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A phase II study of docetaxel and vinorelbine combination chemotherapy in patients with advanced non-small cell lung cancer☆

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Abstract

A phase II study was conducted to determine the efficacy and the safety of docetaxel combined with vinorelbine as first-line chemotherapy in patients with metastatic or unresectable non-small cell lung cancer (NSCLC). 39 patients, median age 54 years (range: 35–69), with stage IIIB (5 patients; 13%) or IV (34 patients; 87%) NSCLC were treated with 75 mg/m^2 docetaxel given intravenously (i.v.) over 1 h on day 1 and with 20 mg/m^2 vinorelbine given i.v. over 15 to 30 min on days 1 and 5. Cycles were repeated every 3 weeks. 9 of the 39 patients had a partial response (overall response rate 23.1%, 95% confidence interval (CI): 11.1–39.3%) with a median duration of response of 20 weeks (95% CI; 17–30). The median survival was 40 weeks (95% CI: 21–49 weeks) with a 1-year survival rate of 31% in the intent-to-treat population. Neutropenia grade IV occurred in 33 patients (92%). 16 patients (41%) experienced febrile neutropenia with a concomitant stomatitis in 9 patients (23%). One patient died due to febrile neutropenia associated with a grade 4 stomatitis and 1 patient due to a septicaemia concomitant with a grade 4 neutropenia. Although the combination of docetaxel and vinorelbine is feasible, the efficacy does not seem to be improved compared with single-agent docetaxel or vinorelbine and the rate of febrile neutropenia is unacceptable in this population with incurable disease. Therefore, different doses and/or schedules are to be explored.

Keywords: Vinorelbrine-doxetaxel combination; Advanced non-small cell lung cancer

1. Introduction

Chemotherapy in advanced non-small cell lung cancer (NSCLC) is increasingly used in several countries as a palliative treatment along with best supportive care. A meta-analysis, using updated data on individual patients from 11 trials (1190 patients), has shown a benefit for cisplatin-based chemotherapy with an absolute improvement in survival of 10% at 1 year compared with best supportive care [1]. In the last decade, the emergence of new drugs has enabled the development of new therapeutic schedules in advanced NSCLC aimed at improving the response rate, the 1-year survival rate and the quality of life of the patients. Amongst these new agents, the efficacy of docetaxel has been demonstrated in phase II trials, where 23–38% objective response rates have been obtained [2–5]. The antimitotic effects of docetaxel lead to the stabilisation of microtubules causing depolymerisation and thereby inducing a mitotic block at metaphase/anaphase during the cell cycle [6]. Conversely, the vinca-alkaloids disrupt mitosis by preventing microtubule assembly [7]. Several phase II studies in NSCLC, testing a new semi-synthetic vinca-alkaloid,

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vinorelbine, have reported objective response rates of 29% [8]. It, therefore, seems logical to combine these two new drugs because of their mechanism of action and their efficacy against NSCLC. *In vitro*, the administration of vinca-alkaloids (vindesine or vinorelbine) followed by docetaxel resulted in synergistic toxicity. Reversing the sequence of drug administration led to antagonism. It is likely that pretreatment of cells with docetaxel renders the tubulin in these cells resistant to the action of vinca-alkaloids [9,10]. Fumoleau and colleagues conducted a phase I combination study of docetaxel with vinorelbine in untreated patients with metastatic breast carcinoma [11]. The recommended dose for further phase II trials was 75 mg/m^2 for docetaxel (day 1) and 20 mg/m^2 (day 1 and day 5) for vinorelbine. Utilising these recommended doses, we undertook a multicentre phase II study of the docetaxel and vinorelbine combination in chemotherapy-naïve patients with advanced NSCLC. Docetaxel was given before vinorelbine because the drug interaction data *in vitro* were unknown at the time of study design.

The first aim of this trial was to determine the efficacy of docetaxel combined with vinorelbine as first-line chemotherapy in patients with metastatic or unresectable NSCLC with evaluation of the objective response rate, duration of response and time to disease progression. The second aim was to characterise the toxicity of this combination in this group of patients.

2. Patients and methods

2.1. Patient eligibility

Patients from 18 to 75 years old with histologically proven stage IV or unresectable stage IIIB NSCLC were eligible. Previous systemic chemotherapy or immunotherapy, including loco-regional treatment, were not allowed. Previous radiotherapy was allowed, but not including a site used to assess response, and only encompassing less than 10% of the total bone marrow. At inclusion, measurable lesions were identified as a lesion of more than 20 mm on computed tomography (CT) scan in two perpendicular dimensions. Other eligibility criteria included: Karnofsky Performance Status (KPS) $\geqslant$60%, a life expectancy $\geqslant$12 weeks, adequate bone marrow reserve, normal renal (serum creatinine $\leqslant$1.25$\times$the upper normal limit of the institution (UNL) or creatinine clearance $\geqslant$65 ml/min) and hepatic function (serum total bilirubin level $\leqslant$1.25$\times$UNL and aspartate aminotransferase (AST)$\leqslant$2.5$\times$UNL) and no instable cardiovascular condition. Signed informed consent was obtained from all patients and the protocol was approved by the local Ethical Committee. Exclusion criteria from the trial were as follows: radiotherapy within the previous 4 weeks, history or presence of central nervous system metastases, pre-existing symptomatic pleural effusion requiring thoracocentesis, ascites or pericardial effusion, current peripheral neuropathy > grade 1 according to National Cancer Institute — common toxicity criteria (NCI — CTC), history of significant neurological or psychiatric disorder (including dementia and seizures), active peptic ulcer, unstable diabetes mellitus or other contra-indication to high-dose corticosteroids, untreated superior vena cava syndrome, history of prior malignancies other than the previously excised or curatively irradiated basal cell skin cancer or *in situ* cancer, and concurrent treatment with investigational drug or participation in another clinical trial within the 30-day period prior to screening for this study.

2.2. Pretreatment and follow-up evaluations

Before therapy, a complete medical history of each patient was obtained and all underwent a physical examination which included a neurological examination, chest X-ray, electrocardiogram (ECG), a complete blood cell count, differential white blood cell count and serum biochemistry analysis (sodium, potassium, total protein, calcium, alkaline phosphatase, AST/alanine aminotransferase (ALT), total bilirubin, lactate dehydrogenase (LDH), and creatinine). A chest CT scan, an abdominal CT scan or an abdominal ultrasound, a brain CT scan and a whole bone scan were performed within the 3 weeks prior to study entry to record all measurable and/or evaluable lesions. During the study, the patients were reviewed every 3 weeks for history, by physical examination, including a neurological examination, and for toxicity symptoms (according to NCI criteria). Complete blood cell count and serum biochemistry analysis were performed every first and third weeks, respectively. CT scans were performed every two cycles at 6-week intervals for tumour response assessment. After removal from the study, patients were observed for at least 1 month after the last treatment to document any late side-effects.

2.3. Treatment plan

Docetaxel was administered intravenously (i.v.) at a dose of 75 mg/m^2 over 1 h on day 1. Vinorelbine was administered at a dose of 20 mg/m^2 as a short (15 to 30 min) i.v. infusion on days 1 and 5. On day 1, vinorelbine was administered immediately after docetaxel. This schedule was repeated every 3 weeks. Prior to docetaxel administration, a premedication was administered, which contained prednisolone or its equivalent (50 mg twice a day *per os* on days $-$1, 1 and 2) and diosmine, 500 mg (2 tablets twice a day *per os* from the first infusion of the treatment until the end of the study). Prophylactic antiemetic regimen with metoclopramide was

allowed from the first cycle. Patients with nausea and vomiting despite these measures could be treated with granisetron or ondansetron.

Dose adjustments were defined for both docetaxel and vinorelbine if haematological or other toxicities occurred, according to the NCI — CTC. A maximum of 6 cycles could be given to patients with stable disease while 3 additional cycles were allowed for patients who achieved a complete or partial response. However, therapy was halted in cases of unacceptable toxic effects or where progressive disease was evident.

2.4. Efficacy and adverse event evaluation

World Health Organization criteria were used to determine the tumour response which was recorded as complete, partial, no change or progressive disease [12]. The duration of complete remission was counted as the interval between complete response documentation and further proof of progression. The duration of partial response or no change was counted from the beginning of treatment until the documentation of progression or the use of a new specific anticancer treatment. The time to progression and survival duration were defined by measuring the time interval from initial dose of docetaxel to the date of progression and death, respectively. All the responses, no change and conflicting observations were checked and reviewed by an external radiologist and an external medical oncologist. Toxicities were assessed according to NCI — CTC criteria, with COSTART classification applied to events not covered by the NCI — CTC.

2.5. Statistical methodology

The study had a two-stage Fleming design [13] which permitted termination of patient accrual after the first 20 patients in the event that less than three responses were observed and allowed determination of active treatment with a response probability $\geqslant 20\%$ in 45 patients with a power of 0.91. All treated patients were evaluable for safety (intent-to-treat population). The overall response, time to progression and duration of response were analysed in the intent to treat population. The Kaplan–Meier estimations were applied to the duration of response, time to disease progression and survival. Response rate was calculated with a 95% confidence interval (CI).

3. Results

3.1. Patient characteristics

Between February 1995 and August 1995, 39 patients were recruited into the study from six French centres. All the registered patients received at least one cycle and were evaluable for the safety analysis. Table 1 lists the baseline characteristics of the treated patients. This population was in general representative of patients usually diagnosed with unresectable NSCLC: with a majority of men (79%), a median age of 54 years (range: 35–69), a median KPS of 80% (range: 60–90%), and metastatic disease in 34 patients (87%) with a huge tumour bulk. The most frequent metastatic sites were bone (41%) and liver (28%).

3.2. Treatment administration

One hundred and seventy-eight cycles were administered in 39 patients during the study period. The median number of cycles per patient was 4 (range: 1–10) and 26 patients (67%) received at least 4 cycles. The majority of cycles (150; 84%) were delivered at the initial combination dose planned in the protocol. Twenty-eight cycles (28; 16%) were administered at a modified dose in 15 patients (38%), because of haematological toxicity (17 cycles; 10%), and also because of grade 3 stomatitis (1

Table 1
Baseline characteristics of treated patients ($n = 39$)

Characteristic	No. of patients (%)
Sex	
Male	31 (79)
Female	8 (21)
Age (years)	
Median (range)	54 (35–69)
Karnofsky performance status	
Median (range)	80 (60–90)
$\geqslant 80$	32 (82)
< 80	7 (18)
Histological subtype	
Adenocarcinoma	16 (41)
Squamous cell carcinoma	11 (28)
Large cell carcinoma	10 (26)
Other	2 (5)
Disease stage	
IIIB (locally advanced)	5 (13)
IV (metastatic)	34 (87)
Main sites of tumour involvement	
Lung	35 (90)
Lymph nodes	25 (64)
Bone	16 (41)
Liver	11 (28)
Adrenal	5 (13)
Pleura	3 (8)
Brain	1 (3)
No. of distant metastases	
1	5 (13)
2	18 (46)
3 or more	16 (41)
Prior therapy	
None	30 (77)
Radiotherapy	4 (10)
Surgery	3 (8)
Radiotherapy + surgery	2 (5)

Table 2
Overall response rate

Response	Intent-to-treat population ($n=39$)	
	n	%
Complete response (CR)	0	0
Partial response (PR)	9	23.1
Response rate (CR + PR) (95% confidence interval)	9	23.1 (11.1–39.3%)
No change (NC)	11	28.2
Progressive disease (PD)	14	35.9
Not evaluable	5	12.8

cycle; 1%). Six cycles (3%) were delayed in 5 patients (13%) due to reasons not related to the drugs under study.

3.3. Efficacy

Follow-up evaluation was performed every 3 months until death. At the time of the cut-off date (6/98), all patients were dead. 9 patients in the intent-to-treat (ITT) population had a partial response, leading to an overall response rate of 23.1% (95% CI: 11.1–39.3%) (Table 2). The lung (23%) and lymph nodes (20%) were the most common responding sites but also the adrenal gland (20%) and liver (14%) showed a fair response. The median duration of response was 20 weeks (95% CI: 17–30 weeks). The median time to progression was 11 weeks (95% CI: 6–13 weeks) and the median survival was 40 weeks (95% CI: 21–49 weeks). The 1 year survival rate in the intent to treat population was 31%.

3.4. Adverse events

The main haematological toxicity (Table 3) was neutropenia, which occurred in 94% of patients. All but 1 patient had a grade 4 neutropenia. The median neutrophil nadir was 0.1×10^9/l (range: 0.0–5.2×10^9/l) occurring at day 9 (range: 6–15) with a median duration of grade 3 or 4 at 6 days (range: 2–14). 16 patients (41%) had experienced a febrile neutropenia, occurring in 25 cycles (14%). Thrombocytopenia was evident in only 4 (11%) of the patients, no grade 4 was reported. 11 patients (28%) experienced at least one neutropenic infection (12 episodes). A septicaemia associated with a grade 4 neutropenia led to a patient's death. Anaemia (above grade 0) was observed in 35 out of 36 patients (97%) evaluable for this toxicity but no grade 4 was recorded. Only 5 patients (14%) developed a grade 3 anaemia. 3 patients received a red blood cell transfusion.

The non-haematological toxicities, possibly related to the treatment, are summarised in Table 4. The most frequent were alopecia in (34 patients, 87%), fever in the absence of infection (22 patients, 56%), asthenia (19 patients, 49%), stomatitis (18 patients, 46%) and infection (14 patients, 36%). Stomatitis was concomitant with febrile neutropenia in 9 patients (23%) and with infection in 4 patients (10%). 2 (5%) and 5 patients (13%) developed a grade 4 and 3 stomatitis, respectively. One patient (3%) died due to febrile neutropenia concomitant with a grade 4 stomatitis whereas 1 grade 3 stomatitis led to treatment discontinuation. 2 patients (5%) experienced a grade 3 hypersensitivity reaction, 1 patient each (3%) a grade 3 or 4 diarrhoea and 1 patient (3%) a grade 3 vomiting.

4. Discussion

Since the large meta-analysis published by the Non-Small Cell Lung Cancer Study Group in 1995 [1] regarding the overall survival of patients with unresectable NSCLC, the cisplatin-based chemotherapy has become standard treatment for this disease. However, this meta-analysis only looked at the so-called old generation of drugs. Since that time, new generations of compounds have been used with reported high response rates when administered as single drugs [14].

Table 3
Haematological toxicity of NCI — CTC grade III/IV in 36 evaluable patients for toxicity

Toxicity	Overall incidence (all grades) patients (%)	Worst NCI — CTC grade			
		III		IV	
		Patients *n* (%)	Cycles[a] *n* (%)	Patients *n* (%)	Cycles[a] *n* (%)
Leucopenia	32 (89)	14 (39)	56 (35)	13 (36)	22 (14)
Neutropenia	34 (94)	0[b]	14 (9)	33 (92)	97 (61)
Thrombocytopenia	4 (11)	2 (6)	2 (1)	0	0
Anaemia	35 (97)	5 (14)	8 (5)	0	0

NCI — CTC, National Cancer Institute — Common Toxicity Criteria.
[a] Patients who were evaluable received 158 cycles.
[b] All the patients with grade 3 neutropenia had had a grade 4 neutropenia.

Table 4
Non-haematological adverse events possibly or probably related to the combination of docetaxel plus vinorelbine ($n = 39$)

Adverse event	Overall incidence (all grades) patient (%)	Worst grade	
		Grade III (%)	Grade IV (%)
Acute			
Fever[a]	22 (56)	2 (5)	0
Stomatitis	18 (46)	5 (13)	2 (5)
Infection	14 (36)	7 (18)	1 (3)
Nausea	6 (15)	0	0
Allergy	5 (13)	2 (5)	0
Diarrhoea	4 (10)	1 (3)	1 (3)
Vomiting	3 (8)	1 (3)	0
Chronic			
Alopecia	34 (87)	27 (69)[b]	Not applicable
Asthenia[c]	19 (49)	15 (38)	3 (8)
Neurosensory	7 (18)	0	0
Neuromotor	1 (3)	0	0
Skin toxicity	1 (3)	0	0
Fluid retention[c]	1 (3)	0	0
Nail disorder[c]	4 (10)	1 (3)	1 (3)

[a] In the absence of infection or neutropenia.
[b] Grade II.
[c] Non-NCI — CTC terms: grade III, moderate; grade IV, severe.

Whether or not cisplatin will remain a critical component of polychemotherapies with the availability of these 'new drugs' is questionable. A more recent meta-analysis, based on published data, which included the new drug, vinorelbine, showed a 2-fold increase in the response rate following combination chemotherapy compared with single-agent chemotherapy. However, the impact on survival was moderate and the toxicity higher [15]. When a platinum analogue or vinorelbine was used as a single agent and compared with combination chemotherapy, there was no difference in survival [15]. The last observation suggests that new drugs may be considered as efficient as cisplatin. Therefore, it is now worthwhile to determine whether new drugs, given alone, are as efficient as combinations and to develop combinations of new drugs excluding cisplatin. Vinorelbine and docetaxel belong to the most efficient drugs available to date [14]. In the present study, the overall response rate for the treated patients was 23.1% with a median survival of 40 weeks and a 1-year survival rate of 31%. In terms of objective responses, this result appears to be inferior to the other cisplatin-based chemotherapy combination reported in NSCLC [14] and is similar to those already published with single drug docetaxel or vinorelbine phase II studies. These inferior results may be explained by two main hypotheses: (1) The prognostic factors of the population included in our study were poor with metastases reported in 87% of the patients, bone metastases in 41% and $\geqslant 3$ organs involved in 41% of the patients, even if the Karnofsky index was $\geqslant 80\%$ for 32/39 (82%) of patients. (2) Upon initiation of the study, the results of the preclinical studies showing an antagonism between the two drugs when docetaxel is administered prior to vinorelbine was unknown. These actual clinical results seem to corroborate these preclinical data. The side-effects noted during this trial are worthy of discussion. The major toxicity was myelosuppression: 33 patients (92%) experienced a grade 4 neutropenia, while 16 patients (41%) developed febrile neutropenia. These very high rates of neutropenia may be explained by the design of the study where vinorelbine was given on day 1 and day 5 and docetaxel on day 1. The nadir of neutropenia related to docetaxel is known to occur on day 7. Therefore, the second administration of vinorelbine occurs during the decrease in neutrophil levels.

It may have been more appropriate to administer docetaxel on day 5 instead of day 1. With regard to the non-haematological toxicities, 18 patients (46%) experienced stomatitis with a NCI grade 3/4 in 7 patients (18%). This mucous toxicity was concomitant with febrile neutropenia in 9 patients (23%). Two deaths were attributed to the study treatment because of a febrile neutropenia concomitant with a grade 4 stomatitis, and a neutropenic septicaemia. Kourousis and colleagues suggested that the prophylactic use of haematological growth factor in combination with docetaxel/vinorelbine decreases the incidence, degree and duration of granulocytopenia [16]. Using a different therapeutic scheme (vinorelbine 25 mg/m^2 at day 1, docetaxel 100 mg/m^2 at day 2 with granulocyte-colony stimulating factor (G-CSF) 150 μg/m^2 from day 3 to day 10), grade 4 neutropenia was reported in 33% of the patients. However, neutropenic fever required hospitalisation in 24% of patients and two fatal sepsis were recorded. The incidence of mucositis was lower than in our study with a WHO grade 3 involving 2% of patients and the absence of grade 4 toxicity. This difference may be explained by the lower total dose of vinorelbine used. As the Fumoleau and colleagues phase I study clearly demonstrated, the occurrence of grade 3/4 stomatitis was more frequent at higher dose levels of vinorelbine [11]. Other toxicities reported in our study were easily manageable. Asthenia was a frequent adverse effect (49% of patients) but was rarely severe (8% of patients exhibiting grade IV toxicity). Despite the use of two antitubulin agents, neurotoxicity observed in 20% of patients was at low grade (1 or 2) and well tolerated. No cardiotoxicity, renal toxicity or hearing toxicity was recorded. Docetaxel is one of the most active new drugs in advanced NSCLC, not only in first-line chemotherapy but also in second-line with an objective response rate of 21% when given as single drug [17]. In an effort to improve the efficiency of this single-agent chemotherapy, new combinations must be investigated with toxicity and quality of life remaining acceptable. Results of our study suggest that although the combination of

docetaxel and vinorelbine is feasible, a new therapeutic schedule must be identified because of its unacceptable toxicity with no benefit in terms of response rate compared with single-agent docetaxel.

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References

1. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *Br Med J* 1995, **311**, 899–909.
2. Francis PA, Rigas JR, Kris MG, *et al*. Phase II trial of docetaxel in patients with stage III and IV non-small-cell lung cancer. *J Clin Oncol* 1994, **12**, 1232–1237.
3. Miller VA, Rigas JR, Francis PA, *et al*. Phase II trial of a 75-mg/m^2 dose of docetaxel with prednisone premedication for patients with advanced non-small cell lung cancer. *Cancer* 1995, **75**, 968–972.
4. Cerny T, Kaplan S, Pavlidis N, *et al*. Docetaxel (Taxotere) is active in non-small cell lung cancer: a phase II trial of the EORTC Early Clinical Trials Group (ECTG). *Br J Cancer* 1994, **70**, 384–387.
5. Fossella FV, Lee JS, Murphy WK, *et al*. Phase II of docetaxel for recurrent or metastatic non-small cell lung cancer. *J Clin Oncol* 1994, **12**, 1238–1244.
6. Ringel I, Horwitz SB. Studies with RP 56 976 (Taxotere): a semisynthetic analogue of Taxol. *J Natl Cancer Inst* 1991, **83**, 288–291.
7. Jordan Ma, Thrower D, Wilson L. Mechanism of inhibition of cell proliferation by vinca-alkaloids. *Cancer Res* 1991, **51**, 2212.
8. Depierre A, Lemarie E, Dabouis G, Garnier G, Jacoulet P, Dalphin JC. A phase II study of Navelbine (Vinorelbine) in the treatment of non-small cell lung cancer. *Am J Clin Oncol* 1991, **14**, 115–119.
9. Hino M, Kobayashi K, Hayashihara K, *et al*. *In vitro* combination effect of docetaxel (RP56976) with vinca-alkaloids on cancer cell line. *Proc Am Assoc Cancer Res* 1995, **36**, 299 (abstract 1780).
10. Aoe K, Ueoka H, Kiura K, *et al*. Synergistic effect of docetaxel (DCT) and vinorelbine (VNB) against *in vitro* growth of a human small-cell lung cancer line. *Proc Am Assoc Cancer Res* 1996, **37**, 375 (abstract 2560).
11. Fumoleau P, Delecroix V, Perrocheau G, *et al*. Docetaxel in combination with vinorelbine as first line chemotherapy in patients with metastatic breast cancer: a phase I, dose finding. *Proc Am Soc Clin Oncol* 1996, **15**, 232.
12. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
13. Fleming T. One sample multiple testing procedure for phase II clinical trials. *Biometrics* 1982, **38**, 143–151.
14. Bunn PA Jr, Kelly K. New chemotherapeutic agents prolong survival and improve quality of life in non small cell lung cancer: a review of the literature and future directions. *Clin Cancer Res* 1998, **5**, 1087–1100.
15. Lillenbaum RC, Langenberg P, Dickersin K. Single agent versus combination chemotherapy in patients with advanced nonsmall cell lung carcinoma. A meta-analysis of response, toxicity, and survival. *Cancer* 1998, **82**, 116–126.
16. Kourousis C, Androulakis N, Kakolyris S, *et al*. First-line treatment of advanced nonsmall cell lung carcinoma with docetaxel and vinorelbine. *Cancer* 1998, **83**, 2083–2090.
17. Fossella FV, Lee JS, Shin DM, *et al*. Phase II of docetaxel for advanced or metastatic platinum refractory non-small cell lung cancer. *J Clin Oncol* 1995, **13**, 645–651.