Randomised phase II study of docetaxel/cisplatin vs docetaxel/irinotecan in advanced non-small-cell lung cancer: a West Japan Thoracic Oncology Group Study (WJTOG9803)

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Unfortunately, non-small-cell lung cancer (NSCLC) is a member of the group of neoplastic diseases that is relatively chemoresistant. Recent meta-analyses show that cisplatin-based chemotherapy improves survival (Non-Small Cell Lung Cancer Collaborative Group, 1995), and it is considered a standard treatment for NSCLC. Most cisplatin-based regimens have substantial toxicities that require close monitoring and supportive care. Thus, there is a need to develop active and less toxic chemotherapy regimens that include new active compounds with novel mechanisms of action.

In the 1990s, several new, active therapies with single-agent response rates of 15–30% became available for NSCLC, including irinotecan, docetaxel, paclitaxel, vinorelbine, and gemcitabine. Because irinotecan and docetaxel were approved for NSCLC earlier than the other drugs in Japan, development of regimens containing irinotecan or docetaxel is more advanced. Docetaxel 60 mg m\(^{-2}\) showed good antitumour activity against advanced NSCLC (Kunitoh et al, 1996), and the combination of docetaxel plus cisplatin (DC) is one of the most effective regimens for advanced NSCLC (Rodriguez et al, 2001; Schiller et al, 2002). Studies in Japan included a phase II study in which DC yielded a response rate of 42% (Okamoto et al, 2002), and a phase III study in which DC was associated with better survival than the vindesine and cisplatin (VC) combination (Kubota et al, 2002).

Irinotecan demonstrated activity similar to that of VC in stage IIIb/IV NSCLC (Negoro et al, 2003), and significant longer overall survival time than VC in stage IV NSCLC (Fukuoka et al, 2000). We reported a phase I study of docetaxel plus irinotecan (DI) in patients with advanced NSCLC, in which a promising response rate of 48% and the median survival time of 48 weeks were achieved (Masuda et al, 2000). Thus, DI appeared to be a promising non-cisplatin-containing regimen.

Based on the above findings, we conducted a randomised trial of DC vs DI in patients with advanced NSCLC to compare the respective response rates, survival data, and toxicity profiles of the two regimens. This was a multicentred phase II study.

PATIENTS AND METHODS

Patients

Patients enrolled in this trial had histologically or cytologically confirmed stage IIIb or IV NSCLC. Patients with stage IIIb disease who were not candidates for thoracic radiation and patients with stage IV disease were eligible if they had not received previous therapy, had measurable disease, and had a Life Expectancy of at least 3 months. Additional entry criteria were age ≥ 20 years, performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale, adequate bone marrow function (leucocyte...
Clinical study protocol.

Institutional review board for human experimentation approved were excluded. All patients gave written informed consent, and the history of any malignancy, symptomatic brain metastases, past history of drug allergy reactions, complication by interstitial pneumonitis, massive pleural effusion or ascites, or serious active infection were excluded. Patients with active concomitant or a recent (<3 years) history of any malignancy, symptomatic brain metastases, past history of drug allergy reactions, complication by interstitial pneumonitis, massive pleural effusion or ascites, or serious active infection were excluded. All patients gave written informed consent, and the institutional review board for human experimentation approved the protocol.

Study evaluations

Pretreatment studies included a complete medical history and physical examination, chest X-ray, electrocardiography, computed tomography (CT) scan of the brain and chest, CT or ultrasound examination of the abdomen, and bone scintigraphy. Blood and blood chemistry studies included complete blood count, liver function test, serum electrolytes, serum creatinine, and blood urea nitrogen. Chest X-ray, blood and blood chemistry analyses, and urinalysis were repeated weekly.

Randomisation and treatment schedule

Patients were randomly assigned to receive the DC regimen or the DI regimen by a minimisation method using stage (IIIB/IV) and treatment institution. The DC regimen was consisting of docetaxel 60 mg m⁻² on day 1 and cisplatin 80 mg m⁻² on day 1, and the DI regimen was consisting of docetaxel 60 mg m⁻² as a 60-min intravenous infusion on day 8 and irinotecan 60 mg m⁻² as a 90-min intravenous infusion on days 1 and 8 (Figure 1). Both regimens were repeated every 3 weeks. Participating researchers at each institution decided the amount of fluid replacement and the type of antiemetic therapy to administer. Standard antiemetic regimen was consisting of 5-HT3 receptor antagonist plus 16 mg dexamethasone intravenously on day 1, before cisplatin chemotherapy administration. In the DI arm, standard antiemetic treatment consisted of 5-HT3 receptor antagonist intravenously before chemotherapy administration on days 1 and 8. Patients received at least two treatment cycles, and those with a complete or partial response after two cycles had treatment continued until there was evidence of disease progression, intolerable toxicity, or patient refusal.

Dose modifications

Toxicity assessment was based on the National Cancer Institute – Common Toxicity Criteria version 2.0. Dose levels and treatment schedule were modified to avoid severe adverse effects. Patients receiving DI had the day-8 docetaxel and irinotecan doses postponed to day 15 if any of the following toxicities was present on day 8: leucocyte count <3000 μl⁻¹, platelet count <100 000 μl⁻¹, diarroea consisting of bloody or watery stools, or increased to two or more diarroea within 24 h, abdominal pain rated mild or worse, hepatic toxicity ≥grade 3, or fever >38.5 °C. If these toxicities occurred on day 15 after skipping the day-8 treatment, DI was stopped in that course.

Patients could receive the next treatment course only if the following criteria were met: leucocyte count ≥4000 μl⁻¹, platelet count ≥100 000 μl⁻¹, AST/ALT <2.0 times the upper limit of normal, total bilirubin ≤1.5 mg d⁻¹, and pulmonary function (PaO₂ ≥60 torr). No change was defined as a 25% increase in the sum of the products of the two IL largest perpendicular diameters of all measurable tumours lasting at least 4 weeks and without appearance of any new lesions. No change was defined as a <50% decrease or a <25% increase of tumor lesions for at least 4 weeks with no new lesions.

| Table 1 | Dose modification criteria |
|---|---|---|
| **Toxocities in previous cycle** | Decrease in docetaxel dose (mg/m²) | Decrease in cisplatin dose (mg/m²) | Decrease in irinotecan dose (mg/m²) |
| Grade 4 neutropenia lasting ≥3 days, leucopenia or thrombocytopenia | 10 | 10 | 10 |
| Grade ≥2 neurotoxicity | 10 | 10 | — |
| Grade ≥2 renal toxicity | — | 20 | — |
| Grade ≥2 hepatic toxicity | 10 | — | 5 |
| Grade ≥3 stomatitis | 10 | — | — |
| Grade ≥2 diarrhoea | — | 10 | — |
| Cancellation of day-8 treatment | — | — | 10 |

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![Figure 1](image)
Progressive disease was defined as development of new-lesions or a 25% increase in the sum of the products of the two largest perpendicular diameters of all measurable tumors. Duration of response in patients who achieved complete or partial response was measured from the start of treatment to the date of disease progression.

Statistical methods
Results of this study were evaluated to determine whether the docetaxel plus irinotecan combination warranted further assessment in a phase III trial. Thus, this study was designed to conduct two randomised phase II studies concurrently. We calculated the number of patients required for each of the two studies based on the Fleming’s single-stage procedure (Fleming, 1982). In both studies, we set response rates of 40% as target activity level and 20% as the lowest level of interest with a power of 0.9 at a one-sided significance level of 0.05. As a result, a total of 100 qualified patients were to be enrolled, with 50 patients in each treatment arm. The primary objective was to estimate the response rate to both regimens, particularly to irinotecan plus docetaxel.

Overall survival and progression-free survival were analysed by the Kaplan–Meier method. The overall survival was measured from study entry to death. The progression-free survival was measured from study entry until the day of the first evidence of disease progression. If the disease had not progressed by the time of this analysis, progression-free survival was considered censored at the time of the analysis. All comparisons between patient characteristics, response rates, and toxicity incidences were performed by Pearson’s $\chi^2$ contingency table analysis.

RESULTS

Patient characteristics
From October 1998 to August 1999, 108 patients were assigned to receive DC ($n = 51$) or DI ($n = 57$). Baseline patient characteristics according to treatment arm are shown in Table 2. Patients were well balanced between the two treatment arms in terms of gender, age, performance status, disease stage, and histologic subtypes. There were 23% stage IIIb patients and 74% had adenocarcinoma. All patients were included in the survival evaluation, and all were assessable for antitumor efficacy and toxicity.

Treatment delivery
Patients in both treatment arms received a median of two treatment courses. Two or more courses were delivered to 72.5 and 71.9%, and four courses to 17.6 and 19.1% of patients in the treatment courses. Two or more courses were delivered to 72.5% of patients in the DC arm, and 46 weeks (95% confidence interval: 37–54 weeks), 40 and 18%, respectively, in the DC arm, and 46 weeks (95% confidence interval: 37–54 weeks), 40 and 18%, respectively, in the DI arm. No significant differences were noted between groups in progression-free survival ($P = 0.33$) or overall survival ($P = 0.50$), although there were trends toward higher 1-year and 2-year survival rates in the DC.

Table 3 Overall response to docetaxel/cisplatin (DC) or docetaxel/irinotecan (DI) in patients with stages IIIb/IV non-small-cell lung cancer

| Response | DC ($n = 51$) No. pts | DI ($n = 67$) No. pts |
|----------|-----------------------|-----------------------|
| Complete response | 0 | 0 |
| Partial response | 19 | 18 |
| No change | 23 | 25 |
| Progressive disease | 6 | 14 |
| NE (TRD) | 3 | 0 |
| Response rate | 37.3%* | 31.6%* |
| 95% Confidence intervals | 24.1–51.9% | 19.9–45.2% |

$\text{pts} = \text{patients}; \text{NE} = \text{not evaluable}; \text{TRD} = \text{treatment-related death}. *P = 0.55.$

![Figure 2](https://example.com) Overall survival according to treatment group, calculated by Kaplan–Meier method. Median survival times were 50 weeks for DC (docetaxel plus cisplatin) and 46 weeks for DI (docetaxel plus irinotecan). $P = 0.50$ between treatment groups.

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clinical neuropathy, were mild and occurred with similar frequency in nonhaematologic toxicities, such as hepatic toxicity and peripheral vs in DI than in DC patients (24 X 2). On the other hand, grade 4 diarrhoea occurred significantly more often in the DC than in the DI arm, respectively. There was a higher rate of grade 4 thrombocytopenia in the DC group and 13 patients the DI group received. Leucopenia and neutropenia were the major toxicities in both groups. As expected, emesis and renal toxicity were more prevalent in patients receiving DC, and diarrhoea occurred more frequently with DI.

Cisplatin has played a prominent role in the treatment of NSCLC, despite a relatively unimpressive single-agent response rate and a relatively severe toxicity profile. In 1995, the Non-Small Cell Lung Cancer Collaborative Group published a pivotal meta-analysis of chemotherapy in lung cancer and demonstrated the advantage of cisplatin-based regimens over best supportive care (Non-Small Cell Lung Cancer Collaborative Group, 1995). In the 1990s, third-generation chemotherapeutic agents, including paclitaxel, docetaxel, vinorelbine, gemcitabine and irinotecan, were shown to have higher response rates often coupled with fewer adverse effects (no renal toxicity, no massive dehydration, less emesis, etc.) than cisplatin. For example, single-agent paclitaxel (Ranson et al, 2000), docetaxel (Roszkowski et al, 2000), or vinorelbine (The Elderly Lung Cancer Vinorelbine Italian Study Group, 1999) significantly improved survival compared with best supportive care in patients with advanced NSCLC. Studies of single-agent gemcitabine (Perng et al, 1997) or irinotecan (Negoro et al, 2003) demonstrated a survival benefit comparable to that of second-generation chemotherapy regimens (cisplatin plus vindesine, cisplatin plus etoposide). Based on the above results, we thought that combination chemotherapy consisting of third-generation agents might improve outcome for patients with advanced NSCLC.

Only one published study compared cisplatin-based and noncisplatin-based regimens that included third-generation agents, which were due to febrile neutropenia and sepsis (one of these patients also developed perforation of the oesophagus). No treatment-related deaths occurred in the DI arm. The difference in incidence of treatment-related deaths was not significant.

Second-line chemotherapy was administered to 61 patients (24 DC and 37 DI patients). A total of 22 patients in the DI group received cisplatin-based second-line chemotherapy and five had partial responses to this treatment (overall response rate, 23%). In particular, nine patients were subsequently treated with vinorelbine containing regimen and three patients had a partial response. Only two patients in the DC group received an irinotecan-containing regimen, one of whom had a partial response. Concerning as second-line chest irradiation, 8 patients in the DC group and 13 patients the DI group received.

Toxicity

Haematologic and nonhaematologic toxicities are listed in Tables 4 and 5. Grade 4 leucopenia and neutropenia occurred in a significantly higher percentage of DI than DC patients (leucopenia 16 vs 4%, P < 0.01; neutropenia 61 vs 43%, P < 0.01). On the other hand, there was a higher rate of grade ≥2 thrombocytopenia in the DC than in the DI arm (14 vs 9%, P < 0.01). Rates of anaemia (decrease in haemoglobin) and febrile neutropenia were similar in both groups.

Nonhaematologic toxicities including grade ≥2 nausea (88 vs 51%, P < 0.01), vomiting (39 vs 14%, P < 0.01), and renal toxicity (increased serum creatinine; 12 vs 2%, P < 0.01) were significantly more prevalent in the DC than in the DI arm, respectively. On the other hand, grade ≥2 diarrhoea occurred significantly more often in DI than in DC patients (24 vs 42%, P = 0.01). Other nonhaematologic toxicities, such as hepatic toxicity and peripheral neuropathy, were mild and occurred with similar frequency in both groups.

Table 4 Haematologic toxicity: maximum toxicity grade in any course

| Toxicity/grade | Docetaxel/ cisplatin (% pts) | Docetaxel/ irinotecan (% pts) |
|----------------|-----------------------------|-----------------------------|
| Leucopenia*    | 31                          | 43                          | 26                          |
| Neutropenia*   | 10                          | 31                          | 42                          |
| Anaemia*       | 47                          | 10                          | 46                          |
| Thrombocytopenia** | 10                          | 4                           | 0                           |
| Febrile neutropenia | 20                          | 0                           | 28                          |

P = patients; *P < 0.01 for grade 4; **P < 0.01 for the sum of grades 2, 3, and 4.

Table 5 Nonhaematologic toxicity: maximum toxicity grade in any course

| Toxicity/grade | Docetaxel/ cisplatin (% pts) | Docetaxel/ irinotecan (% pts) |
|----------------|-----------------------------|-----------------------------|
| Diarrhoea*     | 18                          | 26                          | 12                          |
| Nausea*        | 53                          | 33                          | 18                          |
| Vomiting**     | 33                          | 14                          | 0                           |
| Peripheral neuropathy | 2                 | 2                           | 0                           |
| AST increase   | 8                           | 2                           | 7                           |
| ALT increase   | 14                          | 4                           | 9                           |
| ALP increase   | 8                           | 2                           | 4                           |
| Creatinine increase* | 10                          | 0                           | 2                           |

P = patients; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase. *P < 0.01 for the sum of grades 2, 3, and 4.
agents. Georgoulas et al (2001) conducted a randomised study of cisplatin plus docetaxel (CD) vs gemcitabine plus docetaxel (GD) in 441 advanced NSCLC patients. The noncisplatin regimen provided a comparable response rate (CD 32.4%, GD 30.2%) and median survival time (CD 10 months, GD 9.5 months) but with less toxicity. The authors stated that the non-cisplatin GD regimen would likely be more acceptable to patients based on convenience of administration. However, several randomized trials reported at recent international meetings showed slightly shorter survival times with noncisplatin compared with cisplatin-based combinations. Preliminary results of the EORTC-Lung Cancer Group phase III study of cisplatin plus paclitaxel vs cisplatin plus gemcitabine vs paclitaxel plus gemcitabine in 480 patients with advanced NSCLC revealed superior overall survival and progression-free survival with the cisplatin-based regimens (Van Meerbeeck et al, 2001). Moreover, in a recent Italian–Canadian intergroup study of 501 patients comparing gemcitabine plus vinorelbine with cisplatin plus vinorelbine or gemcitabine, the noncisplatin regimen provided only short-term and sporadic advantages in some quality-of-life components, but there were no significant differences in overall and progression-free survival (Gridelli et al, 2002).

The best known noncisplatin platinum-based chemotherapy regimen is the paclitaxel plus carboplatin doublet. A Southwest Oncology Group study compared vinorelbine plus cisplatin with paclitaxel plus carboplatin. No differences in the overall survival or quality of life were noted between the two treatment groups, but toxicity rates were significantly lower in patients who received paclitaxel plus vinorelbine (Chen et al, 2002). Results of a recent ECOG randomised phase III trial evaluating four platinum-based chemotherapy regimens showed no significant differences in the overall survival, while the paclitaxel plus carboplatin combination was less toxic than cisplatin-based chemotherapy (Schiller et al, 2002). Based on these findings, the paclitaxel plus carboplatin regimen is considered a standard therapy for previously untreated patients with advanced NSCLC, with activity comparable to that of cisplatin-based regimens and better tolerability.

The utility of doublet regimens containing third-generation chemotherapeutic agents for advanced NSCLC thus needs to be evaluated against the paclitaxel plus carboplatin combination, and several such studies were reported or are ongoing. The Hellenic Cooperative Oncology Group is conducting a phase III randomised study of paclitaxel plus carboplatin vs paclitaxel plus gemcitabine, and final results indicate comparable activity, toxicity and total cost of the two regimens in patients with inoperable NSCLC (Kosmidis et al, 2002). The Taiwan group conducted a similar study and found that paclitaxel plus carboplatin and paclitaxel plus gemcitabine had similar efficacy in the treatment of NSCLC, but that paclitaxel plus carboplatin was more cost-effective (Chen et al., 2002).

As mentioned in the introductory paragraphs, we conducted a phase I study of docetaxel plus irinotecan (DI) in patients with advanced NSCLC, and had a promising response rate of 48% and median survival time of 48 weeks (Masuda et al, 2000). Although we recommended docetaxel 50 mg m⁻² on day 1 plus irinotecan 50 mg m⁻² on days 1, 8, and 15 in the phase I study, more than half of patients could not receive irinotecan on day 15 because of haematologic toxicities. Accordingly, the day-15 irinotecan dose was omitted and the day-2 docetaxel dose moved to day 8 and increased from 50 to 60 mg m⁻² in this randomised phase II trial.

It has been reported that second-line chemotherapy compared with best supportive care may increase the overall survival in patients with advanced NSCLC, and more studies in this regard are needed. In a recent study in which patients received cisplatin-based chemotherapy followed by docetaxel or supportive care alone, the median survival was significantly longer in the docetaxel-treated patients (Shepherd et al, 2000). In our study, 52% of patients were treated with second-line chemotherapy. Of these, 19 (33%) DI patients received cisplatin-based second-line chemotherapy, five of whom (26%) responded. Thus, cisplatin-based chemotherapy is capable of exerting antitumour activity in patients who have relapsed after having received noncisplatin-containing regimens. Only two patients in the DC group received an irinotecan-containing regimen, one of whom had a partial response. As there were only two patients, we cannot judge whether irinotecan-containing regimen is effective for the patients after having received cisplatin-containing regimen. In conclusion, docetaxel plus irinotecan combinations may be reasonable treatment options for NSCLC patients who cannot tolerate cisplatin. However, as there was no significant difference in the overall survival and no reduction in overall toxicity, DI has not improved on results obtained with DC. Thus, we will not select docetaxel/irinotecan as the experimental regimen in the next phase III study of first-line treatment of advanced NSCLC.

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