Phase II Study of 3-Hour Infusion of Paclitaxel in Previously Untreated Non-Small Cell Lung Cancer

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ABSTRACT
Paclitaxel has clinical activity in non-small cell lung cancer, with response rates of 21 and 24% in a 24-h infusion. Recent clinical studies have shown that a 3-h infusion of the drug with premedication did not result in hypersensitivity reactions, and that neutropenia was milder in the 3-h than in the 24-h schedule. In this Phase II study, we tried to evaluate the efficacy and toxicity of paclitaxel given over 3 h in patients with previously untreated, unresectable stage III or IV non-small cell lung cancer. In addition, we attempted to investigate the pharmacokinetics and pharmacodynamics of the drug. Paclitaxel was administered i.v. over 3 h at a dose of 210 mg/m² every 3 weeks with premedication of dexamethasone, ranitidine, and diphenhydramine. Heparinized blood samples were obtained from 12 patients for pharmacokinetic studies. Twenty-three (38%) of 60 assessable patients achieved a partial response, with a median duration of 11.2 months, and the 1-year survival rate was 48%. Thirty (50%) patients developed grade 4 neutropenia. Nonhematological toxicities were mild, except for pulmonary toxicity in one (1.7%) patient who required mechanical ventilatory support for 4 days. The duration of the paclitaxel concentration above 0.1 µM correlated well with the percentage of decrease in the absolute neutrophil count. In conclusion, a 3-h infusion of paclitaxel was safe and probably not less effective than a 24-h infusion.

INTRODUCTION
Paclitaxel is a novel antineoplastic agent extracted from the bark of the Pacific yew, Taxus brevifolia (1). The drug blocks cells in G2-M by promoting microtubule assembly and by stabilizing microtubules, and shows a broad spectrum of antitumor activity in experimental models (2–5). The optimum administration schedule of paclitaxel has not been determined, although preclinical studies indicate that schedule may influence the biological effects (6). Early clinical trials of paclitaxel developed a 24-h infusion because of hypersensitivity reactions. In the first Phase I trial of a 3-h infusion conducted in the United States, three of five patients treated with 190 mg/m² or more developed acute dyspnea, generalized erythema, or hypotension, and one of them died despite maximum resuscitation efforts (7). However, it has been demonstrated that paclitaxel can be given safely over 3 h with premedication of dexamethasone, diphenhydramine, and an H2 receptor antagonist (8–10). Moreover, significantly less severe neutropenia was noted in this schedule (9). We observed the same phenomenon in our previous Phase I trial of paclitaxel over 24 h and 3 h (11, 12).

Lung cancer is one of the most common malignancies and causes of deaths from cancer in Japan. In 1990, 36,486 persons died of the disease, which accounted for approximately 17% of all cancer deaths. For the year 2010, the number of deaths from lung cancer is predicted to be 103,714, 2.84 times the number observed in 1990 (13). Advanced non-small cell lung cancer remains incurable, although a few drugs show reproducible response rates of 15–20% and in combination of greater than 30% (14). Two Phase II trials of paclitaxel for the disease using a 24-h infusion revealed overall response rates of 24% and 21%, and median survivals of 40 weeks and 24 weeks, respectively (15, 16). The objective of this study was to assess the efficacy and toxicity of paclitaxel administered over 3 h for advanced non-small cell lung cancer. In addition, we investigated the PK and pharmacodynamics of this schedule.

PATIENTS AND METHODS
Patients with histologically or cytologically proven unresectable stage III or metastatic non-small cell lung cancer having received no prior chemotherapy, radiotherapy, or surgical treatment for the primary lesion were eligible for this study. They were required to meet the following criteria: to be between 15 and 74 years old; to have a Japan Society for Cancer Therapy performance status of 0, 1, or 2; a life expectancy of 3 months or more; measurable lesions; and adequate organ functions as indicated by a leukocyte count ≥ 4,000/µl, a neutrophil count ≥ 2,000/µl, a platelet count ≥ 100,000/µl, a serum bilirubin level ≤ 1.5 mg/dl, a serum creatinine level ≤ 1.5 mg/dl, and a normal electrocardiogram. Patients were excluded if they had symptomatic brain metastasis, active multiple malignancies or acute inflammatory diseases, and a history of severe hypersensitivity reactions. Written informed consent was obtained from all pa-

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The abbreviations used are: PK, pharmacokinetics; ANC, absolute neutrophil count; AUC, total area under the curve; MRT, mean residence time.
Paclitaxel was supplied by Bristol-Myers Squibb K. K. (Tokyo, Japan) as a solution containing 30 mg of the drug in 5 ml 50% polyoxyethylated castor oil (Cremophor EL) and 50% dehydrated alcohol. Patients received 210 mg/m² paclitaxel diluted in 500 ml 5% glucose in a 3-h i.v. infusion. The dose was determined according to the results of the previous Phase I study (12). Premedication consisted of 20 mg dexamethasone (14 h and 7 h before paclitaxel), 50 mg ranitidine, and 50 mg diphenhydramine (30 min before paclitaxel) as described previously (11, 17). Patients were observed closely by continuous electrocardiogram telemetry and by measuring the blood pressure every 30 min during the infusion. The therapy was repeated every 3 weeks if patients had sufficiently recovered from drug-related side effects. Those who responded or whose disease remained stable continued to receive the drug until evidence of disease progression or unacceptable toxicity was noted.

Adverse reactions were graded according to the toxicity criteria of the Japan Society for Cancer Therapy, which are a modification of those devised by the WHO (18). Dose reductions by 30 mg/m² in subsequent cycles were made for those who developed grade 4 leukenopa or thrombocytopenia and for those who developed grade 3 or more nonhematological toxicity. A maximum of two dose reductions were allowed in each patient. Recombinant granulocyte colony-stimulating factor was s.c. injected if patients had a leukocyte count <1000/µl or an neutrophil count of <500/µl that lasted for more than 2 days.

Responses were evaluated using the criteria of the Japan Lung Cancer Society, based on the WHO criteria. A complete response was defined as the disappearance of all measurable, assessable, and secondary lesions for at least 4 weeks, with no new lesion appearing. A partial response was at least a 50% decrease in the product of the two longest perpendicular diameters of bidimensionally measurable lesions for at least 4 weeks without the appearance of new lesions. For patients with unidimensionally measurable disease, a partial response required a 30% or greater decrease in linear tumor measurements. No change was defined as the failure to observe a partial or complete response and no progressive or new lesions for at least 4 weeks. If a objective decrease was <50% but >25% in the size of tumor for more than 4 weeks, or a 50% or greater decrease lasted less than 4 weeks, it was recorded as a minor response. Progressive disease was defined as a 25% or more increase in the size of any measurable lesion or the appearance of new lesions. The response status of all patients considered to have an objective response (complete, partial, or minor response) was confirmed by external review. The duration of overall response was defined as the time from the first day of treatment to the date of first observation of progression.

Pharmacokinetic analyses were performed in 12 consecutive patients admitted to the National Cancer Center Hospital East. Heparinized blood samples were collected before infusion, at 1.5 and 3 h during the infusion, and at 5, 15, and 30 min and 1, 2, 3, 4, 6, 12, 24, and 48 h after the end of the infusion. They were separated by centrifugation at 3000 rpm for 5 min, and the supernatants were stored at −40°C until analyzed. Plasma paclitaxel concentrations were measured by a high-performance liquid chromatographic assay using n-hexyl p-hydroxy benzoate as an internal standard. The concentration was quantified by linear regression analysis of peak height ratio (paclitaxel/n-hexyl p-hydroxy benzoate) versus the standard curve (17). The following PK parameters were obtained: Cmax, AUC, t1/2, MRT, volume of distribution at steady state, and total-body clearance. We also calculated the duration of the paclitaxel concentration above 0.1 µM because our previous study showed the threshold of 0.09 µM to be the best parameter to predict granulocytopenia in the 3-h schedule (17). The percentage of decrease in ANC was calculated according to the following equation:

\[
\text{% of decrease} = \frac{(\text{Pretreatment ANC} - \text{Nadir ANC})}{\text{Pretreatment ANC}} \times 100%
\]

We analyzed the relationship of the percentage of decrease in ANC and clinical responses to the PK parameters.

The study was designed to test the null hypothesis that the response rate was <10% against the alternative that the true response rate was 20% or more. Assuming a one-sided test with a P value of 0.05 and a power of 0.8, the estimated required sample size was 60 patients.

**RESULTS**

Between March 1994 and September 1994, 61 patients entered the study. Of these 61 patients, 60 met all of the eligibility criteria and were objects of the study. One patient was excluded because he was found to have pulmonary metastases from colon cancer and did not receive paclitaxel. The characteristics of the eligible patients are listed in Table 1.

A median number of paclitaxel cycles received by a patient was 3 (range, 1–9), and a total of 188 cycles were delivered. Dose reduction was made in 5 of 60 patients and in 15 of 188 cycles.

Responses are shown in Table 2. Twenty-three and 25 patients had partial responses and no change, respectively. Of the 25 patients, 6 showed a minor response. The response rate in patients with stage IIIA or IIIB was 63.6% (7/11), and that in

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**Table 1** Patient characteristics

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<th>Description</th>
<th>No. of patients entered</th>
<th>No. of patients eligible</th>
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Table 2 Clinical responses

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<th>No. of Patients</th>
<th>CR</th>
<th>PR</th>
<th>NC</th>
<th>PD</th>
<th>NE</th>
<th>% Response rate (95% CI)</th>
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<tr>
<td>Stage II A+II</td>
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<td>7</td>
<td>4</td>
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</table>

* CR, complete response; CI, confidence interval; NC, no change; NE, not assessable; PD, progressive disease; PR, partial response.

Table 3 Toxideties by grade

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<td>Anemia</td>
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<td>Allergic reaction</td>
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<td>Hypotension</td>
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<td>Nausea and vomiting</td>
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<td>Diarrhea</td>
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<td>Hearing loss or tinnitus</td>
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<td>Arrhythmia</td>
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<td>3</td>
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<tr>
<td>ST-T wave change in ECG</td>
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<tr>
<td>Pulmonary toxicity</td>
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* ECG, electrocardiogram.

Fig. 1 Kaplan-Meier survival plot for 60 patients (median survival time, 11.2 months; 1-year survival rate, 48%).

Patients with stage IV was 32.7% (16/49). The overall response rate in 60 patients was 38.3% (95% confidence interval, 26.1–51.8%). The median duration of overall response and survival was 3.2 (range, 2.3–11.1) months and 11.2 (range, 2.0–7.9+) months, respectively. The 1-year survival rate was 48% (Fig. 1).

Toxicities in all cycles of the treatment are summarized in Table 3. Clinically significant hypersensitivity reactions or cardiotoxicity were not observed. Grade 4 neutropenia was observed in 30 (50%) of 60 patients and in 58 (31%) of 188 courses. Median (range) duration of ANC below 500/pA and 1000/pA were 3 days (days 1–13) and 6 days (days 1–14), respectively. Granulocyte colony-stimulating factor was administered in 17 patients. Neutropenic fever was observed in 26 patients, but none of them developed sepsis or other serious infections. Transfusions of packed RBCs were required in two of three patients with grade 3 anemia, and a mild decrease in the erythrocyte count and hematocrit were observed in some other patients. Hematological studies also showed mild thrombocytopenia, eosinophilia, and reticulocytosis.

Neuromuscular and gastrointestinal toxicity were common but rarely severe. Narcotics were required in two patients who experienced grade 3 myalgia and arthralgia. Grade 4 pulmonary toxicity was noted in one patient, who was suspected to have had interstitial pneumonitis because chest X-ray films showed bilateral reticular shadows in the lower lung fields. This patient was doing well during the first cycle of chemotherapy with paclitaxel, but on day 15 in the second cycle, fever and dyspnea appeared and rapidly progressed despite administration of antibiotics. In a chest X-ray, the bilateral reticular shadow was enhanced and spread throughout the lung fields. This patient required a mechanical ventilator for 4 days and 1 g methylprednisolone for 3 days to achieve a complete recovery from the respiratory failure. Pneumonitis in the patient was considered to be closely related to the paclitaxel treatment because a leukocyte migration inhibitory test for the drug was positive. Paclitaxel treatment was discontinued in this patient.

Other miscellaneous toxicities included hiccups, anorexia, malaise and anxiety, and also a decrease in total protein or albumin:globulin ratio and an increase in lactate dehydrogenase.

The PK parameters (mean ± SD) in 12 patients are summarized as follows: Cmax, 6.40 ± 0.85 μg/ml; t½, 14.4 ± 1.5 h; MRT, 7.4 ± 0.5 h; volume of distribution at steady state, 59.1 ± 10.8 liter/m²; total-body clearance, 169 ± 29 ml/min/m²; AUC, 21.3 ± 3.6 μg h/ml; and duration of the paclitaxel concentration above 0.1 μM, 21.4 ± 3.6 h. One patient was excluded from the analysis of neutropenia because leukocyte and platelet counts were elevated throughout the pretreatment.
and treatment periods, which might indicate that the tumor produced substances stimulating the bone marrow. The percentage of decrease in ANC in the 11 patients correlated well with AUC (percentage of decrease in ANC = 40.5 + 1.96 * AUC (μg h/ml); r = 0.705, P < 0.02) and duration of the paclitaxel concentration above 0.1 μM (percentage of decrease in ANC = 40.2 + 1.97 * duration of the paclitaxel concentration above 0.1 μM (h); r = 0.689, P < 0.02) (Fig. 2). The clinical response did not correlate with these parameters.

**DISCUSSION**

This trial showed that paclitaxel administered over 3 h had encouraging activity for non-small cell lung cancer with acceptable toxicity. Although experimental studies in vitro suggest that prolonged exposure to paclitaxel may increase its antitumor effects (19, 20), the correlation between a longer infusion time and a better response or survival has not been recognized in a clinical study (9). The overall response rate of 38.3% and the 1-year survival rate of 48% in this study were as high as those (21 and 42%, respectively) obtained in a Phase II study of paclitaxel given over 24 h in the same population (16). No correlation between clinical response and the duration of the paclitaxel concentration above 0.1 μM, AUC, or other PK parameters was observed.

i.v. infusion of paclitaxel over 3 h has been proved safe with premedication of dexamethasone, diphenhydramine, and an H2 receptor antagonist in recent trials (8–10). In this trial, no clinically significant hypersensitivity reactions or cardiotoxicity were observed. Moreover, leukocyte toxicity was milder than that observed in the two 24-h trials. Grade 4 neutropenia occurred in 50% of the patients in this trial compared with 82% (40/49) of patients in other trials, 4 of whom developed sepsis (15, 16). The incidence and severity of myalgia and arthralgia were almost the same among these trials. Thus, paclitaxel administered over 3 h is less likely to cause serious toxicity when compared with the 24-h schedule (15, 16).

Pulmonary toxicity not associated with general hypersensitivity reactions is a rare event, and, to our knowledge, only two cases have been reported (21, 22). We observed severe drug-induced pneumonitis in one patient, who required mechanical ventilatory support for 4 days. The patient was suspected to have had interstitial pneumonitis because of bilateral reticular shadows in chest X-ray films. Thus, we suggest that paclitaxel should not be administered to patients with this disease.

A 3-h infusion of paclitaxel was safe and probably not less effective than a 24-h infusion. Paclitaxel in this schedule should be investigated further before the best schedule of administration can be established.

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