Original Article · Originalarbeit

Breast Care

Breast Care 2011;6:279–283
DOI: 10.1159/000330946

Published online: August 19, 2011

Re-Challenging Taxanes in Recurrent Breast Cancer in Patients Treated with (Neo-)Adjuvant Taxane-Based Therapy

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Keywords

Docetaxel · Paclitaxel · Adjuvant · Recurrent breast cancer

Summary

Background: Docetaxel and paclitaxel are among the most active substances for the treatment of breast cancer. As both drugs are used today in adjuvant regimens, efficacy data from pivotal trials in the metastatic setting in taxane-naive populations cannot reliably be used as references. **Patients and Methods:** The Taxane Re-Challenge Cohort Study identified participants from 6 prospective (neo-)adjuvant taxane-based studies with recurrent disease and collected data on their subsequent treatment. Out of 381 recurrent patients, 106 (27.8%) were re-challenged with a taxane-based treatment as first- or later-line therapy for recurrent disease. **Results:** Taxanes were used as first-line therapy in 74 patients and showed a response rate of 48.6% (including complete responses in 27.0%). The response rate was dependent on the disease-free interval (<1 year: 34.8%; 1–2 years: 42.9%; >2 years: 63.3%; p = 0.04) and visceral metastasis (present: 62.5%; not present 32.4%; p = 0.01). Patients without visceral metastasis and with a disease-free interval of >2 years achieved the longest overall survival. Hormone and HER2 receptor status were not predictive; however, triple-negative tumors responded in 50.0%. The overall response rate of later-line taxane-based treatment was 28.2%. **Conclusion:** Re-challenging taxanes appears to be effective and therefore represents a reasonable option in this population.

Schlüsselwörter

Docetaxel · Paclitaxel · Adjuvant · Rezidivierter Brustkrebs

Zusammenfassung

Hintergrund: Docetaxel und Paclitaxel gehören zu den aktivsten Substanzen in der Behandlung des Mammakarzinoms. Da sie heute häufig bereits zur adjuvanten Behandlung eingesetzt werden, können Effektivitätsdaten von früheren Studien mit Taxan-naiven, metastasierten Patientinnen nicht mehr als zuverlässig angesehen werden. **Patienten und Methoden:** Für die Taxane Re-Challenge Kohortenstudie haben wir Teilnehmerinnen 6 prospektiver Taxan-basierter (neo-)adjuvanter Studien mit rezidivierter Erkrankung identifiziert und Daten zur weiteren Behandlung gesammelt. Bei 106 (27,8%) von 381 Patientinnen mit einem Rezidiv oder einer Metastase wurde erneut ein Taxan in der ersten oder späteren Behandlung eingesetzt. **Ergebnisse:** Taxane wurden in der Erstlinie bei 74 Patientinnen angewandt und zeigten eine Ansprechrate von 48,6% (inklusive Komplettremissionen in 27,0%). Die Ansprechrate war vom krankheitsfreien Intervall (<1 Jahr: 34,8%; 1–2 Jahre: 42,9%; >2 Jahre: 63,3%; p = 0,04) und dem Vorhandensein viszeraler Metastasen (vorhanden: 62,5%; nicht vorhanden: 32,4%; p = 0,01) abhängig. Patientinnen ohne viszerale Metastasen und mit einem krankheitsfreien Intervall >2 Jahre überlebten am längsten. Hormon- und HER2-Rezeptorstatus waren für das Ansprechen nicht prädiktiv, jedoch sprachen tripelnegative Tumoren in 50.0% auf die erneute Taxan-Therapie an. Die Gesamtansprechrate auf ein erneutes Taxan in der späteren Linie betrug 28.2%. **Schlussfolgerung:** Der Wiedereinsatz von Taxanen erscheint effektiv und steht somit als sinnvolle Option für mit Taxanen (neo-)adjuvant vorbehandelte Patientinnen zur Verfügung.

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Introduction

Taxanes (docetaxel, paclitaxel, nab-paclitaxel) are among the most active substances for the treatment of breast cancer. Overall response rates of 25–69% have been reported when taxanes are used as first-line-treatment of metastatic breast cancer in taxane-naive patients [1–3]. However, as a consequence of the increase in the use of taxanes as therapy for early-stage breast cancer [4], more patients presenting with metastatic disease have been pretreated with taxanes. There is an almost complete lack of data as to how far the efficacy reported for taxanes in the pivotal trials remains stable with this change. First, patients relapsing despite having received (neo-)adjuvant taxane-based treatment might have more aggressive tumors, and second, metastasis of these tumors might be resistant to taxanes. Despite this lack of evidence, current guidelines recommend a re-introduction of a taxane for metastatic disease only after a treatment-free period of 1 year [5].

The Taxane Re-Challenge Cohort Study was conducted to determine the efficacy of taxane-based treatment as first-line or later-line therapy for recurrent or metastatic breast cancer in participants of (neo-)adjuvant taxane-containing chemotherapy trials.

Patients and Methods

Study Design

The Taxane Re-Challenge Cohort Study collected retrospectively data on treatment, efficacy, and outcome of patients with recurrent disease from 6 large-scale, multi-centric, prospective (neo-)adjuvant chemotherapy trials conducted in Germany between 1999 and 2008.

Objectives

Objectives of this study were the overall (complete and partial) response rate of first- and later-line taxane-based treatment, overall survival after relapse, to find the predictors for a better efficacy, and to determine the efficacy specifically in the subgroup of patients with triple-negative tumors.

Patient Characteristics

Eligible patients were identified from the study databases of the adjuvant or neoadjuvant trials of the German Breast Group and the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Breast Study Group [6–15]. All of them had been treated with either docetaxel or paclitaxel as part of their primary treatment (adjuvant or neoadjuvant chemotherapy) and had had a local or distant relapse reported. Overall, information on 381 out of 1100 patients with recurrent or metastatic breast cancer was received, representing 34.6% of all identified patients. 106 patients (27.8%) of those, from 41 centers, had received taxane-based treatment as first- or later-line therapy and were analyzed in this study.

Statistical Analysis

The primary objective of this trial was to show adequate activity of taxane retreatment measured by the objective response rate. Efficacy analysis was performed on the whole population; unavailable responses were considered as treatment failures. Response rates were compared using chi-square tests. Overall survival time was analyzed using Kaplan-Meier estimates. The log-rank test was used to test for differences between overall survival curves. Values of $p < 0.05$ were considered to be statistically significant. The data were analyzed using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient Characteristics

A total of 106 patients who received taxane-based treatment as first- or later-line therapy were enrolled in this cohort study. The median age of the patients was 48 (25–77) years. The baseline characteristics of all patients are given in table 1. 74 patients received re-challenge with a taxane as first-line treatment and 39 patients received taxane re-challenge at a later line (7 patients received both). First-line taxane treatment was given in combination in 44 patients, i.e. with anthracyclines (n = 27), capecitabine (n = 13), trastuzumab (n = 13), bevacizumab (n = 11), platinum compounds (n = 7), gemcitabine (n = 4), and vinorelbine (n = 2). The most frequently used regimens were docetaxel or paclitaxel with doxorubicin and cyclophosphamide. Monotherapy with paclitaxel was given to 17 patients and with docetaxel to 13 patients.

Efficacy and Outcome of Taxane Re-Challenge as First-Line Therapy

The overall response rate in 74 patients receiving re-challenge with taxanes as first-line treatment was 48.6%, consisting of 20 (27.0%) complete and 16 (21.6%) partial remissions. The

Table 1. Baseline characteristics of 106 patients re-challenged with taxanes as treatment for recurrent disease

Parameter	n (%)
Age, years	
< 50	60 (56.6)
50–69	45 (42.5)
> 70	1 (0.9)
ER/PgR status	
Positive	54 (50.9)
Negative	44 (41.5)
Unknown	8 (7.6)
HER2 status	
Positive	22 (20.8)
Negative	62 (58.5)
Unknown	22 (20.7)
Triple (ER/PgR/HER2)-negative status	
Yes	29 (27.4)
No	49 (46.2)
Unknown	28 (26.4)
Taxane type as (neo-)adjuvant chemotherapy	
Docetaxel	54 (50.9)
Paclitaxel	52 (49.1)
Chemotherapy setting	
Neoadjuvant	81 (76.4)
Adjuvant	25 (23.6)
Disease-free-survival until recurrence	
< 1 year	28 (26.4)
1–2 years	30 (28.3)
> 2 years	48 (45.3)
Visceral metastasis	
Yes	47 (44.3)
No	59 (55.7)

ER = Estrogen receptor, PgR = progesterone receptor.

Table 2. Clinical response to first-line taxane-based therapy

First-line therapy	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	Response unknown, n (%)
All (n = 74)	20 (27.0)	16 (21.6)	4 (5.4)	15 (20.3)	19 (25.7)
Docetaxel (n = 39)	6 (15.4)	9 (23.1)	4 (10.3)	10 (25.6)	10 (25.6)
Paclitaxel (n = 35)	14 (40.0)	7 (20.0)	0 (0)	5 (14.3)	9 (25.7)
Monotherapy (n = 30)	6 (20.0)	6 (20.0)	1 (3.3)	7 (23.3)	10 (33.3)
Combination therapy (n = 44)	14 (31.8)	10 (22.7)	3 (6.8)	8 (18.2)	9 (20.5)

CR = Complete response, PR = partial response, SD = stable disease; PD = progressive disease.

Table 3. Univariable analysis on response to first-line-therapy and overall survival according to patient characteristics

Parameter	Patients, n	CR/PR, n (%)	Chi^2, p	Median overall survival, years (95% CI)	Log rank, p
Age					
< 50	40	21 (52.5%)		1.4 (0.5–2.3)	
≥ 50	34	15 (44.1%)	> 0.1	1.3 (0.5–2.1)	> 0.1
ER/PgR status					
Positive	37	19 (51.4%)		1.5 (0.4–2.6)	
Negative	32	15 (46.9%)	> 0.1	1.3 (0.8–1.8)	> 0.1
HER2 status					
Positive	11	7 (63.6%)		4.0 (1.9–6.1)	
Negative	50	26 (52.0%)	> 0.1	1.3 (0.9–1.7)	> 0.1
Triple (ER/PgR/HER2)-negative status					
Yes	24	12 (50.0%)		1.4 (0.4–2.4)	
No	33	19 (57.6%)	> 0.1	1.5 (0.4–2.4)	> 0.1
Taxane as (neo-)adjuvant chemotherapy					
Docetaxel	39	19 (48.7%)		1.3 (1.0–1.6)	> 0.1
Paclitaxel	35	17 (48.6%)	> 0.1	1.2 (0.0–2.5)	
Disease-free interval until recurrence					
≤ 2 years	44	17 (38.6%)		0.9 (0.7–1.1)	0.002
> 2 years	30	19 (63.3%)	0.04	4.0 (1.9–6.1)	
Visceral metastasis					
Present	40	25 (62.5%)		1.0 (0.7–1.4)	
Not present	34	11 (32.4%)	0.01	2.4 (1.1–3.7)	0.04
Taxane as first-line therapy					
Docetaxel	39	15 (38.5%)		2.4 (1.1–3.7)	
Paclitaxel	35	21 (60.0%)	0.06	1.0 (0.5–1.4)	> 0.1

CR = Complete response, PR = partial response, CI = confidence interval, ER = estrogen receptor, PgR = progesterone receptor.

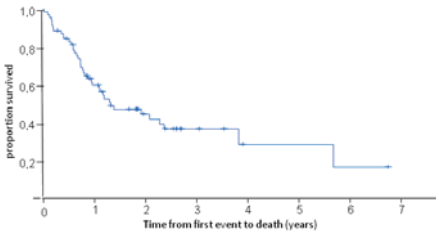

Fig. 1. Overall survival of patients receiving taxane re-challenge as first-line therapy.

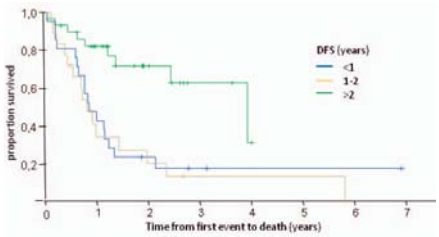

Fig. 2. Overall survival of patients receiving taxane re-challenge as first-line therapy according to the length of the disease-free interval.

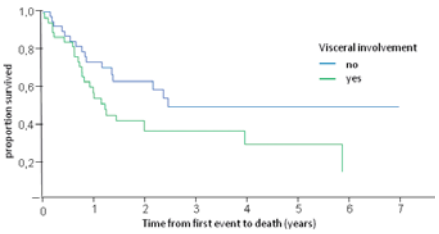

Fig. 3. Overall survival of patients receiving taxane re-challenge as first-line therapy according to the presence of visceral metastasis.

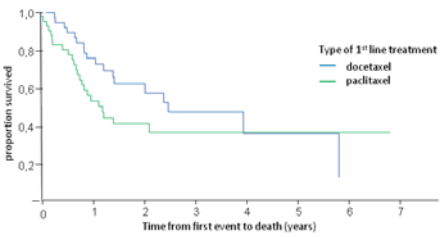

Fig. 4. Overall survival of patients receiving taxane re-challenge as first-line therapy according to the type of taxane used in this setting.

overall response rate was 54.5% with combination therapy and 40% with taxane monotherapy (p = 0.2) (table 2). Patients with a disease-free interval of < 1 year until recurrence showed a response rate of 34.8%, those with 1–2 years, a rate of 42.9%, compared to those with > 2 years having a response rate of 63.3% (p = 0.04). Other factors influencing the response rate were the presence of visceral metastasis (p = 0.01) and the type of taxane used (p = 0.06), whereas age, type of taxane used for (neo-)adjuvant treatment, and hormone and HER2 receptor status were not predictive (table 3). However, there was no difference in response rates in relation to the type of taxane that was used for re-challeng (table 2).

Table 4. Clinical response to later-line taxane-based therapy

Later-line therapy	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	Response unknown, n (%)
Docetaxel (n = 13)	0 (0.0)	2 (15.4)	1 (7.7)	2 (15.4)	8 (61.5)
Paclitaxel (n = 26)	1 (3.8)	8 (30.8)	8 (30.8)	2 (7.7)	7 (26.9)
All (n = 39)	1 (2.6)	10 (25.6)	9 (23.1)	4 (10.3)	15 (38.5)

CR = Complete response, PR = partial response, SD = stable disease; PD = progressive disease.

The median overall survival of these patients was 1.3 years (fig. 1). It was longer in patients with a disease-free interval of > 2 years (median overall survival (in years) for disease-free interval of < 1 year: 0.9; 1–2 years: 0.9; > 2 years: 4.0; p = 0.002) (table 3, fig. 2) and in patients without visceral metastasis (visceral metastasis present: 1.0 year; not present: 2.4 years; p = 0.04) (table 3, fig. 3). Patients treated with docetaxel as first-line treatment showed a trend towards a longer overall survival of 2.4 years compared to those treated with paclitaxel (1.0 year) (p = 0.1) (table 3, fig. 4).

Efficacy of Taxane Re-Challenge at a Later Line

A total of 39 patients were treated with a taxane for recurrent disease as later-line therapy. The median number of preceding regimens for metastatic disease was 3 (range 1–18). The overall response rate of later-line taxane-based treatment was 28.2%. The overall response rate with docetaxel was 15.4% and with paclitaxel 34.6% (table 4). There were 7 patients who received taxane-based treatment as first-line and later-line therapy. With these 7 patients, the best response to the first-line therapy was 1 complete response, and the overall response was 47.1%, (1 (14.3%) complete and 3 (42.9%) partial responses); the best response to later-line therapy was 1 (14.3%) disease stabilization.

Discussion

There is an increasing number of patients with metastatic breast cancer who are pretreated with taxanes in the (neo-) adjuvant situation. Therefore, it is essential to re-assess the efficacy of taxane-based treatment in this group of patients.

In this retrospective multicenter cohort study, we observed an overall response rate of 48.6%, consisting of 27.0% complete and 21.6% partial responses, with a median overall survival of 1.3 years in patients who received taxane-based treatment as first-line therapy. The response rate using taxane monotherapy was 40%, and using combination therapy, 54.5%. This is in the range of what was observed in trials including taxane-naive patients. 5 multicenter phase II trials for first-line treatment of metastatic breast cancer with docetaxel monotherapy of 75 or 100 mg/m^2 reported an overall response rate between 38 and 68% and a median overall survival of 16.4 months across these studies [16], and a phase III study assessing docetaxel and doxorubicin reported a response rate of 48% [17]. Docetaxel in combination with doxorubicin, doxorubicin/cyclophosphamide, and trastuzumab reached response rates of 59, 61, and 77%, respectively [18–20]. The response rate of paclitaxel monotherapy is largely dependent on dosing, infusion time and scheduling, and ranged between 22 and 62% [21, 22]. Combination of paclitaxel with doxorubicin as well as trastuzumab were highly effective, with response rates of 94 and 50%, but the former was associated with significant cardiotoxicity [23, 24].

The observed response rates with re-challenging a taxane appear higher than those with capecitabine, vinorelbine or ixabepilone in a similar setting, which were usually in the range of 20–30% [25].

The strongest predictors for the effect of taxane re-challenge were the presence of visceral metastasis and the duration of the disease-free interval. The observed higher response rate in patients with a longer disease-free interval can be explained by the assumption that tumors with high resistance to taxanes recur earlier. However, the observed response rate of 34.8% in patients with a disease-free interval of < 1 year shows that the use of taxanes in this specific population also represents a valid option. Furthermore, as we received information of approximately 30% of the target population, a selection bias cannot be ruled out.

The response rate of tumor phenotypes according to hormone and HER2 receptor status was not significantly different; however, the rate was highest in HER2-positive tumors (being treated additionally with an anti-HER2 agent). Surprisingly, triple-negative tumors usually considered to be highly resistant to palliative chemotherapy showed a response rate as high as 50%. This is in line with data with anthracyclines and taxanes as neoadjuvant therapy, with a high pathologic complete response rate [26, 27].

The re-challenge of taxanes at a later line resulted in a much lower response rate; however, these patients were heavily pretreated. Due to the small number and the wide heterogeneity of this population, the only firm conclusion that can be drawn from this cohort study is that a third use of taxanes does not seem to result in a clinical benefit for the patient (even with a good response at first line) and should be avoided.

Re-challenging taxane as first- or later-line treatment for patients with recurrent disease after (neo-)adjuvant taxane-based chemotherapy appears to be a reasonable option, also for patients with triple-negative tumors.

Disclosure Statement

This project received unrestricted funding by Sanofi-Aventis, Germany.

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