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Clinical report

Phase II study of docetaxel alternating with cisplatin in chemotherapy-naïve patients with advanced non-small cell lung cancer

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The objective of this study was to evaluate a regimen of full doses of docetaxel and cisplatin, using an alternating schedule, as first-line therapy for patients with inoperable non-small cell lung cancer (NSCLC). The standard concomitant schedule does not allow full doses of both drugs to be administered. We wanted to see if there was an advantage to be gained by administering full doses of both docetaxel and cisplatin, using a different schedule. Docetaxel 100 mg/m^2 was given once every 6 weeks from week 1 and cisplatin (120 mg/m^2 for two doses and 100 mg/m^2 thereafter) once every 6 weeks from week 4, for six cycles (three docetaxel and three cisplatin). Thirty-six of the 44 patients enrolled were evaluable for efficacy. Forty-eight percent of the patients had good (KPS 90–100%) performance status. A median of five cycles was administered, for which no dose reductions were necessary. There were 13 of 36 partial responses (36%; 95% CI 21–54%) and 15 of 36 patients achieved stable disease (42%). The median duration of response was 10.5 months, the median time to progression was 4.5 months and the median survival was 9 months. The 1 and 2 year survival rates were 39 and 16%, respectively. The most frequent grade 3–4 toxicities were nausea (23% of patients), vomiting (18%) and neutropenia (77%). Infections were also common, but not severe. The alternating schedule produced response, toxicity and survival figures that compared favorable with those using the concomitant schedule. This study could serve as a model for future studies of non-cisplatin-containing regimens, in which full doses of docetaxel could alternate with full doses of other new agents active against NSCLC. [© 2000 Lippincott Williams & Wilkins.]

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Introduction

Lung cancer is the main cause of death from malignant disease in both men and women, and may become the leading cause of death in some European countries in the near future.[1] Approximately 80% of lung cancers are non-small cell lung cancers (NSCLC), which include squamous cell carcinoma, adenocarcinoma and large cell (undifferentiated) carcinoma.[2]

Of these patients with NSCLC, 40% present with stage IV disease, 40% with locally advanced stage III disease and 20% with stage I or II disease. Using the old standard therapies of surgery for stage I and II disease, radiotherapy for stage III disease, and best supportive care for stage IV disease, less than 10% of patients were cured.[2] The results of best supportive care alone for advanced NSCLC show that median survival is about 4 months, and that 90% of patients die within 1 year of diagnosis and 98% within 2 years. Cisplatin-based chemotherapy has become an important tool for prolonging survival and for symptom amelioration in patients with stage III and IV NSCLC, either used alone or in combined modality therapies.[2,3] Cisplatin inhibits transcription and replication through its cross-linking (adduction) action on DNA strands.[4] As a single agent it produced response rates of around 15% in advanced NSCLC, with response duration of 2–3 months, median survival of 6–8 months and no long-term survivors, although several meta-analyses have confirmed that regimens using

combinations of cisplatin and older drugs confer a statistically significant improvement in survival, compared to best supportive care.[3,5] Toxicities associated with cisplatin include nausea and vomiting, nephrotoxicity, and ototoxicity.

Since 1990 several new agents have proved to be at least as effective as single agents against NSCLC as the standard cisplatin therapies.[2] These include the two taxoids, docetaxel and paclitaxel, and gemcitabine, vinorelbine, tirapazamine and irinotecan.

Docetaxel, a semi-synthetic taxoid, promotes microtubule assembly and inhibits microtubule depolymerization, thereby blocking cell division in the M phase.[6-8] Phase II studies in 160 patients with NSCLC who received docetaxel (100 mg/m^2 as a 1 h infusion every 3 weeks) reported an overall response rate of 27% in previously untreated patients. Median survival was 9 months, with a 1 year survival rate of 39%.[9] The major dose-limiting toxicity was neutropenia; other toxicities included fluid retention, asthenia and neurotoxicity.

As cisplatin and docetaxel are both active in NSCLC but act by different mechanisms at different points of the cell cycle, combinations of the two drugs might be expected to show synergistic activity. *In vitro* studies have found no evidence of cross-resistance between docetaxel and cisplatin,[10,11] and *in vivo* data from transplantable murine tumors have shown activity, using cisplatin combined with docetaxel, but no synergy.[12] Two phase I clinical studies have evaluated the clinical efficacy of docetaxel plus cisplatin[13,14] and different combination schedules have been investigated in phase II trials.[13-19] The overlapping toxicities of docetaxel and cisplatin have meant that the optimum dose of docetaxel (100 mg/m^2 q 3 weeks) could not be administered in the phase II combination studies because of the risk of additive toxicity. As there is no synergy proven between the two drugs, we designed an alternating schedule for this phase II trial, in an attempt to avoid the toxicities encountered when the drugs are given concomitantly. The alternating schedule was designed to enable the full dose of docetaxel (100 mg/m^2) to be combined with what was at the time considered to be the full dose of cisplatin (120 and 100 mg/m^2) as first-line therapy. The efficacy of this regimen, in terms of objective response rate, time to progression and toxicity, were evaluated in chemotherapy-naïve patients with advanced NSCLC.

Patients and methods

Patients aged 18–75 years with proven metastatic or inoperable, progressive or recurrent NSCLC were eligible for this six-center, open, non-randomized phase II study. All patients were required to have adequate bone marrow function and no history of prior systemic chemo- or immunotherapy. Previous surgery was allowed. Previous radiotherapy was allowed if not directed at a site used to assess response in this study. Patients had to have at least one bi-dimensionally measurable lesion and a Karnofsky performance status (KPS) of 70% or more (WHO PS 0–2).

Exclusion criteria were: pregnant or lactating women or those of childbearing potential who were not using effective contraception; a history of previous malignancy (other than excised or curatively irradiated basal cell skin cancer or cervical cancer *in situ*); patients with, or with a history of, central nervous system metastases; symptomatic peripheral neuropathy or neurological hearing deficit of severity above grade 1 according to the Common Toxicity Criteria of the National Cancer Institute (NCI); radiotherapy within the previous 4 weeks; concurrent treatment with other investigational drugs or participation in another clinical trial within the 30 day period before screening for this study; concurrent treatment with any other anticancer drug; pre-existing symptomatic pleural effusion requiring tapping; and ascites or pericardial effusion. Patients with a history of significant neurological or psychiatric disorders (including dementia and seizures), active infection requiring i.v. antibiotic therapy, active peptic ulcer, unstable diabetes mellitus or other contra-indications to high-dose corticosteroids, or untreated superior vena cava syndrome were also excluded.

The study protocol was approved by the ethics committee at each center, and was carried out in accordance with the Declaration of Helsinki and with the agreement of the appropriate administrators at each center. Fully informed and written consent was obtained from each patient before enrolment into the study.

All patients received docetaxel 100 mg/m^2, administered as a 1 h i.v. infusion, once every 6 weeks from week 1, and cisplatin, administered as a 3 h i.v. infusion, once every 6 weeks from week 4 (i.e. alternating administration of docetaxel and cisplatin, with 3 weeks between each cycle). Cisplatin was given at a dose of 120 mg/m^2 for the first two doses (i.e. cycles 2 and 4) and at 100 mg/m^2 thereafter. Six cycles of treatment (i.e. three doses of docetaxel and three of cisplatin, all at 21 day intervals) were specified by the study protocol, with three additional cycles allowed for any patient who achieved a complete or partial response.

Oral prednisolone 50 mg was given twice daily for up to 5 days with each cycle of docetaxel treatment

(the first two doses being given the day before chemotherapy) to prevent the onset or reduce the severity of any hypersensitivity reaction, skin toxicity or fluid retention. Antiemetic therapy was administered in accordance with normal practice at each center with each cycle of cisplatin treatment and as required on other occasions.

Each patient's medical history was updated and a repeat physical examination with serum biochemistry was carried out every 3 weeks (on each infusion day). Hematological and serum examinations were performed once a week, but increased to once every 2 days in cases of febrile and grade 4 neutropenia. Radiological examinations were repeated every 6 weeks. A repeat ECG was taken on the day of the first infusion and toxicity was evaluated weekly. All assessments were repeated at the end of the study and patients were observed for at least 1 month thereafter to document any late adverse effects. Patients were then followed up every 3 months until death.

Tumor responses were evaluated according to the WHO criteria, every 6 weeks.[20]

Overall response, time to disease progression and duration of response analyses were conducted for the intent-to-treat and the evaluable patient populations, whereas the survival analysis was only carried out on the intent-to-treat patients. Intent-to-treat patients were defined as those who had started at least one treatment infusion. Patients had to have started at least one treatment cycle to be evaluable for toxicity; to be evaluable for efficacy, patient had to have received at least two cycles with at least one follow-up tumor assessment (except patients with early disease progression, who were included in the efficacy analysis in any case).

Adverse events were classified according to NCI CTC criteria or according to the COSTART classification for events not covered by NCI CTC criteria.

A modified two-stage Fleming design was used.[21,22] This ensured that recruitment would be stopped after the first 20 patients (step 1) if no responses were observed. However, if at least three responses were observed among these initial patients, further recruitment to a maximum of 45 patients was permitted (step 2) unless prevented by toxicity results or other medical considerations. The procedure was designed to test the null hypothesis (H_0) that the true response rate was 20% or less against the alternative hypothesis (H_1) that the true response rate was 40% or greater. The significance level was 0.05 and the power was 0.91 when the true response rate was 40%. If at least 14 responses were observed at step 2, the results were considered to be promising.

Categorical data were displayed in contingency tables. Continuous data were summarized with median, minimum and maximum values. Exact confidence intervals for response rates were calculated at the 95% level. Kaplan–Meier estimations were applied to the duration of response, time to disease progression and survival data. Confidence intervals of the median were calculated using Simon's method.[22]

Results

From May 1995 to March 1996, 44 patients were enrolled in the study and form the basis of the intent-to-treat population. Thirty-six patients (82%) were judged evaluable for response. All 44 patients were evaluable for toxicity. Five patients (11%) had previously undergone surgery and/or radiotherapy. The remaining 39 patients (89%) had received no prior treatment. Baseline patient characteristics with tumor details and extent of disease are shown in Table 1.

Fifteen (34%) patients received six or more cycles of the alternating chemotherapy. A total of 209 treatment cycles were administered; the median number of cycles per patient was 5 (range 1–9). Twenty-nine (66%) patients received four or more cycles. Median cumulative dose of docetaxel was 250 mg/m^2 (range 0.3–490) and of cisplatin 299 mg/m^2 (range 60–477). Relative median dose intensities[23] were 0.96 (range 0–1.03) for docetaxel and 1.0 (range 0.5–1.21) for cisplatin.

The overall intent-to-treat response rate was 30% (13 of 44) (95% CI 17–45%), with a corresponding rate of 36% (13 of 36) (95% CI 21–54%) in the evaluable patient population. There were no complete re-

Table 1. Patient characteristics at baseline (n=44)

Characteristic	No. of patients
Sex	
male	34 (77%)
female	10 (23%)
Age (years)	
median (range)	60 (32–74)
<49	6 (14%)
Performance status (Karnofsky score)	
70–80%	23 (52%)
90–100%	21 (48%)
Histological subtype of tumor	
adenocarcinoma	15 (34%)
squamous cell carcinoma	19 (43%)
other	10 (23%)
Stage	
stage IIIB	10 (23%)
stage IV	34 (77%)

sponses and 15 patients (42%) had a stable disease. Of the 13 patients who responded, two had large cell carcinoma, six had adenocarcinoma and five had squamous cell carcinoma. Three had locally advanced disease and 10 had metastatic disease. Two patients had undergone previous local therapy with curative intent (both underwent pneumonectomy, one with post-operative adjuvant radiotherapy). The median duration of response for both the intent-to-treat and evaluable populations was 10.5 months (range 7.5–21.75; 95% CI 8.25–11.25).

The median time to response in the 13 patients with PR was 1.5 months (range 1–5.25). Kaplan–Meier analysis showed a median time to progression of 4.5 months (range 0.25–21.75; 95% CI 3–7.5). Median survival was 9 months (95% CI 6–19); the 1 year survival rate was estimated from the Kaplan–Meier survival curve to be 39%. Seven patients were still alive and well after at least 2 years' follow-up (24–30 months).

The majority of treatment cycles (77% docetaxel and 79% cisplatin) were administered at the planned dosages. Fourteen doses of docetaxel and nine of cisplatin were delayed, mostly because of hematological toxicity. Of the 44 patients treated, 42 (96%) experienced at least one adverse event reported as related to treatment. Twenty-one patients (48%) experienced at least one grade 3 or 4 (NCI) or severe adverse event. The most frequent of these were grade 3 nausea and vomiting, diarrhea, fever in the absence of infection, and allergy (Table 2). Moderate to severe asthenia was reported by 14 patients.

Neuro-sensory defects were observed in 23% of patients and were mild (grade 1 or 2) in all cases. Neurological hearing deficiencies occurred in 20.5% of patients and were always associated with cisplatin treatment. One grade 3 episode was reported and a grade 1 episode led to the discontinuation of treatment after six cycles. Fluid retention was seen in 16% of patients, but was always mild and did not lead to

Table 2. Main acute and chronic non-hematological adverse events considered to be possibly or probably related to study treatment

Acute adverse events						
NCI term	No. of patients (%)	Worst NCI grade (no. of patients)				No. of cycles (%)
		1	2	3	4	
Nausea	33 (75)	9	14	10	0	83 (40)
Vomitting	22 (50)	5	9	8	0	43 (21)
Infection	18 (41)	6	8	3	1	29 (14)
Stomatitis	15 (34)	11	3	1	0	25 (12)
Fever (without infection)	15 (34)	5	8	2	0	24 (12)
Diarrhea	12 (27)	7	2	2	1	14 (7)
Skin	6 (14)	4	2	0	0	11 (5)
Chronic adverse events						
NCI term	No. of patients (%)	Worst NCI grade (no. of patients)				
		1	2	3	4	
Alopecia	37 (84)	9	28	NA	NA	
Neuro-sensory	10 (23)	6	4	0	0	
Neuro-hearing	9 (21)	5	3	1	0	
Neuro-constipation	10 (23)	6	4	0	0	
Non-NCI-listed adverse events						
Event	No. of patients (%)	Worst severity (no. of patients)				
		Mild	Moderate	Severe		
Astenia	19 (43)	5	12	2		
Anorexia	6 (14)	4	1	1		
Nail disorder	5 (11)	4	1	0		
Fluid retention	7 (16)	5	2	0		
Myalgia	5 (11)	3	2	0		

treatment withdrawal.

Neutropenia was the major hematological toxicity observed, occurring in 120 of 198 evaluable treatment cycles. Grade 4 neutropenia occurred in 63% of patients during 65 treatment cycles and grade 3 in 14% of patients during 18 treatment cycles. Median neutrophil nadir was 0.2×10^9/l (range 0–8), occurring at day 8 (range 6–19) with a median duration of grades 3–4 neutropenia of 7 days (range 4–10). Fifteen patients (34%) experienced at least one neutropenic infection (20 episodes in total) and eight patients (18%) experienced febrile neutropenia during nine treatment cycles. Six of these patients received granulocyte colony stimulating factor. None of these toxicities was fatal or led to treatment discontinuation.

Anemia occurred in 72% of patients (133 of 202 evaluable cycles; 64% of docetaxel and 68% of cisplatin treatments) and reached grade 3 in one patient. Three patients received transfused red cells for grade 2 hemoglobinemia. No thrombocytopenia was reported.

Treatment was discontinued in eight patients, with one patient withdrawn for each of the following reasons: weight loss with anorexia and asthenia (cycle 6), allergic reaction (cycle 1), myocardial ischemia (cycle 2), fever in absence of infection (cycle 3), neurological hearing deficit (cycle 6), pulmonary embolism (cycle 3), prolonged neutropenia (cycle 8), and several adverse events (cycles 1, 2, 4 and 5).

None of the four deaths that occurred during treatment (one disease progression, one spontaneous tracheal esophageal fistula, one cardiac failure and one myocardial infarction with rhythm disorder) was considered to be related to the treatment.

Discussion

Several phase II studies of concurrent docetaxel and cisplatin treatment have reported response rates superior to the single-agent results in NSCLC, and with higher median survival times.[15–19] However, none of these studies used full doses of docetaxel (100 mg/m^2) with full doses of cisplatin ($\geqslant$100 mg/m^2) because of dose-limiting hematological toxicities. The alternating administration of cisplatin and docetaxel used in this study allowed the full dose of both drugs to be given and reduced the hematological toxicity associated with concurrent administration of lower doses. According to our schedule, docetaxel 100 mg/m^2 was administered first, followed 3 weeks later by cisplatin 120 mg/m^2 (or 100 mg/m^2 after cycle 5). When administered as first-line therapy, this regimen produced a response rate of 36% (95% CI 20.8–53.8) in 36 evaluable patients with advanced or metastatic NSCLC. The intent-to-treat response rate was 30% (13 of 44). This response rate is as good as any cisplatin–new drug combination and within the range of those reported in two phase II studies in which low doses of docetaxel and cisplatin were administered concurrently to a total of 98 patients with NSCLC.[24] A French study used docetaxel 75 mg/m^2 and cisplatin 100 mg/m^2, administered on days 1, 21 and 42, and once every 6 weeks thereafter, and achieved a response rate of 31% in their intent-to-treat population (33% in the evaluable population);[15] an Australian study used docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2, once every 3 weeks, and achieved a response rate of 30% in the intent-to-treat population (39% in evaluable population).[19] The three study populations are similar, except for a higher proportion of patients with poor performance status (KPS$\leqslant$80%) in our study, 53 versus 35 and 15%, respectively, for the French and the Australian studies. Patients with brain metastases were excluded in all three studies. However, the alternating administration of full doses of both drugs was associated with a slightly increased median duration of response (10 versus 5 and 7 months for the Australian and French studies, respectively). Median time to progression (4 months), 1 year survival rates (39 versus 32 and 35%) and median duration of survival (8 versus 10 and 8 months) were similar.

A major consideration in the design of the alternating regimen was that it should maximize the number of treatment cycles that could be administered for any given cumulative dose in an attempt to improve overall survival. Although a median of five treatment cycles was administered in our study, compared to four cycles in the combination chemotherapy studies,[24] and although the relative dose intensity of each agent in the present study indicates that the full dose of each agent could be administered using an alternating regimen, there was only a trend towards better survival.

The incidence of grade 3 and 4 toxicity or severe adverse events was no greater in our study than those studies using concurrent administration of lower doses[24] (Figure 1), with the exception of the nausea and vomiting associated with high-dose cisplatin therapy. The very low incidence and severity of fluid retention in our study indicated the efficacy of the prophylactic corticosteroid therapy given to all patients before each docetaxel infusion. There was little variation in incidence of grade 3 or 4 febrile neutropenia or infection in the three studies. The rates of infection (41%) and grade 3–4 neutropenia (77%) were fairly high and could have been avoided by administering growth factors prophylactically. This

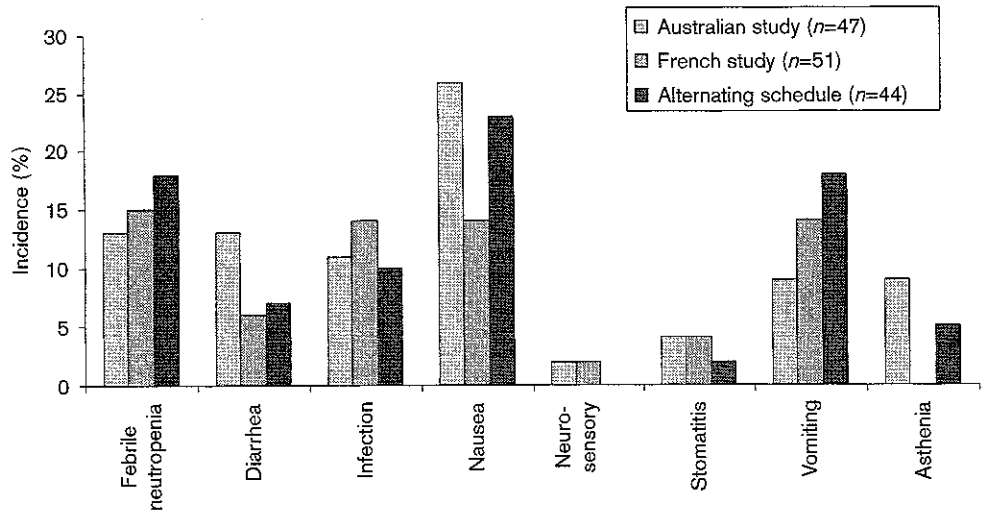

Figure 1. Incidence of NCI grade 3 or 4 and non-NCI-graded severe adverse effects associated with chemotherapy in three phase II studies of combination therapy with docetaxel and cisplatin in patients with NSCLC.

was not recommended in our study protocol, but six patients received growth factor support, at the discretion of the investigator, to alleviate neutropenia.

Triple-drug combination chemotherapy has also been investigated in NSCLC. Data from a study of docetaxel alternating with cisplatin–vinorelbine in 45 patients with stage IIIB or IV NSCLC have indicated additive activity for these agents, but the survival data were not superior to those reported here.[25]

In conclusion, the present study has shown that a regimen of alternately administered docetaxel and cisplatin allows both drugs to be given at full dose. However, although this regimen is clearly active against NSCLC, response rates, survival and toxicity profile are not significantly better than those seen using other docetaxel–cisplatin combination regimens in similar patient populations. As docetaxel and cisplatin act at different times in the cell cycle, it seems preferable to use a combination of the two drugs instead of an alternating schedule. However, this study could serve as a model for future studies of non-cisplatin-containing regimens, in which full doses of docetaxel could alternate with full doses of another new agent active against NSCLC.

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