Phase II study of weekly docetaxel and cisplatin in patients with non-small cell lung cancer

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We conducted a phase II study to examine the efficacy and safety of weekly docetaxel and cisplatin in the treatment of advanced non-small cell lung cancer (NSCLC). Forty chemotherapy-naïve patients (10 with stage IIIB and 30 with stage IV NSCLC) with an Eastern Cooperative Oncology Group performance status of 0–2 and adequate organ functions were enrolled. Chemotherapy consisted of cisplatin (80 mg/m^2) on day 1, and docetaxel (35 mg/m^2) on days 1, 8 and 15, delivered in 4-week cycles consisting of three weekly treatments followed by 1 week of rest. There were 18 partial responses, with an overall response rate of 45% (95% confidence interval 29.6–60.4%) in 40 treated patients. The median survival period was 19.9 months, median progression-free survival was 5.5 months and 1-year survival rate was 69.4%. Hematologic toxicities were mild and included grade 3 or 4 neutropenia in 37.5%. There were no severe infections or septic deaths. Non-hematologic toxicities were generally mild. Grade 3 or 4 transaminase elevations were observed in two patients. Grade 3 events included two cases each of vomiting, and one case each of hypokalemia, diarrhea and creatinine elevations. Weekly docetaxel and cisplatin is an effective and safe combination in the treatment of patients with advanced NSCLC. *Anti-Cancer Drugs* 16:455–460 © 2005 Lippincott Williams & Wilkins.

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Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers. Most patients present with locally advanced stage III or metastatic stage IV disease. A meta-analysis of 52 randomized trials indicated a significant, but modest, survival advantage for patients treated with cisplatin-containing regimens, compared with best supportive care alone [1]. The recent introduction of newer agents, with improved responses rates in NSCLC [1], offers hope for more active combination regimens. Although the current practice of treating patients with stage IV disease includes the addition of newer generation agents such as vinorelbine, gemcitabine, paclitaxel or docetaxel to a platinum agent, no combination has emerged as a gold standard [1,2]. Docetaxel is a semisynthetic taxoid derived from the European yew *Taxus baccata* [3]. It has antitumor activity in NSCLC and shows survival benefits not only in chemotherapy-naïve patients, but also in those patients who have previously received platinum-based chemotherapy [4–8]. *In vitro* studies have shown a lack of cross-resistance between docetaxel and cisplatin [9], and the two drugs appeared to be non-cross-resistant clinically [7]. Moreover, docetaxel and cisplatin resulted in a more favorable overall response and survival rate than vinorelbine and cisplatin [10]. Although the commonly used dose and schedule of docetaxel is 60–100 mg/m^2 every 3 weeks, more than 90% of patients developed grade 3 or 4 neutropenia [4–7]. Recent studies have shown that weekly administration of docetaxel produces a higher dose intensity and less myelosuppression [11–13]. Thus, we conducted a phase I trial of cisplatin and weekly docetaxel for advanced NSCLC in non-elderly (younger than 70 years) patients [14]. From this research, the recommended doses were 80 mg/m^2 cisplatin on day 1, and 35 mg/m^2 docetaxel on days 1, 8 and 15. In that study, a response rate of 44.4% was observed in 18 assessable patients. Based on the phase I study, we conducted the phase II study reported here. The primary endpoint of the current phase II study was response rate. Secondary endpoints included toxicity and survival.

Patients and methods

Patient eligibility

Eligible patients were required to have histologically and/or cytologically proven unresectable stage IIIB or IV NSCLC, be 20–69 years of age, have no previous chemotherapy or radiotherapy, have a performance status (PS) of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale, have a life expectancy of $\geq$ 12 weeks,

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adequate bone marrow reserve (leukocyte count $\geq 4000/mm^3$, neutrophil count $\geq 2000/mm^3$, platelet count $\geq 100\,000/mm^3$ and hemoglobin ≥ 10 g/dl), normal liver (total serum bilirubin ≤ 1.5 mg/dl and AST, ALT less than twice the upper limit of the normal range) and normal renal functions (serum creatinine ≤ 1.5 mg/dl and creatinine clearance ≥ 60 ml/min). Patients with concomitant malignancy, central nervous system metastases, active infectious diseases or other serious medical problems were ineligible. The local ethics committee approved the study and written informed consent was obtained from all patients.

Clinical evaluation

Patients were evaluated prior to treatment with a complete blood cell count, a differential count, routine chemistry measurements, a chest radiograph, a chest computed tomography (CT) scan, an abdominal CT scan, whole-brain magnetic resonance imaging or CT scan and an isotope bone scan. Evaluations performed weekly were complete blood cell count, differential count, routine chemistry measurements, physical examination and toxicity assessment.

Treatment schedule

Chemotherapy consisted of cisplatin ($80\,mg/m^2$) on day 1, and docetaxel ($35\,mg/m^2$) on days 1, 8 and 15 every 4 weeks. Docetaxel was infused i.v. in 200 ml of 5% glucose over 60 min. Cisplatin was administrated along with a program of forced diuresis that included at least 2000 ml of fluids via a 30-min i.v. infusion after docetaxel infusion on day 1. Anti-allergic prophylaxis was given with dexamethasone (12 mg i.v.) 2–3 h before each docetaxel infusion. In the absence of any hypersensitivity reaction, dexamethasone was withheld. An antiemetic, granisetron (3 mg i.v.), was administered 30 min before docetaxel. The prophylactic administration of granulocyte colony stimulating factor (G-CSF) was not permitted. Administration of G-CSF was permitted in patients with grade 4 neutropenia and/or grade 3 febrile neutropenia. Docetaxel was withdrawn if leukocyte count $< 2000/mm^3$ or platelet count $< 75\,000/mm^3$ on days 8 and 15. Subsequent courses of chemotherapy were initiated when leukocyte counts $\geq 4000/mm^3$ and platelet counts $\geq 100\,000/mm^3$ after day 29. If the leukocyte or platelet counts had not returned to these levels by day 1 of the next course of chemotherapy, both drugs were withheld until full recovery. Treatment was carried out for at least two courses, unless unacceptable toxicity or disease progression occurred.

Response and toxicity evaluation

The responses were evaluated according to the WHO criteria [15]. A complete response (CR) was defined as the disappearance of all known tumor mass for at least 4 weeks. A partial response (PR) was defined as a 50% or more decrease in total tumor size for a period of at least 4 weeks. No change (NC) was defined as a less than 50% decrease or a less than 25% increase in total tumor size. Progressive disease (PD) was defined as a more than 25% increase in total tumor size or the appearance of new lesions. Survival times were calculated from the start of treatment using the Kaplan–Meier method. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

Statistical analysis

Overall survival and progression-free survival were analyzed by the Kaplan–Meier method [16]. If the disease had not progressed by the time of this analysis, progression-free survival was considered censored at the time of the analysis. Confidence intervals (CIs) for response rate were calculated at the 95% level.

Results

Patient characteristics

From November 1999 to April 2003, a total of 40 chemotherapy-naïve patients were enrolled in this study (Table 1). All 40 patients were assessable for toxicity and efficacy. The median age of the patients was 60 years (range 32–70). Twenty-five patients were males and 15 were females. PS, clinical stage and histology of the patients were as follows: 14 patients with PS 0, 26 patients with PS 1; 10 patients with stage IIIB, 30 patients with stage IV; 30 patients with adenocarcinoma, nine patients with squamous cell carcinoma, one patient with large cell carcinoma. Thirty-five patients had no prior treatment, while five had undergone surgery.

Treatment delivery and dose intensity

The total number of treatment cycles was 104 and the median number of cycles was 2 (range 1–5). In 96 out of 104 cycles (92%), docetaxel was administered on days 1, 8 and 15 of the treatment (Table 2). The reasons for

Table 1 Patient characteristics

Characteristic	*N*
Patients enrolled	40
Age (years)	
median	60
range	32–70
Sex	
male	25
female	15
PS (ECOG)	
0	14
1	26
Histology	
adenocarcinoma	30
squamous cell carcinoma	9
large cell carcinoma	1
Stage	
IIIB	10
IV	30
Prior treatment	
none	35
surgery	5
radiotherapy	0

skipping of administration on day 8 or 15 included level of transaminase ($n = 1$), patient refusal ($n = 1$), level of creatinine ($n = 1$), WBC $< 2000/mm^3$ ($n = 3$) and others (diarrhea, gastric ulcer) ($n = 2$). Five patients received only one course because of development of progressive disease ($n = 2$), level of transaminase ($n = 1$), level of creatinine ($n = 1$) and patient refusal ($n = 1$). The median actual dose intensity of docetaxel was 24.7 mg/m^2/week (range 8.8–26.3), whereas the projected dose intensity was 26.25 mg/m^2/week.

Response and survival

There were 18 partial responses and 20 patients had stable disease. The overall response rate in the 40 treated patients was 45% (95% CI 29.6–60.4%) (Table 3). The median survival time was 19.9 months (range 3.3–40.6 months) and the median progression-free survival was 5.5 months (range 1.0–36.2 months) (Figs 1 and 2). The 1- and 2-year survival rates were 69.4 and 35.6%, respectively (Fig. 1).

Table 2 **Treatment delivered**

Administered on	No. treatment cycles					Total
	1	2	3	4	5	
Days 1, 8 and 15	36	32	19	8	1	96
Days 1 and 8	2	3	0	0	0	5
Days 1 and 15	1	1	0	0	0	2
Only day 1	1	0	0	0	0	1
Total	40	36	19	8	1	104

Table 3 **Response rate**

Tumor response	*N*
Complete	0
Partial	18
No change	20
Progressive disease	2
Overall response rate [% (95% CI)]	45.0 (29.6–60.4)

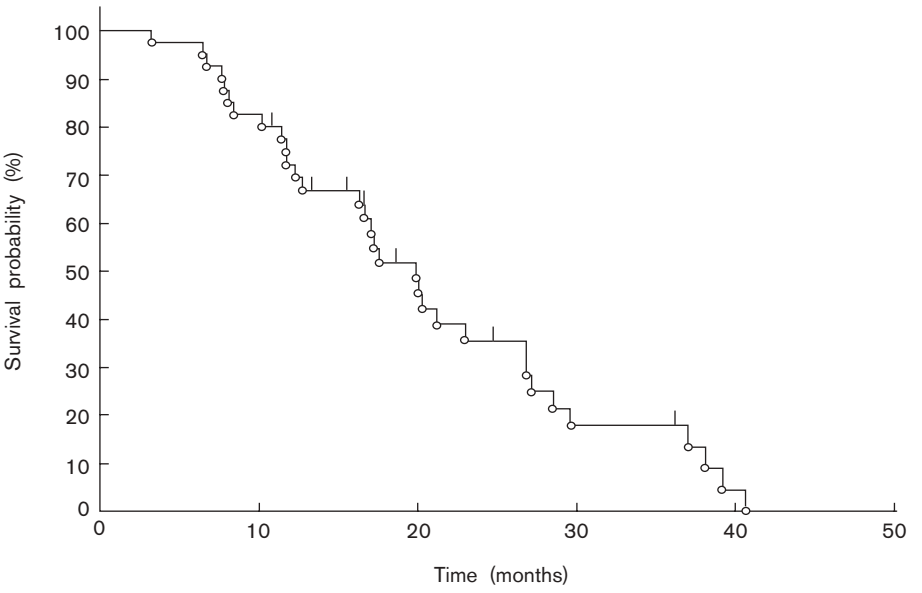
Toxicity

Toxicity was evaluated in all treated patients. The hematologic and non-hematologic toxicities experienced by each patient are listed in Table 4. Grade 3 or 4 neutropenia (37.5%), grade 3 anemia (12.5%) and thrombocytopenia (2.5%) were observed. There were no severe infections, septic deaths or cases of febrile neutropenia. Non-hematologic toxicity was generally mild. Grade 3 or 4 transaminase elevations were observed in two patients, one of whom received chemotherapy with a dose reduction of docetaxel and cisplatin. Grade 3 events were observed in two cases each with vomiting, and one case each with hypokalemia, diarrhea and creatinine elevations. These three patients improved without any interventions. Five patients developed infections, which improved immediately with antibiotic medications. Treatment-related deaths or interstitial pneumonia were not seen in this study.

Second-line chemotherapy

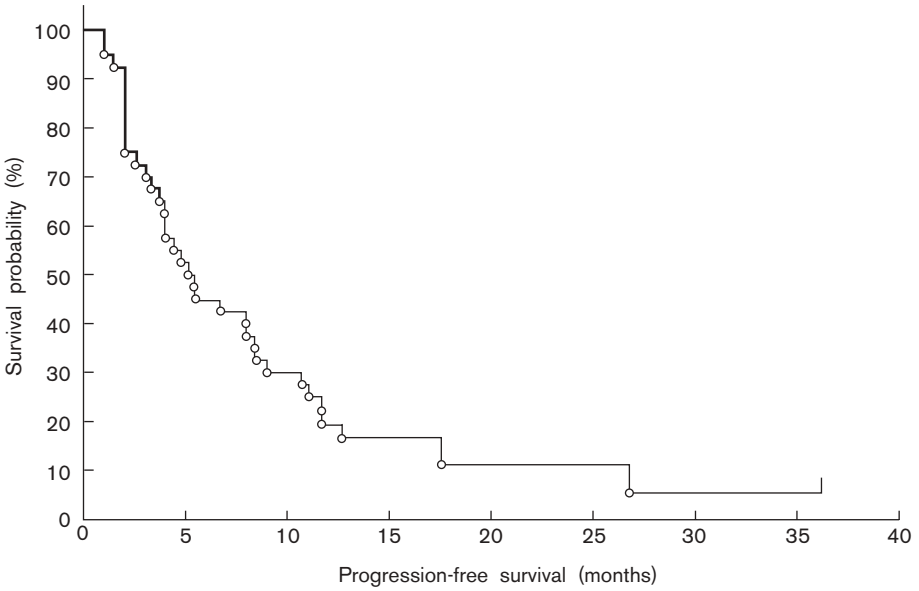
A total of 17 patients received second-line chemotherapy. These patients received gemcitabine-based chemotherapy ($n = 9$), vinorelbine-containing regimen ($n = 2$), carboplatin and paclitaxel ($n = 3$), gefinitib ($n = 2$), and carboplatin combined with weekly docetaxel ($n = 1$). No CR or PR was observed in these 17 patients. Ten patients

Fig. 1



Overall survival time. The median survival time was 19.9 months (range 3.3–40.6 months), and the 1- and 2-year survival rates were 69.4 and 35.6%, respectively.

Fig. 2



The median progression-free survival was 5.5 months (range 1.0–36.2 months).

Table 4 Hematologic and non-hematologic toxicities

	Grade					Grade 3 or 4 (%)
	0	1	2	3	4	
Leukopenia	9	11	16	4	0	10
Neutropenia	11	9	5	8	7	37.5
Anemia	3	16	16	5	–	12.5
Thrombocytopenia	37	2	0	1	0	2.5
Nausea/vomiting	6	17	15	2	–	5
Infection	35	2	1	2	0	5
Transaminase	23	12	3	1	1	5
Hypokalemia	0	0	0	1	0	2.5
Diarrhea	31	5	3	1	0	2.5
Creatinine	35	3	1	1	0	2.5
Rash	34	4	2	0	0	0
Fever	36	3	0	1	0	2.5
Fatigue	26	12	2	0	0	0
Neurotoxicity	37	3	0	0	0	0

received second-line chest irradiation, of which two had a PR. These 10 patients are a distinct group of patients separate to the 17 that received second-line chemotherapy.

Discussion

This is the phase II study designed to evaluate the efficacy and safety of weekly administration of docetaxel (3 consecutive weeks, then 1 week rest) and 4-weekly administration of cisplatin for the treatment of chemotherapy-naïve patients with stage IIIB or IV NSCLC. All enrolled patients ($n = 40$) were evaluated for efficacy and toxicity. There were 18 PRs, with an overall response rate of 45% and the median survival time was 19.9 months. We divided the docetaxel dosages on days 1, 8 and 15 because weekly administration of docetaxel produces higher dose intensity and less myelotoxicity. Moreover, a weekly schedule may be safer than a 3-weekly schedule because treatment on day 8 and/or day 15 can be omitted if severe toxicity is observed. In the current study, the median actual dose intensity of docetaxel was 24.7 mg/m^2/week (range, 8.8–26.3), whereas the projected dose intensity was 26.25 mg/m^2/week with 94% of the planned administration were carried out. Hematologic toxicities were mild in our study. Grade 3 or 4 neutropenia occurred in 37.5% of patients and no febrile neutropenia was detected. Non-hematologic toxicities were also mild. While grade 3 or 4 transaminase elevations were observed in two patients and grade 3 creatinine elevation observed in one patient, all three patients improved without intervention. One patient with grade 3 transaminase elevation received chemotherapy with a dose reduction of docetaxel and cisplatin. Furthermore, none experienced grade 3 or 4 fatigue and neurotoxicity. Several phase II studies describing the every-3-week administration of cisplatin and docetaxel have already been conducted in advanced NSCLC (Table 5). More than 43% of patients developed grade 3 or 4 neutropenia. Febrile neutropenia (9–28%), neurotoxicity (11–58%) and grade 3 or 4 fatigue (18–34%) were also observed [17–21]. Nail disorders (4–4.9%) were observed in some studies [19,20]. Georgoulias *et al.* reported that hematologic toxicity remained high, despite the prophylactic use of G-CSF, and two patients died of sepsis [17]. Similarly, Zalcberg *et al.* reported a high frequency of treatment discontinuation (17%) resulting from toxicity and neutropenic infection (in 11% of

Table 5 Phase II studies of docetaxel and cisplatin in advanced NSCLC

Author	Docetaxel/cisplatin dose (mg/m^2)	No. patients	Stage III (%)	Grade 3 or 4 neutropenia (%)	Febrile neutropenia (%)	Response rate (%)	Median survival time (%)	One-year survival rate (%)
Georgoulias [17]	100/80 day 1 q3 weeks	53	53	43	28	45	48.0 weeks	48
Le Chevalier [19]	75/100 day 1 q3 weeks	51	20	67	16	33	8.4 months	35
Zalcberg [18]	75/75 day 1 q3 weeks	47	32	87	13	30	9.6 months	33
Belani [20]	75/75 day 1 q3 weeks	47	6	74.4	9	32	11.3 months	40
Okamoto [21]	60/80 day 1 q3 weeks	45	0	84	11	42	43.3 weeks	38.7
Niho [23]	35/25 day 1, 8, 15 q4 weeks	37	41	22.2	0	30	12.8 months	54
Tsunoda [28]	25 day 1, 8, 15/80 day 1 q4 weeks	38	42.2	18	0	31.6	11.8 months	46.5
Current study	35 day 1, 8, 15/80 day 1 q4 weeks	40	25	37.5	0	45	19.9 months	69.4

patients), contributing to two treatment-related deaths [18]. On the other hand, Hainsworth *et al.* reported that the administration of weekly docetaxel, 36 mg/m^2, was well tolerated in elderly patients with advanced, previously untreated NSCLC because the hematological toxicities were mild. None of the patients developed grade 4 neutropenia, but fatigue occurred in 10% of the patients [22]. Niho *et al.* reported that treatment of patients with advanced NSCLC with docetaxel 35 mg/m^2 and cisplatin 25 mg/m^2 for 3 consecutive weeks, followed by a week of rest, produced responses comparable to those of the routine 3-weekly administration, with minimal myelosuppression [23]. In our study, myelosuppression was minimal when compared with 3-weekly administration of docetaxel and cisplatin, and no severe toxicities or lung injuries were observed. Le Chevalier *et al.* reported a response rate of 33.3% and a median survival time of 8.4 months with administration of cisplatin at a dose of 100 mg/m^2 [19]. Similarly, other large randomized trials have shown that high doses of cisplatin are not associated with a significantly higher response rate or significantly longer survival [24–26]. Therefore, there is no apparent therapeutic advantage in employing higher doses of cisplatin. Ohe *et al.* divided the cisplatin and docetaxel dosage on days 1, 8 and 15 because full doses of cisplatin were considered too toxic for elderly patients [27]. However, Niho *et al.* reported that a weekly 25 mg/m^2 dose of cisplatin was not dose intensive and nausea or vomiting occurred in 84.5% of patients [23]. In our study, nausea or vomiting occurred in 85% of patients and the toxicity is comparable to the 84.5% of patients observed in their study. Therefore, cisplatin 80 mg/m^2 on day 1, every 4 weeks was administered in our study.

Tsunoda *et al.* reported a phase II study of weekly docetaxel (25 mg/m^2, day 1, 8, 15) combined with cisplatin (80 mg/m^2, day 1) [28]. The study design was novel and similar to our administration schedule except for the different dose of docetaxel. The study showed a response rate of 31.6%, median survival time of 11.8 months and 1-year survival rate of 46.5%, with less hematologic toxicity. Median survival time and 1-year survival rate in our protocol were superior to those recorded in their trial. Weekly administration of 35 mg/m^2 of docetaxel may be more contributory to improvement of survival than 25 mg/m^2 of docetaxel. Other phase II trials, in which patients received cisplatin and docetaxel, overall response rate was 30–45%, median survival time was 8.4–12.8 months and 1-year survival rate was 33–54% (Table 5). With our regimen, although the overall response rate of 45% was similar to the results of the above-mentioned trials, the median survival time of 19.9 months and the 1-year survival rate of 69.4% were superior to those recorded in other trials (Table 5). Although the survival time and survival rate are definitely higher than those published for other trials using a combination of cisplatin and docetaxel, there may be an element of bias because of the patient selection criteria [10 patients (25%) had stage IIIB disease], small sample size and usage of second-line chemotherapy and chest irradiation contributing to an improved survival. The survival time of 19.9 months is extraordinarily long considering that time to progression is only modestly encouraging at 5.5 months. This suggests that the long survival in this trial was not due to this primary treatment regimen, but to subsequent second line therapy. As cisplatin-based chemotherapy regimens may cause severe toxicity in elderly patients, we conducted the eligibility criteria of non-elderly patients aged lees than 70 years. This clearly may have been an additional variable in the prolonged survival and tolerability of this regimen. However, the regimen administered in the current study definitely contributes towards improvement of survival.

In conclusion, the combination of weekly docetaxel and cisplatin is an effective and non-toxic regimen in patients with advanced NSCLC. Prospective randomized trials are warranted to compare weekly docetaxel and cisplatin with 3-weekly administration of docetaxel and cisplatin.

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