Phase II and Pharmacologic Study of Docetaxel as Initial Chemotherapy for Metastatic Breast Cancer

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Purpose: **Because docetaxel (Taxotere, RP 56976; Rhone-Poulenc Rorer, Antony, France) appeared to be active against breast cancer in phase I trials, we performed this phase II study.**

Patients and Methods: **Thirty-seven patients with measurable disease were enrolled. Only prior hormone therapy was allowed, as was adjuvant chemotherapy completed ≥ 12 months earlier. Docetaxel 100 mg/m^2 was administered over 1 hour every 21 days. Diphenhydramine hydrochloride and/or corticosteroid premedication was added after hypersensitivity-like reactions (HSRs) were seen in two of the first six patients. Pharmacokinetic studies were performed during cycle 1 for correlation with toxicity.**

Results: **Thirty-seven patients were assessable. Nineteen (51%) required dose reductions, usually for neutropenic fever. The median nadir WBC count was 1.4 × 10^3/μL. HSRs were noted in 20 patients (54%). At a median cumulative dose of 297 mg/m^2 (range, 99.6 to 424.5 mg/m^2), 30 patients (81%) developed fluid retention, for which 11 (30%) subsequently stopped treatment. The first-cycle plasma area under the concentration-time curve (AUC) did not correlate with toxicity, although an ineligible patient with hepatic metastases (pretreatment bilirubin level 1.8 mg/dL) had an elevated AUC and died of toxicity. Responses were seen at all sites. On an intent-to-treat basis, there were two (5%) complete responses (CRs) and 18 (49%) partial responses (PRs). The overall response proportion (CRs plus PRs) was 54% (95% confidence interval, 37% to 71%). The median time to response was 12 weeks (range, 3 to 15) and the median duration was 26 weeks (range, 10 to 58+).**

Conclusion: **Docetaxel is active for metastatic breast cancer. Neutropenia and fluid retention are dose-limiting. The AUC did not predict toxicity, but caution is warranted when treating patients with liver dysfunction. An understanding of the pathophysiology of the fluid retention may facilitate prevention. Frequent HSR may warrant prophylactic premedication.**

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CHEMOTHERAPY AGENTS, alone or in combination, can induce objective tumor regression and symptom palliation for many patients with metastatic breast cancer. Unfortunately, these responses are almost always of limited duration and cure is exceedingly rare.[1] Recently, a novel diterpene, paclitaxel (Taxol; Bristol-Myers Squibb, Princeton, NJ), derived from the bark of the western yew, *Taxus brevifolia,* was found to be active in the treatment of metastatic breast cancer.[2,3] Unlike the other microtubule toxins in clinical use, such as vincristine or vinblastine, taxanes promote the formation of tubulin dimers and stabilize microtubules against depolymerization.[4] Through various mechanisms, this results in growth inhibition and loss of cell viability. In recent phase II trials, the overall response rate for paclitaxel following little or no prior therapy for metastatic breast cancer was as high as 56% to 62%, but lower in those with more extensive prior treatment.[2,3,5]

Partly because of earlier concerns regarding the long-term availability of paclitaxel, which has been historically derived from the bark of mature yew trees, there has been extensive effort directed at identifying taxane analogs derived from renewable resources. Several years ago, researchers were able to prepare a semisynthetic taxane using a precursor extracted from a renewable resource: the needles of the European yew, *Taxus baccata.* This drug, docetaxel, has been shown to have in vivo activity against a variety of tumors and to have an acceptable toxicity profile in animals.[6] Its mechanism of action is similar or identical to that of paclitaxel in that it enhances microtubule assembly and inhibits the depolymerization of tubulin, which leads to intracellular bundling of microtubules and M-phase cell-cycle blockade.[7,8]

Five human phase I studies have been performed. The highest maximum-tolerated dose (MTD) was seen using a 1-hour infusion schedule and the greatest dose-intensity was achieved using an every-3-week administration

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schedule. A dose of 100 mg/m^2 over 1 hour every 3 weeks, one level below the highest dose reached using this schedule, was recommended for phase II testing.[9-13]

Because testing new agents in extensively pretreated patients can make the demonstration of efficacy more difficult, and because there is no initial therapy for metastatic breast cancer with high likelihood of complete response (CR), we chose to study minimally pretreated patients who had not yet received chemotherapy for metastatic disease.

This phase II study was designed primarily to estimate the major objective response proportion and duration of response to intravenous (IV) docetaxel 100 mg/m^2 every 21 days as first chemotherapy for patients with metastatic breast cancer. We also sought to determine the qualitative and quantitative toxicities associated with the administration of this agent, as well as their reversibility, and to correlate the pharmacologic profile of docetaxel with cycle 1 toxicity.

PATIENTS AND METHODS

Eligibility Criteria

Eligibility criteria included the following: nonlactating female patients, age ≥ 18 years; nonchildbearing potential or using adequate contraception with a negative pregnancy test at study entry; histologically confirmed metastatic breast cancer; metastatic or locally advanced and inoperable disease; bidimensionally measurable and nonirradiated indicator lesions; life expectancy ≥ 12 weeks; Karnofsky performance status ≥ 60%; WBC count ≥ 3,500 cells/μL, absolute neutrophil count (ANC) ≥ 2,000 cells/μL, platelet count ≥ 100,000 cells/μL, creatinine concentration ≤ 2.0 mg/dL, and bilirubin level ≤ 1.5 mg/dL; and stable heart rhythm, no unstable angina, no clinical evidence of congestive heart failure. Previous therapy was allowed only as follows: prior hormone therapy as adjuvant treatment and/or as treatment for metastatic disease must have been stopped at least 1 month before protocol entry; adjuvant chemotherapy had to have been completed at least 12 months before protocol entry and could not have required bone marrow or peripheral-blood stem cell transfusion; and radiotherapy that involved up to 10% of the bone marrow was allowed, but not to a site used to assess response unless a new lesion had subsequently developed in the field. Exclusion criteria included the following: clinically evident brain metastases; history of prior malignancy except completely excised in situ carcinoma of the cervix or nonmelanoma skin cancer; other serious illness; current symptomatic grade II or greater peripheral neuropathy; or concomitant biphosphonate use, use of scalp-cooling device, or use of corticosteroids within 30 days of beginning protocol therapy. The protocol was approved by the institutional review board at Memorial Hospital, and written informed consent was required before protocol therapy was begun.

Measurable disease was defined as tumor masses with identifiable diameters measurable in two dimensions on physical examination, radiograph, or ultrasound. To be considered measurable, computed tomography (CT) and ultrasound-measured lesions had to be at least 2.0 × 2.0 cm, and chest x-ray and skin or lymph node lesions measured by physical examination had to be at least 1.0 × 1.0 cm. Pulmonary lymphangitic metastases, bone lesions, malignant effusions, tumor markers, and abnormal liver function tests did not constitute measurable disease. Any other nonmeasurable lesions were recorded as assessable or nonassessable and monitored. All responses were reviewed and confirmed by a panel of outside physicians, including medical oncologists and radiologists.

Treatment Plan

Study drug. Docetaxel (Taxotere, RP 56976) was supplied by Rhone-Poulenc Rorer (Antony, France) as a concentrated sterile solution that contained a 40-mg/m2 dose in polysorbate 80 in a 15-mL clear-glass vial with a stopper and an aluminum cap. Each vial contained 2 mL of injectable solution. Vials were packed in boxes of 50, labeled in an open manner, and stored protected from light at 4°C.

The initial dosage of docetaxel was 100 mg/m^2, administered as an IV infusion over 1 hour repeated at 21-day intervals. There was no dose escalation; however, dose reductions for all subsequent treatment cycles were made based on hematologic and nonhematologic toxicities using the National Cancer Institute common toxicity criteria. Treatment could also be delayed up to 1 week to allow recovery from acute toxicity. A maximum of two dose reductions was allowed per patient (100 to 75 mg/m^2 to 55 mg/m^2). Patients were taken off study if they did not recover sufficiently to receive treatment within 35 days from their prior dosage.

Premedication. Initially, premedications were not used. However, after we observed acute hypersensitivity reactions (HSRs) in two of the first six patients, a variety of pretreatment regimens that incorporated diphenhydramine, corticosteroids, and cimetidine were used. In case of acute HSR, diphenhydramine 50 mg IV could be administered and it could also be repeated as prophylaxis if the docetaxel infusion was interrupted and then restarted. In such cases, the recommended treatment also included dexamethasone 10 mg IV at least 30 minutes before resumption of the docetaxel infusion. During the first 15 to 30 minutes of docetaxel infusion, a physician or a chemotherapy nurse remained at the bedside. Blood pressure was monitored every 15 minutes during the hour of the infusion.

Duration of therapy. After the initial dose of docetaxel, we planned to administer at least one additional treatment unless disease progression (PD) or intolerable (grade 3 to 4) nonhematologic toxicity precluded further treatment. We planned to continue treatment until dose-limiting toxicity or PD occurred.

Pretreatment Evaluation

A complete history and physical examination were performed before the first cycle of therapy. These included height, weight, vital signs, performance status, tumor measurements, and detailed neurologic examination with quantitative vibration and thermal sensory testing. Laboratory studies included a complete blood cell (CBC) count with differential and platelet count, prothrombin time (PT)/partial thromboplastin time (PTT), and measurements of serum chemistry (AST, alkaline phosphate, total bilirubin, and lactate dehydrogenase [LDH]), serum creatinine, carcinoembryonic antigen (CEA) and CA 15-3, and serum beta-human chorionic gonadotropin (β-HCG; if indicated to rule out pregnancy). An ECG and posteroanterior and lateral chest radiograph were required. If needed to evaluate bidimensionally measurable disease, CT scan, magnetic resonance imaging (MRI), and/or ultrasound were performed. Bone scans were performed if clinically warranted, but were not used to monitor measurable disease.

Evaluation During Treatment

At the end of every cycle, on day 1 (before beginning the infusion for the next cycle), a repeat history and physical examination, which included weight, vital signs, performance status, and tumor measurements, was performed. Neurologic evaluation that included a symptom-evaluation questionnaire and detailed neurologic examination with quantitative vibration and thermal sensory testing was performed again during the first cycle, and a full neurologic examination was performed every other cycle. The chest x-ray, toxicity assessment, and laboratory studies listed earlier (excluding β-HCG) were repeated. During the first two cycles only, a CBC count with differential was performed twice per week; for subsequent cycles, it was performed weekly. If tumor measurements were only obtainable by imaging study (CT, MRI, ultrasound, or radiograph), these studies were performed every 6 weeks (two cycles). Patients with cutaneous lesions were to have serial photographic documentation, along with physical examination measurements, whenever possible. Three weeks after the final treatment cycle, the history and physical examination and all laboratory testing except for the β-HCG were repeated.

Criteria for Response

CR was defined as the disappearance of all clinical evidence of tumor by physical examination or imaging studies for a minimum of 4 weeks. Partial response (PR) was defined as a $\geq$ 50% reduction in the sum of the products of the biperpendicular diameters of all measurable lesions, without the appearance of new lesions, for at least 4 weeks. When there were multiple sites of metastases, the largest masses (up to five) were considered as the index lesions. Stable disease included regression that did not meet the criteria for CR or PR. PD was defined as the appearance of any new lesions, an increase by $\geq$ 25% of an indicator lesion or the sum of the product of the biperpendicular diameters of the measured lesions, or any increase in the estimated size of a nonmeasurable lesion.

Pharmacokinetic Studies

During the first cycle, a limited-sampling strategy was used to allow us to relate interpatient pharmacokinetic variability to various pathophysiologic covariates, to generate individual estimates of systemic exposure to docetaxel (determine the areas under the plasma concentration versus time curve [AUC]), and to use these estimates as prognostic factors for toxicity. The design was based on population pharmacokinetic parameter estimates obtained from phase I data.[14] Four 3-mL heparinized samples were obtained on the first day of the first cycle of docetaxel administration for each patient. Subsequent sampling was performed according to one of four randomly assigned pharmacokinetic protocols. Each sample was centrifuged within 30 minutes of collection at 3,000 rpm for 15 minutes and the plasma was removed to a plastic tube, labeled, flash-frozen, and stored at ≤ -20°C for shipment to Rhone-Poulenc Rorer for analysis. Docetaxel was assayed using high-performance liquid chromatography and UV detection after solid-phase extraction.[15] Individual estimates of docetaxel clearance were obtained using bayesian estimation implemented in the NONMEM program.[16] These estimates allowed computation of the plasma AUC.

Statistical Analysis

Responses. If no responses were observed among the first 14 patients, the predicted true response rate would have been less than 20% with 95% confidence and the trial would have been terminated. Because therapeutic responses were seen, accrual was extended to estimate the response rate better. Response and survival determinations were measured from the date of initiation of docetaxel. All responses were reviewed by a panel of outside experts.

Pharmacology/toxicity. The estimate of the Pearson correlation coefficient was used to examine relationships between toxicity and the AUC.

RESULTS

Demographic Data

Between July 14, 1992 and October 31, 1993, 37 female patients were accrued. Visceral disease was present in 76% of patients and nearly half of the patients had three or more involved organ systems. Patient characteristics are listed in Table 1. All patients were assessable for toxicity. Response was evaluated on an intent-to-treat basis and includes two patients (5%) who only received one cycle of therapy.

Response

There were two (5%) CRs and 18 (49%) PRs, for an objective response proportion (CRs plus PRs) of 54% (95% confidence interval, 37% to 71%). Responses were observed at all sites of metastatic disease. The median time to detection of response was 12 weeks (range, 3 to 15). Four patients (11%) withdrew from study while in PR or CR to receive high-dose chemotherapy. Excluding these four patients, the median response duration was 26 weeks (range, 10 to 58+). Response data and reasons for discontinuation of therapy are listed in Table 2.

Hematologic Toxicity

Leukopenia and neutropenia were both observed in 35 patients (95%) (Table 3). The median number of days to neutrophil nadir was 8 (range, 5 to 22). The median nadir counts and days to nadir were similar across multiple cycles and by dose level.

There were 19 episodes of febrile neutropenia complicating 9% of all treatment cycles. Fifteen episodes were seen at the first dose level (100 mg/m^2), three at the second level (75 mg/m^2), and one at the third level (55 mg/m^2). Six patients (16%) developed neutropenic fever during the first treatment cycle, six (16%) during cycle 2, two (5%) during cycle 3, and five (14%) during subsequent cycles. Infection was documented in six patients (16%) and 13 cycles (6%).

Nonhematologic Toxicities

HSRs. After two of the first six patients (33%) treated developed some form of possible HSR, a variety of premedications were administered to new patients (Table 4).

Table 1. Patient Characteristics

Characteristic	No.	%
Patients entered	37	100
Age, years		
Median	50	
Range	28-71	
Performance status*		
0	2	5
1	23	62
2	6	16
Unknown	6	16
Menopausal status		
Pre-	12	32
Post-	25	68
Specific sites involved		
Lymph nodes	23	62
Lung	18	49
Bone	15	41
Liver	13	35
Pleura	8	22
Breast	7	19
Skin	3	8
Other soft tissue	10	27
Other viscera	1	3
Distribution of sites		
Soft tissue + viscera	13	35
Soft tissue + viscera + bone	8	22
Only soft tissue	7	19
Viscera + bone	5	14
Soft tissue + bone	2	5
Only viscera	2	5
Extent of prior systemic therapy		
None	10	27
Prior hormone therapy only	3	8
Prior adjuvant chemotherapy only	10	27
Both	13	35
Prior anthracycline	18	49
No prior anthracycline	5	14
Time from prior chemotherapy to study entry, months		
Median	23.3	
Range	1-95.1	

*World Health Organization.

Table 2. Response and Outcome (intent-to-treat basis)

Variable	Patients No.	Patients %	95% Confidence Limits
Total no. assessable	37		
CRs	2	5	1-18
PRs	18	49	32-66
CRs + PRs	20	54	37-71
Reason for withdrawal from study:			
PD	16	43	
Toxicity*	14	38	
Consent withdrawn†	6	16	
Lost to follow-up	1	3	

*Includes 1 (2.7%) toxic death.
†Includes 4 (10.8%) treated with high-dose therapy.

In 24 patients (65%), this included diphenhydramine 50 mg IV within 1 hour of commencing docetaxel. In two patients (5%), dexamethasone 20 mg IV was added, and in one patient (3%) each Decadron (dexamethasone; Merck & Co, West Point, PA) and cimetidine 300 mg IV, or cimetidine alone, were added to the diphenhydramine. Because of the small sample sizes and the fact that these interventions were not implemented in a randomized fashion, it is not possible to analyze the impact of specific pretreatment regimens on the incidence of HSR.

In total, 47 (HSRs) occurred in 20 patients (54%). As listed in Table 4, the signs and symptoms felt possibly related to HSR included (in order of frequency) the following: flushing, hypertension, complaints of throat and/or chest tightness, pain, dyspnea, pruritus, bronchospasm, complaints of feeling warm, nausea, crampy abdominal pain, upper respiratory tract angioedema, and lacrimation. An additional three reactions occurred during rechallenge, so that a total of 50 reactions were seen. One patient (3%) withdrew consent subsequent to developing an HSR. However, it is not certain that she actually experienced an HSR, as within several seconds of the initiation of the first docetaxel infusion, and following prophylactic premedication with IV diphenhydramine (50 mg), she developed hypotension, bradycardia, and loss of consciousness. The infusion was stopped and the patient was treated with additional IV diphenhydramine, IV corticosteroids, and supplemental nasal oxygen with complete recovery. The etiology of this patient's reaction remains unclear and may instead be attributable to a cardiac conduction disturbance.

Treatment for HSR was not undertaken for 16 episodes (32%). In three episodes (6%), the infusions were not interrupted, in six (12%) the infusions were stopped and restarted without additional medication, and in 24 (48%)

Table 3. Hematologic Toxicity: All Cycles

Variable	Nadir Median	Nadir Range	Grade 3 No.	Grade 3 %	Grade 4 No.	Grade 4 %
Toxicity						
WBC count ($\times 10^3/\mu L$)	1.4	0.3-28.0	25	68	4	11
ANC ($\times 10^3/\mu L$)	0.2	0-25.5	2	5	32	87
Platelet count ($\times 10^3/\mu L$)	183	33-353	1	3	0	0
Hemoglobin level (g/dL)	9.0	5-31	5	14	0	0

	Patients No.	Patients %	Cycles No.	Cycles %
Febrile neutropenia*	14	38	19	9
Packed RBC transfusions	3	8		

*Grade 3 or 4 neutropenia with fever > 38°C.

Table 4. HSRs

Variable	Patients		Cycles	
	No.	%	No.	%
Overall incidence	20	54	47	22
Cycle no. for first HSR				
1	13	65		
2	4	20		
4	2	10		
6	1	5		
Maximum grade of HSR				
+1	8	22	14	30
+2	9	24	1	2
+3	0	0	25	53
+4	1	3	1	2
Ungraded	2	5		
Signs and symptoms*				
Flushing	16	80	33	70
Hypertension	6	30	8	17
Chest tightness	6	30	11	23
Pain	6	30	9	19
Dyspnea	5	25	10	21
Pruritus	4	20	7	15
Bronchospasm	4	20	5	11
Throat tightness	3	15	4	9
Warm feeling	3	15	4	9
Nausea	2	10	9	19
Crampy abdominal pain	2	10	2	4
Upper respiratory tract angioedema	1	5	3	6
Lacrimation	1	5	2	4
Cycle no. 1 premedications				
None	9	24		
Diphenhydramine	24	65		
+ Decadron	2	5		
+ Decadron + cimetidine	1	3		
Cimetidine + diphenhydramine	1	3		

*The following signs or symptoms occurred in 1 patient (5%) and 1 cycle (2.1%) only: rash, dysesthesia, drug fever, hypotension, anxiety, arrhythmia, cold feeling, loss of consciousness, pressure in head, sneezing, tachycardia, urticaria, and unspecified.

the infusions were stopped and resumed following medication. As earlier, one patient (2%) did not resume therapy following a possible HSR.

Subsequent to experiencing an HSR, antihistamines alone were given to 10 patients (50% of those with HSRs), corticosteroids alone to two patients (10%), and both to 13 (65%).

Other acute toxicities. Two patients (5%) had local reactions. One (3%) had a grade 2 mild local cutaneous erythema at the injection site during cycle 1 that lasted 4 days. This was later diagnosed as an extravasation and did not recur in subsequent cycles. A second patient (3%) had an extravasation reaction with cycle 2.

Twelve patients (32%) experienced nausea (including the two patients who noted this as part of an HSR). It occurred in 13 of 124 cycles (11%) given at 100 mg/m^2 and eight (13%) of 61 given at 75 mg/m^2. Vomiting was observed in seven patients (19%). Seven emetic episodes occurred in 124 cycles (6%) at 100 mg/m^2 and two more among the 61 cycles (3%) at 75 mg/m^2.

At the 100-mg/m^2 dose level, stomatitis occurred in 11 of 124 cycles (9%), and at the 75-mg/m^2 dose level in four of 61 cycles (7%). One ineligible patient (3%) with an elevated pretreatment bilirubin level of 1.8 mg/dL was treated at her request and the request of her primary oncologist and with institutional review board and sponsor (Rhone-Poulenc Rorer) approval. She developed grade 4 neutropenia and grade 4 mucositis with massive gastrointestinal hemorrhage and died on day 12 following the first cycle of therapy. The steady-state docetaxel level (AUC) for this patient was 11.58 μg/mL, which was well above the median for the 34 patients studied (median, 4.59 μg/mL; range, 2.86 to 11.74). Autopsy showed diffuse hemorrhagic enterocolitis.

Except for the signs associated with acute HSR, there was no cardiac toxicity. One patient (3%) was noted to develop an elevated creatinine concentration (grade 2). The total bilirubin level increased in two patients (5%), both with known liver metastases. Mild hypoalbuminemia developed in 33 patients (89%), but in only two (5%) was it severe ($<$ 2 g/dL).

Cutaneous toxicity included erythema in 14 patients (38%), pruritus in 11 (30%), papulae in eight (22%), rash in seven (19%), and desquamation in six (16%). The median cumulative dose received at the onset of cutaneous toxicity was 502 mg/m^2 (range, 96.9 to 588.6). In addition, nail changes, including onycholysis that was considered moderate in two (5%), occurred in eight patients (22%), of whom seven (19%) had additional cutaneous toxicity. Two patients (5%) developed subungual superinfection with *Pseudomonas* that required antibiotic treatment.

Neurologic. Thirty-four patients (92%) underwent baseline testing and, of these, 31 (84%) had at least one follow-up neurologic evaluation. Neurologic toxicity was common (Table 5). Among 34 patients with detailed baseline evaluations, seven (21%) had mild neuropathic symptoms, which were attributed to radiculopathy in five (15%), carpal tunnel syndrome in one (3%), and pure sensory neuropathy in one (3%). Of 31 assessable patients, 29 (94%) developed new or worsened signs or symptoms of peripheral neuropathy. Thirteen (42%) developed both signs and symptoms, 12 (39%) symptoms only, and four (13%) signs only. The symptoms were paresthesias only in 10 (32%), numbness only in six (19%), and both in nine (29%). Symptoms involved both fingers and toes in 18 (58%), toes only in three (10%), and

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