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Paclitaxel and Recombinant Human Granulocyte Colony-Stimulating Factor as Initial Chemotherapy for Metastatic Breast Cancer

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Purpose: **A phase II study of Taxol (paclitaxel; Bristol-Myers Squibb Co, Princeton, NJ) as initial chemotherapy for metastatic breast cancer was conducted. Recombinant human granulocyte colony-stimulating factor (rhG-CSF) was used to ameliorate myelosuppression, the anticipated dose-limiting toxicity.**

Patients and Methods: **Twenty-eight patients with bidimensionally measurable breast cancer who had not received prior chemotherapy for metastatic disease were treated. Taxol was administered at 250 mg/m² as a continuous 24-hour intravenous (IV) infusion every 21 days. rhG-CSF was administered at 5 μg/kg/d subcutaneously on days 3 through 10.**

Results: **Objective responses were observed in 16 of 26 assessable patients (62%; 95% confidence interval, 41% to 80%). There were three (12%) complete responses (CRs) and 13 (50%) partial responses (PRs). Ten of 16 patients (63%) who had received prior adjuvant chemotherapy responded, which included one CR and four PRs among eight patients who had received prior doxorubicin-containing therapy. Responses were observed in all sites of metastatic disease. The median time to first objective response was 5 weeks (range, 1 to 14). Administration of rhG-CSF was associated with a short duration of neutropenia (median, 2 days with absolute neutrophil count < 500 cells/μL). Eight of 26 patients (31%) who received more than one course received subsequent therapy without dose reduction. One hundred seventy-eight cycles of treatment were administered, with a median of six cycles per patient (range, one to 19). Eight courses (4.5%) were associated with admissions for neutropenic fever. Twenty-two patients (79%) did not require admission for neutropenic fever. Treatment was well tolerated. Adverse effects included generalized alopecia in all patients. Myalgias, arthralgias, and peripheral neuropathy were mild. No hypersensitivity reactions and no cardiac toxicity were observed.**

Conclusion: **Taxol is highly active as initial chemotherapy for metastatic breast cancer. Administration of rhG-CSF reduced the incidence, depth, and duration of neutropenia, compared with published prior experience. Further studies of Taxol in breast cancer, including combinations with other active agents, are clearly warranted.**

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THE NOVEL DITERPENE Taxol (paclitaxel; Bristol-Myers Squibb Co, Princeton, NJ), derived from the bark of the western yew, Taxus brevifolia, is one of the most exciting new anticancer drugs.[1,2] Unlike other microtubule toxins in clinical use, such as vincristine or colchicine, Taxol promotes the formation of tubulin dimers and stabilizes microtubules against depolymerization.[3-6] This results in growth inhibition and loss of cell viability.

In the 1960s, bark extracts containing Taxol were found to be active against many murine cancers, including L1210, P388, and P1534 leukemias, Walker 256 carcinosarcoma, sarcoma 180, and Lewis lung carcinoma.[7] Taxol was isolated in 1971. However, because of its limited supply and relative insolubility, and a preclinical testing profile that was not very different from other spindle poisons, clinical trials with the drug were not initiated until the early 1980s. Phase I studies found that profound myelosuppression, specifically noncumulative reversible neutropenia, was dose-limiting.[8-12] Life-threatening type I hypersensitivity reactions were also encountered. These may be at least partially the result of the infusion of a high concentration of Cremophor EL (BASF Aktiengesellschaft), a mixture of polyoxyethylated castor oil and ethanol, used to solubilize the Taxol. In fact, similar hypersensitivity reactions have occurred when Cremophor EL was infused with drugs other than Taxol, such as didemnin B or teniposide.[13] Increasing the duration of the infusion to 24 hours and administering dexamethasone and H_1 and H_2 receptor antagonists before Taxol successfully reduces the incidence of hypersensitivity reac-

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tions.[6-12] Phase I trials of this method of administration have concluded that phase II studies should use 135 to 250 mg/m^2, depending on the degree of the patient's prior exposure to cytotoxic therapy. In these phase I trials, significant anticancer activity was observed in ovarian carcinoma, non–small-cell lung carcinoma, and melanoma.[6-12]

Concerning breast cancer, Taxol is active against the implanted human MX-1 mammary tumor xenograft.[7] In a recent phase II trial in metastatic breast cancer, the overall response rate was 56% (95% confidence interval, 35% to 76%), including a 12% complete response (CR) rate.[14] Hematopoietic growth factors were not used in this study, and myelosuppression was dose-limiting. For this reason, we performed the present trial in which recombinant human granulocyte colony-stimulating factor (rhG-CSF) was administered to ameliorate neutropenia and its morbid consequences.

PATIENTS AND METHODS

Eligibility Criteria

To be eligible for our trial, patients had to have histologically confirmed breast cancer with clinical evidence of bidimensionally measurable metastatic disease. Previous cytotoxic chemotherapy for stage IV disease was not permitted. Patients may have received prior radiation therapy if it was completed ≥ 4 weeks before study entry and if the portals encompassed less than 30% of the marrow-bearing skeleton. Indicator lesion(s) could not have been irradiated previously. Patients could have received prior adjuvant chemotherapy if it was completed 1 year or longer before study entry. One hormonal agent as adjuvant treatment and/or one hormone therapy for metastatic disease were allowed, but hormone therapy must have been discontinued at least 3 weeks before protocol entry. Blastic bone metastases, bone scan abnormalities alone, and pleural or peritoneal effusions were not considered measurable. Lytic bone metastases were acceptable as measurable indicator lesions if they were bidimensionally measurable on plain radiography, magnetic resonance imaging (MRI), or computed tomographic (CT) scan. Patients with stable brain metastases were eligible if at least one other site of measurable disease existed. Patients with carcinomatous meningitis and/or symptomatic lymphangitic pulmonary metastases were ineligible. Other eligibility criteria included the following: total WBC count more than 3,000 cells/μL, absolute granulocyte count ≥ 1,500 cells/μL, hemoglobin ≥ 8 g/dL, platelet count ≥ 100,000 cells/μL, serum creatinine ≤ 1.4 mg/dL, total bilirubin less than 1.5 mg/dL, serum calcium ≤ 10.5 mg/dL, Karnofsky performance status ≥ 60%, and an anticipated survival duration of ≥ 12 weeks. Patients must have recovered from prior surgery, being ≥ 2 weeks from minor surgery and ≥ 3 weeks from major surgery. Patients were ineligible if they had other prior malignancy (except for in situ cervical carcinoma and cured nonmelanoma skin cancer), other serious medical illnesses (including significant cardiac disease or arrhythmia), peripheral neuropathy, severe infection, or malnutrition. Before study entry, all patients gave written informed consent indicating their awareness of the investigational nature of this protocol.

Treatment Plan

Taxol was supplied by the National Cancer Institute as a concentrated sterile solution for intravenous (IV) administration in a 5-mL vial containing 30 mg of Taxol in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, United States Pharmacopeia, 50%. The drug was diluted with either 5% dextrose injection or 0.9% sodium chloride injection. When the study was initiated, shelf-life stability studies had indicated that the solution was stable for at least 12 hours, so the total dose was divided into two consecutive 12-hour infusions, each prepared immediately before administration.[7] Subsequent studies demonstrated that the solution was stable for 24 hours, so the total daily dose was prepared just before the start of therapy.[15] In-line filters, 0.2 μm, were used (IVEX-2, Abbott Laboratories, North Chicago, IL). Only glass containers and polyethylene-lined nitroglycerin tubing were used to avoid leaching of polyvinyl chloride from containers made of this material.

Initial dosage of Taxol was 250 mg/m^2, administered as a continuous IV infusion over 24 hours. Treatment was planned to be repeated every 21 days. Subsequent doses were modified on the basis of hematologic and nonhematologic toxicities (using National Cancer Institute common toxicity criteria) listed in Table 1.[16] The dose was reduced by one level to 200 mg/m^2 if the granulocyte nadir was less than 250 cells/μL or if the platelet nadir was ≤ 50,000 cells/μL, and by two levels to 180 mg/m^2 if infection or bleeding occurred in association with marrow suppression. Subsequent dose reductions followed the same rules. In patients without dose-limiting toxicity, the dose was escalated by two levels to 300 mg/m^2 if the granulocyte nadir was more than 2,000 cells/μL and the platelet nadir was more

Table 1. Dose Modification Scheme

Definition of Dose Levels

Level	Dose (mg/m^2)
−2	180
−1	200
0	250
1	275
2	300

Hematologic Toxicity

Granulocyte Nadir	Platelet Nadir	Dose Modification
> 2,000	and > 100,000	Increase 2 levels
> 1,000 but ≤ 2,000	and/or > 75,000 but ≤ 100,000	Increase 1 level
≥ 250 but ≤ 1,000	or > 50,000 but ≤ 75,000	No change
< 250	or ≤ 50,000	Decrease 1 level
Infection or bleeding		Decrease 2 levels

Nonhematologic Toxicity

Grade	Dose Modification
0-1	Increase 1 level
2	No change
3	Decrease 1 level
4	Decrease 2 levels

than 100,000 cells/μL, and by one level to 275 mg/m² if the granulocyte nadir was more than 1,000 but less than 2000 cells/μL and/or the platelet nadir was more than 75,000 but less than 100,000 cells/μL.

When appropriate, re-treatment was to be held beyond day 22 until hematologic recovery to a granulocyte count ≥ 1,500 cells/μL and platelets more than 100,000 cells/μL, and until gastrointestinal and/or infectious complications resolved. We planned to take patients off study if they did not recover sufficiently to receive treatment within 35 days from their prior dosage. Subcutaneous ports were implanted in patients with poor peripheral venous access before beginning therapy. All patients received the following regimen to prevent hypersensitivity reactions: dexamethasone 20 mg orally at 14 and 7 hours before each Taxol treatment, and diphenhydramine hydrochloride 50 mg, and cimetidine 300 mg IV at 1 hour before Taxol. During the first 30 minutes of Taxol infusion, a physician or a chemotherapy nurse remained at the bedside. Blood pressure was monitored every 15 minutes during the first hour of the infusion.

rhG-CSF (Neupogen, Amgen, Thousand Oaks, CA) at 5 μg/kg/d was specified to be administered subcutaneously on days 3 through 10 of each course (a total of 8 days) or until the absolute neutrophil count recovered to ≥ 2000 cells/μL for 3 consecutive days, even if antibiotic treatment for febrile neutropenia was required. Treatment with rhG-CSF was discontinued if the absolute neutrophil count exceeded 10,000 cells/μL. rhG-CSF was discontinued for at least 48 hours before institution of the next cycle of Taxol.

Duration of Therapy

After the initial dose of Taxol, we planned to administer at least one additional treatment unless there was disease progression or if intolerable (grade 3 to 4) toxicity, excluding neutropenia, precluded further treatment. Due to the limited supply of Taxol, we planned to administer only two courses beyond the best observed response, or to stop treatment when a maximum of 10 cycles were given, unless the tumor was still regressing at 10 cycles.

Pretreatment Evaluation

A complete history and physical examination were performed before the first cycle of therapy. Laboratory studies included a complete blood cell (CBC) count with differential and platelet count, biochemical screening profile, serum creatinine, carcinoembryonic antigen (CEA) and CA 15-3 determinations, serum human chorionic gonadotropin-beta (if indicated to rule out pregnancy), ECG, and posteroanterior (PA) and lateral chest x-rays. CT scan, MRI, and ultrasound were performed as needed to evaluate bidimensionally measurable disease. Bone scans were to be performed if clinically warranted.

Evaluation During Treatment

During treatment, CBC with differential and platelet counts were performed three times per week (each Monday, Wednesday, and Friday) to measure the duration and depth of neutropenia, and to monitor the effect of rhG-CSF. Before each treatment course, a physical examination and a detailed history documenting disease symptoms and the side effects of treatment was obtained. In addition, biochemical screening profile, serum creatinine, CEA, CA 15-3, ECG, and PA and lateral chest x-rays were performed every 3 weeks just before each treatment course. Tumor measurements were required at each cycle if these could be obtained by physical examination or chest x-ray. Otherwise, the measurements were to be obtained every 6 weeks (every two cycles) by CT, MRI, ultrasound, or plain x-ray (guided, if necessary, by bone scan). Patients with cutaneous lesions were to have serial photographic documentation whenever possible.

Criteria for Response

CR was defined as the disappearance of all clinical evidence of active tumor, with complete reossification of bone lesions and absence of disease-related symptoms for a minimum of 4 weeks. Partial response (PR) was defined as a ≥ 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. Minor response (MR) was defined as a decrease of less than 50% but more than 25% in tumor size for at least 4 weeks. Stable disease (SD) was defined as no change in tumor size or a less than 25% increase for at least 4 weeks. Progressive disease (PD) was defined as the unequivocal appearance of any new lesions or an increase of ≥ 25% in the sum of the perpendicular diameters of any measured lesion or in the estimated size of a nonmeasurable lesion. MR, SD, and PD were considered to be treatment failures.

Pharmacokinetic Studies

During the initial treatment cycle, three venous samples were collected from each patient: one before Taxol and two during the last 2 hours of the infusion (between hours 22 and 23) with at least 30 minutes separating these final two samples. At each sampling, 7 to 10 mL of blood was collected in a heparinized tube. This was centrifuged to separate the plasma, which was then transferred to a conical 15-mL polypropylene screw-top tube and stored at −20°C. An aliquot of the infusate from each patient was also stored at −20°C.

Taxol levels in plasma samples were measured by a reverse-phase high-performance high-performance liquid chromatography (HPLC) method described by Jamis-Dow et al.[17] Briefly, cephalomannine was added as an internal standard to 0.5 mL of plasma standard or sample. Each sample or standard was extracted on a C_{18} solid-phase extraction column. The extracts were dried under vacuum, reconstituted in mobile phase, and resolved by HPLC. Samples were chromatographed isocratically, with 45% acetonitrile in water at a flow rate of 1 mL/min. Separation was accomplished on an octadecylsilane (ODS) Hypersyl C_{18}, 5 μmol/L, 100 × 4.6-mm column (Hewlett-Packard Co, Palo Alto, CA) with a C_{18} precolumn insert (Millipore Corp, Milford, MA). Taxol and cephalomannine were quantitated at 230 nm with peak confirmation by diode-array detection.

Statistical Methods

The two-stage phase II design reported by Gehan[18] was applied for this study. Therapeutic responses were seen in the first 14 patients, so accrual was extended to estimate the response rate better. Duration of response and survival determinations were measured from the date of initiation of Taxol.

RESULTS

Patients

Between April 8 and October 24, 1991, 28 patients were accrued to this study (Table 2). The median age was 52 years (range, 30 to 67) and the median Karnofsky performance status was good at 90% (range, 70% to

Table 2. Patient Characteristics

Characteristic	No.	%
No. entered	28	
No. assessable	26	
Age, years		
Median	52	
Range	30-67	
Karnofsky performance status (%)		
Median	90	
Range	70-100	
Menopausal status		
Pre-	9	32
Post-	19	68
Sites of metastatic disease		
Bone	17	54
Lung	10	36
Liver	11	39
Lymph nodes	16	57
Soft tissue	14	46
No. of metastatic disease sites		
1	5	18
2	12	43
≥ 3	11	39
Prior therapy		
No prior adjuvant chemotherapy	11	39
Prior adjuvant chemotherapy	17	61
CMF	8	
CMFVP	1	
CAF	6	
CAMF	1	
CAMFV	1	
Prior hormonal therapy	11	39
Adjuvant only	5	
Metastatic only	2	
Both	4	
Time from prior adjuvant therapy to study entry, months		
Median	20	
Range	12-47	

Abbreviations: C, cyclophosphamide; M, methotrexate; F, fluorouracil; V, vincristine; P, prednisone; A, doxorubicin.

100%). However, 82% of patients had two or more sites of metastatic disease, and 11 (39%) had at least three sites of metastatic disease. Seventeen patients (61%) had received prior adjuvant chemotherapy, with a median time interval from completion of adjuvant chemotherapy to study entry of 20 months (range, 12 to 47). Eight patients had received doxorubicin-containing adjuvant chemotherapy, and nine had received cyclophosphamide, methotrexate, and fluorouracil (CMF) variants. Two patients had received vincristine as part of the adjuvant chemotherapy regimen. Eleven patients (39%) had received hormonal therapy: five in the adjuvant setting, two for treatment of metastatic disease, and four for both.

Therapeutic Responses

Twenty-six of 28 patients entered were assessable for response. The other two patients were not assessable for response, but were evaluated for toxicity. One patient had received her first cycle of treatment when it became necessary to administer radiation therapy for a cervical spine fracture, which became apparent only after a motor vehicle accident. The other patient had received two prior hormone regimens as treatment for stage IV breast cancer, but this information was withheld at the time of study entry. This latter patient had stable disease after four cycles of treatment with Taxol.

Objective responses were observed in 16 of 26 fully assessable patients (62%; 95% confidence interval, 41% to 80%) (Table 3). Three CRs (12%; 95% confidence interval, 2% to 30%) were seen: one patient had complete resolution of supraclavicular lymphadenopathy and pleural effusion, another had disappearance of supraclavicular and cervical lymphadenopathy by physical examination and CT scan, and the third had disappearance of supraclavicular lymphadenopathy and histologically confirmed resolution of diffuse involvement of the skin of the anterior and posterior chest wall. She had received adjuvant radiation to the anterior chest wall, as well as adjuvant doxorubicin-containing chemotherapy. There were 13 PRs (50%; 95% confidence interval, 30% to 70%), which were observed in all sites of metastatic disease.

Hormone receptor status did not appear to influence response. Although menopausal status per se did not influence the probability of response, responses were seen more frequently in women younger than 50 years of age (11 of 14 [79%] *v* five of 12 [42%], $P = .105$, two-sided Fisher's exact test). The median age of patients with responding tumors was 45.5 years (range, 30 to 67), as compared with 55 years (range, 37 to 64) for patients whose tumors did not respond.

Prior adjuvant treatment did not appear to influence response to Taxol (Table 4). Six PRs occurred in the 10 patients who did not receive prior adjuvant chemotherapy. Ten of 16 patients (63%) who had received prior adjuvant

Table 3. Therapeutic Responses

Response	No. of Patients	Percent	95% Confidence Interval
CR	3	12	2-30
PR	13	50	30-70
CR + PR	16	62	41-80
MR	4		
SD	0		
PD	6		

Note. N = 26 patients assessable for response.

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