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CLINICAL TRIAL REPORT

**Hiroshi Sakai · Shuichi Yoneda · Tomohide Tamura
Yutaka Nishiwaki · Akira Yokoyama
Koshiro Watanabe · Nagahiro Saijo**

A phase II study of paclitaxel plus cisplatin for advanced non-small-cell lung cancer in Japanese patients

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Abstract We performed a clinical phase II trial of the combination of paclitaxel and cisplatin in patients with locally advanced (stage IIIB) or metastatic non-small-cell lung cancer (NSCLC) using a 3-h infusion of paclitaxel followed by a 1 to 2-h infusion of cisplatin, with a short premedication regimen. Treatment was repeated every 21 days for at least two cycles. The patients received paclitaxel 180 mg/m^2 followed by cisplatin 80 mg/m^2. Enrolled in the trial were 33 chemotherapy-naive patients with stage IIIB (15%) or stage IV (85%) NSCLC. Their median age was 61 years (range 43–71 years). Of the 33 patients, 10 (30%) were women and 23 (70%) were men, and 82% had adenocarcinoma. With 78 courses of chemotherapy administered, 32 patients were evaluable for toxicity and response. Hematologic toxicities were moderate: Japan Clinical Oncology Group (JCOG) grade 3 or 4 neutropenia occurred in 37% of the cycles (53% of patients). Other toxicities consisted mainly of grade 1 or 2 alopecia and nausea/vomiting, but also included grade 1 or 2 neuropathy (47%), hypotension (grade 1 in 6%, grade 3 in 3%) and allergic reactions (grade 1 or 2 in 16%, grade 3 in 3%). Of 32 patients evaluable for response, a partial response was achieved in 10 (31%; 95% confidence interval 16% to 50%), stable disease was seen in 16 (50%), and disease progression was seen in 2 (6%). The median survival time was 14.8 months and the 1-year survival rate was 56%. These results suggest that the combination of paclitaxel and cisplatin is a well-tolerated and active regimen in Japanese patients with advanced NSCLC. In view of the promising survival outcomes, further evaluation in prospective randomized trials with other regimens is warranted.

Keywords Non-small-cell lung cancer · Paclitaxel · Cisplatin · Premedication · Phase II study

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H. Sakai (✉) · S. Yoneda
Department of Respiratory Disease,
Saitama Cancer Center, 818 Komuro,
Ina, Saitama, 362-0806, Japan
E-mail: hiroshi_sakai@cancer-c.pref.saitama.jp
Tel.: +81-48-7221111
Fax: +81-48-7235197

T. Tamura · N. Saijo
Department of Internal Medicine,
National Cancer Center, Central Hospital,
5-1-1 Tsukiji, chuo-ku, Tokyo, Japan

Y. Nishiwaki
Department of Respiratory System,
National Cancer Center, East Hospital,
6-5-1 Kashiwanoha, Kashiwa-city, Chiba, Japan

A. Yokoyama
Department of Internal Medicine,
Niigata Prefectural Cancer Center,
Niigata Hospital, 2-15-3 kawagishi-cho,
Niigata-city, Niigata, Japan

K. Watanabe
Department of Respiratory System,
Yokohama City Hospital, Okazawacho-56,
Hodogaya-ku, Yokohama-city, Kanagawa, Japan

Introduction

Currently, lung cancer is one of the most common malignancies and a major cause of cancer death in Japan. In the year 2000, over 50,000 individuals died of this disease, accounting for approximately 17% of all cancer deaths. Advanced non-small-cell lung cancer (NSCLC) remains incurable, although a few drugs have shown reproducible single-agent response rates of 15–20%, and response rates in combination of greater than 30% [1]. Paclitaxel has recently been shown to have good activity as a single agent, with response rates of 21% [2] and 24% [3] using a 24-h infusion, and 32% [4] and 38% [5] using a 3-h infusion. Combination with cisplatin, a well-established drug for NSCLC treatment, holds particular promise because both drugs have good efficacy as single agents.

Phase II trials of paclitaxel (3-h infusion) and cisplatin have shown overall response rates of 35–50%, and median survivals of 41 to 43 weeks [6, 7, 8, 9, 10]. The dose-limiting toxicities in a phase I study in Japan evaluating paclitaxel (3-h infusion) combined with cisplatin [11] were neutropenia, leukopenia, and neuropathy. The recommended doses for phase II study were determined to be paclitaxel 180 mg/m^2 and cisplatin 80 mg/m^2, repeated every 3 weeks.

The objective of this study was to assess the efficacy and toxicity of paclitaxel (3-h infusion) and cisplatin for advanced NSCLC.

Patients and methods

Patients

Patients had to fulfill the following eligibility criteria for this study: age more than 20 years and less than 75 years; ECOG performance status of 0 or 1; histologically or cytologically proven diagnosis of NSCLC, stage IIIB (only pleural metastasis or malignant pleural effusion) or IV; clinically measurable disease; adequate marrow, renal and liver functions (hemoglobin ≥9.5 g/dl, white blood cell (WBC) count 4,000–12,000/μl, platelet count ≥100,000/μl, serum creatinine ≤ 1.3 mg/dl, blood urea nitrogen ≤ 25 mg/dl, bilirubin ≤ 1.5 mg/dl); a life expectancy of at least 8 weeks; no prior chemotherapy; no prior radiation therapy to primary tumor, no radiation therapy to major bone marrow areas within 4 weeks prior to study entry; no previous allergic reaction to any drug mixed with the Cremophor solubilizer (e.g. vitamin K, cyclosporin); no symptomatic brain metastases; no active concomitant malignancy; no massive pleural or pericardial effusion requiring tube drainage; and no severe heart or pulmonary disease. Written informed consent was obtained from all patients. This study was conducted in accordance with Japanese Good Clinical Practice (GCP).

Pretreatment and follow-up studies

Prior to entry, patients were required to have a complete history and physical examination, ECOG performance status, biopsy or cytologic examination confirming NSCLC, complete blood cell count, liver and renal function studies, electrocardiogram, chest radiograph, computed tomography of the chest and abdomen, bone scan, and computed tomography or MRI of the brain.

Toxicities were evaluated according to the toxicity criteria of the Japan Clinical Oncology Group (JCOG), which are a modification of those devised by the WHO [12]. All patients were treated on an inpatient basis. Complete blood counts were obtained twice a week and patients were evaluated for treatment response after two courses of therapy by complete clinical/laboratory evaluation.

Responses were evaluated using the criteria of the Japan Lung Cancer Society, based on the WHO criteria.

Drug administration

To prevent hypersensitivity reactions, all patients were premedicated with dexamethasone, diphenhydramine, and famotidine. Dexamethasone 20 mg and famotidine 20 mg were given as an intravenous bolus injection 30 min prior to paclitaxel infusion. Diphenhydramine 50 mg was administered orally 30 min prior to paclitaxel infusion. Patients received paclitaxel 180 mg/m^2 dissolved in 500 ml saline and administered by continuous infusion over 3 h. After standard prehydration, patients received cisplatin 80 mg/m^2 over 1 to 2 h, followed by hydration for a further 24 h. Granulocyte colony-stimulating factor (G-CSF) prophylaxis was not routinely administered. A standard antiemetic regimen with 5-HT3 antagonists was administered after completion of paclitaxel in the event of emesis. Treatment was repeated every 21 days for more than two courses until disease progression, if patients fulfilled the eligibility criteria.

During the entire period of paclitaxel infusion, patients were monitored continuously by a physician. If any symptoms of severe acute hypersensitivity reaction occurred, the paclitaxel infusion was discontinued and standard treatment for anaphylaxis was initiated immediately.

Patients whose disease progressed were considered treatment failures and the therapy was stopped. Patients experiencing severe hypersensitivity reactions producing symptoms such as dyspnea, wheezing, severe hypotension, or generalized urticaria were withdrawn from the study. Chemotherapy was also discontinued in the event of severe prolonged neutropenia (neutrophil count < 2000/μl), thrombocytopenia (platelet count < 100,000/μl), or serum creatinine > 1.3 mg/dl within 14 days before the next scheduled infusion. In this study granulocyte colony-stimulating factor (G-CSF) was given when neutrophil counts fell below 500/μl.

Paclitaxel dose reductions of 30 mg/m^2 were planned in the event of: (1) < 500/μl neutrophil nadirs or < 1000/μl WBC nadirs with G-CSF support; (2) thrombocytopenia nadirs of < 30,000/μl; (3) grade III or IV nonhematologic toxicity; (4) peripheral neuropathy of more than grade 2. Cisplatin dose reductions of 20 mg/m^2 were planned in the event of more than grade 2 elevation of serum creatinine or more than grade 2 peripheral neuropathy.

Statistics

With the threshold efficacy rate set at 25% and the expected efficacy rate at 45%, under conditions of $\alpha = 0.05$ and $\beta = 0.2$, the number of patients in this study was established as 32. Survival time was assessed from various parameters calculated using the Kaplan-Meier method.

Results

From June 1998 through February 1999, 33 patients were enrolled in this study. Patient characteristics are presented in Table 1. Of the 33 patients, 32 were eligible and evaluable for response and toxicities. One patient was not eligible. Although the ineligible patient fulfilled the criteria at the time of enrollment, because of failure

Table 1 Patient characteristics. Values are number of patients, except age in years (none of the 33 patients had received prior therapy)

Enrolled	33
Treated	32
Evaluable for	
Toxicity	32
Response	32
Sex (M/F)	23/10
Age	
Median	61
Range	43–71
ECOG performance status	
0	9
1	24
Stage	
IIIB	5
IV	28
Histology	
Adenocarcinoma	27
Squamous cell carcinoma	5
Unclassified NSCLC	1

to meet one of the criteria (absolute neutrophil count more than 2000/μl) in a test on the day scheduled for administration, it was decided to wait until the neutrophil count had recovered before starting administration. However, recovery from neutropenia was delayed and the 2-week criterion was not met; administration was therefore abandoned.

There were 22 men and 10 women eligible, with a median age of 61 years (range 43 to 71 years), and a median ECOG performance status of 1 (range 0 to 1). Five patients had stage IIIB disease and 27 had stage IV disease. The predominant histologic type was adenocarcinoma (82%). The total and median number of courses were 78 and 2 (range 1 to 4), respectively.

Toxicities

The major toxicity associated with this regimen was myelosuppression. However, the severity was moderate (Table 2). JCOG grade 3–4 leukopenia occurred in 9% and grade 3–4 neutropenia occurred in 53% of patients. No grade 2–4 thrombocytopenia or grade 3–4 anemia occurred. Elevations of SGOT and/or SGPT were commonly observed (38/63%). Elevation of serum ALP occurred in 31% and elevation of serum creatinine occurred in 28% of patients, but were less than grade 2. Grade 3 or 4 hyponatremia occurred in 6% of patients.

Nonhematologic toxicity was generally mild to moderate (Table 2). Nausea and vomiting occurred in 78% of patients, myalgia in 25%, and arthralgia in 38%.

Table 2 Toxicity according to JCOG grade: worst toxicity per patient

Toxicity	JCOG grade ($n=32$)			
	1	2	3	4
Hematologic				
Leukopenia	8	14	3	0
Neutropenia	4	7	11	6
Anemia	5	13	0	0
Thrombocytopenia	1	0	0	0
SGOT elevation	10	1	1	0
SGPT elevation	14	5	1	0
ALP elevation	10	0	0	0
Serum creatinine elevation	3	6	0	0
Hyponatremia	13	4	1	1
Nonhematologic				
Nausea/vomiting	11	12	2	–
Myalgia	2	6	0	0
Arthralgia	7	5	0	0
Neuropathy	11	4	0	0
Alopecia	23	3	–	–
Hypotension	2	0	1	0
Edema	6	1	0	0
Allergic reactions	4	1	1	0
Skin rash	9	3	3	0
Phlebitis	0	1	0	0
Convulsive seizure (due to hyponatremia)	0	0	1	0
Unconsciousness (due to hyponatremia)	0	0	0	1

Sensory neuropathy occurred in 47% of patients; this toxicity was cumulative and became progressively more severe with each treatment course (first course 7/32; second course 9/25; third course 12/15, including four patients with grade 2 toxicities; and fourth course 3/6, including one patient with grade 2 toxicity). Alopecia occurred in 81% of patients. Hypersensitivity reactions, such as hypotension and facial edema, occurred in one patient at grade 3 (3%) and one patient at grade 2 (3%) during paclitaxel infusion. Both patients recovered soon after discontinuation of paclitaxel and administration of methylprednisolone. Grade 3 skin rash occurred in three patients (9%) after completion of the paclitaxel infusion. One patient experienced grade 4 hyponatremia, probably induced by renal dysfunction due to cisplatin. These toxicities had disappeared 7 days after the initial symptoms. No cardiac events were noted. The reason for discontinuing administration was a change in treatment policy in 19 patients (including 4 patients with progressive disease), adverse reactions in 11 patients, and patient refusal in 2 patients.

Response

Among 32 eligible patients, there were no complete responses and 10 partial responses, for an overall response rate of 31.3% (95% confidence interval 16.1–50.0%). There were 16 patients with stable disease, and 2 with progressive disease (Table 3). Four patients were judged to be not evaluable because the period required for "no change" had not been completed. The median survival time was 14.8 months (range 2.2–24.2, Fig. 1). The 1-year survival rate was 56%.

The post-treatment consisted of chemotherapy in 13 patients and radiotherapy in 11 patients (primary focus irradiation in 7 patients, skeletal irradiation in 3 patients, and brain irradiation in 3 patients), and no post-treatment was performed in the other 8 patients.

Discussion

This trial showed the combination of paclitaxel administered over 3 h and cisplatin to have encouraging activity in chemotherapy-naive patients with advanced NSCLC. Although the median number of courses of infusion was only two, the overall response rate of 31% and the 1-year survival rate of 56% were as high as those (35–50% and 33–43%, respectively) obtained in similar phase II studies [6, 7, 8, 9, 10]. The mean survival time of 14.8 months achieved in this study exceeded the those obtained in similar phase II studies (10–12 months) by 3–5 months. While it is impossible to rule out unintended selection bias when choosing the patients for this study, the reasons for this appear to be that radiotherapy was able to be performed as post-treatment in many of the patients, and that other potent chemotherapy was

Table 3 Response (*CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable)

	No. of patients						Response rate (%)
	Total treated	CR	PR	SD	PD	NE	
Overall	32	0	10	16	2	4	31.3[a]
Stage							
IIIb	5	0	3	2	0	0	60.0
IV	27	0	7	14	2	4	25.9
Primary site							
Lung	26	0	10	16	0		38.5
Metastatic site							
Pulmonary	10	0	1	8	1		10.0
Pleural	1	0	0	1	0		0.0
Lymph nodes	11	0	3	8	0		27.3
Brain	1	0	0	1	0		0.0
Liver	2	0	0	2	0		0.0
Histology							
Squamous cell	4	0	3	0	0	1	75.0
Adenocarcinoma	27	0	7	16	1	3	25.9
Unclassified NSCLC	1	0	0	1	0	0	0.0

[a]95% CI 16.1–50.0%

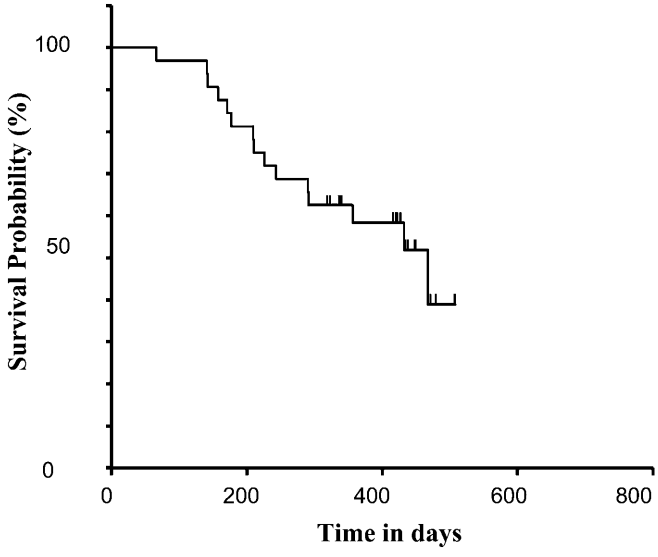

Fig. 1 Overall survival of the 32 patients

able to be incorporated in the therapy of many of the patients because their general condition was favorable.

As expected at the outset, high rates of leukopenia and neutropenia were seen in this study, and these toxicities at grade 3 or more were observed in 9.4% and 53.1%, respectively. However, this regimen was generally feasible, and G-CSF was only used in two patients. Peripheral neuropathy, which is a specific adverse reaction to paclitaxel, was moderate, with no grade 3 toxicity observed, but its incidence and severity tended to increase with the number of courses of treatment administered. These seem to be events that will require attention in the future. Hypersensitivity reactions, including hypotension and skin rashes, were seen, but their incidence was similar to those reported in other studies, and they rapidly resolved after paclitaxel administration was discontinued. Unconsciousness due to hyponatremia was seen in one patient, but this patient also rapidly recovered after administration was discontinued.

These results suggest that the combination of paclitaxel and cisplatin is a well-tolerated and active regimen in Japanese patients with advanced NSCLC. In view of the promising survival outcomes, further evaluation in prospective randomized trials with other regimens is warranted.

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