose: Previous phase II studies have indicated a greatly reduced hematotoxicity of docetaxel-based regimens administered on weekly schedules. The present trial was initiated to randomly compare the toxicity and efficacy of weekly docetaxel versus its standard 3-weekly application. ***Methods:*** Patients previously untreated with chemotherapy for metastatic disease were recruited. Patients aged >60 years or with a Karnofsky Perfomance Status (KPS) of 60–80% were eligible for the D2 study. Patients were randomized to receive docetaxel either on a 3-weekly [75 mg/m^2 every 3 weeks (q3w)] or on a weekly (30 mg/m^2 on days 1, 8, and 15; q4w) schedule. Treatment was continued until a maximum of 8 cycles, unacceptable toxicity, or disease progression. All patients received standard corticosteroid prophylaxis. ***Results:*** Since statistical significance for the primary endpoint (toxicity) was achieved in the interim analysis, the study was closed according to the study protocol (102 of 162 patients). Compared to the standard arm, leukopenia ≥grade 3 was a rare event in the weekly arm of the D2 study (per-patient analysis: 4.2% q1w vs. 51.9% q3w; $p < 0.0001$). No difference was observed between the 2 schedules regarding the occurrence of anemia or thrombocytopenia. With regard to nonhematological toxicity, there was a higher incidence of skin/nail and hepatological toxicity with the weekly schedule, whereas neurotoxicity was observed more often in the standard arm. The rate of omitted doses was significantly increased in the weekly arm (8.6% q1w vs. 0% q3w). The overall response rate was 22.9% in the weekly arm compared to 42.6% in the standard arm ($p = 0.039$). Time to progression was 5.4 (q1w) versus 6.3 (q3w) months ($p = 0.91$), and overall survival was 22.7 (q1w) versus 15.8 (q3w) months ($p = 0.24$). ***Conclusion:*** The present data support the feasibility of both weekly and 3-weekly application of docetaxel. As expected, severe leukopenia seems avoidable in weekly scheduled single-agent docetaxel and may serve as an important treatment option, particularly in elderly patients and patients with a reduced performance status.

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Introduction

Docetaxel (Taxotere; Sanofi-Aventis, Frankfurt, Germany) is one of the most effective antitumor agents currently available for the treatment of breast cancer. In early breast cancer, it is currently considered a standard option in node-positive and high-risk node-negative disease. In metastatic breast cancer (MBC), when compared to doxorubicin, docetaxel showed a significantly superior response rate (RR; 47.8 vs. 33.3%; p = 0.008) and a trend towards a prolonged time to progression (TTP; 26 vs. 21 weeks) [1]. After failure with anthracycline-containing chemotherapy, single-agent docetaxel has demonstrated superior results when compared to mitomycin/vinblastine [RR, TTP, and overall survival (OS)] or methotrexate/5-fluorouracil (RR and TTP). Moreover, it has shown equivalent efficacy when compared to vinorelbine/5-fluorouracil (RR, TTP, and OS) [2–4].

When docetaxel is administered at a standard dose of 100 mg/m^2 [every 3 weeks (q3w)], 70–90% of patients develop grade 3/4 neutropenia [1]. Instead of dose reduction, one strategy to reduce toxicity without growth factor support is to apply docetaxel on a weekly schedule. Several studies have indicated that severe hematotoxicity (grade 3/4) could largely be prevented at weekly doses of less than 40 mg/m^2 without impaired efficacy in the first- or second-line setting [5–9]. Meanwhile, the favorable toxicity profile of weekly scheduled docetaxel has been confirmed in 2 randomized phase III trials without inferior results regarding TTP or OS [10, 11]. A further rationale for weekly docetaxel might be that standard-dose single-agent docetaxel (100 mg/m^2 q3w) frequently needs to be adjusted to 75 mg/m^2 in pretreated, unfit, or elderly patients [12].

Taken together, this evidence provided the basis to conduct the D2 trial which investigated a dose-adjusted 3-weekly regimen (75 mg/m^2) compared to a weekly regimen (30 mg/m^2) in elderly or medically unfit patients.

Patients and Methods

Patient Selection

Patients with MBC were recruited for the trial. None of the patients had received chemotherapy for metastatic disease. The treatment protocol was approved by the local ethics committees and all patients gave their written informed consent before treatment was started.

For the D2 study, patients (aged ≥18 years) were required to have a Karnofsky Performance Status (KPS) of 60–80% or an age ≥60 years. Moreover, patients were required to have histologically proven MBC, bidimensionally measurable disease, and an anticipated survival of at least 12 weeks. Prior to study entry, hepatic, renal, and hematological functions had to be adequate [leukocyte count ≥3.0 × 10^9/l, platelets ≥100 × 10^9/l, hemoglobin ≥8 g/dl, bilirubin ≤1.25 times the normal range, alanine aminotransferase:aspartate aminotransferase (ATL:AST) ratio ≤3 times the normal range, and alkaline phosphatase ≤2.5 times the normal range].

Patients with bone metastases only and/or steroid (estrogen and/or progesterone) receptor expression without prior endocrine treatment were not eligible for the trial. Additional exclusion criteria were active infections, previous or concurrent radiotherapy of more than 25% of marrow-containing bone, clinically overt brain metastases, previous neuropathy ≥grade II, and a history of a second malignancy other than resected basal cell and/or squamous cell carcinoma of the skin. Patients were not eligible for study enrolment if they were pregnant or lactating or if they refused effective contraception.

Treatment Regimen

Patients were randomly assigned to receive docetaxel either on a 3-weekly (75 mg/m^2 q3w) or weekly schedule (30 mg/m^2 days 1, 8, and 15; q4w). Docetaxel was dissolved in 100 ml of 0.9% saline and given by intravenous (i.v.) infusion over 30 min (30 mg/m^2 weekly) or 60 min (75 mg/m^2 q3w), respectively. Treatment was continued until a maximum of 8 cycles, unacceptable toxicity, or disease progression. All patients received standard corticosteroid prophylaxis, antiemetics (routinely 5HT3 antagonists), and growth factors (which were allowed at any point) according to the local standards.

In case of myelosuppression on the day of the planned treatment (leukocytes ≤1,000/μl and platelets ≤50,000/μl), further drug administration was postponed for 1 week until bone marrow recovery occurred (leukocytes ≥2,000/μl and platelets ≥100,000/μl). If there was no recovery within the additional rest of 1 week, the patient was excluded from the study. A reduced dose (–25%) was applied in case of a leukocyte count between 1,000/μl and 2,000/μl and a platelet count between ≥50,000/μl and 100,000/μl. A full dose of docetaxel was administered if the blood counts had risen to leukocytes ≥2,000/μl and platelets ≥100,000/μl.

Patients were excluded from the trial in case of nonhematological toxicity ≥grade 3 (excluding nausea/vomiting). Dose reductions of 25% were required in case of hematological toxicity grade 3 or 4 complicated by fever, infection, or both. Moreover, a reduced dose (–20%) was required in case of grade 3 diarrhea or mucositis.

Data Collection

Drug administration, KPS, and toxicity or adverse events were recorded after every cycle of treatment. Weekly blood counts were performed. Febrile neutropenia was defined as fever (≥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's Common Toxicity Criteria (NCI CTC 2.0) [13]. Imaging studies using ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) were performed after every 2 cycles of treatment.

Response Evaluation

In all patients, tumors were measured by imaging procedures (ultrasound, CT, or MRI) within 14 days prior to entry into the study and subsequently after every 2 cycles of treatment. A standard evaluation comprised of history, a physical examination, and routine laboratory tests (including a complete blood cell count, chemistry profile, and electrolyte determination) was performed before each treatment.

Patient response was assessed according to standard WHO criteria as follows: Complete response (CR) was defined as the disappearance of all known disease as determined by 2 observations not less than 4 weeks apart, while partial response (PR) was defined as a decrease of at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions as determined by 2 observations not less than 4 weeks apart. Stable disease (SD), lasting at least 6 weeks from the start of study (i.e. the first drug administration), was defined as a <50% decrease and a <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 1 bidimensionally or unidimensionally measurable lesion or the appearance of a new lesion. The occurrence of pleural effusion was considered a sign of progression if it was verified by positive cytology.

Study Endpoints and Statistics

The primary study endpoint was hematotoxicity (leukopenia). Assuming grade 3 and grade 4 hematotoxicity rates of 70–95% for the standard regimen and 10–20% for the weekly regimen, the calculated sample size for the primary endpoint was 40 patients (20 for each treatment arm), with a statistical power of 80% using a 5% level of significance (Fishers's exact test).

An interim analysis was planned in 80 recruited patients (40 for each treatment arm) for the primary endpoint using α_1 = 0.0052 and α_2 = 0.048 as the levels of significance (O'Brien and Fleming sequential design).

The calculated sample size for the secondary endpoint (TTP) was 162 patients, with the assumption of the noninferiority of the weekly schedule (TTP q3w = 7 months and TTP q1w = 6.5 months). Sample sizes were calculated using NCSS/PASS 2000 software. Further secondary endpoints were OS and RR. TTP was determined by the interval between the initiation of therapy and the first date that disease progression was objectively documented. OS was measured from the date of the start of treatment to the date of death from any cause. All patients were included in the (intent-to-treat) analysis of TTP and survival.

The probabilities of survival and TTP were estimated by Kaplan-Meier analysis, and confidence intervals for the RR were calculated using methods for exact binominal confidence intervals [14, 15].

Results

Patient Characteristics

Patients were recruited between July 2001 and August 2008. Since statistical significance was achieved for the primary endpoint in the interim analysis, the study was closed before the target recruitment had been reached (102 of 162 patients). The median observation time was 14.4 months (range 1.2–77.7). The patients' characteristics are presented in table 1.

Table 1. Patient characteristics

Characteristics	D2 (n = 102)	
	q1w	q3w
Patients	48	54
Age, years		
Median	73	70.5
Range	58–84	60–82
KPS, %		
Median	80	80
Range	60–100	60–100
Estrogen and progesterone receptor status		
Positive	36	35
Negative	12	17
Unknown	0	2
Menopausal status		
Premenopausal	0	0
Postmenopausal	48	54
HER-2 status		
Positive (IHC 3+ or 2+ and FISH+)	6	6
Negative (IHC 0 or 1+ or 2+ and FISH–)	30	36
Unknown	12	12
Measurable disease sites		
Lung	23	23
Liver	23	27
Lymph nodes	23	23
Skin	8	6
Skeleton	20	24
Disease sites per patient, n		
1	11	15
2	15	14
≥3	22	25
Prior treatment		
Adjuvant chemotherapy	19	24
(including anthracyclines)	10	16
Adjuvant hormonal therapy	31	35

Toxicity

All investigated hematological and nonhematological toxicities are listed in table 2. Compared to the standard arm, leukopenia ≥grade 3 was a rare event in the weekly arm of the D2 study (per-patient analysis: 4.2% q1w vs. 51.9% q3w; $p < 0.0001$). There was no difference regarding the occurrence of anemia or thrombocytopenia between the 2 schedules.

With regard to nonhematological toxicity, neurotoxicity was observed more frequently in the standard regimen (3.7% q3w vs. 0% q1w; $p = 0.01$), whereas skin and nail dis-

Table 2. Toxicity profile (per-patient analysis): hematological and nonhematological toxicity by NCI CTC grade

	A (q3w), %					B (q1w), %					p value (after dichotomization ≤2/≥3)
	0	1	2	3	4	0	1	2	3	4	
Hematological toxicity											
Anemia	18.5	51.8	25.9	3.7	0	27.1	43.8	29.2	0	0	>0.05
Leukopenia	22.2	9.3	16.7	35.2	16.7	43.8	31.4	20.7	4.1	0	<0.0001
Thrombocytopenia	87.0	11.1	0	1.9	0	81.3	18.7	0	0	0	>0.05
Nonhematological toxicity											
Alopecia	20.3	9.2	70.5	0	0	29.2	12.5	58.3	0	0	>0.05
AP	66.7	27.8	5.6	0	0	60.4	27.1	6.3	6.3	0	0.02
Arrhythmias	94.4	3.7	1.9	0	0	93.8	0	4.2	0	2.1	>0.05
Bilirubin	96.3	1.8	1.9	0	0	83.3	6.3	6.3	4.2	0	>0.05
Constipation	74.1	16.7	9.3	0	0	81.3	10.4	4.2	4.2	0	>0.05
Creatinine	77.8	18.5	1.9	1.9	0	79.2	14.6	6.3	0	0	>0.05
Diarrhea	62.9	14.8	11.1	11.1	0	54.2	25.0	12.5	8.3	0	>0.05
Fever	79.6	5.6	5.6	7.4	1.9	87.5	6.3	4.2	2.1	0	>0.05
Fluid retention	72.2	22.2	3.7	1.9	0	81.3	4.2	12.5	2.1	0	>0.05
Gastrointestinal symptoms	90.7	5.6	1.9	1.9	0	100.0	0	0	0	0	>0.05
GGT	38.9	29.6	18.5	12.9	0	39.6	20.8	20.8	10.4	8.3	0.01
Infections	77.8	12.9	1.9	7.4	0	75.0	8.3	10.4	6.3	0	>0.05
Mucositis	64.8	14.8	12.9	7.4	0	64.6	20.8	8.3	4.2	2.1	>0.05
Musculoskeletal disorders	98.1	0	1.9	0	0	93.8	4.2	2.1	0	0	>0.05
Nausea and vomiting	48.2	29.6	14.8	7.4	0	52.1	33.3	10.4	4.2	0	>0.05
Neurotoxicity	59.3	25.9	11.1	3.7	0	54.2	31.3	14.6	0	0	0.01
Edema	79.6	12.9	3.7	1.9	1.9	89.6	4.2	4.2	0	2.1	>0.05
Pain	48.2	24.1	24.1	3.7	0	54.2	14.6	29.2	0	2.1	>0.05
Skin and nail disorders	59.3	12.9	22.2	5.6	0	70.8	8.3	6.3	14.6	0	0.03

Table 3. Toxicity profile: dose modifications

	All (n = 481)	q3w (n = 295)	q1w (n = 186)	p value
Cycles				
Dose reductions[a]	48 (9.98)	26 (8.81)	22 (11.83)	>0.05
Delayed doses[a]	45 (9.36)	23 (7.80)	22 (11.83)	>0.05
Omitted doses[a]	16 (3.33)	0	16 (8.60)	<0.001
Percentage of intended drug delivery	94.6	95.7	92.8	>0.05

[a] Reductions within a cycle; data given as n (%).

orders were observed more often in patients who received weekly scheduled docetaxel (5.6% q3w vs. 14.6% q1w; p = 0.03). Moreover, increased values for AP and GGT were measured significantly more often in the weekly arm.

The median number of applied cycles was 6 (range 1–8) for the standard arm and 4 (range 1–8) for the weekly arm. The median duration of treatment was 105 days (range 5–181) for the standard arm and 97.5 days (range 1–210) for the weekly schedule. There were no significant differences regarding dose reductions, delayed doses, or the percentage of the intended drug delivered within a cycle between the 2 regimens (standard vs. weekly dose). Solely, the rate of omitted doses within the cycle (days 1, 8, and 15) was significantly increased in the weekly arm (8.6% q1w vs. 0% q3w). These data are summarized in table 3.

Efficacy

In an intent-to-treat analysis, 1 CR, 33 PR, 36 SD, and 20 PD were observed. Twelve patients were not evaluable. The overall RR was 33.3% (95% CI 24.3–43.4). The RR in the group of standard docetaxel q3w was approximately twice as high as that of the weekly group (42.6% q3w vs. 22.9% q1w; p = 0.039). Nevertheless, the significantly higher response rate did not result in a significantly improved TTP (5.4 months q1w vs. 6.3 months q3w; p = 0.91) or OS (22.7 months q1w vs. 15.8 months q3w; p = 0.24) (fig. 1). The response and survival data are presented in tables 4 and 5 and in figure 1.

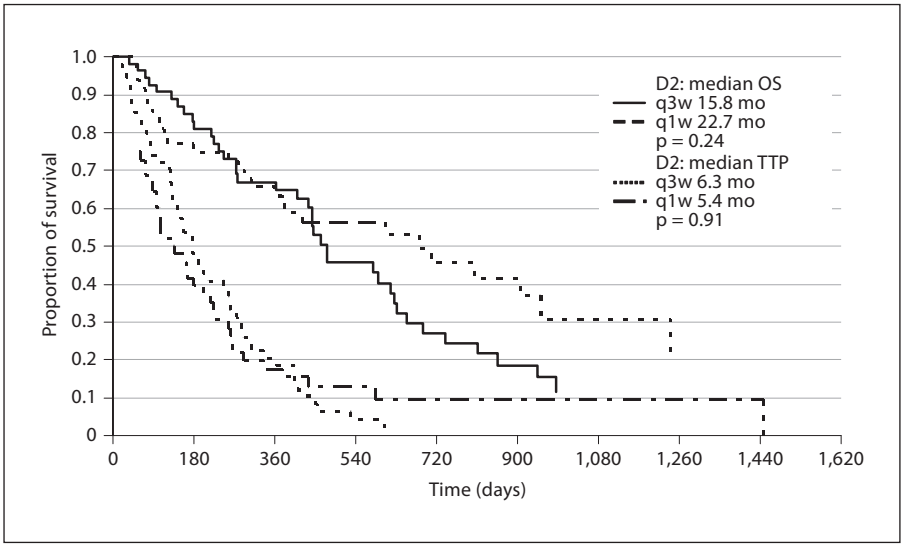

Fig. 1. TTP and OS for the q3w group versus the q1w group. mo = Months.

Table 4. Efficacy: RR (intent-to-treat analysis)

D2	CR	PR	SD	PD	Not evaluable	RR, %	95% CI, %	p
All patients (n = 102)	1	33	36	20	12	33.3	24.3–43.4	
q1w group (n = 48)	0	11	18	12	7	22.9	12.0–37.3	0.039[a]
q3w group (n = 54)	1	22	18	8	5	42.6	29.2–56.8	

[a] RR q1w versus q3w.

Table 5. Efficacy: TTP and OS

D2	q3w		q1w		p value (log-rank test)
	median	range	median	range	
TTP, months	6.3	0.4–20.1	5.4	0.7–48.2	>0.05
OS, months	15.8	1.2–32.8	22.7	1.8–41.4	>0.05

Discussion

Numerous phase II studies have shown a considerably reduced hematotoxicity of weekly scheduled docetaxel with stable efficacy in the first- or second-line setting of MBC [5–9]. These data led to the initiation of the randomized D2 study in July 2001 which compared a dose-adjusted 3-weekly regimen (75 mg/m^2) to a weekly regimen (30 mg/m^2) in elderly or medically unfit patients in first-line MBC.

As expected, leukopenia ≥grade 3 was rarely seen in the weekly arm of the D2 study (per-patient analysis: 4.2% q1w vs. 51.9% q3w; $p < 0.0001$). Due to the high significance of this finding, the study was stopped according to the study protocol after an interim analysis (the primary endpoint was toxicity, i.e. 'leukopenia'; recruited patients: 102 of 162 patients).

Skin and nail disorders are known sequelae of docetaxel [7, 16]. The frequency of these side effects (≥grade 3) was significantly increased in patients who were randomized to the weekly arm (14.6% q1w vs. 5.6% q3w; $p = 0.03$), whereas the rate of neurotoxicity ≥grade 3 was increased in the 3-weekly arm (3.7% q3w vs. 0% q1w; $p = 0.01$). Although these side effects can be a dose-limiting factor even in elderly patients, they did not result in a shorter treatment duration in the weekly arm (105 days q3w vs. 97.5 days q1w). Clinically irrelevant but significant changes in AP and GGT were observed more frequently in patients who received weekly scheduled docetaxel.

Despite a significantly lower hematotoxicity, the rate of omitted doses within a cycle significantly increased in patients who received weekly docetaxel (8.6% q1w vs. 0% q3w; p = 0.001). Except for an increased rate of skin and nail toxicity, we cannot provide any other reasonable explanation for this finding.

With regard to efficacy, the RR was inferior in the weekly arm compared to the standard regimen (22.9% q1w vs. 42.6% q3w; p = 0.039). Nevertheless, the almost doubled RR in the 3-weekly regimen did not result in any improvement regarding TTP or OS. TTP was 5.4 (q1w) versus 6.3 (q3w) months (p = 0.91), and OS was 22.7 (q1w) versus 15.8 (q3w) months, respectively (p = 0.24).

A conclusive statement regarding efficacy is restricted by the fact that the calculated sample size for the secondary efficacy endpoints (TTP and OS) was not reached in the D2 study because the study was terminated prematurely after reaching statistical significance for its primary endpoint in the interim analysis.

However, the present data confirmed the favorable and different toxicity profile of weekly scheduled docetaxel, without any suggestion of inferior results regarding TTP or OS. These data have basically been confirmed in 2 randomized phase III trials by Rivera et al. [10] and Tabernero et al. [11]. Patients who received docetaxel q3w in the study of Rivera et al. [10] experienced a more pronounced toxicity. Despite an inferior RR for the weekly schedule (20.3% q1w vs. 35.6% q3w), patients experienced similar PFS (5.5 q1w vs. 5.7 q3w months; p = 0.46) and OS (18.6 q1w vs. 18.3 q3w months; p = 0.34).

The rather low rate of severe leukopenia associated with weekly docetaxel may permit its combination with an anthracycline. Both agents are considered among the most active single agents for the treatment of early and MBC. Consequently, their combined use is a logical step in the search for highly effective chemotherapy combinations. Numerous phase II trials have investigated a 3-week scheduled anthracycline/taxane regimen with impressively high response rates of 46–88% [17–20]. However, the dose-limiting factor in these trials has been leukopenia, leading to the initiation of phase II trials investigating weekly anthracycline/taxane combinations. Such studies have shown proven efficacy with a manageable toxicity profile [21, 22]. Gamucci et al. [21] reported a considerably low rate of ≥grade 3 neutropenia of 16% of patients who received first-line weekly epirubicin (25 mg/m^2) and docetaxel (25 mg/m^2) for MBC [21]. The regimen was quite effective with a response rate of 60% and a median OS of 25 months. Moreover, Perez-Manga et al. [22] reported on a phase II study which investigated a combination of doxorubicin (50 mg/m^2 q4w) and weekly docetaxel (36 mg/m^2 days 1, 8, and 15; q4w) for locally advanced or metastatic breast cancer (first line) [22]. A consistently low rate of severe neutropenia (≥grade 3) was reported (7%, with 4% febrile neutropenia) and the RR were considerably high, i.e. 93 and 64%, among the locally advanced metastasized patients, respectively.

In conclusion, the results of the D2 study have confirmed the favorable toxicity profile of weekly docetaxel. Regarding efficacy, our study indicated equivalence in terms of TTP and OS. Nevertheless, these data need to be taken with caution due to the premature closure of the trial after reaching statistical significance for the primary endpoint in the interim analysis. The weekly regimen remains a valuable approach in elderly, unfit, or pretreated patients. Since phase II data indicated a greatly reduced hematotoxicity with weekly scheduled docetaxel/anthracycline combinations, a randomized phase III study (D4) has already been conducted to further evaluate this approach.

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