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CLINICAL TRIAL REPORT

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A feasibility study of 1-h paclitaxel infusion in patients with solid tumors

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Abstract The optimal schedule for paclitaxel administration has not yet been determined. This phase I/II study was carried out to evaluate the safety of paclitaxel administration by 1-h infusion in the outpatient setting. A total of 43 patients with advanced pretreated malignancies (18 breast, 18 ovarian, and 7 non-small-cell lung cancers) received at least 2 cycles of paclitaxel given at 175 mg/m^2 in a single dose by 1-h i.v. infusion. This protocol was repeated every 21 days. All patients were premedicated as follows: promethazine given i.m. at 50 mg, dexamethasone given at 16 mg in 250 ml normal saline by i.v. infusion for 20 min and ranitidine given i.v. at 50 mg in 250 ml normal saline over 15 min, all premedication being carried out 1 h before the paclitaxel infusion. In a total of 156 cycles, only 1 patient presented with a hypersensitivity reaction (grade 2 urticaria in 1 cycle) and another patient developed transient facial flushing (in 1 cycle; this was resolved by slowing of the infusion rate) on this schedule of paclitaxel administration. Other adverse side effects were usually mild and well tolerated. Alopecia was universal; myelosuppression was uncommon because our patients were supported with granulocyte colony-stimulating factor (G-CSF, lenograstim) given at 34 IU/day in the presence of a neutrophil count of <500 μl; neutropenia was seen in 50/156 (32%) cycles and was mild. Neurotoxicity was the most serious adverse effect, and all patients experienced mild to severe neuromuscular toxicity, mainly in the form of peripheral sensorimotor neuropathy and myalgias. In conclusion, 1-h paclitaxel administration is safe and reduces the duration of treatment, making its use more convenient and easy in the outpatient setting. A prospective comparison of 1-h versus 3-h paclitaxel infusion in terms of efficacy and toxicity is the subject of our current randomized study.

Key words: Paclitaxel · Infusion · Premedication · Neurotoxicity · Advanced cancer · Outpatient setting

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Introduction

Paclitaxel is the first clinically available taxane, a group of compounds that cause cytotoxicity by stabilizing the microtubules, thereby inhibiting the dynamic reorganization of this network, which is necessary for cell division [1, 2]. Its development has been accompanied by a great deal of anticipation and enthusiasm due to its novel mechanism of action and its wide range of antineoplastic activity.

Paclitaxel has demonstrated substantial activity in resistant ovarian, breast, and lung cancers [3–7]. Severe hypersensitivity reactions caused by paclitaxel were observed early in its clinical development and led to the discontinuation of early trials; such reactions included acute dyspnea, urticaria, and hypotension at a dose of 190 mg/m^2 [8–10] given in a 1-h infusion. Anaphylaxis was thought to be due either to paclitaxel itself or to the Cremophor vehicle in which the former is formulated; the rate of administration was also thought to be an important factor in the development of hypersensitivity reactions [8].

On the basis of these data, two modifications were made in clinical trials. First, premedication with corticosteroids, cimetidine, and diphenhydramine was initiated before treatment with paclitaxel. Second, the duration of the paclitaxel infusion was lengthened to a 24-h period. With these modifications, severe hypersensitivity reactions were largely abolished and occurred in only 1–2% of patients in recently reported studies [8, 11, 12].

Nevertheless, 24-h continuous infusion of paclitaxel was approved by the Food and Drug Administration for routine use. Recently, a 3-h continuous infusion has also proved to be safe, and a recent randomized trial has demonstrated significantly reduced myelosuppression for the shorter infusion schedule with no compromise in the response rate [8, 11, 12]. More recently, some studies attempted the administration of paclitaxel by 1-h infusion in an outpatient setting so as to avoid the need for hospitalization [13–20]. In a phase II trial we attempted to give paclitaxel by 1-h infusion with a simpler premedication protocol.

Table 1 Patients' characteristics

	Number	Percent
Number of patients	43	
Median age (years)	61	
Sex (M/F)	7/36	
ECOG performance status:		
0	5	12
1	30	70
2	8	18
Cancer type:		
Breast	18	
Ovarian	18	
Lung[a]	7	
Number of previous chemotherapy regimens:		
0	0	
1	31[b]	
2	8[c]	
>2	0	

[a] Non-small-cell lung cancer (NSCLC)
[b] 14 cases of breast cancer previously tested with FEC (5-fluorouracil + epirubicin + cyclophosphamide), 10 cases of ovarian cancer with formerly treated carboplatin and ifosfamide, and 7 cases of NSCLC that had relapsed after cisplatin chemotherapy
[c] 4 cases of breast cancer that had undergone CMF (cyclophosphamide + methotrexate + 5-fluorouracil) therapy and, after relapsing, had undergone treatment with high-dose epirubicin and 8 cases of ovarian carcinoma that had been treated with carboplatin and, after relapsing, had been treated with melphalan

Patients and methods

Patients who had advanced cancer and were either resistant or refractory to standard therapy were eligible for the current study; these patients had relapsed following first- or second-line treatment, showing definite measurable evidence of progressive disease at 2 months after the last chemotherapy cycle (see Tables 1, 2). All patients had measurable or evaluable metastatic lesions. Eligibility requirements included the following: (1) histologically proven carcinoma, (2) a Karnofsky score greater than 70, (3) good general health with no history of cardiac disorder or congestive heart failure, and (4) an expected survival of at least 3 months. Patients were ineligible if they had experienced a previous allergic reaction to any drug mixed with the Cremophor solubilizer (e.g. radiocontrast material, vitamin K). The study protocol was submitted to the ethical review board of our hospital. All patients gave written informed consent before study entry.

Before receiving treatment, all patients underwent the following laboratory studies: a full blood count, determination of electrolytes, a serum chemistry profile, determination of prothrombin time, a chest X-ray, and an ECG. Other criteria included unimpaired organ function (creatinine value of <1.5 mg/dl, normal liver-function tests) and no clinical or laboratory (ECHOCG, ECG, nuclear injection fraction, chest X-ray) evidence of congestive heart failure. Additional radiology studies were performed as necessary for the evaluation of tumor extent and to obtain tumor measurements.

All patients received paclitaxel given at 175 mg/m^2 as a single dose by i.v. infusion for 1 h. Cycles were repeated every 21 days. The paclitaxel dose was mixed in 200 ml normal saline and given as a rapid i.v. infusion. Before receiving paclitaxel, all patients were premedicated with 50 mg promethazine given i.m. followed immediately by 16 mg dexamethasone given i.v. in 250 ml normal saline over 20 min, followed by 250 ml normal saline containing 50 mg ranitidine given by 20-min i.v. infusion; the premedication protocol was followed by the administration of paclitaxel.

All patients were treated on an outpatient basis unless they had been hospitalized for other reasons before paclitaxel therapy was initiated. During the entire period of paclitaxel infusion, patients were monitored continuously by a doctor. Vital signs were recorded every 15 min. In any patient complaining of chest pain or other respiratory symptoms the paclitaxel infusion was immediately interrupted and an ECG with clinical examination was performed. If any symptom of severe acute hypersensitivity reaction occurred, the paclitaxel infusion had to be discontinued and standard treatment for anaphylaxis was instituted immediately.

Patients had complete blood counts checked weekly and were evaluated for response to treatment after two courses of therapy by complete clinical/laboratory evaluation. Patients who progressed were considered treatment failures and the therapy was stopped. Those with stable disease or objective tumor responses continued the therapy until tumor progression for a maximum of eight courses.

Patients experiencing severe hypersensitivity reactions producing symptoms such as dyspnea, wheezing, severe hypo- or hypertension, or generalized urticaria were removed from the study. Patients showing mild symptoms of hypersensitivity to paclitaxel were allowed to continue the study but were monitored closely during subsequent courses. Chemotherapy was also discontinued in the event of severe prolonged leukopenia (a neutrophil count of $<2{,}000\times10^9$/l) or thrombocytopenia (a platelet count of $<100\times10^9$/l for more than 2 weeks) or any cardiac event or ECG abnormality. We gave patients granulocyte colony-stimulating factor (G-CSF) in the presence of neutrophil counts of $<500\times10^9$/l. Clinical information related to symptoms was recorded and side effects were graded using the World Health Organization criteria [20].

Dose reductions were planned in cases of (1) <500/μl neutrophil nadirs lasting for >7 days, with G-CSF support; (2) thrombocytopenia nadirs of $<50{,}000$/μl; (3) any case of grade III neurotoxicity or disabling grade III toxicity; or (4) delay of the planned chemotherapy course by 1 week due to neutrophil count of $<1{,}500$/μl and/or a platelet count of $<100{,}000$/μl. The dose of paclitaxel in subsequent cycles was reduced by 20% if any of the above problems was encountered.

Although determination of antitumor activity was not the primary objective of this study, all patients were evaluated for response to

Table 2 Patients' prior chemotherapy and response (*CT* chemotherapy)

Type of cancer	Number of patients	Previous CT		Response			Number of cycles
		First	Second	PR	SD	PD	
Breast	14	FEC[b]	–	3	5	6	47
	4	CMF	Epirubicin	0	2	2	13+8
Ovarian	6	CIF[c]	–	2	4	0	25
	8	CIF	Melphalan	3	3	2	28+19
Lung[a]	4	CV[d]	–	0	3	1	12
	3	PV[e]	–	0	3	0	13

[a] Non-small-cell lung cancer
[b] 5-Fluorouracil + epirubicin + cyclophosphamide
[c] Carboplatin + ifosfamide
[d] Carboplatin + vinblastine
[e] Cisplatin + vinblastine

treatment after the completion of two courses of therapy. Before each administration of the drugs, patients had undergone an evaluation for visible lesions by physical examination, chest X-ray, and ultrasound scans. Computerized tomography (CT) scans were repeated every two cycles. A decrease of 50% or more in the sum of the products of the largest perpendicular diameters of measurables lesions was defined as a partial response (PR), with the complete disappearance of all abnormal laboratory values and clinically evaluable disease constituting a complete response (CR). A 25–50% decrease in tumor dimensions was defined as stable disease (SD). Toxicity was estimated according to WHO criteria [20] and was estimated according to the number of therapy courses completed (see Table 3).

The patients' characteristics are outlined in Tables 1 and 2. Between January and December of 1995 a total of 43 patients entered the study. Their median age was 61 years, there were 7 men and 36 women, and the median performance status (ECOG) was 1. In all, 18 patients had breast cancer, 18 had ovarian carcinoma, and 7 had non-small-cell lung cancer.

Results

All 43 patients were evaluable, having received at least 2 cycles of paclitaxel and a total of 156 cycles of therapy.

Toxicity

In Table 3 we present the toxicity parameters except for myelosuppression. No serious hypersensitivity reaction was encountered with paclitaxel except for one case with mild urticaria that developed during the administration of the drug at the second chemotherapy course. Treatment was threafter discontinued because of disease progression (Table 3). Complete alopecia occurred in all patients. Myalgias of grades 1–3 (87%) and fatigue of grades 1–2 (100%) were not intense in the majority of patients and were the main toxicity problems encountered. The remaining toxicity parameters were nausea of grades 1–2 (44%); emesis of grade 1 (20%); mucositis of grade 1 (8%); headache (23%); peripheral neuropathy (42%), which was always mild; diarrhea (1%); and angina (1%). Two patients developed grade 2 diarrhea during the third and fourth cycles, which was well controlled with loperamide given at 2 mg×3/day p.o. During the fourth cycle one patient had an episode of angina, which was controlled with sublingual nitroid; she continued therapy and experienced no other episode, and no modification of the infusion rate was necessary. We did not notice light-headedness. Most patients experienced mild somnolence because of the promethazine premedication.

Myelosuppression was common but mild or moderate in most patients (Table 4). Nadir neutrophil counts of 1,000–1,500/μl occurred during 26 courses (17%), whereas neutrophil counts of $<1{,}000$/μl occurred during 12 courses (8%) and during 4 courses in 2 patients whose nadirs were <500/μl; all the patients with neutrophil counts of <500/μl received G-CSF at 34 IU/day for 3–5 days. No hospitalization was required for febrile neutropenia. Two patients experienced urinary tract infections and two cases of bronchial pneumonia were managed with oral antibiotics.

Table 3 Nonhematologic toxicities encountered according to the number of cycles involved (total 156)

Adverse effect	Grade (WHO scale)	Number of cycles	Percent
Hypersensitivity reactions:			
Urticaria	0	155	99
	2	1	1
Wheezing/dyspnea	0	156	100
Flushing	0	156	100
Pruritus	0	156	100
Alopecia (number of patients)	4	43	100
Myalgias	0	21	13
	1	38	24
	2	63	40
	3	42	27
Fatigue/weakness	0	0	0
	1	25	16
	2	89	57
	3	42	27
Nausea	0	88	56
	1	29	18
	2	26	16
	3	13	8
Emesis	0	125	80
	1	31	20
	2	8	0
Mucositis	0	143	92
	1	11	7
	2	2	1
Diarrhea	0	154	99
	2	2	1
Light-headedness	0	156	100
Headache	0	121	77
	1	35	23
Peripheral neuropathy	0	66	42
	1	78	50
	2	14	8
Angina		1	1

Table 4 Myelosuppression encountered according to the number of cycles involved (total 156)

	Nadir (cells/μl)	Number of cycles	Percent
Neutropenia	1,500–2,000	12	8
	1,000–1,500	26	17
	500–1,000	8	5
	<500	4	3
Thrombocytopenia	50,000–100,000	7	5
	$<50{,}000$	3	2

All patients who developed severe neutropenia and/or infections had received at least two courses of paclitaxel. These patients required dose reductions to 80% of the starting dose. Thrombocytopenia was infrequent (7%), and no patient suffered hemorrhagic problems related to this toxicity.

Table 5 Patients developing myalgias and peripheral neuropathy in relation to the performance status, number of prior chemotherapy cycles, and number of cycles including Taxol (*CT* Chemotherapy)

Group	Number	ECOG PS			Previous CT cycles (mean value)	Taxol cycles (mean value)
		0	1	2		
Patients without neurotoxicity of myalgia	6	4	2	0	18 (3.0)	15 (2.5)
Patients with myalgias	18	1	16	0	67 (3.3)	60 (3.3)
Patients with neurotoxicity and myalgias	19	0	12	7	83 (4.4)	81 (4.3)
P		0.02	0.02	0.02	0.485	0.472

Table 6 Response according to the number of patients and the number of cycles completed (*NSCLC* Non-small-cell lung cancer)

Cancer type	Number of patients	Number of cycles	Response			
			CR	PR	SD	PD
Breast	18	68	0	3	4	11
Ovarian	18	65	1	4	3	10
Lung (NSCLC)	7	23	0	1	2	4
Total	43	156	1	8	9	25

Among all toxicity parameters examined, we noticed an increased percentage of myalgias and neurotoxicity. In an attempt to analyze these toxicities we noted that only six patients did not present with myalgias and/or neurotoxicity, 18 developed only myalgias, and all 19 patients presenting with neurotoxicity developed myalgias (Table 5). As correlated with other factors that can influence myalgias and neurotoxicity, performance status seemed to be the most important ($P = 0.02$); on the other hand, the number of cycles of previous chemotherapy and the number of cycles of paclitaxel seemed to be higher in patients who developed myalgias and/or neurotoxicity, but the differences were not statistically significant. We also noticed that all 37 patients (Table 5) who developed myalgias and/or neurotoxicity experienced symptoms after the second cycle of paclitaxel.

Response

Only one patient with ovarian cancer had a CR. A PR was seen in three patients with breast cancer, four patients with ovarian carcinoma, and one patient with lung cancer. SD was seen in four patients with breast cancer, three patients with ovarian carcinoma, and two patients with lung cancer. In these heavily pretreated patients the response rate was 3/18 (17%) for breast cancer, 5/18 (28%) for ovarian cancer, and 1/7 (14%) for lung cancer (Table 6).

Discussion

The optimal schedule for paclitaxel administration has not yet been determined. Most recent studies have applied the 3-h infusion protocol. However, in a limited number of studies [13–19], attempts have been made to decrease the infusion duration to 1 h. This is important if one takes into account the hospital stay required for each patient receiving paclitaxel and, hence, the convenience of administration of the drug as a part of outpatient regimens. On the other hand, standard premedication consists of initiation of dexamethasone treatment 12 h before paclitaxel administration to avoid severe life-threatening hypersensitivity reactions. In the present study we tried to reduce the duration of paclitaxel infusion to 1 h, and this proved to be very convenient and safe in the outpatient setting.

Our more extensive experience with promethazine as an H_1 blocker formed the basis for its administration rather than that of diphenydramine, which is used in the majority of standard paclitaxel premedication regimens. It is noteworthy that despite the shorter premedication interval with respect to dexamethasone (1 h before initiation of the paclitaxel infusion, allergic reactions were reduced to a minimum (1%). However, this incidence could represent simply the change of the antihistamine.

With regard to long-term toxicities, we noted that high percentages of patients developed myalgias (87%), fatigue (100%), and peripheral neuropathy (58%). We believe that this cannot be ascribed only to paclitaxel and its rapid schedule of administration, since impaired performance status seems to be the most important determinant of paclitaxel-related toxicities, probably followed by the number of cycles of previous and paclitaxel chemotherapy. Response rates were similar to those reported in other trials of paclitaxel in respective types of tumors.

In conclusion, 1-h paclitaxel administration is safe, reduces the duration of treatment administration from the conventional 3-h regimen, thus making its use more convenient and easy in the outpatient setting. A prospective comparison of 1-h versus 3-h paclitaxel infusion in terms of efficacy and toxicity is the subject of our current randomized study.

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