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ORIGINAL ARTICLE

A dose-escalation study of pemetrexed and docetaxel in non-small-cell lung cancer

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Abstract A phase I study was conducted to determine the maximum tolerated doses (MTD) and the dose-limiting toxicities (DLT) of pemetrexed and docetaxel in patients with advanced unresectable or metastatic non-small-cell lung cancer (NSCLC). Patients were treated with escalating doses of pemetrexed (400–600 mg/m^2 as a 10-min intravenous infusion) and docetaxel (65–85 mg/m^2 as a 1-h intravenous infusion) on day 1, every 3 weeks. An expanded accrual at the level of the recommended dose (RD) had been scheduled. Forty-two patients with metastatic NSCLC were enrolled in the phase I study and 20 additional patients at the RD level. The MTD could not be reached even at the doses of 550 and 85 mg/m^2 for pemetrexed and docetaxel, respectively, which are higher than the recommended dose for each drug given as a single agent. Therefore, the RD was defined at 500 mg/m^2 pemetrexed and 75 mg/m^2 docetaxel. Among the 164 administered chemotherapy cycles (phase I part), there were three episodes of febrile neutropenia whereas 13 (7.9%) and 11 (6.7%) cycles were complicated with grade III and IV neutropenia, respectively. Three patients developed grade III/IV thrombocytopenia. Non-hematologic toxicity was mild with grade III fatigue occurring in three (6.7%) patients. There was no toxic death. The favorable toxicity profile of the regimen was confirmed in patients treated at the RD level. Overall, one complete (CR) and 13 partial responses (PR) (overall response rate = 23; 95% C.I:12.4–33.5%] were documented. The combination of pemetrexed and docetaxel seems to be an effective regimen in NSCLC with acceptable and manageable toxicity, which merits further investigation.

Keywords Pemetrexed · Docetaxel · NSCLC · Phase I study

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Introduction

Lung cancer is the leading cause of cancer death in the United States and Europe, and it has been estimated that more patients will die from lung cancer than prostate, breast and colorectal cancer together [1]. In 2006, lung cancer was in incidence the third most common cancer in Europe and the most frequent reason for death caused by a malignant tumor [2]. Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers and has become the major cause of cancer-related mortality in both men and women. Despite significant advances in the treatment of NSCLC over the past years, the prognosis of the patients with advanced or metastatic disease is poor with a median survival for the newly diagnosed stage IV patients ranging from 8 to 11 months and 5–7 months for those with relapsed disease [2].

Platinum-based combination has emerged as the cornerstone first-line treatment for NSCLC. In two large meta-analyses, cisplatin-based combinations revealed superior responses and improved overall survival (OS) in some subgroups of patients [3, 4]. Moreover, cisplatin has been shown to be superior to carboplatin when is combined with new chemotherapeutic agents (e.g. paclitaxel, docetaxel

and gemcitabine) [3]. Recently, an antibody against vascular endothelial growth factor (bevacizumab) was proved effective in the first-line setting of non-squamous NSCLC, as significantly prolonged the progression-free survival (PFS) [5, 6] and OS [5]. Although these agents are active in NSCLC, they add toxicity which, in some cases, is severe. Nausea, vomiting, anemia, neuro- and nephrotoxicity comprise the most common occurred adverse events. Bevacizumab has also been mainly associated with increased toxicity, hypertension, proteinuria, hemorrhage and gastrointestinal (GI) perforation.

Less toxic and more active regimens are required to be incorporated in the modern oncology armamentarium. Hence, the replacement of platinum compound with new agents has been emerged as an attractive approach for the treatment of NSCLC. Docetaxel promotes the assembly of microtubules from tubulin dimers, inhibits the depolymerization of tubulin that stabilizes microtubules in the cell and, eventually, inhibits DNA, RNA and protein synthesis occurring mainly during the M phase of the cell cycle. On the basis of the results of big randomized trials [7–9], docetaxel has been approved as first-line treatment for NSCLC in combination with cisplatin and as monotherapy in the second-line setting. Docetaxel has shown activity in the first-line setting even with non-platinum combinations; we have previously shown that the docetaxel/cisplatin and the docetaxel/gemcitabine regimens had a comparable efficacy in terms of response rate (RR), PFS and OS with a more favorable toxicity profile for the non-platinum regimen [10].

Pemetrexed is a multitargeted antifolate drug that targets the enzymes thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT) [11]. By inhibition of these enzymes, it affects the synthesis of substrates necessary for cell growth and division and causes cell-cycle arrest in the S phase [12, 13]. It has shown activity against NSCLC and has been approved as front-line treatment in combination with cisplatin as well as monotherapy in the second-line setting for the non-squamous cell carcinomas [14]. In addition, pemetrexed given as maintenance treatment in NSCLC patients who achieve disease control after platinum-based front-line therapy could significantly improve OS and PFS [15].

The fact that both pemetrexed and docetaxel result to a cell-cycle arrest during different phases may imply that they could have an additive or synergistic antitumor effect. Indeed, preclinical data have shown at least additive effect when pemetrexed was combined with docetaxel [16]. The same combination regimen has also been used in clinical trials in solid tumors with promising efficacy and acceptable toxicity. Furthermore, the combination of paclitaxel with pemetrexed was recently tested in patients with NSCLC with encouraging results [17]. These data provide us the rationale to conduct a dose-escalation study of the docetaxel/pemetrexed combination in order to determine the dose-limiting toxicity (DLT) and the maximum tolerated doses (MTD) of the association in patients with advanced or metastatic NSCLC.

Patients and methods

Patient selection

Patients aged >18 years with a pathologically or cytologically confirmed, unresectable locally advanced (stage IIIB with pleural infusion) or metastatic NSCLC who had received prior chemotherapy (maximum one prior chemotherapy regimen) as well as chemotherapy-naïve patients were eligible for the study; in addition, patients with CNS disease were also eligible if they had been irradiated and were clinically stable. Prior surgery or radiotherapy (to less than 25% of bone marrow) was allowed. However, a treatment-free interval of at least 4 weeks was required before study enrollment. Other inclusion criteria were as follows: performance status 0–2 (ECOG); adequate blood counts (absolute neutrophil count >1,500/μl, hemoglobin <10/μl and platelets >100,000/μl); adequate renal function (serum creatinine <2 mg/dl); adequate hepatic function (total bilirubin <2 mg/dl and transaminases <3 times the upper normal limit); adequate cardiac function without unstable angina or myocardial infarction within the last 6 months; no history of other primary cancer; and life expectancy of at least 3 months. All patients signed a written informed consent before study enrollment. The study had been approved by the Ethics and Scientific Committees of our Institution and is registered in ClinicalTrials.gov (NCT00684099).

Treatment

Treatment schedule and dose escalation are shown in Table 1. Docetaxel (Taxotere; Sanofi-Aventis, Bridgewater, USA) was administered as a 1-h intravenous infusion (IV) at escalated doses from 60 to 85 mg/m^2 followed by pemetrexed (Alimta; Eli-Lilly, Indianapolis, USA) given as a 10-min IV infusion, at escalated doses from 400 to 550 mg/m^2; both drugs were given on day 1 every 3 weeks without prophylactic administration of hematopoietic growth factors. The treatment was continued for up to six cycles or occurrence of disease progression or unacceptable toxicity. All patients had standard vitamin supplementation with 1,000 mcg vitamin B12 intramuscular every 9 weeks and folic acid 400 mcg/day per os for the administration of pemetrexed. In addition, standard

Table 1 Dose levels and DLTs

Level (no of patients)	Doses (mg/m^2) D P		No of DLTs	DLT events
	D	P		
1st ($n = 3$ pts)	65	400	–	None
2nd ($n = 6$ pts)	65	450	2	Neutropenia grIV ($n = 1$)
				Febrile neutropenia grIII ($n = 1$)
3rd ($n = 6$ pts)	70	450	1	Thrombocytopenia grIV ($n = 1$)
4th ($n = 6$ pts)	70	500	2	Neutropenia grIV ($n = 2$)
5th ($n = 3$ pts)	75	500	–	None
6th ($n = 6$ pts)	80	500	2	Neutropenia grIV ($n = 1$)
				Rash grIII ($n = 1$)
7th ($n = 6$ pts)	80	550	1	Neutropenia grIV ($n = 1$)
8th ($n = 6$ pts)	85	500	2	Neutropenia grIV ($n = 2$)

premedication with corticosteroids for docetaxel administration was given. The used antiemetic regimen included ondansetron 16 mg intravenously 30 min before chemotherapy administration.

Dose escalation

The following dose levels for docetaxel/pemetrexed have been evaluated: 65/400; 65/450; 70/450; 70/500; 75/500; 80/500; 80/550; 85/500 (mg/m^2) (Table 1). No intrapatient dose escalation was allowed. At least three patients were enrolled at each dose level. If a DLT was observed in one of the first three patients, then three additional patients were enrolled at the same dose level. DLTs were assessed during the first chemotherapy cycle; as DLT was defined the occurrence of any of the following: grade 4 neutropenia or thrombocytopenia; grade 3–4 neutropenia with fever >38.3°C, or a sustained temperature >38°C for more than 1 h [18]; grade 3–4 non-hematologic toxicity; and any treatment delay because of toxicity. Dose escalation was discontinued and the DLT level would be reached if at least 50% of the patients treated at that level developed a DLT (e.g. at least two of three, or three of six patients). The MTD level was defined as the first level below the DLT dose level. At the MTD level, 20 additional patients have to be recruited (a total of 23 patients) in order to further evaluate the tolerance of the regimen at the recommended doses (RD level) for future phase II studies.

Toxicity assessment

Before each chemotherapy cycle, all patients had a detailed toxicity questionnaire and a physical examination in order to define treatment-related adverse events. Hematologic toxicity was assessed weekly with complete blood counts (CBC) with differential and platelet counts; in case of grade III/IV hematologic toxicity, a CBC with differential and platelets count was performed daily until recovery (neutrophils >1,500/μl and platelets >100.000/μl). A complete biochemical profile was performed at baseline and every 3 weeks thereafter. Toxicities were graded according to NCI CTC version 3.0. Day 1 treatment was administered on scheduled dates without any delay or dose reduction if the laboratory inclusion criteria were met; otherwise, day 1 treatment was postponed for up to 7 days until resolution of the prohibitive toxicity. Then, treatment was administered according to the predefined schedule and dose and without any missed dose. If the prohibitive toxicity had not resolved after a 7-day treatment delay, the scheduled treatment was missed and upon resolution of the toxicity, treatment was resumed as a new cycle using doses of the previous dose level. Doses were also reduced to the previous dose level in case of febrile neutropenia (grade II–IV neutropenia with fever >38.0°C in two consecutive measurements at least 1 h apart) [18] or grade III–IV thrombocytopenia with or without bleeding episode.

Tumor response

Although patients were not required to have bidimensionally measurable disease to enter the study, response was assessed according to the standard RECIST criteria for those who did have [19]. Tumor response was assessed every three chemotherapy cycles by appropriate imaging studies, and all responses have to be confirmed by a repeated imaging evaluation 4 weeks later. The duration of response was defined as the time from the day that objective tumor shrinkage was noted for the first time until the time of documented tumor progression or death due to any cause. The time to progressive (TTP) disease and the overall survival were defined as the time from the date of study enrollment until the date of progressive disease and the date of death due to any cause, respectively.

Results

Patients' demographics

Patients' characteristics are presented in Table 2. Between June 2005 and June 2009, a total of 62 patients were enrolled onto the study; forty-two patients were recruited onto the escalation part of the study and 20 at the RD level of the expanded part of the study. The patients' median age was 63 years, and 87% of them had a performance status (ECOG) of 0–1. Fourteen (23%) patients suffering from a squamous cell carcinoma were enrolled in the trial before May 2008 when the published results demonstrated that pemetrexed was mainly active in patients with a non-squamous cell histology (14). From the patients enrolled in the phase I part of the study, 33 (78.6%) had a non-squamous histology whereas in the phase II part of the study, 15 (75%) had a non-squamous histology. Fifty-one (82%) patients had stage IV disease and 21 (34%) were chemotherapy-naïve. Table 2 also indicates that 34 (54.8%) patients had previously received platinum- and 35 (56.5%) taxane-based chemotherapy.

Compliance with the treatment

At the escalation part of the study, a total of 164 chemotherapy cycles were administered in all patients and in all dose levels with a median of 3 cycles/patient (range, 1–9). The median interval between cycles was 21 days (range, 21–33). Eleven (7%) cycles were delayed because of hematologic toxicity ($n = 2$ cycles) as well as for reasons unrelated to the disease or treatment ($n = 9$ cycles). Dose reduction was required in 8 (4.9%) cycles because of hematologic ($n = 6$ cycles) and non-hematologic ($n = 2$ cycles) toxicity. The reasons for treatment discontinuation were as follows: completion of treatment as per protocol ($n = 12$ patients), progressive disease ($n = 25$ patients), toxicity ($n = 3$ patients) and patient's consent withdrawn or lost to follow-up ($n = 3$ patients). Regarding the expansion at the RD level, the rate and the severity of toxicity were similar to that observed during the escalation and significant delays or dose reductions were not required (data not shown).

Table 2 Patient characteristics

No of enrolled patients	62
Age, median (range)	63 (37–80)
Sex (*no*)	
Male	50 (81%)
Female	12 (19%)
Stage (*no*)	
IIIB	11 (18%)
IV	51 (82%)
Performance status (*no*)	
0–1	54 (87%)
2	8 (13%)
Histology (*no*)	
Squamous	14 (23%)
Adenocarcinoma	36 (58%)
Large cell	2 (3%)
Mixed	2 (3%)
Non otherwise specified	8 (13%)
No of prior regimens	
No prior therapy	21 (34%)
1 Regimen	41 (66%)
Prior chemotherapy regimens	
Platinum-based	34 (55%)
Taxane-based	35 (57%)

Dose-limiting toxicities

Table 1 shows the dose-escalation levels, the number of patients enrolled at each dose level and the observed DLTs during the first cycle. The most common DLT was grade III-IV neutropenia or febrile neutropenia observed at dose levels 2 ($n = 2$ patients), 4 ($n = 2$ patients), 6 ($n = 1$ patient), 7 ($n = 1$ patient) and 8 ($n = 2$ patients). Other DLTs included grade IV thrombocytopenia at dose level 3 ($n = 1$ patient) and grade III generalized skin rash leading to treatment delay at dose level 6 ($n = 1$ patient). The MTD has not been reached. However, dose escalation has been discontinued when it was ascertained that the regimen was safe, with an acceptable toxicity profile even at dose levels that exceeded the recommended single agent doses, and it was observed that higher doses of the drugs were not associated with better efficacy results (see below). Therefore, the recommended doses for future studies are docetaxel 75 mg/m2 and pemetrexed 500 mg/m2 on day 1 every 3 weeks (5th dose level = RD level).

Hematologic and non-hematologic toxicity

Table 3 indicates the hematologic toxicity observed in all patients and in all chemotherapy cycles irrespectively of the dose level. A total of 12 (6.7%) and 16 (9.1%) cycles were complicated with grade III and IV neutropenia, respectively; three patients presented grade III ($n = 2$ patients) and IV ($n = 1$ patient) thrombocytopenia; no bleeding episodes were observed, and no platelet transfusions were required. There were four episodes of febrile neutropenia occurring at the 1st, the 2nd, the 5th and the 6th dose levels but none of them occurred during the first chemotherapy cycle. There was no toxic death. One patient developed a non-neutropenic infection requiring hospitalization for intravenous antibiotics and cardio-respiratory support; the patient was uneventfully recovered.

Table 3 Hematologic toxicity in all cycles and dose levels

Level/No of cy	Docetaxel	Pemetrexed ($n = 42$)	Neutropenia no of patients (%)			Anemia no of patients (%)			Thrombocytopenia no of patients (%)			Febrile neutropenia
			Grade			Grade			Grade			
			II	III	IV	II	III	IV	II	III	IV	
1°/7	65	400	–	2 (28.6)	–	1 (14.3)	–	–	–	–	–	GrIII = 1
2°/25	65	450	1 (4.0)	2 (8.0)	1 (4.0)	–	–	–	–	–	–	GrIII = 1
3°/20	70	450	2 (10.0)	2 (10.0)	1 (5.0)	–	1 (5.0)	–	–	–	1 (5.0)	–
4°/28	70	500	3 (10.7)	1 (3.6)	2 (7.1)	6 (21.4)	–	–	–	–	–	–
5°/11	75	500	–	–	–	–	–		–	–	–	GrIII = 1
6°/22	80	500	4 (18,2)	1 (4.5)	1 (4.5)	–	–	–	–	1 (4.5)	–	GrIII = 1
7°/30	80	550	1 (3.3)	2 (6.7)	3 (10.0)	1 (3.3)	–	–	–	–	–	–
8°/23	85	500	3 (13.0)	3 (13.0)	3 (13.0)	1 (4.3)	–	–	–	1 (4.3)	–	–

Non-hematologic toxicity was generally mild. Table 4 shows the incidence of moderate to severe non-hematologic toxicity in all patients and all cycles, irrespectively of the dose levels. The most common toxicity was asthenia, which was grade II in 20 (12.2%) cycles corresponding to 11 (26%) patients and grade III in 3 (1.8%) cycles corresponding to three (7.2%) patients. Other toxicities were mild occurring in less than 5% of the administered cycles. Grade III generalized skin rash was observed in one (0.5%) patient two times. No other severe unexpected toxicities were observed. For the patients treated at the higher dose levels (6–8), the observed toxicity was slightly increased, mainly regarding the hematologic profile. At the RD level, 20 additional patients were enrolled. The toxicity profile of the regimen as well as the incidence of different adverse events was, practically, similar to those observed during the dose-escalation part of the trial. In particular, grade III and IV neutropenia occurred in three patients each, whereas febrile neutropenia was observed in one patient (Table 5).

Antitumor activity

In total, 61 patients were evaluable for response (41 out of 42 patients who were enrolled in the escalation part of the study and 20 patients enrolled in the RD level).One patient without a measurable target lesion was not evaluated for response. Complete response (CR) was achieved in one (1.6%) patient and partial response (PR) in 13 (21.0%) (overall response rate (ORR) = 23; 95% C.I:12.4–33.5%); ten (16.1%) patients experienced stable disease (SD) and 37 (60.7%) progressive disease (PD). The disease control rate was 39%. The treatment was 1st-line for five of the responders (ORR = 25% in chemotherapy-naïve patients; 95% C.I: 6.0–43.9%) and 2nd-line for nine of them. (ORR = 22; 95% CI: 9.3–34.6%) ($p = 0.790$). In addition,

Table 4 Non-hematologic toxicity in all cycles and dose levels

Level/No of cy	Docetaxel	Pemetrexed ($n = 42$)	Nausea/vomiting no of patients (%)		Diarrhea no of patients (%)			Asthenia no of patients (%)			Others
			Grade		Grade			Grade			
			II	III	II	III	IV	II	III	IV	
1°/7	65	400	2 (28.6)	–	–	–		–	–	–	–
2°/25	65	450	–	–	–	–	–	3 (12.0)	–	–	Non-neutropenic infection ($n = 1$)
3°/20	70	450	1 (5.0)	–	1 (5.0)	–	1 (5.0)	1 (5.0)	2 (10.0)	–	–
4°/28	70	500	–	–	2 (7.1)	–	–	4 (14.3)	–	–	–
5°/11	75	500	2 (18.2)	–	–	–	–	1 (9.1)	–	–	–
6°/22	80	500	1 (4.5)	–	1 (4.5)	–	–	3 (13.6)	1 (4.5)	–	Generalized Skin rash GrIII ($n = 2$)
7°/30	80	550	2 (6.7)	–	1 (3.3)	–	–	6 (20.0)	–	–	–
8°/23	85	500	–	–	–	3 (13.0)	–	2 (8.7)	–	–	

Table 5 Toxicity at the RD (docetaxel 75 mg/m^2 plus pemetrexed 500 mg/m^2) level

Grade Toxicity[a]	II no of patients (%)	III no of patients (%)	IV no of patients (%)
Neutropenia	1 (4.3)	3 (13)	3 (13)
Febrile neutropenia	–	1 (4.3)	–
Anemia	7 (30.4)	1 (4.3)	–
Thrombocytopenia	1 (4.3)	–	–
Nausea	1 (4.3)	–	–
Vomiting	1 (4.3)	1 (4.3)	–
Diarrhea	1 (4.3)	–	–
Asthenia	2 (8.7)	–	–

[a] Worst toxicity in all cycles and all patients enrolled in the RD level

four (28.5%) and 10 (21.3%) responses occurred in patients with squamous and non-squamous cell carcinoma, respectively. The only CR was observed in the 8th dose level while the PRs were observed in all dose levels (2nd: $n = 1$; 3rd: $n = 2$; 4th: $n = 1$; 7th: $n = 2$; 8th: $n = 1$) during the escalation part of the study. Regarding the efficacy of the combination in the expanded cohort of patients ($n = 20$) who were treated with the recommended doses, a PR was achieved in six patients (30.0%), SD in four (20.0%) and PD in 10 (50.0%). The overall median response duration was 6.8 months (range, 0.5–16 months) and the overall median TTP 2.8 months (range, 0.5–17.2 months) (the median TTP was 2.8 (range, 0.7–17.2) and 3.3 (range, 0.4–13.1) months for chemotherapy-naïve and pre-treated patients, respectively ($p = 0.845$)). After a median follow-up period of 18.5 months (0.7–38.2 months), the median overall survival (OS) was 10.0 months (range, 0.7–38.2 months); (the median OS was 10.4 (range, 1.4–38.2) and 9.2 (range, 0.7–31.5) months for patients treated in the 1st- and 2nd-line setting, respectively ($p = 0.356$)). The estimated 1-year survival rate for all patients was 40.5% (40.5 and 40.9% for chemotherapy-naïve and pre-treated patients, respectively).

Discussion

The necessity of more active and less toxic chemotherapy regimens for NSCLC patients is of great interest for the oncologists. In the present study, we combined two active drugs (pemetrexed and docetaxel) against NSCLC [7–9, 14, 20] in a dose-escalation trial. It is interesting to note that the MTD has not been reached even at doses that exceeded the recommended doses for monotherapy with each one of them. Thus, given that efficacy results were similar in the high- and low-dose levels, we recommended the dose of 75 mg/m^2 for docetaxel and 500 mg/m^2 for pemetrexed (RD level) for future phase II studies.

The combination of pemetrexed with taxanes (paclitaxel and docetaxel) has been tested in phase I and II studies. The pemetrexed/paclitaxel regimen has been associated with encouraging efficacy results and acceptable toxicity even at doses which approached the recommended dose for each agent in the monotherapy setting [21, 22]. In a phase II study, the combination of paclitaxel with pemetrexed, which was evaluated in chemotherapy-naïve patients with NSCLC, showed an encouraging efficacy with an objective response rate of 39.6% associated with a median survival of 14 months and a favorable toxicity profile [17].

There are a few clinical trials evaluating the pemetrexed/docetaxel combination in patients with solid tumors [23–26]. In a phase I study, 17 patients with solid tumors were treated with a fixed dose of docetaxel (60 mg/m^2 on day 8) combined with escalated doses of pemetrexed (300–600 mg/m^2 on day1); the first level of 300 mg/m^2 for pemetrexed and 60 mg/m^2 for docetaxel was the MTD. Then, the investigators amended the treatment schedule and the same doses of pemetrexed were administered on day 1 and docetaxel on day 15. This sequential modified administration was feasible and well tolerated; at the time of study presentation, the MTD had not been reached (pemetrexed 600 mg/m^2 and docetaxel 60 mg/m^2). Hematologic toxicity was the main adverse event of the combination [26]. In another phase I study, both agents were administered on days 1 and 15. At the dose level of pemetrexed 400 mg/m^2 and docetaxel 40 mg/m^2, the MTD had not been reached [23]. Similar to our study, another phase I trial investigated the administration of pemetrexed and docetaxel on day 1 every 3 weeks, in patients with metastatic disease who had received ≥2 prior regimens of chemotherapy. This study was suspended and the planned phase II study was abandoned due to the limited tolerability and efficacy of this regimen [24]. This is in overt contrast with the favorable toxicity profile that was observed in the current study; this discrepancy could be attributed to the fact that patients suffering from a wide range of tumors, which have a variable sensitivity to both agents, were enrolled in this trial. Based on the tolerability of the docetaxel/pemetrexed regimen, it seems that both the biweekly and the 3-weekly schedule should be preferred for further evaluation.

In the present study, the docetaxel/pemetrexed regimen was well tolerated and neutropenia and fatigue were the most frequently observed adverse events. In the initial clinical trials, pemetrexed was associated with severe toxicity including hematologic toxicity, skin rash, lethargy, nausea and vomiting [27–29]. The incidence of these adverse events was significantly reduced with the administration of vitamin supplementation [30]. Consistently, the

administration of vitamin B12 and folates was standard practice in the current study explaining, thus, the low incidence of severe toxicity.

Although efficacy was not the primary endpoint of the study, the pemetrexed/docetaxel regimen resulted in an ORR of almost 23%, a disease control rate (CR + PR + SD) of 39% and a median overall survival of 10.0 months. These efficacy results should be considered encouraging, given that 66% of the enrolled patients were already pre-treated. Moreover, it should be taken into account that the study was initiated in April 2005, and 23% of the enrolled patients had the diagnosis of squamous cell carcinoma, for which pemetrexed has been recently proved ineffective [14]; therefore, it could be argued that these particular patients could achieve the same clinical response with docetaxel alone.

In conclusion, this dose-escalation study demonstrated that the combination of docetaxel and pemetrexed is well tolerated in patients with NSCLC. The drugs can be safely combined at the recommended, for each agent, monotherapy doses. The antitumor activity of this regimen was promising and its combination with anti-angiogenic agents in non-squamous lung carcinoma could be of great interest in future studies. In addition, we consider that it merits further evaluation in second-line treatment compared to monotherapy with docetaxel, pemetrexed or erlotinib.

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Conflict of interest None declare.

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