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ORIGINAL ARTICLE

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Biweekly paclitaxel in patients with metastatic breast cancer

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Abstract
Background. This study was conducted to evaluate the efficacy and the toxicity of paclitaxel administered as a biweekly 1-h infusion (120 mg/m^2).
Methods. Twenty patients with metastatic breast cancer were enrolled in this study. Paclitaxel was administered at a dose of 120 mg/m^2 by an intravenous 1-h infusion every 2 weeks. The primary objectives of the study were the response rate and toxicity. Pharmacokinetic analysis was conducted in 7 of the 20 patients treated with paclitaxel.
Results. Four of the 20 patients had grade 3 or 4 neutropenia. Arthralgia or myalgia was observed in 8 of the 20 patients. Grade 2 or 3 neurotoxicity was observed in 6 of the 20 patients. In the 20 assessable patients, there was one complete response and eight partial responses. The overall response rate was 45%. The mean time to progression was 5.4 months.
Conclusion. Biweekly paclitaxel may be suitable for patients receiving paclitaxel for palliative therapy, as tolerance was similar to that with the weekly schedule, but with the advantage of increased convenience.

Key words Paclitaxel · Breast cancer · Biweekly

Introduction

Paclitaxel is an active drug in the treatment of metastatic breast cancer, as first-line therapy, as well as for relapsed or refractory disease, even in patients who have failed to respond to prior anthracycline therapy. The optimal dose and schedule for paclitaxel administration for metastatic breast cancer have not yet been defined. Because preclinical data suggested that the duration of exposure was an important factor in the cytotoxic activity of this drug, clinical trials of triweekly 96-h infusions of paclitaxel were performed. However, the administration of 96-h continuous infusions of paclitaxel may be inconvenient for both the clinic and the patients.

Another method of producing extended cumulative exposure is frequent, repetitive drug administration, such as that done with a weekly schedule. Weekly dosing of paclitaxel has been demonstrated to be well tolerated and feasible.[1] Weekly administration of paclitaxel is dose-intense, but has a favorable toxicity profile. In the above report,[1] the tumor response rate to a weekly infusion of paclitaxel was superior to that of triweekly infusion, and the hematological toxicity (neutropenia) was less than that with triweekly infusion, although peripheral neurotoxicity was increased compared with triweekly infusion. Biweekly infusion of paclitaxel is an alternative to the triweekly schedule, but only a small number of clinical trials of biweekly infusion have been reported.[2–4] The present study was developed to demonstrate the feasibility of administering paclitaxel every 2 weeks. The objectives were to evaluate the efficacy and toxicity of biweekly 1-h infusions of paclitaxel (120 mg/m^2).

Patients and methods

Patient population

This study was conducted from January 1, 2000, to March 1, 2002, at Nagoya City University Hospital.

Women with metastatic breast cancer who met the following eligibility criteria were included in this study: aged between 20 and 69 years, a performance status of 0, 1, or 2 (Eastern Cooperative Oncology Group), life expectancy of at least 2 months, leukocyte count of 4000/μl or more, platelet count of 100000/μl or more, total bilirubin level below the upper normal limit (UNL), serum hepatic transaminase

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levels less than twice the UNL, serum creatinine level under the UNL, and normal electrocardiogram. Twenty patients were enrolled and all gave written informed consent to participate in this study.

Study design

Paclitaxel was administered at a dose of 120 mg/m^2 by an intravenous (IV) 1-h infusion, referring to the results of phase I–II trials of biweekly paclitaxel.[2,3] Cycles were repeated every 2 weeks. Therapy was stopped when there was nonmanageable toxicity or evidence of progressive disease. Endocrine therapy was not combined with the biweekly paclitaxel therapy.

Premedication was uniform for all patients, and consisted of the following, to prevent a hypersensitivity reaction: dexamethasone (20 mg IV) 1 h before infusion, and diphenhydramine (50 mg IV) and ranitidine hydrochloride (50 mg IV), each given 30 min before the start of paclitaxel infusion. Neither prophylactic granulocyte-colony stimulating factor (G-CSF) nor prophylactic antibiotic administration was allowed. Toxicity was graded using the National Cancer Institute (NCI) common toxicity criteria. Doses were modified for toxicity on the day of treatment. A 25% reduction in paclitaxel dose was made for an absolute neutrophil count between 500 and 1500/μl. For an absolute neutrophil count of less than 500/μl, paclitaxel was withheld. If the blood counts did not recover within 7 days, paclitaxel was reduced by 25% in subsequent cycles. For other toxicities of grade 3 or more, treatment was withheld until resolution to grade 1 or less or baseline and then restarted with the paclitaxel dose reduced by 25%. Toxicities of grade or less were managed symptomatically, if possible, with no dose reductions.

Response was evaluated using the Response Evaluation Criteria in Solid Tumor (RECIST) guideline.[5] Complete response (CR) was defined as the total disappearance of all target lesions for at least 4 weeks. Partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameters of target lesions for at least 4 weeks, taking as reference the baseline sum of the longest diameters. Progressive disease (PD) was defined as at least 20% increase in the sum of the longest diameters of the target lesions, taking as reference the smallest sum of the longest diameters recorded since the treatment started or the appearance of one or more new lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the longest diameters since the treatment started.

All patients were evaluable for safety from the start of their first treatment cycle. To be evaluable for response, patients had to have received a minimum of two cycles of treatment (i.e., 4 weeks on study) with at least one follow-up tumor assessment.

The primary objectives of the study were to determine the response rate and toxicity. The secondary objective was to determine time to progression, which was calculated from the date of administration of the initial paclitaxel to the date of documented progression, date of last hospital visit, or start of further antitumor therapy.

Pharmacokinetic analysis

Pharmacokinetic analysis was conducted in seven patients treated with paclitaxel who gave written informed consent to participate in the pharmacokinetic study. Serum samples for pharmacokinetic evaluation of paclitaxel were collected from each patient at the time of the first course of therapy. Heparinized blood samples were obtained before the infusion and 0, 0.5, 1, 3, 6, 12, 24, 34, and 48 h after the infusion, and were immediately separated by centrifugation. A portion of the serum sample was stored frozen for the measurement of paclitaxel. Concentrations of paclitaxel in plasma were determined using high-performance liquid chromatography (HPLC) with *n*-hexyl *p*-hydroxybenzoate (Tokyokasei, Tokyo, Japan) as an internal control. The HPLC system consisted of an LC-9A chromatograph system (Shimazu, Kyoto, Japan), water injector, and UV detector at 227 nm. Plasma samples diluted with water were applied to a solid-phase extraction column, (Sep-Pak C_{18} cartridge; Waters Associates, Milford, MA, USA). Internal standard solution diluted with water was added to the column and the column was washed with 2 ml 30% acetonitrile in water. The mobile phase was acetonitrile: 0.01 M KH_2PO_4 (44:55) at a flow rate of 1.5 ml/min. The retention times of paclitaxel and *n*-hexyl *p*-hydroxybenzoate were 12 and 17 min, respectively. The paclitaxel concentration was quantitated by linear regression analysis of the peak height ratio (paclitaxel: *n*-hexyl *p*-hydroxybenzoate) versus the standard curve generated from the solution of paclitaxel with *n*-hexyl *p*-hydroxybenzoate diluted with acetonitrile-2 mM H_3PO_4 (44:55). Pharmacokinetic parameters of paclitaxel were determined by the noncompartmental method (moment method).

Results

Twenty patients were enrolled in this study and were assessed for response and safety. As shown in Table 1, all patients were female, ranging in age from 38 to 69 years (median, 51 years). In 50%, there were two or more metastatic sites. Nine patients had liver metastasis. Seven had received prior anthracycline therapy, and 13 patients had previously received docetaxel therapy. Prior docetaxel had been administered by a triweekly infusion (60 mg/m^2), and the accumulated total dosage of docetaxel was 282.3 mg/m^2. In the 13 patients assessable for prior docetaxel therapy, there were 3 with PR, 9 with SD, and 1 with PD.

Table 2 shows the toxicity profile. One patient had transient marginal grade 4 neutropenia, but received no G-CSF, while another patient had grade 4 neutropenia and was given G-CSF for 3 days. Two patients exhibited grade 3 neutropenia. Alopecia (grade 1 or 2) was the most common

Table 1. Patient characteristics

Characteristic	No.	Percentage
No. of patients	20	
No. assessable for response	20	
No. assessable for toxicity	20	
Age (years)		
Median		51
Range		38–69
Menopausal status		
Pre-	9	45
Post-	11	55
Hormone receptor status		
ER+ and/or PR+	10	50
ER− and PR−	8	40
Unknown	2	10
Metastatic sites		
No. of sites involved		
1	10	50
2	2	10
3+	8	40
Actual sites involved		
Lymph node	5	25
Skin, soft tissue	7	35
Lung, pleura	8	40
Bone	9	45
Liver	9	45
Prior chemotherapy		
Prior adjuvant therapy only	2	10
Prior metastatic therapy only	4	20
Both	12	60
Prior anthracycline therapy	7	35
Prior docetaxel therapy	13	65
Both	5	25
Prior endocrine therapy	10	50

ER, estrogen receptor; PR, progesterone receptor

Table 2. Toxicity profile of biweekly paclitaxel therapy

Toxicity (grade)[a]	No. of patients					
	0	1	2	3	4	3/4 (%)
Leukopenia	6	4	8	2	0	2 (10)
Neutropenia	8	5	3	2	2	4 (20)
Anemia	16	2	2	0	0	0
Nausea	18	1	1	0	0	0
Alopecia	0	3	17	0	0	0
Neurosensory	11	3	5	1	0	1 (5)
Arthralgia/myalgia	12	4	4	0	0	0
Malaise/asthenia	12	4	4	0	0	0
Dysgeusia	19	1	0	0	0	0
Stomatitis	19	1	0	0	0	0

[a] National Cancer Institute (NCI) common toxicity scale

event. Gastrointestinal toxicity, as evidenced by nausea and vomiting, was not severe. Arthralgia or myalgia was observed in 8 of the 20 patients (40%). Grade 2 or 3 neurotoxicity was observed in 6 patients (30%). The relative dose-intensity was 92.6% (55.6 mg/m^2 per week) of the planned dose (60 mg/m^2 per week).

In the 20 assessable patients, 1 had CR, 8 had PR, 9 had SD, and 2 patients had PD (Table 3). The overall response (OR) rate was 45%. The mean time to progression among the patients was 5.4 months (Fig. 1). A 38-year-old woman with multiple lung nodules and local relapse had a CR lasting for 4 months.

Table 3. Response to biweekly paclitaxel therapy

	Response					
	n	CR	PR	SD	PD	OR (%)
All patients	20	1	8	9	2	9 (45)
Prior anthracycline therapy	7	1	2	3	1	3 (43)
Prior docetaxel therapy	13	1	5	6	1	6 (46)
Both	5	1	2	2	0	3 (60)
None	4	0	3	1	0	3 (75)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, overall response

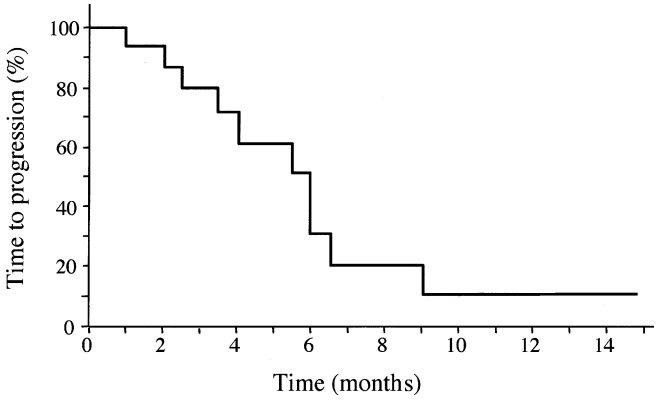

Fig. 1. Time to progression. Mean time to progression in all patients was 5.4 months

The plasma concentration-versus-time curves of paclitaxel for the seven patients in whom pharmacokinetics were studied are shown in Fig. 2. The plasma concentration of paclitaxel began to decline immediately upon cessation of the infusion, in a biexponential fashion. The mean peak plasma concentration (Cmax) was 4.04 μg/ml, and the mean area under the curve (AUC) was 9.92 μg/ml per h. These data suggest nonlinear pharmacokinetics of paclitaxel when given by a 1-h infusion, a result that is compatible with other reports.[6–8]

Discussion

Initial phase I trials with paclitaxel have evaluated a wide range of schedules. Early studies using short infusion times were associated with an unacceptably high frequency of unpredictable hypersensitivity reactions. However, prolonging the infusion time and premedicating patients with steroids and antihistamines prevented these reactions. Therefore, a 24-h infusion schedule was recommended for subsequent trials. With evidence that short infusion times were safe when premedication was administered, it became important to evaluate further the optimal dosage and schedule of administration.

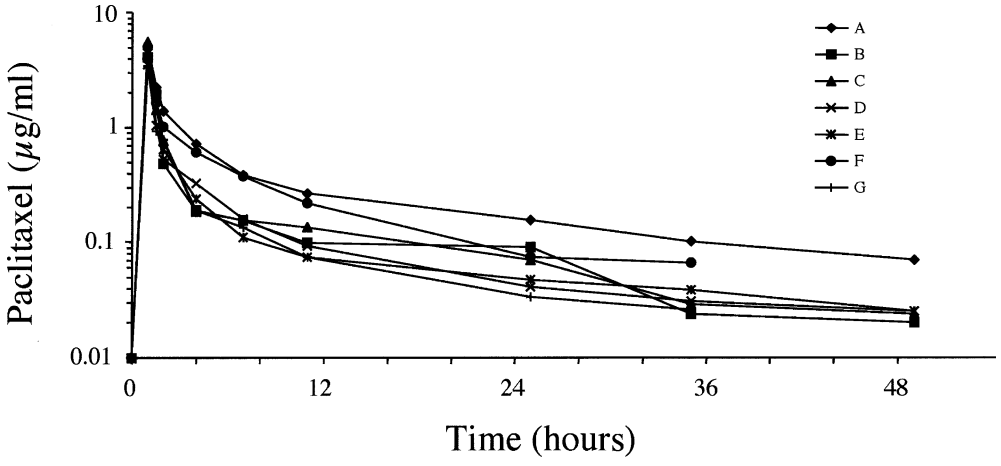

Fig. 2. Concentration versus time curves in seven patients (*A–G*) who received biweekly paclitaxel therapy. Blood samples were obtained before the infusion, and 0, 0.5, 1, 3, 6, 12, 24, 34, and 48 h after the infusion. Concentrations of paclitaxel in plasma were determined using an HPLC method

A study in patients with metastatic breast cancer evaluated triweekly 3-h infusions of paclitaxel in patients randomized to receive either 135 mg/m^2 or 175 mg/m^2. The high-dose arm showed a trend toward an improvement in response rate and overall survival, as well as significant improvement in time to progression.[9] On the other hand, a phase II study demonstrated that the median delivered dose-intensity of a weekly 1-h paclitaxel infusion was 91 mg/m^2 per week, which was higher than that of the triweekly 3-h infusion. Responses were observed in 50% of patients with prior anthracycline therapy. Therapy was well tolerated and was remarkable for the lack of overall and cumulative myelosuppression. Peripheral neuropathy prohibited dose escalation above 100 mg/m^2.[1]

Biweekly schedules for paclitaxel infusion are also dose-intense. A phase I study of solid tumors, including breast cancers, showed the safety of biweekly 3-h infusions (175 mg/m^2).[2] Preliminary results of a phase I–II trial for metastatic breast cancer by Gelmon et al.[3] demonstrated a response rate to biweekly 3-h infusions (100 to 160 mg/m^2) of 61%, and a median time to progression of 221 days. As 75% of the patients in our study had received prior anthracycline and/or docetaxel therapy, paclitaxel 120 mg/m^2 was administered over a 1 h period every 2 weeks. Although the dosage of paclitaxel in this study was lower than that in other trials, the response rate was 45% and the median time to progression was 5.4 months. An overall response rate of 43% was observed in patients who had prior anthracycline therapy. These data supported the results of the randomized clinical trial reported by Nabholtz et al.[9] Therefore, the response to paclitaxel therapy was encouraging in these patients who had prior anthracycline therapy.

Clinical trials have demonstrated that docetaxel is active in patients with paclitaxel-resistant breast cancer, with response rates of 17% to 25%.[10,11] However, there are few reports of the efficacy of paclitaxel in patients with docetaxel-resistant breast cancer. In this study, a response rate of 46% was observed in patients who had prior docetaxel therapy, which seems relatively high. The dose of docetaxel for most patients who had received prior docetaxel therapy in this study had been 60 mg/m^2 every 3 weeks. This dose was lower than the doses used in a substantial number of clinical trials. Therefore, the disease in some of these patients may not have been 'real' docetaxel-resistant disease.

The pharmacokinetics in the present study demonstrated that peak plasma paclitaxel concentrations were similar to those observed with dosages of 105 to 270 mg/m^2 delivered over 3 h,[5] and plasma concentrations remained above 0.01 μmol/l (=0.012 μg/ml) for at least 48 h after a dose of 120 mg/m^2 was administered over a 1-h period. This may have important implications when considering the schedule-dependence of paclitaxel-induced apoptosis.[12–14] Prolonged exposure to relatively low concentrations of paclitaxel, on the order of 0.01 to 0.02 μmol/l, have been shown to induce apoptosis in several different cell lines, including the MCF-7 breast cancer cell line. With the biweekly doses used in the present study, which were lower than the standard doses (i.e., 175 mg/m^2), plasma paclitaxel concentrations of this magnitude can be achieved with acceptable toxicity.

Myelosuppression was remarkably mild. Although grade 3 or 4 neutropenia did occur in four patients, there was no instance of febrile neutropenia, and thrombocytopenia was nonexistent. Neuropathy is an issue with paclitaxel administration. The neuropathies have been typically described as numbness, burning, and tingling, starting in the fingers and toes and moving up into the hands and legs, having a stocking-glove distribution with repeated paclitaxel administration. In this study, grade 2 or 3 neuropathy was observed in six patients (30%). According to the results of weekly paclitaxel therapy in a study by Seidman et al.[1] grade 3 or 4 neutropenia occurred in 14% of patients, 24% exhibited grade 3 neurotoxicity, and grade 3 arthralgia/myalgia was observed in 6% of patients. The toxicity profile of the biweekly paclitaxel therapy in our study was similar to that of the weekly paclitaxel therapy.

Biweekly paclitaxel may be suitable for patients receiving paclitaxel for palliative therapy, because of the convenience of a biweekly schedule in comparison with the weekly schedule, and because tolerance is similar in both regimens. The mild toxicity profile also makes biweekly paclitaxel a viable candidate for combination with other agents.

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