Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan

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Background: To compare the efficacy and toxicity of three platinum-based combination regimens against cisplatin plus irinotecan (IP) in patients with untreated advanced non-small-cell lung cancer (NSCLC) by a non-inferiority design.

Patients and methods: A total of 602 patients were randomly assigned to one of four regimens: cisplatin 80 mg/m2 on day 1 plus irinotecan 60 mg/m2 on days 1, 8, 15 every 4 weeks (IP); carboplatin AUC 6.0 min x mg/mL (area under the concentration–time curve) on day 1 plus paclitaxel 200 mg/m2 on day 1 every 3 weeks (TC); cisplatin 80 mg/m2 on day 1 plus gemcitabine 1000 mg/m2 on days 1, 8 every 3 weeks (GP); and cisplatin 80 mg/m2 on day 1 plus vinorelbine 25 mg/m2 on days 1, 8 every 3 weeks (NP).

Results: The response rate, median survival time, and 1-year survival rate were 31.0%, 13.9 months, 59.2%, respectively, in IP; 32.4%, 12.3 months, 51.0% in TC; 30.1%, 14.0 months, 59.6% in GP; and 33.1%, 11.4 months, 48.3% in NP. No statistically significant differences were found in response rate or overall survival, but the non-inferiority of none of the experimental regimens could be confirmed. All the four regimens were well tolerated.

Conclusion: The four regimens have similar efficacy and different toxicity profiles, and they can be used to treat advanced NSCLC patients.

Key words: carboplatin, cisplatin, gemcitabine, irinotecan, non-small-cell lung cancer, paclitaxel, randomized phase III study, vinorelbine

Introduction

Nearly 60 000 patients in Japan died of lung cancer in 2004, and the mortality rate is still increasing [1]. Even old-generation cisplatin-based chemotherapy provides a survival benefit and symptom relief in patients with inoperable non-small-cell lung cancer (NSCLC) [2]. Several anticancer agents including irinotecan, paclitaxel, docetaxel, gemcitabine, and vinorelbine, were developed in the 1990s and most of them have mechanisms of action that differ from those of the old-generation agents [3–7]. The combinations of platinum and these new agents developed in the 1990s are more useful against advanced NSCLC than old-generation combination chemotherapy, and doublets of platinum and new-generation anticancer agents are considered standard chemotherapy regimens for advanced NSCLC, although no consistent standard regimen has yet been established [8–17].

Two phase III studies comparing cisplatin plus irinotecan (IP) with cisplatin plus vindesine for advanced NSCLC have been conducted in Japan [18, 19]. Fukuoka et al. [20] reported the results of a combined analysis of the 358 eligible stage IV patients in these studies. They carried out a multivariate analysis using the Cox regression model with adjustment for well-known prognostic factors, and the Cox regression analysis demonstrated that treatment with IP was one of significant independent favorable factor. Based on their data, we selected IP for the reference arm in our study.

The Ministry of Health, Labour and Welfare of Japan approved the prescription of paclitaxel, gemcitabine, and...
vinorelbine for NSCLC in 1999 and requested a phase III study to confirm the efficacy and safety of these agents. The Japanese investigators and the pharmaceutical companies decided to conduct a four-arm randomized phase III study for NSCLC, the so-called FACS, Four-Arm Cooperative Study. The purpose of the study was to compare the efficacy and toxicity of three platinum-based combination regimens, carboplatin plus paclitaxel (TC), cisplatin plus gemcitabine (GP), cisplatin plus vinorelbine (NP), with IP as the reference arm.

**patients and methods**

**patient selection**

Patients with histologically and/or cytologically documented NSCLC were eligible for participation in the study. Each patient had to meet the following criteria: clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy, such as malignant pleural effusion, pleural dissemination, malignant pericardial effusion, or metastatic lesion in the same lobe), at least one target lesion > 2 cm, no prior chemotherapy, no prior surgery and/or radiotherapy for the primary site, age 20–74 years, Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, adequate hematological, hepatic and renal functions, partial pressure of arterial oxygen (paO₂) > 260 torr, expected survival > 3 months, able to undergo first course treatment in an inpatient setting, and written informed consent. The study was approved by the Institutional Review Board at each hospital. Written informed consent was obtained from every patient.

**treatment schedule**

All patients were randomly assigned to one of the four treatment groups by the central registration office by means of the minimization method. Stage, PS, gender, lactate dehydrogenase (LDH) and albumin values, and institution were used as adjustment variables. The first group received the reference treatment, 80 mg/m² of cisplatin on day 1 and 60 mg/m² of irinotecan on days 1, 8, and 15, and the cycle was repeated every 4 weeks. The second group received 200 mg/m² of paclitaxel (Bristol-Myers K.K., Tokyo, Japan) over a 3-h period followed by carboplatin at a dose calculated to produce an area under the concentration–time curve of 6.0 min × mg/mL on day 1 and the cycle was repeated every 3 weeks. The third group received 80 mg/m² of cisplatin on day 1 and 1000 mg/m² of gemcitabine (Eli Lilly Japan K.K., Kobe, Japan) on days 1, 8 and the cycle was repeated every 3 weeks. The fourth group received 80 mg/m² of cisplatin on day 1 and 25 mg/m² of vinorelbine (Kyowa Hakko Kogyo Co. Ltd., Tokyo, Japan) over a 3-h period followed by carboplatin at a dose calculated to produce an area under the concentration–time curve of 6.0 min × mg/mL on day 1, and the cycle was repeated every 3 weeks. Each treatment was repeated for three or more cycles unless the patient met the criteria for progressive disease or experienced unacceptable toxicity.

**response and toxicity evaluation**

Response was evaluated according to the Response Evaluation Criteria in Solid Tumors, and tumor markers were excluded from the criteria [21]. Objective tumor response in all responding patients was evaluated by an external review committee with no information on the treatment group. Toxicity grading criteria in National Cancer Institute Common Toxicity Criteria Ver 2.0 were used to evaluate toxicity.

**quality of life assessment**

Quality of life (QoL) was evaluated by means of the Functional Assessment of Cancer Therapy—Lung (FACT-L) Japanese version and the QoL Questionnaire for Cancer Patients Treated with Anticancer Drugs (QoL-ACD), before treatment, immediately before the second cycles of chemotherapy, and 3 and 6 months after the start of treatment [22–24].

**statistical analysis and monitoring**

The primary end point of this study was overall survival (OS), and the secondary endpoints were response rate, response duration, time to progressive disease (TTD), time to treatment failure (TTTF), adverse event, and QoL. The 1-year survival rate of the control group in this study was estimated to be 63% based on the data in published papers, and the 1-year survival rate in the other treatment group was expected to be 50%. The lower equivalence limit for 1-year survival rate was set as $-10\%$. The criterion for the non-inferiority of each treatment was a lower limit of the two-sided 95% confidence interval (CI) of the 1-year survival rate of treatment minus that of control larger than the lower equivalence limit. Because the non-inferiority of each treatment versus the control was to be evaluated independently, a separate null hypothesis was stated for each treatment, and for that reason no multiple comparison adjustment was included in the study. Based on the above conditions and binomial distribution, 135 patients were needed per arm for a one-sided Type I error of 2.5% and 80.0% power. In view of the possibility of variance inflation due to censoring, the sample size was set at 600 (150 per arm).

Central registration with randomization, monitoring, data collection, and the statistical analyses were independently carried out by a contract research organization (EPS Co., Ltd, Tokyo, Japan).

**results**

**patient characteristics**

From October 2000 to June 2002, a total of 602 patients were registered by 44 hospitals in Japan. All patients had been followed up for > 2 years, and 447 patients had died as of June 2004. Of the 602 patients registered, 151 were allocated to the reference treatment, IP, and 150, 151, and 150 patients were allocated to TC, GP, and NP, respectively. Since 10 patients did not receive chemotherapy and 11 patients were subsequently found to be ineligible, 592 patients were assessable for toxicity and 581 patients were assessable for efficacy. Four patients did not receive chemotherapy due to electrolytic disorder, fever, symptomatic brain metastases, and rapid tumor progression in IP, two patients due to refusal and pneumonia in TC, four patients due to lower WBC counts (two patients), rapid tumor progression, and nephritic syndrome in NP. Two patients were ineligible due to wrong stage in IP, two patients were wrong stage and one patient had double cancer in TC, two patients were wrong diagnosis, one patient had massive pleural effusion, one patient received prior chemotherapy in GP, one patient had no target lesions in NP, Age, gender, PS, stage, and LDH and albumin values were well balanced in each arm (Table 1). Fewer patients with adenocarcinoma and more patients with squamous cell carcinoma were, however, entered in three experimental arms than in IP.

**objective tumor response and response duration**

Objective tumor response is shown in Table 2. Forty-five partial responses occurred in the 145 assessable patients in the reference arm, IP, for an objective response rate of 31.0% with a median response duration of 4.8 months. The response rate and median response duration were 32.4% and 4.0 months in TG, 30.1% and 3.5 months in GP, and 33.1% and 3.4 months in NP. The response rates in TC, GP, and NP were not statistically different from the rate in IP according to the results of the $\chi^2$ test.
OS, TTP disease, and TTTF

OS and TTP are shown in Figure 1. Median survival time (MST), the 1-year, and 2-year survival rate in IP were 13.9 months, 59.2%, and 26.5%, respectively. The MSTs, 1-year, and 2-year survival rates were, respectively, 12.3 months, 51.0%, and 25.5% in TC; 14.0 months, 59.6%, and 31.5% in GP; and 11.4 months, 48.3%, and 21.4% in NP. The lower limits of the 95% CI of the difference in 1-year survival rate between IP and TC (−19.6%), GP (−10.9%), and NP (−22.3%) were below −10%, which was considered the lower equivalence limit (Table 2). Thus, the results did not show non-inferiority in three experimental regimens compared with reference treatment. Median TTP and median TTTF were 4.7 and 3.3 months, respectively in IP. Median TTP and TTTF were, respectively, 4.5 and 3.2 months in TC, 4.0 and 3.2 months in GP, and 4.1 and 3.0 months in NP. There were no statistical differences in either TTP or TTTF in TC, GP, or NP, compared with IP according to the results of the generalized Wilcoxon test (Table 2).

hematologic and non-hematologic toxicity

In IP, 47.6% and 83.7% of patients developed grade 3 or worse leukopenia and neutropenia, respectively (Table 3). The incidences of grade 3 or worse leukopenia (33.1%, \( P = 0.010 \)) and neutropenia (62.9%, \( P < 0.001 \)) were significantly lower in GP than in IP. The incidence of grade 3 or worse leukopenia (67.1%, \( P < 0.001 \)) was significantly higher in NP than in IP. Grade 3 or worse thrombocytopenia developed in 5.4% of the patients in IP, and the incidence was significantly higher in GP (35.1%, \( P < 0.001 \)). The incidence of febrile neutropenia in IP was 14.3%, and was significantly lower in GP (2.0%, \( P < 0.001 \)).

Grade 2 or worse nausea, vomiting, anorexia, and fatigue occurred in 60.5%, 51.0%, 65.3%, and 38.8%, respectively, of the patients in IP. The incidences of grade 2 or worse nausea (TC: 25.0%, \( P < 0.001 \), NP: 47.3%, \( P = 0.022 \)), vomiting (TC: 22.3%, \( P < 0.001 \), NP: 36.3%, \( P = 0.011 \)), and anorexia (TC: 32.4%, \( P < 0.001 \), NP: 49.3%, \( P = 0.005 \)) were significantly lower in TC and NP than in IP. Grade 2 or worse diarrhea was

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**Table 1.** Patient characteristics and treatment delivery

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin + irinotecan</th>
<th>Carboplatin + paclitaxel</th>
<th>Cisplatin + gemcitabine</th>
<th>Cisplatin + vinorelbine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessable patients</td>
<td>145</td>
<td>145</td>
<td>146</td>
<td>145</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>97/48</td>
<td>99/46</td>
<td>101/45</td>
<td>101/44</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>62 (30–74)</td>
<td>63 (33–74)</td>
<td>61 (34–74)</td>
<td>61 (28–74)</td>
</tr>
<tr>
<td>PS (0/1)</td>
<td>44/101</td>
<td>44/101</td>
<td>45/101</td>
<td>45/100</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>121</td>
<td>104</td>
<td>108</td>
<td>109</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>16</td>
<td>31</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Others</td>
<td>8</td>
<td>10</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Stage (IIIB/IV)</td>
<td>31/114</td>
<td>28/117</td>
<td>30/116</td>
<td>26/119</td>
</tr>
<tr>
<td>No. of cycles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.0 ± 1.3</td>
<td>3.5 ± 1.5</td>
<td>3.2 ± 1.2</td>
<td>3.1 ± 1.3</td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Range</td>
<td>1–7</td>
<td>1–10</td>
<td>1–7</td>
<td>1–8</td>
</tr>
</tbody>
</table>

PS, performance status; SD, standard deviation.

**Table 2.** Survival, TTP, TTTF, response rate, and response duration

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median survival, months</th>
<th>1-year survival (%)</th>
<th>Difference in 1-year survival from IP</th>
<th>2-year survival (%)</th>
<th>TTP (median), months</th>
<th>TTTF (median), months</th>
<th>Response rate (%)</th>
<th>Response duration (median), months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin + irinotecan</td>
<td>145</td>
<td>13.9</td>
<td>59.2</td>
<td>−</td>
<td>26.5</td>
<td>4.7</td>
<td>3.3</td>
<td>31.0</td>
<td>4.8 (n = 45)</td>
</tr>
<tr>
<td>Carboplatin + paclitaxel</td>
<td>145</td>
<td>12.3</td>
<td>51.0</td>
<td>−8.2% (95% CI −19.6% to 3.3%)</td>
<td>25.5</td>
<td>4.5 (( P = 0.355 ))</td>
<td>3.2 (( P = 0.282 ))</td>
<td>32.4 (( P = 0.801 ))</td>
<td>4.0 (n = 47)</td>
</tr>
<tr>
<td>Cisplatin + gemcitabine</td>
<td>146</td>
<td>14.0</td>
<td>59.6</td>
<td>0.4% (95% CI −10.9% to 11.7%)</td>
<td>31.5</td>
<td>4.0 (( P = 0.170 ))</td>
<td>3.2 (( P = 0.567 ))</td>
<td>30.1 (( P = 0.868 ))</td>
<td>3.5 (n = 44)</td>
</tr>
<tr>
<td>Cisplatin + vinorelbine</td>
<td>145</td>
<td>11.4</td>
<td>48.3</td>
<td>−10.9% (95% CI −22.3% to 0.5%)</td>
<td>21.4</td>
<td>4.1 (( P = 0.133 ))</td>
<td>3.0 (( P = 0.091 ))</td>
<td>33.1 (( P = 0.706 ))</td>
<td>3.4 (n = 48)</td>
</tr>
</tbody>
</table>

\( ^a \)Compared with IP by the generalized Wilcoxon test.

\( ^b \)Compared with IP by the \( \chi^2 \) test.

CI, confidence interval; IP, cisplatin plus irinotecan; TTP, time to progressive disease; TTTF, time to treatment failure.
significantly less frequent in TC (6.8%), GP (8.6%), and NP (11.6%) than in IP (48.3%, \( P < 0.001 \)). The incidences of grade 2 or worse sensory neuropathy (16.9%, \( P < 0.001 \)), arthralgia (21.6%, \( P < 0.001 \)), and myalgia (17.6%, \( P < 0.001 \)) were significantly higher in TC than in IP. Grade 2 alopecia occurred in 30.6% of the patients in IP, and its incidence was significantly higher in TC (44.6%, \( P = 0.013 \)) and significantly lower in GP (15.2%, \( P = 0.001 \)) and NP (8.9%, \( P < 0.001 \)). Grade 2 injection site reactions were more frequent in NP (26.7%) than in IP (4.8%, \( P < 0.001 \)).

A total of five patients died of treatment-related toxicity: three in IP (cerebral hemorrhage, interstitial pneumonia, acute circulatory failure/disseminated intravascular coagulation: 2.0%), one in TC (acute renal failure: 0.7%), and one in NP (pulmonary embolism: 0.7%).

**second-line treatment**

Data on second-line treatment, but not third-line or later treatment, was available in this study, and they showed that...
60%–74% of the patients received chemotherapy and 6%–9% received thoracic irradiation as second-line treatment (Table 4). The percentages of patients in each treatment group who received second-line chemotherapy were not significantly different ($P = 0.081$).

### quality of life

The details of the QoL analysis will be reported elsewhere. No statistically significant difference in global QoL was observed among the four treatment groups based on either the FACT-L Japanese version or the QoL-ACD. Only the physical domain evaluated by QoL-ACD was significantly better in TC, GP, and NP than in IP.

### discussion

Many randomized phase III studies have compared platinum-plus-new-agent doublets in NSCLC, but, this is the first to evaluate the efficacy of an irinotecan-containing regimen in comparison with other platinum-plus-new-agent doublets in NSCLC [14–17]. Although non-platinum-containing chemotherapy regimens are used as alternatives, doublets of platinum and a new-generation anticancer agent, such as TC, GP, and NP, are considered standard chemotherapy regimens for advanced NSCLC worldwide [13–17, 25]. Although the non-inferiority of none of the three experimental regimens could be confirmed in this study, no statistically significant differences in response rate, OS, TTP, or TTTF were observed between the reference regimen and the experimental regimens. All four platinum-based doublets have similar efficacy against advanced NSCLC but different toxicity profiles. Nevertheless, IP was still regarded as the reference regimen in this study because the non-inferiority of none of the three experimental regimens could be confirmed.

OS in this study was relatively longer than previously reported. The estimated 1-year survival rate in the reference arm was 43%, but the actual 1-year survival rate was 59.2%, much higher than expected. The MSTs reported for patients treated with TC, GP, and NP in recent phase III studies have ranged from 8 to 10 months, and in the present study they were 12.3, 14.0, and 11.4 months, respectively [14–17]. One reason for the good OS in this study was the difference in patient selection criteria, for example exclusion of PS2 patients. Ethnic differences in pharmacogenomics have also been indicated as a possible reason for the good OS in this study [26]. The OS in IP in this study, however, was better than in previous Japanese studies [18, 19]. TTP in this study ranged from 4.0 to 4.7 months, and was similar to the TTP of 3.1–5.5 months reported in the literature [15, 16]. OS not TTP was longer in this study.
Table 4. Second-line treatment

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin + irinotecan</th>
<th>Carboplatin + paclitaxel</th>
<th>Cisplatin + gemcitabine</th>
<th>Cisplatin + vinorelbine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>145 (74%)</td>
<td>145</td>
<td>146 (69%)</td>
<td>145</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>107 (60%)</td>
<td>87 (60%)</td>
<td>101 (69%)</td>
<td>95 (66%)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>11</td>
<td>9</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>15</td>
<td>14</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>24</td>
<td>28</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>9</td>
<td>12</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>15</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Thoracic irradiation</td>
<td>8</td>
<td>10</td>
<td>13</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 4. Second-line treatment

than previously reported, and higher 2-year survival rates, 21.4%–31.5%, were observed in the minimum 2-year follow-up in this study. Second-line or later treatments may affect survival, because docetaxel has been established as standard second-line chemotherapy for advanced NSCLC [27, 28]. Gefitinib is also effective as second-line or later chemotherapy for advanced NSCLC, especially in Asian patients, never smokers and patients with adenocarcinoma [29–32]. The toxicity profile of each treatment differed and the toxicity of all four regimens was well tolerated. Overall QoL was similar in the four platinum-based doublets. Only physical domain QoL evaluated by the QoL-ACD was statistically better in TC, GP, and NP than in IP. This finding is presumably attributable to the fact that diarrhea is a statistically less frequent adverse effect of TC, GP, and NP than of IP.

In conclusion, all four platinum-based doublets had similar efficacy for advanced NSCLC but different toxicity profiles. All the four regimens can be used to treat advanced NSCLC patients in clinical practice.

acknowledgements

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references


