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Phase II Trial of Biweekly Paclitaxel and Gemcitabine as Second-Line Chemotherapy for Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy

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A phase II study was conducted to evaluate the feasibility and efficacy of biweekly administration of paclitaxel and gemcitabine in patients with non-small cell lung cancer (NSCLC) who had been treated previously with platinum-based chemotherapy. Paclitaxel (150 mg/m²) and gemcitabine (1,000 mg/m²) were administered biweekly for at least 4 cycles. Thirty-one patients with a median age of 64 years (39-75 years) were enrolled in this study (stage IIIB/IV : 11/20, PS 0/1/2 : 13/16/2). Partial response was observed in 7 cases (23 %), and stable disease was seen in 18 cases (58 %). Median survival time was 8.8 months with a one-year survival rate of 41.9 %. Hematological toxicities were mild and neutropenia of grade 3 or above was observed in one patient (3 %). Non-hematological toxicities were also mild, including neurotoxicity (3 %). Biweekly paclitaxel and gemcitabine combination chemotherapy was effective and tolerated well as second-line therapy against NSCLC. *Shinshu Med J 59 : 411—418, 2011*

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I Introduction

In recent years, the efficacy of second-line chemotherapy has been established in phase III clinical trials for patients with advanced non-small cell lung cancer (NSCLC)[1]. Two chemotherapeutic agents, docetaxel and pemetrexed, and the biological agent erlotinib are currently approved for clinical use in patients with advanced NSCLC[2)-5)]. However, the improvements in survival after these therapies are modest and other novel agents have become available for patients with NSCLC over the past decade. Therefore, it is still important to conduct clinical trials to evaluate the activity of other agents as second-line treatment for NSCLC.

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Among the agents useful for NSCLC, paclitaxel is the first clinically available taxane the cytotoxicity of which is derived from suppression of the functions of mitotic microtubules[6]. Gemcitabine (2',2'-difluoro-2'-deoxycytidine) is also a novel pyrimidine nucleoside analog[7]. Both agents have yielded response rates of 21 %-26 % in advanced NSCLC with only mild toxicities when used in single-agent regimens[8]. Platinum in combination with paclitaxel or gemcitabine has been studied extensively and shown response rates in the 21 %-62 % range in first-line chemotherapy for NSCLC[9)-12)]. However, little information is available regarding the activity and feasibility of paclitaxel plus gemcitabine when used as second-line chemotherapy for NSCLC. These agents appear promising due to their specific mechanism of action and favorable toxicity profiles[13)-15)].

Previously, we conducted a phase I study of a biweekly combination of paclitaxel and gem-

citabine and the results indicated recommended doses of 150 mg/m² for paclitaxel and 1,000 mg/m² for gemcitabine[16]. The present study was performed to further evaluate the effectiveness and safety of biweekly administration of paclitaxel and gemcitabine as second-line therapy for patients with advanced NSCLC who had been unsuccessfully treated with platinum-based chemotherapy.

II Method and Subjects

A Patient eligibility

Patients with histologically or cytologically confirmed stage IIIB or IV NSCLC in whom first-line chemotherapy with a platinum-containing regimen had failed or who had relapsed were eligible for this study. Other criteria were as follows: 1) age≧20 and≦75 years; 2) Eastern Clinical Oncology Group (ECOG) performance status 0 to 2; 3) adequate bone marrow function (neutrophil count≧2×$10^3/\mu$L, hemoglobin≧10 g/dL, platelet count≧100×$10^3/\mu$L), normal hepatic function (total bilirubin level≦1.5× and AST≦2× the upper normal limits), and renal function (creatinine≦1.5 mg/dL, creatinine clearance≧60 mL/min). Individuals with peripheral neuropathy were excluded. Patients with a history of partial response after prior paclitaxel chemotherapy were permitted to participate in the present study. In addition, patients were excluded from the trial for any of the following reasons: 1) active infection; 2) severe heart disease; 3) past history of hypersensitivity to drugs; 4) pleural or pericardial effusion requiring drainage; 5) active brain metastasis; or 6) pregnancy. Patients with other concurrent active malignancy were also excluded. No other concomitant anticancer therapy or experimental drug administration of any type was permitted. Written informed consent was obtained from each enrolled patient. The study was undertaken in accordance with the Declaration of Helsinki.

B Pretreatment evaluation

Before enrollment in the present study, all patients underwent clinical and physical examination. General condition, medical history, performance status, differential blood cell counts, routine laboratory tests, and urinalysis results were obtained before the study. Electrocardiography, chest radiography, chest computed tomography (CT), abdominal ultrasound and/or CT scan, and whole-brain CT scan or magnetic resonance imaging (MRI) and isotope bone scan were also performed in all cases.

C Toxicity and response evaluation

During the study period, complete differential blood cell counts were obtained weekly. Routine chemistry measurements were performed biweekly before chemotherapy. If necessary, additional examinations of blood samples were performed. Examination of chest CT was performed after four cycles of chemotherapy for detailed tumor measurements. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria Version 2[17]. Tumor assessment by chest CT was performed after four cycles of chemotherapy. Response Evaluation Criteria in Solid Tumors (RECIST) was used for evaluation of tumor response[18]. All responses were evaluated carefully and confirmed by independent verification. Toxicities were expressed at the highest grade during chemotherapy and the delivery and compliance of the treatment were evaluated for the first four cycles of paclitaxel/gemcitabine administration.

D Treatment delivery and dose reduction

On day 1 of each chemotherapy cycle, paclitaxel (150 mg/m²) was administered first as an intravenous infusion over 1 h followed by gemcitabine (1,000 mg/m²) intravenously over 30 min. Paclitaxel (Taxol) and gemcitabine (Gemzar) were diluted in 250 mL and 100 mL of normal saline, respectively. To avoid hypersensitivity reactions, the following standard premedication was administered: dexamethasone 20 mg intravenously (IV), diphenhydramine 50 mg IV, and cimetidine 150 mg IV. These drugs were administered 30 min prior to paclitaxel administration. Chemotherapy cycles were repeated every 2 weeks. Recombinant human G-CSF was not given prophylactically. Administration of subsequent chemotherapy was allowed when absolute

neutrophil and platelet counts were more than $1.5\times10^3/\mu L$ and $75\times10^3/\mu L$, respectively. If these variables did not return to adequate levels by a maximum of 2 weeks, doses of both agents were reduced by 20 %. Similarly, the dose reduction was adjusted in cases showing chemotherapy-induced febrile neutropenia or grade 4 hematological toxicity lasting for 4 days. Patients with disease progression at any cycle of chemotherapy or presenting with grade 3 or 4 nonhematological toxicity and requiring hospitalization were withdrawn from the study.

E Statistics

The main endpoint of this study was the response rate. Secondary endpoints were toxicities and overall survival. Response and survival rates were both calculated on an intent-to-treat basis. Overall survival was calculated from the date of initiation of this regimen to death or date of last follow-up (cutoff date : 31 March 2008). The Kaplan-Meier method was used to determine the medians of the time-related parameters.

III Results

A Patient characteristics

A total of 31 patients were enrolled in the study between August 2000 and January 2006. The clinical characteristics of the patients are summarized in Table 1. The study population consisted of 23 men and 8 women, with a median age of 67 years (range 39-75 years). Of the 31 patients, 29 had a PS of 0 or 1, and 2 had a PS of 2. Adenocarcinoma histology was noted in 26 patients. Eleven patients had stage IIIB disease and the remaining 20 had stage IV disease. All patients had been previously treated with platinum-containing regimens as first-line chemotherapy ; 26 received platinum compound plus docetaxel, and the remaining 5 patients had been treated with platinum compound plus paclitaxel.

B Treatment delivery

A total of 161 cycles of biweekly administration of paclitaxel and gemcitabine were performed with a median of 4 cycles (range 1-20). Treatment delivery was evaluated during the first four cycles of chemotherapy. A delay of one week until the next cycle occurred because of neutropenia (3 cases), non-neutropenic infection or fever (3 cases), and other reasons unrelated to treatment (2 cases). Pulmonary toxicity developed after only one cycle in one patient and disease progression was observed after two cycles in one patient, and chemotherapy was subsequently discontinued. Dose modification of these agents was not performed. Thus, 111 cycles of chemotherapy received the intended first four cycles, resulting in a completion rate of 89.5 % (111/124 cycles).

C Toxicity

Toxicities were assessed in all patients. Hematological toxicities were generally mild, as shown in Table 2. Grade 3 neutropenia occurred in only one patient (3 %) and none developed neutropenic fever during the present chemotherapy regimen. Interestingly, there were no cases of severe thrombocytopenia or anemia during therapy. Nonhematological toxicities are summarized in Table 3. Grade 2 and 3 peripheral sensory neurotox-

Table 1 Patient characteristics

Characteristic	No.	%
Sex		
Male	23	74
Female	8	26
Age (years)		
Median	67	
Range	39-75	
Performance status		
PS0	13	42
PS1	16	52
PS2	2	6
Histology		
Adenoca.	26	84
Squamous cell ca.	2	6
Large cell ca.	3	10
Stage		
IIIb	11	35
IV	20	65
First line chemotherapy		
cisplatin+docetaxel	25	81
carboplatin+paclitaxel	3	10
nedaplatin+paclitaxel	2	6
carboplatin+docetaxel	1	3

Table 2 Hematological toxicities

Toxicity	Grade (No.)					Grade≧3 (%)
	0	1	2	3	4	
Leukopenia	21	7	3	0	0	0
Neutropenia	19	5	6	1	0	3
Thrombocytopenia	30	1	0	0	0	0
Anemia	24	4	3	0	0	0

Table 3 Non-hematological toxicities

Toxicity	Grade (No.)					Grade≧3 (%)
	0	1	2	3	4	
Nausea	19	10	2	0	0	0
Diarrhea	27	3	1	0	0	0
Constipation	28	3	0	0	0	0
Neuropathy	15	7	8	1	0	3
Myalgia	19	11	1	0	0	0
Eruption	27	2	2	0	0	0
Alopecia	11	10	10	0	0	0
Edema	31	0	0	0	0	0
Infection without neutropenia	28	1	1	1	0	3
Liver dysfunction	28	3	0	0	0	0
Renal dysfunction	31	0	0	0	0	0
Pneumonitis	30	0	0	0	1	3

icities were observed in 8 cases (28 %) and one case (3 %), respectively. One patient developed severe pulmonary toxicity after only one cycle of chemotherapy, which resulted in a fatal outcome. No patients showed an allergic reaction to therapy or developed edema during chemotherapy.

D Efficacy

All 31 patients were included in the analyses of tumor response and survival. Partial response was observed in 7 patients (23 % ; 95 % confidence interval (CI) 9.6 %-41.1 %), and stable disease was seen in 18 patients (58 %) (Table 4). Among the 7 patients who responded to prior docetaxel plus platinum compound chemotherapy, one patient achieved a partial response (14 %) to the gemcitabine and paclitaxel regimen. On the other hand, among 19 patients who failed to response to the docetaxel-containing chemotherapy regimen, 5 patients showed a partial response (26 %) to the gemcitabine and paclitaxel regimen. There were no significant differences in response rate related to previous responses to docetaxel.

Table 4 Response rate

Overall response	30	No. (%)
Partial response (PR)		7 (23 %) (95 %CI 9.6-41.1 %)
Stable disease (SD)		18 (58 %)
Progressive disease (PD)		5 (16 %)
Not evaluated	1	(only 1 cycle)

The overall survival curve is shown in Fig. 1. Median survival time was 8.8 months (95 %CI 4.9-15.0 months), and 1-year survival rate was 41.9 % (95 %CI 24.6 %-59.3 %).

Ⅳ Discussion

The results of the present study indicated that paclitaxel plus gemcitabine administered biweekly could be combined safely for treatment of patients with NSCLC who had relapsed after or were resistant to platinum-based chemotherapy. The response rate was 23 % and median survival time

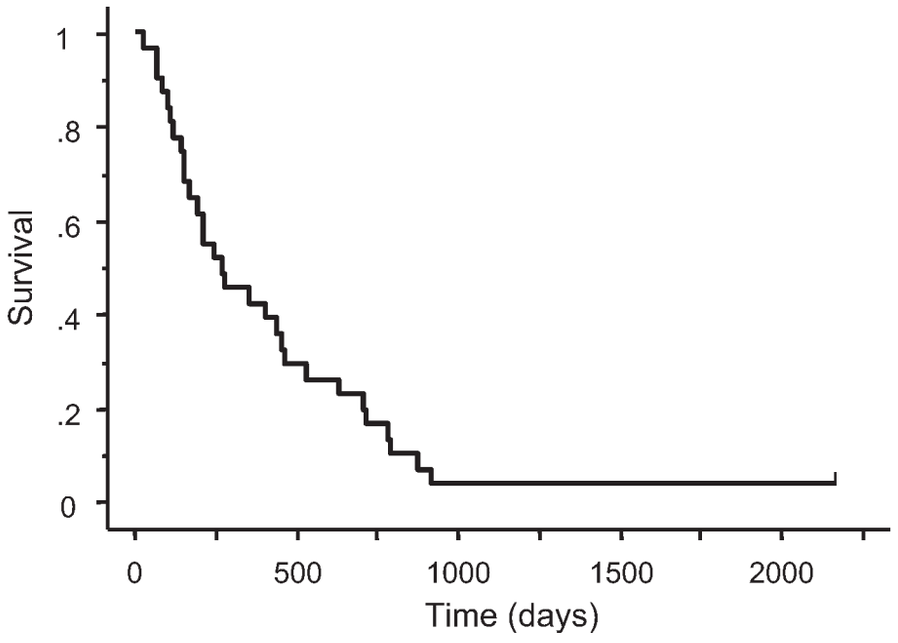

Fig. 1 Overall survival when treated with paclitaxel and gemcitabine as second-line chemotherapy in patients with non-small cell lung cancer (n=31).
The median survival time was estimated as 8.8 months (95 %CI 4.9-15.0 months), and 1-year survival rate was 41.9 % (95 %CI 24.6 %-59.3 %).

was 8.8 months with a 1-year survival rate of 41.9 %, which were promising results as second-line chemotherapy. Furthermore, the toxicity profiles were also acceptable.

Several studies using a combination of paclitaxel and gemcitabine as second-line therapy in patients with NSCLC have been reported. Mori et al.[19] conducted weekly administration of paclitaxel (100 mg/m² on days 1 and 8) and gemcitabine (1,000 mg/m² on days 1 and 8) in patients with NSCLC and reported a response rate of 32.5 % and MST of 41.7 weeks. Androulakis[20] also reported an overall response rate of 18 % and MST of 47 weeks. The dose settings were: paclitaxel, 175 mg/m² day 8; and gemcitabine, 900 mg/m² days 1 and 8. These findings were almost identical to our results obtained by biweekly administration of paclitaxel (150 mg/m²) and gemcitabine (1,000 mg/m²), although survival benefit was slightly lower in the present study[19)-21)]. To our knowledge, no clinical studies have shown the superiority of a doublet regimen over single-agent chemotherapy in second-line treatment of NSCLC. Gemcitabine in combination with docetaxel failed to show a survival benefit compared with docetaxel alone in patients with previously treated NSCLC. Several studies, including the present study, demonstrated that combined gemcitabine and paclitaxel in second-line chemotherapy provided a relatively high response rate compared with studies using docetaxel. Thus, paclitaxel plus gemcitabine is a potentially useful novel regimen, which should be examined in phase III clinical trials as second-line chemotherapy for patients with NSCLC.

In the initial planning stages of this study, there was no patient selection for previous agents in combination with platinum. However, all patients enrolled in the present study were treated with chemotherapy regimens that included taxanes. Little information is available regarding the influence of previous administration of docetaxel on subsequent paclitaxel activity in patients with NSCLC. The superior activity of docetaxel in second-line therapy is comparable to those of vinorelbine and ifosfamide[4]. However, the response and survival benefit of subsequent docetaxel therapy were in-

dependent of the previous use of paclitaxel[22]. The current paclitaxel and gemcitabine therapy regimen showed a response rate of 23 % in patients treated previously with a docetaxel-containing regimen. In addition, the 26 % response rate of paclitaxel plus gemcitabine in patients who failed to response to docetaxel-including chemotherapy regimens suggested partial non-cross-resistance between docetaxel and paclitaxel, gemcitabine, or the combination therapy. The present study suggested that paclitaxel is also promising as second-line therapy in patients with NSCLC previously treated with docetaxel.

In the present study, hematological toxicities were mild. In particular, thrombocytopenia was infrequent. Grade 3-4 thrombocytopenia was observed in 30 %-50.4 % of cases treated with a combination of platinum plus gemcitabine[9)11)12)]. Isla et al.[15)] performed a Phase II study of biweekly paclitaxel (150 mg/m^2) and gemcitabine (2,000 mg/m^2) as first-line chemotherapy against NSCLC and reported that no thrombocytopenia exceeding grade 3 was observed. Similar findings at a lower frequency of thrombocytopenia were observed in other studies using gemcitabine and paclitaxel[14)21)]. However, weekly administration of paclitaxel and gemcitabine showed an incidence rate of thrombocytopenia exceeding grade 3 of 12.5 %. Therefore, the administration of combined paclitaxel and gemcitabine every two weeks appeared to show a reduced rate of thrombocytopenia.

Neurotoxicity was seen frequently in cases treated with paclitaxel-containing regimens. In particular, cumulative peripheral neuropathy could be the dose-limiting toxicity of paclitaxel. The neurotoxicity observed in the present study may have been due to paclitaxel or the previous use of docetaxel or paclitaxel. Although patients with preexisting neuropathy were excluded from the present study, the incidences of neurotoxicity exceeding grade 3 (3 %) were low and were similar to those in other reports[23)-25)]. As it has been demonstrated that gemcitabine combined with paclitaxel did not lead to worse neurotoxicity than that observed with paclitaxel as single therapy[14)26)], we believe that our data support this.

One patient in the present study showed severe pulmonary toxicity. It has been reported that gemcitabine combined with docetaxel increases the risk of pulmonary toxicity compared to docetaxel alone[27)]. Based on reports in the literature, the rates of pulmonary toxicity in paclitaxel plus gemcitabine combination are low compared with those associated with docetaxel plus gemcitabine. Thus, it is unlikely that the combination of paclitaxel and gemcitabine could be associated with increased pulmonary toxicity. However, pulmonary adverse events should be noteworthy toxicities in any chemotherapy regimen.

In summary, a biweekly regimen of a combination of paclitaxel (150 mg/m^2) and gemcitabine (1,000 mg/m^2) was well tolerated and showed good activity as second-line therapy in patients with NSCLC who had relapsed after or developed resistance to platinum-based chemotherapy. The results of our trial suggest that this is a candidate regimen for second-line treatment in NSCLC with a well-tolerated schedule of administration.

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