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ORIGINAL ARTICLE

A randomised phase II trial of two sequential schedules of docetaxel and cisplatin followed by gemcitabine in patients with advanced non-small-cell lung cancer

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Abstract
Purpose The aim of this study was to determine the activity and toxicity of two sequential chemotherapy regimens in the first-line treatment of advanced non-small-cell lung cancer (NSCLC).
Methods Eighty-eight chemonaive patients with stage IIIB/IV NSCLC were randomised to receive either three cycles of 75 mg/m^2 cisplatin plus 75 mg/m^2 docetaxel, both administered on day 1 every 21 days, followed by three cycles of 1,200 mg/m^2 gemcitabine on days 1 and 8 every 3 weeks (arm A), or three cycles of 25 mg/m^2 cisplatin plus 25 mg/m^2 docetaxel on days 1, 8 and 15 every 28 days, followed by three cycles of 1,200 mg/m^2 gemcitabine on days 1 and 8 every 3 weeks (arm B).
Results Of the evaluable patients, 61% in arm A ($n = 41$) and 36% ($n = 44$) in arm B completed treatment as per the protocol. The best tumour response rates were as follows (arm A and arm B): complete response: 2.4 and 2.3%; partial response: 39 and 20.4%; stable disease: 26.8 and 13.6%; and progressive disease: 31.8 and 45.4%. The median progression-free and overall survival were 3.9 and 12.3 months in arm A, respectively, 3.1 and 7.7 months in arm B. Grade 3–4 adverse events were more common in arm A. Grade 3–4 neutropenia was the main toxicity observed (56.1% in arm A and 11.4% in arm B).
Conclusions Our data demonstrate the feasibility of a sequential approach of cisplatin plus docetaxel followed by single-agent gemcitabine. Weekly administration of platinum-docetaxel is associated with an improved safety profile but lower efficacy than the conventional three-weekly schedule (registration ID 2004-001044-72).

Keywords Non-small-cell lung cancer · Docetaxel · Gemcitabine · Cisplatin · Sequential chemotherapy · First-line chemotherapy

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Introduction

In recent years, most efforts to improve the treatment of advanced non-small-cell lung cancer (NSCLC) have focused on the development of new drugs and new treatment regimens. However, to date, few data have been published on the optimal duration of chemotherapy, particularly for platinum-based therapies [1–4]. The ASCO (American Society of Clinical Oncology) guidelines recommend that first-line chemotherapy for advanced NSCLC be administered for a maximum of six cycles, with earlier interruption in non-responders after the fourth cycle [5]. More recently, several randomised trials and a meta-analysis [6] have demonstrated the potential benefit of prolonged treatment with non-cross-resistant agents, which may be administered either until disease progression (maintenance) [7–9] or for a defined number of cycles (consolidation) [10].

Sequential chemotherapy is the sequential administration of non-cross-resistant chemotherapy for a defined number of cycles [11] and can be considered a 'halfway' approach between standard chemotherapy and the maintenance/consolidation strategy. Day hypothesised that sequential chemotherapy could be superior to concurrent therapy, allowing for the delivery of a larger number of drugs at optimal doses with limited toxicity [12]. Sequential administration could also allow drug resistance to be circumvented at the molecular level. Such a schedule typically involves the planned sequential administration of additional agents with different mechanisms of action for a pre-specified number of cycles. Unlike the switch from first- to second-line treatment, the sequential approach does not require documented disease progression to switch from one treatment to another.

TAX 326 was the only study to show a significant difference between two platinum doublets in both efficacy and safety, with cisplatin-docetaxel displaying improved response rates and median survival times and a better tolerability and quality of life over vinorelbine-cisplatin [13]. These results have recently been confirmed in a meta-analysis of all randomised controlled trials comparing docetaxel- and vinca alkaloid-based chemotherapy for first-line therapy of advanced NSCLC [14].

This randomised phase II study was conducted to evaluate the antitumor activity of the same drug sequence—three cycles of cisplatin-docetaxel followed by three cycles of gemcitabine—with the administration of cisplatin-docetaxel either once every 3 weeks or once a week for 3 weeks for the first part of the sequence. This approach combines decreased cisplatin exposure with the possibility of offering patients both docetaxel and gemcitabine.

Indeed, the weekly administration of docetaxel and cisplatin for 3 consecutive weeks has been associated with minimal myelosuppression and preserved antitumor activity in the treatment of chemonaive patients with advanced NSCLC [15].

Patients and methods

Eligibility

The eligibility criteria were age 18–70 years and histologically or cytologically confirmed advanced NSCLC (clinical stage IIIB with malignant pleural effusion or supraclavicular lymph node metastasis or stage IV disease). Patients with central nervous system (CNS) metastases were eligible provided that they were asymptomatic or had minor, clinically stable symptoms and did not require immediate treatment or had already completed successful therapy (e.g. radiation therapy or steroids). Other eligibility criteria included: the presence of at least one measurable lesion according to RECIST (Response Evaluation Criteria in Solid Tumors) [16]; a WHO (World Health Organization) performance status (PS) of 0–1; and adequate bone marrow, liver, and kidney function.

Previous radical surgery (more than 30 days before study entry) was allowed; however, post-surgical progressive disease had to be pathologically confirmed. Previous radiation therapy was allowed to $<25\%$ of the bone marrow as long as the irradiated area was not the only source of measurable disease. No prior chemotherapy or biologic therapy was permitted. Patients were excluded in the case of a prior malignancy other than NSCLC, carcinoma in situ of the cervix, non-melanoma skin cancer or any other cancer type unless it was diagnosed and surgically treated at least 5 years before with no subsequent evidence of recurrence. Patients with weight loss $\geq 5\%$ in the previous 3 months or with a pre-existing peripheral neuropathy higher than grade 2 were not accepted. Patients with any uncontrolled concomitant systemic disorder, as well as pregnant or lactating women, were also excluded. This trial was approved by all the ethic committees of participating centres, and all patients provided informed written consent.

Pre-treatment evaluation and treatment

At baseline, all patients had a complete history and physical examination, complete blood work-up, ECG, chest X-ray and a computed tomography scan of the chest and abdomen. Other scans were taken if clinically indicated.

After stratification by the stage of disease at trial entry (stage IIIB vs. stage IV), patients were randomised to receive one of the following treatment regimens: arm A, 75 mg/m^2 docetaxel over 30–60 min on day 1 immediately followed by 75 mg/m^2 cisplatin over 30–60 min on day 1, repeated every 21 days for three cycles, followed by

1,200 mg/m^2 gemcitabine on days 1 and 8, repeated every 21 days for three cycles; arm B, 25 mg/m^2 docetaxel over 30 min on days 1, 8 and 15 immediately followed by 25 mg/m^2 cisplatin over 30–60 min on days 1, 8 and 15, repeated every 28 days for three cycles, followed by 1,200 mg/m^2 gemcitabine on days 1 and 8, repeated every 21 days for three cycles. Randomization lists had been prepared with the use of permuted blocks of different sizes and a 1:1 ratio. Prior to the administration of docetaxel, the patients were premedicated with oral corticosteroids starting the day before docetaxel infusion and continuing during the day of infusion and the day after. Prior to and after the administration of cisplatin, appropriate hydration and antiemetics were given at the discretion of the individual investigator. Independent of the response achieved after the first three cycles, in the absence of unacceptable toxicity or disease progression, patients in both arms were shifted to three cycles of gemcitabine. Treatment was discontinued in the case of unacceptable toxicity as determined by the attending physician in agreement with the study coordinators, treatment delay longer than 2 weeks or the patient's refusal. Once patients discontinued the protocol treatment, they were followed up for survival every 3 months. At the time of progression, treatment was left up to the investigators.

Dose modification and treatment delay

Dose modifications were based on both haematological and non-haematological toxicity according to the study protocol. Complete blood counts (CBC) were obtained weekly during each cycle. Toxicities were recorded and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 [17]. Briefly, an absolute neutrophil count $\geq 1.5 \times 10^9$/L and a platelet count $\geq 100 \times 10^9$/L were required before each cycle of therapy. Any modifications in the dose made according to the protocol for haematological and non-haematological adverse events were permanently maintained.

A treatment delay of longer than 3 weeks for any toxicity or of at least 2 weeks for haematological, hepatic, renal or neurological toxicity resulted in treatment discontinuation.

Response assessment

Patients were assessed every three cycles for an objective response according to the RECIST version 1.0 [16]. Responses were assessed by attending physicians; a central review evaluation was not required. Best overall response is the best response observed from the start of treatment until disease progression.

Statistical considerations

The primary endpoint of the trial was the assessment of the overall response rate in each arm. No formal statistical comparison between the two arms was planned into the protocol. The sample size was calculated using Fleming's single-stage procedure [18]. From a review of the literature, it was assumed that a regimen should be associated with an overall response rate (CR + PR) of at least 40% to warrant further studies, whereas a regimen associated with a response rate $\leq$20% warrants no interest. For a power of 90% against the hypothesis of a response rate $\geq$40% and a 5% false positivity rate against the hypothesis of a response rate $\leq$20%, 42 patients were to be enrolled in each arm. Each regimen would therefore be considered sufficiently active to deserve further study if at least 14 objective responses were seen. The efficacy and safety analyses were based on a modified intention-to-treat population, including all randomised patients who received at least one study drug administration. The objective response rate of each treatment arm is provided with its two-sided 95% exact confidence interval.

Secondary endpoints included progression-free, overall survival and safety. Progression-free survival and overall survival curves were estimated using the Kaplan-Meier method [19].

Tolerability is described in terms of the frequency of grade 3–4 adverse events for each patient, treatment discontinuations due to an adverse event, treatment-related serious adverse events and toxicity-associated deaths in each treatment group.

Results

Between 4 May 2005 and 31 October 2006, a total of 88 patients were enrolled at 15 participating centres. Forty-three and forty-five patients were assigned to arms A and B, respectively. Three patients (two in arm A and one in arm B) did not receive any study drugs due to patient refusal after randomisation. All patients included in the modified intention-to-treat population (arm A, $n = 41$; arm B, $n = 44$) were treated according to the regimen assigned at the end of the randomisation process. Two patients in arm B were found to be ineligible at the end of the first treatment cycle due to the presence of concomitant bladder cancer and incorrect staging, respectively. According to the definition of the modified intention-to-treat population, each patient was included in all efficacy and safety analyses (Fig. 1). No other relevant protocol deviations occurred. The baseline patient characteristics are listed in Table 1. The median age was 60 years (range: 42–71) and 64 years (range: 44–70) in arms A and B, respectively. Most patients were men

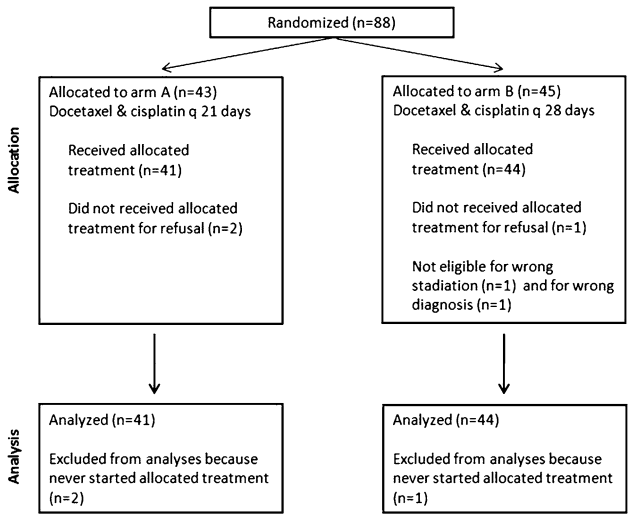

Fig. 1 CONSORT diagram

Table 1 Characteristics of assessable patients

	Arm A (q 3 weeks) $n = 41$	Arm B (weekly) $n = 44$
Median age (range), years	60 (42–71)	64 (44–70)
Sex, *n* (%)		
Male	30 (73)	35 (80)
Female	11 (27)	9 (20)
ECOG PS, *n* (%)		
0	26 (63)	27 (61)
1	15 (37)	17 (39)
Histology, *n* (%)		
Adenocarcinoma	21 (51)	19 (43)
Large cell	4 (10)	1 (2)
Squamous	6 (15)	14 (32)
Other	10 (24)	10 (23)
Stage, *n* (%)		
IIIB	6 (15)	6 (14)
IV	35 (85)	38 (86)

(73.2 and 79.5% in arms A and B, respectively) and had stage IV disease (85.4 and 86.4% in arms A and B, respectively) and a WHO PS of 0 (63.4 and 61.4% in arms A and B, respectively). An imbalance in the distribution of patients with adenocarcinoma versus squamous cell histology was observed between the two arms (Table 1).

Treatment administration

The median number of administered courses was six (range: 1–6) in arm A and three (range: 1–6) in arm B. The proportion of patients receiving six cycles was in arm A 25 of 41 (61%) and in arm B 16 of 44 (36%).

Of the 41 patients in arm A, 38 (92%) completed the first part of the sequence, whereas 61% completed the treatment as per the protocol. Of the 44 patients in arm B, 32 (73%) completed the first part of the sequence, and 36% completed the treatment as per the protocol. During the first three courses of the sequential regimen, treatment compliance—calculated as the percentage of drugs administered according to the number of courses actually received relative to the expected total amount—was ≥80% in 100% of patients in arm A and in 84% of patients in arm B.

Overall, 93% of the patients in arm A and 82% of the patients in arm B received at least 80% of the expected total amount of drugs.

Response and survival

Following the first three cycles of chemotherapy, in arm A, the overall response rate (ORR) was 34.1% (95% C.I. 20.6–50.7%), and the SD and PD were recorded in 34.1 and 31.8% of patients, respectively. In arm B, the ORR was 18.2% (95% CI 8.7–33.2%). SD and PD were observed in 18.2 and 45.4% of patients, respectively (Table 2).

At the end of the treatment, patients in arm A achieved an ORR of 22% (95% CI 10.6–37.6%). SD and PD were recorded in 17.1 and 58.5% of patients, respectively. In arm B, the ORR was 13.6% (95% CI 5.2–27.4%). SD and PD were observed in 4.5 and 56.9% of patients, respectively (Table 2).

The best response for arm A was 41.5% in ORR (95% CI 26.7–57.8%). SD was recorded in 26.8% and PD in 31.8% of patients. In arm B, the ORR was 22.7% (95% CI 12–38.2%). SD and PD were observed in 13.6 and 45.4% of patients, respectively (Table 2).

The median progression-free survival was 3.9 months (95% CI 2.6–7.1) in arm A and 3.1 months (95% CI 2.4–4.9) in arm B (Fig. 2); the median overall survival was 12.3 months (95% CI 6.5–18.9) in arm A and 7.7 months (95% CI 6.3–10.4) in arm B (Fig. 3).

Toxicity

After the first three cycles of chemotherapy, the incidence of grade 3–4 leucopoenia and neutropenia was in arm A 12.2 and 46.3%, and 0% in arm B. For the overall treatment period, grade 3–4 leucopoenia and neutropenia were 19.5 and 56.1% of patients in arm A and 4.5 and 11.4% of patients in arm B (Table 3).

Incidence of grade 3–4 fatigue and diarrhoea was 12.2 and 9.8% of patients in arm A and 2.3 and 2.3% of patients in arm B (Table 3); incidence of grade 3–4 pain, pulmonary toxicity and stomatitis was in arm B 11.4, 11.4 and 6.8%, respectively, and 7.3, 2.4 and 2.4% of patients, respectively, in arm A (Table 3).

Table 2 Distribution of patients by response after three and six cycles and best overall tumour response by treatment arm

	After 3 cycles		After 6 cycles		Best response	
	Arm A *n* (%)	Arm B *n* (%)	Arm A *n* (%)	Arm B *n* (%)	Arm A *n* (%)	Arm B *n* (%)
CR	0	1 (2.3)	1 (2.4)	0	1 (2.4)	1 (2.3)
PR	14 (34.1)	7 (15.9)	8 (19.6)	6 (13.6)	16 (39)	9 (20.4)
SD	14 (34.1)	8 (18.2)	7 (17.1)	2 (4.5)	11 (26.8)	6 (13.6)
PD	13 (31.8)	20 (45.4)	24 (58.5)	25 (56.9)	13 (31.8)	20 (45.4)
ED	0	4 (9.1)	0	4 (9.1)	0	4 (9.1)
NE	0	4 (9.1)	1 (2.4)	7 (15.9)	0	4 (9.1)

Arm A ($n = 41$): docetaxel and cisplatin q 21 days; Arm B ($n = 44$): docetaxel and cisplatin q 28 days

CR complete response, *PR* partial response, *SD* stable disease, *PD* progression disease, *ED* early death, *NE* not evaluable

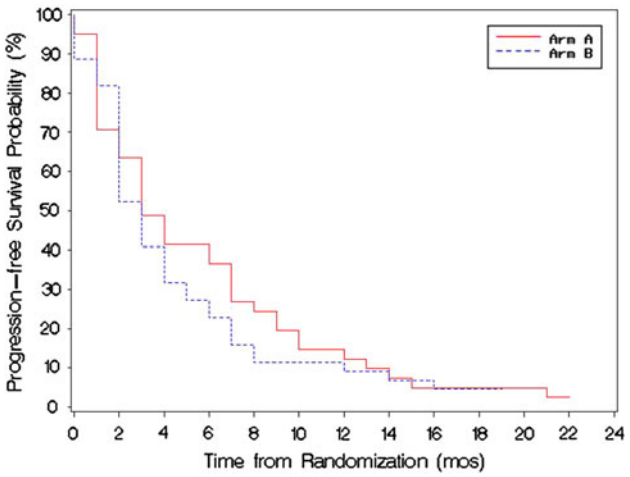

Fig. 2 Kaplan–Meier progression-free survival plot by treatment arm. *Arm A*: docetaxel and cisplatin q 21 days; *Arm B*: docetaxel and cisplatin q 28 days

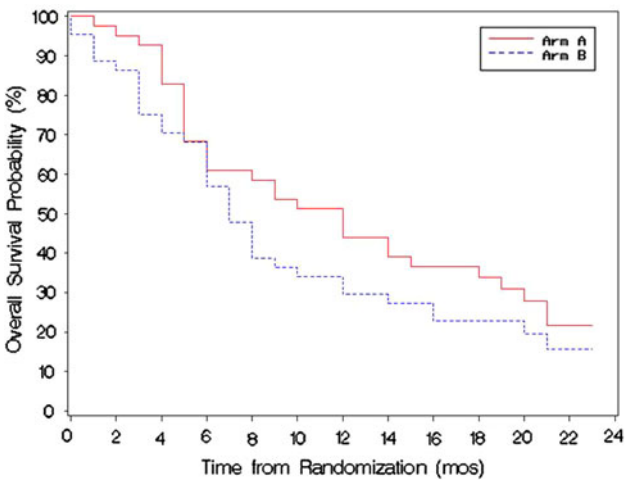

Fig. 3 Kaplan–Meier overall survival plot by treatment arm. *Arm A*: docetaxel and cisplatin q 21 days; *Arm B*: docetaxel and cisplatin q 28 days

One treatment-related death occurred in arm B. Five patients in arm A and 5 in arm B required hospital admission for non-fatal serious adverse events. Seven patients on arm A and 1 on arm B have been withdrawn from the study. Four patients (1 arm A and 3 arm B) have been withdrawn after one cycle due to mediastinic syndrome, pneumonitis, anaphylactic reaction and pulmonary embolism. One patient has abandoned the treatment after two cycles due to stomatitis. Two patients have left after two cycles due to chest abdominal pain and worsened performance status and one patient after five cycles due to heart attack.

Discussion

Our study results suggest that the weekly schedule provides poorer efficacy with better haematological toxicity compared with the standard schedule. Both regimens were well tolerated, with 41 of 85 (48%) patients completing the planned six cycles, but the proportion of patients receiving six cycles of treatment was higher in arm A than in arm B (61% vs. 36%). However, a median of four standard treatment cycles (range: one to six) represents the usual standard of care; therefore, it is unlikely that the observed difference affected the outcomes of the study.

The incidence of grade 3–4 leucopoenia and neutropenia was higher in arm A. Arm B resulted in an increased incidence of grade 3–4 pain, pulmonary toxicity and stomatitis compared with arm A. On the other hand, arm A was associated with an increased incidence of grade 3–4 fatigue, diarrhoea and alopecia compared with arm B. However, compared with similar clinical trials, no increase in the incidence of treatment-related adverse events was seen in either arm.

This trial was designed in an effort to overcome the lack of clinically significant progress in the treatment of advanced NSCLC through the use of ‘old’ drugs, which

Table 3 Distribution of patients by the presence of grade 3–4 haematological and non-haematological toxicities and treatment arm (overall treatment period)

Toxicity	Treatment arm	
	Arm A (41 pts) *n* (%)	Arm B (44 pts) *n* (%)
Haematological toxicities		
Anaemia	1 (2.4)	2 (4.5)
Leucopoenia	8 (19.5)	2 (4.5)
Neutropenia	23 (56.1)	5 (11.4)
Thrombocytopenia	0	2 (4.5)
Non-haematological toxicities		
Fatigue	5 (12.2)	1 (2.3)
Cough	0	2 (4.5)
Diarrhoea	4 (9.8)	1 (2.3)
Nausea	2 (4.9)	0
Neuromotor	2 (4.9)	0
Pain	3 (7.3)	5 (11.4)
Pulmonary	1 (2.4)	5 (11.4)
Stomatitis	1 (2.4)	3 (6.8)
Alopecia	3 (7.3)	0
Fever w/o infection with neutropenia	1 (2.4)	0
Fever w/o infection w/o neutropenia	1 (2.4)	0
Presence of infection w/o neutropenia	0	2 (4.5)

Arm A: docetaxel and cisplatin q 21 days; Arm B: docetaxel and cisplatin q 28 days

were administered here with a relatively novel treatment strategy. A solid theoretical rationale exists for the sequential administration of different chemotherapy regimens over the standard concurrent treatment. Recently, a clinical trial in castration resistant prostate cancer patients demonstrates that the different sequences of administration of anti-cancer agents have a clear impact on the toxicity of treatment and potential implications on the efficacy of the same [20].

Furthermore, there is strong evidence that prolonged chemotherapy administration is not better in terms of efficacy than three to four cycles of a specific regimen [1–4]. Several phase II trials have evaluated the activity and toxicity of a sequence of a doublet followed by a single agent. Most of these treatments consist of a platinum-based doublet followed by a taxane, either paclitaxel or docetaxel [21–27]. In a phase II trial of 44 chemonaive NSCLC patients, Hosoe et al. [23] evaluated a non-platinum sequential regimen with gemcitabine-vinorelbine for three cycles followed by docetaxel for three cycles. Interestingly, a 47.7% response rate was reported, with a median survival time of 15.7 months and a 1-year survival rate of 59%. Based on these results, a phase III trial comparing this non-platinum sequential triplet (vinorelbine and gemcitabine followed by docetaxel) with a standard platinum combination (carboplatin + paclitaxel) has been conducted. However, the experimental regimen did not result in better overall survival than the standard regimen of paclitaxel plus carboplatin [28].

Sequential chemotherapy is an appealing approach to increasing the number of non-cross-resistant agents delivered up front. A regimen of a platinum-based doublet followed by a single agent, including third-generation agents, is feasible in patients with good performance status and has yielded promising results with acceptable toxicity. Considering the promising results of these studies, the recommended trial design to draw meaningful conclusion should be a randomized comparison between sequential regimens and standard cisplatin-based chemotherapy. Data from the ongoing randomised phase III trials comparing these regimens with combination chemotherapy are expected soon.

Conclusion

This trial demonstrates the feasibility of a sequential approach using cisplatin plus docetaxel followed by gemcitabine in treatment of advanced NSCLC. However, the hypothesis of similar efficacies with a better toxicity profile in favour of weekly cisplatin plus docetaxel compared with the standard combination is not supported by our data. This trial gives evidences of better activity for arm A, with a small difference in haematological toxicity in favour of arm B that does not support the use of this alternative schedule, at least in fit patients.

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Conflict of interest Francesco Grossi, Filippo de Marinis, Vittorio Gebbia, Ferdinando Riccardi, Orazio Caffo, Teresa Gamucci, Francesco Ferraù, Mario Nardi, Luca Moscetti, Luca Boni, Enzo Galligioni have no conflicts of interest. Davide Dondi is full employee of Sanofi-Aventis.

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