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Weekly Paclitaxel in Pretreated Metastatic Breast Cancer: Retrospective Analysis of 52 Patients

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BALTALI, E., ALTUNDAG, K., OZISIK, Y., GULER, N. and TEKUZMAN, G. *Weekly Paclitaxel in Pretreated Metastatic Breast Cancer: Retrospective Analysis of 52 Patients*. Tohoku J. Exp. Med., 2004, **203** (3), 205-210 —— Single-agent paclitaxel has been shown to be effective as both first- and second-line treatment of metastatic breast cancer, and the efficacy and tolerability of weekly administration of paclitaxel has generated much interest. Fifty-two patients with pretreated metastatic breast cancer who were admitted to Hacettepe University between January 2001 and June 2002 were retrospectively analyzed in this study. Paclitaxel was administered weekly in a dose of 80 mg/m^2 over 1 hour. The median number of cycles delivered was 20 weeks (range, 8 to 24). The median delivered dose was 2400 mg (range, 960 to 3840 mg). At a median follow-up of 12.3 months (range, 6 to 17), all patients were assessable for response and toxicity. A complete response and partial response were observed in 7 (13.5%), and 19 (36.5%) patients, respectively. Overall response rate was 50%. Median duration of response was 10 months (range, 3 to 16). Therapy was generally well tolerated, and toxicities were manageable. Severe leukopenia was seen in two (4%) patients. Based on these results, we conclude that weekly paclitaxel is a well-tolerated and highly effective regimen in pre-treated metastatic breast cancer. ———— metastatic breast cancer; weekly paclitaxel; chemotherapy

Although fewer than 10% of patients initially diagnosed with early-stage breast cancer present with distant metastases, an estimated 20% to 30% of patients will eventually develop them (Ellis et al. 2000). The primary aim of treatment of metastatic breast cancer is palliation; treatment improves length and quality of life without hope of cure (Fossati et al. 1998), and few patients with metastatic disease are long-term survivors (Ellis et al. 2000). New treatment options are needed because many of these patients have previously received chemotherapy, either as adjuvant therapy or for metastatic disease. Tolerability of treatment for metastatic breast cancer is an important consideration.

Single-agent paclitaxel has been shown to be effective as both first- and second-line treatment of metastatic breast cancer (Perez 1998). Overall

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rates of 21% to 62% have been reported in trials evaluating paclitaxel at doses of 135 to 250 mg/m^2 administered by either 3- or 24-hour infusion as initial or subsequent therapy to women with metastatic breast cancer (Nabholtz et al. 1996; Bishop et al. 1999; Smith et al. 1999; Paridaens et al. 2000). Neutropenia is the most common toxicity in these studies.

Recently, the efficiacy and tolerability of weekly administration of paclitaxel given in a 1-hour infusion has generated much interest. Weekly paclitaxel at doses of 80 to 100 mg/m^2 have produced an overall response rate of 2.1% to 86% (Perez et al. 2001; Luck and Roche 2002). The rationale for this approach is that more frequent delivery of moderate doses may achieve greater efficacy than standard doses every 3 weeks (Seidman et al. 1998). Dose-dense paclitaxel may inhibit tumor regrowth between cycles and limit the emergence of malignant cell populations resistant to chemotherapy. More frequent exposure to paclitaxel may enhance its apoptotic and antiangiogenic effects (Belotti et al. 1996; Milross et al. 1996). Reduced incidence of side effects, including neutropenia and peripheral neutropenia, is another advantage of weekly administration of paclitaxel.

Materials and Methods

Patients with metastatic breast cancer, with measurable disease who were admitted to Hacetepe University between January 2001 and June 2002 were eligible for evaluation in this study. Patients were required to be $\geqq$18 years of age; have an Eastern Cooperative Oncology Group performance status $\leqq$2; have life expectancy exceeding 3 months; have bilirubin and creatinine levels less than 1.25×the upper limits of normal, and have an absolute neutrophil count above 1.5×10^9/liter. Patients may have received up to two prior chemotherapy regimens for metastatic disease. Previous treatment with taxane administration on a 3-week schedule was allowed.

The criteria for exclusion included patients with known hypersensitivity; New York Heart Association class 3 or 4 disease; pre-existing peripheral neuropathy higher than grade 1; pregnancy and/or and breast feeding; a corrected serum calcium level of $\geqq$12 mg/100 mL at study entry; and a second primary cancer except for basal cell carcinoma of the skin and cervical carcinoma in situ.

Pre-treatment staging procedures included a complete history and physical examination, complete blood count and liver and kidney function tests, chest x-ray, bone scan and x-ray of metastatic bones, abdominal and pelvic ultrasonography, electrocardiography and echocardiography. Computed tomography of the chest, liver, abdomen, or cranium was performed when clinically indicated.

Paclitaxel was administered weekly in a dose of 80 mg/m^2 over 1 hour. Pre-medications consisted of intravenous diphenhydramine 50 mg and H_2 blocker (such as intravenous ranitidine 50 mg), and intravenous dexamethasone 16 mg all administered 30 to 60 minutes before treatment. If no hypersensitivity reactions were seen after first paclitaxel administration, the dose of dexamethasone was reduced by half each consecutive week. Treatment continued until the disease progressed or severe toxicity occurred. Physical examination, complete blood count and toxicity assessment were performed weekly. Serum chemistry was assessed every 2 weeks. Dose modifications were evaluated according to guidelines of the European Organization for Research and Treatment of Breast Cancer Cooperative Group (1998). Adverse effects were determined according to World Health Organization (1999) criteria. Mild toxicity indicates grade 1, and grades increase up to grade 4 as the severity of toxicity increases.

Tumor measurements were obtained every eight cycles to evaluate response. All responses were confirmed by a second measurement after an additional 4 weeks. Response criteria were as follows: (a) complete response, a disappearance of the primary tumor clinically and radiologically; (b) partial response, a tumor reduction of $\geqq$50%;

(c) stable disease, a tumor reduction of <50%, or an increase in tumor size of <25%; and (d) progressive disease, an increase in tumor size of ≧25% or appearance of any new lesion. Statistical analysis was evaluated by the χ^2 test. Duration of response was calculated from the day the response was first recorded until the day of disease progression.

Results

Fifty-two patients were retrospectively analyzed. Patient characteristics are listed in Table 1. The median age of the patients was 49 (range, 28 to 70). A majority of patients (90%) had an Eastern Cooperative Oncology Performance status of 0 or 1. The majority of patients (89%) had received adjuvant or neoadjuvant treatment. All patients who had positive hormone receptor status had received tamoxifen in the adjuvant or neoadjuvant setting. A total of 20 (38%) patients had received prior taxane therapy in the metastatic setting (8 patients with paclitaxel, 12 patients with docetaxel). All patients had received anthracycline containing regimens in the metastatic or adjuvant or neoadjuvant setting (Table 1).

The median number of cycles delivered was 20 weeks (range, 8 to 24). The median delivered dose was 2400 mg (range, 960 to 3840 mg).

At a median follow-up of 12.3 months (range 6 to 17), all patients were assessable for response and toxicity. Complete response or partial response was observed in seven (13.5%), and 19 (36.5%) patients, respectively. The overall response rate was 50%. There were 5 (10%) patients categorized as stable diseases, and 21 (40%) categorized as progressive diseases. the clinical benefit was 60% (Table 2). These overall response rates were not statistically different between patients who had received prior therapy with taxane and those who had not (55% vs. 45%). Response rates were different between patients with visceral metastases and those with soft-tissue metastases. Progressive disease was more commonly seen in patients with visceral metastases than in patients with soft-tissue me-

Table 1. *Patient characteristics*

	No.	%
Total no. of patients	52	100
Median age	49	
Range	28-70	
Menopausal status		
Premenopausal	20	38
Postmenopausal	32	62
ER status		
Negative	16	31
Positive	28	54
Unknown	8	15
Performance status (ECOG)		
0	32	62
1	15	28
2	5	10
Site of metastasis		
Soft tissue	20	38
Bone	16	31
Liver	8	15
Lung	4	8
Other	4	8
Prior chemotherapy		
Adjuvant therapy	32	62
Neoadjuvant therapy	14	27
Metastatic therapy	52	100
Prior therapy		
Taxane	20	38
Anthracycline	52	100

ER status, estrogen receptor status;
ECOG, Eastern Cooperative Oncology Group.

Table 2. *Response to therapy*

Response	No. of patients	%
CR	7	13.5
PR	19	36.5
SD	5	10
PD	21	40
Total	52	100

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

tastases (52% vs. 24%) (Table 3). Median duration of response was 10 months (range 3 to 16). Median duration of response for metastases that were either visceral or soft tissue only was 8.5 months and 16 months, respectively.

Therapy was generally well tolerated, and effects of toxicities were manageable. Grade 3 or 4 leukopenia was seen in two (4%) patients. No neutropenia-associated fever occurred in these patients, who had received two different chemotherapy regimens for metastatic disease. Of 52 patients, 2 (3.5%) and 5 (10%) developed grade 1 and 2 peripheral neuropathy. Gastrointestinal toxicities (stomatitis, nausea-vomiting, diarrhea) were rarely seen. and grades 1 and 2 were easily manageable (Table 4).

TABLE 3. *Response to therapy according to metastatic sites*

Response	No. (%)		
	Soft tissue	Visceral	Total
CR	5 (24)	2 (6)	7 (13.5)
PR	9 (43)	10 (32)	19 (36.5)
SD	2 (9)	3 (10)	5 (10)
PD	5 (24)	16 (52)	21 (40)
Total	21 (100)	31 (100)	52 (100)

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

TABLE 4. *Treatment-related toxicity*

	Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
Nausea-vomiting	14	27	4	7.5	0	0	0	0
Stomatitis	3	6.5	1		0	0	0	0
Diarrhea	3	6.5	2	3.5	0	0	0	0
Hepatotoxicity	3	6.5	1	2	0	0	0	0
Anemia	3	6.5	0	0	0	0	0	0
Leukopenia	9	17	3	6.5	1	2	1	2
Neuropathy	5	10	2	3.5	0	0	0	0
Alopecia	6	13	10	19.5	5	10	0	0
Nail disorder	7	14	1	2	0	0	0	0
Arthralgia/myalgia	9	17	4	7.5	2	3.5	0	0

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

DISCUSSION

Metastatic breast cancer is still considered an incurable disease, and the primary aim of treatment is palliation. The best that can be expected of treatment is that it will improve length and quality of life, and there is no hope of cure (Fossati et al. 1998). Tolerability of treatment is an important consideration and the efficacy and tolerability of weekly administration of paclitaxel given in 1-hour infusion has generated much interest. Weekly paclitaxel at doses of 80 to 100 mg/m^2 has produced an overall response rate of 2.1% to 86% (Perez et al. 2001; Luck and Roche 2002).

We observed that weekly paclitaxel therapy was well tolerated and showed some efficacy in patients who had received one or two chemotherapy regimens for metastatic disease.

We found an overall response rate of 50% with weekly paclitaxel (80 mg/m^2) in pre-treated metastatic breast cancer patients. The clinical benefit was 60%. Our results were comparable

with response rates observed in other phase II weekly paclitaxel studies, although the eligibility criteria of these studies were different (Perez et al. 2001; Gori et al. 2002; Luck and Roche 2002).

As increasingly more patients are receiving anthracyclines in the adjuvant setting, the use of taxanes as front-line chemotherapy will increase. In the first reported study of weekly paclitaxel administered as first-line chemotherapy for metastatic breast cancer, paclitaxel 100 mg/m^2 resulted in a 40% overall response rate and 67% clinical benefit. Time to progression was 189 days, the duration of response was 180 days, and overall survival was 544 days (Wist et al. 2004). Thus, this study has shown that weekly paclitaxel as first-line therapy for metastatic or advanced breast cancer produces comparable response rates and less toxicity than when the drug is given every 3 weeks. More studies are warranted to demonstrate its role as front-line treatment.

Another study evaluated the activity and toxicity of weekly paclitaxel, 80 mg/m^2 as first-line chemotherapy in elderly patients (>70 years of age) with hormone-refractory metastatic breast cancer. Of 23 patients who were evaluable for response, 10 had partial responses (38%), and 9 had stable disease (35%), while 4 had disease progression (15%). The median duration of response was 194 days (>6 months). Overall, treatment was relatively well tolerated (Ten Tije et al. 2004). This study also showed that weekly paclitaxel at this dose and schedule is an effective treatment regimen in the elderly patient with metastatic breast cancer, and that this treatment is feasible. Thus, weekly regimens may be more suitable for elderly patients and those with a lower performance status.

The toxicity profile of weekly paclitaxel was also favorable. Only two patients (4%) developed grade 3 or 4 leukopenia without any fever. No grade 3 or 4 neuropathy was observed to cause reduction of the dose or cancellation of the treatment. Gastrointestinal toxicities were usually grade 1 or 2 and manageable.

Minimal toxicity and satisfactory efficacy may provide an opportunity to combine this regimen with other agents including trastuzumab. A Phase IIb randomized study showed the superiority of a weekly paclitaxel and trastuzumab combination over single agent weekly paclitaxel (Gasparini et al. 2003). Direct comparison of weekly paclitaxel with 3-weekly paclitaxel may enlighten us as to the efficacy and toxicity profiles of these regimens.

In conclusion, weekly paclitaxel is well tolerated and a highly effective regimen in pretreated metastatic breast cancer.

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