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ORIGINAL ARTICLE

Response rates of taxane rechallenge in metastatic breast cancer patients previously treated with adjuvant taxanes

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Summary

Purpose: *This study was conducted to determine the efficacy of taxane-based regimens in patients with metastatic breast cancer pre-treated with taxanes in adjuvant treatment and also to assess the response rates of taxanes in each treatment line.*

Methods: *The data of 939 breast cancer patients, who had received adjuvant taxane-based chemotherapy, were reviewed retrospectively. In 191 of them local/distant recurrences were detected. The treatments that were given when metastases occurred and the responses were recorded. Response rates (RRs), clinical benefit rates/CBR (complete response/CR + partial response/PR + stable disease/SD) and progression-free (PFS) and overall survival (OS) values were determined. RRs to the most frequently used protocols in our institutes (capecitabine-based and taxane-based regimens) were compared.*

Results: *Of 191 patients, 11 didn't receive treatment and for the remaining 180 patients 45 (24%) received taxane-based therapies, 89 (49.4%) received capecitabine-based therapies, 28 (15.6%) received hormonotherapy and 18 (10%) received other chemotherapeutics. The RR for first-line taxane regimen was 58.5%, consisting of 5 CRs (12%) and 19 PRs (46%). Menopausal status, histological grade, estrogen/progesterone receptors, cerbB2 status, having PFS > or ≤ 2 years and the site of metastases did not predict response to first-line taxane treatment. For the 2nd and 3rd or later line therapies, RRs of taxane rechallenge were above 40%.*

Conclusion: *Rechallenging with taxanes after (neo)adjuvant taxane exposure seems to be a reasonable option even in 3rd or further line treatments with high response rates.*

Key words: *breast cancer, rechallenge, response rates, taxanes.*

Introduction

Taxanes are among the most active chemotherapeutic agents used in breast cancer. In the metastatic setting, overall RRs of 25-70% have been reported when used at first line in taxane-naive patients with metastatic breast cancer (MBC) [1]. Moreover, there is cumulative evidence that addition of a taxane to an antracycline-based treatment improves both DFS and OS in early-stage breast cancer patients [2,3]. However, as there is an increasing tendency for the use of taxanes in adjuvant treatment of high-risk early-stage breast cancer, more patients presenting with MBC have previous taxane exposure. So, consideration has to be given to the benefits of taxane rechallenge in the metastatic setting.

The concept of rechallenging an active chemotherapeutic agent after a pre-defined interval is a valid option in some tumor types. It has been proposed in the management of ovarian cancer, Hodgkin's disease and small cell lung cancer in

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selected patient groups [4-6]. However, data on taxane rechallenge in breast cancer is scarce. First, patients relapsing after (neo) adjuvant taxane treatment might have different response rates compared with those reported in pivotal trials of taxane-naive patients in the metastatic settings. Second, whether the length of taxane-free period has an impact on response rate after re-introduction is not known. Current guidelines and clinical trial registries recommend re-use of taxanes for MBC after an arbitrary and variable (6-12 months) period of prior taxane exposure [7,8] despite the lack of prospective randomized data. Since some other chemotherapeutics including capecitabine, gemcitabine, vinorelbine or combinations of these agents are also available, the optimum time and sequence to use taxanes along with other chemotherapy options is debatable in taxane pretreated patients.

This retrospective study was conducted to determine the efficacy of taxane-based regimens in patients with MBC pre-treated with taxanes in adjuvant treatment and also to assess the response rates of taxanes in each treatment line. This study also aimed to compare the clinical outcomes and RRs of taxanes with other agents in this setting.

Methods

This study was approved by Baskent University Institutional Review Board (Project No:KA14/166).

The data of 939 patients with MBC diagnosed and treated between 2007 and 2014 in two cancer centers (Baskent University Hospital, Department of Medical Oncology and Hacettepe Institute of Oncology) who had received adjuvant taxane (paclitaxel or docetaxel) based chemotherapy were retrospectively reviewed. Besides demographic variables of the patients, characteristics of the tumor and metastatic sites, treatments that were given when recurrence/metastases occurred and responses were recorded. RRs, CBR: CR + PR+ SD and PFS and OS values were determined. RRs to the most frequently used protocols in MBC in our institutes (capecitabine-based and taxane-based regimens) were compared.

Progression-free survival-1 (PFS1) was defined as the time interval from breast cancer diagnosis to the date of first recurrence or metastases and PFS2 was the time to second progression.

Statistics

Statistical analyses were made by SPSS version 17.0. For patient and tumor characteristics, descriptive statistical methods were used. Chi-square test was used to compare differences between categorical variables. Kaplan-Meier curves were generated to obtain survival probabilities and log rank test was used to compare the curves between groups. P levels <0.05 were considered to be statistically significant.

Results

Of 939 patients who had received adjuvant taxane, local/distant recurrences were detected in 191 (20.3%) of them. All further analyses were performed in these patients. Median age was 44 years (range 19-73) and only 1 patient was male (0.5%). Median tumor size was 4 cm (range 0.8-16) and median number of total and metastatic axillary lymph nodes were 23 (range 1-77) and 9 (range 0-56) respectively. Baseline patient and tumor characteristics are displayed in Table 1.

Median follow up of the patients was 46.4 months (range 13.3-189) and median PFS1 was 25.4 months (range 1-143). At first recurrence, 45 patients (24%) received taxane-based treatment (74% monotherapy, 26% combination), 89 (49.4%) received capecitabine-based treatment (85% monotherapy, 15% combination), 28 (15.6%) received

Table 1. Baseline characteristics of patients and tumors

Parameters	*N (%)*
Menapousal status	
Pre	109 (57.1)
Post	69 (36.1)
Peri	12 (6.3)
Estrogen receptors	
Positive	125 (65.4)
Negative	64 (33.5)
Progesterone receptors	
Positive	120 (62.8)
Negative	69 (36.1)
cerbB2	
Negative	116 (60.7)
Positive	65 (34)
T stage	
T1	14 (7.3)
T2	105 (55)
T3	56 (29.3)
T4	12 (6.3)
N Stage	
N0	7 (3.7)
N1	41 (21.5)
N2	50 (26.2)
N3	89 (46.6)
Adjuvant treatment	
Anthracycline	182 (95.3)
Paclitaxel	67 (35.1)
Docetaxel	124 (64.9)
Trastuzumab	48 (25.1)
Radiotherapy	176 (92.1)
Sites of first metastases	
Local	17 (8.9)
Bone and soft-tissue	66 (34.6)
Visceral	106 (55.5)

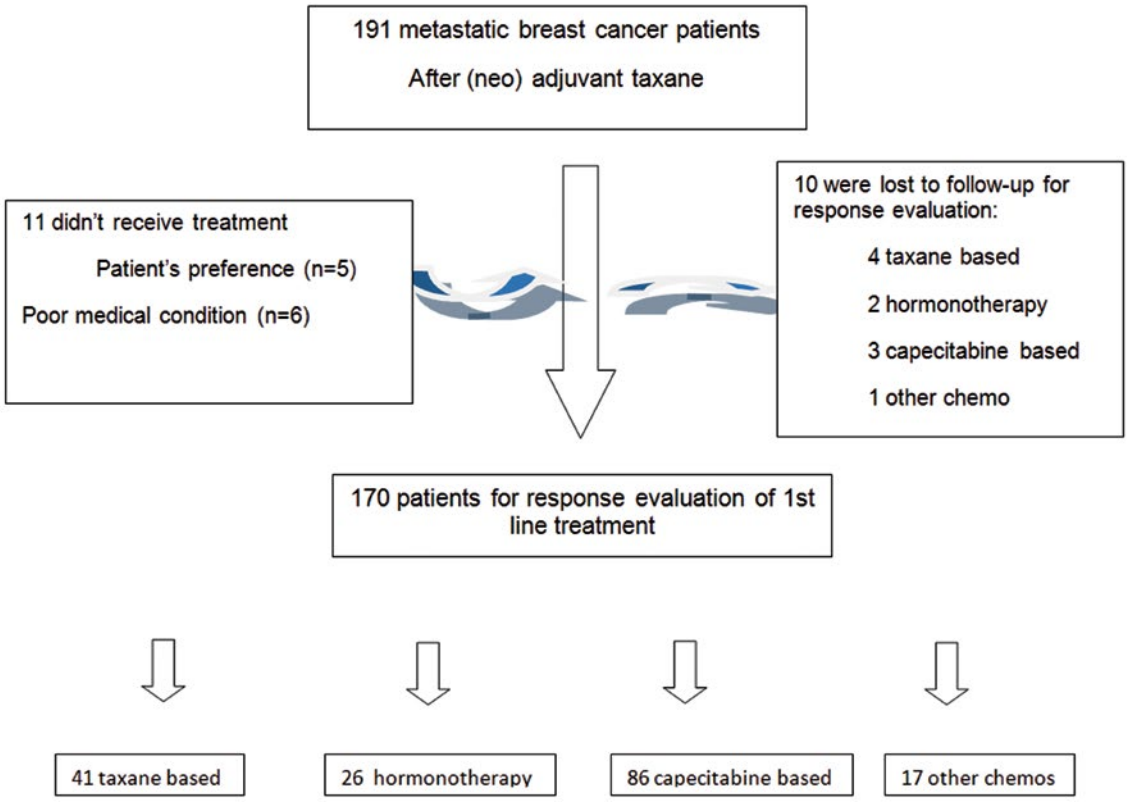

Figure 1. Analytical diagram of the patient population.

Table 2. Responses to first-line treatments

Treatments (N)	*CR N (%)*	*PR N (%)*	*SD N (%)*	*PD N (%)*	*p value*
Taxane-based (41)	5 (12.2)	19 (46.3)	7 (17.1)	10 (24.4)	
Hormonotherapy (26)	7 (26.9)	9 (34.6)	5 (19.2)	5 (19.2)	
Capecitabine-based (86)	15 (17.4)	35 (40.7)	20 (23.3)	16 (18.6)	0.29
Other chemo (17)	1 (5.9)	3 (17.6)	5 (29.4)	8 (47.1)	

For abbreviations see text

hormonotherapy and 18 (10%) received other chemotherapeutics. The analytical diagram of the 191 patients is shown in Figure 1. PFS1 was similar in taxane re-challenge group and in those receiving other first line regimens (26 vs 28 months, respectively, p=0.585). When disease progression occurred after first-line treatments, 56% of those who had received taxane as first line treatment received capecitabine-based regimens and 54% of those who had received capecitabine as first-line received taxane-based regimens thereafter.

Because 10 patients were lost to follow-up, RRs rates were evaluated in 170 patients. The overall RR for first-line taxane regimen was 58.5% consisting of 5 CRs (12%) and 19 PRs (46%).The RRs to first-line taxane-based and non-taxane-based treatments were similar (p=0.29) and are given in Table 2. Patients who received first-line taxanes and had PFS1 ≤ 2 years had similar RRs (p=0.30) and time to second recurrence (PFS2) (p=0.65) compared with those who had PFS1 >2 years. Menopausal status, histological grade, estrogen/progesterone receptor, cerbB2 status and the site of metastases did not predict response to first-line taxane treatment. Thirty-one patients had received taxanes at second line and 34 had received at third or further lines. The overall RRs and CBRs of taxanes at first-line and subsequent lines are summarized in Table 3.

Table 3. Response rates of taxane re-challenge in treatment lines

1st line %	*2nd line %*	*≥3 rd line %*
58.5	45.2	41.2
75.6	68.9	55.9

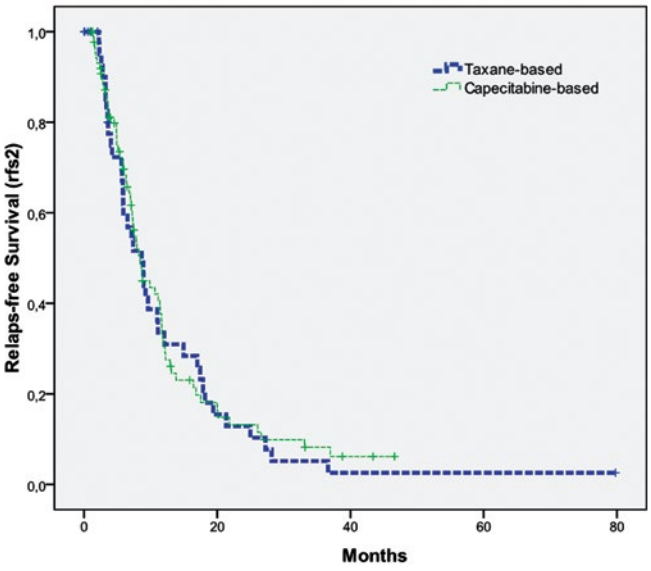

Figure 2. Relapse free survival after first recurrence in taxane and capecitabine treated groups (median 8.7 vs 8.4 months, respectively; p=0.751).

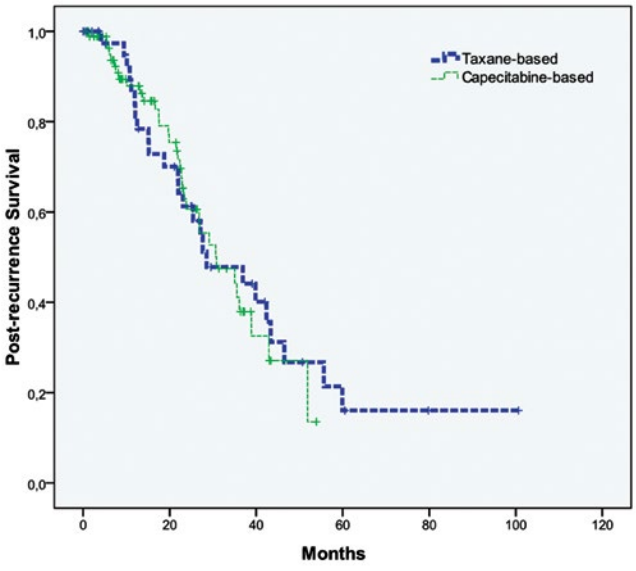

Figure 3. Overall survival after first recurrence in taxane and capecitabine treated groups (median 28.5 vs 30.8 months, respectively; p=0.801).

The RRs and CBRs of those who had received the same taxane vs a different taxane in the adjuvant and metastatic setting were similar (p=0.86 and 0.46, respectively). RFS2 of the patients that received the same taxane both in adjuvant and metastatic setting was 8.9 months, whereas it was 6.5 months in those who had different taxanes in adjuvant and metastatic treatments (p=0.77).

Being the most commonly used 2 regimens in our study, we seperately compared outcomes of the patients who received taxane-based (group T) and those who received capecitabine-based (group C) regimens at the first recurrence. The RRs (58.5 vs 58.1%, respectively, p=0.64) and CBRs were similar (75.6 vs 81.4%, respectively, p=0.603). Progression free survival after first recurrence (PFS2) was 8.7 vs 8.4 months respectively in group T and group C (p=0.751) (Figure 2). Post recurrence median OS was 28.5 vs 30.8 months respectively in group T and group C (p=0.801) (Figure 3). Median OS from the time of diagnosis were 67.6 vs 70.3 months respectively in group T and group C (p=0.814). Of note, patients in group T had higher rate of visceral metastases (73.3 vs 51%, respectively), while those in group C had higher rate of local recurrence or bone/soft tissue metastases (24.5 vs 48.3%) (p=0.005). Estrogen receptor, progesterone receptor and cerbB2 positivity rates and histological grades were similar in groups T and C (p=0.53, 0.53, 0.11 and 0.73, respectively).

Discussion

Patients with breast cancer and symptomatic visceral metastases or that are endocrine treatment-refractory should receive chemotherapy in the metastatic setting. Once anthracyclines and taxanes have been used in the adjuvant treatment, the evidence regarding the utility and sequence of subsequent chemotherapeutics is limited. In this retrospective study, we found an overall RR of 58.5% with taxane re-challenge in the first-line setting, and also 2nd and ≥3rd line taxane rechallenge responses were quite high. These are comparable with the RRs reported in the trials of first-line taxane treatment in patients with MBC. In the phase III trials of docetaxel and paclitaxel as single agents or combined with anthracyclines and/or trastuzumab in taxane-naive patients, the reported RRs were between 48% and 62% [9,10]. Since the RRs in our study are similar to the previously reported RRs of taxanes in taxane-naive patients, taxane reintroduction seems to be appropriate at any line in metastatic setting in previously treated patients in the adjuvant setting.

Data for rechallenging with taxanes in breast cancer originate mainly from phase II pharmacokinetic studies about cross-resistance between docetaxel and paclitaxel or from retrospective studies in patients with MBC. In a phase II study designed for schedule-dependent resistance for paclitaxel in MBC, overall RR of 26.9% with median response duration of 6 months was achieved with 96-hr paclitaxel infusion after progression on short taxane administration in metastatic setting [11]. In another retrospective analysis on weekly paclitaxel administration in MBC after docetaxel exposure, an overall RR of 19.5% was found. Docetaxel resis-

tance pattern (primary resistance, secondary resistance, short/long intervals) was found to be strongly correlated with paclitaxel responses (response rates were 8.3, 17.9 and 36.8% respectively) [12]. In the docetaxel rechallenge studies in patients with MBC after paclitaxel exposure in any metastatic line therapy, similar RRs (18.1-25%) were obtained both in resistant and refractory cases, proving partial cross-resistance between these two agents [13,14].

In a retrospective analysis, the efficacy of docetaxel rechallenge after a minimum docetaxel-free interval of 3 months was evaluated in 72 patients with MBC who had an objective response or stable disease after docetaxel treatment in the metastatic setting. It was found that 76% of the patients obtained a benefit (PR + SD >6 weeks+biochemical response for patients with no RECIST evaluation available) from docetaxel rechallenge used in 2nd, 3rd or ≥4th line chemotherapy. Median time to progression (TTP) and OS values after docetaxel rechallenge were reported as 5.7 and 10.2 months, respectively. Docetaxel-free interval (<6 vs ≥6 months) did not predict TTP in this study [15].

The results of all these previous taxane rechallenge studies have demonstrated that treatment with taxanes in patients with prior exposure to taxanes can yield objective responses, an evidence that makes taxane rechallenging a reasonable option in patients with MBC. But in most of these studies, prior taxane exposure was mostly in the metastatic setting. The number of patients who had received previous taxane in (neo) adjuvant setting was quite low and the RRs of these patients to taxane rechallenge were not separately evaluated [16,17]. In the phase III AVEREL trial evaluating bevacizumab in combination with docetaxel and trastuzumab as first line therapy in Her2(+) MBC, hazard ratios for PFS were nearly identical in patients who received prior taxane therapy and in those who did not (0.81 vs 0.83). Previous adjuvant taxane was permitted if received ≥ 12 months before random assignment in this study [18]. Another study evaluating the efficacy of docetaxel and sunitinib in first-line treatment of MBC also showed that prior taxane exposure was not associated with PFS [19]. Despite supplying data on taxane rechallenge, the use of bevacizumab, trastuzumab or sunitinib along with docetaxel confounds response rates, limiting thus the evaluation of taxane efficacy in these studies.

Recently, Guo et al. [20] have evaluated retrospectively the outcomes and efficacy of taxane rechallenge in 106 patients with MBC who had previous taxane exposure in the (neo)adjuvant setting. The overall RRs were 48.6% for the 74 patients who had taken first-line taxane-based treatments and 28.2% for ≥2nd line taxane treatments. For these 74 patients, the median OS was 1.3 years and median DFS and presence of visceral metastases were predictors of OS. Median OS in patients with DFS ≤2 years (N=44) and >2 years (N=30) were 0.9 and 4 years, respectively (p=0.002). In our study, ≥2nd line taxane rechallenge RRs were noticeably higher. We have detected a RR of >40% (2 CRs and 12 PRs) in patients who had received taxanes in ≥3rd line setting, which is quite high for such a heavily pretreated group of patients. Different from the study by Guo et al. [20], disease free interval did not predict efficacy of subsequent taxane rechallenge in patients treated with (neo)adjuvant taxanes. Since the number of patients who had relapses within 12 months after adjuvant taxane treatment was low (N=2) in our study, no sound conclusion about those patients can be drawn with our data.

The retrospective nature and the heterogeneity of the other treatments given are the limitations of our study. However, the RR of taxane rechallenge in any line seems to be prosperous and comparable to other non-taxane based treatment regimens. So, rechallenging with taxanes after (neo)adjuvant taxane exposure seems to be a reasonable option even in 3rd or further line treatments with high RRs.

Conflict of interests

The authors declare no confict of interests.

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