Phase II Trial of a Novel Paclitaxel Schedule As Single-Agent, First-Line Therapy for HER-2/*neu*-Negative Metastatic Breast Cancer: A Community-Based Study

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Abstract

Purpose: To determine the response rate (RR), progression-free survival (PFS), and toxicity in patients with HER-2/*neu*-negative metastatic breast cancer treated with first-line paclitaxel in a de-escalating dosing schedule.

Patients and Methods: Between August 1999 and December 2000, 73 patients were enrolled. Paclitaxel was administered on day 1 (175 mg/m²) and on days 8 and 15 (80 mg/m² each) in each 4-week cycle (1 week of rest). Doses were de-escalated with the aim of reducing toxicity. An Eastern Cooperative Oncology Group performance status of 0, 1, or 2 was found in 55%, 41%, and 4% of patients, respectively. Median age was 59 years (range, 38 to 84 years), and 86% of patients had received prior surgery; 60%, adjuvant chemotherapy; and 59%, radiation therapy.

Results: Based on an intention-to-treat analysis (N = 73), there were five patients with a complete response (6.8%), 16 with a

partial response (21.9%), 17 with stable disease (23.3%), and 23 with progressive disease (31.5%) for an RR of 28.7%. Twelve patients (16.4%) were not assessable for response due to toxicity (seven patients, mainly neuropathy), withdrawal of consent (two patients), early death (two patients), or noncompliance (one patient). Median PFS was 6.5 months (range, < 1 to 36.1 months), median survival was 22.8 months (range, < 1 to 36.1 months), and median duration of response was 8.8 months (range, 3.0 to 31.8 months). Patients (n = 72) were evaluated for toxicity. Grade 3 to 4 treatment-related toxicities occurring in more than 5% of patients included neutropenia (22.2%), neuropathy (18.1%), fatigue (6.9%), and leukopenia (5.6%).

Conclusion: In a unique de-escalating schedule, this study of single-agent paclitaxel produced a response rate similar to other single-agent paclitaxel schedules, in first-line therapy for metastatic breast cancer, published in the literature. However, this schedule is not recommended for the therapy of metastatic breast cancer because of the higher rate of toxicity.

Introduction

Excluding skin cancer, breast cancer is the most common type of cancer among women and the leading cause of cancer death for women in the United States.¹ Although standard treatment options for metastatic breast cancer (MBC) may prolong survival, an effective cure remains elusive for the majority of women. Hence, the search for effective agents and treatment schedules continues.

Paclitaxel is considered an effective first-line therapeutic choice for MBC in women who have failed adjuvant anthracycline breast cancer therapy.² Paclitaxel has shown clinical activity in the refractory and relapse settings.³⁻⁶

The schedule of treatment for first-line MBC with paclitaxel may be a key factor in optimizing outcome, toxicity, and compliance. Previous studies conducted at The University of Texas M.D. Anderson Cancer Center and Memorial Sloan-Kettering Cancer Center have established paclitaxel as a potent antitumor agent.^{7,8} These two groups administered one 24-hour infusion of 250 mg/m² every 3 weeks (q3) to produce response rates (RRs) of 56% and 62%, respectively. Similar RRs, without the high degree of neutropenia have been observed when the infusion was shortened from 24 hours to 3 hours.^{7,9-11} Many first-line MBC studies report that 3-hour infusions q3 with doses of paclitaxel ranging from 175 to 225 mg/m² have produced RRs of 30% to 60%.¹²⁻¹⁴

In an effort to further minimize toxicity, the weekly administration of lower doses of paclitaxel is gaining increased acceptance; compared with q3 schedules, higher cumulative doses can be achieved with weekly dosing. This affects the dosing intensity, which potentially increases the cytoreductive potential of the therapy.¹⁰ In one study using high weekly doses (175 mg/m²), there was a higher response rate seen than with the low weekly doses (80 mg/m²). However, this high dose schedule was associated with unacceptable toxicity, specifically neurotoxicity.¹⁵

In our current study, we evaluate a novel paclitaxel dosing schedule as single-agent first-line therapy with an initial high dose therapy in week 1, followed by a de-escalated weekly dose of 80 mg/m² for weeks 2 and 3 of a 4-week schedule, with the aim to reduce neurotoxic effects and produce a better RR. The basis for the current dosing, and an initial dose of 175 mg/m², was prior work done by Sikov et al.¹⁵ Weekly dosing at 80 mg/m² was used by Perez et al.¹⁶ and was later confirmed by Seidman et al.¹⁷

Patients and Methods

Study Design

This was an open-label, multicenter, phase II clinical trial conducted between August 1999 and December 2000 in the community-based US Oncology Research Inc network. The protocol was approved by a central institutional review board,

and all patients signed an informed consent form before being admitted onto the study.

Patients

Patients were required to have histologically confirmed adenocarcinoma of the breast with locally advanced (stage IIIB) or metastatic (stage IV) measurable disease, and be HER-2–negative (HER-2/*neu* 0 or 1+ by immunohistochemistry). Full recovery for ≥ 4 weeks since radiotherapy and for ≥ 3 weeks since major surgery, were necessary for inclusion. Patients were required to have a performance status (PS) of 0, 1, or 2 on the Eastern Cooperative Oncology Group (ECOG) scale. Adequate bone marrow (absolute neutrophil count [ANC] $\geq 1,500$ cells/L and platelet count $\geq 100,000$ cells/L), renal (creatinine ≤ 2.0 mg/dL), and hepatic (serum bilirubin ≤ 1.5 mg/dL, AST and ALT $\leq 1.5 \times$ the institutional upper limit of normal [ULN]) threshold values were required. Patients also had to have a negative pregnancy test if applicable, and a life expectancy ≥ 3 months.

Exclusion criteria included prior chemotherapy for advanced or metastatic disease, or concurrent treatment with immunotherapy, hormonal therapy, or trastuzumab (Herceptin; Genentech, South San Francisco, California). Parenchymal brain metastases not responding to treatment, serious intercurrent medical or psychiatric illnesses, or a history of other malignancy without ≤ 5 years that could have affected the diagnosis or assessment of MBC were also conditions for exclusion.

Treatment Regimen

Supportive care, including antiemetics, blood products, and hematopoietic growth factors, was provided as medically appropriate. Patients received 175 mg/m^2 of paclitaxel administered intravenously over 60 minutes on day 1. On days 8 and 15, patients received a lower dose of paclitaxel (80 mg/m^2) administered intravenously over 60 minutes. After this 3-week cycle, there was 1 week of no treatment. Patients were premedicated with 10 mg dexamethasone, 25 mg diphenhydramine, and either 300 mg cimetidine or 50 mg ranitidine approximately 30 to 60 minutes prior to paclitaxel administration.

Dose Modification

Dose escalation of paclitaxel was not permitted. Dose modifications for paclitaxel were based on blood counts obtained on the day of treatment, and the presence of nonhematologic toxicities. Only the week-1 paclitaxel dose was modified, and reductions from the 175-mg/m^2 planned amount were 150 mg/m^2 and 125 mg/m^2 for the first and second level decreases, respectively. Regardless of the initial dose level, the paclitaxel dose for weeks 2 and 3 remained at 80 mg/m^2 .

Doses of paclitaxel were not altered if the ANC count was $\geq 1,500$ cells/L and if the platelet count was $\geq 100,000$ cells/L. If the ANC was between 500 and 1,500 cells/L or the platelet count was 50,000 to 99,999 cells/L, then the dose was decreased by one level. If the ANC was less than 500 cells/L or the platelet count was less than 50,000 cells/L, the dose was withheld.

Patients who experienced $\geq$ grade 3 peripheral neuropathy had their paclitaxel dose reduced by one level in subsequent cycles. For all other toxicities that were $\geq$ grade 3, treatment was withheld (except anemia) until resolution to $\leq$ grade 1, or baseline if baseline was greater than grade 1. Treatment was then restarted if medically appropriate, with a dose reduction of one level. Toxicities $\leq$ grade 2 were managed symptomatically without a dose reduction. Patients who were delayed for longer than 14 days (excluding rest week) from their scheduled dose were taken off study treatment. Severe hypersensitivity reactions resulted in immediate discontinuation of paclitaxel. Patients continued to receive study treatment until disease progression, intolerable toxicities, or withdrawal of consent.

Assessments

Validation of inclusion and exclusion criteria, completion of informed consent, a pregnancy test (if applicable), and a medical history were completed at screening. A physical examination, including vital signs, height and weight, assessment of ECOG PS, CBC with differential and platelet count, tumor assessments, and laboratory tests (total bilirubin, serum creatinine, AST, ALT, alkaline phosphatase, serum calcium, blood urea nitrogen) were conducted at screening, prior to each cycle, and at the end of therapy. Toxicity was assessed prior to each cycle and at the end of therapy. At follow-up, a CBC with differential and platelet count, a survival assessment, and laboratory tests were performed.

Toxicity and Response Criteria

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Patients were assessable for response if they received two or more cycles, developed rapid tumor progression, or died of progressive disease (PD) prior to response evaluation. The primary study end point was the percentage of patients who achieved an objective response (CR or PR).¹⁸ A complete response (CR) required the disappearance of all known disease for ≥ 4 weeks without any new lesions. A partial response (PR) was defined as a $\geq 50\%$ decrease of the sum of products in measurable lesions for ≥ 4 weeks without any new lesions. Stable disease (SD) was defined as a less than 25% increase of the sum of products in measurable lesions without any new lesions. PD was defined as a greater than 25% increase of the sum of the products in measurable lesions or the appearance of new lesions. Secondary end points were duration of response (DoR), progression-free survival (PFS), and survival.

Statistical Analysis

It was estimated that 73 eligible patients and an observed response rate of 35% or greater would provide an acceptable level of accuracy ($\pm 11\%$) with CIs of 95% or greater. A minimum response of 24% would be expected, based on prior results of a phase II study.¹⁶ The primary efficacy parameter of this study was the objective response rate, (ORR; CR + PR). Secondary efficacy parameters included median time to response, DoR, PFS, and survival. The duration of response was defined as the

interval between the date of onset of the PR or CR and the date that progressive disease occurred or the last date of follow-up for patients who did not progress. PFS was defined as the interval between the start date of treatment and the date of occurrence of progressive disease or death due to any cause, or last date of contact for surviving patients. Survival was calculated from the first day of treatment to the last date of follow-up for surviving patients or until the date of death. Patients who withdrew from the study to undergo high dose chemotherapy with stem cell support transplantation (or any other treatment) were censored as of the date they began alternative therapy in the duration of response and time to disease progression. PFS and survival were estimated using the method of Kaplan and Meier.¹⁹ All patients treated were assessable for toxicity if they received at least one dose of study chemotherapy. SAS version 8.0 was used to run the analysis.

Results

Patient Characteristics

A total of 73 eligible patients with metastatic breast cancer were included in this phase II trial of weekly paclitaxel as first line of therapy. The demographics of these patients, tumor characteristics, and metastatic sites at presentation, are listed in Table 1.

Response to Treatment

Based on an intention-to-treat analysis (N = 73) there were five CRs (6.8%) and 16 PRs (21.9%). The ORR (CR + PR) was 28.7% (95% CI, 19.6% to 40.1%). There were also 17 SDs (23.3%), and 23 PD (31.5%). Among the 17 SD patients, 14 (82.4%) had stable disease for > 6 months and the clinical benefit ratio (CR + PR + SD; $\geq$ 6 months) was 57.4% (95% CI, 45% to 69.8%). Twelve patients (16.4%) were not assessable for response due to the following reasons: seven for treatment failure due to toxicity (mainly neuropathy), two due to withdrawal of consent, two due to early death, and one for noncompliance. Table 2 summarizes the response to treatment.

Median time to response for the 21 responders was 1.7 months (range, 1 to 5.2), and the median DoR was 8.8 months (range, 3.0 to 31.8). Dose delay, attributed to neuropathy, sensory neuropathy, neutropenia, or sepsis occurred in 11% of the patients. The median number of cycles completed was four (range, one to 14). Seventy of the 73 patients went off study due to progressive disease (49%); toxicity (32%) including neurotoxicity, allergic reaction, fatigue; withdrawal of consent (6%); death (3%); protocol deviation (3%); and other reasons (7%) including intercurrent diabetes, lack of insurance and lost to follow-up.

At least 90% of patients were able to receive the full dose on day 1 of every cycle. Nine patients had prior taxanes, for an average of 2 months, on various cycles. The median interval from last taxane dose to first dose of study drug was 19 months, and the response rate in this group of nine patients was 44%. The response rate for patients who had received prior nontaxane chemotherapy was 37% ($P = .72$).

Table 1. Patient Demographics

Characteristic	Patients	
	No.	%
Total eligible patients	73	
Race/ethnicity		
White	59	80.8
Black	9	12.3
Hispanic	2	2.7
Other	3	4.1
Age, years		
Median	59.2	
Range	38.4-84.3	
ECOG performance status		
0	40	54.8
1	30	41.1
2	3	4.1
Prior therapy		
Prior surgery	63	86.3
Prior radiotherapy	43	58.9
Prior adjuvant chemotherapy	44	60.3
No. of sites of involvement at baseline		
1	24	32.9
2	27	37.0
3	10	13.7
$\geq$ 4	9	12.3
Initial sites of metastasis		
Visceral (excluding liver)	50	68.5
Hepatic	25	34.2
Soft tissue	36	49.3
Bone	32	43.8
Other	2	2.7

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Survival

Forty-six (95.7%) of the 73 subjects who died, died of PD. The remaining patient died of cardiac arrhythmia. The estimated 1- and 2-year overall survival rates were 63% and 47%, respectively, with a median of 22.8 months (range, < 1 to 36.1 months), as shown in Table 3. The estimated 1- and 2-year PFS rates were 29% and 18%, respectively. Median PFS was 6.5 months (range, < 1 to 36.1 months). There were no statistically significant differences in PFS and survival between patients with liver metastases and patients with other sites of metastasis at the start of the study.

Toxicity

Among the eligible patients, 72 out of 73 received one or more doses of drug therapy and were assessable for toxicity. Grades 2

Table 2. Best Response to Treatment

	Patients		95% CI
	No.	%	
Total eligible patients	73		
Best response			
Complete response	5	6.8	3.2 to 13.6
Partial response	16	21.9	13.9 to 32.8
Stable disease	17	23.3	14.2 to 34.7
Progressive disease	23	31.5	21.1 to 43.4
Not assessable	12	16.4	

to 4 treatment-related adverse events are summarized in Table 4. The most frequent treatment-related grade 3 to 4 toxicities included neutropenia (22.2%), neuropathy (18.1%), fatigue (6.9%), and leukopenia (5.6%). The incidence of grade 1 and 2 alopecia was 58.3%. There were no treatment-related deaths during the study.

Discussion

This investigation used a novel regimen of weekly paclitaxel in which cycles consisted of a high load dose (175 mg/m²) administered on day 1, a lower dose (80 mg/m²) given on days 8 and 15, and no therapy given during days 16 through 28. The rationale behind this schedule was to achieve the high RR observed in high-dose weekly paclitaxel studies while avoiding the subsequently elevated toxic profiles also seen in this treatment schema by giving a lower dose during weeks 2 and 3. A rest week was also incorporated to allow time for WBC counts to recover. We observed a RR (CR + PR) of 28.7% and an SD rate of

23.3%. The corresponding clinical benefit rate (CR + PR + SD; ≥ 6 months) was 47.9% with this schedule.

Studies by Sato et al and Sikov et al support these data.^{20,21} Sato et al obtained a similar RR (40.4%), time to progression (TTP; 4.8 months), and median survival (15.8 months) when they dosed patients with 80 mg/m² for 3 weeks with 1 week of rest.²⁰ Sikov et al reported similar results for RR (42%), TTP (4 months), and survival (20 months) in arm C (80 mg/m²/wk $\times$ 15 weeks).²¹ Toxicity was again remarkably low as neutropenic and neuropathic incidence rates of only 8% each were observed. These levels of toxicity have also been observed in a number of second-line weekly paclitaxel studies in which patients with MBC were dosed with 50 to 100 mg/m² and achieved RR ranging from 25% to 62%.²²⁻²⁴ Hence, the use of standard-dose weekly paclitaxel showed at least similar outcome data (and in some cases better) when compared with the current study (high-dose weekly paclitaxel followed by standard-dose weekly paclitaxel). In this clinical trial, patients with HER-2-positive disease were excluded because of the discovery of the favorable interaction of trastuzumab and a variety of chemotherapy agents in other HER-2-positive breast cancer trials.

Monitoring of neurotoxicity was particularly important during treatment with paclitaxel. The absolute dose of paclitaxel per course is integral to the incidence of neurotoxicity, while the role of cumulative dose, treatment duration, and infusion schedule as potential risk factors remain in question.²⁵ du Bois et al²⁵ determined that higher doses of paclitaxel per course showed a significant impact on neurotoxicity, while the different infusion schedules were of minor importance. Moreover, Tate et al²⁶ observed that weekly paclitaxel administration reduced neurotoxicity when compared to dosing every 3 weeks.

In the current study, the majority of neurotoxicity cases were observed between cycles 2 to 4 indicating that neurotoxicity was evident early in the treatment timeline, appeared to be directly correlated with the initial high load dose as suggested by du Bois, and appeared to be independent of the cumulative dose. With only four patients showing neurotoxic signs after four cycles of treatment, this suggests that an early identification of patients who will subsequently have a neurotoxic adverse event can be made. Seidman et al. also reported superior response rates when comparing weekly paclitaxel to paclitaxel given every 3 weeks although weekly paclitaxel caused more grade 3 sensory/motor neuropathy.¹⁷

The 18.1% incidence of grade 3 to 4 neuropathy combined with a remaining adverse event profile consisting of only four grade 3 to 4 toxicities above 5% (neutropenia, 22.2%; fatigue, 6.9%; pain and leukopenia, 5.6% each; alopecia [grades 1 to 2], 58.3%) is comparable to observations made by Sikov et al²¹ and suggests that the de-escalating schedule of paclitaxel used in this regimen is deliverable but with high rates of toxicity. There was a 32% discontinuation rate due to toxicity, and almost 10% of patients were nonevaluable due to toxicity in the present study. The regimen was therefore determined too toxic as prescribed.

Table 3. Estimated Overall Survival and Progression-Free Survival (N = 73)

	Patients	
	No.	%
Estimated overall survival		
Median		22.8
Range		<1-36.1
Survival	47	
1 year		63
2 years		47
3 years		23
Estimated progression-free survival		
Median		6.5
Range		<1-36.1
Progression-free	61	
1 year		29
2 years		18
3 years		11

Table 4. Treatment-Related Toxicities $\geq$ Grade 2 in More Than 5% of Patients

Adverse Event by Body System	Grade 2	Grade 3	Grade 4	Total and % of AEs	
				No.	%
Hematologic					
Anemia	8	0	0	8	11.1
Leukopenia	6	4	0	10	13.9
Neutropenia	6	11	5	22	30.6
Nonhematologic					
Alopecia	36	0	0	36	50.0
Arthralgia	6	2	0	8	11.1
Bone pain	2	2	0	4	5.6
Constipation	4	0	0	4	5.6
Fatigue	15	5	0	20	27.8
Myalgia	8	2	0	10	13.9
Nausea	3	2	0	5	6.9
Neuropathy	7	11	2	20	27.8
Pain	4	2	0	6	8.3
Paresthesia	5	2	0	7	9.7
Weakness	6	0	0	6	8.3

NOTE. Percentage of total adverse events is based on the number of patients known to have received at least one dose of drug (n = 72).

Weekly treatment with paclitaxel continues to provide significant RR, PFS, and survival advantages in patients with HER-2–negative MBC. Our novel de-escalating approach shows similar efficacy when compared with standard-dose weekly paclitaxel; however, it is not recommended for administration to patients with metastatic disease, in any practice setting, because it is too toxic.

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Appendix

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Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict existed for drugs or devices used in a study if they are not being evaluated as part of the investigation.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
David Loesch			BMS		BMS; Eli Lilly; AstraZeneca	BMS; AstraZeneca; Eli Lilly		

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