ARTICLES

Phase II Trial of Taxol, an Active Drug in the Treatment of Metastatic Breast Cancer

Frankie Ann Holmes, Ronald S. Walters, Richard L. Theriault, Arthur D. Forman, Lesley K. Newton, Martin N. Raber, Aman U. Buzdar, Debra K. Frye, Gabriel N. Hortobagyi*

Taxol, an antimicrotubule agent, has shown promise for efficacy in treatment of breast cancer, but severe hypersensitivity reactions led to cessation of many phase I clinical trials. Consequently, investigators and the National Cancer Institute recommended that phase I and II studies of this agent use 24-hour infusions and antiallergic medications. Using a premedication regimen effective in preventing hypersensitivity reactions, we have performed a phase II trial of taxol in patients with metastatic breast cancer. Taxol was administered to 25 patients at a dose of 250 mg/m^2 by 24-hour infusion every 21 days. These patients had received only one prior chemotherapy regimen, either adjuvant to surgery or for metastatic disease; all but two had received doxorubicin. In 60% of the patients, the dominant site of disease was the viscera. All patients were assessable. In April 1991, at a median time on study of 9 months (range, 5-13+ months), the objective response rate was 56% (12% complete and 44% partial; 95% confidence interval, 35%-76%). Disease progressed in only 8% of the patients. The median number of courses of therapy was 11. Granulocytopenia was the dose-limiting toxic effect, but neutropenia with fever occurred in only 5% of 232 courses. A chronic glove-and-stocking neuropathy developed in most patients, but no allergic reactions occurred. We conclude that taxol is an active agent in the treatment of metastatic breast cancer and that it warrants continued study. Currently, we are conducting a phase I trial of taxol plus doxorubicin. Future trials should address the optimal effective dose, the optimal sequencing of combinations, mechanisms of drug resistance in tumors, and dose-limiting toxic effects (particularly cardiac toxic effects of taxol given as a single agent or in drug combinations). [J Natl Cancer Inst 83:1797–1805, 1991]

The development of antimicrotubule agents has been one point of light in the treatment of the epidemic of breast cancer. Preliminary studies with vinorelbine (Navelbine; Burroughs Wellcome Co., Research Triangle Park, N.C.), a semisynthetic derivative of vinblastine that acts in a similar but more selective way, have shown responses in 50% of patients with metastatic breast cancer (*1,2*). The general mechanism of action of antimicrotubule agents is inhibition of tubulin polymerization and of microtubule formation.

Taxol is a microtubule agent isolated by Walls' group at Research Triangle Institute, Research Triangle Park, from the stem bark of *Taxus brevifolia*, the western (Pacific) yew (*3,4*). Unlike all other antimicrotubule agents, taxol acts by promoting the formation of unusually stable microtubules, inhibiting the normal dynamic reorganization of the microtubule network required for mitosis and cell proliferation (*5*). Early development of this drug was stymied by the relative unavailability of the bark and difficulty in solubilizing the compound. However, the novel mechanism of action and the activity of taxol in the intraperitoneally implanted B16 melanoma murine tumor were impetuses for further development. Potential efficacy in the treatment of breast cancer was suggested by the activity of taxol in the subrenally

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F. A. Holmes, R. S. Walters, R. L. Theriault, A. U. Buzdar, D. K. Frye, G. N. Hortobagyi, Section of Breast Medical Oncology, Department of Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Tex.

A. D Forman, L. K. Newton, Division of Medicine, Department of Neuro-Oncology, The University of Texas M. D. Anderson Cancer Center.

M. N. Raber, Clinical Trials Administration, Department of Medical Oncology, The University of Texas M. D. Anderson Cancer Center.

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**Correspondence to:* Frankie Ann Holmes, M.D., The University of Texas M. D. Anderson Cancer Center-Box 95, 1515 Holcombe Blvd., Houston, TX 77030.

implanted human MX-1 mammary tumor xenograft, although it was not effective in the subcutaneously implanted murine $CD8F_1$ mammary tumor (*6*).

Rowinsky et al. (*5*) have comprehensively summarized the development of taxol. The dose-limiting toxic effect of taxol in most phase I clinical trials was neutropenia, but clinically important neurotoxic effects also occurred. In addition, however, hypersensitivity reactions, including hypotension and death, were observed. These reactions, which led to cessation of many phase I trials, were thought to be consistent with toxic effects from the diluent Cremophor EL, a mixture of 50% alcohol and polyethoxylated castor oil (*7*). After considering the problem, investigators and the National Cancer Institute recommended that phase I and II studies of taxol use 24-hour infusions and an antiallergic premedication regimen consisting of dexamethasone given orally and diphenhydramine with either cimetidine or ranitidine given intravenously (*8*). The recommended dose and schedule for phase II testing of taxol are 250 mg/m^2 by 24-hour infusion repeated every 21 days. Our article presents the results of the phase II study performed in patients with metastatic breast cancer at The University of Texas M. D. Anderson Cancer Center.

Patients and Methods

Eligibility Criteria

Eligible patients for this study had histologically diagnosed breast cancer with documented measurable or evaluable metastatic disease that was progressing on current therapy; a Zubrod (*9*) performance status less than 3 [Karnofsky scale >70% (*10*)]; an expected survival of more than 12 weeks; adequate function of the bone marrow, liver, and kidney; and a maximum of one prior regimen of chemotherapy (either adjuvant to surgery or for metastatic disease) with or without biologic therapy. Before treatment, all patients were advised of the investigational nature of this study, signed an informed consent document approved by The University of Texas M. D. Anderson Cancer Center Surveillance Committee, and were registered with the central data management office.

Treatment

Drug preparation. Taxol was supplied in 30-mg ampules, which we diluted with either a 0.9% sodium chloride injection or a 5% dextrose injection to a final concentration of 0.3-1.2 mg/mL. Because initial shelf-life data indicated that the solution was stable for at least 8 hours, the total dose was divided into thirds, and one third of the total dose was prepared just prior to each of three consecutive 8-hour infusions. Subsequent stability studies indicated the solution was stable for at least 12 hours, so the total dose was halved, and one half of the dose was prepared just prior to each of two consecutive 12-hour infusions (*6*). To prevent leaching of taxol from containers composed of polyvinyl chloride, only glass or polyolefin containers and polyethylene-lined nitroglycerin tubing were used. Because some particulate matter occurs after dilution, in-line filtration with 0.2-μm filters is necessary; this procedure does not affect the concentration of the final solution.

Dose level. Taxol was administered by 24-hour infusion every 21 days. The standard premedication regimen used to prevent hypersensitivity reactions (*8*) consisted of dexamethasone (20 mg) given orally 14 and 7 hours before taxol and cimetidine (300 mg) and diphenhydramine (50 mg) given intravenously 1 hour before taxol.

The starting dose level of taxol was 250 mg/m^2 for patients with a low risk of myelosuppression and 200 mg/m^2 for those with a high risk. Criteria for a high risk of myelosuppression were prior irradiation to 30% of the marrow-bearing bones, prior treatment with mitomycin, or poor hematologic tolerance to previous chemotherapy manifested by need for dose reductions due to neutropenia with fever. The dose level was reduced for toxicity as follows: 200, 180, 160, or 130 mg/m^2. A dose reduction of one level was planned for grade 3 toxic effects or an absolute granulocyte count of less than $250/mm^3$; a dose reduction of two levels was planned for grade 4 toxic effects. There was no maximum number of dose reductions per patient. When subsequent experience revealed that even lower granulocyte count nadirs were not associated with infections, doses were not reduced for any degree of neutropenia. All patients were treated and observed for 26 hours in the ambulatory treatment center.

Duration of therapy. The planned duration of therapy was at least two courses unless disease progression was rapid; at least three courses if there was no change in disease and if grade 3 or 4 toxic effects, excluding neutropenia, did not occur; and 12 months after a complete remission or after maximum response in patients who had partial remission. Patients who clearly had disease progression before receiving taxol and who had no change were to continue treatment until 1) toxic effects were intolerable, 2) there was clinical evidence of progressive disease, or 3) there had been no change for 6 months. Patients could stop treatment at any time by their expressed intent.

Pretreatment Evaluation

Pretreatment evaluation included a medical history with documentation of prior therapies and estrogen receptor status. An estrogen receptor value greater than 10 fmol/mg of cytosol protein was considered positive. A physical examination with attention to the peripheral nerves was performed. Laboratory evaluation included a complete blood cell count with platelet count and leukocyte differential count, sequential multiple analysis (total protein albumin, calcium, phosphorus, blood urea nitrogen, creatinine, uric acid, glucose, bilirubin, alkaline phosphatase, alanine aminotransferase, and lactate dehydrogenase), and assays of the markers carcinoembryonic antigen and CA 15-3. All patients had appropriate radiographs and scans to document the extent of the metastatic disease. These procedures included chest radiographs, ultrasound or computed tomography of the liver, isotope bone scan, and bone radiographs or computed tomography of the affected areas. Disease was categorized by the dominant site of metastasis, i.e., the site with the poorest prognosis. The dominant sites in order of decreasing risk were viscera, bone, and soft tissue. The extent of disease was also categorized by the number of organ systems involved. For example, a patient with pulmonary nodules, liver metastases, pleural effusion, chest wall disease, and lymphadenopathy would be classified as having visceral-dominant disease with five sites.

Evaluation During Treatment

Vital signs (blood pressure, pulse, respirations, and temperature) were measured before the start of therapy. The blood pressure and pulse were measured every 30 minutes twice during the infusion of the premedication and every 15 minutes twice after the infusion of taxol started. Thereafter, vital signs were measured every 4 hours during infusion. Because experience with taxol at this institution did not reveal cardiac problems, patients did not have monitoring of the cardiac rhythm except during measurement of the vital signs.

Evaluation Between Courses

After the infusion was completed, patients were evaluated with a complete blood cell count twice weekly until the pattern of neutropenia was established. Thereafter, these blood tests were performed weekly, except during the expected period of neutropenia (days 8-15), when they were done twice weekly to allow more precise documentation of the duration of neutropenia. Before each course, a history of disease symptoms and toxic effects of the treatment was obtained. All patients had a physical examination with attention to areas of disease and toxic effects. Toxic effects were graded by the National Cancer Institute's Common Toxicity Criteria (*11*). Physical examination of the peripheral nerves was performed by a neurologist (A. D. Forman or L. K. Newton) after every three or four courses or every 3 months. Radiographs or scans of areas of disease were evaluated after every two courses until there was evidence of response or disease progression. Thereafter, in responding patients, the disease was evaluated after every four courses.

Assessment of Response

All responses were graded according to standard criteria (*12*). The duration of response was defined as the time from the first evidence of response until the first evidence of progressive disease. The time to response or disease progression was defined as the time from the start of therapy until the first evidence of response or progressive disease, respectively.

Complete remission was defined as disappearance of all evidence of tumor for at least 4 weeks, improvement of bone lesions as evidenced by scan and complete reossification as shown by x ray, normal levels of the markers carcinonoembryonic antigen and CA 15-3, and no clinical symptoms of cancer. Partial response was defined as a 50% or greater decrease in the sum of the products of the perpendicular diameters of all measured lesions persisting for at least 4 weeks, appearance of no new lesion(s), improvement of bone lesions as evidenced by scan and some reossification as shown by x ray, and decreased levels of markers. Minor response was defined as a decrease in size of any measurable lesion too small or too brief to meet the criteria for a partial response. No change was defined as no change in tumor size or less than a 25% increase in tumor size for at least 4 weeks. Progressive disease was defined as the appearance of an unequivocally new lesion or an increase of 25% or more in the sum of the products of the perpendicular diameters of any measured lesion or in the estimated size of a nonmeasurable lesion.

Results

Response

Twenty-five patients were enrolled from January through August 1990. All patients were assessable. Results are current as of April 1991. Responses in the initial 12 responding patients were reviewed and confirmed on October 11, 1990, by the Cancer Therapy Evaluation Program, Division of Cancer Treatment, at the National Cancer Institute.

Patient characteristics are shown in Table 1. The dominant site of disease in 60% of the patients was visceral. Eighteen patients (72%) had bidimensionally measurable disease; of the seven patients (28%) with evaluable disease, three (12%) had bone metastasis only.

Responses are shown in Table 2. The complete remission rate was 12%; the overall response rate was 56% (12% complete remission and 44% partial response; 95% confidence interval = 35%-76%). Of the three patients with complete remission, two had measurable disease in the soft tissue and one had nodular lung metastases; in the last, complete remission was confirmed

Table 1. Characteristics of patients and tumors and prior treatment

	No. of patients
Entered in study	25
Assessable	25
Age, y	
Median: 51	
Range: 34-70	
Zubrod performance status	
Median: 1	
Range: 0-2	
Disease-free interval, mo	
Median: 18	
Range: 0-94	
Estrogen receptor status	
Negative	9
Positive	14
Unknown	2
Estrogen receptor value, fmol/mg*	
Median: 25.5	
Range: 10-433	
Prior therapy	
Hormone therapy	15
Chemotherapy	
Adjuvant	14
For metastatic disease	11
Doxorubicin	23
Doxorubicin-resistant†	6
Dominant disease site	
Soft tissue	6
Bone	4
Viscera	15
No. of sites	
Median: 2	
Range: 1-10	
No. of organ systems involved	
Median: 2	
Range: 1-6	

*Of estrogen receptor positive.
†Doxorubicin resistance is defined in the "Results" section.

Table 2. Responses in 25 patients

Response to taxol	No. of patients	Duration, mo	Time to progressive disease, mo
Complete	3	5, 8+, 12+	6, 9+, 13+
Partial	11	3, 4, 4, 5, 8, 3+, 3+, 5+, 6+, 6+, 13+	5, 7, 7, 9, 12, 8+, 9+, 10+, 11+, 11+, 13+
Minor	8	—	2, 3, 4, 4, 4, 8+, 10+, 10+
No change	1	—	6
Progressive disease	2	—	1, 2

by computed tomography of the chest and continues. One patient who had complete remission of soft-tissue disease has relapsed. The other patient with complete remission of soft-tissue disease remains disease free after discontinuing taxol. Partial responses were seen in patients who had soft-tissue (12%), bone (8%), and visceral disease (24%). Examples of partial responses in viscera and bone are shown in Figs. 1 and 2. Of eight patients with a minor response, three continue to receive taxol. In only two patients (8%) did taxol fail to cause any regression or stabilization of tumor. The median time to response was 3.5 months (range, 1-7 months), and the median duration of response was greater than 5 months (range, 3-13+ months). Eleven patients continue to respond favorably in this

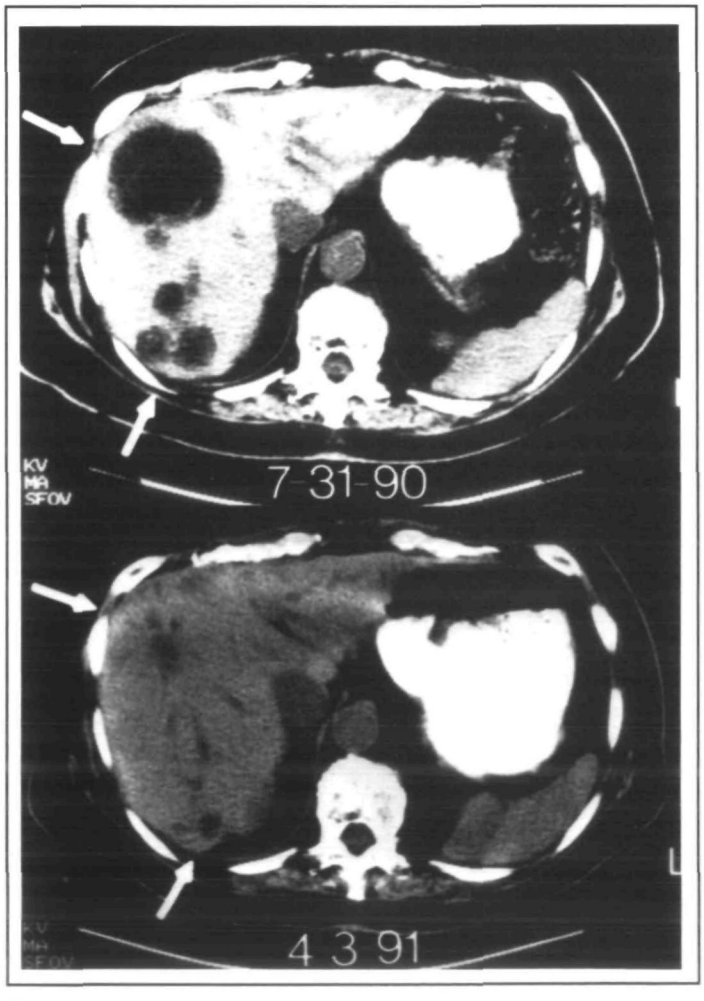

Fig. 1. Partial response in viscera: dramatic reduction in size of liver lesions seen after 14 courses of taxol.

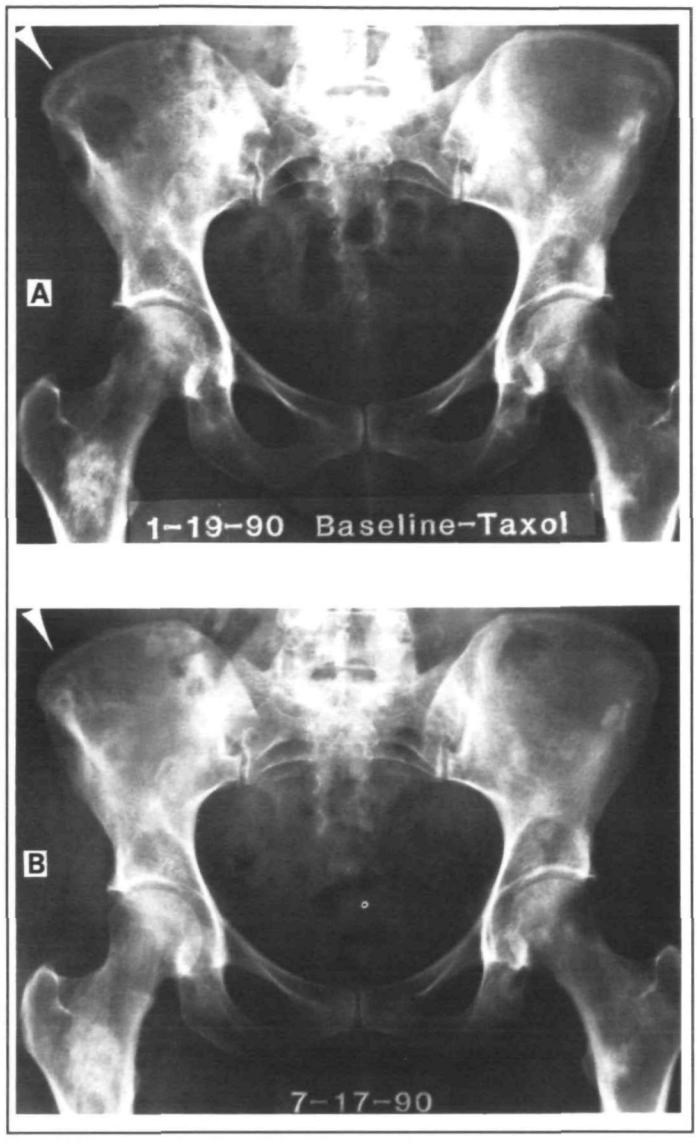

Fig. 2. Panel A: baseline pelvis film showing large lytic lesions in right ilium. Panel B: Partial response in bone showing blastic healing of lesions in right ilium after eight courses of taxol.

study. Fourteen patients have experienced disease progression, and eight of these have died (Fig. 3).

Both the median time on study and the median time to disease progression for all patients were 9 months (range, 5-13+ months). The median time to disease progression for patients who remained in the study was greater than 10 months. The median number of courses per patient was 11 (range, 2-19), and the median cumulative dose of taxol per patient was 2160+ mg/m^2 (range, 450-4050+ mg/m^2).

Response by Prior Therapy

Responses were evaluated in relation to prior therapy. Correlation of responses with prior chemotherapy is shown in Table 3. Slightly more responses occurred in patients who had received adjuvant therapy. Both of the patients whose disease progressed during taxol therapy were in the group that had previously received chemotherapy for metastatic disease.

Patients with metastatic disease who had progressive disease without an intervening response while receiving doxorubicin or

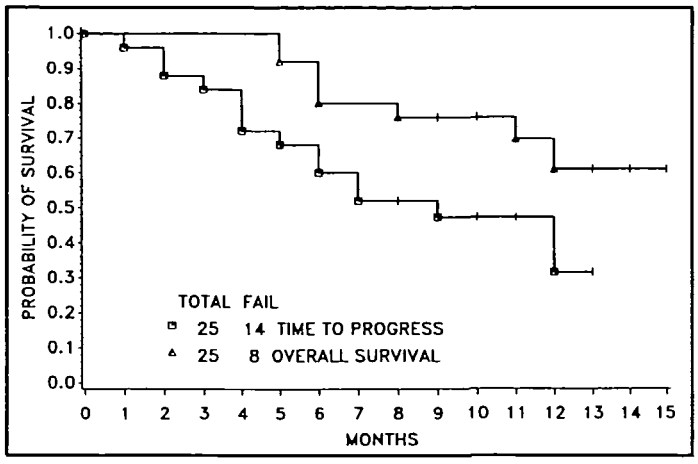

Fig. 3. Time to progression and overall survival curves for 25 patients treated with taxol.

within 6 months of receiving doxorubicin in an adjuvant setting were considered to have primary resistance to doxorubicin. Patients with metastatic disease who were receiving doxorubicin and had progressive disease after an initial response were considered to have secondary doxorubicin resistance.

Twenty-three patients had received doxorubicin-based regimens. Of six patients with primary or secondary resistance to doxorubicin, two had a partial response, two had a minor response, and two had progressive disease. The two patients who had not received doxorubicin had been treated with a methotrexate-based adjuvant regimen. One of these patients relapsed during adjuvant therapy but had a minor response to taxol, which further demonstrates the efficacy of taxol.

None of the patients with a complete remission or progressive disease had received prior hormonal therapy. Of 11 patients who had partial remissions, eight had received hormonal therapy and three had responded. Of eight patients with a minor response, five had received hormonal therapy and three had responded. In one patient, the hormonal therapy was given as an adjuvant therapy, then discontinued before relapse. The patient with no change was receiving adjuvant hormonal therapy when she relapsed.

The performance status did not correlate with response, except that all three patients with a complete remission had a performance status of 0. The estrogen receptor status did not correlate with response. The response and the estrogen receptor status, respectively, were as follows: complete remission, two negative and one unknown; partial response, six positive, four negative, and one unknown; minor response, seven positive and one negative; no change, one negative; progressive disease, one positive and one negative.

Hematologic Toxic Effects and Dose Levels

As of April 1991, 258 courses have been administered, of which 232 are assessable for toxic effects. At that time, data on laboratory tests for 26 courses had not been received. Neutropenia was the dose-limiting toxic effect in all but four patients, who had grade 3 myalgias.

Table 4 shows the number of patients treated at each dose level in specific courses, the number who required dose reduction, and the reasons for dose reduction. Seven patients were initially treated at the 200-mg/m^2 level because of poor hematologic tolerance to prior adjuvant chemotherapy (three patients), prior irradiation to marrow-bearing sites (three patients), and prior treatment with high-dose chemotherapy and stem cells (one patient). Seven patients required no dose reductions during the entire treatment period. Doses were altered in only 32 (14%) of the 232 courses evaluated. Of these 32 courses, in 26 courses (11% of all courses), doses were reduced by one

Table 3. Number of responses by prior chemotherapy treatment

Response to taxol	Chemotherapy adjuvant to surgery: No. of patients (N = 14)	Chemotherapy adjuvant to surgery: Prior regimen*	Chemotherapy for metastasis: No. of patients (N = 11)	Chemotherapy for metastasis: Prior regimen*	Chemotherapy for metastasis: Response to prior regimen†
Complete	2	FAC × 6–MVb × 4 FAC × 8	1	FAC × 6	IV-NED
Partial	6	VACp × 9–hIFN × 12 FACVp × 9–MVb × 6 VACp × 3–VbMF × 6 FAC × 6 CMFVp × 12 VACp × 3–XRT–VbMF × 10	5	F(THP-A)C × 10 FAC × 12 AC × 2–CEP (↑dose‡) × 2 ACp × 10 + T × 12 FACT × 9–CMFT × 12	PR PR PR IV-NED PR
Minor	6	FACVp × 8–MVb × 6 FACVp × 8–M × 3–Vb × 3 VACp × 7 FACV × 9–CMFVp × 1 CMF × 4 Lp × 1–FAC × 9–CMF × 1–Lp × 6	2	FAC × 11 FAC × 9–Vb × 6	PR PR
No change	0		1	FAC × 9	NC
Progressive disease	0		2	FAC–Prem × 7 FAC × 7	PR PD

*A, doxorubicin; C, cyclophosphamide; E, etoposide; F, fluorouracil; hIFN, human interferon α (Cantell; Finnish Red Cross, Finland); Lp, melphalan; M, methotrexate; p, prednisone; P, cisplatin; Prem, Premarin; T, tamoxifen; THP-A, pirarubicin; V, vincristine; Vb, vinblastine; XRT, x-ray therapy.

†IV-NED, stage IV but no evident disease; PR, partial response; NC, no change; PD, progressive disease.

‡High-dose chemotherapy with autologous peripheral stem cell infusions.

Table 4. Number of patients treated at each dose level in specified courses

Course No.	No. of patients Treated	No. of patients Requiring dose reductions	Reason for reductions*	No. of patients treated with 250 mg/m^2	200 mg/m^2	180 mg/m^2	160 mg/m^2	130 mg/m^2
1	25	7	High risk	18	7	—	—	—
2	25	13	G (8) GI (3) GIN (2)	9	12	4	—	—
3	23	6	G(3), GI (2), N (1)	6	11	3	3	—
6	19	1	I	4	9	2	2	2
9	15	1	N	2	7	3	1	2
12	13	2	I	2	6	5	—	—
15	5	0		1	4	—	—	—

*High-risk = prior x-ray therapy and poor tolerance to prior chemotherapy; G = absolute granulocyte count <250/mm^3; I = infection; N = neurotoxicity. Values in parentheses = No. of patients.

dose level; of these 26 courses, in 13 courses (6% of all courses), doses were reduced only because the granulocyte count nadir was less than 250/mm^3. The reasons for dose reduction in the remaining courses were as follows: infection (10 courses, 4%), neurotoxic effects (five courses, 2%), and both infection and neurotoxic effects (two courses, 1%). In 10 courses (4%), doses were increased one dose level. The number of dose level reductions and the number of patients treated at those levels were as follows: one dose level reduction, four patients; two reductions, four patients; three reductions, four patients; and four reductions, one patient. Two patients required dose reduction to 130 mg/m^2, and both had partial responses.

Hematologic toxic effects in specific courses are shown in Table 5. The median granulocyte count nadir was consistently 100-200/mm^3 for the majority of the courses; despite dose reduction, the range at all dose levels included 0/mm^3. The median hemoglobin level remained above 10 g/dL; only three patients required transfusion of packed red blood cells. No patient experienced thrombocytopenia with a platelet count less than 50 000/mm^3.

Analysis of hematologic effects by dose level, independent of course number, as shown in Table 6, again demonstrates the same pattern of profound myelosuppression at all levels.

Nonhematologic Toxic Effects

Myalgias. A unique toxic reaction was the occurrence of pain in the muscles and bones, similar to a prodrome of influenza or the syndrome seen with high doses of vinblastine or etoposide. Myalgias occurred in most patients (Table 7), began 3-6 days after treatment, and lasted 3-6 days. The lower extremities and pelvis were usually involved, but the upper extremities were also occasionally involved. The intensity of this reaction varied among patients, but it was directly related to the dose of taxol.

In patients whose symptoms required treatment, one or more of the following medications were useful: hydrocodone (5 mg) with acetaminophen (500 mg) every 4-6 hours; ibuprofen (600-

Table 5. Median lowest recorded granulocyte and platelet counts and hemoglobin by specified course*

	Course No. (No. of patients) 1 (25)	2 (25)	3 (23)	6 (19)	9 (12†)
Dose, mg/m^2					
Median	250	200	200	200	200
Range	200-250	180-250	160-250	130-250	130-250
Granulocyte count nadir, cells/mm^3					
Median	100	200	100	100	300
Range	0-1000	0-600	0-1100	0-900	0-1800
Day of granulocyte count nadir					
Median	8	12	13	13	12.5
Range	7-15	8-16	10-16	9-17	8-16
Platelet count nadir, × 10^3/mm^3					
Median	165	191	190	192	201
Range	63-353	76-320	72-347	87-245	54-380
Day of platelet count nadir					
Median	8	8	9	8	8
Range	4-15	7-12	4-15	7-12	7-16
Hemoglobin nadir, g/dL					
Median	10.8	10.5	10.8	10.7	10.9
Range	6.7-14.0	7.4-13.8	8.1-13.4	8.2-13.3	9.2-11.9
No. of transfusions	2	1	0	0	0

*Courses 1-3 were chosen because almost all patients received three courses and the denominator was large enough to show any acute effects. Courses 6 and 9 were chosen to demonstrate chronic effects.

†Blood cell counts were available for analysis only on 12 of 15 patients treated in course 9 (*see* Table 4) at the time of analysis.

Table 6. Median lowest recorded granulocyte and platelet counts by dose level and number of courses

	Dose level, mg/m^2				
	250	200	180	160	130
No. of patients (No. of courses)	18 (68)	18 (109)	7 (27)	4 (14)	2 (14)
Granulocyte count nadir, cells/mm^3					
Median	200	200	100	100	100
Range	0-1700	0-1800	0-1200	0-1000	0-300
Median day of granulocyte count nadir	11	12	12	14	12
No. of days granulocyte count <500/mm^3					
Median	7	7	7	7	9
Range	3-15	2-15	3-11	5-11	4-14
Platelet count nadir, × 10^3/mm^3					
Median	196	180	191	224	210
Range	101-353	54-320	72-262	147-380	185-286
No. of days platelet count <100 × 10^3/mm^3					
Median	0	3	7	0	0
Range	0	2-7	7	0	0

Table 7. Highest grade of nonhematologic toxic effects experienced

Toxic effect	No. of patients (%) with toxic effects of		
	Grade 1	Grade 2	Grade 3
Myalgia/arthralgia	3 (12)	17 (68)	4 (16)
Neuropathy	9 (36)	13 (52)	2 (8)
Nausea only	3 (12)	3 (12)	—
Nausea/vomiting	4 (16)	5 (20)	—
Anorexia	7 (28)	2 (8)	—
Diarrhea	8 (32)	15 (60)	1 (4)
Stomatitis	13 (52)	8 (32)	—
Dysgeusia	9 (36)	1 (4)	—
Infection or fever during neutropenia*	6 (24)	9 (36)	2 (8)
Alopecia	—	25 (100)	—
Skin rash	14 (56)	1 (4)	—
Fatigue	6 (24)	7 (28)	9 (36)
Cardiac rhythm	2 (8)	1 (4)	1 (4)
Sneezing	1 (4)	—	—
Onycholysis	3 (12)	2 (8)	—
Hypomagnesemia	7 (28)	—	—

*Neutropenia = <1000 granulocytes/mm^3.

800 mg) every 6-8 hours; amitriptyline (25-50 mg) daily; propoxyphene (65-130 mg) every 3 hours; acetaminophen (325 mg) with codeine (30-60 mg) every 3-4 hours; and immediate-release morphine (30-60 mg orally) or hydromorphone (4 mg orally) every 2-3 hours. In four patients, these symptoms were dose limiting and required dose reduction; in one of these four patients, large doses of hydromorphone given orally were required. In the patient with lung metastases in complete remission who had received 14 courses at the 250-mg/m^2 level, the duration of the myalgias gradually increased so that she was never pain free between courses.

Cardiac toxic effects. At the time this study was started, cardiac toxic effects had not been reported. Subsequently, some patients who had received cisplatin and taxol in another study experienced ventricular ectopy, and the National Cancer Institute issued a letter alerting all investigators using taxol about this toxic effect (*13*).

Only four cardiac events occurred in our study. One patient, who had a prolapsed mitral valve, experienced atypical chest pain associated with ventricular ectopy 3 days after her second infusion. Subsequent cardiac evaluation (medical history, physical examination, serial serum cardiac enzyme levels, serial electrocardiograms, and an echocardiogram) showed no abnormality. It is not clear whether this event was related to taxol.

In the other three patients, however, sinus bradycardia (two patients) or sinus arrest (one patient) occurred during the infusion. Before we received the letter from the National Cancer Institute, one patient known to have asymptomatic sinus bradycardia was entered in the study. During routine evaluation of this patient's vital signs during course 2, a pulse of 45 beats per minute was noted. A 12-lead electrocardiogram was obtained immediately and gave normal results. The pulse was normal 10 minutes later, and the infusion continued uneventfully. The patient received seven additional courses of taxol and had no symptoms of cardiac toxic effects.

After we received the letter, a second patient was noted to have a pulse rate of 56 beats per minute nearly 12 hours after the start of the infusion of taxol, during course 18. The pulse immediately rose to 61 beats per minute, and continuous cardiac monitoring was begun. During that infusion, a number of other episodes of sinus bradycardia from 44 to 60 beats per minute were observed. The patient was asymptomatic. Continuous recording of the electrocardiogram by Holter monitoring during course 19 revealed a few other episodes of asymptomatic sinus bradycardia. A medical history and physical examination by a cardiologist and an echocardiogram revealed no abnormality. No subsequent therapy was administered because the patient had completed 1 year of treatment and was in complete remission.

The third patient reported "dizziness" 2 days after completing course 8 of taxol. A 48-hour Holter monitor recording, obtained after the infusion of taxol in course 9, showed only a few premature atrial contractions and premature ventricular contractions thought to be related to prior therapy with doxorubicin. Before course 9, the serum magnesium level was borderline low at 1.7 mmol/L (normal level, 1.8-2.8 mmol/L); therefore, intravenous magnesium was administered 24 hours before course 9, and oral

supplementation has been given since that time. The magnesium level was determined again and was normal before the start of course 9. Monitoring during and for 48 hours after the infusion of taxol in course 10 revealed several episodes of sinus pause, one for longer than 2 seconds. The patient has remained asymptomatic, and these episodes have resolved spontaneously. Evaluation by echocardiogram revealed normal results. Despite monitoring during courses 11 and 12, no further cardiac abnormalities occurred, and the patient continues to receive taxol without cardiac monitoring.

Neurotoxic Effects

Acute and chronic neurotoxic effects were seen. A few patients reported acute tingling of the fingertips and toes within 24 hours after the infusion. This symptom merged into the myalgia syndrome. The chronic effect was a cumulative glove-and-stocking sensory neuropathy associated with complete loss of deep tendon reflexes (grade 1 toxic effect), which occurred in most patients. Some patients experienced painful paresthesias with hyperalgesia. These paresthesias were most severe on the plantar surfaces, but they progressed to the mid-calf (stocking distribution) in some patients, at which time dose reduction was necessary. Diminution of fine motor skills (e.g., buttoning or putting on earrings) occurred but generally did not progress after doses were reduced. Evaluation of the deep tendon reflexes 4 months after the last course in one of the patients who discontinued taxol after attaining a complete remission revealed that the deep tendon reflexes were uniformly present except in the right quadriceps.

Other Toxic Effects

Table 7 lists all the nonhematologic toxic effects by grade. Most of these effects were mild. After the National Cancer Institute's alert about cardiac toxic effects in patients who had been treated with cisplatin and thus were at risk for total-body magnesium depletion, serum magnesium levels were obtained before each course in all patients.

Seven patients had hypomagnesemia (range, 1.3-1.7 mmol/L). In three patients, the hypomagnesemia had no obvious cause, and magnesium was administered orally or, before a course, intravenously. The other four patients received magnesium intravenously as well as orally to normalize serum levels before taxol was administered. One of these four patients had glucose intolerance, controlled with oral hypoglycemic agents; the other three were receiving thiazide diuretics, but only two took them regularly.

A majority of patients experienced the typical cutaneous reaction to high doses of dexamethasone (Decadron; Merck & Co., Inc., West Point, Pa.). This reaction was an erythematous rash involving one or more of the following sites: the forehead and malar regions of the face and the sun-exposed area of the chest and upper torso. This rash was self-limited, and no therapy was given. Three patients received prophylactic antibiotics. One patient received antibiotics for one course, and another for two courses. A third patient, who developed a grade 3 infection despite initial treatment with 200 mg/m^2 taxol, received prophylactic trimethoprim-sulfamethoxazole twice daily from day 10 to day 18 of all of the subsequent eight courses; this patient continues in the study.

A more detailed perspective on the incidence of toxic effects can be seen in Table 8, which compares the incidence of toxic effects by patients and by number of courses. This table demonstrates that, while many patients experienced at least one toxic effect, this effect generally occurred in only a few courses. The majority of patients tolerated therapy quite well.

Discussion

Although drug-supply problems limited this study to 25 patients and, thus, the confidence intervals were wide, the results clearly show that the efficacy of taxol for metastatic breast cancer is similar to or better than that of most currently used drugs. Despite the supply problems, future studies must address the following issues.

First, the optimal effective dose for taxol is not known. The ovarian cancer studies suggest that taxol is active as a single agent at doses of 110-175 mg/m^2 (*5*). Even though most patients (72%) in our study required a dose reduction, their tumor responses continued. Determination of the dose-response curve will address the problems of the peak dose-related toxic effects (myalgias and neuropathy), optimal doses for combination therapy, and limited drug supply.

A second and closely related issue is determination of dose-limiting toxic effects. While myelosuppression is profound, it is brief. Patients with absolute granulocyte counts of 0/mm^3 did not necessarily develop infectious complications in this study. However, in a phase II study in patients with ovarian cancer, McGuire et al. (*14*) reported three episodes of sepsis directly implicated in the death of two patients. When taxol is used as a single agent, infectious complications should be the surrogate for neutropenia, and doses should not be reduced for neutropenia alone. Use of hematopoietic growth factors may abrogate this problem by reducing the severity of myelosuppression and enhancing recovery of the granulocyte counts. However, myalgias and sensory neuropathy, which are peak dose related, and stomatitis may become the major dose-limiting toxic effects.

Table 8. Incidence of grade 2 or 3 toxic effects by patients and courses

Toxic effect	% of patients (N = 25)	% of courses (N = 232)
Neutropenia <500/mm^3	100	85.8
Infection during neutopenia	8	0.9
Fever during neutropenia*	36	4.7
Diarrhea		
Grade 2	60	13.8
Grade 3	4	0.4
Stomatitis—grade 2	32	6.0
Myalgia/arthralgia—grade 3	16	3.0
Neuropathy		
Grade 2	52	15.1
Grade 3	8	0.9

*Neutropenia = <1000 granulocytes/mm^3.

Third, the cardiac toxic effects of taxol given as a single agent or in combinations, especially with other cardiotoxic drugs, must be clarified. Although most patients in this study had no clinically important adverse effects, Rowinsky et al. (*15*) reported ventricular tachycardia, ventricular ectopy, and myocardial infarction in patients who received taxol with cisplatin. Two patients who received taxol as a single agent experienced serious atrioventricular conduction delay; one was complete, requiring a temporary pacemaker. On the other hand, Lampidis et al. (*16*) demonstrated some promising effects of taxol on cardiac cells in vitro when it was used in combination with other drugs. They found that exposure to vinblastine resulted in cardiostimulatory activity, which was blocked by pretreatment or simultaneous treatment with taxol. Similarly, they observed that cardiac arrhythmias induced by doxorubicin were reversed by treatment with taxol.

Fourth, taxol should be studied in combination with other active agents, such as doxorubicin and cyclophosphamide. The optimal sequencing of any combination to maximize efficacy and to minimize toxicity is not clear. Citardi et al. (*17*) evaluated the effect of the sequence of administration of taxol and cisplatin on cytotoxic effects in taxol-resistant L1210 cells. They found maximal cytotoxicity when taxol preceded cisplatin. Although preliminary findings in an initial report by Rowinsky et al. (*18*) showed no difference in the severity of toxic effects observed in 25 patients treated in a phase I study, the full report by Rowinsky et al. (*19*) clearly demonstrated impaired taxol clearance, which had the same effect as increasing the taxol dose by 33%, when cisplatin was given first. This sequence caused significantly greater myelosuppression than the reverse sequence. In addition, an unconfirmed observation by Blumenschein et al. (*20*) suggested that the sequencing of doxorubicin and vinblastine influenced response rate. The incidence of partial remissions was halved, and no complete remissions were observed when doxorubicin was given after vinblastine, compared with one complete remission and a partial remission rate of 58% (11 of 19 patients) with the reverse sequence. Preliminary results of our phase I trial of the combination of taxol and doxorubicin also suggest that the sequencing of drugs may profoundly affect the incidence of stomatitis.

Fifth, the mechanisms of resistance to taxol should be clarified in the clinic. Alterations in tubulin and a membrane-associated phosphoglycoprotein have been demonstrated in cell lines (*5*). Reversal of resistance associated with the membrane phosphoglycoprotein was possible with calcium channel blockers. Interestingly, the vehicle for taxol, Cremophor EL, has been shown to reverse resistance mediated by overexpression of the P-glycoprotein membrane pump (*21,22*).

We are currently evaluating the combination of taxol and doxorubicin in a phase I trial. The dose of taxol will be escalated as tolerated; the dose of doxorubicin will be fixed and infused over 48 hours. All patients will have continuous cardiac monitoring and 72-hour Holter monitors. Filgrastim (Neupogen; Amgen Inc., Thousand Oaks, Calif.) will be administered to ameliorate myelosuppression, and dose-limiting neutropenia will be defined as documented infection or fever during granulocytopenia (<500 granulocytes/mm^3) or failure of the granulocyte count to recover to greater than 1500/mm^3 by day 21. If there is evidence of potential therapeutic antagonism, the sequence of drug administration will be reversed. The National Cancer Institute is also studying this combination with escalating doses of both agents given in a different schedule.

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