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Docetaxel Administered Every Two Weeks as Second-line Chemotherapy for Advanced Non-small Cell Lung Cancer: A Phase II Study

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Abstract. *Background: The aim of this phase II study was to evaluate efficacy and toxicity of single-agent docetaxel, administered every two weeks as second-line treatment for patients with recurrent non-small cell lung cancer (NSCLC). Patients and Methods: Forty-eight patients with confirmed NSCLC were enrolled in this trial. The median age was 56.5 years (range 43-76), median PS was 1, and the main histology type was adenocarcinoma (54%). Only 8% of patients had previously received paclitaxel. Patients received docetaxel i.v., 50 mg/m^2 over 1 hour, on day 1 every 2 weeks. Results: The overall response rate was 8.3% (95% Confidence Interval 0.5-16.1%). The median time to disease progression, median survival time and 1-year survival rate were 3 months, 6 months and 21%, respectively. Grade 3-4 neutropenia was registered in 47% of patients, with only 1 patient (2%) experiencing febrile neutropenia. Non-hematological toxicity was mild (grade 1-2) and consisted mainly of asthenia (19%) and diarrhea (10%). Conclusion: The bi-weekly schedule of docetaxel showed an activity comparable to the standard tri-weekly 75 mg/m^2 schedule as second-line treatment for recurrent NSCLC. Though non-hematological toxicity is significantly reduced, myelosuppression is still a matter of concern.*

Docetaxel can be considered the standard second-line treatment in patients with advanced non-small cell lung cancer (NSCLC) who relapse after a platinum-based front-line therapy (1). This conclusion is based onto two phase III trials (TAX 317 and TAX 320) that compared docetaxel to best supportive care (2) and to an alternative low active regimen, containing vinorelbine or ifosfamide (3), respectively. Docetaxel showed to be superior to the control groups, in terms of survival, response rate and improvement in quality of life and disease-related symptoms. Although previous phase II trials in this setting had established the optimal docetaxel dose at 100 mg/m^2, administered *i.v.* every 3 weeks (4-7), this schedule caused a significant number of toxic deaths in the phase III studies. For this reason, docetaxel administered at 75 mg/m^2 every 3 weeks was registered in the USA and in Europe for second-line treatment in NSCLC, and was to be considered the control group for any other forthcoming study in this setting. However, despite the good activity shown by this drug, with a response rate of nearly 7% and a median survival time of almost 6 months, this schedule resulted in being very toxic. Grade 3-4 neutropenia and febrile neutropenia were recorded in 54% and 8% of patients, respectively (3). The main goal of second-line treatment in refractory NSCLC is the palliation of symptoms, which can be successfully obtained by means of chemotherapy. Drug-related toxicity is an issue of concern, and new schedules must be explored in the attempt to reduce the toxicity of the tri-weekly administration. The dose intensity planned with a docetaxel schedule of 75 mg/m^2 every 3 weeks is 25 mg/m^2/week. In the present phase II study, the efficacy of docetaxel administered at the dose of 50 mg/m^2 every 2 weeks, a schedule that maintains the same dose intensity as the tri-weekly regimen, was examined.

Patients and Methods

The eligibility criteria were as follows: histologically or cytologically confirmed recurrent metastatic NSCLC previously treated with one chemotherapy regimen; paclitaxel, but not docetaxel, was allowed as previous treatment; ECOG performance status 0-2; age >18 years; life expectancy >12 weeks; bidimensionally or unidimensionally measurable, or otherwise evaluable tumor lesions; adequate

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hematological (absolute neutrophil count [ANC] $\geq 2.0 \times 10^3$/mcl; platelets $\geq 100 \times 10^3$/mcl), liver (total serum bilirubin within normal limit; aspartate aminotransferase [ASAT] and/or alanine aminotransferase [ALAT] ≤2.5 x upper limit of normal range [ULN]; alkaline phosphatase [AP] ≤2.5 x ULN, unless bone metastases were present in the absence of liver disorder) and renal (creatinine ≤1.5 mg/dl) functions. More than 3 weeks had to have elapsed since last radiotherapy. Patients with symptomatic brain metastasis or symptomatic peripheral neuropathy were excluded. Patients underwent baseline assessment by history and physical examination, complete blood count and serum chemistry profiling. Staging was performed with chest X-ray and CT scan of the thorax and upper abdomen. Radionuclide bone scan and/or imaging of the brain were not routinely performed, unless clinically indicated by specific symptoms or previously demonstrated metastatic disease to the bone or the brain. Tumor measurements were performed within 4 weeks prior to second-line chemotherapy. Patients received docetaxel, 50 mg/m^2 as a 1-hour intravenous infusion every 2 weeks. One cycle of treatment consisted of 2 administrations of docetaxel and was repeated every 28 days. All patients received dexamethasone 8 mg orally twice daily, or alternatively, prednisone 50 mg orally twice daily, for 4 doses: –24 h, –12 h, +24 h, +36 h, starting the day before each infusion of docetaxel until the day after. RECIST criteria were used to evaluate response (8), while toxicity was assessed according to the National Cancer Institute common toxicity criteria (9). An absolute granulocyte count $\geq 1.5 \times 10^3$/mcl and a platelet count $\geq 100 \times 10^3$/mcl were required before each administration of therapy.

Dose modifications were as follows: patients experiencing grade 4 neutropenia lasting more than 7 days, or febrile grade 4 neutropenia were retreated with a dose reduction of 25%; in case of fluid retention, diuretic treatment was performed if grade 2, removal from study if grade 3; in case of peripheral neuropathy, a 25% dose reduction was applied if grade 2, removal from study if grade 3; in case of hypersensitivity reactions, removal from study after one severe reaction; in case of diarrhea, dose reduction of 25% if grade ≥3. The dose was omitted and postponed until recovery if patients had grade >2 neutropenia or grade >1 thrombocytopenia or any other grade >2 non-hematological toxicity (but alopecia) before any administration of docetaxel. The use of granulocyte-colony stimulating factor (G-CSF) was not recommended as prophylactic, but was allowed at the discretion of the treating physician.

The primary end-point of this phase II study was the response rate to docetaxel as second-line treatment in NSCLC patients.

The sample size was calculated according to Simon's two-stage mini-max design (10). An overall response rate (CR+PR) of 5% was considered to be ineffective, whereas a rate of 20% was assumed to be of potential interest. This design yielded an $\alpha=0.05$ with 80% power. According to this design, at least 1 out of 13 patients had to achieve this end-point in the first stage of the trial to proceed to the second stage of the study, where at least another 30 evaluble patients had to be enrolled. Survival was estimated by the Kaplan-Meier actuarial method (11), and calculated from the date of starting treatment to death or to the last follow-up (overall survival) and to the radiographic evidence of tumor regrowth (progression-free survival).

Results

From May 2002 to December 2003, 48 patients entered the study. The patient characteristics are listed in Table I. There were 36 males and 12 females (75% and 25%, respectively), with a median age of 56.5 years (range 43-76). The patient ECOG performance status (PS) was 0 in 10 patients (21%), 1 in 32 (66%) and 2 in 6 (12%). Histology types were adenocarcinoma in 54%, squamous-cell carcinoma in 29% and non-further specified NSCLC in 16% of patients, respectively. Two or more sites of metastases were present in 48% of patients. Previous chemotherapy consisted of platinum-based doublets or triplets in 92% of patients. No patient had received docetaxel, while 4 patients (8%) had previously received paclitaxel. The response to prior chemotherapy is also shown in Table I. Eleven patients (23%) received palliative radiotherapy shortly before or after docetaxel administration. All 48 patients were evaluable for toxicity. The total number of cycles of docetaxel administered was 125, with a median of 3 cycles per patient (range 1-6). The delivered dose intensity for all patients was 23.9 mg/m^2/week or 95.7% of the programmed dose intensity.

As summarized in Table II, toxicity was globally mild. Severe myelosuppression occurred in 47% of patients, with 8% of patients experiencing grade 4 neutropenia. Only one case of febrile neutropenia was registered (2%). Anemia was never higher than grade 2 (6% of patients), and the platelet count at any control was >100,000/mcl. Overall, 149 vials of G-CSF were used, in 29% of cycles. Sixty % of G-CSF vials were administered to treat neutropenia, while 40% of vials were used prophylactically in subsequent cycles. Overall, the non-hematological toxicity was very mild and consisted mainly of fatigue (19% of patients) and diarrhea (10% of patients). Dose modification or reduction was necessary in 20% of cycles, and was always due to neutropenia, except in 3 patients (1 patient with grade 2 diarrhea the day of programmed administration of docetaxel, 2 patients with grade 2 nail changes). No cases of fluid retention were registered.

Five patients were non-evaluable for response: 2 patients were lost to follow-up for unavoidable palliative radiotherapy and 3 patients for having received only 1 administration of second-line docetaxel. In this second group, treatment was suspended due to worsening of the PS, but not due to toxicity. On an intent-to-treat basis, no complete response and 4 partial responses were observed, for an overall response rate of 8.3% (95% confidence interval [CI] 0.5-16.1%). In 10 patients (21%) the disease remained stable, for an overall disease control rate (PR+SD) of 29%. Finally, 29 patients (60%) experienced progressive disease (Table III). None of the patients who received paclitaxel in the first-line setting responded to docetaxel. Moreover, neither patient PS, nor response to prior chemotherapy nor platinum-sensitivity were predictors of response to docetaxel. The overall survival and progression-free survival are shown in Figure 1. Forty events have been registered (83%). The median follow-up in 8 censored patients was 10.5 months. The median survival time was 6 months, with a 1-year survival rate of 21%. The

Table I. *Characteristics of 48 patients entered in the study.*

Characteristics	No. of patients	Percentage
Gender		
Male	36	75
Female	12	25
Age (yrs)		
Median	56.5	
Range	43-76	
ECOG Performance Status		
0	10	21
1	32	66
2	6	12
Previous Chemotherapy		
Cis or Carbo or Oxa + Gem or Vin	36	75
Cis containing triplets	8	17
Cis and Pac containing triplets	4	8
Other	4	8
Response to prior chemotherapy		
Partial response	15	31
Stable disease	18	37
Progressive disease	15	31

Abbreviations: Cis, cisplatin; Carbo, carboplatin; Oxa, oxaliplatin; Gem, gemcitabine; Vin, vinorelbine; Pac, paclitaxel

Table II. *Treatment toxicity (48 patients).*

	Toxicity grading		
Event	G 1-2 (%)	G 3 (%)	G 4 (%)
Neutropenia	6 (12)	19 (39)	4 (8)
Anemia	3 (6)	0	0
Fatigue	9 (19)	0	0
Diarrhea	5 (10)	0	0
Nail Changes	3 (6)	0	0
Mucositis	2 (4)	0	0
Paresthesias	1 (2)	0	0
Hiccups	1 (2)	0	0

median progression-free survival was 3 months. The only factor significantly associated with a longer survival was the overall disease control obtained with docetaxel; the median survival time of patients with PR or SD was 13.5 months, compared to 4.5 months of patients who were non-evaluable or experienced PD (log-rank $p=0.0006$). Thirteen patients (27%) received further treatment after docetaxel failure (gemcitabine, 1 patient, gefitinib, 10 patients, gemcitabine/gefitinib, 1 patient, vinorelbine/gefitinib, 1 patient). Finally, 15 patients (31.2%) were elderly (age ≥70 years) or aged <70 years but with a performance status of 2. When compared with the overall population, docetaxel seemed to reach a comparable efficacy in this particular subset of unfit patients, with 1 partial response observed (6%), without an increase in hematological toxicity (grade 4 neutropenia recorded in 20% of patients).

Table III. *Response to treatment (ITT: 48 patients).*

Best response	No. of patients	Percentage
Partial response	4	8.3*
Stable disease	10	21
Progressive disease	29	60
Non-evaluable	5	10.4

*95% Confidence interval (CI) 0.5-16.1%

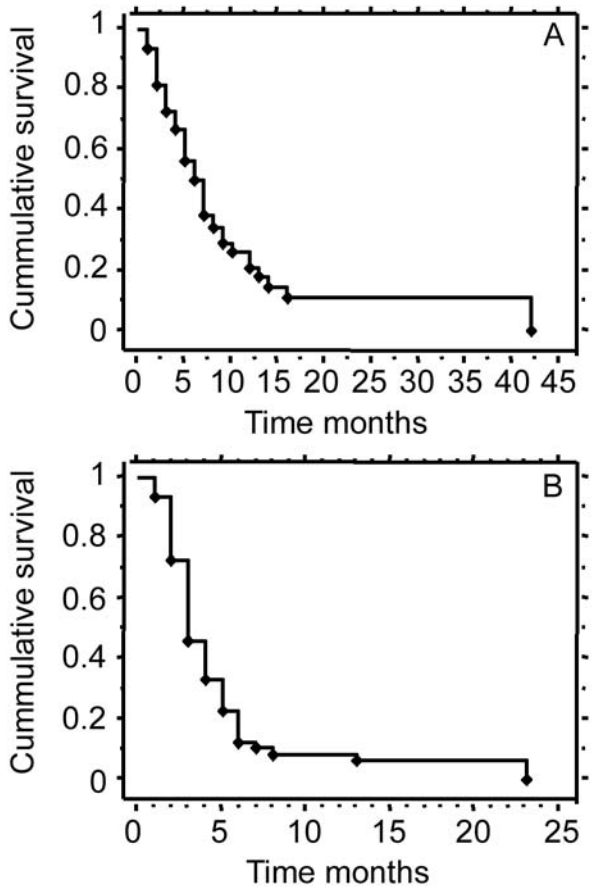

Figure 1. *Overall survival (A) and time to progression (B). Median survival time: 6 months; median time to progression: 3 months; 1-year survival rate: 21%.*

Discussion

This phase II study confirms the activity of docetaxel as second-line treatment for recurrent NSCLC patients. The response rate reached with this bi-weekly schedule was 8.3%, similar to the response rate obtained by the tri-weekly 75 mg/m^2 schedule in phase III (2, 3, 12, 13) and phase II randomized trials (14, 15), but slightly lower than the response rate obtained by the tri-weekly 100 mg/m^2 schedule in early phase II trials (13.8-21.7%) (4-7) (see Table IV).

Table IV. *Summary of phase II and III studies on tri- and bi-weekly docetaxel as second-line treatment for NSCLC.*

Study	Phase	No. of pts	Docetaxel dose (mg/mq) and schedule	RR %	MST months	Grade 3-4 neutropenia %	Febrile neutropenia %
TAX 317 (2)	III*	55	75 q3w	5.5	7.5	67.3	1.8
TAX 317 (2)	III*	49	100 q3w	6.3	5.9	85.7	22.4
TAX 320 (3)	III*	125	75 q3w	6.7	5.7	54.0	8.0
TAX 320 (3)	III*	125	100 q3w	10.8	5.5	77.0	12.0
Fossella (4)	II	42	100 q3w	21.0	11.0	81.0	16.0
Gandara (5)	II	80	100 q3w	16.0	7.0	88.5	14.0
Gridelli (6)	II	23	100 q3w	21.7	5.0	0	0
Mattson (7)	II	58	100 q3w	13.8	7.2	n.r	8.0
Quoix (14)	IIR	93	75 q3w	8.6	4.7	44.0	6.7
Quoix (14)	IIR	89	100 q3w	7.6	6.7	72.7	6.8
Gervais (15)	IIR	62	75 q3w	4.8	5.8	48.4	6.5
Vazquez (16)	II	43	50 q2w	20.0	4.0	41.0	16.0
Present study	II	48	50 q2w	8.3	6.0	47.0	2.0

Abbreviations: No. of pts, number of patients; RR, response rate; MST median survival time; IIR, randomized phase II study; q3w, tri-weekly schedule; q2w, bi-weekly schedule; n.r., not reported.
*Cited only phase III trials with docetaxel as experimental arm, not as control arm

Also comparable with the tri-weekly schedule were median time to progression (3 months), median survival time (6 months) and 1-year survival rate (21%). Variables related to patient and tumor characteristics that can predict the response to docetaxel must still be identified. In the TAX 317 trial (2), the strongest predictive factor was the lack of progression on first-line cisplatin chemotherapy, while in the TAX 320 (3) this variable showed only a trend. Moreover, in this latter trial, patient PS (0-1 *vs.* 2) was a good prognostic factor, but was not predictive. Finally, paclitaxel exposure in first-line treatment did not impact the response to subsequent docetaxel (2, 3, 12). While in our study all patients who responded to docetaxel had not received paclitaxel in a front-line setting, and had a PS of 0-1, these factors were not predictive of response to docetaxel. To our knowledge, the activity of bi-weekly docetaxel as single-agent in second-line chemotherapy for NSCLC has been explored in only one other phase II trial reported by Vazquez *et al*. (16) Though in both studies platinum-based combination chemotherapy was the main first-line treatment used, in the Spanish trial there was a higher rate of cisplatin-based triplets compared to our study (51% and 8%, respectively). Despite this, these authors reported a very high response rate (20% *vs.* 8.3% in the present study), with no definite factors as predictive of response.

Regarding toxicity, myelosuppresion was the main adverse event reported in our study. Though of short duration, and with only one episode of febrile neutropenia registered, hematological toxicity was the main reason for treatment delay and dose reduction, as well as for G-CSF use. Grade 3-4 neutropenia was experienced by 47% of patients; these data are noticeably lower than those reported with the tri-weekly 100 mg/m^2 schedule (77-88%), but not so different from that reported with the tri-weekly 75 mg/m^2 schedule (40.2-67.3%). Interestingly, in the Spanish trial (16) only 16% of patients treated with this bi-weekly 50 mg/m^2 schedule experienced grade 3-4 neutropenia, and no cases of febrile neutropenia were registered. Finally, the delivered dose intensity in our study was 95.7%, in line with the results for the same schedule reported in the Spanish trial.

Non-hematological toxicity was very mild in the present study, reaching only grade 2 in all cases. Fluid retention was never observed, maybe due to the prophylaxis performed with steroids at full dose, the same schedule as the one used in the tri-weekly 75 mg/m^2 administration. The most common side-effect was asthenia (19% of patients) which, as reported by Shepherd *et al*. in the TAX 317 study, is a typical symptom in lung cancer patients with active and progressive disease, and is present in even 47% of patients treated with best supportive care alone (2). Finally, sensory neuropathy was reported in only 1 patient, but was not experienced by any of the 8 patients who received paclitaxel or oxaliplatin as first-line treatment. Interestingly, with the same bi-weekly schedule of docetaxel used in the Spanish trial, neuropathy was reported in 19% of patients.

Second-line chemotherapy for advanced NSCLC patients, progressing after a platinum-based front-line treatment is being administered worldwide in current clinical practice, mostly with single-agent strategies. Docetaxel has been the

leading drug in this setting. Though phase II studies had indicated the optimal dose of docetaxel as 100 mg/m^2 every 3 weeks, the results of phase III trials reduced the recommended dose to 75 mg/m^2. The overall hematological and non-hematological toxicity showed by this latter schedule limits its administration to patients with good performance status. The present study confirmed the activity of the bi-weekly schedule of docetaxel, with a manageable hematological toxicity, and a very low non-hematological toxicity. This schedule might then be compared in a phase III trial with the standard schedule or with the weekly administration, which in previous randomized studies has shown an impact on survival and on global quality of life similar to the tri-weekly schedule, but with significantly less toxicity (13, 17, 18).

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