A Phase II Randomized Study of Paclitaxel Plus Carboplatin or Cisplatin against Chemo-Naive Inoperable Non-small Cell Lung Cancer in the Elderly

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Abstract: Paclitaxel plus carboplatin (CAR) or cisplatin (CIS) has shown activity in the treatment of advanced non-small cell lung cancer (NSCLC). Our aim was to determine whether paclitaxel plus platinum is an appropriate regimen for chemo-naive NSCLC in patients aged 70 years or older. Patients were randomized into paclitaxel plus CAR or paclitaxel plus CIS treatment arms. Treatment consisted of paclitaxel 160 mg/m² and carboplatin at AUC = 6 (predicted using measured clearances and the Calvert formula) IV infusion on day 1 every 3 weeks, or paclitaxel 160 mg/m² and cisplatin 60 mg/m² IV on day 1 every 3 weeks. In total, 81 patients were enrolled from September 2000 to February 2005, including 40 who received CAR treatment and 41 who received CIS treatment. In all, 152 cycles of CAR (median, four cycles per patient) and 172 cycles of CIS (median, four cycles per patient) were given. Each arm had one complete response and 15 partial responses to the treatment, with overall response rates of 40% and 39%, respectively. Myelosuppression was mild in both arms, and there was no statistical difference between the two arms. Alopecia (P < 0.001), peripheral neuropathy (P = 0.017), and fatigue (P < 0.001) were more severe in the CIS treatment arm than in the CAR treatment arm. Median time to disease progression was 6.6 months in the CAR arm and 6.9 months in the CIS arm. Median survival time was 10.3 months in the CAR arm and 10.5 months in the CIS arm. In conclusion, paclitaxel plus CAR treatment is feasible in elderly patients and has similar activity. However, paclitaxel plus CAR had less non-hematological toxicity than paclitaxel plus CIS.

Key Words: Carboplatin, Cisplatin, Elderly, Non-small cell lung cancer, Paclitaxel.

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immunotherapy; with a performance status of 0 to 2 on the World Health Organization (WHO) scale; with bidimensionally measurable disease; and with an adequate bone marrow reserve and a white blood cell count $\geq 4000/mm^3$, platelets $\geq 100,000/mm^3$, and hemoglobin $\geq 10$ g/dl, were eligible for the study. Patients with signs or symptoms of brain metastases, inadequate liver function (serum bilirubin $> 1.5$ times and alanine aminotransferase/aspartate transaminase $> 3$ times upper limit normal), or inadequate renal function (serum creatinine $> 1.5$ times upper limit normal) were excluded from the study. Patients were randomized into the paclitaxel plus carboplatin (CAR) or paclitaxel plus cisplatin (CIS) treatment arm by an outside center not involved in the study, with staging and performance status as stratification factors.

Initial work-up included the documentation of the patient’s history, a physical examination, and a performance score. A complete blood cell count, urinalysis, serum biochemistry profile, electrocardiograph, chest roentgenography, whole-body bone scan, brain computed tomographic scan, and chest computed tomographic scan (including liver and adrenal glands) were also performed.

Paclitaxel 160 mg/m$^2$ was given as a 3-hour IV infusion, followed by carboplatin at AUC = 6 (predicted using measured clearances and the Calvert formula) IV for 1 hour on day 1 of every 3 weeks in the CAR arm, or paclitaxel 160 mg/m$^2$ IV on day 1 and cisplatin 60 mg/m$^2$ IV for 1 hour on day 1 of every 3 weeks in the CIS arm. The maximal number of cycles that were planned for patients enrolled in the study was six, unless there was disease progression, intolerable toxicities, or patient refusal. All patients received dexamethasone (10 mg IV at $-12$ and $-6$ hours), cimetidine (300 mg IV), and diphenhydramine (50 mg IV) before paclitaxel administration. In addition, adequate hydration, and granisetron and metopropramide were administered in the CIS and CAR arms, respectively, as anti-emetics.

For dose adjustments in the subsequent cycle, a 50% reduction in the initial dose of paclitaxel and an 80% reduction in the initial dose of carboplatin or cisplatin were instituted when the patient experienced grade 4 neutropenia or thrombocytopenia. This more marked than usual dose modification was based on the concept of “do no harm and safety first” with respect to the elderly patients. Subsequent escalation of the original dosage was allowed providing the patient tolerated the doses given at the 50% level, followed by the 75% level. In the area of non-hematological toxicities, patients were excluded from further study if they experienced grade 3 or worse neuropathy.

A complete blood cell count was repeated before every injection and during the nadir period (day 9 to day 11 after chemotherapy). Serum biochemistry analysis was performed before every course of chemotherapy and during the course, if clinically indicated. The study was designed to enroll at least 35 qualified patients in each arm. This calculation assumes that the true moderate to severe (grades 2 to 4) toxicity induced by the more toxic regimen was 10% higher than that of a safer regimen in terms of specific toxicity items; peripheral neuropathy was the primary end point in the present study. The use of this specific toxicity item, instead of response rate, which is usually used as the primary end point in phase II studies, was based on the fact that paclitaxel plus carboplatin or cisplatin has been found to have similar efficacy or survival benefit in non-elderly patients with NSCLC in studies such as the ECOG-1594. Thus, in the present study, we focused on toxicity that could be more severe in degree or more frequent in elderly patients, instead of the response rate. We assumed that the safer regimen had 15% grade 2 to 4 peripheral neuropathy and that the toxic regimen had 25% grade 2 to 4 peripheral neuropathy, with a power of 0.85 and a $P$ value of 0.05, and that each treatment group required at least 35 qualified patients.

Response and study drug-related toxicities were evaluated according to WHO criteria. Patient responses were reevaluated after three cycles of treatment and when the patient was off study. All adverse events were recorded regardless of whether they were thought to be the result of chemotherapy.

Overall survival and time to disease progression were analyzed using the Kaplan-Meier estimation method. Time to disease progression was calculated from the date of initiation of treatment to the date of disease progression or death. If disease progression had not occurred by the time of this analysis, progression-free survival was considered censored at the time of the last follow-up. Survival time was measured from the date of initiation of treatment to the date of death. If death had not occurred, survival time was considered censored at the last follow-up. All comparisons of response rates and toxicity incidences were performed by using the ANOVA test.

## RESULTS

From September 2000 to February 2005, 81 patients were entered into the study, including 40 patients randomly assigned into the CAR arm and 41 into the CIS arm. Patient ages ranged from 70 to 87 years, with mean ages of 76 years in the CAR arm and 75 years in the CIS arm. The clinical characteristics of these patients are listed in Table 1. There was no significant difference in clinical characteristics between the two arms of treatment, except that all female patients were randomized into the CIS arm. Under the principle of intent to treat, all patients were assessable for toxicity profile and treatment response.

A total of 324 cycles of paclitaxel-based treatment was administered, including 152 cycles in the CAR arm and 172 cycles in the CIS arm. The mean and median number of treatment cycles per patient was 3.8 and 4 in the CAR arm and 4.2 and 4 in the CIS arm, respectively (Table 1).

After three cycles of treatment, each arm had one patient with a complete response and 15 patients with a partial response, with an overall response rate of 40% (95% CI, 24.8%–55.2%) in the CAR arm and 39% in the CIS arm (95% CI, 24.1%–53.9%) (Table 2). The disease control rate (patients with a complete response, partial response, and stable disease) was higher in the CIS arm ($P = 0.225$).

The median time to disease progression was 6.6 months in the CAR arm and 6.9 months in the CIS arm (Figure 1). The median survival of the entire study population was 10.5 months (95% CI, 3.3–17.7 months), with a 1-year survival
rate of 48.6%. The median survival time was 10.3 months in the CAR arm and 10.5 months in the CIS arm. The 1-year survival rate was 49.7% in the CAR arm and 47.1% in the CIS arm (Figure 2).

The treatment-related toxicities were mild in degree, mainly hematological, and easy to manage (Table 3). The incidence of WHO grade 3 or 4 hematological toxicity was: leukopenia 15%, anemia 12.5%, and thrombocytopenia 7.5% in the CAR arm; and leukopenia 4.9%, anemia 9.8%, and thrombocytopenia 2.4% in the CIS arm. There was no statistically significant difference in hematological toxicities between the two treatment arms. There were several other non-hematological toxicities (Table 4). Peripheral neuropathy, fatigue, and alopecia were more severe in the CIS arm.

**DISCUSSION**

It has been shown that age has an impact on the treatment of NSCLC. The use of paclitaxel plus cisplatin has proven to be a well-tolerated and quite active regimen, with a 1-year survival of approximately 40% in stage IV patients aged less than 70 years. Paclitaxel plus non-cisplatin combinations, such as paclitaxel plus carboplatin, may prove to be reasonable alternatives for patients with NSCLC who cannot tolerate cisplatin and for patients with a compromised performance status and organ function, such as renal function impairment or congestive heart failure. The response rate and median survival in phase II studies of paclitaxel plus carboplatin in patients aged less than 70 years ranged from 30 to 45% and 38 to 55 weeks, respectively. The response rate in the CAR arm $(P = 0.017, <0.001, \text{and} <0.001, \text{respectively})$, especially grade 2 peripheral neuropathy, which occurred in 53.7% of patients receiving CIS treatment but in only 17.5% of patients in the CAR arm.
and median survival of our elderly patients who received paclitaxel plus cisplatin or carboplatin were also within the range of studies involving younger patients.

Paclitaxel plus cisplatin was found to have a better response rate than paclitaxel plus carboplatin in the four-arm ECOG-1594 study, although there was no statistically significant difference. In contrast, less toxicity and slightly better median and 1-year survival was found in patients receiving paclitaxel plus carboplatin treatment, although also with no statistically significant difference. Most patients in the ECOG-1594 study were younger than ours, and their performance status was better than that of ours. However, our patients had a better response rate and survival. A Japan-SWOG common-arm analysis of paclitaxel plus carboplatin treatment also showed a significant difference in toxicity profiles and survival between Japanese and American patients. The racial difference that seems to exist between Caucasian and East Asian populations requires further pharmacogenomic study.

The largest phase III randomized trial comparing paclitaxel plus carboplatin treatment with paclitaxel plus cisplatin treatment was performed by Rosell et al.22 The study enrolled 618 patients who received paclitaxel 200 mg/m² plus either carboplatin at AUC = 6 or cisplatin 80 mg/m² once every 3 weeks. In this study, 71% of patients were aged less than 65 years, with a mean age of 58 years, and 83% of patients had a performance status of 0 or 1. In contrast, the mean age of our patients was 76 years, and all patients were 70 years or older; only 56% of our patients had a performance status of 0 or 1. Median survival was 9.8 months in the cisplatin arm and 8.5 months in the carboplatin arm in their study (P < 0.05), whereas it was 10.5 and 10.3 months, respectively, in our study. The response rate was also higher in our study than theirs. There was no difference in peripheral neuropathy in their study. Although we used a lower dose of paclitaxel and cisplatin, peripheral neuropathy occurred more frequently in our patients who received cisplatin than carboplatin, which implies that cisplatin is not a good choice for elderly patients when paclitaxel is used. However, this combination is appropriate for younger patients, as reported by Rosell et al.22

Phase II studies (such as ours) usually have a higher response rate than phase III studies, and older patients frequently have a better response rate than younger patients when same regimens are used. Other phase II studies using paclitaxel plus carboplatin, either weekly or every 3 weeks, also showed that this regimen is relatively well tolerated in elderly patients, with a response rate of approximately 25 to 45% and a median survival time of 9.2 to 14.7 months.23–27 In addition, a study from Korea with attenuated doses of paclitaxel and carboplatin (135 mg/m² and AUC = 5, respectively, every 3 weeks) also showed a good response rate of 40% and median survival of 8.6 months.28

Based on previous studies and this study, treatment with paclitaxel plus cisplatin induces more peripheral neuropathy than paclitaxel plus carboplatin.10,13 This side effect is more marked in elderly patients who probably already have preexisting systemic disease that exacerbates and worsens the situation. In the present study, we reduced the paclitaxel dosage in both arms and used a relatively low dose of

### TABLE 3. Hematological Toxicity Per Patient

<table>
<thead>
<tr>
<th>Toxicity grade</th>
<th>Paclitaxel + carboplatin (%)</th>
<th>Paclitaxel + cisplatin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1-2</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>27.5</td>
<td>57.5</td>
</tr>
<tr>
<td>Anemia</td>
<td>10</td>
<td>77.5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>87.5</td>
<td>5</td>
</tr>
</tbody>
</table>

*ANOVA test.

### TABLE 4. Non-Hematological Toxicity per Patient

<table>
<thead>
<tr>
<th>Toxicity grade</th>
<th>Paclitaxel + carboplatin (%)</th>
<th>Paclitaxel + cisplatin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>80</td>
<td>12.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>92.5</td>
<td>5</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>45</td>
<td>32.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>65</td>
<td>12.5</td>
</tr>
<tr>
<td>Alopecia</td>
<td>57.5</td>
<td>35</td>
</tr>
</tbody>
</table>

*ANOVA test.

*Worst of any course, n = 40 in the paclitaxel plus carboplatin arm, n = 41 in the paclitaxel plus cisplatin arm.

**Two patients in the paclitaxel plus carboplatin arm had leukopenic fever and recovered.**
cisplatin, 60 mg/m² every 3 weeks, which had been demonstrated to be safe and effective in Chinese patients,²⁹ with the intention of preventing the occurrence of severe treatment-related toxicities, especially neuropathy. The patients in the CIS arm still experienced more fatigue and peripheral neuropathy than those in the CAR arm, whereas other parameters showed similar therapeutic indexes in both arms. Peripheral neuropathy and fatigue or weakness are issues deserving of attention because these effects easily disable or impair the normal daily activities of elderly patients, who generally already have some difficulty with mobility and are likely to be disabled even more by peripheral neuropathy and weakness. Although weakness can improve within 2 weeks after stopping chemotherapy, neuropathy can last for more than 4 months in our patients. Thus, it is not appropriate to use paclitaxel with cisplatin in elderly patients.

Other regimens commonly used for elderly patients include vinorelbine alone or with gemcitabine. Vinorelbine single-agent treatment is considered a standard regimen for elderly chemo-naïve patients with NSCLC, after the Elderly Lung Cancer Vinorelbine Italian Study Group and Multi-center Italian Lung Cancer in the Elderly Study studies showed its effectiveness.³₀,³¹ In addition, neuropathy is not the main problem when using this agent.

In conclusion, carboplatin, instead of cisplatin, should be used in elderly patients when combining paclitaxel treatment, because peripheral neuropathy and fatigue occur more frequently in elderly patients receiving paclitaxel plus cisplatin treatment.

REFERENCES