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CLINICAL TRIAL REPORT

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Docetaxel and granulocyte colony-stimulating factor in patients with advanced non-small-cell lung cancer previously treated with platinum-based chemotherapy: a multicenter phase II trial

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Abstract *Purpose*: To investigate the activity of docetaxel and granulocyte colony-stimulating factor support (G-CSF) in patients with advanced non-small-cell lung cancer (NSCLC) previously treated with cisplatin. *Patients and methods*: A total of 60 patients with locoregional and metastatic NSCLC who had relapsed or progressed after first-line treatment with cisplatin-based regimens were enrolled into the trial. Docetaxel at 100 mg/m^2 was given as a 1-h infusion with G-CSF (rhG-CSF given s.c. at 150 μg/m^2) support from day 2 to day 8 every 3 weeks; all patients received premedication with corticosteroids. *Results*: In all, 1 (1.6%) and 14 (23.3%) patients achieved a complete response (CR) and a partial response (PR), respectively, for an overall response rate of 25% (95% CI 14.0–35.9%); stable disease (SD) and progressive disease (PD) were documented in 18 (30%) and 27 (45%) patients, respectively. The median duration of response was 20 weeks and the median time to tumor progression was 28 weeks. The median overall survival was 32 weeks and the 1-year survival rate was 23%. A total of 263 courses were given at a median of 3 cycles/patient. Grade 3 and 4 neutropenia occurred in 11 (18%) and 14 (23%) patients, respectively, with 18 (30%) patients requiring hospitalization for neutropenic fever; 1 patient died of sepsis. Grade 2 peripheral neuropathy occurred in 9 patients (15%) and grade 3 asthenia, in 4 (7%). Other toxicities were mild. *Conclusions*: Docetaxel has considerable single-agent activity in patients with NSCLC who have relapsed or progressed after first-line chemotherapy with cisplatin-based regimens.

Key words Docetaxel · Non-small-cell lung cancer · Chemotherapy · Second-line treatment

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Introduction

Non-small-cell lung cancer (NSCLC) is one of the most common tumors in men [2]. Although early stages could be cured by surgery, the majority of patients have unresectable or metastatic disease at the time of diagnosis. Systemic chemotherapy can be used in these patients, and recent meta-analysis studies have provided evidence that cisplatin-based chemotherapy confers a moderate absolute improvement of 10% in survival at 1 year in comparison with the best supportive care [22].

For patients with refractory or recurrent disease after an initial response to platinum-based first-line chemotherapy, treatment options are very limited and the results of available second-line chemotherapy regimens are disappointing. Docetaxel, synthesized from the noncytotoxic precursor 10-deacetylbacatin III [5, 19], promotes microtubule assembly and inhibits depolymerization to free tubulin, resulting in blockage of the cells in the M phase of the cell cycle [11, 25]. Phase II studies of docetaxel given at a dose of 100 mg/m^2 every 3 weeks (q3w) have resulted in response rates ranging from 23% to 38% in chemotherapy-naive patients with NSCLC [3, 6, 8]. At lower doses (75 mg/m^2 q3w and 60 mg/m^2 q3w) the response rate obtained in chemotherapy-naive patients was 25% and 19%, respectively [18, 21]. Docetaxel is also active as second-line

treatment, since a 21% partial response rate has been reported in 44 patients with cisplatin-refractory NSCLC, with the median survival being 42 weeks [7]; in addition, three studies published in abstract form have also reported a 15–20% response rate in a similar patient population [3, 9, 26].

Confirmation of the antitumor activity of docetaxel in patients who have failed first-line platinum-based chemotherapy is of great importance since it could open the way for the development of new active docetaxel-containing regimens for this particular poor-prognosis group of patients. For this purpose we conducted a multicenter phase II trial of docetaxel in previously treated patients with NSCLC. The main dose-limiting toxicity of docetaxel is grade 3/4 neutropenia or/and neutropenic fever [3, 6, 8]; in addition, it seems that lower doses of docetaxel are less active than higher ones [18, 21]. Therefore, to achieve good dose intensity in the present study, all patients prophylactically received recombinant human granulocyte colony-stimulating factor support (rhG-CSF).

Patients and methods

Patients and staging

Patients with histologically or/and cytologically confirmed, bidimensionally measurable stage III_B or IV NSCLC who had relapsed or failed to respond to prior first-line platinum-based chemotherapy were eligible for the study. A minimal interval of 4 weeks from the last chemotherapy course was required. Other inclusion criteria were an age of 18–75 years; a performance status (World Health Organization, WHO) of 0–2; adequate hematologic parameters (absolute granulocyte count ≥1500/dl, platelet count ≥120,000/dl); adequate renal (serum creatinine level ≤1.5 mg/dl) and hepatic (serum bilirubin level ≤1.5 mg/dl) function; and normal cardiac function (as assessed by clinical examination and electrocardiogram). Prior radiotherapy was allowed, provided that measurable lesions were outside the fields of radiation. Patients with irradiated brain metastases could be enrolled, provided that the brain lesions were radiographically stable or improved and that the clinical manifestations were improved. Patients were considered ineligible if they had a history of second malignancy (except for non-melanomatous skin cancer or in-situ cervical carcinoma), severe infection, malnutrition, or symptomatic peripheral neuropathy. The protocol was approved by the ethics committees of the participating hospitals. All patients gave written informed consent to participate in the study.

Patients' evaluation

Pretreatment evaluation included a complete medical history; a physical examination; a complete blood count (CBC) with differential and platelet count; a standard biochemistry profile; an electrocardiogram (ECG); chest X-rays; computed tomography (CT) of the chest, abdomen, and brain; and a whole-body bone scan. Magnetic resonance imaging was performed if indicated.

During treatment, CBC was performed weekly. In cases of grade 3/4 neutropenia or grade 4 thrombocytopenia, CBC was performed daily until the absolute granulocyte count (AGC) was $>1{,}200$/dl and the platelet count was $>50{,}000$/dl. A detailed medical history was taken and a physical examination was performed before each course of treatment for assessment of the status of disease and the toxicity of treatment. Biochemistry tests, ECG, and chest X-rays were performed every 3 weeks. A clinical neurologic evaluation was performed every 3 weeks; motor and sensory conduction velocity measurements and vibration tests were performed if neurotoxicity of grade ≥2 was detected. Lesions that could be assessed by clinical examination or by chest X-rays were evaluated before each cycle, whereas those assessable by ultrasound and/or CT were evaluated after every three cycles.

Chemotherapy regiment

Docetaxel (Rhone-Poulenc Rorer Pharmaceuticals Inc, Collegeville, Pa., USA) was given at a dose of 100 mg/m^2 as a 1-h infusion every 3 weeks. All patients received premedication consisting of dexamethasone given orally at 16 mg at 14 and 7 h before docetaxel treatment and at 16 mg/12 h for 3 additional days posttreatment. In addition, ondansetron (given at 8 mg i.v. before the infusion of docetaxel and then at 8 mg b.i.d. orally for 3 days after treatment) was given to all patients. Treatment was continued until there was evidence of disease progression or unacceptable toxicity. All patients received rhG-CSF (150 μg/m^2 from day 2 to day 8).

Dose adjustment criteria

Grade 4 thrombocytopenia or grade 4 neutropenia and/or neutropenic fever required a 25% dose reduction in subsequent courses. Grade 4 vomiting, grade 2 peripheral neuropathy, and all other toxic effects of grade ≥3 also mandated a 25% dose reduction. Patients with grade 1 or 2 fluid retention were allowed to continue treatment at the initial dose with concomitant administration of oral furosemide. A maximum of two 25% dose reductions (to 75 and 55 mg/m^2) was permitted; patients who continued to present dose-limiting events after two dose reductions were removed from the study.

Response and toxicity evaluation

Evaluation of a complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) was based on the WHO criteria [15]. The duration of response was calculated from the time at which the CR and PR criteria were first met until the first documentation of clinical progression. The time to tumor progression (TTP) was calculated from the time of the first docetaxel administration to the first objective evidence of tumor progression. Survival was estimated from the enrollment into the docetaxel + rhG-CSF protocol until death. Toxicity criteria were those adopted by WHO [20].

Statistical analysis

All patients who received at least two courses of chemotherapy were evaluable for response, and all patients receiving at least one course were evaluated for toxicity and survival. The TTP and overall survival were calculated using the Kaplan-Meier method [15]. Confidence limits for the response rate were the usual large-sample estimates based on binomial distribution. Comparisons of individual values were performed using the chi-square test.

Results

Demographic data

The characteristics of the 60 patients enrolled into the study are presented in Table 1. All but nine patients had stage IV disease, and 43% of the patients had a

Table 1 Patients' characteristics

	n	%
Patients accrued	60	
Age (years):		
Median	61	
Range	36–75	
Sex:		
M	49	82
F	11	18
Stage:		
Locoregional	9	15
Metastatic	51	85
Performance status (WHO):		
0	26	43
1	22	37
2	12	20
Histologic subtype:		
Squamous-cell carcinoma	26	43
Adenocarcinoma	22	36
Large-cell carcinoma	1	2
Bronchoalveolar carcinoma	4	7
Adenosquamous carcinoma	1	2
Poorly differentiated carcinoma	6	10
Prior treatment:		
Surgery	16	26
Radiotherapy	22	37
None	22	37
Prior chemotherapy:		
1 regimen	47	78
≥2 regimen	13	22
Numbers of metastatic sites:		
1	9	15
2	29	48
≥3	22	37
Prior response to platinum-based chemotherapy:		
CR + PR	10	17
SD	20	33
PD	30	50

performance status of 0. In 22 patients (37%), radiotherapy was given with curative intent. In all, 10 of 60 patients (17%) had initially responded (CR or PR) to platinum-based regimens. Docetaxel was given after a median of 4 (range 4–116) weeks from the last cisplatin-containing chemotherapy regimen.

Response to treatment and survival

All patients were evaluable for the response to treatment. A CR was observed in 1 patient with locoregional disease (1.7%) and a PR was achieved by 14 patients (23.3%), for an overall response rate of 25% (95% confidence interval 14.0 ± 35.9%). SD was observed in 18 (30%) cases and PD, in 27 patients (45%). Responses were documented at all sites of tumor localization, including the lung (14 responses in 59 patients; 24%), mediastinal or/and cervical lymph nodes (9 responses in 40 patients; 23%), liver (1 response in 13 patients; 8%), and skin (1 response in 4 patients; 25%).

The response was not associated with the time that had elapsed from the last CDDP-containing regimen, the histology, the stage of disease, the performance status, or the number of prior chemotherapy regimens. Conversely, a significantly higher response rate was observed in patients who had responded to prior platinum-based chemotherapy (5 of 10 patients; 50%) than in nonresponders (10 of 50 patients; 20%; $P < 0.05$; Table 2).

The median time to an objective response was 7 (range 3–12) weeks, corresponding to the third treatment course. The median duration of response was 20 (range 8–24) weeks and the median duration of SD was 12 (range 4–52) weeks. The median time to tumor progression for the responders was 28 (range 4–60) weeks. At a median follow-up of 36 (range 4–76) weeks, 51 patients (85%) are dead. All but two patients died because of PD. The median overall survival was 32 (range 4–76) weeks and there was no statistically significant difference in survival according to response [CR + PR: median 36 (range 16–60) weeks; SD + PD: median 20 (range 4–76) weeks], histology, or performance status. The 1-year survival rate was 23% (Fig. 1).

Compliance with treatment and toxicity

A total of 263 treatment courses were delivered. The median number of cycles per patient was 3 (range 1–9), and the median interval between cycles was 21 (range 21–28) days. Treatment was delayed in 23 cycles for toxicity and in 12 cycles for patients' personal reasons unrelated to their treatment or disease. The toxicity-related delays were due to febrile neutropenia (9 cycles), grade 3/4 neutropenia (5 cycles), grade 4 thrombocytopenia (1 cycle), acute renal failure due to aminoglycoside administration (1 course), upper gastrointestinal (GI) bleeding (1 cycle), bowel obstruction (1 cycle), grade 3 diarrhea (1 cycle), pericardial effusion (1 cycle), and nonneutropenic infections (3 cycles). In all, 3 patients refused to continue treatment for reasons related directly to treatment (1 due to grade 3 allergic reactions and 2 because of grade 3 asthenia), and 5 patients (8%) were withdrawn from the study because of upper GI bleeding (1 patient), severe allergic bronchospasm (1 patient), bowel obstruction (1 patient), and cardiac arrhythmia (2 patients). The main reason for dose reduction was neutropenia; 9 patients (15%) received reduced doses because they developed, at least once, an AGC of < 500/dl during treatment. The median dose intensity was 33 mg/m^2 per week (range 21–33 mg/m^2 per week), exactly the planned dose.

Toxicity was evaluated in all patients. Myelosuppression was the main toxicity. Grade 3/4 neutropenia occurred in 25 (41%) cases and grade 3/4 anemia occurred in 9 (15%) patients; grade 3/4 thrombocytopenia was infrequent, but 1 patient required hospitalization for platelet transfusions (Table 3). Overall, 28 cycles (11%) were complicated by fever and neutropenia (median

Table 2 Response to docetaxel according to the response to previous platinum-based chemotherapy

Platinum-based chemotherapy		Response to docetaxel (number of patients)					
		CR	PR	SD	PD	CR + PR	
						number of patients	%
CR	$n = 3$	–	2	1	–	2	66.6
PR	$n = 7$	1	2	2	2	3	42.8
SD	$n = 20$	–	4	10	6	4	20.0
PD	$n = 30$	–	6	5	19	6	20.0

Table 3 Hematologic toxicity of docetaxel as determined for all patients ($n = 60$) and all courses ($n = 256$)

Toxicity	Number of patients (%)		Number of courses (%)	
	Grade 1 + 2	Grade 3 + 4	Grade 1 + 2	Grade 3 + 4
Anemia	41(68)	9(15)	89(35)	24(9)
Neutropenia	9(15)	25(41)	33(13)	62(24)
Thrombocytopenia	10(17)	2(3)	25(10)	4(2)

duration 3 days; range 2–5 days), corresponding to 11 patients (18%). In all, 24 (85%) febrile episodes occurred during the first 2 cycles. All patients required hospitalization and positive blood cultures were documented in four cases. There was one death due to sepsis.

The nonhematologic toxicity is detailed in Table 4. Hypersensitivity reactions were typically characterized by flushing and/or skin erythema; however, one patient developed relatively severe bronchospasm with wheezing, necessitating his withdrawal from the study, whereas another, who developed hypotension, refused further treatment; in all cases, additional administration of dexamethasone and diphenhydramine resulted in resolution of the allergic reactions. Peripheral sensory neuropathy seemed to be cumulative since it occurred after the third docetaxel course in 13 patients (22%); however, no modification of the treatment plan was required because of neurotoxicity. Asthenia also seemed to be cumulative since it always occurred after the third docetaxel course. Two patients developed cardiac arrhythmias following the first course of docetaxel administration. Finally, 6 patients (10%) developed nonneutropenic infections of the respiratory system.

Discussion

In vitro studies using the ovarian cell lines 41McisR, CH1cisR, and OVCAR-3carboR have shown a lack of cross-resistance between CDDP and docetaxel [13, 17]; in addition, docetaxel given at a dose of 100 mg/m^2 has shown substantial activity in patients with advanced ovarian cancer refractory to cisplatin or carboplatin [1, 14, 16, 23]. This lack of cross-resistance might be attributed to the different mechanisms of both action [11, 24, 25] and resistance [4, 12, 27] of these drugs.

Four studies of single-agent docetaxel have been conducted in patients with NSCLC who had received prior CDDP-based chemotherapy [3, 7, 9, 26]; overall, 27 objective responses (17.4%) were achieved in 155 patients, with the response rate ranging from 15% to 22%. The 25% rate of objective responses along with the

Table 4 Nonhematologic toxicity by patient: any cycle of docetaxel ($n = 60$)

Toxicity	Grade (WHO)							
	1		2		3		4	
	n	%	*n*	%	*n*	%	*n*	%
Nausea/vomiting	8	13	3	5	–	–	–	–
Diarrhea	6	10	7	12	1	2	1	2
Mucositis	6	10	4	7	1	2	–	–
Alopecia	7	12	53	88	–	–	–	–
Nail changes	15	25	10	17	–	–	–	–
Hypersensitivity reactions	12	20	2	4	2	4	–	–
Peripheral edema	7	12	5	8	–	–	–	–
Pleural effusion	1	2	–	–	–	–	–	–
Arrhythmia	–	–	1	2	1	2	–	–
Peripheral neuropathy	15	25	9	15	–	–	–	–
Asthenia	3	5	13	22	4	7	–	–
Hyperlacrimation	5	8	3	5	–	–	–	–

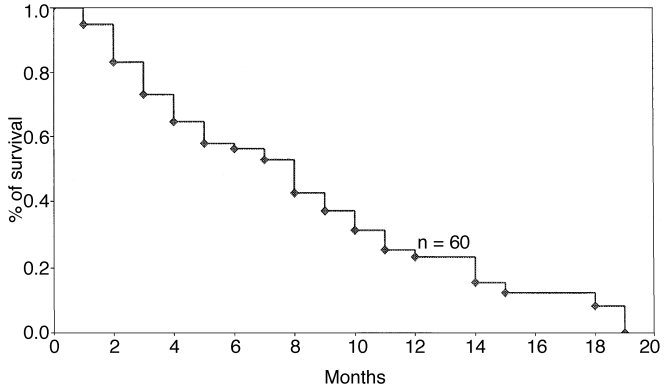

Fig. 1 Survival of patients treated with docetaxel (Kaplan-Meier analysis)

1.6% rate of CRs observed in the present study are in agreement with the results of the above-mentioned studies. Moreover, the median survival was 32 weeks in the present study and 42 weeks in Fossella et al.'s trial [7]; this observation raises the question as to whether second-line docetaxel might have any impact on the patients' survival, but additional randomized studies are needed to answer this question.

Docetaxel given as second-line treatment showed a statistically significantly higher degree of activity in patients with CDDP-sensitive (ORR = 50%) than in patients with CDDP-refractory (ORR = 20%) tumors (Table 2). However, the small number of patients who had previously responded to platinum-based chemotherapy limits the statistical power of this observation. We recently reported that patients with NSCLC who had responded to first-line cisplatin-based chemotherapy demonstrated a higher probability to respond to a second-line paclitaxel-gemcitabine combination [10]. Therefore, it seems that a prior response to cisplatin-based chemotherapy could select a subgroup of patients with taxane-sensitive tumors. However, that 20% of the patients with cisplatin-refractory or CDDP-resistant tumors also experienced objective responses to second-line docetaxel further supports the knowledge that there is no complete cross-resistance between docetaxel and platinum derivatives [7, 13, 17, 23].

The antitumor activity of docetaxel was not dependent on the histologic subtype of NSCLC; this observation contrasts with that of Fossella et al. [7], who observed a trend toward a higher response rate in adenocarcinomas than in nonadenocarcinomas. Moreover, the stage, the performance status, and the number of prior chemotherapy regimens do not have any impact on the probability of a response to second-line docetaxel; whether this observation might be due to the loss of the well-known predictive value of these parameters after the administration of first-line regimens or to some other reason (i.e., patient selection) is not yet clear. Finally, the survival was not statistically significantly different in patients who responded and those who failed to respond to second-line docetaxel; this observation clearly indicates that in patients with NSCLC the response to chemotherapy is not always associated with a survival benefit.

The dose-limiting toxicity of docetaxel in the present study was neutropenia, as had also been the case in chemotherapy-naive patients [3, 6, 8, 18, 21]; the neutropenia was not cumulative since 85% of neutropenic episodes occurred during the two first courses of chemotherapy. The febrile neutropenia was of short duration and was easily manageable with i.v. antibiotics and rhG-CSF; however, one patient died of sepsis. Similarly, Fossella et al. [7] reported that 57% of their patients developed febrile neutropenia and hospitalization was necessary in 7 (16%) cases. Anemia and thrombocytopenia were infrequent, as has previously been reported [7]. Therefore, our results suggest that the incidence of severe hematologic toxicity in heavily pretreated patients with NSCLC is not significantly different from that reported in chemotherapy-naive patients treated with an identical regimen of docetaxel [6, 8, 18]. The role of the prophylactic administration of rhG-CSF in the incidence of neutropenic episodes remains unclear.

Other acute toxicities include hypersensitivity reactions, which were the reason for treatment refusal in two patients; however, in the majority of cases, hypersensitivity reactions were mild, probably as a result of the prophylactic use of corticosteroids [21], and no modification of the treatment plan was required. Despite prior treatment with cisplatin-based chemotherapy, neurotoxicity was mild, as previously noted in Fossella et al.'s study [7]. A more serious complaint was grade 3 asthenia in four patients, which forced two of them to refuse further treatment.

Fluid-retention syndrome, which was relatively frequent in Fossella et al.'s series [7], was not a major problem in our study; thus, only grade 1–2 peripheral edema occurred in 12 patients (20%), and it was easily manageable with oral furosemide. This low incidence of fluid-retention syndrome in the present study could be attributable to the systematic premedication with corticosteroids, as has previously been reported [21].

In conclusion, the results of the present study confirm and extend the available experience concerning the efficacy of docetaxel in patients with NSCLC who have failed first-line platinum-based chemotherapy. Although docetaxel is more effective in patients who have demonstrated an initial tumor sensitivity to platinum derivatives, it also demonstrates a substantial degree of activity (20%) in cisplatinum-refractory or CDDP-resistant tumors. Therefore, docetaxel could be a very interesting drug in the development of second-line chemotherapy regimens for patients with advanced NSCLC.

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