Phase I Trial of Docetaxel and Vinorelbine in Patients with Advanced Nonsmall Cell Lung Carcinoma

Vincent A. Miller, M.D.[1]
Kenneth K. Ng, M.D.[1]
Lee M. Krug, M.D.[1]
Wendy Perez, B.A.[1]
Barbara Pizzo, R.N.[1]
Robert T. Heelan, M.D.[2]
Mark G. Kris, M.D.[1]

[1] Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, New York, New York.

[2] Department of Radiology, Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, New York, New York.

Presented in part at the American Society of Clinical Oncology Annual Meeting, Los Angeles, California, May, 1998.

Supported, in part, by Rhône-Poulenc Rorer, Inc., Collegeville, PA.

Dr. Miller has received speaking honoraria and is on the Advisory Committee for Glaxo Wellcome and has also received research funding and speaking honoraria from Rhône-Poulenc Rorer and is a member of its Advisory Committee.

Dr. Kris has acted as a consultant for Glaxo Wellcome and Rhône-Poulenc Rorer, has received research funding from Rhône-Poulenc Rorer, has received honoraria from Glaxo Wellcome, has provided paid expert testimony for Rhône-Poulenc Rorer, and is a member of the Advisory Committee for Rhône-Poulenc Rorer.

Dr. Miller is the recipient of an American Cancer Society Clinical Oncology Career Development Award.

Address for reprints: Vincent A. Miller, M.D., Thoracic Oncology Service, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

Received July 13, 1999; revision received November 12, 1999; accepted November 23, 1999.

BACKGROUND. With preclinical evidence of synergy, this dose-finding trial examining the combination of docetaxel and vinorelbine given with prophylactic filgrastim for the treatment of patients with nonsmall cell lung carcinoma was undertaken.

METHODS. Twenty-seven patients with advanced nonsmall cell lung carcinoma received vinorelbine as an intravenous push immediately followed by docetaxel as a 1-hour intravenous infusion once every 2 weeks at 1 of 7 different dose levels. Vinorelbine was escalated from 15 mg/m^2 (Level I) to 45 mg/m^2 (Level VII) and docetaxel was increased from 50 mg/m^2 (Level I) to 60 mg/m^2 (Level VII). Prophylactic corticosteroids and filgrastim were employed prospectively.

RESULTS. After completion of dose Level VII, accrual was terminated because Phase II dose intensity of both agents had been reached and further escalation was believed to be unsafe. At dose Level VII, one episode of first-cycle febrile neutropenia and a death after three treatment cycles due to *Haemophilus influenzae* sepsis (Grade 5 toxicity according to the Common Toxicity Criteria of the National Cancer Institute) without neutropenia were noted. In all, 209 treatment cycles were administered and febrile neutropenia was observed in only 4 of these treatments (1.9%). Bacteremia occurred in three patients (four episodes) in the absence of neutropenia. Symptomatic onycholysis was observed in three patients. Clinically significant peripheral neuropathy and fluid retention were rare. Confirmed partial responses were noted in 10 patients for a response rate of 37% (95% confidence interval, 20–57%).

CONCLUSIONS. Docetaxel at a dose of 60 mg/m^2 and vinorelbine at a dose of 45 mg/m^2, both given every 2 weeks, can be combined safely to achieve Phase II dose intensity of both agents. An ongoing Phase II trial will define the activity of this treatment combination. ***Cancer* 2000;88:1045–50.**

KEYWORDS: chemotherapy, docetaxel, vinorelbine, nonsmall cell lung carcinoma.

Docetaxel and vinorelbine are active agents in the treatment of advanced nonsmall cell lung carcinoma (NSCLC). Docetaxel is a semisynthetic taxoid prepared from a precursor compound derived from the needles of the European yew, *Taxus baccata,* which exerts antitumor effects through promotion of microtubule assembly and inhibition of tubulin depolymerization.[1] Phase II trials of this agent (60–100 mg/m^2 every 3 weeks) have reported major response rates ranging from 19–38% and median survivals of 7–14 months with the average of these being just under 11 months, thus making docetaxel one of the most active agents ever tested in NSCLC.[2] Nearly all these studies used a dose of 100 mg/m^2 given as a 1-hour infusion.[3] Vinorelbine is a semisynthetic vinca alkaloid approved in the U.S. as a single agent or in combination with cisplatin for the treatment of

NSCLC.[4] At least 1 study has suggested that a vinorelbine dose of 25–30 mg/m^2/week is associated with higher response rates than a dose of 20 mg/m^2/week.[5] An extensive body of preclinical in vivo and in vitro data suggests synergistic, or at least additive, antitumor effects when docetaxel and vinorelbine are combined and administered at approximately the same time; alternate schedules may result in increased toxicity or lessened efficacy.[6–8] Thus, in 1995 we undertook a Phase I trial of the combination of docetaxel and vinorelbine. Because docetaxel is associated with febrile neutropenia in 24% of patients[2] and vinorelbine has been reported to cause Grade 3/4 neutropenia in 50% of patients,[4] we reasoned that the combination would likely result in febrile neutropenia in $\geq$ 40% of patients and thus prophylactic filgrastim would be needed to attain the minimal dose intensities of each agent associated with reproducible clinical antitumor activity.[9] We initially attempted to give docetaxel, 75 mg/m^2, on Day 1, with vinorelbine, 15 mg/m^2/day, on Days 1–3 and planned retreatment every 21 days. Despite prophylactic filgrastim, initiated 24 hours after the completion of vinorelbine, febrile neutropenia developed in 4 of 4 treated patients and an alternative schedule was studied. In designing this new schedule we hoped that smaller, more frequent doses might allow maintenance or improvement of dose intensity, obviate hematologic toxicity, and allow for more frequent interaction between the putatively synergistic agents. In addition, we chose to give filgrastim beginning 48 hours after vinorelbine because of the long terminal half-life of that agent (27 hours).[10] We believed it was possible that administering filgrastim just 24 hours after the completion of chemotherapy might have prematurely recruited neutrophil precursors that then were subjected to residual vinorelbine and that actually may have magnified neutropenia. We initiated this modified Phase I trial combining docetaxel and vinorelbine, given at the same time, with the goal of determining whether clinically relevant doses of both agents could be given safely in combination on a novel every-2-weeks schedule.

PATIENTS AND METHODS

Eligibility

All patients had AJCC Stage IIIB (malignant pleural or pericardial effusion) or Stage IV[11] disease and a Karnofsky performance status $\geq$ 60%. All patients treated had measurable indicator lesions; however, measurable or evaluable indicator lesions were not required. No radiotherapy to major bone marrow areas was allowed within 4 weeks of treatment initiation. Patients were permitted to have received one prior chemotherapy regimen, exclusive of taxanes or vinca alkaloids. Laboratory requirements for eligibility included an absolute neutrophil count (ANC) $\geq$ 2000/mm^3, platelet count $\geq$ 100,000/mm^3, serum bilirubin $\leq$ the upper limit of normal (ULN), aspartate aminotransferase $\leq$ 1.5 times the ULN, alkaline phosphatase $\leq$ 5 times the ULN, and creatinine $\leq$ 2.0 mg/dL. Patients with symptomatic brain metastases or symptomatic peripheral neuropathy $\leq$ Grade 2 (according to National Cancer Institute Common Toxicity Criteria) were excluded. Written informed consent was obtained from all patients and the protocol was approved by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center.

Treatment Plan

Before therapy, all patients had a complete history and physical examination, complete blood count, electrolytes, glucose, hepatic and renal biochemical tests, electrocardiogram, and a computed tomography (CT) scan of the chest and any other sites of known disease. Other scans were performed if clinically indicated. Patients were evaluated weekly for toxicity (using the Common Toxicity Criteria of the National Cancer Institute) during the first 6 weeks and subsequently on days of treatment. Patients with Grade 4 neutropenia associated with fever (single oral temperature $>$ 38.5 °C or 3 elevations $>$ 38 °C) requiring treatment with intravenous antibiotics were to be retreated after recovery with a 25% reduction in the doses of both agents. Tumor response assessment by CT scans was performed after 2 cycles of therapy (4 weeks) and then every 6 weeks thereafter. Categories of response included complete, partial, no change, and progression. Partial response was defined as a $\geq$ 50% decrease in the sum of the products of the greatest dimensions of measurable lesions in the absence of any new or progressive lesions. Major response designation (complete, partial) required confirmation on a second scan obtained $\geq$ 4 weeks after the first such scan documenting the major response. Initial treatment was comprised of two cycles. Duration of response and survival were measured from the date of the first treatment. All imaging studies of indicator lesions were reviewed by a reference radiologist (R.T.H.).

A minimum of three evaluable patients were entered at each dose level (Table 1). Dose-limiting toxicity (DLT) was defined as $\geq$ Grade 3 nonhematologic toxicity or Grade 4 emesis, Grade 4 neutropenia lasting $\geq$ 7 days or with fever requiring parenteral antibiotics, or Grade 4 thrombocytopenia occurring during the first cycle (2-week period) of therapy. Doses were escalated until a DLT was observed in at least one of three patients adequately observed at a given dose

TABLE 1
Dose Levels of Docetaxel and Vinorelbine[a]

Level	Vinorelbine	Docetaxel	No. of patients
I	15	50	6
II	20	50	3
III	25	50	3
IV	30	50	3
V	37.5	50	3
VI	45	50	3
VII	45	60	6

[a] Doses are in mg/m^2 every 2 weeks.

level. If only one of three patients experienced a DLT, three additional patients were to be entered at that level. If no additional DLT then was observed, escalation continued. If two or more patients encountered a DLT, dose escalation was to cease and that dose was considered the maximum tolerated dose (MTD). No intrapatient dose escalation was permitted.

Docetaxel and vinorelbine were administered in the outpatient department. Vinorelbine (Navelbine®) was prepared according to manufacturer's instructions (Glaxo Wellcome, Research Triangle Park, NC), diluted in 125 mL of normal saline, and given as a 6–10 minute intravenous push. Docetaxel (Taxotere®; Rhone-Poulenc Rorer, Collegeville, PA) was packaged, dispensed, and stored as previously reported.[1] Docetaxel was administered as a 1-hour infusion immediately after the completion of vinorelbine. All patients received dexamethasone, 8 mg orally, for 5 doses given every 12 hours, starting 24 hours before planned chemotherapy administration. No other antiemetics were employed routinely. Filgrastim was given as a subcutaneous injection at a dose of 5 μg/kg starting 48 hours after treatment, and continued for a minimum of 6 days, and until the ANC was $\geq$ 10,000/mm^3.

RESULTS

From February 1996 through July 1997, 27 patients with pathologically confirmed NSCLC were enrolled, all of whom were treated and assessable for response and toxicity. All patients had measurable indicator lesions. Patient characteristics are summarized in Table 2. A total of 209 treatments were administered. In 190 of these full doses of both drugs were delivered. In 19 and 11 treatments, respectively, docetaxel and vinorelbine were given at 75% of the planned doses. The overall calculated dose intensity (planned/delivered dose $\times$ 100) was 98% for docetaxel and 99% for vinorelbine. The median number of treatments was 6 (range, 2–26). The median delivered dose intensity at the highest dose level was 30 mg/m^2/week for docetaxel and 23 mg/m^2/week for vinorelbine.

TABLE 2
Pretreatment Patient Characteristics

	No.	%
Entered	27	
Measurable disease	27	100
Stage IIIB	4	15
Stage IV	23	85
Women	10	37
Karnofsky PS		
80–90%	23	85
60–70%	4	15
Weight loss $\geq$ 5%	7	26
Elevated LDH	9	33
Bone metastases	6	22
Median age (yrs)	55	
Range	37–75	
Cell type		
Adenocarcinoma	21	78
Squamous	3	11
NSCLC, not specified	3	11
Prior treatment		
Surgery	7	26
Chemotherapy	3	11
Radiotherapy	2	7

PS: performance status; LDH: lactate dehydrogenase; NSCLC: nonsmall cell lung carcinoma.

Toxicity

Toxicity data are summarized by dose level in Table 3. One patient treated on dose Level I developed febrile neutropenia after the first cycle of treatment and thus this cohort was expanded to treat an additional three patients. Because no other first-cycle DLT was observed, dose escalation ensued. Infection, frequently without neutropenia, was the most commonly observed serious adverse event. Three patients died while on study after having received five, five (one each at dose Levels III and VI), and three (dose Level VII) treatments, respectively. All developed dyspnea and nonneutropenic fever approximately 24–48 hours before seeking medical evaluation. One patient died of *Haemophilus influenzae* bacteremia and pneumonia (Grade 5 infection) (Table 3). The other two patients had extensive preexistent lung disease and evidence of pulmonary infiltrates on radiologic studies and physical examination. Their underlying lung disease, the delay in seeking medical attention, and the clinical course made it unlikely that the study combination was a contributor to their subsequent deaths from progressive respiratory failure. Six patients received dose reductions for the following reasons: onycholysis (three patients), neutropenic fever (two patients), and

TABLE 3
Toxicity by Dose Level of Docetaxel and Vinorelbine (Highest NCI Toxicity Grade-No. of Patients)

	I (n = 6)	II (n = 3)	III (n = 3)	IV (n = 3)	V (n = 3)	VI (n = 3)	VII (n = 6)	Cumulative (n = 27)
Toxicity	**0 1 2 3 4**	**0 1 2 3 4**	**0 1 2 3 4**	**0 1 2 3 4**	**0 1 2 3 4**	**0 1 2 3 4**	**0 1 2 3 4**	**0 1 2 3 4**
Alopecia	0 3 3	0 2 1	0 1 2	0 1 2	0 3	0 2 1	0 2 4	0 11 16
Neurosensory	2 3 1 0 0	1 2 0 0 0	1 2 0 0 0	1 2 0 0 0	2 1 0 0 0	3 0 0 0 0	4 2 0 0 0	14 12 1 0 0
Local skin/soft tissue	2 2 0 2 0	1 1 1 0 0	2 1 0 0 0	0 2 0 1 0	1 2 0 0 0	2 0 1 0 0	3 2 1 0 0	11 10 3 3[a] 0
Nausea	3 3 0 0 0	1 2 0 0 0	2 1 0 0 0	2 1 0 0 0	1 1 1 0 0	1 2 0 0 0	5 0 1 0 0	15 10 2 0 0
Anemia	1 2 2 1 0	1 1 1 0 0	0 0 1 2 0	0 1 2 0 0	0 1 1 1 0	1 1 1 0 0	0 1 3 2 0	3 7 11 6 0
Myalgias/arthralgias	5 1 0 0 0	3 0 0 0 0	2 1 0 0 0	1 2 0 0 0	2 1 0 0 0	2 0 1 0 0	2 4 0 0 0	17 9 1 0 0
Diarrhea	2 3 1 0 0	3 0 0 0 0	2 1 0 0 0	0 1 2 0 0	2 1 0 0 0	2 1 0 0 0	4 1 0 1 0	15 8 3 1 0
Emesis	5 1 0 0 0	2 0 1 0 0	2 1 0 0 0	2 1 0 0 0	2 1 0 0 0	2 1 0 0 0	5 0 1 0 0	20 5 2 0 0
Fever	4 0 2 0 0	2 1 0 0 0	3 0 0 0 0	3 0 0 0 0	2 0 0 1 0	3 0 0 0 0	3 1 2 0 0	20 2 4 1 0
Neutropenia	3 0 1 0 2	3 0 0 0 0	2 0 0 1 0	3 0 0 0 0	2 1 0 0 0	3 0 0 0 0	3 1 0 0 2	19 2 1 1 4
Infection	5 0 0 1 0	3 0 0 0 0	1 0 0 1 1	2 0 1 0 0	2 0 1 0 0	2 0 0 0 1	5 0 0 0 1[b]	20 0 2 2 3[b]

NCI: National Cancer Institute.
[a] Onycholysis.
[b] One patient died of *Haemophilus influenzae* sepsis (Grade 5 toxicity).

transient elevation of serum transaminase (one patient). Clinically relevant fluid retention, peripheral neuropathy, and thrombocytopenia were rare.

Response and Survival

Ten confirmed partial responses were documented (major response rate 37%; 95% confidence interval, 20–57%). Four additional patients attained a partial response that could not be confirmed (disease progression, death on study, lost to follow-up) on the follow-up CT scan. Response by dose level was recorded as follows: I: two of six patients; II: none of the three patients; III: one of three patients; IV: one of three patients; V: two of three patients; VI: one of three patients; and VII: three of six patients. One of three patients previously treated with chemotherapy achieved a partial response. The median duration of response measured from the date of first treatment was 11 months (range, 4–18+ months) and was 6.8 months (range, 2–16+ months) when measured from date of first documentation of partial response status. One patient continued to respond at 18+ months. The median survival was 9 months and the 1-year survival proportion was 33%.

DISCUSSION

This study sought to determine whether clinically relevant doses of docetaxel and vinorelbine could be given safely in combination when administered every 2 weeks with prophylactic filgrastim and corticosteroids to patients with advanced NSCLC. However, our dose escalation schema was somewhat arbitrary and alternative dosing regimens might well be feasible (e.g., docetaxel, 70 mg/m^2, and vinorelbine, 35–40 mg/m^2, every 2 weeks). Although the formal definition of MTD was not reached (two first-cycle DLTs), it was believed that the dose Level VII death from sepsis after three treatments and the episode of neutropenic fever after the first cycle in another patient treated at this level made further dose escalation inadvisable. The low observed rate of incidence of febrile neutropenia could be explained, in part, by the use of filgrastim. Although the use of this growth factor may be appropriate in a clinical trial setting, this practice cannot routinely be extrapolated to everyday patient care. We chose to give a minimum of 6 doses of filgrastim and required that an ANC $\geq$ 10,000/mm^3 be reached because of the profound neutropenia observed with our original schedule. An initial complete blood count was obtained after 6 days of filgrastim and only if ANC requirements were not met was this test repeated. It is thus conceivable, although unlikely, that fewer days of filgrastim therapy might have sufficed, particularly at lower dose levels. The role of corticosteroids in contributing to observed nonneutropenic infections also should be considered. Although no persistent or profound lymphopenia or Cushingoid features were observed, 40 mg of dexamethasone given every 14 days is approximately equivalent to 10–15 mg of prednisone daily and thus could have added to immunosuppression. Other investigators have attempted to use lower doses of peritreatment corticosteroids.[12] After the septic death at dose Level VII, we chose to add prophylactic ciprofloxacin, 500 mg, twice daily for 7 days on

Days 3–9, for subsequent patients treated on this trial and all patients on our Phase II study of the combination.[13] Anecdotally, we believe this has decreased the incidence rate of nonneutropenic infections. The issue of pulmonary "reactions" with the combination has been raised by this study, other studies of the combination, and with nearly all new agents used in treating NSCLC.[4,14–16] Recognition of the potential for these reactions, early evaluation by a pulmonologist, and prompt treatment with corticosteroids in the absence of an infectious etiology appear paramount to a successful recovery. Using these supportive measures, our recommended Phase II doses of vinorelbine, 45 mg/m^2, followed by docetaxel, 60 mg/m^2, provide 75% and 90–120%, respectively, of Phase II single agent dose intensity. Similarly, drug delivery was comparatively high at dose Level VII (and lower dose levels). In a pivotal Phase III trial, only a 71% dose intensity of vinorelbine (21 mg/m^2/week) when used in combination with cisplatin or 83% (25 mg/m^2/week) when given as monotherapy was achieved.[17] To our knowledge, few other trials of vinorelbine report data regarding doses of drug actually delivered.

Our study was undertaken in part because of diverse and extensive preclinical evidence of additive or even synergistic interactions between the taxanes (docetaxel or paclitaxel) and vinorelbine in a variety of common solid tumors. Hino et al. showed that vinorelbine followed by docetaxel resulted in synergistic killing in the human NSCLC cell line PC-9, whereas treatment in the reverse order resulted in antagonism.[6] Similarly, when paclitaxel and vinorelbine were applied at or near the same time to the melanoma cell lines G361 and StM111a, synergy was noted at relatively low, clinically achievable concentrations.[18] In vivo, the combination of vinorelbine and paclitaxel resulted in a significantly greater proportion of cures of transplanted P388 murine leukemia than either agent alone.[19] In a variety of murine-borne solid tumors against which docetaxel was assessed in doublets with a panel of other agents, vinorelbine was found to provide the greatest increase in the combination toxicity index, a measure of the likelihood that the clinical toxicities would be nonoverlapping, whereas simultaneously resulting in the best enhancement of antitumor effect. This effect is believed to be independent of any pharmacokinetic interaction between the drugs.[20]

Clinically, the suggestion of schedule dependence appears to be supported because one trial that used a Day 1 vinorelbine, Day 2 docetaxel schedule reported seemingly greater toxicity despite the use of prophylactic filgrastim. In this trial, individuals received vinorelbine, 25 mg/m^2, followed by docetaxel, 100 mg/m^2, and, despite the fact that 70% of patients had a World Health Organization performance status of 0, febrile neutropenia was observed in 24% and 4 treatment-related deaths occurred.[21] Thus, we believe an every-2-weeks schedule as reported in the current study or, alternatively, a weekly schedule to be the only ways in which clinically relevant dose intensity of both component agents, particularly vinorelbine, can be delivered reliably.[14] A recent study using the combination of vinorelbine and docetaxel weekly in previously treated NSCLC patients defined the MTD without filgrastim to be vinorelbine, 20 mg/m^2/week, and docetaxel, 25 mg/m^2/week. Neutropenia and febrile neutropenia were dose-limiting and with filgrastim, Phase II doses of vinorelbine (20 mg/m^2/week) and docetaxel (35 mg/m^2/week) were recommended for untreated patients.

One proposed explanation for the antitumor synergism of these agents, which have seemingly antagonistic mechanisms of action, is that both, despite their differing effects on microtubules, result in phosphorylation and associated inactivation of the protooncogene *bcl*-2 gene, which is overexpressed in some cases of NSCLC.[22] Inactivation of *bcl*-2 protein may permit unopposed action of *bax* protein, a proapoptotic protein. Our ongoing Phase II study will define the activity of this combination and correlate baseline expression of and serial changes in *bcl*-2 protein and *bax* protein with response to the combination in a multivariate analysis including known prognostic factors in NSCLC.

REFERENCES

1. Miller VA, Rigas JR, Francis PA, Grant SC, Pisters KMW, Venkatraman ES, 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;75:968–72.
2. Miller V. Docetaxel (Taxotere^R) in the management of advanced non-small cell lung cancer (NSCLC). *Lung Cancer* 1997;18(Suppl 2):136.
3. Cortes JE, Pazdur R. Docetaxel. *J Clin Oncol* 1995;13(10): 2643–55.
4. Miller V, Kris M. Vinorelbine for treatment of advanced non-small cell lung cancer. *Med Lett Drugs Ther* 1995;37: 72–3.
5. Berthaud P, Le Chevalier T, Ruffie P, Baldeyrou P, Arriagada R, Besson F, et al. Phase I-II study of vinorelbine (Navelbine^R) plus cisplatin in advanced non-small cell lung cancer. *Eur J Cancer* 1992;28A(11):1863–5.
6. Hino H, Kobayashi K, Hayashihara K, Aoyama A, Shibuya M, Kudo S, et al. In vitro combination effect of docetaxel (RP56976) with vinca alkaloids on cancer cell lines. *Proc Am Assoc Cancer Res* 1995;36:299.
7. Aoe K, Ueoka H, Kiura K, Tabata M, Shibayama T, Harada M, et al. Synergistic effect of docetaxel (DCT) and vinorelbine (VNB) against in vitro growth of a human small-cell lung cancer cell line. *Proc Am Assoc Cancer Res* 1996;37:375.

8. Bissery MC, Vrignaud P, Bayssas M, Lavelle F. Preclinical in vivo activity of docetaxel-containing combinations. *Proc Am Soc Clin Oncol* 1995;14:489.
9. American Society of Clinical Oncology. Update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based clinical practice guidelines. *J Clin Oncol* 1996;14(6):1957–60.
10. Wargin WA, Lucas VS. The clinical pharmacokinetics of vinorelbine (Navelbine). *Semin Oncol* 1994;21(5 [Suppl 10]):21–7.
11. Beahrs OH, Henson DE, Hutter RVP, Kennedy BJ. Handbook for staging of cancer. Philadelphia: J.B. Lippincott Company, 1993.
12. Hainsworth JD, Burris HA, Erland JB, Thomas M, Greco FA. Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. *J Clin Oncol* 1998; 16(6):2164–8.
13. Krug LM, Kris MG, Grant SC, Heelan RT, Pizzo BA, Perez W, et al. Phase II trial of dose dense docetaxel plus vinorelbine with prophylactic filgrastim (G-CSF) in advanced non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 1999;18: 1775 (abstract).
14. Johnston E, Crawford J, Garst A, Bjurstrom L, Campagna L, Anderson E, et al. Phase I trial of weekly docetaxel (D) and vinorelbine (V) in advanced non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 1999;18:476a.
15. Vander Els NJ, Miller V. Successful treatment of gemcitabine toxicity with a brief course of oral corticosteroid therapy. *Chest* 1998;114:1779–81.
16. Ramanathan RK, Belani CP, Reddy VV. Transient pulmonary infiltrates: a hypersensitivity reaction to paclitaxel. *Ann Intern Med* 1996;124(2):278.
17. Le Chevalier T, Brisgand D, Douillard JY, Pujol JL, Alberola V, Monnier A, et al. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicenter trial including 612 patients. *J Clin Oncol* 1994;12(2):360–7.
18. Photiou A, Shah P, Leong LK, Moss J, Retsas S. In vitro synergy of paclitaxel (Taxol) and vinorelbine (Navelbine) against human melanoma cell lines. *Eur J Cancer* 1997;33(3): 463–70.
19. Knick V, Eberwein D, Miller CG. Vinorelbine tartrate and paclitaxel combinations: enhanced activity against in vivo P388 murine leukemia cells. *J Natl Cancer Inst* 1995;87(14): 1072–7.
20. Baille P, Vernillet L, Vergniol JC, Pasquier O, Bruno R, Azli N, et al. Docetaxel (D) pharmacokinetics (PK): influence of coadministered drugs in phase I combination studies *Proc Am Soc Clin Oncol* 1998;17:189a.
21. Kourousis C, Androulakis N, Kakolyris S, Souglakos J, Maltezakis G, Metaxaris G, et al. First-line treatment of advanced nonsmall cell lung carcinoma with docetaxel and vinorelbine. *Cancer* 1998;83(10):2083–90.
22. Haldar S, Basu A, Croce C. Bcl2 is the guardian of microtubule integrity. *Cancer Res* 1997;57:229–33.