



phase I trial of docetaxel and vinorelbine in patients with advanced non-small cell lung cancer

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Abstract. Advanced non-small cell lung cancer (NSCLC) remains a difficult cancer to treat, and evolution of platinum-free regimens in a first-line setting is ongoing. This was a dose-finding study on the docetaxel and vinorelbine combination. Docetaxel was given at 60 mg/m² on day 1 only, and vinorelbine was given on days 1 and 15 starting at 20 mg/m², then escalated to 30 and 40 mg/m² in two dose cohorts. Each cycle lasted 28 days. The maximum tolerated dose was 60 mg/m² docetaxel and 30 mg/m² vinorelbine. Twenty-one patients were enrolled and showed an overall response rate of 9.5%, with stable disease documented in 33% of patients. The dosage schedule of this combination resulted in acceptable toxicities. The median time to progression was 5.86 months (95% CI 2.50-9.22), and median survival was 10.96 months (95% CI 1.42-20.51) with a 1-year survival rate of 50%. This combination may be important for patients with NSCLC.

Introduction

There is a palliative benefit of chemotherapy for advanced non-small cell lung cancer in previous studies and meta-analyses in terms of survival and improvement of quality of life (1-6). Docetaxel is active as a single agent and in combination with platinum and non-platinum agents as treatment in chemo-naïve or previously treated advanced non-small cell lung cancer (NSCLC) patients. The dose-limiting toxicity of docetaxel is short-lived neutropenia, which develops in 75-85% of patients (7,8). However, only 12% of patients developed neutropenic fever. In patients showing

good performance with NSCLC recurring after platinum-based regimens, an objective response rate of 7-10% and a longer time-to-progression compared to best supportive care (9), vinorelbine or ifosfamide is reported with docetaxel (10). In the TAX 326 trial, improved quality of life and survival with docetaxel and cisplatin was demonstrated in comparison with the combination of vinorelbine and cisplatin (11).

Vinorelbine is a third generation vinca alkaloid with activity in NSCLC. The dose-limiting toxicity of vinorelbine is neutropenia, with 54% of patients developing grade 3-4 neutropenia (12). Vinorelbine has response rates of 12-31% in NSCLC (12,13). Based on the single agent activity of vinorelbine in NSCLC, Le Chevalier *et al* undertook a phase III multicenter trial comparing cisplatin and vindesine, cisplatin and vinorelbine, and single-agent vinorelbine (14). As anticipated, the response rate (30% overall) and median survival (40 weeks) were significantly improved in the cisplatin and vinorelbine arm. The most intriguing data to emerge from this study were comparable response and survival rates for cisplatin and vindesine (19% response rate and 32-week median survival) and single-agent vinorelbine (14% response rate, 31 week median survival). The results suggest that single-agent vinorelbine is a reasonable option for patients who might be intolerant of the nephrotoxicity, neurotoxicity, and ototoxicity associated with cisplatin use.

Testing of docetaxel demonstrates additive to synergistic activity with a wide variety of drugs including vinorelbine (15,16). There is minimal overlapping toxicity except neutropenia. With vinca alkaloids, docetaxel could be delivered at 80-100% of the MTD without severe toxicity in murine models and xenograft studies (16). There is schedule dependence in cell lines treated with taxanes and vinorelbine *in vitro*, with better efficacy when vinorelbine was given before taxanes (17,18). This has not been shown specifically for docetaxel. In a non-randomized phase II study, Sanchez *et al* showed that scheduling docetaxel prior to vinorelbine resulted in a marginally better response rate (19).

In order to avoid excessive hematologic toxicity and derive an effective and safe combination regimen using these two drugs, a schedule with a long cycling interval and docetaxel given prior to vinorelbine was chosen. A phase I trial in patients with recurrent or newly diagnosed stage IIIB or IV NSCLC was conducted to determine the maximum tolerated dose and dose-limiting toxicities.

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Table I. Dose escalation schema.

Cohort	Docetaxel (mg/m ²) ^a	Vinorelbine (mg/m ²) ^a	No. of patients	No. of cycles administered
1	60	20	10	17.5
2	60	30	6	25.5
3	60	40	5	14.5

^aDocetaxel was administered on day 1 and vinorelbine was administered on days 1 and 15 of a 28-day cycle.

Patients and methods

Patients were eligible for the trial if they had histologically or cytologically confirmed stage IIIB or IV or recurrent non-small cell lung cancer and no more than one previous chemotherapeutic regimen. Other eligibility criteria included an ECOG performance status of 0-2, age ≥ 18 , and measurable disease. Patients with previously irradiated lesions needed documented progression to be eligible, and patients with pleural effusions, ascites, and bone metastases were not eligible. Adequate hematological marrow function (ANC ≥ 1500 cells/mm³; hematocrit $\geq 30\%$; platelets $\geq 100\,000$ /mm³; hepatic function total bilirubin ≤ 34 μ mol/l; AST/ALT less than twice the upper limit of normal levels); and renal function (creatinine ≤ 177 μ mol/l) were required.

Exclusion criteria included prior therapy with docetaxel or vinorelbine, uncontrolled infection, pregnancy, active CNS metastases, chemotherapy within 4 weeks prior to study entry; nitrosourea or mitomycin C treatment within 6 weeks prior to study entry, radiotherapy to the chest, pelvic or spine within 4 weeks prior to study entry, known history of HIV infection or life expectancy < 3 months. Written informed consent was obtained from all patients, and the trial was approved by the Human Studies Committee of the Washington University Medical Center.

Treatment schedule. This was a phase I study of once monthly docetaxel with twice monthly vinorelbine. Vinorelbine was administered on days 1 and 15, starting with 20 mg/m² then dose escalated to 30 and 40 mg/m² (Table I). Docetaxel was administered at 60 mg/m² on day 1 after vinorelbine infusion in all cohorts. Both agents were given in a 28-day cycle. Premedication with dexamethasone 8 mg po was given twice daily for 5 days starting one day prior to docetaxel.

Six patients were accrued at each dose level. Dose escalation occurred when the sixth patient in a cohort completed the first cycle and only if no more than 1 of 6 patients in that cohort experienced a DLT. If, in any cohort, 2 of 6 patients developed DLT, dose escalation ceased and the previous dose level was considered the maximum tolerated dose (MTD). If no more than 1 of 6 patients at dose level 40 mg/m² experienced DLT, this dose was considered the MTD. If any of the six patients in any cohort did not complete the first cycle of treatment, for reasons other than DLT, another patient was added to replace the patient in that cohort. There was no intra-patient dose escalation.

Table II. Patient characteristics.

Characteristics	No. of patients
Age	
Median	63
Range	45-78
Sex	
Male	16
Female	5
ECOG performance status	
0	9
1	11
2	1
Stage	
IIIB	5
IV	16
Histology	
Adenocarcinoma/adenosquamous	13
Squamous/others	8
Prior radiotherapy	9

Dose-limiting toxicity was defined as any of the following events: grade 4 neutropenia for > 7 days or grade 4 neutropenia associated with fever $\geq 38.5^{\circ}\text{C}$ of any duration; grade 4 thrombocytopenia; or grade > 3 non-hematologic toxicity (excluding nausea and vomiting, alopecia, anorexia, stomatitis, and esophagitis/dysphagia) occurring during the first cycle (28 day period) of therapy. Administration of 6 cycles of therapy was planned unless a patient developed clear-cut disease progression or dose-limiting toxicity, or requested withdrawal from study.

Toxicity monitoring and dose modifications. Patients underwent a complete history and physical examination every 2 weeks by either the principal investigator or co-investigators. Safety assessments were based on physical examination findings, vital signs, laboratory tests, performance status, symptoms/toxicity, and clinical adverse events. Adverse events observed before, during and after drug treatment administered by the study were recorded and graded according to standard NCI Common Toxicity Criteria version 2.

Cycle 1

Cohort	Dose (mg/m ²)		ANC x10 ³ /μl ^d	Hb g/dl ^d	Plts x10 ³ /μl ^d
	Docetaxel	Vinorelbine			
1	60	20	3.70 (0.00-13.72)	10.8 (7.3-13.6)	223 (166-302)
2	60	30	1.80 (0.03-9.25)	10.2 (8.0-11.4)	208 (106-304)
3	60	40	0.60 (0.05-2.27)	10.9 (9.5-13.4)	341 (149-468)

Cycles 2-6

Cohort	Dose (mg/m ²)		ANC x10 ³ /μl ^d	Hb g/dl ^d	Plts x10 ³ /μl ^d
	Docetaxel	Vinorelbine			
1	60	20 ^a	3.47 (0.16-8.66)	11.6 (9.5-12.9)	278 (165-587)
2	60	30 ^b	0.56 (0.01-2.20)	9.3 (7.3-10.7)	292 (69-760)
3	60	40 ^c	-	-	-

^aIncludes 2 cycles administered to one patient enrolled in cohort 2, but dose-reduced to the doses in this cohort because of grade 4 neutropenia. ^bExcludes 2 cycles administered to one patient whose vinorelbine was dose-reduced twice to 15 mg/m² and not included in this analyses, includes 8 cycles from three patients enrolled in cohort 3 and subsequently dose reduced, and excludes 2 cycles from one patient whose dose of docetaxel and vinorelbine were reduced due to grade 4 neutropenia. ^cAll five patients enrolled at this level received only 1 cycle and were dose reduced due to myelosuppression. ^dData expressed as mean nadir count (range).

Table IV. Non-hematologic cycle 1.

Toxicity	Cohort 1		Cohort 2		Cohort 3	
	Grade 3 Patients (%)	Grade 4 Patients (%)	Grade 3 Patients (%)	Grade 4 Patients (%)	Grade 3 Patients (%)	Grade 4 Patients (%)
Gastrointestinal						
Constipation		1 (4.8)				
Nausea/vomiting			1 (4.8)			
Infection						
Fever with neutropenia			1 (4.8)		1 (4.8)	
Neurology						
Depression		2 (9.5)				
Seizure			1 (4.8)			
Pain						
Arthralgia/myalgias	1 (4.8)					

Complete blood counts were obtained weekly, and a comprehensive metabolic panel was obtained prior to the start of each cycle. Therapy was delayed by one week for ANC ≤ 1500 cells/mm³ or platelets $\leq 25,000$ /mm³. The vinorelbine dose was reduced by 25% for the remaining treatments if either of these events resulted in a delay lasting >7 days or a fever $\geq 38.5^\circ\text{C}$ associated with an ANC ≤ 500 cells/mm³ of any duration. A second reduction of 25% was made if a patient had a subsequent episode that met these criteria.

Response criteria. Patient response was evaluated after every 2 cycles of treatment. Response data were collected and defined according to World Health Organisation (WHO) criteria (20).

Results

Patient characteristics. There were 21 patients enrolled in the trial between February 1998 and May 2000. The baseline patient characteristics are described in Table II. Five patients had stage IIIB and 16 patients had stage IV disease. Most of the patients were male. A majority had a performance status of 1. Two patients received previous chemotherapy, and 9 patients had prior radiotherapy.

Dose escalation was done in the manner described (Table I). In cohort 1, patient 4 had an episode of febrile neutropenia, and it was decided to add six more patients to this cohort. Of these six additional patients, two did not complete cycle 1

Table V. Best response.

Response	No. of patients	%
Partial response	2	9.5%
Stable disease	4	19.0%
Progressive disease	10	47.6%
Not evaluable ^a	5	23.8%

^aFive patients were not evaluable for response as they did not complete 2 cycles.

due to a gunshot wound and severe depression, respectively. As there was no other DLT in these patients attributed to the study agents, patients were entered in cohort 2. Four patients in cohort 2 had greater than grade 4 neutropenia, and one required dose reduction. One patient had a seizure-like reaction within minutes of infusion of docetaxel. The infusion was stopped and given the next day without incident. The etiology of this grade 3 non-hematologic event was unclear, and five other patients were treated without incident. Patients were then enrolled in cohort 3. Five patients in this cohort received only 1 cycle of chemotherapy as two of them had DLTs defined as neutropenic fever, and dose reductions were subsequently required. The MTD was therefore determined to be 60 mg/m² docetaxel on day 1 and 30 mg/m² vinorelbine on days 1 and 15.

Toxicities. Encountered toxicities are shown in Tables III and IV. The main hematologic toxicity encountered was grade 3/4 neutropenia in eleven (52%) patients (Table III). Three (14%) patients had neutropenic fever. A reduction in the dose of vinorelbine was required for two patients in cohort 2 and all five patients in cohort 3. Per investigator discretion, 1 of the five patients in cohort 3 was administered a dose reduction of vinorelbine and docetaxel. None of the patients required growth factor support or prophylaxis. The frequency of grades 3 and 4 non-hematologic toxicities was <5% at each dose level. There was no treatment-related mortality.

Response and survival. All analyses were on an intent-to-treat basis. Only four patients completed the planned 6 cycles of therapy. Most patients completed between 2 to 4 cycles of treatment (median =2). There were 16 patients who were evaluable for response (Table V). Partial response was achieved in two patients (9.5%) in cohort 2. There were no complete responses. Stable disease was achieved in 4 (19.0%) patients.

Discussion

Several chemotherapeutic agents such as taxanes, topoisomerase I inhibitors, gemcitabine and vinorelbine have documented single agent activity in NSCLC. Platinum-based combination therapy with these newer agents is the current standard of care in advanced NSCLC. A comparison of these different platinum-based regimens in treatment of naïve patients does not show clear benefit of one over the other in terms of survival, and the overall impact of these regimens on survival remains modest (21).

Non-platinum combinations may be associated with decreased toxicity and improved efficacy. Several investigations in a first-line setting have studied the administration of docetaxel and vinorelbine at 3 weekly intervals (22,23). This resulted in high rates of grade 3/4 neutropenia and some treatment-related mortality as a result of neutropenic sepsis. Response rates were 27.0% and 36.6% in the two above-mentioned studies. The concomitant use of prophylactic filgrastim support allowed the use of 60 mg/m² docetaxel and 45 mg/m² vinorelbine given every 2 weeks in a chemo-naïve population (24,25). Overall response rates of 51% were achieved with acceptable rates of febrile neutropenia. In the salvage setting, weekly doses of docetaxel and vinorelbine also had significant hematological toxicity. In one study dose modifications were required in 91% of patients (26); in another trial, toxicity was unacceptable and the trial was stopped without producing any meaningful response (27).

In this dose-finding study, the MTD was determined to be 60 mg/m² docetaxel on day 1, and 30 mg/m² vinorelbine on days 1 and 15. Hematologic toxicities in the absence of prophylactic growth factor support are among the lowest in all phase I/II studies described so far.

The overall response rate was only 9.5%. Though the response rate is low, stable disease was achieved in 33% of patients. In patients with recurrent and advanced disease, achieving stable disease with low toxicity constitutes an important palliative endpoint (28). This is more significant in light of current data that support limiting the administration of chemotherapy to 3-4 cycles in patients with newly diagnosed advanced NSCLC (29,30). Although an endpoint was not specified in this trial, the median time to progression and median survival achieved are comparable to historical data of current first-line platinum-based regimens. This is encouraging and supports further investigation of non-platinum-containing regimens. Nevertheless, interpretation across studies and the small number of patients in this study limit further conclusions.

Docetaxel and vinorelbine dosed according to the schedule in this study have a tolerable toxicity profile and achieve responses and rates of stable disease that translate into a meaningful duration of response and survival. Dose-limiting toxicity was neutropenia. This remains an important combination for patients with advanced NSCLC. Future studies of docetaxel will need to exploit synergism with other drugs that can improve efficacy without concomitant dose-limiting toxicity.

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