Dose-Dense Vinorelbine and Docetaxel with Filgrastim Support in Patients with Advanced Nonsmall Cell Lung Carcinoma

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BACKGROUND. Vinorelbine and docetaxel are active single agents in the treatment of nonsmall cell lung carcinoma (NSCLC) and may provide enhanced activity when combined in a dose-dense fashion. The efficacy and safety of this combination was assessed when it was administered every 14 days with Filgrastim support in a community practice setting.

METHODS. This open-label study was conducted at 12 community oncology practices in the United States. Sixty-one chemotherapy-naive patients with Stage IIIB/IV NSCLC received vinorelbine 45 mg/m^2 followed by docetaxel 60 mg/m^2 on Day 1 and Filgrastim 5 mcg/kg beginning on Day 2, with cycles repeated every 14 days.

RESULTS. Among 61 enrolled patients, 44% of patients had either a complete or partial response as their best response, and 27% of patients had confirmed complete or partial responses. The median time to confirmed response was 1.9 months (95% confidence interval [95% CI], 0.9–2.3 mos), and the median duration of confirmed response was 6.0 months (95% CI, 3.1–14.4 mos). The median time to disease progression was 4.9 months (95% CI, 3.8–5.8 mos). With a median follow-up of 14.3 months, the median survival was 12.9 months (95% CI, 8.1–14.3 mos), and the 1-year survival rate was 56% (95% CI, 43–69%). The relative dose intensity was 94% for vinorelbine and 93% for docetaxel. Febrile neutropenia occurred in 9 patients (15%) and during 9 of 351 cycles (3%).

CONCLUSIONS. It was possible to administer dose-dense vinorelbine and docetaxel chemotherapy with Filgrastim support, beginning in the first cycle, to patients with NSCLC who were treated in a community practice setting. ***Cancer* 2005;104: 1956–61.** *© 2005 American Cancer Society.*

KEYWORDS: neutropenia, Filgrastim, chemotherapy, nonsmall cell lung carcinoma, dose-dense.

Each year in the United States, over 170,000 individuals are diagnosed with lung carcinoma, and > 160,000 will die from the disease.[1] Of all deaths attributed to cancer, lung carcinomas are the most common, accounting for 32% of cancer deaths in men and 25% of cancer deaths in women. Among patients with newly diagnosed lung carcinoma, approximately 80% have nonsmall cell lung carcinoma (NSCLC), and > 70% of patients will present with advanced-stage disease at diagnosis.[2] The prognosis for patients with advanced NSCLC is dismal; because, even with treatment, the 5-year survival rate is < 10%.[3] Standard, first-line therapy for NSCLC generally consists of a platinum-containing doublet.[4] However, these regimens may be inappropriate for some patients, and alternative therapies are needed.

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Vinorelbine and docetaxel both are active single agents in the treatment of NSCLC and have demonstrated enhanced activity when combined in vitro.[5–7] Although both drugs affect tubulin, they have different mechanisms of action. Vinorelbine disrupts mitosis by preventing tubulin monomers from polymerizing into microtubules, whereas docetaxel blocks mitosis by promoting the assembly of stabilized microtubules and inhibiting depolymerization. The synergistic effect of these agents in vitro suggested a possible use for combination therapy in a clinical setting.

The efficacy and safety of vinorelbine and docetaxel administered in a 21-day cycle was explored previously in 3 clinical trials. In 1 study (n = 39 patients),[8] docetaxel at a dose of 75 mg/m^2 given on Day 1 followed by vinorelbine 20 mg/m^2 on Days 1 and 5 achieved an overall response rate of 23%, a median survival of 40 weeks, and a 1-year survival rate of 31%. In addition, a high rate of neutropenia was reported (92% of patients had Grade 4 neutropenia; 41% of patients had febrile neutropenia). The second study (n = 41 patients),[9] in which the dose and timing of the chemotherapeutic agents were modified (vinorelbine 25 mg/m^2 on Day 1 followed by docetaxel 100 mg/m^2 on Day 2), and recombinant human granulocyte colony-stimulating factor (G-CSF) was added, achieved a 37% response rate, a median survival of 5 months, and a projected 1-year survival rate of 24%. Grade 3/4 neutropenia occurred in 46% of those patients, and 24% of the patients were hospitalized for neutropenic fever. In a third, recently reported study (n = 42 patients),[10] the authors investigated 3 21-day schedules of docetaxel 75 mg/m^2 and vinorelbine 20 mg/m^2 (docetaxel on Day 1 and vinorelbine on Days 1 and 6; vinorelbine on Days 1 and 6 and docetaxel on Day 6; and docetaxel on Day 1 and vinorelbine on Days 6 and 15) with G-CSF prescribed in subsequent cycles after an episode of febrile neutropenia. The combination of docetaxel on Day 1 and vinorelbine on Days 1 and 5 yielded good response (43%) and survival rates (overall survival, 16 mos; 1-yr survival rate, 78%) but frequent myelotoxicity (64% of patients had Grade 3/4 neutropenia; 43% of patients had febrile neutropenia).

Toxicity associated with this combination of chemotherapeutic agents was reduced when vinorelbine was administered immediately prior to docetaxel and then followed by G-CSF support.[11] Using this dosing sequence, a 14-day schedule of the vinorelbine and docetaxel combination was investigated in a Phase II, single-center trial (n = 35 patients).[12] Vinorelbine 45 mg/m^2 followed by docetaxel 60 mg/m^2 on Day 1 with Filgrastim support beginning on Day 2 attained a 51% response rate with only 14% of patients experiencing febrile neutropenia. The median survival in the study was 14 months, and the 1-year survival rate was 60%. Because of the encouraging results obtained with the 14-day schedule, the current study was undertaken to substantiate the findings in a community setting. Tumor response, overall survival, time to disease progression, and toxicities were assessed among patients with advanced NSCLC who received dose-dense vinorelbine and docetaxel with Filgrastim support in a community practice setting.

MATERIALS AND METHODS

Patient Selection

Patients older than 18 years who were chemotherapy naive and had histologically or cytologically documented Stage IIIB or IV NSCLC were entered into the study. In addition, patients were required to have a life expectancy $>$ 2 months, a Karnofsky performance status $\geq$ 70%, an absolute neutrophil count (ANC) $\geq$ 2000/mm^3, and a platelet count $\geq$ 100,000/mm^3. Other study entry requirements included a serum creatinine level $\leq$ 2.0 mg/dL, aspartate and alanine transferase levels $\leq$ 1.5 times the upper limit of normal, and a bilirubin level at or below the upper limit of normal. In addition, patients must not have had major thoracic or abdominal surgery or any radiation therapy within the 2 weeks before study entry. Patients with previous malignancies (within 5 yrs of enrollment), active infection or fever $\geq$ 38.2 °C, significant nonmalignant disease (human immunodeficiency virus infection, uncontrolled hypertension, unstable angina, congestive heart failure, poorly controlled diabetes, or uncontrolled atrial or ventricular cardiac arrhythmias), or recent angioplasty or myocardial infarction were excluded from the study.

The protocol and informed consent forms were approved by the appropriate Institutional Review Board before an investigator enrolled any patients into the study. All patients (or their legal representatives) provided written informed consent to participate in the study before any study-specific procedure was performed.

Study Treatments and Procedures

Patients received open-label vinorelbine and docetaxel chemotherapy every 14 days with Filgrastim support. On Day 1 of each chemotherapy cycle, vinorelbine 45 mg/m^2 was administered over 6–10 minutes by slow intravenous push, followed by a 1-hour infusion of docetaxel 60 mg/m^2. Filgrastim 5 mcg/kg was given daily on Days 2–14 or until the patient's ANC was $\geq$ 10,000/mm^3.

Disease response was evaluated at the end of Cycles 2, 5, and 8. Patients continued treatment for up to eight cycles if they had either a complete or partial

response or stable disease. Patients with disease progression were required to withdraw from the trial. Patients who tolerated the chemotherapy well and appeared to have continued benefit were permitted to continue treatment beyond eight cycles. Cycles administered beyond Cycle 8 were excluded from dose intensity calculations but included in all other assessments.

Statistical Methods

Baseline characteristics, response, and adverse events were tabulated. The time to disease progression and the 1-year survival rates were determined using the Kaplan–Meier method. Relative dose intensity was calculated as the dose intensity of each chemotherapeutic agent divided by the corresponding standard dose in mg/m^2 per week averaged across the number of delivered regimen cycles (up to 8 cycles, because only 4 patients had a longer treatment).

A complete response was defined as disappearance of all measurable or evaluable disease, signs, symptoms, and biochemical changes related to the tumor with no new lesions. A partial response was defined as a reduction $\geq$ 50% from pretreatment measurements in the sum of the products of the greatest perpendicular dimensions of all measurable lesions lasting at least 4 weeks posttherapy with no new lesions and no progression of existing lesions. For patients with evaluable disease only, response was defined as a definite decrease in tumor size agreed on by 2 independent investigators for at least 4 weeks. Stable disease was defined as a reduction $<$ 50% and an increase $<$ 25% in the sum of the products of the 2 greatest perpendicular dimensions of all measured lesions and the appearance of no new lesions. Disease progression was defined as 1 of the following: 1) an increase in the product of the greatest perpendicular dimensions of any new measured lesion by $>$ 25% over the size at study entry, 2) the appearance of new areas of malignant disease, or 3) a 2-level deterioration in performance status, $>$ 10% loss of pretreatment weight, or increasing symptoms that should initiate a new evaluation for extensive disease. The best response was defined as the best outcome from all disease response assessments. A confirmed response was based on 2 evaluations at least 4 weeks apart. Febrile neutropenia was defined as an ANC $<$ 500/mm^2 and a body temperature $\geq$ 38.2 °C and was documented as an adverse event by the investigator.

RESULTS

Study Population

Patients from 12 community practices in the United States were entered into the study between November 1999 and June 2002. Of 63 screened patients, 61 patients met the study entry criteria and were enrolled into the study. Two of the 61 patients withdrew consent and did not receive study medication. Those two patients were included in demographic, disease progression, and survival summaries, but not in dose-intensity or toxicity assessments.

TABLE 1
Pretreatment Patient Characteristics (N = 61 patients)

Characteristic	No. of patients (%)
Age in yrs	
Median	61.4
Range	40.5–79.4
Male gender	34 (55.7)
White race	49 (80.3)
Karnofsky performance status	
100%	13 (21.3)
90%	23 (37.7)
80%	16 (26.2)
70%	9 (14.8)
Elevated lactate dehydrogenase	17 (27.9)
Metastases	
Bone	11 (18.0)
Liver	9 (14.8)
Adrenal	6 (9.8)
Other (pancreas, spleen, kidney)	6 (9.8)

The median age of the study participants was 61 years (age range, 41–79 yrs) (Table 1). Eighty percent of the patients were white, and 56% were male. Most patients had a Karnofsky performance status $\geq$ 80%.

Twenty-eight of 61 patients (46%) completed the study. The most common reasons for early withdrawal were disease progression (15%), intolerable adverse events (10%), patient request (10%), and administrative or investigator decision (10%). Three patients died while they were receiving study treatment, one due to disease progression and two due to adverse events (sepsis and sudden death). Three additional patients died due to disease progression within 30 days after the last dose of study drug.

Response

Of 55 patients with tumor response data, 3 patients (5%) had a complete response as their best evaluation, and 21 patients (38%) had a partial response as their best evaluation (Table 2). A complete or partial response was confirmed for 15 patients (27%), including 3 patients (5%) who had a complete response and 12 patients (22%) who had a partial response. For patients with confirmed responses, the median time to response was 1.9 months (95% confidence interval [95% CI], 0.9–2.3 mos), and the median duration of response was 6.0 months (95% CI, 3.1–14.4 mos).

TABLE 2
Objective Response (N = 55 patients)

Response	No. of patients (%)	
	Best response	Confirmed response
Complete response	3 (5)	3 (5)
Partial response	21 (38)	12 (22)
Stable disease	23 (42)	31 (56)
Progressive disease	8 (15)	9 (16)
Overall response rate	24 (44)	15 (27)

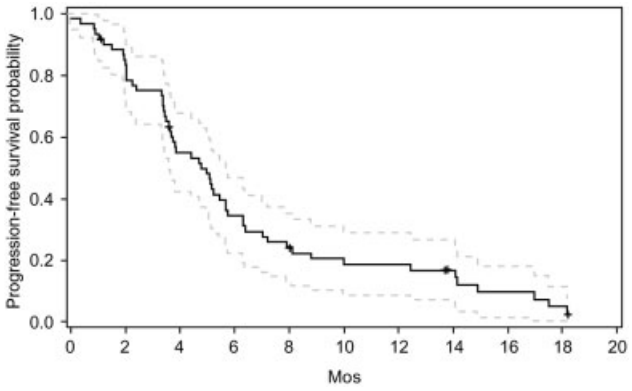

FIGURE 1. This chart illustrates the time to disease progression (solid line) in patients with nonsmall cell lung carcinoma who received dose-dense vinorelbine and docetaxel chemotherapy administered with Filgrastim support. Dashed lines (on both sides of the solid line) indicate 95% confidence intervals, and crosses represent censored observations.

Time to Progression and Overall Survival

The median time to disease progression was 4.9 months (95% CI, 3.8–5.8 mos) (Fig. 1). With a median follow-up of 14.3 months, the median survival was 12.9 months (95% CI, 8.1–14.3 mos), and the 1-year survival rate was 56% (95% CI, 43–69%) (Fig. 2).

Relative Dose Intensity

In total, 351 cycles of chemotherapy were administered to 59 patients, and 28 of 59 patients (47%) completed ≥ 8 cycles of chemotherapy. The maximum number of cycles given was 11, although only 9 patients received > 8 cycles. The relative dose intensity ± standard deviation was 94% ± 11% for vinorelbine and 93% ± 10% for docetaxel. Ten patients (17%) received at least 1 cycle of chemotherapy with < 75% of the prescribed vinorelbine dose, and 14 patients (24%) received at least 1 cycle with < 75% of the prescribed docetaxel dose. Fourteen of 59 patients (24%) had ≥ 1 cycle delayed by ≥ 7 days. The mean (± standard deviation) duration of the dosing delay was 8.8 days (± 2.7 days). Because the reasons for dose modification usually were not provided, assessment of causality was not performed.

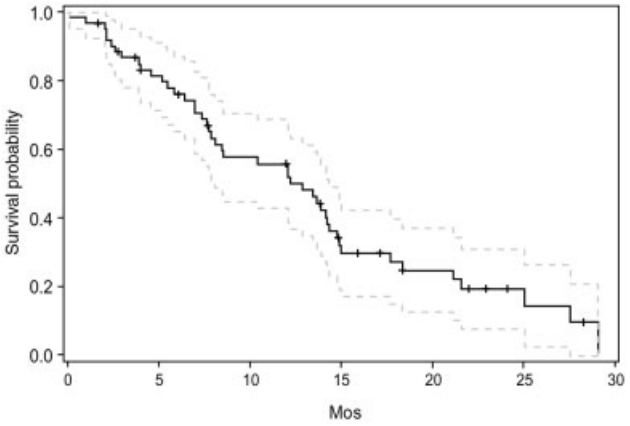

FIGURE 2. This chart illustrates the survival (solid line) of patients with nonsmall cell lung carcinoma who received dose-dense vinorelbine and docetaxel chemotherapy administered with Filgrastim support. Dashed lines (on both sides of the solid line) indicate 95% confidence intervals, and crosses represent censored observations.

TABLE 3
Grade 3/4 Adverse Events Occurring in ≥ 5% of Patients (N = 59 patients)

Grade 3/4 adverse event	No. of patients (%)
Neutropenia[a]	11 (19)
Anemia	7 (12)
Asthenia	7 (12)
Febrile neutropenia	7 (12)
Dyspnea	5 (8)
Fatigue	4 (7)
Nausea	4 (7)
Emesis	4 (7)
Hypotension	3 (5)

[a] Includes febrile neutropenia.

Toxicity

Grade 3/4 adverse events that occurred in ≥ 5% of patients are shown in Table 3. Anemia, asthenia, and febrile neutropenia were the most commonly reported Grade 3/4 events and were reported in 7 patients each (12%). Two patients had fatal adverse events (sepsis and sudden death), and 8 patients (14%) withdrew from the study due to intolerable adverse events, most of which were considered related to either vinorelbine or docetaxel therapy. Overall, febrile neutropenia occurred in 9 patients (15%) and in 9 of 351 cycles (3%). Thirteen patients (22%) reported mild-to-moderate bone pain. Increased lacrimation was reported by 11 patients (19%), and nail disorders were reported by 7

patients (12%). All reports of nail disorders were mild to moderate in severity, and the investigator believed that most events probably or definitely were related to docetaxel therapy.

DISCUSSION

In this open-label study of dose-dense vinorelbine and docetaxel chemotherapy given with Filgrastim support, the confirmed tumor response rate was 27%. The median survival was 12.9 months, and the 1-year survival rate was 56%. Most adverse events were consistent with those reported by patients with NSCLC undergoing chemotherapy. Few neutropenic complications were observed, and only 9 patients (15%) had febrile neutropenia in 9 of 351 cycles (3%).

The survival and toxicity data from our study are similar to those previously reported by Miller et al. at Memorial Sloan Kettering Cancer Center.[12] In their small ($n = 35$ patients), single-center trial, a confirmed major response rate of 51% (16 partial responses and 2 improvements) was attained, with a median survival of 14 months and a 1-year survival rate of 60%. Febrile neutropenia occurred in 5 of 35 patients (14%) and 5 of 384 treatments (1%). Their adverse event profile was similar to that observed in our current study, although the incidence of individual adverse events differed from our findings. Despite similarities in 1-year survival, confirmed response rates differed between the 2 studies (27% vs. 51%). The reason for our lower response is unclear, although it may be due at least in part to varying definitions of response. Response has not always correlated with survival in studies conducted in this patient population,[13,14] leading to an emphasis on survival as a more clinically relevant endpoint. Our study results support the survival and toxicity data reported by Miller et al. and suggest that a 14-day regimen of vinorelbine and docetaxel can be used in the community practice setting as well as in a major cancer center.

First-line therapy for patients with NSCLC frequently consists of a two-drug, platinum-based regimen (cisplatin or carboplatin in combination with paclitaxel, docetaxel, vinorelbine, gemcitabine, or irinotecan). Response rates associated with these regimens generally range from 30% to 45%, with a median survival of 8–11 months and a 1-year survival rate between 30% and 45%.[4] In a large ($n = 1155$ patients) study that compared 4 different platinum doublets (gemcitabine/cisplatin, docetaxel/cisplatin, paclitaxel/carboplatin, and paclitaxel/cisplatin), the median survival was between 7 months and 8 months, and the 1-year survival rate ranged from 31% to 36%.[15] Newer single agents, such as paclitaxel, docetaxel, vinorelbine, and gemcitabine, are perceived as less toxic than platinum-containing compounds, but they have produced inferior survival rates when administered as single agents rather than in combination with carboplatin or cisplatin.[16,17] The efficacy results from both our study and the study reported by Miller et al.[12] at least are comparable to the results obtained from platinum-based doublets and may suggest improved survival. However, most patients in our study had a Karnofsky score $\geq$ 80%, and our clinical experience with this combination suggests that its use should be limited to patients who have a good performance status.

The results of the current study are encouraging and support further investigation. Dose-dense regimens are being investigated in a variety of clinical settings and already have demonstrated improvement in survival compared with standard-dose regimens among patients with breast carcinoma,[18] lymphoma,[19,20] and small cell lung carcinoma.[21] The 1-year survival rates both in our study (56%) and in the study reported by Miller et al. (60%)[12] suggest that a dose-dense vinorelbine/docetaxel regimen may offer similar benefit in patients with NSCLC and warrants further study. In an ongoing Cancer and Leukemia Group B study (CALGB 30303), the CALGB currently is investigating the feasibility of delivering docetaxel and cisplatin in a dose-dense regimen with pegfilgrastim and darbepoetin alfa support in patients with NSCLC. The use of once-per-chemotherapy-cycle pegfilgrastim instead of daily Filgrastim would reduce the number of injections required to provide neutrophil support and could improve the ability to administer these dose-dense regimens. Larger, randomized trials are needed to explore further and confirm our findings, either in the adjuvant or neoadjuvant treatment setting, in patients who have a good performance status or earlier stage NSCLC.

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