

Phase II Trial of Adjuvant Chemotherapy with Bi-Weekly Carboplatin Plus Paclitaxel in Patients with Completely Resected Non-small Cell Lung Cancer

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Abstract. *Background:* Adjuvant chemotherapy improves the prognosis of patients with non-small cell lung cancer (NSCLC) after a complete resection despite unacceptable toxicity and low compliance. *Methods:* A total of 67 patients were enrolled in a multi-institutional study. The patients received chemotherapy with carboplatin (CBDCA) area under the curve of 3 and paclitaxel (PTX) 90 mg/m² every 2 weeks for six cycles after surgery. *Results:* Fifty patients (74.6%) completed all cycles of therapy. The presence of grade 3 and 4 toxicities of neutropenia were 13.4, and 3.0%, respectively. Non-haematological adverse effects were infrequent and no treatment-related death was registered. The estimated disease-free survival and overall survival at 2 years were 89.0% and 88.8%, respectively. *Conclusion:* A bi-weekly schedule of CBDCA and PTX as adjuvant chemotherapy showed an acceptable toxicity and favourable feasibility in Japanese NSCLC patients after complete tumor resection. Consequently, it is desirable to validate this regimen in a future randomized clinical trial.

Lung cancer is the most common cause of cancer death in the majority of developed countries (1). It is a malignancy with a poor prognosis, and approximately 30% of all patients with NSCLC demonstrate a recurrence of the tumour and die despite undergoing a complete surgical resection (2). This suggests that occult metastases are present at the time of surgical intervention. Therefore, adjuvant chemotherapy is needed to improve the prognosis of patients who undergo a complete resection.

Recently, the benefits of adjuvant chemotherapy have been demonstrated using mainly cisplatin (CDDP)-based chemotherapy (3). However, still many problems remain. For example, an inpatient setting is required over a long duration to achieve safe treatment without good drug compliance. Furthermore, treatment related deaths sometimes occur with CDDP chemotherapy, even though it might prevent recurrence in an adjuvant setting (4-7). On the other hand, carboplatin (CBDCA) combined with paclitaxel (PTX) is one of the key treatment regimens (8), with severe neutropenia being the predominant toxicity. Therefore, it is necessary to establish the adjuvant use of CBDCA+PTX by means of a new strategy. Sledge is currently undertaking a phase I study of a bi-weekly regimen with CBDCA plus PTX for metastatic breast cancer (9, 10).

The purpose of this study was to test the adverse events (AE) and disease-free survival (DFS) as primary endpoints and a perfect completion rate as a secondary endpoint for patients with stage IB-III NSCLC in a multi-institutional study.

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Key Words: NSCLC, adjuvant chemotherapy, carboplatin, paclitaxel, treatment compliance, surgical resection.

Patients and Methods

Eligibility criteria. Patients were eligible for the main trial if they fulfilled the following local criteria for pathological diagnosis of stage IB, II, IIIA, or IIIB (pm1) NSCLC (11) after a curative lobectomy and a systematic mediastinal lymphadenectomy: age 80 years or younger; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; a leukocyte count of 4,000 / μ l and a neutrophil count of 2,000 / μ l or greater; haemoglobin level 9.5 g/dl or greater; a platelet count 100,000 / μ l or greater; serum bilirubin level less than 1.5 mg/dl; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels equal to or less than 2 times the institutional normal and creatinine less than 1.5 mg/dl. The patients were ineligible if they had concurrent malignancy, uncontrollable complications, severe postoperative morbidity, previous treatment other than surgery, hypersensitivity to agents, the possibility of being pregnant, and other conditions such as hepatic inflammation as judged by the attending physician.

Treatment schedule and trial design. This was a multi-institutional prospective study. A dose of 90 mg/m² PTX and CBDCA (area under the curve (AUC) of 3 and were given intravenously on day 1 and thereafter every 2 weeks for a maximum of six cycles. The treatment was started within 8 weeks of surgery, mainly in an outpatient setting. Calvert's formula was used to calculate the dose of the AUC for CBDCA (12), whereas the creatinine clearance was determined with the formula by (13). A short premedication of 20 mg of dexamethasone, 5 mg of d-chlorpheniramine maleate and 50 mg of ranitidine was administered intravenously 30 minutes before the patients received PTX. CBDCA and PTX were dissolved in physiological saline or 5% glucose to a volume of 250 ml, and were administered by intravenous drip infusion over 30 min and 60 min, respectively.

Complete blood cell counts were measured before the beginning of a new treatment course. Treatment was delayed 1 week if the leukocyte count was less than 3,000 / μ l or the platelets were less than 100,000 / μ l. The patient was withdrawn from the study if these conditions were not resolved within 2 weeks. The dose of PTX was reduced to 80 mg/m² or the dose of CBDCA was reduced to AUC 2.5 only once through a full course when the neutrophil count was 1,000 (/ μ l), the patient had a fever of 38.0°C or higher, or the platelet count was 25,000 / μ l or less within previous treatment. The dose of PTX was reduced to 80 mg/m² when grade 3 non-haematological toxicities occurred. The therapy was terminated when grade 4 non-haematological toxicities occurred. The maximum grade on the NCI Common Toxicity Criteria for Adverse Events (AEs) was reported for haematological and non-haematological toxic effects (14). Patients did not receive prophylactic granulocyte colony-stimulating factor (G-CSF) during any cycle. The treatment was discontinued if there was intolerable toxicity or withdrawal of consent. The choice of any subsequent treatment depended on the institute. The Institutional Review Board approved this study and informed consent was obtained either from the patient or from the patient legal guardians.

Observations and evaluations. The primary endpoints of this study were AE and disease-free survival (DFS) with the chemotherapy protocol, while the secondary endpoint was compliance to this regimen in the adjuvant setting. All eligible patients who received any part of treatment were considered assessable for toxicity. The complete blood count was repeated weekly. The blood chemistry studies and serum levels of tumour markers were repeated every two

Table I. Patient characteristics.

Characteristic	Number (%) (n=67)
Gender	
Male	50 (75)
Female	17 (25)
Histology	
Adenocarcinoma	41 (61)
Squamous cell carcinoma	21 (31)
Large cell carcinoma	3 (4)
Adenosquamous cell carcinoma	1 (2)
Pleomorphic carcinoma	1 (2)
Pathological stage	
IB	24 (36)
IIA	2 (3)
IIB	14 (21)
IIIA	21 (31)
IIIB	6 (9)

cycles. DFS was calculated from a date of treatment initiation to the date of documented progression. Overall survival (OS) was calculated from first day of treatment to the date of death. The follow-up periods after accrual closure were 6, 18, and 24 months.

Statistical analysis. The events considered in the DFS were locoregional or distant recurrence and death without a recurrence. The Kaplan-Meier method was used to estimate the probability of survival, and survival differences were analyzed by the log-rank test. The terminal event of the overall survival analysis was death attributable to cancer or non-cancer causes. The statistical difference was considered to be significant if the *p*-value was less than 0.05. The data were analyzed using the Stat View software (Abacus Concepts, Inc., Berkeley, CA, USA).

Results

Patient characteristics. Seventy-two patients were enrolled into this multi-institutional trial from July 2001 to September 2003. Five of the 72 patients enrolled were excluded from the final analysis; 4 due to ineligibility criteria and one patient due to not receiving the study therapy. A total of 67 patients were evaluable and their characteristics are shown in Table I. The 67 patients included 50 males and 17 females, with a median age of 64 years (range, 33-79 years). They included 41 adenocarcinomas, 21 squamous cell carcinomas, 3 large cell carcinomas, 1 adenosquamous cell carcinoma and 1 pleomorphic carcinoma. Twenty-four patients were in stage IB, 16 in II, 21 in IIIA, and 6 in IIIB. None of the patients received either induction or postoperative radiotherapy.

Toxicity. Grade 3 and 4 leukocytopenia and neutropenia were observed in 13.4 and 3.0%, respectively (Table II). Grade 4 leukocytopenia was not observed, and grade 4 neutropenia was found in only 2 cases (3.0%). No grade 3/4 anemia or

Table II. Worst adverse events.

Toxicity	Grade 3	Grade 4	Frequency (%)
Leukopenia	2	0	3.0
Neutropenia	7	2	13.4
Appetite loss	2	0	3.0
Constipation	1	0	1.5
Diarrhoea	1	0	1.5
Abdominal pain	1	0	1.5
Colitis	1	0	1.5
Peripheral nerve disorder	1	0	1.5
General fatigue	3	0	4.5
Arthralgia	1	0	1.5
Myalgia	1	0	1.5

Table III. Severe toxicities classified by age.

Age (years)	Grade 3/4	Frequency (%)
<60 (n=21)	4	19.0
60-69 (n=26)	2	7.7
70-79 (n=20)	3	15.0
Total (n=67)	9	13.4

thrombocytopenia was observed. The frequency of grade 3/4 toxicities was 4.5% or less and no grade 4 adverse events were observed. No treatment-related death was registered. Table III shows the main haematological and the non-haematological toxicities (grade 3 and 4) classified by age. The frequency of grade 3/4 toxicities in patients younger than 60 years, 60-69 years, and 70-79 years were 19.0%, 7.7%, and 15.0%, respectively. The rate of patients with haematological toxicities did not tend to be higher in the elderly patients than that in the younger patients (Table III).

Survival. There were 16 events (9: alive with recurrence, 5: death with recurrence; 2: death without cancer) in 67 patients. The overall median follow-up period for all patients was 23.0 months. The 2-year DFS and OS rate of the 67 patients was 89.0% and 88.8%, respectively. The 2-year DFS rate of patients with stage IB-II and III tumours was 94.9% and 80.8%, respectively (Figure 1A). The 2-year OS rate of patients with IB-II disease was 97.5% and that of patients with III-IV was 77.3%, respectively (Figure 1B). Advanced stage NSCLC tends to have a poor prognosis, although there was no patients with statistically significant difference between stage IB-II and III for disease survival. Thirteen out of 14 patients who had developed recurrent disease showed systemic disease. There was not a significant relationship between pathological stage and the number of recurrences (stage IB-II: 15.0%, III: 29.6%, $p=0.15$; Table IV).

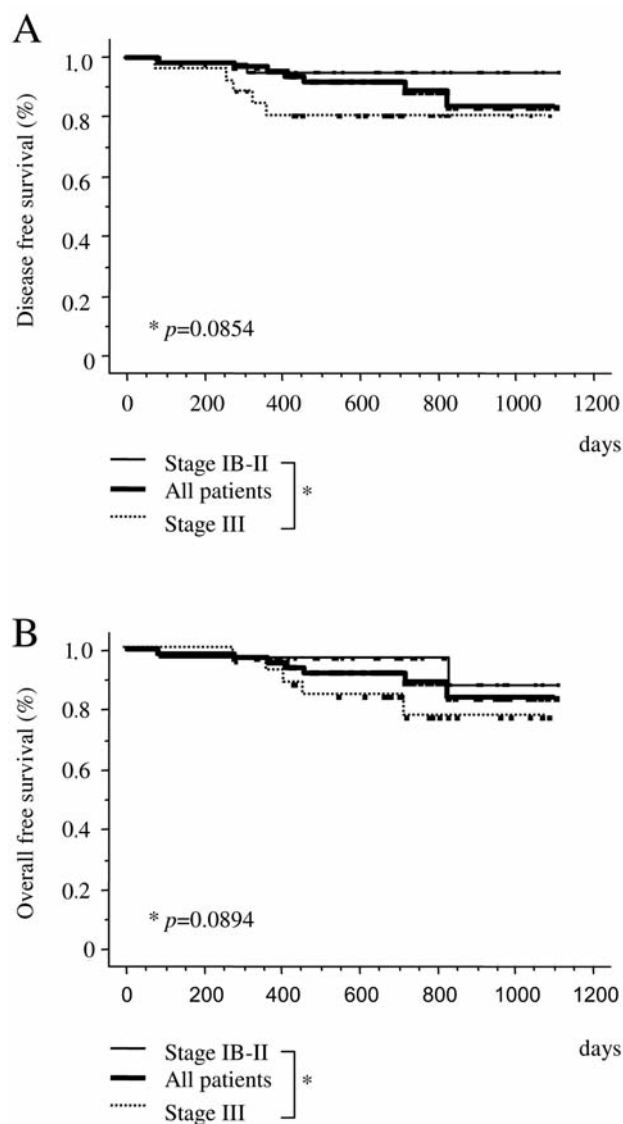


Figure 1. Disease-free (A) and overall (B) survival of treated patients.

Chemotherapy compliance. Fifty patients completed all cycles of therapy and therefore, the perfect completion rate was 74.6% (Table V). The median number of treatment cycles for all patients was 5.1. Some patients did not complete all cycles because of rejection in 5 cases, alopecia in 4 cases, gastrointestinal toxicity in 3 cases, and haematological toxicity in 2 cases (Table VI). The completion rate in patients less than 60 years, 60-69 years, and 70-79 years were 85.7%, 73.1%, and 65.0%, respectively. There was a decreasing tendency with aging. The transition rate of patients to outpatient status in all cycles was 98.0% (Table VII).

Table IV. Pathological stage and type of recurrence.

Pathological stage	No. of cases	No. of recurrent cases	Local (%)	Systemic (%)
IB	24	3 (12.5)	0	3
IIA	2	0 (0.0)	0	0
IIB	14	3 (21.4)	0	3
IIIA	21	6 (28.6)	1	5
IIIB	6	2 (33.3)	0	2
Total	67	14 (20.9)	1 (1.5)	13 (19.4)

Discussion

Recent randomized phase III trials have been conducted to determine therapies to reduce the risk of relapse and death for NSCLC patients after a surgical resection (4-7). Consequently, the ASCO guidelines in advanced NSCLC recommend platinum-based doublet regimens for those patients with a good performance status (15). No single specific platinum-based doublet is recommended. A vinorelbine (VNR) and cisplatin (CDDP) regimen as adjuvant therapy improved the OS in patients with stages II to IIIA NSCLC. However, it is not sufficiently useful to administer CDDP in an outpatient setting because CDDP requires hydration to prevent renal toxicity, which also adds a risk for lung oedema with a reduced vascular bed after a lung resection. CBDCA is more favorable with less toxicity than most of the anticancer drugs for advanced lung cancer. However, the results of adjuvant chemotherapy in combination with CBDCA are still uncertain. PTX has a so-called platelet-sparing effect when administered in combination with CBDCA (16), while CBDCA and PTX have been reported to be just as efficacious as VNR plus CDDP, but less toxic for the treatment of advanced NSCLC (17). Recently, CALGB reported a significantly better survival advantage for patients who had tumours ≥ 4 cm NSCLC at stage IB in postoperative administration of CBDCA and PTX (8). In fact, the combination of CBDCA and PTX is one of the standard regimens for the treatment of advanced NSCLC patients (18, 19). However, only 27% of patients treated with CBDCA (AUC6) and PTX (225 mg/m²) every 3 weeks completed chemotherapy as planned (17).

In vitro experiments with lung cancer cell lines showed that prolonged exposure to PTX above a threshold concentration was more efficacious than a short exposure to a higher drug concentration (20). Furthermore, reducing the interval between treatments has also been suggested to minimize the occurrence of drug-resistant cell clones and re-growth (21). One clinical study recommended weekly split treatment because weekly PTX has a better safety profile and seems to be as effective as the equivalently dosed schedule every 3

Table V. Chemotherapy compliance classified according to age.

Age (years)	Completion rate	Median no. of cycles
<60 (n=21)	85.7% (18/21)	5.6
60-69 (n=26)	73.1% (19/26)	5.0
70-79 (n=20)	65.0% (13/20)	4.8
Total (n=67)	74.6% (50/67)	5.1

Table VI. Reasons for discontinuation of therapy.

Reason	No. of patients (%)
Patient rejection	5 (7.5)
Alopecia	4 (6.0)
Gastrointestinal toxicity	3 (4.5)
Haematological toxicity	2 (3.0)
Depressive state	1 (1.5)
Bronchitis	1 (1.5)
Death without recurrence	1 (1.5)
Total (n=67)	17 (25.4)

Table VII. Transition rate of patients to outpatient status.

No. of cycles	1	2	3	4	5	6
Inpatient	61	14	2	2	2	1
Outpatient	6	46	56	53	51	49
Total	67	60	58	55	53	50
Transition rate (%)	9.0%	76.7%	96.6%	96.4%	96.2%	98.0%

weeks (22). However, no clear efficacy advantage of a weekly schedule is evident (23) and the versatility of CBDCA and PTX regimen was confirmed (24). Briefly, tri-weekly and weekly regimens have both advantages and disadvantages. Conner *et al.* reported that a bi-weekly schedule had less non-haematological toxicity for advanced NSCLC, compared to a three-week regimen (10). There might be some large differences between intense chemotherapy for the patients with a tumour burden and the adjuvant setting for the postoperative patients that are macroscopically tumour free. Therefore, the current study investigated the AE, DFS, and compliance by bi-weekly regimen in a multi-institutional study. Recently, this bi-weekly combination was reported to be well tolerated (25, 26) and produce an objective response rate (ORR) of 35.1% and overall survival of 11.9 months, with a more favorable toxicity profile than an every 3 weeks regimen for advanced NSCLC patients (27).

Table VIII. Prospective trial by CBDCA+PTX.

Authors (ref)	Stage	No. of patients	Schedule	Grade 3/4 neutropenia	2-Years survival	Completion rate
Strauss <i>et al.</i> (8)	IB	173	CBDCA (AUC6) and PTX (225 mg/m ²) every 3 weeks for four cycles	35%	DFS: 75% OS: 90%	86%
Yamashita <i>et al.</i> (28)	IB-IIIA	61	CBDCA (AUC 5) and weekly PTX (70 mg/m ²) every 4 weeks for four cycles	34%	DFS: 51% OS: 85%	69%
Maruyama <i>et al.</i> (29)	IB-IV	34	CBDCA (AUC 5) and PTX (175 mg/m ²) every 3 week for four cycles	77%	-	79%
This study	IB-III	67	CBDCA (AUC3) and PTX 90 mg/m ² every 2 weeks for six cycles	13.4%	DFS: 89% OS: 89%	75%

There are only three reports using CBDCA and PTX in an adjuvant setting in Table VIII (8, 28, 29). The frequency of grade 3/4 neutropenia in the previous reports was 34-77%. The frequency of grade 3/4 neutropenia in Japanese patients is much higher than in Caucasian patients with the same tri-weekly schedule (8, 29). The difference might depend on ethnic differences in population-related pharmacogenomics (30). The frequency of severe neutropenia in only 13% in the current series suggested that a bi-weekly regimen has a better safety profile.

The 2-year DFS and OS rates were 89.0% and 88.8%, respectively, in this trial and better than previous reports (8, 28, 29). The data regarding survival are still preliminary and must be followed up. Compliance with the chemotherapy protocol was also acceptable in this regimen. An increasing number of patients are presently undergoing outpatient chemotherapy as an alternative to inpatient chemotherapy (31). Furthermore, the transition rate to outpatient treatment using this regimen was 98.0%, which had the added advantage of reducing medical care costs by shortening hospital stays and also cutting the cost of inpatient services.

Conclusion

Adjuvant chemotherapy with a bi-weekly schedule of CBDCA and PTX showed an acceptable toxicity and a favorable feasibility in Japanese patients with NSCLC. The main limitation of this study is the small number of the patients enrolled, and therefore, when evaluating this treatment regimen, it is important to employ a reference arm for randomised clinical trials.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Received April 8, 2010

Revised May 11, 2010

Accepted May 14, 2010