A Multi-Center, Phase II Clinical Trial of Genexol[®] (Paclitaxel) and Cisplatin for Patients with Non-Small Cell Lung Cancer

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Purpose: A combination of paclitaxel and cisplatin is an effective and safe regimen for advanced non-small cell lung cancer (NSCLC). We conducted a multi-center, phase II trial to evaluate the efficacy and safety of Genexol[®] (paclitaxel) and cisplatin in patients with NSCLC.

Materials and Methods: Chemotherapy-naïve patients having histologically confirmed NSCLC were enrolled. Genexol[®] was administered at 175 mg/m² as a 3-hour intravenous infusion and cisplatin at 75 mg/m² as an intravenous infusion on day 1 every 3 weeks.

Results: Twenty-five of 27 patients that were entered from 5 hospitals between Jan 2001 and Aug 2001 received chemotherapy. On an intent-to-treat basis, 9 patients (36%) achieved a partial response, 7 patients (28%) a stable disease, and 5 patients (20%) progressed. The overall response rate was 36% (95% CI, 17 to 55%). The

median duration of the response was 7.8 months (95% CI, 6.6 to 9.0 months). The median time to progression was 7.4 months (95% CI, 5.3 to 9.5 months), and median overall survival was 13.3 months (95% CI, 10.8 to 15.9 months) for the intent-to-treat population. The major toxicity was hematological, with grade 3 and 4 neutropenia in 10% (10/106) of the total cycles. The non-hematologic toxicity was mild, and grade 3 emesis was observed in 2 patients (8%). One patient experienced a moderate degree hypersensitivity reaction.

Conclusion: The results suggest that a combination of Genexol[®] and cisplatin is an effective and well-tolerated regimen for patients with NSCLC. (*Cancer Research and Treatment* 2003;35:30-34)

Key Words: Non-small cell lung neoplasm, Chemotherapy, Genexol[®], Paclitaxel, Cisplatin

INTRODUCTION

Lung cancer is the second most common cancer and the leading cause of cancer deaths in Korea (1,2). Non-small cell lung cancer (NSCLC) comprises about 84% of all lung cancer in Korea (1). Cisplatin-based chemotherapy has been proved to have survival benefit in NSCLC (3). Of the many cisplatin-based

regimens, paclitaxel and cisplatin is considered one of the most effective regimens for advanced NSCLC (4~6).

Previously paclitaxel (Taxol[®]; Bristol-Myers Squibb Company, Princeton, NJ) was produced via a semi-synthetic process from *Taxus baccata*, but another paclitaxel (Genexol[®], Samyang Genex Corporation, Korea) was produced from *Taxus chinensis* via plant cell and tissue culture technology. Pre-clinical trials showed similar antitumor effects for Genexol[®] which was comparable to the paclitaxel produced by the former method. In a phase II trial with metastatic breast cancer patients, Genexol[®] showed no less response than the former paclitaxel with no considerable toxicity other than that previously reported (7).

We conducted a multi-center, phase II trial to evaluate the efficacy and safety of Genexol[®] and cisplatin in patients with NSCLC.

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MATERIALS AND METHODS

1) Patients

The patients in this study were entered from 5 hospitals between Jan 2001 and Aug 2001. The chemotherapy-naïve patients with histologically confirmed, inoperable locally advanced or metastatic NSCLC were eligible for the study. They were required to be between 18 and 75 years of age, to have an ECOG performance status of 0 to 2, and to have an estimated survival period of more than 3 months. Prior radiotherapy and surgery were permitted if they were completed at least 4 weeks before entry into the study. All patients were required to have at least one clinically or radiographically measurable lesion, and to have adequate hematologic, renal, and hepatic functions defined as follows: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, serum creatinine $\leq 1.5 \times$ upper normal limit (UNL), total bilirubin $\leq 1.25 \times$ UNL, AST and ALT $\leq 3.0 \times$ UNL, and alkaline phosphatase $\leq 3.0 \times$ UNL. All patients gave their written informed consent to participate in the study, which was approved by the local institutional review boards.

Patients were ineligible if they had a history of a different type of cancer other than NSCLC, atrial or ventricular arrhythmia or congestive heart failure, preexisting peripheral neuropathy more than grade 1, acute myocardial infarction within 6 months before enrollment, active infections, or any other underlying medical condition that would interfere with participation in the study.

2) Treatment scheme

Genexol[®] was supplied by Samyang Co. as a concentrated sterile solution for intravenous administration in a 5 ml vial containing 30 mg of paclitaxel in polyoxyethylated castor oil and dehydrated alcohol (Cremophor EL/ethanol).

The patients received paclitaxel 175 mg/m² as a 3-hour intravenous infusion, followed by cisplatin 75 mg/m² as an intravenous infusion on day 1. The paclitaxel was always given before the cisplatin administration with the premedication as follows: hydrocortisone 100 mg (or corresponding drugs) IV, pheniramine maleate 45.5 mg (or corresponding drugs) IV, cimetidine 300 mg (or corresponding drugs) IV and ondansetron 8 mg (or corresponding drugs) IV 30 minutes before the paclitaxel. Before and after the cisplatin administration, adequate hydration procedure was taken to reduce the nephrotoxicity.

The treatment was repeated every 3 weeks and the chemotherapy planned for up to 6 cycles if the disease progression, or substantial toxicity did not develop. After 6 cycles, the test drugs were administered continuously at the discretion of investigator.

3) Dose modification and discontinuation

For patients not achieving a hematologic recovery on the scheduled day of treatment, a complete blood count (CBC) was taken weekly until the ANC reached $1.5 \times 10^9/L$, and the platelet count reached $100 \times 10^9/L$. If a hematologic recovery was still not achieved by day 35 of treatment, the patient was withdrawn from the study.

In the event of hematologic and severe non-hematologic

toxicities occurring at any time during treatment, the patients was treated at three dose levels (0, -1, -2) as follows: patients were started at dose level 0, in which they received paclitaxel, 175 mg/m², plus cisplatin, 75 mg/m². If the ANC $\leq 0.5 \times 10^9/L$ persisted for more than 1 week, the platelet count $\leq 25 \times 10^9/L$ persisted for more than 1 week, pyogenic neutropenia or infection, severe hemorrhage, grade 3 neurotoxicity, or grade 3 mucositis was observed, the dose of paclitaxel was decreased to level -1 (paclitaxel 140 mg/m²). If the above toxicities occurred after dose reduction, the dose of paclitaxel was decreased to level -2 (paclitaxel 112 mg/m²). If other major toxicities occurred, excluding alopecia, nausea and vomiting greater than grade 2, administration of the drugs were discontinued. Administration of the drugs were also discontinued if they had symptomatic arrhythmia or an atrioventricular block (except first degree), grade 4 neurotoxicity, or grade 3 neurotoxicity that was not reversible within 2 weeks after dose reduction.

4) Efficacy and toxicity assessment

A pretreatment evaluation was performed within 3 weeks of the therapy initiation, including full history, physical examination, CBC, biochemical screening profile, chest X-ray, chest CT and site-specific imaging. The definition of a response followed the standard WHO criteria, and the duration of a response was calculated from the first day of treatment to the date of first observation of a progressive disease, or the last examination for the responding patients. The time to progression was calculated from the first day of treatment to the date of first observation of a progressive disease, or the last examination, and the overall survival from the first day of treatment to the date of death or the last follow-up.

All the patients who received at least one cycle of chemotherapy were considered evaluable for toxicity. The toxicities observed were evaluated according to the National Cancer Institute-Common Toxicity Grading (NCI-CTG) criteria in relation to the test drug. The severity of any toxicities not defined in the NCI-CTG were graded as 1=mild, 2=moderate, 3=severe or 4=very severe.

5) Statistical analysis

Analysis of the clinical efficacy was performed according to an intent-to-treat analysis. Kaplan-Meier estimates were used in the analysis of all the time-to-event variables (duration of response, time to progression, overall survival), and the 95% confidence interval (CI) for the median time to event was computed.

The actually delivered dose-intensity (DI) was calculated as the ratio of the total dose (expressed in milligrams) per meter squared actually received by the patient, divided by the actual total treatment duration expressed in weeks. In this calculation, the end of treatment duration was considered to be 3 weeks after day 1 of the last cycle of chemotherapy. The relative DI was calculated as the ratio of the actually delivered DI to the DI planned by the protocol.

The SPSS (SPSS, Inc, Chicago, IL) for Windows packages were used for the statistical computation.

RESULTS

1) Patient characteristics (Table 1)

A total of 27 patients were entered from 5 hospitals between Jan 2001 and Aug 2001. Of these 27 patients, 2 were considered ineligible: one because of an incorrect diagnosis (small cell lung cancer), and the other because of brain metastasis. Therefore 25 patients received the test drugs. The majority of patients had an ECOG performance status of 1, and the majority of the tumors were adenocarcinomas or squamous cell carcinomas. The median time from the initial diagnosis to the study was 11 days (range, 2 to 51 days).

2) Efficacy

Among the 25 patients who received the test drugs, 4 were not considered evaluable for their response: 2 stopped treatment

Table 1. Patient characteristics

Characteristics	No (%)
Total number of patients	25
Age (years)	
Median	58
Range	40 ~ 72
Sex	
Male	14 (56%)
Female	11 (44%)
Smoking history	
No	10 (40%)
Yes	15 (60%)
Performance status ECOG	
ECOG 0	2 (8%)
ECOG 1	23 (92%)
Pathology	
Adenocarcinoma	14 (56%)
Squamous cell carcinoma	8 (32%)
Others	3 (12%)
Stage	
III	7 (28%)
IV	18 (72%)

Table 2. Response to combination chemotherapy

Response	No (%)
Complete response	0
Partial response	9 (36%)
Stable disease	7 (28%)
Progressive disease	5 (20%)

Of 25 eligible patients, 4 patients could not be evaluated. Percentages were calculated on an intent-to-treat basis.

after 1 cycle of chemotherapy, with no evidence of disease progression, due to voluntary withdrawal, and 2 stopped after 2 cycles, with no evaluation of response, due to the patients' refusals.

According to an intent-to-treat analysis, 9 patients (36%) achieved a partial response, 7 (28%) a stable disease, and 5 (20%) progressed. Thus, the overall response rate was 36% (95% CI, 17 to 55%) (Table 2).

The median follow-up duration was 12.3 months (range, 0.5 to 18.1 months). The median duration of response was 7.8 months (95% CI, 6.6 to 9.0 months). The median time to progression and overall survival were 7.4 months (95% CI, 5.3 to 9.5 months) and 13.3 months (95% CI, 10.8 to 15.9 months), respectively, for the intent-to-treat population (Fig. 1, 2).

3) Drug delivery

A total of 106 cycles of chemotherapy were given to the 25 patients. The median number of cycles received was four, ranging from one to six cycles. Twelve of the patients received the full six cycles of chemotherapy. A dose reduction of the paclitaxel was required in only one patient, due to fever with grade IV neutropenia, but a dose reduction of the cisplatin was

Fig. 1. Time to progression curve

Fig. 2. Overall survival curve

not required. A treatment delay was needed in 8 cycles with patients. The relative DIs for the paclitaxel and cisplatin were both 0.97.

4) Toxicity

The treatment was generally well tolerated, and there were no toxic deaths. The hematologic toxicity was mild (Table 3). Grade 3/4 neutropenia appeared in 10% of the total cycles, and one episode of neutropenic fever occurred, but no neutropenic sepsis was observed. Grade 3/4 thrombocytopenia was not noted, and grade 3/4 anemia occurred in 4% of the cycles (grade 3 only).

The non-hematologic toxicity was also mild (Table 4). There

Table 3. Hematologic toxicity of combination chemotherapy (106 cycles)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	15 (14%)	5 (5%)	2 (2%)	1 (1%)
Neutropenia	13 (12%)	16 (15%)	7 (7%)	3 (3%)
Anemia	60 (57%)	27 (25%)	4 (4%)	—
Thrombocytopenia	2 (2%)	1 (1%)	—	—

Table 4. Non-hematologic toxicity of combination chemotherapy

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Emesis	7 (28%)	10 (40%)	2 (8%)	—
Diarrhea	1 (4%)	1 (4%)	1 (4%)	—
Alopecia	3 (12%)	15 (60%)	1 (4%)	—
Myalgia	10 (40%)	6 (24%)	—	—
Peripheral neuropathy	12 (48%)	5 (20%)	—	—
LFT* abnormality	6 (24%)	2 (8%)	1 (4%)	—

*Liver function test

were two patients (8%) with grade 3 emesis, one (4%) with grade 3 diarrhea, one (4%) with grade 3 alopecia, and one (4%) with grade 3 hyperbilirubinemia. There were no grade 4 non-hematologic toxicities.

DISCUSSION

A cisplatin-containing regimen is considered the choice for chemotherapy in advanced NSCLC as it resulted in a small, but statistically significant, improvement in survival (3~5). Since the 1990's, several new chemotherapeutic agents, such as paclitaxel, docetaxel, gemcitabine, and vinorelbine, have been introduced, and are widely used in advanced NSCLC (4~6). Many phase II and III studies have reported that combination regimens of new agents and a cisplatin were more active, and/or less toxic, than the cisplatin alone or traditional cisplatin-based regimens (4,5). To date, no regimen, among combination regimens of new agents and a cisplatin, have been identified as superior in terms of their efficacy (4~6).

We reported here the result of a phase II clinical trial of a new paclitaxel, Genexol[®] and cisplatin, in patients with NSCLC, to evaluate its efficacy and safety.

We observed a response rate of 36%, with a median duration of response of 7.8 months, in an intent-to-treat analysis. The response rate and the duration of response were not less than the previously reported results for paclitaxel and cisplatin in advanced NSCLC (6,8~15) (Table 5).

The median time to progression, and the overall survival were 7.4 and 13.3 months, respectively, which were no less than the results of the other studies where paclitaxel and cisplatin were used for the treatment of NSCLC (6,8~12,14, 15) (Table 5). The median overall survival and 1-year survival rate were somewhat higher than those of the other studies, but small sample size of this study suggests the possibility of incidental findings.

We observed one patient who experienced a moderate degree of hypersensitivity reaction, accompanied by dyspnea, urticaria, and itching, during the second cycle. After the infusion time

Table 5. Comparison with previous studies in terms of efficacy

Reference No.	Trial type	Paclitaxel dose (mg/m ²)	Cisplatin dose (mg/m ²)	Response rate	Overall survival (months)	1-year survival rate	TTP* (months)
This	II	175 (3) [†]	75	36%	13.3	63%	7.4
6	III	135 (24) [†]	75	22%	7.8	31%	3.4
8	III	175 (3) [†]	80	27%	8.1	30%	4.1
9	III	250 (24) [†]	75	28%	10.0	40%	5.0
9	III	135 (24) [†]	75	25%	9.5	37%	4.0
10	III	175 (3) [†]	80	41%	9.7	43%	5.4
11	II	175 (3) [†]	75	42%	10.0	33%	—
12	II	175 (3) [†]	100	35%	10.0	35%	—
13	II	135 (3) [†]	75	50%	—	—	—
14	II	180 (3) [†]	80	31%	14.8	56%	—
15	II	145 (3) [†]	60	37%	12.5	—	—

*Time to progression, [†] Infusion time (hours)

of Genexol[®] was changed to 24 hours, instead of 3 hours, no further hypersensitivity reaction occurred. A severe hypersensitivity reaction from paclitaxel has been known to develop in 1 to 2% of cases during the 3-hour infusion, and to be satisfactorily managed with conventional strategies for hypersensitivity (16).

Peripheral neuropathy, which is a specific adverse reaction to paclitaxel and cisplatin, was moderate, and no grade 3 toxicity observed.

Neutropenia, at grade 3 or more, was observed in 10% of the total cycles. When the first cycle was only considered, the incidence of neutropenia was 20% (5/25). Seven patients (28%) experienced grade 3/4 neutropenia. In the previous studies using 3-hour infusion of paclitaxel and cisplatin for NSCLC, it was reported that 50% of the patients underwent grade 3 or more neutropenia (8,10,11,14). In contrast, with a 24-hour infusion, more frequent neutropenia at grade 3 or more (6,9) were observed. We observed one episode of neutropenic fever, but no treatment-related mortality was noted.

As a whole, no considerable toxicity, other than that previously reported for paclitaxel and cisplatin regimens, was observed in this study.

CONCLUSIONS

A combination of new paclitaxel, Genexol[®] and cisplatin is an effective and well-tolerated regimen for patients with NSCLC.

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