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ORIGINAL ARTICLE

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

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Abstract
Background Docetaxel and cisplatin combination chemotherapy is established first-line chemotherapy for advanced non-small cell lung cancer (NSCLC). We evaluated a weekly schedule of docetaxel and cisplatin for efficacy and tolerability in patients with chemotherapy-naive NSCLC.
Methods Patients enrolled in this study had stage IIIB or IV NSCLC with measurable disease, no prior chemotherapy, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2. Treatment consisted of docetaxel 40 mg/m^2 and cisplatin 35 mg/m^2 given on D1 and D8 every 3 weeks. Patients were evaluated for response after every 2 cycles of treatment.
Results Thirty six patients were enrolled, and 35 underwent treatment. Of these, 29 were males and 7 females, median age was 61 years (range, 38–68). About 31 patients had ECOG PS 0-1 and 4 patients had ECOG PS 2. Fifty seven percentage (20/35) of patients had adenocarcinoma and 74.3% (26/35) had stage IV disease. A total of 153 cycles of chemotherapy were administered. Of the 35 patients treated, 17 (48.6%) achieved partial response, 11 (31.4%) showed stable disease, and 6 (17.1%) had progressive disease. Median duration of response was 5.3 months (95% CI: 4.2–6.2 months), and median time to disease progression was 4.6 months (95% CI: 2.9–6.3 months). Estimated overall survival at 1 year was 65.7%. The major hematologic toxicity was myelosuppression. Grade 3 or 4 anemia occurred in 6 cycles, and grade 3 or 4 neutropenia was observed in four cycles. Major non-hematologic toxicities were grade 3 nausea in three patients and grade 3 fatigue in two patients. Three patients developed pneumonia and one patient had infectious colitis. There were no treatment-related deaths in this study.

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Conclusions Weekly schedule of docetaxel and cisplatin as first-line treatment for NSCLC had good efficacy and manageable toxicity.

Keywords Non-small cell lung cancer · Taxotere · Cisplatin · Combination chemotherapy · Chemo-naive

Introduction

Lung cancer, the leading cause of cancer-related mortality in Korea, presents with advanced disease in the majority of patients at the time of diagnosis [1]. Some meta-analysis of randomized trials with NSCLC demonstrated the benefits of cisplatin-based chemotherapy over palliative care in improving overall survival rates and providing symptom relief [2, 3]. Following the introduction of new agents in the 1990s, cisplatin combination chemotherapy with new agents, such as docetaxel, vinorelbine, gemcitabine, and paclitaxel, has been found to increase median overall survival to 9–10 months and established as a standard therapy.

Docetaxel is a semi-synthetic taxoid derivative from the rare Pacific yew tree *Taxus Baccata* [4] and active against NSCLC [5, 6]. Stabilization of microtubule by docetaxel results in inhibition of mitotic cell division between metaphase and anaphase and initiation of apoptosis [7]. Docetaxel and cisplatin double regimen therapy appears to have no cross-resistance in vitro and in clinical study [8, 9] and has been demonstrated to produce favorable responses and good overall survival rates compare to vinorelbine and cisplatin combination [10, 11]. In phase II/III clinical trials with docetaxel and cisplatin in patients with NSCLC, median survival has been reported to be between 8.4 and 13 months [12–14]. These trials lead us to choose docetaxel and cisplatin as a first-line chemotherapy in advanced NSCLC. The usual recommended schedule for docetaxel is 60–100 mg/m^2 and cisplatin 60–100 mg/m^2 every 3 weeks; however, myelotoxicity is a limitation of treatment. In advanced NSCLC, improving survival without severe treatment-related toxicity is major challenge in the management.

A weekly regimen of docetaxel showed similar efficacy and lower toxicity than a 3-weekly infusion in phase I clinical trials [15–17]. We experienced that weekly schedule of cisplatin has similar efficacy and better toxicity profile than 3-week administration in our previous trial [18], and several other studies showed that fractionated schedule of docetaxel and cisplatin has similar efficacy to the conventional schedule [19–21]. The optimal schedule for administration of the two drugs has not yet been determined. Based on our clinical trial and several trials reported recently, we planned to conduct a fractionated schedule of docetaxel and cisplatin to reduce severe hematologic toxicity while preserving efficacy. Our primary endpoint was response rate, and secondary endpoint was toxicity, progression free survival, and overall survival rate.

Patients and methods

Study design

This study was designed as an open-label, multicenter, prospective single-arm phase II trial of combination chemotherapy with fractionate dose of docetaxel and cisplatin in metastatic or unresectable locally advanced NSCLC. The primary endpoint was the response rate to treatment, assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Secondary endpoints were response duration, time to disease progression, toxicity, and overall survival.

Patient eligibility

Eligibility criteria were as follows: histologically confirmed NSCLC (squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and adenosquamous cell carcinoma), stage IIIB (not suitable for chemoradiation) or IV disease, Eastern Cooperative Oncology Group Performance Status (ECOG PS) $\leq$2, age $\geq$18 years, measurable disease by RECIST criteria, no prior chemotherapy, adequate function of bone marrow [absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l], liver [serum bilirubin level $\leq$1.5 mg/dl, AST and ALT $\leq$ 2.5 of upper normal limit(UNL), and alkaline phosphatase $\leq$5 of UNL], and kidney [creatinine level $\leq$1.5 mg/dl]. Patients with any of the following were excluded: presence of active infection, severe uncontrolled heart disease, uncontrollable hypertension or diabetes mellitus, myocardial infarction during the preceding 6 months, active gastric or duodenal ulcers, pregnancy, and any previous or concurrent malignancy other than non-melanomatous skin cancer or in situ cancer of the uterus or cervix. All patients gave written informed consent. The study protocol was approved by the institutional review board at each study center, and the study was conducted in compliance with the Helsinki Declaration and Korean Good Clinical Practice.

In the 2 weeks before initiation of treatment, patients underwent a full medical checkup—a complete medical history was taken and physical examination done, ECOG PS was determined, and the following laboratory tests were performed: complete blood cell count (CBC), serum biochemistry (hepatic and renal function tests and electrolytes), urinalysis, and electrocardiogram. Chest radiographs

and computerized tomography (CT) scans of all disease sites were obtained in the 3 weeks prior to study enrollment.

Treatment schedule

A total of six cycles of the planned chemotherapy were given, with repeat dosing at 3-week intervals. All patients were admitted during the first cycle of chemotherapy. Docetaxel 40 mg/m^2 and cisplatin 35 mg/m^2 were administered on days 1 and 8. Docetaxel was dissolved in 250 ml of 5% dextrose solution and infused over 30 min, with 16 mg dexamethasone given 30 min before infusion. On completion of docetaxel infusion, cisplatin dissolved in 150 ml of 0.9% saline was administered intravenously over 30 min, with adequate intravenous hydration ensured (750 ml of normal saline was given over 60 min before cisplatin, and 1,000 ml given over 90–120 min after). Prophylactic intravenous and oral 5HT3 antagonist were used to decrease nausea and vomiting. G-CSF prophylaxes were not permitted. For patients to proceed beyond the second cycle, ANC had to be $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, and toxicities resolved to $\leq$grade 1. After four cycles of treatment, the decision whether two additional cycles were needed was made based on response and toxicity.

Dose modification and discontinuation of treatment

At the scheduled day of drug administration, if the ANC was $<1.5 \times 10^9$/l and/or platelet count $<100 \times 10^9$/l, or if grade 2 non-hematologic toxicities were present, chemotherapy was delayed for up to a maximum of 1 week. In subsequent weeks, administration of both drugs was reduced or omitted if toxicity occurred, and this was done according to the following dosage adjustment criteria: if ANC ranged from 1.0 to 1.5×10^9/l and/or platelet count was 75–99.9 $\times 10^9$/l, 75% of full doses of both drugs were given; if ANC ranged from 0.75 to 0.99×10^9/l and/or platelet count was 50–74.9 $\times 10^9$/l, 50% of full doses were given; chemotherapy was not given if ANC was $<0.75 \times 10^9$/l and/or platelet count $<50 \times 10^9$/l. After dose reduction, resumption of initial dose was not permitted. Patients were removed from the study if more than two dose reductions occurred, counts were inadequate by day 36, or grade 3 or 4 non-hematologic toxicity did not resolve by day 1 of the next cycle. Treatment was discontinued when any of the following occurred: radiographic or clinical evidence of cancer progression, deterioration of health or the attending physician believed it was in the patient's best interest to stop therapy, intolerable toxicity, or the patient's refusal to continue treatment. Once treatment was stopped, post-study follow-up and subsequent therapy were managed by the attending physician.

Response and toxicity assessment

Patients had CBC tests done before days 1 and 8 of treatment, and all laboratory tests including CBC, serum biochemistry, and chest radiographs were rechecked on day 1 of each cycle. Tumor responses were evaluated after every two cycles of chemotherapy, based on the measurements of tumor lesions on CT scans.

Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, of the National Cancer Institute (NCI). The most severe degree of toxicity experienced during treatment was recorded for each patient.

Statistical analysis

According to the mini-max two-stage phase II study design by Simon, 33 patients were required for a statistical power of 80% and a false positive rate of 5%, with lower activity level rate of 5%, and a lower and higher activity level of 20% and 40%, respectively. Assuming a drop-out rate of 10%, 37 patients had to be accrued.

The response rates and their 95% CIs were estimated based on the exact binomial distribution. Duration of response was measured from the time that measurement criteria were met for response to the first date that progressive disease was documented. Progression free survival (PFS) was measured from the start of treatment to evidence of progression of cancer. Overall survival (OS) was measured from the start date of treatment to the date of death from any cause. PFS and OS were estimated using the Kaplan–Meier method using SPSS statistical software programs. Toxicity was summarized descriptively by frequency distributions for $\geq$ grade 2 toxicity events.

Results

Patients

From November 2005 to June 2008, a total of 36 patients from six sites in South Korea were enrolled. One patient withdrew consent before the beginning of treatment. The median duration of follow-up for this study was 10.6 months. As of 1 April 2009, 24 patients had died.

The demographic and baseline characteristics of the 35 patients are summarized in Table 1. At study entry, 74.3% (26/35) of patients presented with metastatic disease and 57.1% (20/35) had adenocarcinoma. The median age was

Table 1 Patients' characteristics

Number of patients	$N = 35$
Age (years)	
Median	62
Range	38–68
Sex	
Male	28
Female	7
Performance status (ECOG)[a]	
0–1	31
2	4
Disease stage	
IIIB	9 (25.7%)
IV	26 (74.3%)
Histology	
Adenocarcinoma	20 (57.1%)
Squamous cell carcinoma	11 (31.4%)
Unclassified	4 (11.5%)

[a] *ECOG* Eastern Cooperative Oncology Group

62 years (range, 38–68), and 80% (28/35) of patients were male. The median time interval from diagnosis to study entry was 1.71 weeks (range 0–150.29). Overall, two patients (5.7%) underwent prior surgery, and two patients (5.7%) had palliative radiotherapy before study entry.

Clinical efficacy

Response rate was calculated via intent-to-treat analysis. The overall response rate was 48.57% (95% CI, 31.15–65.99%), and all responses were partial responses; there were no complete responses (Table 2). Six (17.1%) patients had progressive disease, and of these, four had progressive disease after two cycles of chemotherapy; 12 (34.3%) patients had stable disease. The mean (±standard deviation) duration of response was 5.9 (±3.05) months. Median PFS was 4.6 months (95% CIs, 2.9–6.3 months) (Fig. 1), and median OS was 11.8 months (95% CIs, 5.8–17.7 months) (Fig. 2). One- and 2-year survival rates were 65.7 and 31.9%, respectively.

Toxicity

A total of 153 cycles were administered, with the median number of cycles administered per person being four cycles (range, 2–6). Table 3 shows any grade 2 or greater toxicities occurring in the 35 patients. Grade 3 and 4 hematologic toxicities included anemia (17.1%) and neutropenia (11.5%). Two patients experienced grade 2 febrile neutropenia; this was treated with antibiotics and the patients subsequently recovered.

Overall, 46% (16/35) of patients reported grade 3 or 4 non-hematologic toxicities. The most common and severe toxicities were grade 3 and 4 infections (four patients affected; two had bacterial pneumonia, one had atypical pneumonia, and one had infectious colitis), and three patients discontinued treatment because of side effects (two had pneumonia and one had paronychia). Azotemia occurred in one patient but renal function was restored after discontinuation of chemotherapy. There were no hypersensitivity reactions.

Salvage chemotherapy on progression

Twenty nine of the 35 patients subsequently received second-line chemotherapy, and of these, a further 17 received third-line chemotherapy.

Second-line chemotherapy was administered as follows; pemetrexed in 12 patients, gemcitabine-containing regimen in 10 patients, gefitinib in 4 patients, and erlotinib in 2 patients. Four patients received a fourth line of chemotherapy. Salvage chemotherapy had a positive effect on survival time. Patients who received second-line chemotherapy had longer survival times (median of 15.9 months; range, 10.04–21.76 months) than those who did not (median of 5.77 months; range, 2.65–8.89 months) ($P < 0.0001$).

Discussion

This is a phase II clinical trial evaluating the efficacy and toxicity of a fractionated schedule of docetaxel and

Table 2 RECIST clinical response criteria on intent-to-treat population

Type of response	Number of patients ($n = 36$)	%	95% CI
Complete response	0	0	–
Partial response	17	48.57	31.15–65.99
Stable disease	12	34.29	17.74–50.83
Progressive disease	6	17.14	4.01–30.28
Not assessable for response or withdrew before starting	1	–	–

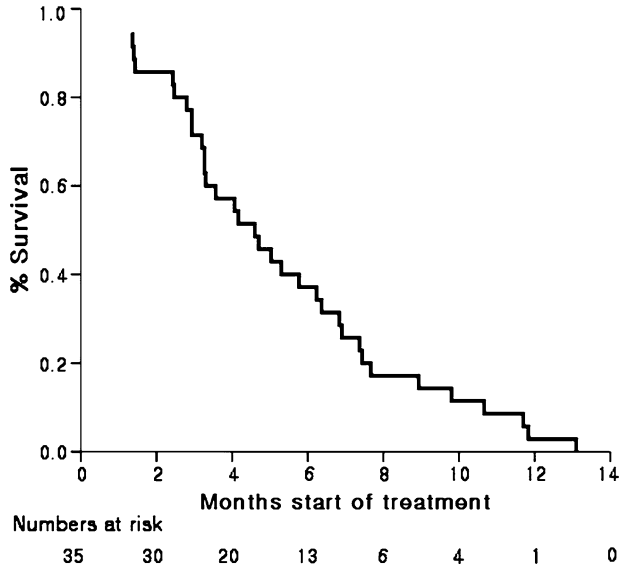

Fig. 1 Progression-free survival of 35 patients

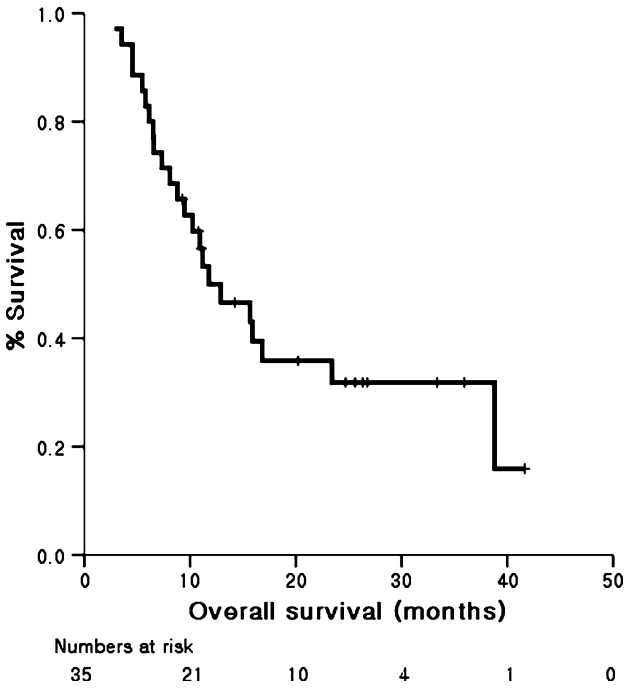

Fig. 2 Overall survival of 35 patients

cisplatin in patients with chemotherapy-naive stage IIIB or IV NSCLC. The outcome of the study is promising—overall response rate was 48.6% (95% CI, 31.15–65.99%), with median PFS of 4.6 months (95% CI, 2.9–6.3 months). This outcome is comparable to that consistently reported for standard cisplatin-based doublet regimen treatments (approximately 17–37% response rate with PFS of 7.4–11.3 months) [10, 11, 22]. Grade IV neutropenia occurred in only one patient and grade IV anemia in two patients. Although four patients developed pneumonia, none of them died from it; however, treatment was interrupted in two patients. The toxicity profile in this schedule of treatment is similar to the least severe ones that have been reported in the literature.

In ECOG clinical trial, docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 were administered in 3-week schedule. They reported that median survival was 7.4 months (6.6–8.8) and response rate was 17% [22]. About 69% of patients experienced grade 3 and 4 neutropenia, 11% of them underwent febrile neutropenia, thereafter, high level of toxicity was remained the problem to solve. In TAX 326 study, conventional dose of docetaxel and cisplatin combination showed median survival of 11.3 months and response rated of 31.6% [10]. The toxicity profile in the same study was also miserable; grade 3 and 4 neutropenia was 74.8%. Although the regimen of docetaxel 60–100 mg/m^2 every 3 weeks is a commonly used one, 69–74.8% of patients have been known to develop grade 3 or 4 hematologic toxicities with this regimen [10, 11, 22]. To decrease the incidence of severe adverse events, weekly docetaxel administration has become an attractive option for the treatment of advanced stage NSCLC. Randomized phase III trials comparing weekly and 3-weekly administration of docetaxel in patients with previously treated NSCLC have shown comparable efficacies of both treatment regimens [15, 23, 24]. These trials also reported similar efficacies and less toxicity with the weekly regimen compared to the 3-weekly one. In a randomized phase II study, Gervais et al. [15] suggested that weekly docetaxel at 40 mg/m^2 could be an alternative option to the 3-weekly regimen in patients with previously treated NSCLC. In their study, median time to progression was similar and less toxicity observed with the weekly regimen compared to the 3-weekly one, and response rate also showed a trend toward better disease control with the former treatment than the latter (32.2 vs. 25.4%). Gredelli et al. [23] focused on quality of life (QOL) issues and found that results were similar for global QOL in patients given the 3-weekly and weekly regimens. Moreover, Gervais et al. [15] and Camps et al. [25] demonstrated that weekly docetaxel is effective and well tolerated. These trials elicited several phase I clinical trials in the previously untreated advance NSCLC [17, 26, 27]. The dose intensity of these studies is between 18.75 and 26.25 mg/m^2/week. Sato et al. suggested that the dose of docetaxel to be combined with CDDP 80 mg/m^2 on day 1 is 35 mg/m^2 per week on days 1, 8, and 15. They reported that most common non-hematologic toxicity appeared between day 8 and 15 [17]. Based on these results, we choose the schedule that consisted of docetaxel 40 mg/m^2 on days 1 and 8 every 3 weeks; dose intensity of docetaxel was 26.67 mg/m^2/week.

Table 3 Toxicity profile

Toxicity	Grade 2		Grade 3		Grade 4	
	Number of patients	%	Number of patients	%	Number of patients	%
Anemia	14	40	4	11.4	2	5.7
Neutropenia	0	0	3	8.6	1	2.9
Febrile neutropenia	2	5.7	0	0	0	0
Thrombocytopenia	1	2.9	1	2.9	0	0
Fatigue	1	2.9	2	5.7	0	0
Adrenal insufficiency	2	5.7	0	0	0	0
Diarrhea	3	8.6	2	5.7	1	2.9
Dysphagia	1	2.9	0	0	0	0
Stomatitis	4	11.4	0	0	0	0
Nausea	10	28.6	3	8.6	0	0
Vomiting	4	11.4	1	2.9	0	0
Infection with normal ANC	2	5.7	3	8.6	1	2.9
Hypocalcemia	0	0	0	0	1	2.9
Neuropathy	3	8.6	0	0	0	0
Azotemia	1	2.9	0	0	1	2.9
Nail change	0	0	1	2.9	0	0

Table 4 Dosage and administration

Result	Docetaxel	Cisplatin
Number of cycles of chemotherapy		
Total	153	153
Median (range)	4 (2–6)	4 (2–6)
Dose-reduced cycles		
No.	12	14.5
%	7.84	9.5
Delayed cycles		
No.	17	
%	11.1%	
Planned dose intensity (%)[a]	26.7 mg/m^2/week (100%)	23.3 mg/m^2/week (100%)
Actual dose intensity (%)[b]	24.0 mg/m^2/week	21.0 mg/m^2/week
Relative dose intensity (%)[c]	90.0%	90.1%

AUC area under the curve

Relative dose intensity = actual dose/planned dose × 100%

[a] Planned dose intensity: planned dose per week

[b] Actual dose intensity: dose patient received per week

[c] Relative dose intensity: actual dose/planned dose × 100%

We also planned to modify the administration schedule of cisplatin. The required cisplatin dose in a 3-week treatment regimen is 70–80 mg/m^2 (23–27 mg/m^2/week). Administration of these high doses of cisplatin should be accompanied by vigorous hydration and meticulous preparation to reduce the incidence of toxicity. Although cisplatin is the mainstay of treatment for NSCLC, renal toxicity, nausea, and vomiting are main restriction of treatment. In the conventional schedule of docetaxel and cisplatin, 44% of renal toxicity, 83% of nausea, and 57% of vomiting were reported [28]. Several clinical studies [20, 21, 29, 30] have suggested that weekly administration of cisplatin may have similar efficacy and less toxicities to 3-weekly cisplatin given in combination chemotherapy. We recently reported on the weekly administration of cisplatin with gemcitabine in chemotherapy-naïve NSCLC patients [18]. In this study, we showed that gemcitabine with weekly cisplatin had similar efficacy (response rate of 51%) to and less toxicity than the 3-weekly regimen.

Several trials have evaluated the efficacy and toxicity of weekly administration of docetaxel and cisplatin for NSCLC in the first-line setting (Table 5). Four of these studies divided the dose of docetaxel [31–34], and two studies separated the dose of both drugs [20, 21] into 4-weekly cycles. The response rates to the chemotherapy regimens ranged from 27 to 45%, and the median survival times ranged from 10.1 to 12.8 months [20, 21, 31–34]. Planned dose intensity of docetaxel in these studies ranged from 18.75 to 26.25 mg/m^2/week, levels which are somewhat lower than the 3-weekly regimens (25 mg/m^2/week).

Table 5 Summary of relevant clinical trials in patients with advanced stage NSCLC

Author	Regimen	Number of patients	RR (%)	TTP (M)	OS (M)	PDI	ADI	Common grade 3 or 4 toxicities more than 5%
Niho (2002) [21]	D 35 mg/m^2 d1,8,15 C 25 mg/m^2 d1,8,15 q 4w	33	27	5.1	12.8	26.25 18.75	23.8	Neutropenia (25%), anemia (14%)
Tsunoda (2004) [33]	D 25 mg/m^2 d1,8,15 C 80 mg/m^2 d1 q 4w	38	31.6	NA	11.8	18.75 26.7	NA	Neutropenia (18%)
Kaira (2005) [31]	D 35 mg/m^2 d1,8,15 C 80 mg/m^2 d1 q 4w	40	45	5.5	19.9	26.25 26.7	24.7	Neutropenia (37.5%), Anemia (12.5%)
Tartarone (2005) [32]	D 25 mg/m^2 d1,8,15 C 80 mg/m^2 d1 q 4w	31	40	6.4	10.1	18.75 26.7	18.75	Neutropenia (6%), nausea (6%), febrile neutropenia (6%)
Park (2007) [34]	D 35 mg/m^2 d1,8,15 C 75 mg/m^2 d1 q 4w	43	39	3.9	10.0	26 18.75	23.1 98%	Neutropenia (9%), anemia (28%), stomatitis (24%), Fatigue (44%), Nausea/vomiting (35%), peripheral neuropathy (21%), diarrhea (14%), skin toxicity (21%), nail toxicity (16%),
Han (2009) [20]	D 25 mg/m^2 d1,8,15 C 20 mg/m^2 d1,8,15 q 4w	48	39.6	10.9	10.9	18.75 15	17.25[a]	Anemia (17.3%), Neutropenia (8.7%), stomatits (10.9%), diarrhea (10.9%), Neuropathy (10.9%), Nail toxicity (8.7%)
Current study	D 40 mg/m^2 d1,8 C 35 mg/m^2 d1,8 q 3w	35	48.57	4.6	11.8	26.7 23.3	24	Anemia (17.1%), Neutropenia (11.5%), diarrhea (8.6%), nausea (8.6%)

D docetaxel; *C* cisplatin; *RR* response rate; *TTP* median time to progression; *OS* median overall survival; *M* months; *NA* not available; *a* abstract available in English; *b* carboplatin; *PDI* planned dose intensity (mg/m^2/week)

[a] Calculated from the data the authors presented

Our hypothesis was that with a 2-weeks-on and 1-week-off schedule of chemotherapy, non-hematologic toxicities would be reduced compared with the 3-weeks-on and 1-week-off type of schedule, and both these regimens would be similarly efficacious. Park et al. [34] compared two different administration schedules of docetaxel. In that study, he reported that overall response rate (40% in the 3-weekly regimen and 39% in the weekly regimen, $P = 0.74$) and median PFS (4.3 months in the 3-weekly regimen and 3.9 months in the weekly one, $P = 0.08$) was not significantly different between the two arms. The authors explained that this lack of difference resulted from the reduced dose intensity of the weekly arm compared to the 3-weekly one (88 vs. 97%). About 21% omitted the day 8 dose of docetaxel because of cytopenia, and the planned dose intensity was lower in the weekly arm than the 3-weekly one (25 vs. 18.75 mg/m^2/week). There were more frequent reports of thrombocytopenia and neutropenia in the 3-weekly arm; but more fatigue, nausea/vomiting, peripheral neuropathy, and skin toxicity in the weekly arm resulted in no difference in QOL between the two arms. Our study changed the administration of the chemotherapy from a 4-weekly schedule to a 3-weekly one to increase the density of the dose. The actual dose intensity in our study is fairly comparable to the 3-weekly regimen (24.0 mg/m^2/week: range, 16.52–26.7 mg/m^2/week for docetaxel, and 24.0 mg/m^2/week: range, 16.52–26.7 mg/m^2/week for cisplatin) (Table 4). A relatively high dose intensity of both drugs could explain the high response rate in our study. The median OS in our study is quite consistent with the survival rates seen with platinum doublet therapy, as has been previously reported [10, 11, 22].

Conclusion

We performed the present study to prove the hypothesis that weekly administration of docetaxel and cisplatin has comparable efficacy and better toxicity profiles, especially in the previously untreated patients. Although our study has the limitation of a phase II clinical trial design, fractionated schedule of docetaxel and cisplatin is an alternative

regimen in patients with chemotherapy-naive stage IIIB or IV NSCLC. Our study demonstrated comparable response rates and less toxicity for this regimen compared with the platinum doublet regimen currently being used. The result of this trial suggests conducting phase III clinical trial to prove clinical efficacy and less toxicity of fractionated schedule of docetaxel and cisplatin.

Conflict of interest statement None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References

1. Bae J, Won Y, Jung K, Park J (2002) Annual report of the Korean central cancer registry program 2000: based on registered data from 131 hospitals. Cancer Res Treat 34:77–83
2. Non-small Cell Lung Cancer Collaborative Group (1995) Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 311:899–909
3. Marino P, Pampallona S, Preatoni A, Cantoni A, Invernizzi F (1994) Chemotherapy vs supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. Chest 106:861–865
4. Clarke SJ, Rivory LP (1999) Clinical pharmacokinetics of docetaxel. Clin Pharmacokinet 36(2):99–114
5. Cerny T, Kaplan S, Pavlidis N, Schoffski P, Epelbaum R, van Meerbeek J, Wanders J, Franklin HR, Kaye S (1994) Docetaxel (Taxotere) is active in non-small-cell lung cancer: a phase II trial of the EORTC early clinical trials group (ECTG). Br J Cancer 70:384–387
6. Kunitoh H, Watanabe K, Onoshi T, Furuse K, Niitani H, Taguchi T (1996) Phase II trial of docetaxel in previously untreated advanced non-small-cell lung cancer: a Japanese cooperative study. J Clin Oncol 14:1649–1655
7. Yvon AC, Wadsworth P, Jordan MA (1999) Taxol suppresses dynamics of individual microtubules in living human tumor cells. Am Soc Cell Biology 10:947–959
8. Fossella FV, Lee JS, Shin DM, Calayag M, Huber M, Perez-Soler R, Murphy WK, Lippman S, Benner S, Glisson B, Chasen M, Hong WK, Raber M (1995) Phase II study of docetaxel for advanced or metastatic platinum-refractory non-small cell lung cancer. J Clin Oncol 13:645–651
9. Kelland LR, Abel G (1992) Comparative in vitro cytotoxicity of taxol and Taxotere against cisplatin-sensitive and -resistant human ovarian carcinoma cell lines. Cancer Chemother Pharmacol 30:444–450
10. Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szczesna A, Fidias P, Millward M, Belani CP (2003) Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 21:3016–3024
11. Kubota K, Watanabe K, Kunitoh H, Noda K, Ichinose Y, Katakami N, Sugiura T, Kawahara M, Yokoyama A, Yokota S, Yoneda S, Matsui K, Kudo S, Shibuya M, Isobe T, Segawa Y, Nishiwaki Y, Ohashi Y, Niitani H (2004) Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: the Japanese Taxotere Lung Cancer Study Group. J Clin Oncol 22:254–261
12. Georgoulias V, Ardavanis A, Agelidou A, Agelidou M, Chandrinos V, Tsaroucha E, Toumbis M, Kouroussis C, Syrigos K, Polyzos A, Samaras N, Papakotoulas P, Christofilakis C, Ziras N, Alegakis A (2004) Docetaxel versus docetaxel plus cisplatin as front-line treatment of patients with advanced non-small-cell lung cancer: a randomized, multicenter phase III trial. J Clin Oncol 22:2602–2609
13. Georgoulias V, Androulakis N, Dimopoulos AM, Kourousis C, Kakolyris S, Papadakis E, Apostolopoulou F, Papadimitriou C, Vossos A, Agelidou M, Heras P, Tzannes S, Vlachonicolis J, Mavromanolakis E, Hatzidaki D (1998) First-line treatment of advanced non-small-cell lung cancer with docetaxel and cisplatin: a multicenter phase II study. Ann Oncol 9:331–334
14. Zalcberg J, Millward M, Bishop J, McKeage M, Zimet A, Toner G, Friedlander M, Barter C, Rischin D, Loret C, James R, Bougan N, Berille J (1998) Phase II study of docetaxel and cisplatin in advanced non-small-cell lung cancer. J Clin Oncol 16:1948–1953
15. Gervais R, Ducolone A, Breton JL, Braun D, Lebeau B, Vaylet F, Debieuvre D, Pujol JL, Tredaniel J, Clouet P, Quoix E (2005) Phase II randomised trial comparing docetaxel given every 3 weeks with weekly schedule as second-line therapy in patients with advanced non-small-cell lung cancer (NSCLC). Ann Oncol 16:90–96
16. Hainsworth JD, Burris HA III, Erland JB, Thomas M, Greco FA (1998) Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. J Clin Oncol 16:2164–2168
17. Sato K, Tsuchiya S, Minato K, Takei Y, Watanabe S, Saitoh R, Mori M (2001) A phase I study of weekly docetaxel and cisplatin in advanced non-small cell lung cancer. Lung Cancer 33:69–73
18. Kim JH, Lee DH, Shin HC, Kwon JH, Jung JY, Kim HJ, Song HH, Lee KS, Zang DY, Ahn JS, Park YL, Lee JA (2006) A phase II study with gemcitabine and split-dose cisplatin in patients with advanced non-small cell lung cancer. Lung Cancer 54:57–62
19. Firvida JL, Amenedo M, Rodriguez R, Gonzalez A, Salgado M, Ramos M, Losada G (2004) Docetaxel plus fractionated cisplatin is a safe and active schedule as first-line treatment of patients with advanced non-small cell lung cancer: results of a phase II study. Invest New Drugs 22:481–487
20. Han K, Cao W, Che J, Bo S, Guo X, Huang G, Ma L, Sun L, Gao C, Zhong B, Cao Z, Tucker SJ, Wang D (2009) First line chemotherapy with weekly docetaxel, cisplatin in elderly patients with advanced non-small cell lung cancer: a multicenter phase II study. J Thorac Oncol 4:512–517
21. Niho S, Ohe Y, Kakinuma R, Kubota K, Matsumoto T, Ohmatsu H, Goto K, Nishiwaki Y (2002) Phase II study of docetaxel and cisplatin administered as three consecutive weekly infusions for advanced non-small cell lung cancer. Lung Cancer 35:209–214
22. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH (2002) Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92–98
23. Gridelli C, Gallo C, Di Maio M, Barletta E, Illiano A, Maione P, Salvagni S, Piantedosi FV, Palazzolo G, Caffo O, Ceribelli A, Falcone A, Mazzanti P, Brancaccio L, Capuano MA, Isa L, Barbera S, Perrone F (1996) A randomised clinical trial of two docetaxel regimens (weekly vs 3 week) in the second-line treatment of non-small-cell lung cancer. The DISTAL 01 study. Br J Cancer 91:1996–2004
24. Schuette W, Nagel S, Blankenburg T, Lautenschlaeger C, Hans K, Schmidt EW, Dittrich I, Schweisfurth H, von Weikersthal LF, Raghavachar A, Reissig A, Serke M (2005) Phase III study of second-line chemotherapy for advanced non-small-cell lung cancer with weekly compared with 3-weekly docetaxel. J Clin Oncol 23:8389–8395

25. Camps C, Massuti B, Jimenez A, Maestu I, Gomez RG, Isla D, Gonzalez JL, Almenar D, Blasco A, Rosell R, Carrato A, Vinolas N, Batista N, Giron CG, Galan A, Lopez M, Blanco R, Provencio M, Diz P, Felip E (2006) Randomized phase III study of 3-weekly versus weekly docetaxel in pretreated advanced non-small-cell lung cancer: a Spanish Lung Cancer Group trial. Ann Oncol 17:467–472
26. Hainsworth JD, Burris HA III, Litchy S, Morrissey LH, Barton JH, Bradof JE, Greco FA (2000) Weekly docetaxel in the treatment of elderly patients with advanced nonsmall cell lung carcinoma. A Minnie Pearl cancer research network phase II trial. Cancer 15;89(2):328–333
27. Koizumi T, Tsunoda T, Fujimoto K, Nomura H, Hirai K, Koyama S, Okada K, Kubo K (2001) Phase I trial of weekly docetaxel combined with cisplatin in patients with non-small cell lung cancer. Lung Cancer 34:125–131
28. Zalcberg J, Millward MJ, Bishop JF, McKeage M, Zimet A, Toner G, Friedlander M, Barter C, Rischin D, Loret C, James R, Bougon N, Berille J (1998) Phase II study of docetaxel and cisplatin in advanced non-small-cell lung cancer. J Clin Oncol 16:1948–1953
29. Shepherd FA, Cormier Y, Burkes R, Evans WK, Goss G, Klimo P, Feld R, Taylor M (1997) Phase II trial of gemcitabine and weekly cisplatin for advanced non-small cell lung cancer. Semin Oncol 24:S8-27–S28-30
30. Berardi R, Porfiri E, Scartozzi M, Lippe P, Silva RR, Nacciarriti D, Menichetti ET, Tummarello D, Carle F, Piga A, Cellerino R (2003) Elderly patients with advanced non-small cell lung cancer. A pase II study with weekly cisplatin and gemcitabine. Oncology 65:198–203
31. Kaira K, Takise A, Minato K, Iwasaki Y, Ishihara S, Takei Y, Tsuchiya S, Saito R, Sato K, Mori M (2005) Phase II study of weekly docetaxel and cisplatin in patients with non-small cell lung cancer. Anticancer Drugs 16:455–460
32. Tartarone A, Romano G, Iodice G, Capobianco A, Coccaro M, Bochicchio A, Di Leo P, Ardito R, Di Renzo N (2005) Cisplatin and weekly docetaxel as first-line therapy in patients with advanced non-small cell lung cancer a phase II study. Tumori 91:131–134
33. Tsunoda T, Koizumi T, Hayasaka M, Hirai K, Koyama S, Takabayashi Y, Fujimoto K, Kubo K (2004) Phase II study of weekly docetaxel combined with cisplatin in patients with advanced non-small-cell lung cancer. Cancer Chemother Pharmacol 54:173–177
34. Park SH, Choi SJ, Kyung SY, An CH, Lee SP, Park JW, Jeong SH, Cho EK, Shin DB, Hoon Lee J (2007) Randomized phase II trial of two different schedules of docetaxel plus cisplatin as first-line therapy in advanced nonsmall cell lung cancer. Cancer 109:732–740