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Phase I and Pharmacokinetic Study of Paclitaxel by 24-Hour Intravenous Infusion

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Paclitaxel, a new antitubular agent, appears to be one of the most promising single agents for the chemotherapy of various solid tumors. The primary objectives of this phase I study of paclitaxel using 24-h continuous intravenous infusions were to determine the maximum tolerated dose of paclitaxel administered by this schedule to Japanese patients with solid tumors and to evaluate the pharmacokinetics of paclitaxel. Eighteen patients received one of five doses of paclitaxel, 49.5, 75, 105, 135 or 180 mg/m^2. Premedication with diphenhydramine, dexamethasone, and ranitidine was used to prevent acute hypersensitivity reactions. Pharmacokinetic data were obtained from all 18 patients. Dose-limiting toxicities observed at 180 mg/m^2 consisted of grade 4 granulocytopenia associated with grade 3 infection. No severe HSRs or cardiac toxicity were detected. Reversible toxicities observed included liver dysfunction, alopecia, peripheral neuropathy and myalgias. Pharmacokinetic studies performed using high-performance liquid chromatography demonstrated that plasma concentrations of paclitaxel increased during the 24-h infusion and declined immediately upon cessation of the infusion with a half life of 13.1–24.6 h (75–180 mg/m^2). Less than 10% of paclitaxel was excreted in the urine within 72 h. The peak plasma concentrations and the areas under the concentration-versus-time curves increased linearly with the dose administered. Antitumor activity was observed in one patient with pulmonary metastasis from pharyngeal cancer. Based on these studies a phase II trial dose of 135 mg/m^2 administered over 24 h was chosen.

Key words: Paclitaxel — Phase I study — Pharmacokinetics

Paclitaxel is a new antimitotic agent derived from the bark of the Pacific yew tree. It has a unique mechanism of action that has been investigated in clinical trials in Western countries.[1)] Although earlier trials in the United States demonstrated activity against certain solid tumors, the use of paclitaxel was limited because of restricted availability of the drug and its low solubility in water. In addition, severe acute hypersensitivity reactions (HSRs), such as bronchospasm, hypotension, stridor and arrhythmias, were reported.[2,3)] In order to prevent HSRs, in 1985 the National Cancer Institute (United States) recommended paclitaxel administration as a 24-h infusion with antiallergic premedication consisting of steroids, and H1- and H2-histamine blockers. Using this administration schedule, the incidence of HSRs decreased to approximately 3%. The antitumor activity of paclitaxel has been demonstrated against a variety of solid tumors, such as ovarian cancer, breast cancer, and non-small cell lung cancer. The pharmacokinetic characteristics of paclitaxel administered as a 24-h infusion, however, have not been well described, especially at dose levels below 200 mg/m^2. The primary objectives of this phase I study using 24-h continuous infusions were to determine the maximum tolerated dose (MTD) of paclitaxel administered using this schedule to Japanese patients with solid tumors and to evaluate the pharmacokinetics of paclitaxel at low dose levels.

PATIENTS AND METHODS

Patient selection All patients had histologically or cytologically proven solid tumors refractory to conventional therapy or with no effective therapy. Eligibility criteria included: (1) age 15–74; (2) Eastern Cooperative Oncology Group (ECOG) performance status[4)] 0–2; (3) recovery from the toxic effects of the 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, creatinine clearance $\geq$60 ml/min, urea nitrogen $\leq$25 mg/dl), and hepatic function (total bilirubin $\leq$1.5 mg/dl, transaminase and alkaline phosphatase $\leq 2\times$upper normal limits); (5) stable sinus rhythm with no clinical heart disease; and (6) absence of moderate or severe peripheral neuropathy. The study was approved by the National Cancer Center Institutional Review Boards, and written informed consent was obtained from all patients in accordance with government guidelines (Good Clinical Practice (GCP) by the Ministry of Health and Welfare of Japan) and institutional guidelines. Central registration by fax to the

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Department of Health Science, Faculty of Medicine, University of Tokyo was employed.

Drug administration and dose escalation Paclitaxel was supplied by Bristol-Myers Squibb K.K. as a solution containing 30 mg of the drug in 5 ml of 50% polyoxyethylated castor oil (Cremophor EL) and 50% dehydrated alcohol. Paclitaxel was administered as a 24-h intravenous infusion. Half of the total dose was diluted in 500 ml of 5% dextrose and infused over 12 h for 2 treatments. Only glass bottles and polyethylene-lined nitroglycerin tubing were used. In-line filtration with a 0.22 μm filter was also performed for all infusions. To prevent the HSRs reported in the previous studies, the following premedications were used: (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 performed during the infusion of paclitaxel. The starting dose of 49.5 mg/m^2 represented 3.3 $\times$ n (1/3 TDL in dogs), and dose escalation to 75 (5n), 105 (7n), 135 (9n), and 180 (12n) mg/m^2 was performed in accordance with a modified Fibonacci scale.[5] At least three patients were treated at each dose level. Three additional patients were entered at the same dose level if dose-limiting toxicity (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 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 examination Physical examinations and routine laboratory studies were performed weekly. Complete blood counts (CBCs) were also performed on day 8 and every two or three days for two weeks. Routine laboratory studies included CBC, differential WBC count, total protein, albumin, total cholesterol, electrolytes, blood urea nitrogen, creatinine, total bilirubin, SGOT, SGPT, LDH, alkaline phosphatase and urinalysis. An ECG was performed before and 24 h after therapy. Toxicities were evaluated according to ECOG common toxicity criteria.

Pharmacokinetic studies Serum and urine samples for 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, 3, 6, 12, 18, and 24 h during the infusion, as well as at 5, 15, 30 min and 1, 2, 3, 4, 6, 12, 18, 24, 36 h after the infusion. Urine samples were collected in 24-h increments for 3 days from the start of therapy. Plasma and urinary paclitaxel concentrations were determined by high-performance liquid chromatography (HPLC) according to the modified Grem method developed at Bristol-Myers Squibb K.K.[6] Pharmacokinetic parameters of paclitaxel were determined by the noncompartmental method (moment method).

RESULTS

Twenty patients were entered into this study between October 1991 and August 1992. Two patients were considered ineligible to participate in the study and were excluded before paclitaxel treatment. One patient had undergone radiotherapy just before entry into this study, and the WBC count was less than 4,000/mm^3 in the other patient. Fifteen patients were treated in a dose escalation phase to determine the MTD. Three other patients were treated at the MTD level (180 mg/m^2) with granulocyte colony stimulating factor (G-CSF) after the determination of the MTD (see "Discussion"). The characteristics of the 15 patients in the dose escalation phase are shown in Table I. All patients had good performance status, and their median age was 59 years. Nine of the patients had non-small cell lung cancer, and the others had miscellaneous solid malignancies. Nine patients had previously undergone chemotherapy. The patients received a total of 23 courses of therapy with doses ranging from 49.5 to 180 mg/m^2. Toxicities in the first course were evaluated in these 15 patients.

Toxicity The toxicities are shown in Tables II and III. Granulocytopenia was the principal toxicity of paclitaxel. The nadir was usually observed between day 10 and 12, and it resolved by day 15 to 23. Grade 4 granulocyto-

Table I. Patient Characteristics

Number of patients	15
Males/females	9/6
Median age (range)	59 years (37–70)
Performance status 0/1/2	6/9/0
Prior therapy	
Chemotherapy (C)	1
C+Radiotherapy (R)	3
C+Surgery (S)	3
C+R+S	2
R+S	2
S	2
None	2
Tumor type	
Lung (non-small)	9
Colorectal	3
Head and neck	2
Uterine (cervix)	1

Unless otherwise specified, values represent numbers of patients.

Table II. Toxicity by Dose Level

Level	Dose (mg/m^2)	No. of patients	Myelotoxicities				Other toxicities (≥grade 2)	
			Leukopenia[a]		Granulocytopenia[b]			
			Grade 3	Grade 4	Grade 3	Grade 4	No. of patients	
1	49.5	3	1	0	1	1	GPT 2°	1
							Total bilirubin 2°	2
2	75	3	0	0	1	1	Anemia 2°	3
3	105	3	1	0	1	2		
4	135	3	3	0	0	3	Anemia 2°	1
							Fever 2°	1
							Total bilirubin 2°	2
5	180	3	3	0	0	3	GPT 2°	1
							Fever 2°	3
							Infection 3°	2
							Alopecia 2°	1

a) Median time to nadir: day 11 (8–17).
b) Median time to nadir: day 12 (10–17).

Table III. Toxicity by Grade

	Grade (N=15)			
	1	2	3	4
Leukopenia	1	6	8	
Granulocytopenia		2	3	10
Anemia	4	4		
Thrombocytopenia				
Elevation of transaminase	4	2		
Elevation of total bilirubin		4		
Flushing	3			
Eruption	2			
Alopecia	4	1		
Emesis	1			
Stomatitis	1			
Hiccup	1			
Myalgias	2			
Arthralgias	1			
Bone pain	1			
Weakness	1			
Peripheral neuropathy	1			
Dysgeusia	1			
Arrhythmia	3			
Fever	2	4		
Infection			2	

Unless otherwise specified, values represent numbers of patients.

penia was observed beginning at the starting dose (49.5 mg/m^2). All patients in level 4 (135 mg/m^2) and level 5 (180 mg/m^2) experienced grade 3 leukopenia and grade 4 granulocytopenia. No grade 4 leukopenia was observed at any dose level. The duration of grade 4 granulocytopenia was less than seven days, except in one patient. Anemia was mild, and no thrombocytopenia was observed. Some patients experienced mild decrease in RBC count, hematocrit or reticulocyte count. No patients experienced severe HSRs. Transient flushing and skin eruption were observed in three and two patients, respectively. Mild liver toxicities, including transaminase elevation and total bilirubin elevation were observed in six and four patients, respectively. These toxicities usually appeared between day 2 to 9, and resolved within 2 to 9 days. Other miscellaneous toxicities included mild elevation of LDH and decrease of total protein or albumin. In the second course, grade 1 elevation of alkaline phosphatase was observed in one patient. Two patients experienced transient myalgia, arthralgia, or bone pain. Mild peripheral neuropathy in one patient and transient muscle weakness in another patient were also observed. Transient and mild cardiac toxicities during infusion included asymptomatic bradycardia in one patient (lowest heart rate 48 per minute), solitary ventricular premature beats in one patient and supraventricular premature beats in one patient. Neutropenic fever above 38°C was observed in two of three patients at 135 mg/m^2 and in all three patients at 180 mg/m^2. At a level of 180 mg/m^2, grade 3 infection was observed in two out of the three patients. One developed bilateral pneumonia with transient respiratory failure, and the other experienced a mild hypotensive state as a result of bacterial tonsillitis. These toxicities were considered dose-limiting, and the MTD was determined to be 180 mg/m^2. There were no treatment-related deaths.

Pharmacokinetics The pharmacokinetic parameters in all 18 patients are summarized in Table IV. Fig. 1 shows plasma concentration-versus-time curves for five doses of paclitaxel. The plasma concentration of paclitaxel gradually increased during the 24-h infusion and began to

Table IV. Mean Pharmacokinetic Parameters of Paclitaxel Administered as a 24-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	49.5	3	0.087	2.8	117	554	1.51	15.6
2	75	3	0.187	19.1	267	247	5.12	30.4
3	105	3	0.179	24.6	394	386	5.05	30.8
4	135	3	0.409	17.1	165	246	9.52	23.0
5	180	6	0.575	13.1	151	270	11.31	21.2

Renal excretion $<10\%/72$ h. Cmax, maximum plasma concentration; $T_{1/2}$, half-life; Vdss, volume of distribution at steady state; CL, total clearance; AUC, area under the plasma concentration $\times$ time curve; MRT, mean residence time.

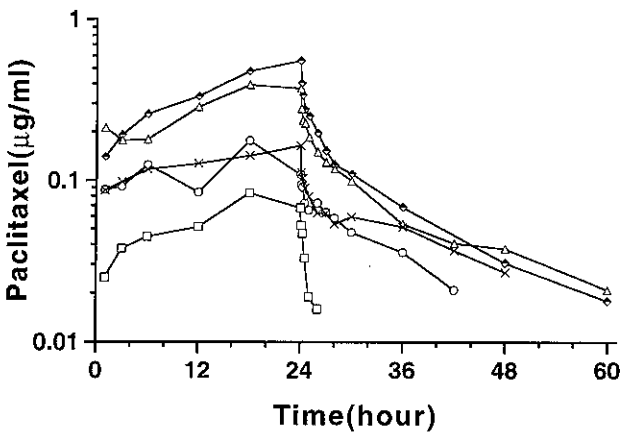

Fig. 1. Concentration versus time curves for five doses of paclitaxel given as 24-h infusions. Paclitaxel was administered as a 24-h continuous infusion at doses of 49.5 (□), 75 (×), 105 (○), 135 (△), and 180 (◆) mg/m^2. Curves, means of 3 or 6 patients.

decline immediately upon cessation of the infusion. Plasma half-lives ranged from 2.8 to 24.6 h. Both the peak plasma concentrations (Cmax) and area under the curve (AUC) of paclitaxel were linearly correlated with the paclitaxel dose (Pearson correlation coefficient, $r=0.892$ & $P<0.01$ for Cmax, $r=0.916$ & $P<0.01$ for AUC). There was a significant correlation between the Cmax values and AUC ($r=0.922$, $P<0.01$). Urinary excretion of paclitaxel over 72 h was less than 10% of the dose administered. The percentage decrease in granulocyte count was significantly correlated with the AUC of paclitaxel ($r=0.707$, $P<0.01$).

Response No complete or partial responses were observed in this study. About 30% regression of a metastatic pulmonary tumor was observed in one patient with pharyngeal cancer treated with three courses of paclitaxel at 135 mg/m^2. This minor response continued for 4 months.

DISCUSSION

Paclitaxel is a new plant-derived anticancer agent which expresses a unique antimitotic action by binding to microtubules.[7,8] The mechanism of the antitumor effect of paclitaxel lies in promotion of the polymerization of tubulin. In phase I and phase II studies in the United States, antitumor activity has been observed in ovarian cancer, non-small cell lung cancer, breast cancer, and other solid tumors.[9] Considerable activity has been documented in cisplatin-refractory ovarian cancer, suggesting lack of cross resistance to cisplatin.[10,11] The MTD was determined to be 180 mg/m^2 in this study. Granulocytopenia associated with infection was the major DLT of paclitaxel. Severe HSRs reported in previous studies in the United States were not observed (with the use of premedications). Peripheral neuropathy and cardiac toxicities were mild and infrequent. The plasma paclitaxel levels gradually increased during 24-h infusion and declined immediately after cessation of the infusion. Plasma half lives ranged from 2.8 to 24.6 h. Both the Cmax and AUC of paclitaxel linearly correlated with the paclitaxel dose administered, suggesting linear pharmacokinetics of paclitaxel in the dose range of 49.5 to 180 mg/m^2. Three phase I studies of paclitaxel using 24-h infusions have been carried out in the United States. The MTDs in these studies were 200, 275, and 390 mg/m^2, and the DLTs were granulocytopenia, peripheral neuropathy, and mucositis, respectively.[12-14] The MTDs in these studies were quite different from the MTD of 180 mg/m^2 in our study. There may be a large discrepancy between the definition of MTD in these studies and our own. The two studies from the United States were conducted in patients with melanoma and acute leukemia. Myelotoxicity was not included in the DLT criteria. However, the great difference in MTDs compared with the studies conducted in the United States, suggests that there are reasons other than difference in DLT criteria, such as limited sample size and inter-patient variability. We recommend a paclitaxel dose of 135 mg/m^2 for phase II

study. Two phase II studies in non-small cell lung cancer recently reported in the United States employed paclitaxel at doses of 250 and 200 mg/m^2,[15,16] and response rates of 20.8% and 24.0%, respectively, were obtained. Whether paclitaxel would provide a response rate of more than 20% at a dose of 135 mg/m^2 is unknown. One possible method of increasing the dose intensity of paclitaxel may be the use of G-CSF. After determining the MTD, we treated three patients with 180 mg/m^2 of paclitaxel without severe myelotoxicities or infection using G-CSF. G-CSF was administered at a dose of 50 μg/m^2 daily by subcutaneous injection when the WBC or granulocyte count fell below 2,000/mm^3 and 1,000/mm^3, respectively. Sarosy *et al.* reported a phase I study of paclitaxel and G-CSF in patients with refractory ovarian cancer.[17] Another method of increasing paclitaxel dose intensity is to change the administration schedule. Recently 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 was no different with infusion schedules using premedication, and that myelotoxicity was less severe with the 3-h infusion.[18] A 3-h infusion might also be more suitable for patients receiving paclitaxel for palliative therapy, because outpatient administration would be possible. A phase II study of paclitaxel by 24-h infusion has been initiated in non-small cell lung cancer by our study group. We are also planning a phase I study of paclitaxel by 3-h infusion in an attempt to find a better administration method.

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