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Phase I Study of Paclitaxel by Three-hour Infusion: Hypotension Just after Infusion Is One of the Major Dose-limiting Toxicities

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The primary objectives of this study were to determine the maximum tolerated dose (MTD) of paclitaxel administered by 3-h infusion to patients with solid tumors, and to characterize the pharmacokinetics of a 3-h infusion in comparison with those of a 24-h infusion. Twenty-seven patients each received one of six levels of paclitaxel, 105, 135, 180, 210, 240 and 270 mg/m^2, with premedication. Two patients given 240 mg/m^2 and one patient given 270 mg/m^2 unexpectedly had grade 3/4 hypotension just after finishing the paclitaxel infusion. Peripheral neuropathy was also dose-limiting at 270 mg/m^2. Although granulocytopenia was significantly less severe than with a 24-h infusion, more than half of the patients experienced grade 4 toxicity at doses of 240 or 270 mg/m^2. Severe hypersensitivity reactions (HSRs) were not observed. Pharmacokinetic studies using high performance liquid chromatography demonstrated proportionally greater increases in the peak plasma concentration and area under the curve, and decreases in clearance and volume of distribution with increasing dose, suggesting non-linear pharmacokinetics of paclitaxel when given by 3-h infusion. The MTD of paclitaxel given as a 3-h infusion was determined to be 240 mg/m^2 with dose-limiting toxicities of granulocytopenia, peripheral neuropathy and hypotension. Hypotension just after infusion, induced by 3-h infusion of paclitaxel, is a new observation which has not been reported previously. The recommended dose for phase II study is 210 mg/m^2. Although hypotension was observed as an unexpected toxic effect, paclitaxel could be administered safely over 3 h with premedication and proper monitoring, resulting in reduced myelotoxicity and with no increase in the incidence of HSRs as compared with a 24-h infusion.

Key words: Paclitaxel — Phase I study — Non-linear pharmacokinetics

Paclitaxel, a novel antitubular agent derived from the bark of the Pacific yew tree, has a broad spectrum of antitumor activity *in vitro* and *in vivo*.[1,2] Unlike other tubulin-binding agents such as vinca alkaloids, which promote microtubule disassembly, paclitaxel shifts the equilibrium toward microtubule assembly and stabilizes microtubules by preventing depolymerization.[3,4]

In initial clinical trials of paclitaxel in the United States using 1, 3, 6 or 24-h infusion schedules, severe acute hypersensitivity reactions (HSRs) such as bronchospasm, angioedema and urticaria were observed.[5,6] Based on observations that the incidence of HSRs appeared to be related to shorter duration of infusion and a direct release of histamines probably caused by the Cremophor EL vehicle,[7] the National Cancer Institute (United States) recommended use of a longer infusion duration and prophylactic antiallergic medication comprising corticosteroids and H_1- and H_2-histamine antagonists for further trials of paclitaxel. Subsequent phase II studies in the United States performed using a 24-h infusion schedule and including premedication, showed significant antitumor activity in a number of solid tumors such as ovarian,[8] breast,[9] and non-small-cell lung cancer.[10,11]

In 1991, we conducted a phase I study of paclitaxel by 24-h infusion at the National Cancer Center Hospital.[12] In this study, the maximum tolerated dose (MTD) was determined to be 180 mg/m^2, the dose-limiting toxicity (DLT) being granulocytopenia associated with infection. However, interim analysis of the European-Canadian ovarian paclitaxel trial comparing high- vs. low-dose and 24-h vs. 3-h infusion suggested that the incidence of HSRs in the 3-h infusion was similar to that observed with 24-h infusion when premedication was included, and that neutropenia was significantly less severe with a 3-h infusion.[13] A shorter infusion duration would be preferable if it had the same efficacy as a longer infusion without any increase in toxicity. The primary objectives of this study of paclitaxel using a 3-h infusion were to determine the MTD in patients with solid tumors and to characterize the pharmacokinetics of paclitaxel in 3-h compared to 24-h infusion.

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PATIENTS AND METHODS

Eligibility Only patients with histologically or cytologically proven solid tumor, refractory to conventional therapy or with no effective therapy, were candidates for this study. Eligibility criteria included: (1) age 15–74 yr; (2) Eastern Cooperative Oncology Group (ECOG) performance status[14] 0, 1, or 2; (3) recovery from the toxic effects of previous therapy; (4) adequate bone marrow function (WBCs $\geq$4,000/mm^3, hemoglobin $\geq$10.0 g/dl, platelets $\geq$100,000/mm^3), renal function (creatinine $\leq$1.5 mg/dl, urea nitrogen $\leq$25 mg/dl), and hepatic function (total bilirubin $\leq$1.5mg/dl, transaminase and alkaline phosphatase $\leq 2\times$ upper normal limits); (5) stable sinus rhythm with no clinical heart disease; (6) absence of $\geq$ grade 2 peripheral neuropathy due to previous chemotherapy. Pregnant patients were excluded. All patients gave informed written consent according to the government guidelines (Good Clinical Practice (GCP) by the Ministry of Health and Welfare of Japan) and institutional guidelines. The study protocol was approved by the Institutional Review Boards of the National Cancer Center. Central registration by fax to the Department of Health Science, Faculty of Medicine, University of Tokyo, was employed.

Drug administration Paclitaxel was supplied by Bristol-Myers Squibb K. K. (Tokyo) as a concentrated sterile solution containing 30 mg of the drug in 5 ml of 50% polyoxyethylated castor oil (Cremophor EL) and 50% dehydrated alcohol. Paclitaxel was diluted in 500 ml of 5% dextrose in water and administered as a 3-h intravenous infusion every 3 weeks. Polypropylene bottles and polyethylene-lined nitroglycerin tubing with in-line filters of 0.22 μm were used for all infusions. To prevent HSRs, patients were premedicated with (1) dexamethasone 20 mg intravenously, 14 and 7 h before paclitaxel; (2) ranitidine 50 mg intravenously, 30 min before paclitaxel; and (3) diphenhydramine 50 mg orally, 30 min before paclitaxel. Continuous electrocardiogram (ECG) telemetry was obtained during the paclitaxel infusion.

Dose escalation The starting dose of 105 mg/m^2, (7n, where n=1/3 toxic dose low in dogs) was chosen from the results of our previous phase I study of 24-h infusion,[12] and dose escalation to 135 (9n), 180 (12n), 210 (14n), 240 (16n), and 270 (18n) mg/m^2 was performed in accordance with a modified Fibonacci scale.[15] At least three patients were treated at each dose level. Three additional patients were entered at the same dose level if DLT was observed in one of the first three patients. The MTD was defined as the dose level at which two patients out of three to six patients experienced DLT. DLT was defined as (a) $\geq$ grade 3 non-hematologic toxicity, (b) grade 4 leukopenia or thrombocytopenia, or (c) grade 4 granulocytopenia lasting for more than seven days. The final determination of MTD or further dose escalation was made by a monitoring committee consisting of three independent members (two medical oncologists and one biostatistician).

Pretreatment and follow-up studies Physical examinations and routine laboratory studies were performed weekly. Complete blood counts (CBCs) were also performed on day 7 and every two or three days for two weeks. Routine laboratory studies included CBC, differential white blood cell count, total protein, albumin, total cholesterol, electrolytes, blood urea nitrogen (BUN), creatinine, total bilirubin, SGOT, SGPT, LDH, alkaline phosphatase and urinalysis. An ECG was obtained before, and 24 h after therapy. Toxicities were evaluated according to ECOG common toxicity criteria. ECOG criteria[16] were used for evaluating the response in patients with measurable or evaluable diseases.

Pharmacologic studies Plasma and urine samples for the pharmacokinetic evaluation of paclitaxel were collected from all patients at the time of their first course of therapy. Heparinized blood samples were obtained before infusion, at 1.5 h during infusion, and at the end of infusion, as well as at 5, 15, 30 min and 1, 2, 3, 4, 6, 12, 24, 48 h after infusion. Urine samples were collected for 3-h infusion and then over 72 h, in 12-h increments twice, and then in 24-h increments twice. Plasma was separated, and plasma and urine samples were stored at below -20°C until analysis. Concentrations of paclitaxel in plasma and urine were determined by high-performance liquid chromatography (HPLC) according to the modified Grem method[17] developed at Bristol-Myers Squibb K. K. Pharmacokinetic parameters of paclitaxel were determined by the noncompartmental method (moment method).

RESULTS

Thirty patients were registered for the study between March and December 1993. Three patients did not receive paclitaxel. One patient with acute infection was considered to be ineligible, and two other patients were lost to the study without paclitaxel administration during transient stoppage of accrual due to the appearance of hypotension as an unexpected toxic effect. Twenty-seven patients received 48 total courses of paclitaxel at one of the six dose levels. The characteristics of the 27 patients are listed in Table I. Table II shows dose-limiting toxicities at each step of the dose escalation, and Table III shows all toxicities observed using the ECOG common toxicity grading.

Hypotension Three of 27 patients experienced grade 3 or 4 hypotension just after finishing the paclitaxel infusion. The fourth patient (#17) at level 5 (240 mg/m^2) was hypotensive 5 min after finishing the paclitaxel infusion,

and required a dopamine or noradrenaline infusion for 8 days. Bronchospasm, stridor, flushing and other common symptoms of HSRs were not observed. ECG showed only non-specific ST-T changes, and the ejection fraction measured by echocardiography was normal. Peripheral edema was not observed. Patient #17 had no symptoms except hypotension and could speak and take food during the dopamine infusion. The pharmacokinetic data from this patient were no different from those of the other four patients studied at level 5. After his complete recovery from hypotension, we concluded that this toxicity could have been an HSR rather than a dose-dependent toxicity, and the study was restarted. However, at level 6 (270 mg/m^2), grade 3 hypotension requiring dopamine for several hours was observed in one patient (#26) and grade 1 hypotension was also observed in two other patients. For safety, the dose was reduced to 240 mg/m^2, but grade 3 hypotension was observed in the first patient (#27). All these toxicities occurred within 5 min of finishing the paclitaxel infusion. In two patients with grade 3 hypotension (#26 and #27), blood pressure and heart rate were stable until the end of the infusion. They looked and felt sleepy during the last 30 min of paclitaxel

Table I. Characteristics of Patients

Number of patients	27
Males/Females	18/9
Median age (range)	53 years (38–65)
PS (0/1/2)	7/20/0
Prior therapy	
None	6
Chemotherapy (C)	3
Surgery (S)	1
C+Radiotherapy (R)	3
C+S	9
C+S+R	5
Tumor types	
Lung	16
Breast	3
Head and neck	3
Colorectal	2
Esophagus	1
Ovary	1
Unknown primary	1

Unless otherwise specified, values represent numbers of patients. PS, performance status.

Table III. Toxicity by Grade

	Toxicity grade[a)]			
	1	2	3	4
Leukopenia	4	10	11	
Granulocytopenia	2	3	8	11
Anemia (Hb)	7	8	1	
Thrombocytopenia	1			
Elevation of transaminase	9	5	1	
Elevation of T-bilirubin		7	1	
Hypotension	2		2	1
Myalgia	6	7	2	
Arthralgia	4	5		
Bone pain	1	3		
Peripheral neuropathy	10	6	1	
Nausea	4	3	1	
Vomiting	4	2		
Fever	4	3		
Alopecia	19	2		
Stomatitis	2	1		
Eruption	1	1		
Dysgeusia		1		
Diarrhea	4			
Flushing	3			
Headache	1			
Arrhythmia	3			
ST-T changes on ECG	4			

Values represent numbers of patients. n=27.
a) ECOG common toxicity criteria.

Table II. Dose-limiting Toxicities by Step

Step	Dose (mg/m^2)	No. of patients	Hypotension Grade[a)]				Peripheral neuropathy Grade[a)]			Granulocytopenia Grade[a)]		
			1	2	3	4	1	2	3	3	4	(duration)
1	105	3	—	—	—	—	1	2	—	2	—	
2	135	3	—	—	—	—	1	—	—	1	—	
3	180	3	—	—	—	—	—	1	—	1	3	(4, 4 days)
4	210	3	—	—	—	—	2	—	—	—	1	(5)
5	240	6	—	—	—	1	3	—	—	2	2	(1, 4)
6	270	6	2	—	1	—	2	2	1	1	4	(2, 3, 5, 5)
7	240	1	—	—	1	—	—	1	—	—	1	(2)
8	210	2	—	—	—	—	1	—	—	1	1	(4)

a) ECOG common toxicity criteria.

infusion, but could respond to questions correctly. Three to five min after finishing the paclitaxel infusion, their blood pressures rapidly dropped and ECGs showed sinus arrhythmias with rates varying from 50 to 100/min. These patients responded well to dopamine and recovered within 2 to 8 h. Therefore, we concluded that this toxicity was both dose-dependent and dose-limiting. Two additional patients were treated with paclitaxel at 210 mg/m^2 and hypotension was not observed.

Hematologic toxicity Grade 4 leukopenia was not observed, although grade 3 leukopenia was evident at the starting dose level (105 mg/m^2). Grade 4 granulocytopenia was observed at dose levels above 180 mg/m^2. The granulocytopenia was significantly less severe than that experienced previously with a 24-h infusion.[12] The nadir occurred between day 7 and day 17. The median duration of grade 4 granulocytopenia was 4 days, and did not exceed 7 days. Three patients, two with grade 3 or 4 hypotension (#26 and #17) and one with grade 2 fever (#24) receiving 270 mg/m^2 paclitaxel, were given granulocyte colony-stimulating factor (G-CSF) subcutaneously. Anemia and thrombocytopenia were mild. There was grade 1, 2, and 3 anemia in seven, eight and one patient, respectively. Only one patient had grade 1 thrombocytopenia, and none of the patients had grade 2 or greater. Some patients experienced mild decrease in RBC count, hematocrit or reticulocyte count.

Neuromuscular toxicity Arthralgia or myalgia was observed in 20 of the 27 patients (74%). These toxicities were not cumulative, usually occurred at day 2 of paclitaxel administration, and were resolved within 5 days. Non-narcotic analgesics were effective for this pain. Two patients receiving 240 mg/m^2 and 270 mg/m^2, respectively, had grade 3 myalgia requiring narcotics. Grade 2 or 3 peripheral neuropathy was observed in six and one patient, respectively, during their first course of treatment. This toxicity was typically described as numbness and tingling with a stocking-glove distribution. Grade 3 toxicity occurred in one patient receiving 270 mg/m^2 paclitaxel. One patient experienced grade 2 peripheral neuropathy at 270 mg/m^2 paclitaxel and refused the second course of treatment because of this toxicity. Peripheral neuropathy was expected to be the dose-limiting toxicity in these patients.

Hepatic toxicity Elevation of transaminase and total bilirubin was observed in 15 and 8 patients, respectively. These toxicities occurred 1 to 6 days after the administration of paclitaxel, were resolved within several days, and were mild and transient with one exception. One patient treated with 240 mg/m^2 paclitaxel had grade 3 elevation of SGPT lasting for more than 1 week, which was considered to be dose-limiting. Other miscellaneous toxicities included mild elevation of LDH and decrease of albumin.

Cardiac toxicity There was no clinically significant cardiac toxicity. Solitary premature supraventricular or ventricular beats during or after the paclitaxel infusion were observed in three patients, and transient, mild, non-specific ST-T changes on ECG were observed in four patients. Two patients who experienced grade 3 hypotension had sinus arrhythmia. No bradycardia or conduction disturbance was recorded.

Other toxicity Severe hypersensitivity reactions such as bronchospasm were not observed. Mild flushing and eruption were seen in 3 and 2 patients, respectively. There was no clinically significant problem with nausea and vomiting. Prophylactic use of antiemetics was not necessary. Alopecia was common. Seven patients had neutropenic fever which was resolved in a few days. Other toxicities included mouth feeling dry, skin pain and flash vision. Mild elevation of BUN was seen in 5 patients.

Responses Twenty-six patients were evaluable. One patient with heavily pretreated refractory ovarian cancer receiving 240 mg/m^2 paclitaxel achieved a partial response, and went on to receive a total of six courses of paclitaxel. Sixteen patients had stable disease and 9 had progressive disease.

Pharmacology Plasma concentration-versus-time curves for 6 doses of paclitaxel are shown in Fig. 1. The plasma concentration of paclitaxel increased during the 3-h infusion, and began to decline immediately upon cessation of the infusion in a bi-exponential fashion. The mean pharmacokinetic parameters for paclitaxel given as a 3-h infusion are summarized in Table IV. Plasma half-lives ranged from 9.9 to 16.0 h. The peak plasma concentration (Cmax) and area under the curve (AUC) at the

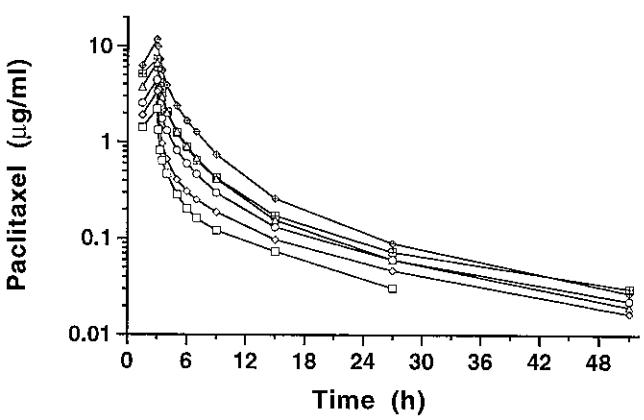

Fig. 1. Concentration versus time curves for six doses of paclitaxel given as 3-h infusions. Paclitaxel was administered as a 3-h intravenous infusion at a dose of 105 (□), 135 (◇), 180 (○), 210 (△), 240 (⊞), or 270 (◈) mg/m^2. Curves, means of 3 to 7 patients.

Table IV. Mean Pharmacokinetic Parameters of Paclitaxel Administered as a 3-Hour Infusion

Level	Dose (mg/m^2)	No. of patients	Cmax ($\mu g/ml$)	$T_{1/2}$ (h)	Vdss ($liter/m^2$)	CL ($ml/min \cdot m^2$)	AUC ($\mu g \cdot h/ml$)	MRT (h)
1	105	3	2.222	9.9	74.7	223	7.88	7.24
2	135	3	3.368	16.0	113.1	214	11.22	10.24
3	180	3	4.468	13.7	81.7	190	16.46	9.06
4	210	5	6.744	13.3	58.9	179	23.18	7.05
5	240	7	7.700	14.6	55.6	151	26.63	7.57
6	270	6	11.881	11.6	33.6	112	40.71	6.47

Renal excretion $<15\%/75$ h. Cmax, maximum plasma concentration; $T_{1/2}$, half-life; Vdss, volume of distribution at the steady state; CL, total clearance; AUC, area under the plasma concentration $\times$ time curve; MRT, mean residence time.

same doses were significantly higher compared with those in the previous study using a 24-h infusion.[12] A proportionally greater increase in Cmax and AUC was observed with increasing dose. The total clearance (CL) and volume of distribution at the steady state (Vdss) decreased with increasing dose. These observations suggest non-linear pharmacokinetics of paclitaxel when given by 3-h infusion, and this is compatible with other reports.[18, 19] The urinary excretion of paclitaxel over 75 h was less than 15% of the dose administered. Pharmacodynamic analyses will be reported separately.

DISCUSSION

In this study, we concluded that paclitaxel could be administered safely by a 3-h infusion without increasing the incidence of hypersensitivity reactions compared with a 24-h infusion. The recommended dose for phase II study is 210 mg/m^2. These results are compatible with those of Schiller *et al.*[20] In their study, the MTD and DLT were 250 mg/m^2 and neutropenia, respectively, when administered alone, and 300 mg/m^2 and peripheral neuropathy, respectively, when administered with G-CSF. The recommended dose for phase II study was 210 mg/m^2 without G-CSF and 250 mg/m^2 with G-CSF.

The dose-limiting toxicities in this study, in which paclitaxel was administered without G-CSF, were not only myelosuppression but also peripheral neuropathy and unexpected hypotension just after finishing the paclitaxel infusion. As shown in Table II, there was grade 3 liver toxicity in one patient and grade 4 hypotension in one out of 6 patients at level 5 (240 mg/m^2). Additional grade 3 hypotension was observed in one patient treated with 240 mg/m^2 paclitaxel. At level 6 (270 mg/m^2), there was grade 3 hypotension in one patient, grade 1 hypotension in two and dose-limiting peripheral neuropathy in two patients. Therefore, we considered that hypotension just after infusion was a dose-dependent and dose-limiting toxicity.

This type of hypotension has not been reported previously. The hypotension in this study was different from that reported as a symptom of HSRs by other groups for several reasons. First, all hypotensive episodes in our study occurred immediately after finishing the paclitaxel infusion, whereas 78% and 94% of HSRs occurred within 10 and 90 min of the start of paclitaxel infusion, respectively.[6] Second, other reported symptoms of HSRs such as bronchospasm, stridor, urticaria and flushing were not seen in the present study. Hypotension in the previous studies was thought to be caused by histamine release induced by the Cremophor EL vehicle.[7] It is unusual that the hypotensive episodes in this study were not accompanied by any other hypersensitivity features. The cause of the hypotension observed in this study may be a lowered systemic vascular resistance, because hypotension occurred suddenly, responded well to dopamine, and cardiac function was normal during the hypotensive episode. Peripheral edema was not observed. The mechanisms of systemic vasodilation induced by paclitaxel itself or its vehicle Cremophor EL are unknown. One possibility may be a release of some cytokine such as tumor necrosis factor, or interleukin-1. However, we have no evidence to support this speculation.

Granulocytopenia was significantly less severe than with a 24-h infusion. In our previous study using a 24-h infusion, grade 4 granulocytopenia was observed from the starting dose level (49.5 mg/m^2) and all of the patients had grade 4 granulocytopenia at dose levels of 135 mg/m^2 and 180 mg/m^2.[12] In this study, seven out of 13 patients (54%) receiving 240 or 270 mg/m^2 paclitaxel had grade 4 granulocytopenia. Although grade 4 granulocytopenia lasted for less than 7 days, we considered that it was one of the dose-limiting toxicities.

Peripheral neuropathy was observed with higher incidence than with the 24-h infusion. In the previous study, only one of 18 patients had grade 1 peripheral neuropathy.[12] However, 17 of 27 patients (63%) had peripheral neuropathy, which was dose-limiting for two of them.

Furthermore, peripheral neuropathy appeared to be cumulative. If a 3-h schedule is to be used as standard method for paclitaxel infusion, peripheral neuropathy would be a major dose-limiting factor, especially in patients with chemosensitive tumors such as ovarian, breast and small-cell lung cancer. Arthralgia or myalgia was observed in 74% of the patients. These toxicities were of short duration, were not cumulative, and responded well to analgesics. Arthralgia or myalgia was never dose-limiting despite the surprisingly high incidence.

This study as well as our previous study showed a higher incidence of liver toxicity, including elevation of transaminase and elevation of total bilirubin compared with the studies in the United States.[21] Liver toxicity in our studies occurred 1 to 6 days after paclitaxel administration and was resolved within a few days. This discrepancy in the incidence of liver toxicity between this study and studies in the United States may be due to the frequency of blood sampling rather than differences in sensitivity between western and Japanese patients.

The Cmax and AUC were significantly higher at the same doses compared with a 24-h infusion. Proportionally greater increases in Cmax and AUC and decreases in CL and Vdss with increasing dose suggest non-linear pharmacokinetics of paclitaxel given by 3-h infusion, as has already been reported by Sonnichsen *et al.*[18] and Gianni *et al.*[19] Low urinary excretion (less than 15% of the administered dose over 75 h) indicates that non-renal excretion is the main route for elimination. Pharmacokinetic parameters obtained in this study are compatible with those in the study of Schiller *et al.*[20] This indicates that there are no differences in pharmacokinetics of paclitaxel between patients in the United States and those in Japan.

In this study, the MTD of paclitaxel given as a 3-h infusion was estimated to be 240 mg/m^2 with DLTs of granulocytopenia, peripheral neuropathy and hypotension just after finishing the infusion. The recommended dose for phase II study is 210 mg/m^2. Although an unexpected toxicity of hypotension was observed, paclitaxel could be administered safely under premedication with proper monitoring, with reduced myelotoxicity and no increase in the incidence of HSRs compared with a 24-h infusion. A 3-h infusion would be preferable if it could be demonstrated to have the same efficacy as a 24-h infusion.

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