A Phase II Study of Weekly Docetaxel-Cisplatin As First-Line Treatment for Advanced Non-small Cell Lung Cancer

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Introduction: The combination of docetaxel and cisplatin is an effective first-line regimen in patients with advanced non-small cell lung cancer. However, the recommended three-weekly schedule is associated with frequent neutropenia and infections. Because of the toxicity of cisplatin, patients may need to be hospitalized to ensure adequate hydration. The aim of this study was to assess the efficacy and tolerability of a weekly schedule of docetaxel and cisplatin.

Patients and Methods: Patients with inoperable stage International Union Against Cancer IIIB (malignant effusion) or IV non-small cell lung cancer received docetaxel (35 mg/m^2, 30 minutes infusion) and cisplatin (25 mg/m^2, 30 minutes infusion) on days 1, 8, and 15, every 4 weeks for 4 to 6 cycles. Ondansetron (8 mg) and dexamethasone (8 mg) were given intravenously before chemotherapy. The patients received oral dexamethasone 2 × 4 mg daily from the day before until the day after chemotherapy. NK1-antagonists were given at the investigator's discretion. The majority of patients was treated in outpatient departments. Safety was assessed using CTCAE v3.0. The primary end point was response rate (RECIST).

Results: Forty-four patients were included. Twelve of 44 patients achieved an objective response (11 partial, 1 complete, intent-to-treat response rate 27%). Median time to progression was 4.4 months (95% confidence interval: 4.0–4.7) and median survival 9.6 months (95% confidence interval: 2.9–16.2). Patients received a median of three full cycles. Four patients (9%) required dose reductions. No cases of febrile neutropenia or grade 2 to 4 thrombocytopenia were observed. One patient (2%) experienced grade 3/4 nausea and vomiting.

Conclusions: Weekly docetaxel-cisplatin demonstrated comparable efficacy with three-weekly schedules. Although the frequencies of neutropenia and febrile neutropenia were low, non-neutropenic infections remained a problem. Because of relatively short hydration, the schedule can be safely administered in an outpatient setting.

Key Words: Docetaxel, Cisplatin, NSCLC, Chemotherapy, Neutropenia.

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In recent years, the outcome of patients with local and locally advanced non-small cell lung cancer (NSCLC) has modestly improved. In the metastatic setting, improved patient selection and novel drugs have facilitated some advance, although survival in most patients with advanced disease remains very limited.[1–3] As a result, treatment tolerability and comfort of administration are gaining increased attention.

The recommended three-weekly schedule of docetaxel and cisplatin is frequently associated with neutropenia and subsequent neutropenic infections.[1,3,4] Moreover, patients receiving full-dose cisplatin frequently require hospitalization to ensure appropriate pretreatment and posttreatment hydration. Hospitalization has a substantial negative impact on quality of life, which is important when considering the dramatically shortened survival time of patients with advanced disease.

Weekly administration may facilitate outpatient administration of the combination. After Ohe et al.[5] evaluated maximum tolerable doses of weekly docetaxel/cisplatin in their phase I study, phase II data were published by Niho et al.[6] in 2002 and by Ohe et al.[7] in 2004 with efficacy results comparable with those of three-weekly schedules. In this study, we investigated the tolerability and efficacy of a weekly schedule of docetaxel and cisplatin in the first-line treatment of advanced NSCLC in Caucasian patients.

PATIENTS AND METHODS

This noncomparative, open-label phase II study was performed in three medical centers in Germany, including two pulmonologist departments and one hematology/oncology department. The patients were accrued between August 2004 and September 2006.

Eligible patients had International Union Against Cancer stage IIIB (malignant effusion) or stage IV non-small cell

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lung cancer and were chemonaive. Eastern Cooperative Oncology Group performance status had to be ≤2. Adequate organ function was defined as absolute neutrophil counts $\geq 1.5 \times 10^9$/liter, platelet count $\geq 100 \times 10^9$/liter, and total bilirubin ≤1.25 × the upper limit of normal and plasma creatinine within the normal limits. Brain metastases were not excluded. All subjects signed informed consent before entering the study. The study protocol had been approved by the responsible ethics committee at Charité Universitätsmedizin Berlin, Germany.

Patients were treated with docetaxel (35 mg/m^2, 30-minute infusion) and cisplatin (25 mg/m^2, 30-minute infusion) on days 1, 8, and 15 of each 28-day cycle. The number of scheduled cycles was 4 to 6 depending on the decision of the local investigator. The treatment protocol specified a total hydration volume of 2750 ml (including chemotherapy solutions) delivered during 3.5 hours on each treatment day. Ondansetron (8 mg) and dexamethasone (8 mg) were given intravenously as premedication and 4 mg of dexamethasone was administered orally twice daily from the day before until the day after each chemotherapy. NK-1 antagonists were administered at the local investigator's discretion.

The primary end point was response to treatment (assessed according to RECIST). The secondary end points comprised median overall survival and 1-year survival, median time to progression, and toxicity (National Cancer Institute Common Toxicity Criteria version 3.0).

A Simon two-stage optimal design was used.[8] With $\alpha = 0.05$ and $\beta = 1\text{-}0.80$, a null hypothesized response rate of 0.20 and an alternative response rate of 0.40 were assumed. Therefore, three responses were needed among the first 13 subjects (first stage) to proceed to the full accrual of 44 patients. The upper limit of second-stage rejection was 12 responses in the 44 evaluable patients.

RESULTS

Accrual and Administration of Treatment

Forty-four patients were enrolled, all of whom were evaluable for safety. Forty patients received at least one full cycle and were evaluated for efficacy. Baseline characteristics are presented in Table 1. The majority of the patients was treated in outpatient departments. The median number of full cycles administered was 3. Seventeen patients (38.6%) received ≥4 treatment cycles.

The chemotherapy dose had to be reduced in four patients (9.1%). Reasons for reduction included nausea (one patient), fatigue/asthenia (two patients), and frequent bronchopulmonary infections (one patient). Of the patients, 24, 14, four, one, and one had total delays of 0, 1, 2, 3, and 4 weeks during their treatment, respectively. The calculated dose density per cycle was 92/92%, 90/90%, 90/91%, 91/91% for cycles 1, 2, 3, and 4, respectively.

Response and Survival

In the intent-to-treat analysis, 12 patients (27.3%) demonstrated a treatment response. One patient (2.3%) had a complete response and 11 patients (25.0%) had a partial response. Thus, the prespecified criteria for efficacy according to the statistical model were not met (at least 13 responders required). Sixteen patients (36.4%) were observed as having a stable disease. Progressive disease was observed in eight patients (18.2%), and a further eight patients (18.2%) were not evaluable for response.

The median overall survival time was 9.6 months (95% confidence interval: 2.9–16.2), with 45.5% ($n = 20$) of the patients surviving for ≥1 year, median time to progression was 4.4 months (95% confidence interval: 4.0–4.7). For details see Figures 1 and 2.

TABLE 1. Patient Baseline Characteristics

Characteristics	*N*	Percentage
Total patient number	44	100
Age (range, 46–74 yr; median, 62 yr)		
≥65 yr, *n* (%)	13	29.5
≥70 yr, *n* (%)	6	13.6
Female	12	27.3
Tumor histology		
Squamous cell carcinoma	13	29.5
Adenocarcinoma	23	52.3
Large cell carcinoma	2	4.5
Undifferentiated/other	6	13.6
Tumor UICC stage		
IIIB	5	11.4
IV	39	88.6
WHO/ECOG performance status		
0	10	22.7
1	27	61.4
2	7	15.9

UICC, International Union Against Cancer; WHO, World Health Organization; ECOG, Eastern Cooperative Oncology Group.

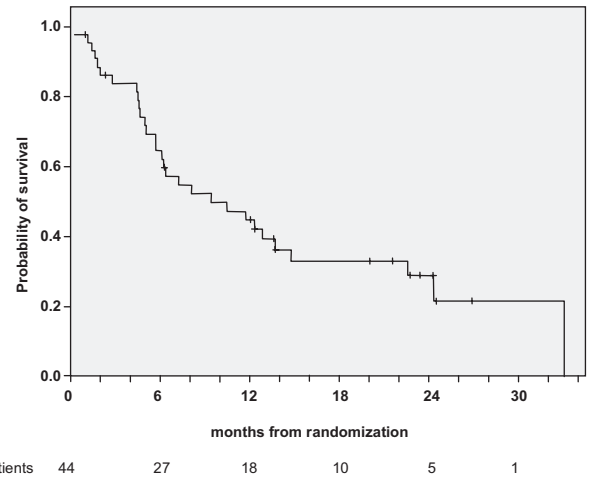

FIGURE 1. Overall survival.

Tolerability

Severe hematologic toxicity was rare, and no cases of febrile neutropenia or grades 2 to 4 thrombocytopenia occurred (Table 2). Only one patient (2%) experienced grade 3 nausea and vomiting, whereas mild nausea was common.

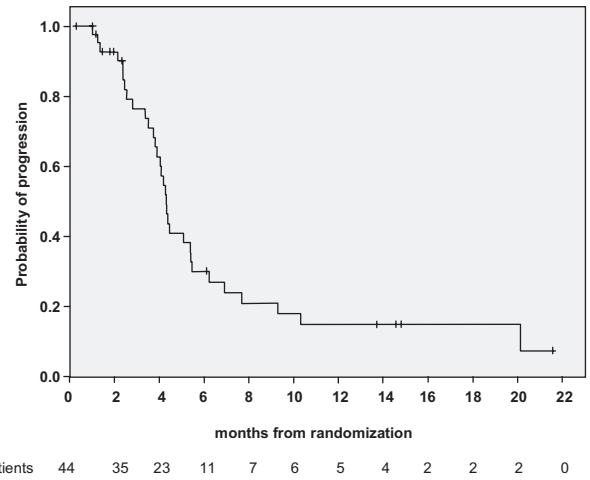

FIGURE 2. Time to progression.

TABLE 2. Grade 3/4 Toxicities (National Cancer Institute Common Toxicity Criteria version 3.0), $n = 44$

Grade 3/4 Adverse Events	*N*	Percentage
Leukopenia/neutropenia	2	4.5
Neutropenic infections	0	0
Thrombocytopenia	0	0
Infection without neutropenia	2	4.5
Nausea and vomiting	1	2.3
Diarrhea	2	4.5
Fatigue/asthenia	3	6.8
Mucositis	1	2.3

Moreover, several patients suffered from moderate to severe fatigue ($n = 11$ [25%] with grades 2–3).

Five patients (11%) died during therapy for reasons that were not unequivocally attributable to tumor progression. Causes of death included bacterial meningitis with normal neutrophil counts ($n = 1$), pneumonia with normal neutrophil counts ($n = 1$), suspected pulmonary arterial embolism ($n = 1$), diagnosed pulmonary arterial embolism ($n = 1$), and unknown cause ($n = 1$; death at home and autopsy not performed). Two patients (4%) died within 30 days after inclusion. These patients were termed as early death (pulmonary arterial embolism [$n = 1$] and unknown cause [$n = 1$]). In addition, one patient suffered from a grade 4 infection with normal neutrophil counts (pneumonia), and another seven patients had non-neutropenic grade 2/3 infections (the majority was with nonsevere pneumonia and tracheobronchitis). Infections occurred both early and late during the course of treatment.

DISCUSSION

In this study, we demonstrated that a regimen of docetaxel and cisplatin administered weekly is feasible. The relatively low hydration time and volume makes outpatient administration easier than in schedules with three-weekly cisplatin. Because we observed only 12 responses, the specified criteria for demonstrating efficacy (13 intent-to-treat responders) was not met. Nevertheless, the response rate and time-to-event measures for progression and survival were in line with published three-weekly regimens with docetaxel and cisplatin[1,3,4] but were slightly inferior to other weekly studies.[6,7] In the studies published by Schiller et al.,[1] Fossella et al.,[3] and Georgoulias et al.,[4] the three-weekly docetaxel/cisplatin objective response rates ranged from 17 to 36.5%. Time to progression was in the range 3.7 to 5.5 months, whereas overall median survival was between 7.4 and 11.3 months.

Phase I results on weekly schedules of docetaxel and cisplatin were first published in 2001 by a Japanese group.[5] With a fixed dose of 25 mg/m^2 cisplatin, the docetaxel dose was stepwise escalated. The docetaxel dose was up to 45 mg/m^2 for patients $\leq$74 years of age and up to 25 mg/m^2 for patients $\geq$75 years of age when given as three consecutive weekly treatments every 4 weeks. Dose-limiting toxicities were neutropenia, infections, and asthenia/fatigue. The same group conducted a phase II study in which the recommended schedule for nonelderly patients (35 mg/m^2 of docetaxel and 25 mg/m^2 of cisplatin for three consecutive weekly treatments every 4 weeks) was applied to a population of 37 patients with advanced NSCLC.[6] Enrolled patients were $<$74 years of age and possessed a good performance status (Eastern Cooperative Oncology Group 0 or 1). With an overall response rate of 27% and a median survival of 12.8 months, the combination provided comparable efficacy with three-weekly schedules. Hematologic toxicity was unusual, and none of the patients suffered from febrile neutropenia or severe infections. Mild to moderate nausea and vomiting and diarrhea were common nonhematologic adverse events. The same investigators published further phase II data later in 2004[7] from a series of 34 elderly patients (75 years of age or older). The basis of their treatment schedule was the recommended dose from the former phase I study, in particular 20 mg/m^2 of docetaxel and 25 mg/m^2 of cisplatin for 3 consecutive weeks with 1 week off treatment. They observed excellent results with 52% response rate and a median overall survival of 15.8 months. None of the patients suffered from grade 3/4 infections, and severe nausea and vomiting was only observed in one patient (3%).

The present chemotherapy schedule demonstrated low hematologic toxicity. Leukopenia/neutropenia or febrile neutropenia were uncommon. Only two patients (4%) suffered from grade 3/4 neutropenia, whereas none of the subjects had febrile neutropenia. In former studies with three-weekly application of docetaxel and cisplatin, severe hematologic toxicity occurred more frequently. In the two largest study populations treated with 75 mg/m^2 of docetaxel and 75 mg/m^2 of cisplatin every 3 weeks, 75/69% of the patients had grades 3 and 4 neutropenia, respectively, and 5/10% developed febrile neutropenia.[1,3] In the large study giving 100 mg/m^2 of cisplatin and 80 mg/m^2 of docetaxel every 3 weeks (with primary prophylactic granulocyte-colony stimulating factor support), 28% of the patients had grade 3/4 neutropenia and 9% suffered from febrile neutropenia.[4] Thus, in this study, hematologic side effects were markedly reduced.

Moreover, severe nausea and vomiting were infrequently observed, whereas a considerable number of patients complained of milder nausea. Mild to moderate fatigue was also common. Docetaxel is known for its potential to cause infections without neutropenia. In a retrospective study conducted by Souglakos et al.,[9] docetaxel-based chemotherapy caused 2.4/2.8-fold more nonneutropenic infections than with paclitaxel-based or taxane-free schedules. This may be related to severe CD4-lymphopenia. In this study, although we observed hardly any high-grade neutropenia, two patients died of infections and one had serious (grade 4) pneumonia. Other patients required oral antibiotics during their course of chemotherapy for less serious complications.

The weekly administration of chemotherapy may result in higher doses of dexamethasone. The protocol comprised 9 days of high-dose dexamethasone in every 28-day cycle, which may contribute to the development of infections. Although additional corticosteroids to prevent or treat delayed nausea and vomiting were generally not necessary, exposure is probably markedly higher than in three-weekly schedules.

However, the treatment compliance of three full cycles in median (12 weeks) was similar to other published studies of docetaxel/cisplatin combinations (15/12 weeks/not recorded in the three-weekly schedules[3,4,1] and 8/12 weeks in the Japanese weekly studies[6,7]).

This study has certain limitations. In recent months, study results that have become available contradict the paradigm of homogeneity of all non-small lung cancers under chemotherapy.[10] Therefore, from today's point of view, the relatively general selection criterion "non-small cell lung cancer" seems to be suboptimal, and the particular histologies possibly warrant more precise patient stratification. This was unknown at the time of study initiation. With a relatively low-dose density of 75 mg/m^2/4 wk (18.75 mg/m^2/wk) in this study, cisplatin was obviously slightly underdosed when compared with common three-weekly schedules. However, this was not associated with clearly inferior efficacy or advantages or disadvantages in compliance to treatment. The data available from studies with weekly cisplatin and docetaxel in advanced NSCLC are currently limited to Japanese patients. Although this study confirms the observed low hematologic toxicity, we were not able to confirm the extraordinarily long survival previously mentioned in these publications. From today's viewpoint, it seems that Asian populations include more light or never smokers and females who have a favorable prognosis or exhibit a better outcome to more novel targeted second-line agents.[11,12]

In summary, the combination of docetaxel and cisplatin given weekly demonstrated less hematologic toxicity and febrile neutropenia, whereas nonneutropenic infections remain a problem. Although the statistical needs for demonstrating efficacy were not met, the efficacy was comparable with three-weekly schedules when given as first-line chemotherapy for advanced NSCLC. Because hydration volumes are relatively low with this schedule, safe outpatient administration is feasible.

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REFERENCES

1. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.
2. Scagliotti GV, De Marinis F, Rinaldi M, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol* 2002;20:4285–4291.
3. Fossella F, Pereira JR, von Pawel J, et al. 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* 2003;21:3016–3024.
4. Georgoulias V, Ardavanis A, Agelidou A, et al. 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* 2004;22:2602–2609.
5. Ohe Y, Niho S, Kakinuma R, et al. Phase I studies of cisplatin and docetaxel administered by three consecutive weekly infusions for advanced non-small cell lung cancer in elderly and non-elderly patients. *Jpn J Clin Oncol* 2001;31:100–106.
6. Niho S, Ohe Y, Kakinuma R, et al. Phase II study of docetaxel and cisplatin administered as three consecutive weekly infusions for advanced non-small cell lung cancer. *Lung Cancer* 2002;35:209–214.
7. Ohe Y, Niho S, Kakinuma R, et al. A phase II study of cisplatin and docetaxel administered as three consecutive weekly infusions for advanced non-small-cell lung cancer in elderly patients. *Ann Oncol* 2004; 15:45–50.
8. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989;10:1–10.
9. Souglakos J, Kotsakis A, Kouroussis C, et al. Nonneutropenic febrile episodes associated with docetaxel-based chemotherapy in patients with solid tumors. *Cancer* 2002;95:1326–1333.
10. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543–3551.
11. Willsie SK, Foreman MG. Disparities in lung cancer: focus on Asian Americans and Pacific Islanders, American Indians and Alaska Natives, and Hispanics and Latinos. *Clin Chest Med* 2006;27:441–452.
12. Huxley R, Jamrozik K, Lam TH, et al. Asia Pacific Cohort Studies Collaboration. Impact of smoking and smoking cessation on lung cancer mortality in the Asia-Pacific region. *Am J Epidemiol* 2007;165:1280–1286.

