Paclitaxel Administered by 1-Hour Infusion

Preliminary Results of a Phase I/II Trial Comparing Two Schedules

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Background. **Paclitaxel currently is administered by prolonged intravenous infusion because of the occurrence of severe hypersensitivity reactions in patients in early clinical trials. However, intensive premedication probably is more important in eliminating allergic reactions than is the length of infusion. The authors evaluated the feasibility of two paclitaxel schedules using a 1-hour, outpatient infusion.**

Methods. **Fifty-six patients with advanced, refractory malignancies were randomized to receive one of two paclitaxel schedules: 135 mg/m^2 administered as a single dose over 1 hour, or 135 mg/m^2 administered in divided daily doses for 3 days, each over 1 hour. All patients were premedicated with dexamethasone, diphenhydramine, and cimetidine.**

Results. **No serious hypersensitivity reactions occurred with either schedule of paclitaxel. In addition, other adverse effects were usually mild and easily tolerated. Other than alopecia, which occurred in all patients, myelosuppression was the most common severe toxicity. However, grade 3 leukopenia occurred in only 19% of treatment courses, and grade 4 leukopenia (nadir < 1000/μL) occurred in only 2%. Nine patients required hospitalization for treatment of infection associated with neutropenia. No significant differences in toxicity were observed when the two paclitaxel regimens were compared. Although it is too early to assess the results adequately, preliminary findings showed that thus far 11 of 56 patients (20%) had a partial or complete response to therapy. Responses were observed in patients with breast, ovarian, and lung cancer.**

Conclusions. **Paclitaxel can be safely administered in a 1-hour infusion in an outpatient setting, either as a single dose or in divided doses for three days. Severe hypersensitivity reactions did not occur in 162 treatment courses, and neutropenia was mild in most patients. Incorporation of this dose and these schedules of paclitaxel into combination chemotherapy regimens should be feasible. An investigation of higher paclitaxel doses given in a 1-hour infusion is currently in progress. *Cancer* 1994; 74:1377–82.**

Key words: paclitaxel, Phase II trial, 1-hour infusion schedules, hypersensitivity reactions.

The clinical development of paclitaxel has been accompanied by a great deal of anticipation and enthusiasm due to the novel mechanism of action of this drug and its wide range of antineoplastic activity. Paclitaxel is the first clinically available taxane, a group of compounds that cause cytotoxicity by stabilizing the microtubules and thereby inhibiting the dynamic reorganization of this network necessary for cell division.[1] Paclitaxel concentrations as low as 0.05 μmol/l promote microtubule assembly in vitro;[2] serum levels greater than 10 times this high can be achieved in humans with clinically tolerable doses.[3,4] Despite relatively limited clinical trials, paclitaxel has demonstrated substantial activity in resistant ovarian cancer, breast cancer, and lung cancer.[5–8]

Severe hypersensitivity reactions caused by paclitaxel were observed early in its clinical development and led to discontinuation of early trials. Kris et al. reported severe reactions characterized by acute dyspnea, urticaria, and hypotension immediately after the initiation of paclitaxel infusion in 3 of 5 patients receiving total doses greater than 190 mg/m^2.[9] Similar observations were made by Grem et al; two of their first nine patients experienced anaphylaxis.[10] These patients were receiving paclitaxel over 1 hour on a daily schedule for 5 consecutive days, so that daily doses of paclitaxel were low (5–15 mg/m^2/day). In both reports, anaphylaxis usually occurred with the first dose of paclitaxel and began within minutes after the infusion was initiated. Anaphylaxis was thought to be due either to

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the paclitaxel itself or to the cremophor vehicle in which paclitaxel is formulated; the rate of administration was also thought to be an important factor in producing hypersensitivity reactions.

As a result of these observations, two important modifications were made in subsequent clinical trials. First, premedication with corticosteroids, cimetidine, and diphenhydramine was initiated before treatment with paclitaxel. Second, the duration of paclitaxel infusion was lengthened, so that in most subsequent trials, paclitaxel was administered by continuous infusion over a 24-hour period. With these modifications, severe hypersensitivity reactions were largely abolished and have occurred in only 1–2% of patients in recently reported studies.[11,12]

Because two changes in the technique of paclitaxel administration were made simultaneously, it is unclear whether the premedication or the prolonged schedule of administration was responsible for decreasing hypersensitivity reactions. Nevertheless, the 24-hour continuous infusion was approved by the Federal Drug Administration for routine use. More recently, 3-hour continuous infusions have also proven safe, and a recent randomized trial demonstrated significantly reduced myelosuppression with the shorter infusion schedule.[12] Because myelosuppression is less with a 3-hour infusion, it is possible that tumor cytotoxicity is also decreased; however, response rates in relapsed ovarian cancer were not significantly different with 3-hour versus 24-hour infusions.[12] The administration of paclitaxel by 3-hour infusion simplifies its use, because hospitalization can be avoided. However, a 3-hour infusion is still rather cumbersome for routine use in the outpatient setting.

The current preliminary report principally describes the toxicity results of a prospective, randomized study evaluating two different schedules of paclitaxel administered by a 1-hour infusion. We administered paclitaxel either by a 1-hour infusion on a single day or in 1-hour doses on three consecutive days. Giving paclitaxel by 1-hour infusion is easier and more economical than using longer infusions; either schedule can be easily administered in the outpatient setting. Toxicity of these two 1-hour paclitaxel regimens are reported in detail along with preliminary efficacy data.

Patients and Methods

Patients who had advanced cancer and were either resistant or refractory to standard therapy were eligible for the current study. Sensitive tumor types (e.g., breast cancer, ovarian cancer, limited stage small cell lung cancer, non-Hodgkin's lymphoma) were eligible only if they had progressed after standard treatment. Other patients with primarily resistant tumor types (e.g., non-small cell lung cancer) were eligible for this treatment as first-line therapy. Although all types of malignancies were considered for this Phase I/II study, an attempt was made to enter patients with ovarian, breast, or lung cancer, because these tumor types had been previously demonstrated to be sensitive to paclitaxel. All patients had measurable or evaluable metastatic lesions. Eligibility requirements included the following: leukocyte count greater than or equal to 3000/μl; platelet count greater than or equal to 90,000/μl; Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; and expected survival of at least 10 weeks. Patients were ineligible if they had a history of congestive heart failure, second- or third-degree heart block, or an acute myocardial infarction within 4 months before study entry. Patients who had experienced previous allergic reactions to any drugs mixed with cremophor solubilizer (e.g., radiocontrast material, vitamin K) were also ineligible. All patients gave written informed consent before study entry.

Before receiving treatment, all patients had the following laboratory studies: complete blood count, differential platelet count, electrolytes, chemistry profile, prothrombin time, partial thromboplastin time, chest X-ray, and electrocardiogram. Additional radiologic studies were performed as necessary for evaluation of tumor extent and to obtain tumor measurements.

Patients were stratified according to performance status (ECOG 0 and 1 versus ECOG 2) and primary disease site and were then randomized by a random card system to one of two schedules of paclitaxel. All patients received paclitaxel at a dose of 135 mg/m^2; this was either administered as a single dose given over 1 hour or given on 3 consecutive days for over 1 hour each day. Doses were repeated every 21 days. To administer paclitaxel over 1 hour, the dose was mixed in 250 ml normal saline and administered as a rapid intravenous infusion.

Before receiving paclitaxel, all patients were premedicated with 20 mg dexamethasone given orally 12 hours and 4 hours before therapy. In addition, the following drugs were administered intravenously 30 minutes before paclitaxel infusion: dexamethasone, 20 mg; diphenhydramine, 50 mg; and cimetidine, 300 mg. In patients receiving the 3-day schedule, premedications were administered on each day of treatment.

All patients were treated as outpatients unless they were hospitalized for other reasons before paclitaxel therapy was initiated. During the entire infusion of paclitaxel, patients were monitored continuously by a nurse. Vital signs were recorded every 15 minutes. Patients did not have continuous cardiac monitoring; however, any patient complaining of chest pain or other respiratory symptoms immediately had the paclitaxel infusion stopped and an electrocardiogram performed.

If any symptoms of severe acute hypersensitivity reactions occurred, the paclitaxel infusion was to be discontinued and standard treatment for anaphylaxis instituted immediately.

After paclitaxel administration, patients had complete blood counts checked weekly. Patients were evaluated for response to treatment after two courses of therapy. In addition to remeasurement of metastatic lesions, patients had electrolytes, screening chemistries, and electrocardiograms repeated. Patients with progressive disease were considered treatment failures and removed from the study. Those with stable disease or objective tumor response were eligible to continue therapy until tumor progression occurred or for a maximum of 12 courses.

No dose escalation was planned during this study. Patients experiencing severe hypersensitivity reactions with symptoms including dyspnea, wheezing, severe hypotension or hypertension, or generalized urticaria were removed from the study. Immediate treatment for severe hypersensitivity reactions was available and included administration of epinephrine, 0.35–0.5 ml subcutaneously; diphenhydramine, 50 mg intravenously; and normal saline, 250 ml/hour. Epinephrine could be repeated every 15 minutes until symptoms subsided; nebulized albuterol, 0.3 ml, was available if wheezing was a prominent symptom. Patients with mild symptoms of hypersensitivity to paclitaxel were allowed to continue on study but were monitored closely during subsequent courses. At the initiation of the study, it was decided to terminate the study prematurely if 2 of the first 5 patients treated experienced severe (Grade 4) hypersensitivity reactions or if 5 of the first 10 patients experienced severe myelosuppression.

Dose reductions for myelosuppression were based on the day 21 leukocyte count. If the leukocyte count was greater than 3500/μl, a full dose was administered. Criteria for dose reductions were as follows: leukocyte count 2500–3500/μl, 75% dose administered; leukocyte count less than 2500/μl, treatment delayed 1 week and then a 75% dose administered. Dose reductions based on platelet counts were as follows: platelets less than 75,000/μl, treatment withheld 1 week and then a 75% dose administered; platelets 75,000–125,000/μl, 75% dose given; platelets greater than 125,000/μl, full dose given. With the exception of alopecia and myalgias, patients experiencing other Grade 3 or 4 toxicities (as determined using ECOG toxicity criteria), received a 75% dose of paclitaxel on subsequent cycles. This dose was administered on day 21 if the treatment-related toxicity had already resolved and was delayed 1 week if symptoms persisted on day 21.

Although determination of antitumor activity was not the primary objective of this study, all patients were evaluated for treatment response after completion of two courses of therapy. All patients were assigned response categories using standard definitions. Complete response required the complete resolution of all objective evidence of tumor for at least 3 months. Partial response occurred when measurable lesions decreased by 50% or more in the product of perpendicular diameters for at least 1 month and no new lesions appeared. Minimal response occurred when the objective decrease in size was less than 50% but greater than 25% in the products of perpendicular diameters for at least 1 month with no new lesions. Stable disease occurred when measurable lesions changed by less than 25% in the products of perpendicular diameters and no new lesions appeared during treatment. Progressive disease occurred when measurable lesions increased by more than 25% during treatment.

In consenting patients, blood and urine samples were obtained for pharmacokinetic studies. Results of pharmacokinetic analyses will be reported at a later time. The toxicities encountered with the two taxol schedules were compared using the standard chi-square test applied at a significance level of $P = 0.05$.

Patient characteristics are outlined in Table 1. Between March 1993 and August 1993, 56 patients entered the study. The median age was 57 years (range, 30–73 years). Most patients (69%) had an ECOG performance status of 1. Eighty-four percent of patients had either breast, lung, or ovarian cancer. Eighty-seven

Table 1. Patient Characteristics (n = 56)

Characteristic	No. (%)
Median age (range)	57 (30–73)
Sex (male/female)	20/36
ECOG performance status	
0	8
1	39
2	9
Cancer type	
Breast	17
Lung, non-small cell	16
Ovarian	9
Lung, small cell	5
Colorectal	2
Non-Hodgkin lymphoma	1
Prostate	1
Sarcoma	1
Hypopharynx	1
Adenocortical	1
Parotid (adenocystic)	1
Pancreas (neuroendocrine)	1
No. of previous chemotherapy regimens	
0	7
1	18
2	15
> 2	16

percent of patients had received previous chemotherapy; 55% had received two or more previous regimens. Twenty-eight patients received the 1-day paclitaxel schedule and 28 received the 3-day schedule.

Results

The 56 patients in the current study have received 162 courses of paclitaxel. Ninety courses were administered by the 1-day schedule, whereas 72 courses were administered by the 3-day schedule. Twenty-nine patients have been removed from the study, whereas 27 are continuing to receive paclitaxel. The number of courses received ranged from one to eight; 29 patients have received more than two courses, and 11 of these patients remain on study. Four patients were removed from study after receiving only one course of paclitaxel; all of these patients were withdrawn prematurely because of rapidly progressive tumor. All 56 patients were evaluable for toxicity.

Toxicity

No serious hypersensitivity reactions were encountered with either paclitaxel schedule. Allergic symptoms were seen in 6 of 162 courses; 5 of these were ECOG Grade 1 reactions and one was a grade 2 reaction, as shown in Table 2. Four episodes occurred with the 3-day schedule and two occurred with the 1-day schedule. All hypersensitivity reactions occurred on the first day of treatment.

Table 2. Nonhematologic Toxicity

Adverse effect	Grade (ECOG scale)	Total	1-Day schedule	3-Day schedule
Hypersensitivity reactions				
Urticaria	1	1	0	1
	2	1	0	1
Wheezing/dyspnea	1	1	1	0
Flushing	1	2	1	1
Pruritus	1	1	1	0
Alopecia	4	56	28	28
Myalgias	1	9	7	2
	2	14	7	7
	3	9	4	5
Fatigue/weakness	1	5	2	3
	2	16	10	6
	3	5	3	2
Nausea	1	9	4	5
	2	6	4	2
	3	2	1	1
Emesis	1	4	3	1
	2	2	0	2
Mucositis	1	7	2	5
	2	3	3	0
Diarrhea	1	2	1	1
	2	3	3	0
Light-headedness	1	2	1	1
Headache	1	2	0	2
Peripheral neuropathy	1	1	1	0

Values are no. of patients.

Table 3. Myelosuppression

	Nadir	Total (%)	1-Day schedule	3-Day schedule
Leukeopenia (leukocyte)	3000–3900	17 (10%)	7	10
	2000–2900	32 (20%)	19	13
	1000–1900	30 (18%)	12	18
	< 1000	4 (2%)	3	1
Thrombocytopenia (platelet)	75,000–99,000	3 (2%)	3	0
	50,000–74,000	6 (4%)	5	1
	25,000–49,000	6 (4%)	5	1
	< 25,000	2 (1%)	2	0

Values are no. of episodes.

Myelosuppression was common but was mild or moderate in most patients (Table 3). Nadir leukocyte counts of 1000–2000/μl occurred during 30 courses (18%), whereas Grade 4 toxicity (leukocyte count < 1000/μl) occurred in only 4 instances (2%). Nine hospitalizations in eight patients were required for treatment of infections associated with neutropenia. In five instances, blood cultures were positive. Two patients had localized infections (one patient had pneumonia and the other had Groshong catheter infection). All patients received intravenous antibiotics and recovered from these episodes. All episodes of Grade 4 neutropenia and all hospitalizations for neutropenia and fever occurred in patients who had received two or more previous chemotherapy regimens.

Duration of Grade 3 and 4 neutropenic episodes was generally brief, and treatment delays were necessary in only two treatment courses. Three patients required dose reductions to 75% of the starting dose after Grade 3 or 4 neutropenia. Cytokines were used only in patients hospitalized with neutropenia and fever. The two schedules of paclitaxel were not significantly different with regard to the incidence of severe neutropenia.

Thrombocytopenia was infrequent, and Grade 3 or 4 thrombocytopenia occurred in only 8 of 162 courses (5%). No patients had hemorrhagic problems related to thrombocytopenia.

Toxicities other than myelosuppression are outlined in Table 2. Total alopecia occurred in all patients. Myalgias and fatigue occurred 57% and 46% of patients, respectively. However, these side effects were usually mild; only nine patients (16%) had Grade 3 my-

algias and five patients (9%) had Grade 3 fatigue. Because all patients in the current study had advanced cancer, it is probable that fatigue was multifactorial in some instances. Gastrointestinal symptoms were uncommon, and only one patient experienced severe (Grade 3) nausea. Only one patient experienced mild (Grade 1) peripheral neuropathy.

Responses

Although the assessment of toxicity was the primary objective of this study, all patients were also evaluated for tumor response. Forty-eight of 56 patients were evaluable for response; the remaining 8 patients are considered treatment failures because they declined rapidly as a result of their cancer and did not receive two full courses of therapy.

Eleven of 56 patients (20%) had major responses to paclitaxel (two complete responses, nine partial responses). Seven responding patients received the 1-day schedule, and four patients (including both patients with complete response) received the 3-day schedule. Responses were distributed by tumor type as follows: breast cancer, 6 of 17 (35%); ovarian cancer, 3 of 9 (33%); and non-small cell lung cancer, 2 of 16 (13%). Twenty-seven additional patients had either stable disease or minimal response after two courses of therapy, and many of these are still receiving therapy. The patients with stable disease or minimal response will be reevaluated for response status after four courses are administered. The final response rate and the duration of response is unknown, because a sizable number of patients are continuing therapy.

Discussion

Paclitaxel has demonstrated a wide range of antineoplastic activity; however, its role in the treatment of cancer has not yet been defined. To date, most studies have evaluated paclitaxel as a single agent in patients with advanced, refractory neoplasms. Although activity has been observed, it is unlikely that the use of paclitaxel in this way will have any major effect on overall treatment results. As with other active antineoplastic agents, paclitaxel is most likely to have an effect when used in combination with other drugs at a time when patients still have sensitive tumors. However, the dose and schedule of paclitaxel used in reported Phase II studies, particularly in breast cancer, make successful combination with other agents problematic due to toxicity. Therefore, the optimal dose and schedule of paclitaxel administration remain undefined, as well as its use in combination regimens.

In the current preliminary report, we present new data concerning the schedule of paclitaxel administration. The 1-hour schedules we have investigated have several potential advantages. First, recent data have shown that the same dose of paclitaxel is less myelosuppressive when given over 3 hours versus 24 hours.[12] A 1-hour infusion may further lessen toxicity. Second, reduction of myelosuppression (and perhaps other paclitaxel-related adverse effects) may allow escalation of dose and/or successful combination with other myelosuppressive agents. Finally, a short infusion would allow paclitaxel to be easily administered to outpatients, thereby creating an easier treatment for patients as well as reducing the cost of therapy.

The major adverse effect of paclitaxel that led to the adoption of a 24-hour continuous infusion schedule was the occurrence of severe hypersensitivity reactions. In the current study, we unequivocally demonstrated that paclitaxel can be safely administered by a 1-hour infusion when adequate premedications are given. We encountered no severe hypersensitivity reactions in 162 courses; only six patients had mild allergic reactions. Severe hypersensitivity reactions to paclitaxel are therefore prevented by the premedication schedule, and with adequate premedication the length of infusion appears unrelated to hypersensitivity reactions.

Both of the paclitaxel schedules reported in the current study were well tolerated with respect to myelosuppression. Despite the fact that many of these patients were heavily pretreated, Grade 3 or 4 myelosuppression was uncommon, and only nine hospitalizations resulted from infections associated with neutropenia (5% of total courses). The duration of neutropenia was short, even though cytokines were not used, and treatment at 21-day intervals was easily tolerated. Although these data do not allow definitive comparison with paclitaxel infusions of other durations, the myelosuppression produced by our 1-hour schedules seems similar to that reported for 3-hour paclitaxel infusions and less than that reported for 24-hour infusions. The 3-day schedule is particularly interesting in this respect, because toxicity was not increased despite the probable increased chronicity of exposure to paclitaxel with this schedule.

Except for alopecia, which was severe in all patients, other adverse effects were uncommon with these two schedules of paclitaxel administration. Both regimens were easily tolerated, and no statistical differences between these regimens with respect to any adverse effect were documented.

Although assessment of treatment toxicity was the major goal of this trial, tumor response was also evaluated. The response data are preliminary, because many patients are currently receiving treatment, and a final report concerning treatment efficacy will await longer follow-up. However, we have already observed objective responses in patients with refractory ovarian can-

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