Phase II Study of Carboplatin and Weekly Paclitaxel in Advanced Non-small Cell Lung Cancer

MEGUMI NAKADATE1,6, KOICHI YAMAZAKI1,6, JUN KONISHI1,6, ICHIRO KINOSHITA2,6, NORIAKI SUKOH3,6, MASAO HARADA3,6, KENJI AKIE4,6, SHIGEAKI OGURA4,6, TAKASHI ISHIDA5,6, MITSURU MUNAKATA5,6, HIROTOSHI DOSAKA-AKITA2,6, HIROSHI ISOBE3,6 and MASAHARU NISHIMURA1,6

1First Department of Medicine, Hokkaido University School of Medicine, Sapporo;
2Department of Medical Oncology, Hokkaido University Graduate School of Medicine, Sapporo;
3Department of Respiratory Disease, National Hospital Organization Hokkaido Cancer Center, Sapporo;
4Department of Respiratory Medicine, Sapporo City General Hospital, Sapporo;
5Department of Pulmonary Medicine, Fukushima Medical School, Fukushima;
6Hokkaido Lung Cancer Clinical Research Group, Japan

Abstract. Background: The optimal schedule of taxane administration has been an area of active interest in several clinical trials. Patients and Methods: To evaluate the efficacy and toxicity of carboplatin and weekly paclitaxel combination chemotherapy, a phase II study was conducted for chemo-naive, advanced non-small cell lung cancer (NSCLC) patients. Patients received paclitaxel 100 mg/m² on days 1, 8 and 15, and carboplatin with the target dose of area under the curve of 6 on day 1 every 28 days. Results: Forty patients were enrolled. Overall response rate and survival at one year by intent-to-treat analyses was 35% and 57.5%, respectively. The median survival time was 12.2 months. Twenty-two patients (56%) had grade 3 or greater neutropenia. Grade 3 sensory and motor neuropathy were seen in one patient (3%). Conclusion: Carboplatin and weekly paclitaxel combination chemotherapy is an active and feasible regimen for patients with advanced NSCLC.

Lung cancer represents a major health problem in the industrialized world. In the United States, approximately one third of male cancer deaths and one quarter of female cancer deaths are secondary to lung cancer (1). In Japan, lung cancer is the most common mortality site from malignant neoplasms in men, and secondary mortality site in women, which accounted for approximately 22.3% and 12.3%, respectively, of all malignant neoplasms in 2003 (2). Efforts at early detection and treatment have been frustrating to date and, hence, the overall prognosis remains poor.

Non-small cell lung cancer (NSCLC) constitutes approximately 80% of all cases of lung cancer and most cases are not candidates for curative surgery at the time of diagnosis. The median survival of patients with stage IIIB and IV NSCLC ranges from 6 to 8 months and only 20-30% survive for 1 year.

Paclitaxel (Taxol; Bristol-Myers Squibb) is a clinically active anticancer drug that inhibits cell division by promoting the assembly of microtubules and stabilizing the tubulin polymers in the G2/M phase of the cell cycle (3). Consequently, paclitaxel causes the formation of abnormal bundles of microtubules during the cell cycle, and has antiangiogenic activity (4). Carboplatin (Paraplatin; Bristol-Myers Squibb) is a less toxic analogue of cisplatin, which is thought to inhibit DNA synthesis by forming interstrand and intrastrand cross-linking of DNA molecules.

The Eastern Cooperative Oncology Group (ECOG) compared third-generation chemotherapy regimens, which included cisplatin and paclitaxel, cisplatin and gemcitabine, cisplatin and docetaxel, and carboplatin and paclitaxel. No differences in survival were noted, and carboplatin and paclitaxel had the lowest degree of toxicity. Therefore, the ECOG selected carboplatin and paclitaxel as its reference regimen (5). The combination of carboplatin (area under the curve (AUC)=6) and paclitaxel (225 mg/m²) administered every 3 weeks is the most commonly used regimen in the United States. The response rate with this regimen ranges from 17% to 25%, with median survival times averaging approximately 8 months (5-7). While the
regimen is well tolerated, it is associated with a 10% to 17% incidence of grade 3 neuropathy (5-7).

Weekly regimens of paclitaxel and carboplatin were developed in an effort to increase efficacy and reduce toxicity. Belani et al. studied various regimens and found that paclitaxel (paclitaxel 100 mg/m² weekly for 3 of 4 weeks) plus carboplatin (AUC = 6 on day 1) was the most effective and least toxic combination (8). For example, this regimen had a response rate of 32%, a median survival time of 49 weeks, and a 1-year survival rate of 47%. Comparisons with previous studies using the standard 3-weekly schedule of paclitaxel and carboplatin indicated that the weekly regimens achieved favorable efficacy with a highly tolerable toxicity profile (8).

In Japan, a phase I trial of carboplatin plus weekly paclitaxel was conducted by the Kansai Clinical Oncology Group in advanced NSCLC, and the recommended dose of paclitaxel was 70 mg/m² on days 1, 8 and 15 in combination with carboplatin (AUC=6) on day 1 of a 4-week cycle (9). The dose of paclitaxel was much lower than in Belani et al.’s study. In order to reconfirm the dose of paclitaxel, a phase I trial of weekly paclitaxel (on days 1, 8 and 15) with carboplatin (on day 1) of a 4-week cycle for advanced NSCLC was previously conducted (10). The maximum tolerated dose was reached at 110 mg/m² for weekly paclitaxel with the dose limiting toxicity, infection with neutropenia. A dose of 100 mg/m² was concluded as the recommended phase II dose. Based on this preceding study, the present phase II study was conducted to assess the efficacy and safety of monthly carboplatin combined with weekly paclitaxel in patients with chemo-naive advanced NSCLC.

**Patients and Methods**

**Eligibility.** The eligibility criteria included the following: pathologically and/or cytologically proven NSCLC, cancer unresectable and unsuitable for radical radiotherapy, no prior treatment for lung cancer and/or no prior pleurodesis from using antitumor drugs, stage IIIIB or IV disease that was not curable with chemoradiation treatment as the first choice, having measurable lesions, an ECOG performance status of 2 or less, age between 20 and 75 years old, adequate organ function (leukocyte count ≥4,000 mm⁻³, hemoglobin level ≥9.5 g/dl, platelet count ≥100,000 mm⁻³, total bilirubin level <1.5 mg/dl, AST/ALT ≤twice normal, serum creatinine level ≤1.5 mg/dl, PaO₂ ≥70 torr), life expectancy of 3 months or more, and written informed consent. Exclusion criteria included serious concomitant systemic disorders, unstable angina and/or myocardial infarction and/or congestive heart failure detected within 3 months, uncontrolled or self-injected-insulin diabetes mellitus, uncontrolled hypertension, active infection, interstitial pneumonia or pulmonary fibrosis defined on chest X-ray, uncontrolled pleural effusion, active gastric ulcer, other active malignancy, history of severe hypersensitivity or hypersensitivity to the study drug or polioxyetilene, severe superior vena cava syndrome, local recurrence after surgery, regular use of steroid, and pregnant or lactating woman. Patients who had undergone previous surgery for their lung cancer were eligible. Previous radiotherapy was permitted, provided it was not given to the target lesion used to assess response. This trial was reviewed by the Protocol Review Committee of the Hokkaido Lung Cancer Clinical Research Group and the Institutional Review Board of all participating institutions.

**Treatment schedule.** Patients received paclitaxel at a dose of 100 mg/m² on days 1, 8 and 15 every 28 days. Paclitaxel was administered as an intravenous (i.v.) infusion over 1 h with premedication including 20 mg of dexamethazone, 50 mg of diphenhydramine, and 50 mg of ranitidine, administered i.v. in principle 30 min before therapy (11, 12). Carboplatin was administered on day 1 every 28 days over a 1 h infusion with the target dose of AUC=6 modeled after the method developed by Calvert et al. (13). Glomerular filtration rate (GFR) was substituted by the calculated value using Cockcroft’s equation (14). Patients with a response or stable disease continued treatment for four cycles unless there was disease progression or unacceptable toxicity.

**Dose modification.** With regard to dose modification within a cycle, the paclitaxel was skipped on day 8 and/or day 15 if the leukocyte count was <2,000 mm⁻³, absolute neutrophil count was <1,000 mm⁻³, the platelet count was <75,000 mm⁻³ on the basis of the blood counts, fever >38°C, ECOG performance status 3 or more within 24 h of the day of scheduled treatment, and/or any grade 3/4 non-hematological toxicities, except appetite loss, nausea and vomiting.

The subsequent course of chemotherapy begun after confirmation of leukocytes ≥3,000 mm⁻³, an absolute neutrophil count ≥1,500 mm⁻³, platelet count ≥100,000 mm⁻³, total bilirubin level <2.0 mg/dl, AST/ALT ≤twice normal, serum creatinine level ≤1.5 mg/dl, no grade 3/4 non-hematological toxicity, no active infection, and/or ECOG performance status less than 3.

Doses of carboplatin and paclitaxel were modified based on observed toxicity. The dose of paclitaxel was reduced by 10 mg/m² and the AUC of carboplatin was reduced by 1 and 0.5 at every cycle (Table I) if the following toxicities were seen: 3 days or more of grade 4 neutropenia, fever >38°C and/or infection with more than grade 2 neutropenia, platelet count <20,000 mm⁻³, >grade 2 non-hematological toxicity excluding anorexia, nausea, vomiting and/or omitting paclitaxel on days 8 and/or 15 in the previous cycle. If there was grade 2 or more neurotoxicity, only the dose of paclitaxel was reduced by 10 mg/m². If bone marrow recovery was delayed for more than 2 weeks, therapy was terminated.

**Table I. Dose modifications.**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Carboplatin (AUC)</th>
<th>Paclitaxel (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>-1</td>
<td>5</td>
<td>90</td>
</tr>
<tr>
<td>-2</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>-3</td>
<td>3.5</td>
<td>70</td>
</tr>
</tbody>
</table>

Abreviation: AUC, area under the curve.
Evaluation Criteria in Solid Tumors (15). A complete response (CR) required disappearance of all evidence of disease for at least 4 weeks. A partial response (PR) required a 30% or greater decrease in the diameters of all measured lesions for at least 4 weeks. Progressive disease (PD) was defined as a >20% increase in the diameters of the measured lesions or the appearance of any new lesions. Stable disease (SD) was defined as not meeting the criteria for PR or PD. Time to progression was measured from the day of registration to death or the date of objective disease progression. Overall survival was measured from the day of registration to death. The Kaplan-Meier technique (16) was used for both. Toxicity was evaluated according to National Cancer Institute Common Toxicity Criteria version 2 (17).

Statistical consideration. The study was planned according to Simon’s minimax design (18) to compare a response probability of 20% under the null hypothesis and 40% under the alternative hypothesis, with a 5% alpha level and a power of 80%. With this design, the accrual of 40 patients was required.

Results

Patient characteristics. A total of 40 patients were enrolled into this phase II study from March 2004 to December 2004. The demographics of these patients are listed in Table II. One patient was not treated because of rapid deterioration of the disease after registration. Thirty-nine patients who received at least one cycle of chemotherapy were evaluable for response and toxicity. Of all 40 patients, at baseline, the median age was 64 years (range, 44-74 years). Twenty-seven patients were male and the baseline PS score included 50% with a PS of 0, 42.5% with a PS of 1 and 7.5% with a PS of 2. Tumor histology included 32 patients with adenocarcinoma, 4 patients with squamous cell carcinoma, 2 patients with large cell carcinoma and 2 patients with tumors of unclassified histology. There were 8 patients with stage IIIIB disease, 31 patients with stage IV disease and 1 patient with recurrence after surgery. Five patients were not assessable for response. One patient was not treated, 1 patient went abroad, 1 patient deteriorated rapidly and 2 patients were removed from the study by the treating physicians.

Treatment administration. Treatment administration is shown in Table III. Out of the 39 patients treated, 29 completed at least two cycles of therapy (74.4%), and 11 completed four cycles of therapy (28.2%). A total of 98 cycles of treatment were administered (median, 2; range, 1-4). Five patients were treated with four cycles (12.8%) without dose modification. In the 39 patients receiving one cycle of therapy, an average dose of 261 mg/m² of paclitaxel and AUC=6 of carboplatin were administered. In the 29 patients receiving the second cycle of therapy, an average dose of 253 mg/m² and AUC=5.8 of carboplatin were administered. In the 19 patients receiving the third cycle and 11 patients receiving the fourth cycle of therapy, an average dose of 239 mg/m² and 221 mg/m² of paclitaxel, and AUC=5.4 and 5.0 of carboplatin, respectively, were administered.

Toxicity. The number and rates of hematological and non-hematological toxicities associated with this combined chemotherapy are shown in Table IV. All thirty-nine patients who received at least 1 cycle of chemotherapy were assessed for toxicity. Toxicity ≥ grade 3 in the patients included neutropenia (56%), leukopenia (46%), anemia (26%), thrombocytopenia (13%), anorexia (15%), nausea (15%), vomiting (10%), infection without neutropenia (10%), sensory neurotoxicity (3%) and motor neurotoxicity (3%). No treatment-related death was observed.
Response and survival. Table V shows the response and survival data of the present study. The intent-to-treat analysis shows a 35% (14/40) response rate (RR), with 27.5% (11/40) achieving SD, 25% (10/40) experiencing PD, and 12.5% (5/40) being non-assessable for response. Per protocol and among the 35 assessable patients, there were 14 PRs (40.0%), 11 SDs (31.4%), and 10 PDs (28.6%), to give an objective RR of 40.0% with no complete responses.

The survival curve is shown in Figure 1. The median survival time was 12.2 months (95% confidence interval, 8.4-16.1 months) and the estimated 1-year survival rate was 57.5%. The median time to progression was 5.2 months (95% confidence interval, 3.6-6.9 months). The median duration of response for the 14 responders was 4.4 months (range, 2.3 to 8.9 months).

Discussion

In the present study, a phase II trial of weekly paclitaxel (100 mg/m² on days 1, 8, and 15) in combination with carboplatin (AUC=6 on day 1) was conducted for patients with advanced NSCLC. The 100 mg/m² dose of paclitaxel was greater than the dose previously reported by the Kansai Clinical Oncology Group (70 mg/m²) (9), while it was equivalent to the dose reported in Belani et al.’s study (8). As a result, a 35% response rate, median survival time of 372 days and a 57.5% estimated 1-year survival rate were achieved. Regarding toxicity, although ≥ grade 3 leukopenia and neutropenia were seen in almost half the patients, there was no infection with neutropenia. Sensory or motor neurotoxicity ≥ grade 3 was as low as 3% and there were no treatment related deaths. Taken together, the combination of carboplatin and weekly paclitaxel is an active and feasible regimen, even at 100 mg/m² of paclitaxel, for Japanese NSCLC patients.

Table VI summarizes the phase II studies of carboplatin and weekly paclitaxel for chemo-naïve NSCLC patients. Compared with the previous reports by the Kansai Clinical Oncology Group (9, 19), the response rate of the present study was lower, while the median survival and 1-year survival rates of the present study were almost equivalent to those studies. Moreover, the response rate, median survival and 1-year survival of the present study were almost equivalent to other previous reports (8, 20, 21).

Initially, Belani et al. reported a randomized phase II study comparing 3 different schedules of weekly paclitaxel and carboplatin. The combination of carboplatin (AUC=6, on day 1) with weekly paclitaxel (100 mg/m²/week on days 1, 8,
and 15) every 4 weeks resulted in a better therapeutic index than the other two schedules (8). However, a recent report of a phase III trial comparing this regimen with the standard 3-weekly carboplatin and paclitaxel failed to show a survival or response benefit of the weekly approach, although the incidence of neuropathy and arthralgia were lower with the weekly regimen (22). In the trial design, 4 cycles of therapy were delivered, followed by maintenance weekly low-dose paclitaxel or observation in responding patients. The maintenance therapy with weekly paclitaxel might have contributed to overall improvement in outcome in both arms of the study. On the other hand, in another randomized phase II trial comparing 3-weekly carboplatin/paclitaxel with carboplatin and weekly paclitaxel in a 3-week cycle in advanced non-small cell lung cancer, patients on the 3-weekly regimen experienced more severe myalgia/arthralgia and the survival experiences seemed unfavorable compared with the weekly regimen (median survival time and 1-year survival rates were 6.6 vs. 8.7 months and 16% vs. 27%, respectively) (21). Further studies will be required to determine the survival benefit of the combination therapy of carboplatin with weekly paclitaxel for patients with NSCLC.

Since paclitaxel is a phase-specific agent, frequent or continuous schedules offer the greatest theoretical benefit (23). Depending on the duration of exposure, cellular cytotoxicity can be achieved at relatively low concentrations of this drug, around 0.01 μmol/L (24, 25). On the other hand, myelosuppression was related to the duration of exposure to plasma paclitaxel concentrations above 0.05 μmol/L (26). In our previous study of weekly paclitaxel, the interval during which the plasma paclitaxel concentration remained above 0.01 μmol/L was more than 144 hours, and above 0.05 μmol/L was 27.9±4.11 hours (10). Thus, a weekly schedule of paclitaxel extended the duration above 0.01 μmol/l and above 0.05 μmol/l of the plasma paclitaxel concentration, as compared to a 3-weekly regimen. The pharmacokinetic data of paclitaxel might explain the favorable response rate of a weekly schedule, despite weakened intensity of carboplatin every 4 weeks, compared with the 3-weekly regimen. In addition to exposure duration issues, cellular cytokinetic considerations imply that frequent exposure to cytotoxic agents with brief intervals between exposures affords less opportunity for the emergence and regrowth of drug-resistant cell clones (27). On the other hand, grade 3/4 neutropenia was seen in more than half of the patients in the present study, which although compatible with the pharmacokinetic data, was tolerable.

Weekly administration of paclitaxel is dose-intense, but also has a favorable toxicity profile (27, 28). Non-hematological toxicity was less common with weekly paclitaxel regimens. In the present study, only 1 patient (3%) developed grade 3 peripheral neuropathy. Peripheral neuropathy may begin as soon as 24 to 72 hours after treatment with higher doses (>250 mg/m²) but usually occurs only after multiple courses at conventional doses. Clinically peripheral neurotoxicity occurs at cumulative doses of around 1500 mg/m² given at weekly doses of more than 110 mg/m² (29, 30). Thus, weekly paclitaxel in combination with carboplatin was a favorable regimen with respect to neuropathy, compared to the standard 3-weekly regimen.

In conclusion, the combination of carboplatin and weekly paclitaxel is an active and feasible regimen in patients with NSCLC. Furthermore, the weekly approach is an acceptable alternative to the conventional 3-weekly regimen of paclitaxel and carboplatin.

References

---

Table VI. Phase II studies of carboplatin and weekly paclitaxel in chemo-naive NSCLC patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Carboplatin AUC (mg/m²)</th>
<th>Paclitaxel (mg/m²)</th>
<th>No. of patients</th>
<th>Response rate (%)</th>
<th>Median survival time</th>
<th>1-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belani CP (8)</td>
<td>6</td>
<td>100</td>
<td>132</td>
<td>32</td>
<td>49 weeks</td>
<td>47</td>
</tr>
<tr>
<td>Kansai clinical oncology group (19)</td>
<td>6</td>
<td>70</td>
<td>46</td>
<td>52.2</td>
<td>395 days</td>
<td>51.1</td>
</tr>
<tr>
<td>Fabi A (20)</td>
<td>6</td>
<td>100</td>
<td>42</td>
<td>42</td>
<td>14 months</td>
<td>59</td>
</tr>
<tr>
<td>Socinski MA (21)</td>
<td>6</td>
<td>75</td>
<td>80</td>
<td>36</td>
<td>8.7 months</td>
<td>27</td>
</tr>
<tr>
<td>The present report</td>
<td>6</td>
<td>100</td>
<td>40</td>
<td>35</td>
<td>12.2 months</td>
<td>57.5</td>
</tr>
</tbody>
</table>

Abbreviations: NSCLC, non-small cell lung cancer; AUC, area under the curve.


Received April 26, 2006
Accepted June 22, 2006