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Original Paper

Docetaxel (Taxotere®) Plus Cisplatin: an Active and Well-tolerated Combination in Patients with Advanced Non-small Cell Lung Cancer

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The activity of the combination of intravenous docetaxel 75 mg/m^2 plus cisplatin 100 mg/m^2 administered every 3 weeks for 3 cycles then every 6 weeks was investigated in 51 chemotherapy naive patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). The population was 92% male, with a median age of 54 years and median performance status of 1; 80% of patients had metastatic disease, including 37% with bone involvement. All patients received prophylactic premedication (ondansetron, dexamethasone plus cetirizine) and standard hyperhydration. With a median of 4 treatment cycles (range 1–9), 14 of 42 evaluable patients responded (overall response rate 33.3%, 95% CI 19.6–49.6%); the median response duration was 7.3 months, median survival 8.4 months, and 1-year survival rate 35%. The most common adverse event was neutropenia, occurring in two-thirds of patients. Neurosensory effects were cumulative but generally mild. No treatment-related deaths occurred. This combination of docetaxel/cisplatin showed activity in advanced NSCLC. While it was not clearly superior to single-agent docetaxel, due to differences in prognostic factors among the patients in open trials, a randomised study would be needed to demonstrate definitively whether cisplatin adds to the activity of docetaxel or not. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

LUNG CARCINOMA is a leading cause of cancer death in both men and women in Western countries [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of cases of lung cancer. The prognosis for patients with NSCLC is poor; only one-third present with resectable disease and more than half of these die despite treatment. Once the disease becomes metastatic, the median survival time is generally around 5–6 months [1, 2].

Single-agent chemotherapy for NSCLC achieves relatively low response rates and limited survival benefit. Cisplatin-containing regimens generally produce superior response rates and survival times compared with non-cisplatin-containing combinations of old generation agents and have consistently demonstrated improved survival rates in patients with advanced disease when compared with alternative management strategies [3]. However, although the combination of cisplatin and vinca alkaloids or etoposide are among the most widely used, there is no well-established standard regimen for the treatment of advanced NSCLC [1].

As the efficacy of a combination depends primarily on the activity of its components, the recent introduction of new generation agents, with improved response rates in NSCLC [2, 4], offers hope for more active combination regimens. In early NSCLC trials, single-agent docetaxel (Taxotere®) 100 mg/m^2 every 3 weeks produced response rates of 30% in previously untreated patients and 20% in cisplatin-refractory or -resistant patients [5]. The latter results implied a lack of cross-resistance between docetaxel and cisplatin, probably

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due to their different mechanisms of action. The adverse effect profiles of docetaxel [5] and cisplatin [6] indicated that additive myelosuppression would be unlikely, but that overlapping neurotoxicity, nausea and vomiting might occur.

A phase I dose-finding study of the combination of docetaxel and cisplatin reported a maximal tolerated dose of docetaxel 75 mg/m^2 and cisplatin 100 mg/m^2 every 3 weeks [7]. Dose-limiting toxicities were febrile neutropenia, diarrhoea and increased creatinine levels. The combination of 75 mg/m^2 of both agents given every 3 weeks achieved a 44% response rate, with no dose-limiting toxicity [7]. However, as it has been suggested that cisplatin should be administered at doses > 80 mg/m^2 in combination regimens [8] and because docetaxel and cisplatin were not actively synergistic in preclinical studies [9], a combination of docetaxel 75 mg/m^2 plus cisplatin 100 mg/m^2 was selected for this study.

PATIENTS AND METHODS

Patient selection

Male and female patients aged 18–75 years with histologically proven, bidimensionally measurable, locally advanced or metastatic NSCLC were eligible. All patients were chemotherapy naïve, had a Karnofsky performance status (KPS) $\geq$ 60% and a life expectancy $\geq$ 12 weeks. Previous surgery and radiotherapy were permitted, unless radiotherapy had been administered to a site used to measure response or had involved more than 10% of the total bone marrow. Radiotherapy had to have been completed at least 4 weeks before study entry. Adequate bone marrow, renal and hepatic function (neutrophil count $\geq 2\times10^9$/l, platelet count $\geq 100\times10^9$/l, creatinine clearance $\geq$ 65 ml/min, creatinine and total bilirubin levels within normal limits and aspartate aminotransferase levels $\leq$ 2.5 times the upper normal limit for the institution) were also required.

Exclusion criteria were: brain or leptomeningeal metastases; symptomatic peripheral neuropathy > grade 1 according to National Cancer Institute Common Toxicity Criteria (NCI-CTC); other current or previous malignancies; other serious medical conditions; pre-existing symptomatic pleural effusion; ascites or pericardial effusion. Concomitant treatment with other anticancer or experimental drugs or haematopoietic growth factors was not permitted. The study protocol was approved by the relevant ethics committees and all patients gave written informed consent.

Pretreatment and follow-up evaluation schedule

Baseline investigations included medical history; full neurological and physical examination; KPS determination; complete blood count; serum and urine biochemistry; creatinine clearance; radiological tumour assessments including chest X-ray; chest computer tomography (CT) scan; abdominal CT scan or ultrasound; brain CT scan; electrocardiogram (ECG); and audiogram; and bone scan if indicated. Tumour response, neurological examinations and ECGs were reassessed every 2 cycles. Blood counts were performed weekly, or every 2 days if febrile or grade IV neutropenia occurred. Other assessments were repeated every 3 weeks. All patients were monitored for 1 month after their last treatment cycle to detect any late adverse effects and were then followed up every 3 months until death. Patients could be offered second-line treatment (chemotherapy, radiotherapy or surgery) according to presentation and clinical symptoms.

Treatment plan

Docetaxel was diluted in 250 ml of 5% glucose and infused intravenously (i.v.) over 1 h. One hour later, cisplatin was infused i.v. over 1 h in a mixture of 3% sodium chloride and 10% mannitol. The starting doses were 75 mg/m^2 for docetaxel and 100 mg/m^2 for cisplatin. If significant haematological suppression or nonhaematological adverse effects ($\geq$ grade III) occurred, the docetaxel dose was reduced to 55 mg/m^2 in subsequent cycles. Docetaxel could be delayed for up to 2 weeks if the blood counts had not recovered or adverse events resolved by day 21. For grade II peripheral neuropathy, the doses of both drugs were reduced (cisplatin to 80 mg/m^2 and docetaxel to 50 mg/m^2). Treatment was withdrawn in cases of peripheral neuropathy $\geq$ grade III or severe ($\geq$ grade III) diarrhoea. The cisplatin dose was reduced by 50% if creatinine clearance fell to 45–54 ml/min, and was withheld until the next cycle if creatinine clearance fell below 45 ml/min.

Premedication comprised ondansetron (8 mg i.v. at 4, 8 and 12 h after chemotherapy, 8 mg orally at + 20 and + 28 h then every 8 h for 4 days); parenteral dexamethasone 20 mg twice daily on days-1 and 1, and once daily on day 2; and oral cetirizine 10 mg 5 and 1 h before chemotherapy. Standard hyperhydration was given with cisplatin.

To minimise the risk of cumulative neurotoxicity, treatment was divided into an induction phase (administered every 3 weeks for 3 cycles) and a maintenance phase (every 6 weeks). Treatment was continued until disease progression or unacceptable adverse effects developed. Patients with stable disease received 6 cycles, while those achieving complete or partial responses continued for 3 cycles after maximal response.

Response and tolerability evaluation

Tumour responses were classified as complete, partial, no change or progressive disease according to World Health Organization criteria [10]. The duration of response was measured from the first chemotherapy infusion to the first documentation of disease progression. The time to progression and survival duration were defined as the times from the first chemotherapy infusion to the first objective evidence of tumour progression and death, respectively. Adverse effects were evaluated according to NCI-CTC criteria, or graded mild, moderate or severe if not included in this classification.

Statistical methods

The study had a two-stage Fleming design [11] which allowed recruitment to be terminated after the first 15 patients if no objective response occurred and allow determination of active treatment with a response probability $\geq$ 30% in 35 evaluable patients, with a power of 0.93. All treated patients were evaluated for safety (intent-to-treat population). Patients had to receive at least 2 cycles to be evaluable for response unless disease progression occurred before the second cycle, in which case the patient was classed as early progression. Data were expressed as medians and ranges, and Kaplan–Meier curves were constructed for survival data. Analyses were performed using SAS software (version 6.08) and exact 95% confidence intervals (95% CI) were calculated using StatXact software.

RESULTS

Patient characteristics

Between April 1994 and December 1995, 51 patients were enrolled at three centres in France; baseline clinical

characteristics are shown in Table 1. The median age was 54 years (range, 34–75). KPS was > 80% for 90% of the patients and over 80% had metastatic disease. The most common disease sites were the lung, and lymph nodes and 37% had bone metastases. Only 6 patients had not received previous anticancer treatment (either as surgery or thoracic radiotherapy) and none had received previous chemotherapy.

Of the 51 patients treated, 42 (82%) were evaluable for response according to the predefined criteria in the protocol. Reasons for non-evaluability were: lack of baseline imaging data allowing strict measurability ($n = 3$), missing tumour assessment data after the first treatment cycle ($n = 1$), early deaths during the first treatment cycle not related to study medication ($n = 3$; 1 progressive disease, 2 intercurrent diseases), withdrawal due to early disease progression ($n = 1$), and intercurrent disease ($n = 1$).

Efficacy

14 of the 42 evaluable patients achieved a major objective response, including one complete response (Table 2). The overall response rate was 33.3% (95% CI: 19.6–49.6%). Responders received 4–9 treatment cycles, with half receiving 6 cycles. The response rate was similar in patients with adenocarcinoma and squamous cell carcinoma. 12 responders had metastatic disease, 11 of whom had ≥ 2 organs involved. Responses were most common in lung and lymph node targets, but improvements were also observed in pleural, adrenal and bone metastases.

The median time to first response (intention-to-treat) was 1.44 (range 1.2–2.8) months. The median duration of response in both treated and evaluable patients was 7.3 months (range 4.1–11.3) (95% CI: 6.3–11.1 months). The median time to progression was 3.7 months (range 0.2–11.1 months; 95% CI: 2.6–5.8 months) in the intent-to-treat population, and 4.1 months in evaluable patients. The median intent-to-treat survival time was 8.4 months (95% CI: 6.7–11.2 months), and the 1-year survival rate was 35%.

Table 1. *Baseline patient characteristics*

	Patients *n* (%)
Patients entered *n*	51
Median age (years) range	54 (34–75)
Male/female	47/4 (92/8)
Karnofsky performance status (median, range)	90 (70–100)
Disease stage:	
IIIb (locally advanced)	10 (20)
IV (metastatic)	41 (80)
Histological subtype:	
Adenocarcinoma	22 (43)
Squamous cell	24 (47)
Large cell	5 (10)
Disease sites:	
Lung	45 (88)
Liver	8 (16)
Pleura	7 (14)
Bone	19 (37)
Lymph nodes	35 (69)
Adrenal	9 (18)
Other viscera	8 (16)
Previous therapy:	
None	45 (88)
Surgery	1 (2)
Radiotherapy	3 (6)
Surgery + radiotherapy	2 (4)

Table 2. *Response rates in* 42 *evaluable patients with locally advanced or metastatic NSCLC treated with a combination of docetaxel plus cisplatin*

Response	Patients ($n = 42$)	Per cent (95% CI)
Complete response	1	2.38
Partial response	13	30.95
Overall response	14	33.33 (19.6–49.6)
No change	14	33.33
Progressive disease	14	33.33

CI, confidence interval.

Treatment administration

A total of 214 treatment cycles were administered to the 51 patients. The median number of cycles per patients was 4 (range, 1–9), and 31 (61%) patients received ≥ 4 cycles (Table 3). The median cumulative doses of docetaxel and cisplatin, as well as the relative dose intensity for both drugs, were almost 100% of the planned figures. Most cycles (94%) were delivered at the planned dose. The dose was reduced in 13 cycles (8 patients), primarily due to neurosensory symptoms after receiving at least 4 cycles. Treatment was delayed in 10 cycles (8 patients) mostly for technical problems not related to the study drugs. Haematological suppression led to treatment delay in only 1 patient. The most common reason for treatment discontinuation was disease progression (32 patients, 63%). Of these, the best overall response was PR in 4 patients and NC in 12 patients. 7 patients discontinued treatment after 6 cycles; 2 after 5 cycles; 7 after 4 cycles; 7 after 3 cycles; and 9 after 1 or 2 cycles. 8 patients (16%) discontinued treatment because of treatment-related adverse events: 5 for neurosensory side-effects (after 5 to 8 cycles), 1 for loss of hearing after 5 cycles, 1 after a hypersensitivity reaction during the fourth cycle and 1 with fever in absence of infection after the first cycle. 2 patients withdrew consent (after 6 and 7 cycles), 2 discontinued due to disease complications (1 with dyspnoea after 1 cycle, and 1 with tumour-related cervical neuralgia after 5 cycles) and 4 completed the protocol (up to 9 cycles).

Haematological toxicity

Grade III/IV neutropenia occurred in 67% of patients and 58% of the 193 evaluable cycles (Table 4). The median time to neutrophil nadir was 11 days (range, 6–16), and recovery generally occurred within 7 days. 8 (16%) patients were hospitalised with febrile neutropenia during 11 (5%) cycles. This

Table 3. *Treatment administration*

Total no. of cycles administered	214
Median no. of cycles (range)	4 (1–9)
Median cumulative dose mg/m^2 (range):	
Docetaxel	299 (74–668)
Cisplatin	399 (99–901)
Relative dose intensity:	
Docetaxel	0.99 (0.75–1.18)
Cisplatin	0.99 (0.75–1.18)

Table 4. Incidence of haematological toxicity (total and grade NCI-CTC III/IV) in 51 patients with NSCLC treated with a combination of docetaxel 75 mg/m² plus cisplatin 100 mg/m² every 3 weeks

Toxicity	Overall incidence by patient (%)	NCI-CTC grade III Patients *n* (%)	III Cycles *n* (%)	IV Patients *n* (%)	IV Cycles *n* (%)
Leucopenia	41 (80)	12 (24)	28 (14)	5 (10)	12 (6)
Neutropenia	42 (82)	10 (20)	44 (23)	24 (47)	68 (35)
Anaemia	44 (86)	4 (8)	4 (2)	1 (2)	1 (0.5)
Thrombocytopenia	9 (18)	0	0	1 (2)	1 (0.5)

NCI-CTC, National Cancer Institute-Common Toxicity Criteria.

was accompanied by grade IV thrombocytopenia in 1 patient and by a grade 1 increase in creatinine levels in another. All responded to i.v. antibiotics and continued chemotherapy. 1 (2%) patient developed grade IV sepsis, whilst grade III infections occurred in a further 6 (12%). Six infectious episodes required hospitalisation. All infections responded within 6–9 days to antibiotics and/or appropriate symptomatic treatment. A further 2 patients were hospitalised with isolated fever, leading in one case to study discontinuation. Severe anaemia and thrombocytopenia were uncommon.

Nonhaematological adverse events

Nonhaematological adverse events are listed in Table 5. 19 (37%) patients experienced at least one grade III/IV adverse event, the most common being nausea, vomiting and, infection (14% each). Hypersensitivity reactions occurred in 4 (8%) patients during 5 (2%) cycles. Only 1 patient developed a NCI grade III reaction which led to discontinuation of treatment during cycle 4. Neurological symptoms appeared to be related to the cumulative doses of both docetaxel and cisplatin, occurring after a median of 4 (range, 1–6) cycles. The symptoms were generally mild. 2 patients developed grade III cardiac dysrhythmias, 1 of whom was hospitalised on two separate occasions; this patient also had concomitant, nausea, vomiting and hypotension. Both responded following treatment with deslanoside for 2–4 days. There were no treatment-related deaths during the study.

Table 5. Incidence of nonhaematological adverse effects possibly or probably related to treatment in 51 patients with NSCLC treated with a combination of docetaxel 75 mg/m² plus cisplatin 100 mg/m² every 3 weeks

Adverse event	Overall incidence by patient (%)	Grade III	Grade IV
Acute			
Allergy	4 (8)	1 (2)	0
Cardiac dysrhythmia	3 (6)	2 (4)	0
Constipation	1 (2)	0	0
Diarrhoea	23 (45)	3 (6)	0
Fever*	13 (25)	0	0
Infection	11 (22)	6 (12)	1 (2)
Nausea	34 (67)	7 (14)	0
Stomatitis	5 (10)	0	0
Vomiting	21 (41)	7 (14)	0
Chronic			
Alopecia	44 (86)	6 (12)†	Not applicable
Asthenia‡	25 (49)	18 (35)	0
Fluid retention‡	4 (8)	0	0
Hearing	8 (16)	0	0
Nail disorder‡	3 (6)	2 (4)	0
Neuromotor	1 (2)	1 (2)	0
Neurosensory	17 (33)	1 (2)	0
Skin toxicity	3 (6)	0	0

*In the absence of infection or neutropenia. †Grade II. ‡Non-NCI-CTC terms: grade III, moderate; grade IV, severe.

DISCUSSION

This phase II study demonstrated that docetaxel 75 mg/m² can safely be combined with cisplatin 100 mg/m² in the treatment of patients with locally advanced or metastatic NSCLC. The combination showed activity in this clinical setting; following administration of a median of 4 treatment cycles, a response rate of 33% was achieved in evaluable patients. Although a response rate of this magnitude is not clearly superior to docetaxel monotherapy [5], because of the differences in prognostic factors among the patients enrolled in open trials a randomised study would be required in order to demonstrate definitively whether cisplatin adds any clinical benefit compared with docetaxel alone.

Although the response rate in this study was lower than the 44–46% reported in earlier phase I studies of docetaxel plus cisplatin [7, 12], given the poor prognostic factors of this population (80% of patients with metastases, 40% with ≥ 3 organs involved and 40% with bone metastases) the 33% response rate is encouraging. This response rate also compares well with established cisplatin-based regimens for NSCLC, including cisplatin plus vinca alkaloids, etoposide ± ifosfamide, and mitomycin-C [1, 13]. In addition, the need to use submaximal doses of docetaxel because of potentially overlapping toxicity may have contributed to the degree of response.

Cisplatin has also been combined with other new agents such as paclitaxel and gemcitabine in an attempt to improve activity in NSCLC. However, although response rates of 26–47% have been reported with paclitaxel plus cisplatin [14, 15], this combination was associated with dose-limiting, residual neurotoxicity. In order to reduce the neurotoxicity, paclitaxel plus carboplatin is also being investigated.

The antimetabolite gemcitabine has demonstrated synergistic activity with cisplatin, and response rates of 38–54% have been achieved with this combination [16–18]. However, most patients had locally advanced disease and neither 1 year survival, nor tolerance, appear to be better than in the present study.

The median survival of 8.4 months in this study is within the same range as the durations reported for combinations of cisplatin plus etoposide, paclitaxel (± granulocyte colony-stimulating factor) [14, 15], vinorelbine [13, 19] and vindesine [20]. The survival duration in our present study represents an improvement compared with the 6 months expected in patients with metastatic NSCLC [1]. In addition, patient benefits such as reduction of tumour bulk and disease stabilisation were observed even in those without an objective response.

The combination was well tolerated, with 61% of patients receiving ≥ 4 cycles, and >90% receiving the full planned doses. The adverse effect profile is similar to that reported in earlier studies [7, 12, 21], without toxic deaths.

Occurrences of grade III/IV neutropenia, neutropenic infections and febrile neutropenia during this study were similar to those observed with docetaxel monotherapy [5]. However, although severe anaemia and thrombocytopenia were uncommon, the incidence was increased compared with docetaxel monotherapy; both toxicities have been reported with cisplatin, which may affect erythropoietin-producing cells as a result of nephrotoxicity [6].

Prophylactic corticosteroids reduced the overall incidence of hypersensitivity reactions to 8% (severe in only 1 patient) compared with the 34% rate previously reported with docetaxel monotherapy [5]. Routine premedication also resulted in low rates of skin toxicity and fluid retention, whereas 14% of patients experienced grade III nausea and vomiting despite premedication.

Neurotoxicity occurred in 35% of patients, but it was generally mild even in those who discontinued treatment because of this adverse event. Only 2 (4%) patients experienced grade III neurological effects, and this toxicity occurred after 6–8 cycles. Low neurotoxicity is an important consideration with regard to the other new platinum-containing combinations, assuming that the docetaxel-cisplatin combination is at least as effective as the established cisplatin-based regimens in the treatment of patients with locally advanced or metastatic NSCLC.

A docetaxel-cisplatin combination (with cisplatin given at 75 mg/m^2 every 3 weeks) is currently being investigated in a large, ongoing randomised phase III study in the USA (Eastern Cooperative Oncology Group), which should clarify the place of this combination in this setting.

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