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ORIGINAL ARTICLE

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Phase I/II trial of biweekly docetaxel and cisplatin with concurrent thoracic radiation for stage III non-small-cell lung cancer

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Abstract *Objectives*: We conducted phase I and II studies of biweekly docetaxel and cisplatin with concurrent radiotherapy, followed by consolidation chemotherapy with the same drugs in patients with locally advanced, unresectable non-small-cell lung cancer (NSCLC). Our objectives were to define the maximum-tolerated dose and dose-limiting toxicity (DLT) in the phase I study, and to determine the response rate, toxicity, and survival rate at the recommended dose (RD) in the phase II study. *Methods*: Patients with unresectable stage IIIA and IIIB NSCLC were studied. Six to eight cycles of docetaxel and cisplatin were administered at 2-week intervals. In the phase I study, patients received four dose levels: level 1, docetaxel/cisplatin = 30/40 mg/m^2; level 2, 35/40; level 3, 40/40; and level 4, 45/40. Radiotherapy was delivered at a rate of 2 Gy per fraction/day up to a total dose of 60 Gy over the course of 6 weeks, during the first three cycles of chemotherapy. *Results*: DLT comprised neutropenia at level 4 in the phase I study ($n=15$), and level 3 was considered the RD. In the phase II study ($n=46$), two patients had a complete response (4.3%) and 34 had a partial response (73.9%), for an overall response rate of 78.2% [95% CI (66.3–90.2%)]. The survival rate was 69.1% at 1 year and 39.6% at 2 years, with a median survival time of 19.1 months. Leukopenia, neutropenia, anemia, and radiation esophagitis were the most common toxic reactions, with Grade ≥ 3 reactions occurring at rates of 77, 70, 17, and 8%, respectively. *Conclusion*: Biweekly docetaxel and cisplatin with concurrent RT was active and well tolerated in patients with unresectable stage III NSCLC.

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Introduction

Several studies and meta-analyses have demonstrated that chemotherapy combined with radiotherapy improves the outcomes of patients with locally advanced unresectable stage III non-small-cell lung cancer (NSCLC), as compared with radiotherapy alone [1–3]. Full-dose cisplatin-based chemotherapy with concurrent thoracic radiotherapy has produced encouraging results, albeit with relatively severe toxicity. Studies directly comparing concurrent with sequential administration of cisplatin-based chemotherapy plus radiation have shown that concurrent treatment is significantly more effective, but is associated with more severe acute toxic reactions [4, 5].

Studies using preclinical models have shown that docetaxel is a potent radiosensitizer [6, 7]. Docetaxel enhances the sensitivity of cells to radiation primarily during the radiosensitive G_2/M phase of the cell cycle [8]. Studies in rodents suggest that docetaxel also stimulates the infiltration of tumors by immune cells, which then participate in the antitumor action of anticancer drugs, either alone or in combination with radiotherapy [9]. Cisplatin is most often used in patients who concurrently receive radiotherapy. Several phase I/II studies have assessed the therapeutic usefulness of docetaxel and cisplatin with

concurrent thoracic radiotherapy for locally advanced NSCLC. In all of these studies, docetaxel and cisplatin were administered weekly in conjunction with 60 Gy of radiation. The main adverse effects of this regimen were radiation esophagitis and neutropenia [10, 11].

A biweekly regimen of paclitaxel plus gemcitabine has been reported to be well tolerated with minimal hematologic and neurologic toxicity as compared with other weekly regimens of chemotherapy and to have an acceptable response rate and a reasonable median survival time [12].

To further explore the clinical activity of docetaxel and cisplatin, we conducted a phase I/II trial to evaluate safety, toxicity, response, and survival in patients with stage III NSCLC who received biweekly docetaxel and cisplatin plus concurrent thoracic radiation, followed by consolidation chemotherapy with the same drugs.

Patients and methods

Eligibility

Patients with pathologically confirmed, unresectable stage IIIA or IIIB NSCLC were eligible for study. Patients with stage T3N1 disease, malignant pleural effusion, pericardial effusion, or pleural dissemination were excluded. Other eligibility criteria included the following: (1) no previous treatment, including radiotherapy, chemotherapy, and surgery; (2) lesions that could be measured or assessed; (3) an age of 18–75 years; (4) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and (5) a life expectancy of 3 months or longer. Patients also had to have an absolute granulocyte count of $\geq$2,000 per μl, a hemoglobin concentration of $\geq$10 g/dl, a platelet count of $\geq$100,000, and a serum creatine level of $\leq$the upper limit of normal or a 24-h creatinine clearance of at least 50 ml/min. In addition, the results of liver function tests had to be $\leq$2.0 times the upper limit of normal, the PaO_2 in a sample of arterial blood $\geq$70 torr, and the cardiac function normal. Pulmonary function tests of vital capacity, FEV_1, and carbon monoxide diffusing capacity of the lung were also required. Patients were excluded if they had apparent evidence of pulmonary fibrosis on computed tomography (CT) or were women who were pregnant. This study was approved by our institutional review board, and all patients provided their informed consent before enrollment. Before study entry, all patients underwent staging investigations, including physical examination, chest radiography, CT of the chest and abdomen, magnetic resonance imaging of the brain, bone scintigraphy, and fiberoptic bronchoscopy with biopsy.

Phase I study

A phase I study was initially performed to determine the maximum-tolerated doses (MTDs) and recommended doses (RDs) of docetaxel and cisplatin for phase II studies when given with 60 Gy of concurrent thoracic radiotherapy to patients with locally advanced and surgically unresectable NSCLC.

Patients received 6–8 cycles of chemotherapy with docetaxel and cisplatin at 2-week intervals (Fig. 1). First, an intravenous infusion of docetaxel was given over the course of 90 min on day 1. An intravenous infusion of cisplatin (40 mg/m^2) was administered over the course of 1 h on the same day. The dose of docetaxel was escalated in increments of 5 mg/m^2 from 30 to 45 mg/m^2, until dose-limiting toxicity (DLT) was reached (Table 1). Starting with dose level 1, at least three patients were entered per dose level. Once they had all completed one cycle of treatment with no DLT, subsequent patients were entered to receive the next highest dose level. If DLT occurred in one or two of the three patients initially given a particular dose level, then three more patients received the same dose level to define the frequency of that toxicity. If at least four of six patients had DLT, the dose level was defined as the MTD, and no further patients were treated; otherwise, three other patients received the next highest dose level. The RD for the phase II study was the dose level immediately below the MTD. All patients received dexamethasone (8 mg) and a 5-hydroxytriptamine type III receptor blocker for antiemetic therapy.

Dose-limiting toxicity was defined according to the National Cancer Institute Common Toxicity Criteria as $\geq$Grade 3 anemia; Grade 4 thrombocytopenia, neutropenia, or febrile neutropenia lasting 3 days or longer; $\geq$Grade 3 radiation esophagitis; and $\geq$Grade 3 nonhematologic toxicity, including renal, hepatic, neurologic, cardiac, skin, and pulmonary toxicity and excluding alopecia and nausea/vomiting.

Radiation therapy

Chest irradiation also began on day 1 for all patients. Two different radiation target volumes were considered: the initial large-field target volume included the primary and mediastinal lymph nodes, and the boost target volume included the primary, involved nodes ($\geq$10 mm along the short axis). The large-field target volume (40 Gy) was given first, followed by the boost target volume (20 Gy), delivered in a dose of 2 Gy/day 5 days/week for 6 weeks (Fig. 1). The target volume of the primary tumor included the complete extent of the

Day	1	15	29	43	57	71
DOC	↓	↓	↓	↓	↓	↓
CDDP	↓	↓	↓	↓	↓	↓
TRT	2 Gy/day, Total 60 Gy					

Fig. 1 Treatment schedule. *DOC* docetaxel, *CDDP* cisplatin, *TRT* thoracic radiotherapy

Table 1 Dose escalation schedule

Level	Docetaxel (mg/m^2/q2w)	Cisplatin (mg/m^2/q2w)	Pts
1	30	40	3–6
2	35	40	3–6
3	40	40	3–6
4	45	40	3–6

visible primary tumor, as defined radiographically with a 2.0-cm margin around the mass. The target volume of the lymph nodes included the bilateral mediastinal and ipsilateral hilar lymph nodes with a 2.0-cm margin. If involved by tumor, the supraclavicular lymph nodes were irradiated with a 2.0-cm margin. The subcarinal lymph nodes were also irradiated if involved by tumor; the field was extended inferiorly to 3.0 cm below the carina. All hematologic and nonhematologic toxic reactions were recorded weekly. All radiation treatment records were sent to the Kyoto Prefectural University of Medicine Affiliate Network data management center, where they were reviewed for quality assurance.

Phase II study

The objectives of the phase II study were to assess the response rate, toxicity, and survival rate in patients receiving the same regimen of concurrent chemoradiotherapy at the RD.

Response and toxicity

During treatment, complete blood counts and serum chemical examinations were done two or three times a week; urinalysis and chest radiography were performed at least weekly; and chest CT was done monthly. Toxicity was graded according to the ECOG common toxicity criteria. Acute esophageal and pulmonary toxicity due to radiation was graded according to the Radiation Therapy Oncology Group (RTOG) criteria. After treatment, the patients underwent physical examinations, comprising mainly chest radiography or CT, at 1- to 3-month intervals for the first 2 years and at 6-month intervals subsequently. Response was evaluated on the basis of the results of clinical examinations and chest CT scans. Response was defined as (1) a complete response (CR) if all target lesions disappeared and (2) a partial response (PR) if the sum of the longest diameters of target lesions decreased by at least 30%. Response had to be maintained for at least 4 weeks with no lesion recurrence. Stable disease (SD) was defined as less than a 30% reduction or less than a 20% increase in the sum of the longest diameters of target lesions, maintained for 8 weeks or longer.

Dose adjustments and evaluations during treatment

Before each administration of the study treatment, the dose was adjusted. If the neutrophil count was less than 1,000 per μl, the platelet count was less than 70,000 per μl, or ≥Grade 2 nonhematologic toxicity other than nausea/vomiting and alopecia occurred, subsequent chemotherapy was delayed until the neutrophil count was more than 1,000 per μl, the platelet count was more than 70,000 per μl, or nonhematologic toxicity other than nausea/vomiting and alopecia resolved to ≤Grade 1. If Grade 3 or 4 radiation esophagitis developed, or the PaO_2 dropped by 10 torr from the baseline value, radiation was withheld until radiation esophagitis resolved to ≤Grade 2, or the PaO_2 returned to within 10 torr from the baseline value. If febrile Grade 3 neutropenia, Grade 4 neutropenia, or Grade 4 thrombocytopenia occurred, radiation was withheld until the neutrophil count was at least 1,000 per μl and the platelet count was at least 70,000 per μl. If febrile Grade 3 neutropenia, Grade 4 hematologic toxicity, or Grade 3 or 4 nonhematologic toxicity other than nausea/vomiting and alopecia occurred, the dose of docetaxel was reduced by 5 mg/m^2 in the following cycle.

Statistical analysis

Overall survival was defined as the interval between the start of therapy to death or the last follow-up evaluation. The survival curve was calculated by the Kaplan–Meier method (Fig. 1).

Results

Patients' characteristics

Between June 2000 and May 2002, 15 patients were enrolled in the phase I study, and between November 2002 and October 2004, 46 patients were enrolled in the phase II study. In the phase I study, the patients comprised 12 men and 2 women, with a median age of 64 years (range 36–75 years). Five (33%) patients had adenocarcinoma, nine had (60%) squamous cell carcinoma, and one (7%) had mucoepidermoid carcinoma. The ECOG performance status was 0 in eight patients and 1 in seven; one patient had stage IIIA disease, and 14 had stage IIIB disease. Patients' characteristics in the phase II study are shown in Table 2. Eleven patients had stage IIIA disease, and 35 had stage IIIB disease.

Phase I study

Toxicity

At dose level 1, there was one episode of Grade 3 leukopenia. At dose level 2, one of three patients had Grade 3 neutropenia. At dose level 3, two of three patients had Grade 3 neutropenia. At dose level 4, two of the first three patients had Grade 4 neutropenia, and three additional patients received the same dose level. Four of the six patients had Grade 4 neutropenia, thus defining the

Table 2 Patients' characteristics (phase II, $n=46$)

	Number of patients (%)
Sex	
Male/female	38/8 (82.6/17.4)
Age	
Median	63
Range	36–75
Performance status	
0/1	26/20 (56.5/43.5)
Body weight loss (/6 months)	
≥5%/<5%	6/40 (13.0/87.0)
Histology	
Adenocarcinoma	18 (39.1)
Squamous cell carcinoma	23 (50.0)
Large cell carcinoma	1 (2.2)
Not specified	4 (8.7)
Stage	
IIIA/IIIB	11/35 (23.9/76.1)

Table 3 Treatment delivery (phase II, $n=46$)

	Number of patients (%)
Total dose of radiotherapy	
Median	57.8
Range	20–60
60 Gy	42 (91.3)
<60 Gy	4 (8.7)
Delay in radiotherapy[a]	
Median, days	4.6
Range, days	0–24
0 day	24 (57.1)
1–5 days	7 (16.7)
6–15 days	6 (14.3)
≥15 days	5 (11.9)
Number of chemotherapy	
6–8	34 (73.9)
≤5	12 (26.1)

[a] In the 42 patients who received a full dose of 60 Gy

DLT. Dose level 4 was determined to be the MTD, and dose level 3 was used as the RD for the phase II study. None of 15 patients had Grade 3 or 4 nonhematologic toxicity.

Response

Among 15 patients in phase I study, 1 (6.7%) had a CR, 12 (80%) had a PR, and 2 (13.3%) had SD.

Phase II study

Administered dose

Of the 46 eligible patients, 42 received the full dose of 60 Gy irradiation. The median dose was 57.8 Gy (range 20–60 Gy). Of the 42 patients who received the full dose, 18 patients required a rest from radiation because of neutropenia ($n=13$), radiation esophagitis ($n=4$), or radiation pneumonitis ($n=1$). In these patients, treatment was delayed 0–24 days, with a median delay of 4.6 days. Of the 46 eligible patients, 34 (73.9%) received 6–8 cycles of biweekly docetaxel and cisplatin (Table 3).

Toxicity

Toxicity is described in Table 4. Leukopenia was the most clinically significant toxicity and occurred in conjunction with neutropenia. Grade 3 or 4 leukopenia or neutropenia was observed in 35 (77%) and 32 (70%) patients, respectively. As for nonhematologic toxicity, Grade 3 or 4 radiation esophagitis occurred in four patients (8%).

Response and survival

Among the 46 patients evaluated, two (4.3%) had a CR and 34 (73.9%) had a PR, for an overall response rate of 78.2% [95% CI (66.3–90.2%)]. Eight (17.4%) patients had SD, and two (4.3%) had progressive disease. The survival rate was 69.1% at 1 year and 39.6% at 2 years. The median survival time was 19.1 months (Fig. 2).

Table 4 Toxicity (phase II, $n=46$)

Grade	2	3	4
Hematological toxicity			
Leukopenia	8 (17)	26 (57)	9 (20)
Neutropenia	9 (20)	19 (42)	13 (28)
Anemia	23 (50)	6 (13)	2 (4)
Thrombocytopenia	1 (2)	1 (2)	0 (0)
Nonhematological toxicity			
Esophagitis	16 (35)	2 (4)	2 (4)
Pneumonitis	15 (33)	1 (2)	0 (0)
Pleural effusion	10 (22)	1 (2)	0 (0)
Liver dysfunction	3 (7)	1 (2)	0 (0)
Renal dysfunction	0 (0)	0 (0)	0 (0)

Values in parentheses are in %

Pattern of failure

Twenty-one patients had disease failure. Distant metastasis alone was the primary site of disease failure in 11

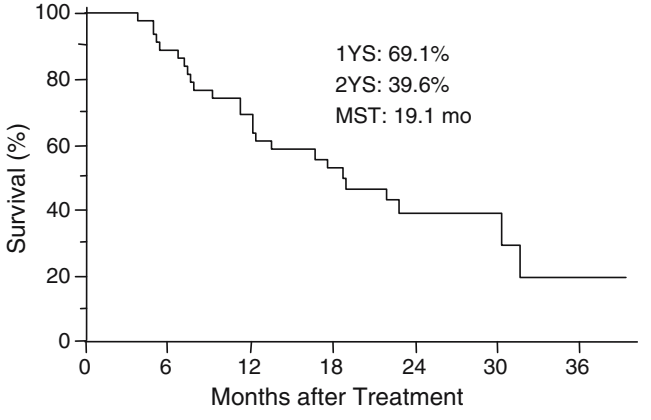

Fig. 2 Kaplan–Meier survival curves. *1 YS* 1-year survival rate, *2 YS* 2-year survival rate, *MST* median survival time

patients, and nine had only locoregional progression. Only one patient had both distant metastasis and locoregional progression. Failure sites in distant metastasis were as follows: brain ($n=5$), bone ($n=2$), adrenal gland ($n=2$), and lung ($n=1$).

Discussion

A number of randomized clinical trials have provided evidence that radiotherapy plus cisplatin-based chemotherapy improves survival as compared with radiotherapy alone in patients with surgically unresectable stage III NSCLC [1–3]. When combined with radiotherapy, chemotherapy may play a cytotoxic role and eradicate distant micrometastases or a radiosensitizing role and improve local control, or both. Recently, two randomized trials, one done by the West Japan Lung Cancer Group [4] and the other by the RTOG [5], have directly compared sequential and concurrent chemoradiotherapy regimens. Both demonstrated superior survival with concurrent treatment. However, these trials were designed and performed before the use of newer agents such as docetaxel and gemcitabine. Pilot studies of carboplatin plus paclitaxel have also reported good results [13–15].

Concurrent chemoradiotherapy including both radiosensitizing agents and dose levels of chemotherapy effective against micrometastases may yield the best outcomes. Because distant metastases remain the major cause of treatment failure, effective chemotherapy or other systemic antitumor agents will most likely be required to further improve current levels of response and survival. Cancer and Leukemia Group B Study 39801, a randomized phase III trial, reported that the addition of induction chemotherapy before concurrent chemoradiotherapy improved median survival by 2.6 months as compared with concurrent chemoradiotherapy alone [16]. Recently, two strategies have emerged to optimize the delivery of chemotherapy and radiation for stage III NSCLC: one is induction chemotherapy followed by concurrent chemoradiation, and the other is concurrent chemoradiation followed by consolidation chemotherapy. However, for many new agents, DLT requires that lower doses be given during concurrent chemoradiotherapy [17, 18]. In Cancer and Leukemia Group B Study 9431, Vokes et al. [18] examined whether cisplatin plus recently developed anticancer drugs could be used for induction chemotherapy followed by concurrent chemoradiotherapy. Two cycles of cisplatin-based chemotherapy with gemcitabine, vinorelbine, or paclitaxel were given as induction chemotherapy, followed by two additional cycles of the same drugs with concurrent radiotherapy. In Vokes' study, the doses of gemcitabine, vinorelbine, or paclitaxel used for concurrent chemoradiotherapy were about half of those used for induction chemotherapy. In CALGB 39801, Vokes et al. [19] evaluated whether the addition of induction chemotherapy before chemoradiotherapy would result in improved survival. Patients were randomly assigned to either immediate chemoradiotherapy consisting of weekly carboplatin and paclitaxel or two cycles of carboplatin and paclitaxel followed by identical chemoradiotherapy. In Vokes' report, the addition of induction chemotherapy to immediate concurrent chemoradiotherapy was associated with a 2.6-month increase in median survival. Gandara et al. [20] reported in SWOG 9504 that consolidation treatment with docetaxel after concurrent chemoradiotherapy was feasible and tolerable. In their study, patients initially received cisplatin 50 mg/m^2 on days 1, 8, 29, and 36 and etoposide 50 mg/m^2 on days 1–5 and 29–33, with concurrent radiotherapy. Consolidation treatment with docetaxel was then given 4–6 weeks after chemoradiotherapy. Median survival was 26 months, and 1-, 2-, and 3-year survival rates were 76, 54, and 37%, respectively. In SWOG 0023, Kelly et al. [21] evaluated whether or not concurrent chemoradiotherapy followed by consolidation treatment with docetaxel and maintenance treatment with gefitinib was feasible and beneficially affected survival. Maintenance therapy with gefitinib had no effect on survival as compared with placebo, and the study was terminated.

Docetaxel has well-defined cytotoxic activity in patients with NSCLC [22–27] and appears to potentiate the effects of ionizing radiation against a variety of cell lines. The use of cisplatin and docetaxel with concurrent radiotherapy is a relatively promising approach for unresectable NSCLC, a potentially curable disease. We evaluated the response to combination chemotherapy with cisplatin and docetaxel plus concurrent radiotherapy followed by consolidation chemotherapy with the same drugs. Treatment schedules remain a central issue in the search for a balance between a good response rate and low toxicity. Several studies have assessed the response to docetaxel and platinum plus concurrent radiotherapy. Kiura et al. [11] reported that treatment with cisplatin 40 mg/m^2 on day 1 and docetaxel 40 mg/m^2 on days 1 and 8 every 3 weeks with 60 Gy of concurrent radiotherapy was associated with Grade 3 or 4 neutropenia in 60% of patients, Grade 3 or 4 thrombocytopenia in 24%, and Grade 3 or 4 esophagitis in 19%. Wu et al. [10] performed a phase I study of weekly docetaxel and cisplatin with concurrent radiotherapy. Cisplatin and docetaxel were administered at weekly intervals for 6 weeks in conjunction with 63 Gy of radiation. The RDs were determined to be cisplatin 20 mg/m^2 and docetaxel 20 mg/m^2. DLT was esophagitis. Choy et al. [28] reported a phase I study of weekly docetaxel and carboplatin with concurrent radiotherapy. Carboplatin and docetaxel were administered weekly over the course of 6 weeks in conjunction with 60 Gy of radiation. Choy et al. showed that docetaxel 20 mg/m^2 weekly for 6 weeks plus carboplatin (AUC 2) with concomitant radiotherapy was a feasible regimen, with esophagitis as DLT.

In our study, cisplatin and docetaxel were administered at 2-week intervals for 6–8 cycles. During the first three cycles, cisplatin and docetaxel were given with 60 Gy of radiation. Patients then received 3–5 cycles of consolidation chemotherapy with the same drugs. DLT

comprised neutropenia at a dose of 45 mg/m^2 of docetaxel with cisplatin 40 mg/m^2, and the RD was determined to be docetaxel 40 mg/m^2 with cisplatin 40 mg/m^2 in our phase I study. Isla et al. [12] reported that a biweekly regimen is well tolerated with minimal toxicity, maintaining a response and a survival benefit in patients with metastatic NSCLC. However, it remained unclear whether a biweekly regimen of concurrent chemoradiotherapy would have the same effect in patients with locally advanced NSCLC. Our results suggested that biweekly cisplatin and docetaxel could be administered in full doses together with thoracic irradiation. Our study is considered unique in this respect. In our phase II study, the main toxic reactions were neutropenia and radiation esophagitis, but the frequency of Grade 3 or 4 radiation pneumonitis was low. However, the degree of radiation esophagitis was lower than that usually occurring in patients who receive concurrent chemoradiotherapy [11, 13]. This difference might be related to biweekly treatment. The response rate and survival time with this regimen were promising: the 1- and 2-year survival rates were 69.1 and 39.6%, respectively, with a median survival time of 19.1 months. We considered these outcomes to be favorable as compared with results obtained with other currently used regimens. Combination chemotherapy with biweekly docetaxel and cisplatin plus concurrent RT thus was active and well tolerated in patients with unresectable stage III NSCLC.

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