www.journalofcancerology.com PERMANYER J Cancerol. 2015;2:75-9

JOURNAL OF CANCEROLOGY CLINICAL CASE

Weekly Paclitaxel for Metastatic Breast Cancer in Patients Previously Exposed to Paclitaxel

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ABSTRACT

Background: Retreatment with weekly paclitaxel in heavily pretreated breast cancer patients has been reported before with varying results, but has not been addressed specifically. **Methods:** Patients with metastatic breast cancer, histologically confirmed with measurable disease, previously exposed to weekly paclitaxel in the adjuvant or neoadjuvant setting or as therapy for metastatic disease were treated with paclitaxel 80 mg/m^2 body surface area, weekly for three weeks with an interval of one week rest (four-week cycle). **Results:** 18 patients were enrolled from December 2011 to July 2013; 100% of the patients had received paclitaxel previously, 39% neoadjuvant, 17% adjuvant, 44% in the metastatic setting. Of the patients, 56% were in the fifth line, 28% in the third line, and 16% in the fourth line. Thirty-three percent of the patients received paclitaxel more than a year before, 11% more than four years, and 56% more than seven years. Grade 3 neutropenia was observed in 12%, and one case of grade 4 neutropenia was observed. There were no deaths due to toxicity. Grade 1 peripheral neuropathy was observed in 34% of the patients, grade 2 in 22%, and grade 3 in 12%. Two patients had therapy withheld due to neuropathy. Progression-free survival was 6.2 months for the whole group. Partial responses were seen in 28% and stable disease in 61%. Two patients had progressive disease. **Conclusions:** Retreatment with this schedule of weekly paclitaxel was well tolerated and effective in controlling metastatic breast cancer after multiple lines of therapy. (J CANCEROL. 2015;2:75-9)

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Key words: Metastatic breast cancer. Weakly paclitaxel. Retreatment with paclitaxel. Heavily pretreated breast cancer.

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Received for publication: 26-12-2014
Accepted for publication: 20-01-2015

BACKGROUND

Metastatic breast cancer is an incurable disease by current standards. Survival is approximately 25% at five years[1-3].

Treatment of metastatic breast cancer is aimed at prolonging survival and palliation of symptoms with improvement of quality of life. There are multiple systemic therapies, which are selected according to toxicity, performance status, comorbidities, and previously delivered therapy. Patient preference for schedule, delivery route, and toxicity is taken into account for decision-making regarding treatment. There is a tendency to use sequential monotherapy as opposed to combination therapy since there is no strong evidence for survival advantage using the latter. Guidelines suggest several drugs that are in use for treatment, with anthracyclines and taxanes being the preferred initial options[2,3].

Paclitaxel is a drug that is obtained from the pacific yew tree *(taxus brevifolia)* discovered in 1963. Its mechanism of action is in the cytoskeleton, interfering with tubulin de-polymerization[1].

Response rates have been reported from 21 to 62% with dosing ranging from 135 to 250 mg/m^2 of body surface area. Neuropathy is dose limiting and myelosuppression is frequently observed. Weekly dosing at 80 mg/m^2 has been reported with response rates at 50-68% with minimal myelosuppression and good tolerance[2].

There are few studies reporting monotherapy with paclitaxel, which has been used in different lines of therapy, reporting response rates that vary from 30 to 60% with progression-free survival of 4.7 months. In these studies, 20-30% of patients had been previously exposed to paclitaxel. These patients were not specifically analyzed[2-9].

To our knowledge, there is no previous report on retreatment with weekly paclitaxel in patients previously exposed to paclitaxel. We conducted this phase II study to evaluate disease control and progression-free survival in heavily pretreated patients with metastatic breast cancer.

MATERIAL AND METHODS

Phase II nonrandomized clinical trial, compared against the literature. Approval of the Ethics Committee of the University Hospital, UANL, was obtained. We included patients with histopathological diagnosis of metastatic breast cancer confirmed by the Department of Pathology.

Patients older than 18 years were included, Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, with adequate bone marrow, kidney and liver function, with measurable disease by clinical or imaging studies. Exclusion criteria were patients with isolated disease in the central nervous system or exclusive bone disease. All patients had to have received paclitaxel during pretreatment, either in neoadjuvant, adjuvant, or metastatic disease treatment, for at least a period of 12 months to be considered for retreatment.

Paclitaxel 80 mg/m^2 intravenously was administered for three hours on day 1 and then weekly for three weeks with one week off (four-week cycle). Premedication consisted of prednisone 20 mg orally administered every 12 hours from the day before chemotherapy and the day of administration, plus ondansetron 8 mg, ranitidine 50 mg, chlorpheniramine 10 mg, and dexamethasone 8 mg administered intravenously 30 minutes before application of chemotherapy. Treatment was continued until disease progression or toxicity. Patients with positive HER2/neu continued treatment with trastuzumab to standard doses (two patients). In case of grade 2 hematological toxicity or motor or sensory neuropathy, the weekly paclitaxel dose was decreased by 10 mg/m^2 without interruption of therapy.

Table 1. Characteristics of the patients

	Number	%
Age - years (median)	51.5 (32-68)	
ECOG		
– 0	4	22
– 1	12	67
– 2	2	11
Number of metastatic sites		
– 1	6	33
– 2	5	28
– 3 or more	7	39
Sites of metastasis		
– Lung	10	27
– Soft tissue	9	24
– Bone	7	19
– Central nervous system	5	13
– Liver	2	5
– Others	4	11
Receptor status		
– HR (+), HER2/neu (–)	12	68
HR (–), HER2/neu (–)	4	22
– HR (+), HER2/neu (+)	1	5
– HR (–), HER2/neu (+)	1	5
Number of prior therapy lines received		
– 2	5	28
– 3	3	16
– 4	5	28
– 5 or more	5	28
Previous exposure to taxanes		
– Neoadjuvant	7	39
– Adjuvant	3	17
– Metastatic disease	8	44
Free time to taxanes		
– 1-3 years	6	33
– 4-6 years	2	11
– More than 7 years	10	55

Non-hematologic toxicity was evaluated clinically every week and complete blood cell counts, platelet counts, and serum chemistries assessed before each cycle (every four weeks). Toxicity was evaluated according to National Cancer Institute common toxicity criteria guidelines.

Clinical response was evaluated every three cycles.

Statistical analysis with 18 patients was deemed enough for this first analysis, considering $p = 0.05$ as significant for response and progression-free survival, using an SPSS system.

RESULTS

From December 2011 to July 2013, 18 patients were enrolled; 17 female patients and one male. Age range was 32 to 68 years with a mean of 51.5 years. On the ECOG scale, 22% corresponded to an ECOG 0, 67% 1, and 11% 2.

The number of metastatic sites was 33% with one site, 28% with two sites, and 39% with three or more sites, being predominantly visceral metastases in lung and liver (Table 1).

Table 2. Response rates and progression-free survival

	CR	PR	SD	PD	PFS
Present study*	0%	28%	61%	11%	6.2 months
Perez, et al. 2001[3]	0%	15%	33%	51%	4.7 months
Chang, et al. 2007[5]	0%	21.7%	43.5%	34.8%	4 months
Baltali, et al. 2004[6]	13.5%	36.5%	10%	40%	10 months

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; PFS: progression-free survival. *No retreatment with paclitaxel in all patients.

Table 3. Toxicity in present study

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Neutropenia	4 (22)	3 (17)	2 (12)	1 (6)
Thrombocytopenia	4 (22)	0 (0)	0 (0)	0 (0)
Anemia	7 (40)	6 (34)	1 (6)	0 (0)
Febrile neutropenia	0 (0)	0 (0)	0 (0)	0 (0)
Neuropathy	6 (34)	4 (22)	2 (12)	0 (0)
Vomiting	2 (12)	0 (0)	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)
Stomatitis	3 (17)	1 (6)	0 (0)	0 (0)
Edema	0 (0)	0 (0)	0 (0)	0 (0)

Previous exposure to taxanes was: 39% of patients had received neoadjuvant paclitaxel, 17% adjuvant, and 44% for metastatic disease.

The number of lines of prior therapy received was: two lines 28%, three lines 16%, four lines 28%, and five lines or more 28%.

The interval from the initial treatment with paclitaxel was 1-3 years in 33% of patients, from 4-6 years in 11%, and more than seven years in 55% (Table 1).

As for the state of receptors, 22% of patients were triple negative, 68% were hormone receptor positive and HER2/neu negative, 5% were hormone receptor positive and HER2/neu positive, and 5% were hormone receptor negative and HER2/neu positive (Table 1).

The progression-free survival for all patients was 6.2 months.

Complete responses were not observed; partial response was obtained in 28%, and 61% remained with stable disease, and progression appeared in 11% of patients (Table 2).

Grade 3 and 4 toxicities occurred in a small percentage of patients, reporting neutropenia in three patients, anemia in one patient, and peripheral neuropathy in two patients (Table 3).

DISCUSSION

There are very few trials reporting retreatment with paclitaxel in metastatic breast cancer. There is a phase II study from MD Anderson[3], which included

211 patients, of which 90% were previously treated with chemotherapy, and 25% had received previous taxane therapy; paclitaxel was administered as first-line in 31% of patients, in 50% as second-line, and in 19% as third-line. Progression-free survival was 4.7 months in the whole group, and 2.7 months in the third-line patients.

In our trial, all the patients had received paclitaxel previously and 72% received it in fourth or subsequent lines of therapy. Of the patients in this study, 61% had prolonged stable disease as compared to 33% in the published experience. The progression-free survival in these 18 patients is well above that reported in other studies. The interval between receiving paclitaxel for the first time was correlated with the progression-free survival, observing that a greater interval between first exposure and retreatment went together with longer disease-free survival, probably reflecting less drug resistance with greater time elapsing between drug exposures. In conclusion, retreatment with paclitaxel in patients with metastatic breast cancer is feasible and effective, with acceptable toxicity. In our institution, we are continuing accrual for a larger experience following these results.

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