Biweekly docetaxel as second-line chemotherapy of patients with advanced non-small cell lung cancer: a phase II study of the Galician Lung Cancer Group (GGCP 006-00)

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This phase II trial assessed the antitumoral activity and toxicity of docetaxel 50 mg/m^2 (1-h i.v. infusion) administered every 2 weeks as second-line treatment in 45 patients with advanced non-small cell lung cancer (NSCLC). A total of 251 infusions (median 4 per patient) were administered. The actual and relative median dose intensity values were 24.2 mg/m^2/week and 0.97, respectively. Thirty-seven patients were evaluable for tumor response. The overall response rate was 20% [95% confidence interval (CI) 8–32%] and included one complete response (2%) and eight partial responses (18%). Stable disease was found in seven patients (16%). With a median follow-up of 4 months, the median time to disease progression was 2.8 months (95% CI 1.9–3.7), the median overall survival was 4.0 months (95% CI 3.4–4.6) and the 1-year survival rate was 23% (95% CI 9–37). The every-2-weeks docetaxel schedule was well tolerated. Grade 3/4 non-hematological toxicities showed rates of 5% or less of patients and 2% or less of cycles. The main grade 3/4 hematological toxicity was neutropenia (16% of patients and 8% of cycles). No febrile neutropenia was found. Nevertheless, one toxic death was reported. We conclude that the biweekly docetaxel schedule showed an antitumoral activity similar to that found with the every-3-weeks or weekly docetaxel schedule in a second-line setting for advanced NSCLC. This antitumoral effect was associated with a marked reduction in hematological toxicity, therefore suggesting that this new docetaxel schedule might be useful in the design of combined second-line schedules for treating NSCLC. *Anti-Cancer Drugs* 15:489–494 © 2004 Lippincott Williams & Wilkins.

Introduction

The role of second-line treatments following an initial first-line chemotherapy with a platinum- or a taxane-based regimen is extremely relevant in an aggressive, chemotherapy-resistant disease like non-small cell lung cancer (NSCLC) [1,2]. However, until recently no agents have been available for second-line chemotherapy in NSCLC [3]. Docetaxel is a chemotherapeutic agent that has been extensively studied in this setting. Several phase II trials evaluated docetaxel monotherapy in platinum-treated patients with NSCLC and showed response rates ranging from 14 to 24%, a median survival greater than 7 months and, when reported, 1-year survival rates ranging from 25 to 44% [4]. The regimen most studied in these phase II trials was docetaxel 100 mg/m^2 every 3 weeks and the promising results found promoted two phase III randomized trials (the TAX 317 study and the TAX 320 study) on docetaxel in second-line chemotherapy of NSCLC patients [5,6].

These two phase III trials confirmed docetaxel as an active second-line chemotherapy in NSCLC patients; in particular, the 75 mg/m^2 dose administered every 3 weeks showed an acceptable benefit:risk ratio. Response rates were low (around 7%), but survival was improved with respect to supportive care [5]. Moreover, an improvement in the 1-year survival rate was found (32–37 versus 19% with control regimens of vinorelbine or ifosfamide) [6]. Thus, docetaxel is the first cytotoxic agent to be registered in the US and Europe for second-line chemotherapy in NSCLC [7]

The goals of second-line treatment of patients with NSCLC are palliative [3]. Therefore, the decision to offer second-line chemotherapy should follow a balanced discussion of the potential risks and benefits of the proposed treatment. Docetaxel given every 3 weeks significantly prolongs survival and offers clinically meaningful benefits as second-line chemotherapy to NSCLC

patients [7]. However, other regimens need to be studied in order to improve the clinical benefit:toxicity ratio of second-line docetaxel chemotherapy. For example, weekly docetaxel has been studied in the second-line setting in phase II trials [8–10] and in several phase III randomized trials [11–13], and has shown a similar response rate and survival, but a more favorable toxicity profile. Weekly docetaxel has also been studied as third-line therapy for advanced NSCLC, with good results [14].

To our knowledge, no data is currently available on biweekly docetaxel monotherapy as second-line chemotherapy in NSCLC patients. Two Italian studies have reported the use of docetaxel every 2 weeks in advanced NSCLC patients, but combined with gemcitabine [15] or irinotecan [16]. This combined biweekly schedule was based on data obtained in phase I trials showing that the 2-week schedule was related to an increased tolerance compared to the combined 3-week schedule [17].

The present phase II trial assessed the antitumoral activity and toxicity of docetaxel 50 mg/m^2 administered every 2 weeks as second-line treatment of patients with advanced NSCLC.

Methods
Selection of patients
A total of seven Spanish hospitals participated in this study. The trial protocol was conducted following the Declaration of Helsinki and Good Clinical Practice guidelines, and all patients provided their written informed consent. Patients were included if they were > 18 years old and had histologically confirmed NSCLC, advanced or metastatic disease untreated with radiotherapy, progression after at least one prior chemotherapy regimen (no requirements for previous chemotherapy were considered), bidimensionally measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2, a life expectancy > 12 weeks and adequate organ function. The laboratory requirements before inclusion in the study were the following: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, Hb ≥ 10 g/dl, serum creatinine ≤ 1.6 mg/dl [in limit values, creatinine clearance had to be ≥ 60 ml/min, bilirubin $\leq 1 \times$ upper normal limit (UNL), transaminases (AST and ALT) $\leq 2.5 \times$ UNL and alkaline phosphatase $\geq 2.5 \times$ UNL; if AST and/or ALT $\geq 1.5 \times$ UNL were concomitant with alkaline phosphatase $\geq 2.5 \times$ UNL, the patients were excluded from the study]. Biochemical and hematological analyses were repeated before each infusion. Patients with clinically controlled cerebral metastases were also included.

The patients were excluded from the study if they showed other histological types different than NSCLC or if they had prior neuropathy grade 2 or grater, other severe concurrent diseases (congestive heart failure below class II NYHA, myocardial infarction during the previous 6 months, uncontrolled hypertension or ventricular arrhythmia, ischemic cardiopathy requiring nitrate treatment, second- or third-degree cardiac blockage, or HIV infection), hypersensitivity to the study drug, hypercalcemia and other neoplasias except for resolved carcinoma of cervix uteri, cutaneous basal carcinoma or other tumors resolved for at least 10 years before inclusion. Other antitumoral concomitant treatments were not allowed and, if needed, corticosteroid therapy had to be started 6 months or more before inclusion and at low doses.

Chemotherapy regimen
The patients were treated with 50 mg/m^2 of docetaxel (Taxotere; Aventis, Spain) (1-h i.v. infusion) on days 1 and 14. All patients were given dexamethasone 8 mg p.o. 3 times: twice before (12 and 1 h) and once after (12 h) docetaxel infusion. Equivalent drugs (methylprednisolone 40 mg p.o. or prednisolone 50 mg p.o.) could also be administered. Each cycle included two infusions and was repeated every 4 weeks. Treatment was to be administered until disease progression, unacceptable toxicity or consent withdrawal. Except for prophylactic antiemetic treatment, other concomitant therapies (i.e. chemotherapy, immunotherapy, hormonal therapy or radiotherapy) were not allowed.

Both ANC $\geq 1.5 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l were required to administer a new chemotherapy cycle. Dose modifications were planned for severe toxicity. In those cases showing grade 3 toxicity (except for alopecia, nausea and vomiting), febrile neutropenia or grade 4 thrombocytopenia, the docetaxel dose was reduced to 75% of the initial dose. Doses reduced for toxicity could not be re-escalated and a delay higher than 2 weeks excluded the patient from the study. The treatment was also discontinued in those patients showing severe fluid retention (pleural, pericardial or ascites) or severe cutaneous toxicity.

Evaluation of efficacy and toxicity
Response to treatment was evaluated after the patients had received two chemotherapy cycles and classified according to WHO criteria [18]. All the patients were evaluated during each treatment cycle and upon completion of the treatment schedule for toxicity. The patients were monitored for clinical and laboratory toxicity, and were asked to report any occurrence of adverse experiences to the investigator. All toxicities were documented and graded according to the National Cancer Institute Common Toxicity Criteria [19]. After the end of the study, the patients were evaluated in follow-up visits once every 2 months.

Data analysis

A sample size of 42 patients to be enrolled was determined assuming a minimal objective response rate of 21% with a power of 80%, an α value of 0.05. and a withdrawal rate of 10% (Fleming's single-stage procedure) [20].

The primary end-point for this study was overall response rate. Secondary end-points were time to disease progression and survival. Objective response rates were calculated with 95% confidence intervals (CI). Time to disease progression was defined as the period of time from the start of the treatment to the first progression or death. Survival was calculated from the date of first treatment administration to the date of death by any cause. Actuarial survival curves were constructed using the method of Kaplan and Meier [21]. Both, toxicity and efficacy analyses were performed on the intent-to-treat (ITT) population, i.e. on patients who received at least one dose of the study treatment.

Results

Patient characteristics

Forty-five patients were enrolled into the study. Their main baseline characteristics are shown in Table 1. Histological diagnosis showed epidermoid carcinoma (57%) and adenocarcinoma (38%) in most patients. The median baseline ECOG PS was 1 and most patients showed stage IV disease (61%). The median number of target lesions was 2 and the median number of metastatic sites was 1. Metastases were mainly located in lung (51%), bone (19%) and lymph nodes (12%). All patients received one prior chemotherapy regimen. Only one patient (2%) received single-agent, non-platinum chemotherapy. Thirty-three (73%) of the patients who

Table 1 Patient characteristics at baseline (*n*=43)[a]

Characteristic	*n*	%
Age (years)		
median	60	
range	40–74	
WHO performance status		
0	8	19
1	28	65
2	7	16
Disease stage		
IIIA	4	10
IIIB	12	29
IV	25	61
No. metastatic sites	36	86
No. of sites involved		
0	10	23
1	19	44
≥ 2	14	33
Disease sites[b]		
bone	8	19
liver	4	9
lung	22	51
lymph nodes	5	12

[a]Data available only for 43 patients out of 45 enrolled.
[b]Some patients showed more than one metastatic site.

received prior combined chemotherapy regimens were treated with platinum-based chemotherapy. The prior chemotherapy regimens most often reported were paclitaxel/cisplatin/gemcitabine (30%) and cisplatin/vinorelbine/gemcitabine (21%).

Chemotherapy

A total of 119 chemotherapy cycles (median 2, range 1–8) and 251 infusions (median 4, range 1–16) were administered during the study. Eleven infusions (4%) required dose reduction due to hematological toxicity (three patients in one infusion, two patients in two infusions and one patient in four infusions). Twenty-four infusions (20%) were delayed in 17 patients (38%) due to hematological toxicity (10 infusions), non-drug related causes (nine infusions) and non-hematologic toxicity (five infusions). The absolute and relative median dose intensity values (RDI) were 24.2 mg/m^2/week and 0.97, respectively.

Response

On an ITT basis, all patients were included in the efficacy analysis (Table 2). One patient (2%) had a CR and eight (18%) had a PR, with an overall response rate of 20% (95% CI 8–32). The CR was found in a patient who had previously received paclitaxel and cisplatin, and four out of five PRs were found in patients who had previously received paclitaxel and cisplatin, respectively. Stable disease was observed in seven patients (15%) and 21 patients (47%) progressed during the period of active treatment studied. No clear differences in antitumoral response were found between patients previously treated with platinum compounds (23%, *n* = 26) or with paclitaxel (26%, *n* = 19).

Eight patients were considered no evaluable for efficacy. Five of these patients died during the study due to cardiorespiratory arrest (*n* = 2), pneumonia (*n* = 1), stroke (*n* = 1) and toxicity (grade 4 neutropenia and massive hemoptysis, *n* = 1). One patient died after receiving an infusion although the relationship with the study drug was unclear. The other two not evaluable patients showed non-measurable disease and withdrawal due to neurological worsening after the first chemotherapy cycle, respectively.
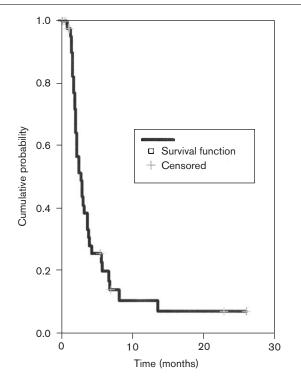
With a median follow-up of 4 months (range 0.2–26), the median time to disease progression was 2.8 months (95%

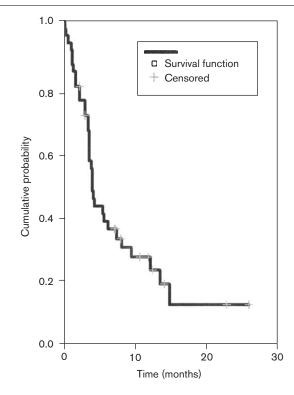**Table 2 Overall response rate (ORR) to treatment (*n*=45)**

	n	%
Complete response	1	2
Partial response	8	18
Stable disease	7	15
Progressive disease	21	47
Not evaluable	8	18
ORR [% (95% CI)]	20 (8–32)	

Fig. 1

Time to progression ($n=45$).

Fig. 2

Overall survival ($n=45$).

CI 1.9–3.7) (Fig. 1) and the median overall survival was 4.0 months (95% CI 3.4–4.6) (Fig. 2). The 1-year survival rate was 23% (95% CI 9–37).

Toxicity

All patients were evaluated for safety. The toxicity profile revealed a good tolerance, especially for non-hematological toxicities (with rates of 5% or less of patients and 2% or less of cycles). Hematological and non-hematological toxicities per cycle and per patient are shown in Table 3. The main grade 3/4 hematological toxicity was neutropenia (16% of patients and 8% of cycles). No febrile neutropenia was reported. Nevertheless, one toxic death was found due to grade 4 neutropenia and massive hemoptysis.

Discussion

This study shows that docetaxel 50 mg/m^2 administered every 2 weeks is an active regimen for the second-line chemotherapy of advanced NSCLC patients. The overall response rate found was 20% and included one complete response. This response rate fell into the range found in previous phase II trials on docetaxel 75–100 mg/m^2 administered every 3 weeks (14–24%) [4] and was more than twice that found in phase III trials on docetaxel 75 mg/m^2 administered every 3 weeks: 7.1 [5] and 6.7% [6] (Table 4). Nevertheless, the patients in these two

phase III trials were heavily pretreated: 27 [5] and 35% of patients [6] had received more than two prior regimens whereas all patients treated here have only received one prior chemotherapy regimen. Response rate is very much influenced by the characteristics of prior therapy and the comparisons showed here must be taken with caution.

Docetaxel 25–43 mg/m^2 given weekly in the second-line setting of NSCLC has shown a lower response rate (10, 11 and 17%) in three phase II trials [8–10], but a similar response rate (23%) in a further phase II study in the third-line setting [14]. Several phase III trials have compared weekly docetaxel with the every-3-weeks schedule as second-line chemotherapy for NSCLC [11–13]. All these randomized trials have shown a reduced toxicity when docetaxel is given at a lower weekly dose, but the data from some of these studies suggest that efficacy (i.e. response rate or survival) could be also reduced [13].

The docetaxel doses studied in phase II trials conducted with the every-3-weeks schedule in the first-line setting ranged from 60 to 100 mg/m^2 and lower doses appeared to have less anticancer activity than higher doses [22,23]. Most phase II studies of docetaxel administered every 3 weeks for previously treated NSCLC patients were conducted in European and American countries using a

Table 3 Treatment-related toxicity

Toxicity	Patient (n=44)[a]		Cycle (n=123)[b]	
	Grade I/II	Grade III/IV	Grade I/II	Grade III/IV
Hematological				
anemia	23 (52%)	3 (7%)	66 (54%)	4 (3%)
leukopenia	17 (39%)	3 (7%)	40 (33%)	5 (4%)
neutropenia	11 (25%)	7 (16%)	25 (20%)	10 (8%)
Non-hematological				
asthenia	10 (23%)	1 (2%)	12 (10%)	1 (1%)
diarrhea	9 (21%)	2 (5%)	10 (8%)	2 (2%)
eye toxicity	2 (5%)	1 (2%)	5 (4%)	1 (1%)
nausea/vomiting	11 (25%)	1 (2%)	15 (12%)	1 (1%)
neuropathy	6 (14%)	2 (5%)	12 (10%)	2 (2%)
Pain	–	1 (2%)	–	1 (1%)

[a]One patient died after the first infusion and no toxicity data was available.
[b]One patient received 4 additional cycles after progression in cycle 4.

Table 4 Docetaxel in the second-line setting using different schedules

Reference	Regimen	n	OR (%)	TTP (weeks)	OS (months)	1-year survival (%)	Grade 3/4 neutropenia (% patients)
Every 3 weeks[a]							
24	60 mg/m^2 every 3 weeks	22	18	13.7	7.8	25	73
5	75 mg/m^2 every 3 weeks	55	6	10.6	7.5	37	67
6	75 mg/m^2 every 3 weeks	125	7	8.5	5.7	32	54
6	100 mg/m^2 every 3 weeks	125	11	8.4	5.5	21	77
Every week							
9	35 mg/m^2 every week	36	11	NR	5.6	NR	0
8	36 mg/m^2 every week	31	10	NR	8.0	31	3
10	43 mg/m^2 every week	26	17	NR	12	46	0
Every 2 weeks							
present study	50 mg/m^2 every 2 weeks	45	20	12.2	4.0	23	16

OR, overall response; TTP, time to progression; OS, overall survival; NR, not reported.
[a]Only data from phase III trials are shown.

dose of 100 mg/m^2, but further phase II trials confirmed 75 mg/m^2 as suitable for second-line setting [5,6]. A phase II study conducted in Japan showed a similar response rate (18%) with a low docetaxel dose (60 mg/m^2) administered every 3 weeks as second-line chemotherapy in NSCLC patients [24]. Nevertheless, the results of this Japanese study must be interpreted with caution due to racial differences affecting docetaxel metabolism and response.

Overall, the response rate found in the present study suggest that docetaxel 50 mg/m^2 administered every 2 weeks show at least a similar antitumoral activity than other regimens used in second-line chemotherapy for NSCLC patients. No clear differences in antitumoral response were found between patients previously treated with platinum compounds (23%, $n = 26$) or with paclitaxel (26%, $n = 19$). Nevertheless, the low number of patients studied does not allow deriving any conclusions from these findings that should be confirmed in randomized, large-scale phase III trials.

The median time to disease progression (2.8 months, 12.2 weeks) fell in the range of 8.0–17.4 weeks found with other schedules (Table 4), but the overall survival (4.0 months) was closer to the lowest value of the range previously found with other second-line docetaxel regimens in NSCLC (5.5–12.0 months) (Table 4). Due to the poor prognosis of advanced NSCLC patients, it is not surprising to find unclear survival differences in the early months or in the median survival between treatments. We found here a 1-year survival rate of 23%, which is higher than the 11% found with best supportive care [5] and fell into the range of 21–32% found with docetaxel administered every 3 weeks [6]. Therefore, the biweekly docetaxel schedule seems to offer a survival benefit like that found with the every 3 weeks docetaxel schedule.

The TAX 317 and TAX 320 phase III studies showed a modest non-hematological toxicity for docetaxel every 3 weeks [5,6]. In accordance with this finding, we report here that grade 3/4 diarrhea, nausea/vomiting or neuropathy appeared in less than 5% of patients. In contrast, whereas the TAX 317 and TAX 320 trials had reported grade 3/4 neutropenia in 54–77% of patients [5,6], only 16% of the patients in the present study showed grade 3/4 neutropenia. Moreover, no febrile neutropenia was found. This meaningful reduction in hematological toxicity agrees with the results of previous trials on weekly docetaxel second-line schedule, which maintained the antitumoral activity of the drug, but improved the hematological toxicity profile [8,9,11,14]. However, one

case of toxic death was reported in the present phase II study. The rate of toxic death found here (2%) is similar (2%) or lower (6%) to that found with docetaxel 100 mg/m^2 every 3 weeks [6]. Further trials conducted in a large number of patients are required to clarify whether this was an unusual finding, especially taking into account the excellent toxicity profile found in most patients studied.

In conclusion, docetaxel 50 mg/m^2 administered every 2 weeks as second-line chemotherapy in advanced NSCLC patients seems to show a similar antitumoral activity to that found with the every-3-weeks or the weekly docetaxel schedules. Similar survival benefit and a remarkable reduction in hematological toxicity were reported compared to the tri-weekly schedule, suggesting that this new schedule might be useful in designing second-line combination therapies for NSCLC. To date, the combination of biweekly docetaxel with gemcitabine or irinotecan has been evaluated. The lack of neutropenia and associated febrile episodes with this docetaxel schedule may be particularly important for previously treated patients or for patients at high risk for myelotoxic complications with chemotherapy. Nevertheless, the finding of one toxic death during the present phase II study requires additional clinical trials in order to confirm the good clinical benefit–toxicity relationship found for most patients included in the present study.

Acknowledgments

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