HHS Public Access

Author manuscript

Am J Clin Oncol. Author manuscript; available in PMC 2016 November 22.

Published in final edited form as:

Am J Clin Oncol. 2010 April ; 33(2): 148–152. doi:10.1097/COC.0b013e318199fb99.

Phase II Study of Vinorelbine and Docetaxel in the Treatment of Advanced Non–Small-Cell Lung Cancer as Frontline and Second-Line Therapy

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Abstract

Objectives—Combination chemotherapy with third-generation, nonplatinum agents (ie, gemcitabine, vinorelbine, taxanes, or camptothecins) represents a well-tolerated frontline treatment option for metastatic non–small-cell lung cancer and might play a role as salvage therapy as well. The aim of this phase 2 study was to investigate the use of docetaxel and vinorelbine in the frontline and second-line setting in patients with incurable non–small-cell lung cancer.

Patients and Methods—Seventy-eight patients (42 untreated, 36 previously treated) were administered vinorelbine (20 mg/m^2) on days 1 and 8 and docetaxel (75 mg/m^2 for untreated patients; 60 mg/m^2 for previously treated patients for cycle 1, increased to 75 mg/m^2 for the subsequent cycles in the absence of grade 3 fever/neutropenia) on day 8, repeated every 21 days, with routine filgrastim support.

Results—The most common grade 3 to 4 nonhematologic toxicities were diarrhea, dyspnea, fatigue, and nausea/vomiting (5% each). Grade 3 to 4 granulocytopenia occurred in 55% of the patients, however only 5% experienced febrile neutropenia. Response rates were 13% in the chemotherapy-naive cohort and 9% in previously treated patients. Median time to progression was 2.9 and 3.0 months and median overall survival was 15.0 and 6.2 months, for the frontline and second-line patients, respectively.

Conclusions—Compared with historical controls, in the first-line setting, the combination of docetaxel and vinorelbine did not demonstrate increased efficacy advantages over platinum- or other nonplatinum-based doublets. In the second-line setting, single agent chemotherapy is as

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effective as, and less toxic than the docetaxel-vinorelbine combination, and the former remains the cytotoxic treatment of choice.

Keywords

non–small-cell lung cancer; docetaxel; vinorelbine; frontline; second-line

Platinum-based doublets constitute the cornerstone of frontline treatment of metastatic non–small-cell lung cancer (NSCLC), yielding a median overall survival in the range of 8 to 11 months in the latest trials.[1,2] Despite the higher response rate obtained with combination chemotherapy as compared with single agents, the former treatment strategy is associated only with a modest improvement in survival at the cost of an increased incidence of adverse events.[3] Nonplatinum, single-agent chemotherapy represents an alternative to platinum combinations (particularly in the elderly and poor performance status patients), with a more favorable side effect profile. Furthermore, there is demonstrated enhancement of quality of life and overall survival of single-agent chemotherapy as compared with placebo.[4,5] The most widely used chemotherapy agents in this setting include gemcitabine,[4,6] vinorelbine,[5–7] and taxanes.[8,9] More recently, first-line single-agent docetaxel has been compared with vinorelbine and has been demonstrated to attain equivalent survival rates, with a significant improvement in disease-related symptoms.[7] Single-agent chemotherapy is also considered the standard-of-care for salvage treatment of patients with NSCLC. Docetaxel, pemetrexed, and more recently the biologic agent erlotinib are the current FDA-approved drugs for this indication.[10–12]

At the time of the conception of this trial, nonplatinum based doublets with newer agents were considered a promising strategy for the treatment of NSCLC, which could result in similar (if not improved) survival rates from single agent chemotherapy and/or platinum-base doublets and possibly a more favorable toxicity profile. Indeed, a recent meta-analysis published by D'Addario et al examined the role of nonplatinum based combination regimes for frontline therapy for metastatic NSCLC and supports this hypothesis.[13] This study demonstrated, in general, superiority in response rates and survival for platinum-containing regimens versus nonplatinum based chemotherapy. Nonetheless, the incidence of side effects (especially those commonly associated with cisplatin, such as nephrotoxicity and nausea/vomiting) was significantly higher for the former strategy. Anemia, neutropenia, and thrombocytopenia were also more common in the platinum-treated group (possibly related with the use of carboplatin). However, when platinum-based doublets were compared with third-generation-based nonplatinum combinations only (ie, combinations of gemcitabine, vinorelbine, taxanes or camptothecins), overall survival was similar between the 2 groups.[13] Therefore, the use of nonplatinum third-generation-based combination chemotherapy could represent an alternative to platinum-based doublets, associated with similar efficacy outcomes and less toxicity (especially as it pertains to neutropenia, thrombocytopenia, and nausea/vomiting, as demonstrated in the meta-analysis by D'Addario et al[13]). This strategy warrants further study both in the frontline and salvage setting. We present the results of a phase II trial of the combination of docetaxel and vinorelbine in 2 separate cohorts of untreated and previously treated patients with incurable NSCLC.

METHODS

This was an open-label, single-arm, phase II trial conducted at The University of Texas M. D. Anderson Cancer Center. The study was approved by the Institutional Review Board and was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

Patient Eligibility

Inclusion criteria included patients with radiographically evaluable and histologically documented NSCLC, who were not otherwise candidates for surgery, radiotherapy, or combined modality therapy with curative intent; ECOG performance status of 0 to 2; life expectancy ≥3 months; age ≥18 years.

Exclusion criteria included: presence of brain metastases (unless treated and stable); hepatic dysfunction (defined as aspartate aminotransferase [AST] or alanine aminotrasferase [ALT] > 1.5× the upper limit of normal [ULN] and alkaline phosphatase ≥ 2.5 × ULN, or AST or ALT > 2.5 × ULN, or total bilirubin >ULN); previous radiotherapy to the target lesion or pelvis; peripheral neuropathy grade ≥2 from any cause; pregnant or lactating women, or any woman not using adequate methods of birth control; use of any biologic, immunologic or experimental agent within 30 days of study entry; prior chemotherapy with a taxane (except paclitaxel) or vinorelbine.

Treatment Plan

Before study entry, all patients were required to sign an informed consent statement. Baseline evaluation included a complete history and physical examination, serum chemistry and hematologic tests, and imaging studies for assessment of evaluable lesions. If all eligibility criteria were met, patients initiated treatment with 1 of the following regimens:

Previously untreated patients (frontline arm): vinorelbine 20 mg/m^2 IV on days 1 and 8 every 21 days and docetaxel 75 mg/m^2 on day 8 every 21 days. Previously treated patients (second-line arm): vinorelbine 20 mg/m^2 IV on days 1 and 8 every 21 days and docetaxel 60 mg/m^2 on day 8 every 21 days for the first course, followed by an increase in the docetaxel dose from 60 to 75 mg/m^2 in the subsequent courses if no grade 3 fever/neutropenia was recorded. Premedication consisted of dexamethasone 8 mg po every 12 hours, initiating 24 hours prior to the taxane's infusion (total of 6 doses). Prophylactic granulocyte-colony stimulating factor (filgrastim 5 mcg/kg subcutaneous) was given to all patients on days 2 to 6 and 10 to 14. For patients with a complete response, partial response or stable disease after 2 cycles, therapy was continued for 2 cycles after maximum response. In case of neutropenia and/or thrombocytopenia, treatment was delayed until absolute neutrophil count was ≥1500/mm^3 and platelets ≥100,000/mm^3 (blood cell counts were rechecked every 48 hours). Dose reductions (25%) of both chemotherapy drugs were done for all subsequent courses if grade 4 neutropenia (lasting >7 days) or neutropenic fever was documented. For patients with abnormal liver function tests while on study (ie, normal bilirubin, alkaline phosphatase ≤ 5 × ULN, and AST or ALT 1.6–5 × ULN), chemotherapy was not withheld, but the

docetaxel dose was reduced by 25%. None of the patients experienced an increase in bilirubin > ULN or alkaline phosphatase, AST, or ALT ≥ 5 × ULN.

Toxicities were recorded and graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. Chest x-rays were repeated prior to every treatment and computerized tomography or magnetic resonance imaging were repeated every 2 cycles.

Patients were discontinued from the study if they experienced progressive disease, unacceptable toxicity, or were noncompliant with protocol requirements.

Study Endpoints and Statistical Analysis

The primary end point of the study was determination of response rate in the 2 cohorts of patients (frontline arm and second-line arm). Additional endpoints included evaluation of time to progression, overall survival and toxicity.

Patients were considered evaluable for response if they received a minimum of 2 courses of treatment or showed rapidly progressive disease after 1 course of treatment. All patients who received at least 1 dose of any of the drugs were evaluable for toxicity.

The criteria for response were defined as follows: complete response—total disappearance of all cancerous lesions and evaluable clinical evidence of cancer without development of new lesions documented on at least 2 measurements which are at least 4 weeks apart; partial response—a minimum of 50% reduction in the size of all measurable lesions as indicated by the sum of the products of the longest perpendicular diameter of all measurable lesions, associated with stable or improved performance status (all conditions must be fulfilled on at least 2 evaluations at least 4 weeks apart); stable disease—patient fails to qualify for partial response, complete response or disease progression, and performance status and symptoms are stable, on at least 2 evaluations separated by at least 8 weeks; progressive disease—increase of 25% or more in the size of any lesion as measured by the sum of the products of the greatest length and maximum width, or appearance of any new lesions, or significant worsening in performance status or cancer related symptoms.

Time to progression was defined as the period of time, on study, from the first day of treatment to the time when progressive disease or treatment related toxicity resulted in discontinuation of treatment. Overall survival was defined as the period of time from the first day of treatment to the date of death.

The 2 cohorts of patients were analyzed separately for the efficacy endpoints. A Simon's optimal 2 stage design was used, with type I and type II error rates of 0.1 and 0.1, respectively. For the frontline arm, a sample size of 37 patients was estimated to target a 40% response rate and consider the combination for future trials. Accrual to this cohort would be discontinued earlier if there were <4 responses among the first 17 patients accrued. For the second-line arm, the target response rate was 20% so as to consider the combination for future studies. The total sample size was estimated as 37 patients. Accrual to this cohort would be discontinued earlier if no responses were documented among the first 12 patients.

RESULTS

Patients Characteristics

Between November 1998 and June 2001, 78 patients were enrolled in the study (42 in the frontline arm and 36 in the second-line arm). Their baseline characteristics are described in Table 1.

Treatment Characteristics

A total of 301 cycles were delivered to all enrolled patients (median number of cycles/patient: 3.5, range: 1–12). Seven patients in the frontline arm required a dose reduction. Six patients in the second-line arm had the dose of docetaxel escalated from 60 to 75 mg/m^2 for the second cycle. Three patients in the second-line arm required a single dose reduction and 1 patient required 2 dose reductions (Table 2). The median time on treatment for the frontline arm and second-line arm was 10.1 and 11.4 weeks, respectively. The reasons for study discontinuation in each arm are described in Table 2.

Toxicity

Hematologic toxicities were common among both treatment arms and consisted mainly of granulocytopenia (55%: grade: 3 or 4). However, febrile neutropenia occurred in only 4 patients (5%), with 1 patient having sepsis. The most common grade 3 to 4 nonhematologic toxicities were diarrhea, dyspnea, fatigue and nausea/vomiting (4 patients each: 5%), followed by stomatitis and non-neutropenic infections (3 patients each: 4%). Eight patients experienced grade 2 neuropathy. The complete list of adverse events (grades: 2–4) are outlined in Table 3.

Efficacy

Thirty-eight and 32 patients were evaluable for response in the frontline and second-line arms, respectively. The response rates for the frontline arm and second-line arm were 13% (95% confidence interval: 4.4 –28.0) and 9% (95% confidence interval: 2.0– 25.0), with disease control rates of 74% (95% confidence interval: 56.9–86.6) and 81% (95% confidence interval: 63.6 –92.8), respectively (Table 4).

The median time to progression was 2.9 months in the frontline arm and 3.0 months in the second-line arm. The median overall survival was 15.0 and 6.2 months in the frontline and second-line arms, respectively.

DISCUSSION

With currently available agents, the achievable goal of treatment in stage IV NSCLC is palliation of symptoms and improvement in survival, albeit modest. Therefore, the identification of treatments that are both tolerable and effective is greatly desired.

The combination of docetaxel and vinorelbine has been previously investigated in several phase 2 trials of patients with advanced NSCLC.[14–19] Various dose levels and schedules have been used, with the most important side effects consisting of hematologic toxicities

(and febrile neutropenia, in particular). In one of the first reports utilizing this combination chemotherapy, Kourousis et al described an incidence of 24% of neutropenic fever among 46 patients treated with vinorelbine 25 mg/m^2 on day 1 and docetaxel 100 mg/m^2 on day 2, repeated every 21 days, despite prophylactic granulocyte-colony stimulating factor.[14] Subsequent trials focused on administering the drugs in different doses and intervals, in an attempt to improve the adverse events profile. Bennouna et al[15] and Munoz et al[16] used 3-week cycles of docetaxel 75 mg/m^2 on day 1 and vinorelbine 20 mg/m^2 on days 1 and 5, whereas other investigators employed weekly vinorelbine (15–20 mg/m^2) with docetaxel given weekly (25–30 mg/m^2)[17,18] or every 3 weeks (60 mg/m^2).[19] Febrile neutropenia remained a concern in all of these studies, with incidences ranging from 25% to 70%. Other adverse events observed included stomatitis, diarrhea, and pulmonary toxicity.

In the present trial, the chemotherapy doses employed were vinorelbine 20 mg/m^2 on days 1 and 8 and docetaxel 75 mg/m^2 (or 60 mg/m^2 for the first cycle in previously treated patients) on day 8, repeated every 21 days. Routine prophylactic granulocyte-colony stimulating factor was mandatory. We found this regimen to be well-tolerated. The most common grades 3 to 4 nonhematologic adverse events consisted of diarrhea, dyspnea, fatigue, and nausea/vomiting (5% each). Grade 3 to 4 granulocytopenia occurred in 55% of the patients, however febrile neutropenia was observed in only 4 patients (5%). Growth factor support, therefore, appears to be an important aspect for minimizing neutropenic infections in NSCLC patients receiving combination vinorelbine and docetaxel. This is consistent with the findings of 2 other trials, which documented a relatively lower incidence (14%–15%) of febrile neutropenia in patients receiving docetaxel 60 mg/m^2 and vinorelbine 45 mg/m^2 in a dose-dense, every-2-week schedule supported with filgrastim (although grade 3–4 non-neutropenic infections, pulmonary toxicities, fatigue, and nausea/vomiting were frequently observed in those studies).[20,21] Hence, from a toxicity standpoint, the treatment schema used in our protocol seems tolerable and safe. Nonetheless, the requirement for filgrastim support may incur substantial inconveniences to the patients if this regimen is translated to routine clinical practice (eg, need for daily injections, possibility of bone pain, and increased costs).

For efficacy analysis, the endpoints should be separately evaluated for the 2 cohorts of patients (ie, frontline and second-line), since response rates and prognosis are substantially different among these 2 populations. In the largest phase 3 randomized trials of chemotherapy-naive patients performed to date, cisplatin-based doublets elicited a response rate of 19% to 32%, median time to progression of approximately 3.7 months and median overall survival of 8 to 11.3 months.[1,2] Single agent vinorelbine, docetaxel, and gemcitabine were associated with response rates of 20%, 23%, and 19%, in randomized phase 3 trials, respectively.[4,5,7] The response rate (13%) observed in our study did not reach the prespecified target of 40%. This is in accordance with other phase 2 studies demonstrating response rates between 23.1% and 36.6% in chemotherapy-naive patients receiving variations of the docetaxel-vinorelbine combination in 21-day cycles.[14,15,22] The time to progression observed in this study (2.9 months) was also lower than in the phase 3 trials by Schiller et al[1] and Fossella et al.[2] This could be due to differences in the definition of time to progression (which included discontinuation of treatment because of toxicity as an event in the present trial, but not in the aforementioned studies). Additionally, our study called for discontinuation of treatment 2 cycles after reaching maximum response. This could have led

to an abbreviated treatment period in patients with stable disease/partial response. Indeed, the median treatment period was 10.1 weeks (for the frontline cohort) in this study as compared with 15 to 18 weeks in the first-line phase 3 study by Fossella et al.[2] Extended first-line treatment has been demonstrated to prolong time to progression, but not overall survival.[23] This is further illustrated by the favorable median survival in the present study (15 months), despite a short progression-free survival. Whereas the prolonged overall survival in this trial could just reflect selection bias, it may also suggest that patients are able to tolerate further therapy after progression on the doublet. Additionally, one cannot rule out the possibility that docetaxel–vinorelbine indeed contributed to a favorable survival outcome by eliciting disease control in a significant proportion of patients (74%). Recently, Lara et al demonstrated that disease control rate is a better predictive factor of overall survival than response rate.[24]

The high disease control rate and the long overall survival observed in this trial also argue against a potential antagonistic effect of the combination of docetaxel and vinorelbine in vivo. This has been a concern, given that the former drug is a microtubule stabilizer and the latter a microtubule depolymerizing agent. Nonetheless, this combination has been demonstrated to be synergistic in prostate,[25] breast,[26] and lung[27] cancer in vitro models, and we do not believe that the outcome data of the present trial (especially pertaining to the disease control rate) support in vivo antagonism between the 2 drugs.

For the second-line patients, docetaxel or pemetrexed (the current standard-of-care cytotoxic treatment options) are associated with response rates, median time to progression and median overall survival in the ranges of 7.1% to 9.1%, 2.7 to 2.9 months, and 7.0 to 8.3 months, respectively.[10,11] Our response rate of 9% is similar to these prior trials, as is the median survival of 6.2 months. In previously treated patients, other studies have found response rates of chemotherapy combinations with the same drugs in the range of 0% to 20.8%.[16–19]

In conclusion, the results obtained in the present clinical trial do not support further evaluation of the combination of docetaxel and vinorelbine for the palliative treatment of NSCLC. For chemotherapy-naive patients, this doublet does not seem to add additional benefit to the currently available cytotoxic treatments. However, given the favorable side-effects profile, the superiority of third-generation nonplatinum based doublets over other nonplatinum combinations (as demonstrated by a recent meta-analysis[13]), and a 15-month overall survival in a phase 2 setting observed in this study, this might still represent a reasonable treatment option in selected patients. An example is the use of the combination of docetaxel and vinorelbine in patients with lung cancers that overexpress both excision repair cross-complementing group 1 (a marker of cisplatin resistance) and ribonucleotide reductase subunit 1 (a marker of gemcitabine resistance) genes. Selection of patients for use of docetaxel and vinorelbine, based on molecular profile, has been found to be a promising strategy in a feasibility phase II study.[28] Future randomized trials may definitively determine whether biomarker analysis will be useful in identifying individuals that are most likely to benefit from this combination.

For previously treated patients, combination chemotherapy still remains investigational and docetaxel with vinorelbine, in the doses and schedule studied herein, does not seem to confer neither a toxicity nor an efficacy advantage. Dose dense regimens, as evaluated by Miller at al.[20] and Page et al[21] as frontline treatment may represent a suitable alternative, albeit with increased incidence of side effects.

Acknowledgments

The authors thank for the assistance provided by the research nurses and data managers. This work was conducted under the auspices of the Lung Cancer Program of M. D. Anderson Cancer Center.

Supported in part by a grant from Sanofi-Aventis (former Rhone-Poulenc Rorer Inc.).

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TABLE 1

Baseline Characteristics of Eligible Patients

Characteristic	No. Patients (%) N = 78
Median age, yr (range)	61 (32–80)
Performance status	
1	75 (96%)
2	3 (4%)
Sex	
Female	33 (42%)
Male	45 (58%)
Histology	
Non–small-cell carcinoma, NOS	36 (46%)
Adenocarcinoma	32 (41%)
Squamous cell carcinoma	10 (13%)
Stage	
IIIA	1 (1%)
IIIB	7 (9%)
IV	70 (90%)
Brain metastases	
None	69 (88%)
Previously treated, controlled	9 (12%)
No. prior systemic treatments	
0	42 (54%)
1	29 (37%)
2	7 (9%)
Prior systemic treatments*	
Platinum-based	36 (100%)
Nonplatinum-based	5 (14%)

*All previously treated patients (N = 36) received a platinum-based doublet prior to entering this study. Additionally, 5 out of 7 patients with 2 prior systemic treatments received a nonplatinum-based regimen, while 2 received a different second-line, platinum-based regimen.

TABLE 2

Treatment Characteristics and Reasons for Study Discontinuation

	Frontline	Second-Line
No. patients	42	36
Total number of cycles	167	134
Median No. cycles/patient (range)	3.5 (1–8)	3.5 (1–12)
No. patients (% of patients) with dose escalation for second cycle	Not applicable	6 (17%)
No. patients (% of patients) with dose reductions		
No dose reductions	35 (83%)	32 (89%)
1 level	7 (17%)	3 (8%)
2 levels	0	1 (3%)
Median time on treatment (wk)	10.1	11.4
No. patients (% of patients) discontinuing treatment due to		
Completion of all planned cycles	4 (10%)	5 (14%)
Toxicities	3 (7%)	8 (22%)
Disease progression	21 (50%)	17 (47%)
No response	3 (7%)	0
Refused	1 (2%)	0
Intercurrent illness	3 (7%)	0
Death	1 (2%)	1 (3%)
Other	6 (14%)	5 (14%)

TABLE 3

Worst Toxicities by Grade (2–4) Per Patient

	No. Patients (%) N = 78		
Grade	**2**	**3**	**4**
Hematologic toxicities			
Anemia	39 (50%)	6 (8%)	—
Thrombocytopenia	1 (1%)	1 (1%)	—
Granulocytopenia	10 (13%)	8 (10%)	35 (45%)
Febrile granulocytopenia		1 (1%)	3 (4%)
Nonhematologic toxicities			
Alopecia	22 (28%)	—	—
Fatigue	16 (21%)	4 (5%)	—
Dyspnea	10 (13%)	4 (5%)	—
Nausea/vomiting	7 (9%)	4 (5%)	—
Cough	9 (12%)	1 (1%)	—
Diarrhea	5 (6%)	4 (5%)	—
Neuropathy	8 (10%)	—	—
Stomatitis	5 (6%)	2 (3%)	1 (1%)
Arthralgia/myalgia	5 (6%)	1 (1%)	—
Infection	3 (4%)	3 (4%)	—
Constipation	3 (4%)	2 (3%)	—
Anorexia	3 (4%)	1 (1%)	—
Edema	2 (3%)	1 (1%)	—
Pain	3 (4%)	—	—
Abdominal pain/cramping	2 (3%)	—	—
Dehydration	2 (3%)	—	—
Headache	1 (1%)	1 (1%)	—
Hearing loss	1 (1%)	1 (1%)	—
Hematuria	2 (3%)	—	—
Pruritus	2 (3%)	—	—
Supraventricular arrhythmia	—	2 (3%)	—
Chest pain	—	1 (1%)	—
Hyperglycemia	—	—	1 (1%)
Muscle weakness	—	1 (1%)	—
Dry eyes	1 (1%)	—	—
Esophagitis	1 (1%)	—	—
Hemoptysis	1 (1%)	—	—
Hemorrhoids	1 (1%)	—	—
Hot flashes	1 (1%)	—	—
Hypotension	1 (1%)	—	—
Insomnia	1 (1%)	—	—
Hyperkalemia	1 (1%)	—	—

	No. Patients (%) N = 78		
Grade	**2**	**3**	**4**
Rash/desquamation	1 (1%)	—	—

TABLE 4

Response Rates in Evaluable Patients

	Frontline N = 38		Second-Line N = 32	
	Response N (%)	95% Confidence Interval	Response N (%)	95% Confidence Interval
Complete response (CR)	0	—	0	—
Partial response (PR)	5 (13%)	—	3 (9%)	—
Stable disease (SD)	23 (61%)	—	23 (72%)	—
Progressive disease (PD)	10 (26%)	—	6 (19%)	—
Overall response (CR + PR)	5 (13%)	4.4–28.1	3 (9%)	2.0–25.0
Disease control (CR + PR + SD)	28 (74%)	56.9–86.6	26 (81%)	63.6–92.8