Gemcitabine and Vinorelbine in Advanced Nonsmall Cell Lung Carcinoma

A Phase II Study

Rogerio Lilenbaum, M.D.
Roberto Cano, M.D.
Michael Schwartz, M.D.
Leonard Siegel, M.D.
Jose Lutzky, M.D.
Mark Lewis, M.D.
Elisa Krill, M.D.
Luis Barreras, M.D.
Enrique Davila, M.D.

Mount Sinai Community Clinical Oncology Program, Mount Sinai Comprehensive Cancer Center, Miami Beach, Florida.

BACKGROUND. The authors conducted a Phase II study to evaluate the activity of the combination of gemcitabine and vinorelbine in patients with advanced nonsmall cell lung carcinoma (NSCLC).

METHODS. Patients were eligible if they had Stage IIIB (malignant pleural effusion) or Stage IV NSCLC, no prior chemotherapy, and Cancer and Leukemia Group B performance status (PS) 0–2. Patients with brain metastases were eligible if they were neurologically stable after brain irradiation. Thirty-three patients from participating institutions were enrolled. One patient was ineligible due to untreated brain metastases. Patients were treated with gemcitabine 1250 mg/m^2 over 30 minutes (1000 mg/m^2 for the first 6 patients) and vinorelbine 25 mg/m^2 over 6 minutes, both administered intravenously on Days 1 and 8 every 21 days. Treatment was planned for a total of six cycles or more if the patient had persistent benefit. Growth factors were not allowed.

RESULTS. Among all 32 eligible patients, there were 8 partial responses, for an overall response rate of 25% (95% confidence interval [CI], 11.5–43.4%). The median survival time was 8.3 months and the 1-year survival rate was 38% (95% CI, 24–59%). Patients with PS 0–1 had a median survival of 11.7 months and a 1-year survival rate of 48%. Grade 3 and 4 neutropenia was observed in 13% and 25% of the 148 treatment cycles, respectively. One patient died of neutropenic sepsis. Only 2 episodes of Grade 3 and 4 thrombocytopenia were observed. Nonhematologic toxicity was minimal.

CONCLUSIONS. Gemcitabine and vinorelbine is an active and well-tolerated regimen in patients with advanced NSCLC, with response and survival rates at least comparable to those achieved with standard platinum-based regimens. This combination may be particularly suitable for the elderly or for patients who cannot tolerate more toxic platinum-based regimens. ***Cancer* 2000;88:557–62.**

Supported in part by educational grants from Eli Lilly and Company and Glaxo Wellcome. Dr. Lilenbaum is a member of the speaker bureaus of these companies.

The authors thank Jim Herndon, Ph.D., for the statistical analysis; Lisa Soontupe, R.N., and Nancy Cisneros, R.N., for data management; and Clara Gallego for manuscript preparation.

Address for reprints: Rogerio Lilenbaum, M.D., Mount Sinai Comprehensive Cancer Center, 4306 Alton Road, Miami Beach, FL 33140.

Received April 26, 1999; revision received July 27, 1999; accepted July 27, 1999.

Nonsmall cell lung carcinoma (NSCLC) is the leading cause of cancer-related deaths in the U.S.[1] The majority of newly diagnosed NSCLC patients present with disease beyond the scope of surgical cure and depend on systemic chemotherapy to improve their outcome. Until the beginning of this decade, only a few chemotherapeutic agents had demonstrated reproducible activity in NSCLC: cisplatin, vindesine, vinblastine, ifosfamide, mitomycin, and possibly carboplatin and etoposide.[2] Combination regimens involving these agents have been shown to prolong the survival of patients with advanced NSCLC when compared with supportive care alone.[3] However, this benefit is usually modest, and toxicity associated with these agents can be significant, leading to a perceived negative impact on quality on life.

Several new agents have been developed in recent years, and among these, vinorelbine, a new semisynthetic vinca alkaloid, and gemcitabine, a novel nucleoside analog, have demonstrated convincing activity as single agents in the treatment of advanced NSCLC patients.[4] When used in combination with cisplatin, both of these agents have shown improved response and survival rates when compared with cisplatin alone or other traditional combinations.[5–8] However, toxicity associated with these regimens remains substantial, and it appears that the relatively mild toxicities of vinorelbine and gemcitabine as single agents are greatly enhanced when they are used in combination with cisplatin.

Based on the individual activity of these agents and their distinct mechanisms of action, we conducted a Phase II study of the combination of gemcitabine and vinorelbine in the treatment of patients with advanced NSCLC. Our main objective was to define an active and well-tolerated non-platinum-based regimen that could be administered according to a convenient outpatient schedule.

PATIENTS AND METHODS

Patient Eligibility

Patients with histologically or cytologically documented Stage IIIB (malignant pleural effusion) or Stage IV NSCLC were eligible if they were age 16 years or older and had bidimensionally measurable or evaluable disease, no prior chemotherapy, and a Cancer and Leukemia Group B (CALGB) performance status of 0–2. Patients with brain metastases were eligible if they were neurologically stable after whole-brain irradiation and had at least one other measurable or evaluable lesion. Patients who received thoracic radiotherapy were eligible only if they had measurable or evaluable disease outside the irradiation field. Adequate renal (serum creatinine <1.5 mg/dL), hepatic (bilirubin <1.5 times the upper limit of normal range), and hematologic (granulocytes $>1500/\mu$L, hemoglobin >10g/dL, and platelet count $>100{,}000/\mu$L) parameters were required. Patients with a nonrecurrent primary tumor surgically resected more than 5 years prior to study entry without administration of adjuvant chemotherapy or radiotherapy were eligible. Patients with uncontrolled infection, patients with a psychiatric condition that would preclude informed consent, and pregnant women or nursing mothers were excluded. All patients signed a written informed consent form approved by the Mount Sinai Medical Center Institutional Review Board.

Pretreatment evaluation consisted of a complete history and physical examination, posteroanterior and lateral chest X-ray, complete blood cell count, and serum chemistry analysis. Computed tomographic (CT) scans of the chest to the level of the adrenal glands were obtained in all patients. CT scan of the abdomen and radionuclide bone scans were performed when clinically indicated. All pretreatment laboratory work was obtained within 14 days of study entry, whereas X-rays or CT scans utilized for tumor measurements were obtained within 4 weeks of study entry. A complete blood cell count was repeated every week, and the serum chemistry analysis was repeated on Day 1 of each treatment cycle. Relevant studies for tumor measurement were repeated every two treatment cycles.

Treatment Regimen

Treatment was administered in the outpatient setting. Gemcitabine was initially given at a dose of 1000 mg/m^2 intravenously over 30 minutes on Days 1 and 8. After no significant toxicity was observed in the first 6 patients, the dose was escalated to 1250 mg/m^2 in all subsequent patients. No further dose escalations were planned or carried out. Vinorelbine was given at a dose of 25 mg/m^2 intravenously over 6 minutes on Days 1 and 8 following gemcitabine administration. An antiemetic regimen consisting of a serotonin antagonist and dexamethasone was recommended. Growth factors were not routinely allowed. Cycles were repeated every 21 days to a planned maximum of 6 cycles. Patients who continued to benefit were permitted to receive additional cycles at the discretion of the attending physician. Chemotherapy was discontinued in patients with progressive disease or unacceptable toxicity.

A complete blood count was obtained in every patient on Days 1, 8, and 15 of each cycle. Dose modifications based on hematologic toxicity were made as follows: On Day 1 of each treatment cycle, a granulocyte count above $1500/\mu$L and a platelet count above 100,000 were required. Otherwise, treatment was withheld for up to 2 weeks until both the granulocyte count and the platelet count returned to the required levels. If the counts failed to return to the required levels after a 2-week delay between treatment cycles, treatment was discontinued and patients were removed from the study. On Day 8 of each cycle, patients who had a granulocyte count <1500 and/or a platelet count $<100{,}000$ had their treatment withheld, and the chemotherapy resumed at 80% of the original doses of both agents on Day 1 of the subsequent cycle. Patients who developed febrile neutropenia or Grade 4 neutropenia and/or thrombocytopenia for more than 4 days in any given cycle also had the doses of both agents reduced by 20% in all subsequent cycles.

Dose adjustments were also made for nonhema-

tologic toxicities. For hepatic dysfunction defined as bilirubin >1.5 times the upper limit of normal range, the dose of vinorelbine was reduced by 50%; for a bilirubin level >3.0 times the upper limit of normal range, vinorelbine was withheld. For neurologic toxicity, defined as Grade 2 peripheral neuropathy, vinorelbine was withheld until the toxicity resolved and then resumed at 50% of the original dose. For Grade 3 or 4 peripheral neuropathy, vinorelbine was discontinued. For all other toxicities that exceeded Grade 2 (except alopecia, nausea, or vomiting), the dose of both gemcitabine and vinorelbine was reduced by 20%.

Response and Toxicity Criteria

Standard CALGB response criteria were used. Response was always assessed by CT scans. A complete response (CR) was defined as disappearance of all measurable or evaluable disease for a minimum of 4 weeks. A partial response (PR) was defined as a reduction of 50% or greater in the sum of the products of the perpendicular diameters of all indicator lesions; this reduction was required to last a minimum of 4 weeks, during which no new lesions could appear. Progressive disease (PD) was defined as an increase in the product of 2 perpendicular diameters of any measured lesion by 25% over the size at entry on study, or the appearance of new areas of malignant disease. Stable disease (SD) included lesions that did not meet the criteria for response or progression.

Statistical Analysis

The primary objective of this trial was to define the activity of gemcitabine and vinorelbine in patients with advanced NSCLC. The study had an 80% power, with a level of significance of 0.05, to test the hypothesis that H0: $P < 0.20$ versus $P > 0.40$, where P denoted the response rate as defined above. Overall survival and failure free survival were analyzed using the Kaplan–Meier estimation method. Survival was defined as the time between initiation of treatment and death. If death had not occurred, survival time was considered censored at the last follow-up time. Failure free survival was defined as the time between initiation of treatment and failure (i.e., death or disease progression). If failure had not occurred at the time of this analysis, failure free survival was considered censored at the time of the last follow-up.

RESULTS

Patient Characteristics

Between May 1997 and April 1998, 33 patients were enrolled in the study: 22 from Mount Sinai Medical Center and 11 from member institutions of the Community Clinical Oncology Program (CCOP). One patient was considered ineligible due to untreated brain metastases discovered on a CT scan of the brain performed prior to enrollment. The characteristics of the 32 eligible patients are depicted in Table 1. There were 16 women and 16 men, with a median age of 67 years (range, 45–83 years). Fourteen patients were older than 70 years and 4 patients were older than 80 years. Twenty-five patients (78%) had a CALGB performance status of 0–1 and 7 (22%) had a performance status of 2. The predominant histology was adenocarcinoma (63%). Twenty-two patients (69%) had Stage IV disease, 5 (16%) had Stage IIIB, and 5 (16%) had recurrent disease. Five patients had undergone previous surgery: two wedge resections, one wedge resection and volume-reduction surgery, and two lobectomies. Four patients (13%) had previously had brain metastases, and a total of 6 patients had received prior radiation therapy: 4 to the brain, 1 to the left pelvis, and 1 to the chest.

TABLE 1
Patient Characteristics

Characteristic	No.	%
No. of patients	32	
Gender		
Male	16	50
Female	16	50
Age, yrs		
Median	67	
Range	45–83	
PS		
0–1	25	78
2	7	22
Stage		
IV	22	69
IIIB	5	16
Recurrent	5	16
Histology		
Adenocarcinoma	20	63
Squamous carcinoma	3	9
Large cell carcinoma	3	9
NOS/other	6	19

PS: Cancer and Leukemia Group B performance status; NOS: not otherwise specified.

Toxicity

A total of 148 cycles were administered, with a median of 4 cycles per patient. The incidence and severity of myelosuppression for all cycles are shown in Table 2. A total of 12 patients (38%) experienced at least 1 episode of Grade 3 (13%) or Grade 4 (25%) neutropenia. Most of these episodes were observed in later cycles, with only 4 episodes seen in the first cycle. Febrile neutropenia was observed in only 3 patients (9%), 1 in the first cycle and 2 in the second cycle.

TABLE 2
Hematologic Toxicity (All Cycles)

	Toxicity scale grading		
Event	2	3	4
Neutropenia	5 (16%)	4 (13%)	8 (25%)
Febrile neutropenia		3 (9%)[a]	
Anemia	13 (41%)	0	0
Thrombocytopenia	4 (13%)	1 (3%)	1 (3%)

[a] One patient died of neutropenic sepsis.

TABLE 3
Nonhematologic Toxicity (All Cycles)

	Toxicity scale grading		
Event	2	3	4
Nausea/emesis	0	2 (6%)	0
Constipation	2 (6%)	1 (3%)	0
Peripheral neuropathy	2 (6%)	0	0
Phlebitis	2 (6%)	0	0
Skin rash	2 (6%)	0	0
Fatigue	3 (9%)	3 (9%)	0
Alopecia	6 (19%)	0	0

There was one treatment-related death due to neutropenic sepsis, which occurred after the administration of the second dose during the first cycle. The patient was an 83 year old female who presented with fever, hypotension, and positive blood cultures, and died within 48 hours of hospital admission, despite administration of broad spectrum antibiotics and filgrastim. As illustrated in Table 2, the frequency and severity of anemia and thrombocytopenia were very modest; there was only one episode of Grade 4 thrombocytopenia. Dose reductions according to protocol guidelines were necessary for 8 patients (25%) due to hematologic toxicity, and for 3 of these patients the dose was reduced more than once.

Nonhematologic toxicities were generally mild (Table 3). Three patients (9%) experienced Grade 3 nausea and emesis, although no Grade 2 toxicity was observed. Mild constipation was recorded for 6 patients (19%) and for 1 patient it was severe. There was no incidence of Grade 3 or 4 peripheral neuropathy, but 2 patients required dose reduction of vinorelbine due to Grade 2 neuropathy. The symptoms resolved in all instances. Two patients developed phlebitis at the site of injection, which resolved with conservative measures. Two patients developed a skin rash, which subsided without a change in the dose of gemcitabine. It is noteworthy that alopecia was almost never observed before at least four cycles of treatment and was always partial. Total alopecia was not observed. Moderate-to-severe fatigue was observed in 6 patients (19%) and was usually cumulative.

TABLE 4
Response Rate

	No.	%
Complete response	0	
Partial response	8	25[a]
Stable disease	17	53
Progressive disease	3	9
Early death	2	6
Unevaluable[b]	2	6

[a] 95% confidence interval: 11.5–43.4%.

[b] One patient was lost to follow-up after 2 cycles and 1 patient discontinued protocol treatment in favor of alternative therapy.

Response and Survival

All 32 eligible patients were included in an intention-to-treat analysis (Table 4). There were 8 partial responses, for an overall response rate of 25% (95% confidence interval [CI], 11.5–43.4%). Two patients died before a formal response assessment was made (1 patient of neutropenic sepsis and 1 patient of rapidly declining performance status after a cardiac event), 1 patient was lost to follow-up after 2 treatment cycles and died 4 months after study entry, and a fourth patient discontinued protocol treatment in favor of alternative treatment after 1 cycle of chemotherapy. He was still alive 14 months after protocol entry. Two patients who responded were treated with gemcitabine 1000 mg/m^2 and the other 6 patients at 1250 mg/m^2. All responses were observed after the initial two cycles of therapy, but a few patients demonstrated continued tumor shrinkage with subsequent cycles.

The median follow-up duration was 13 months (range, 12–22 months). The median survival for all eligible patients was 8.3 months and the 1-year survival 38% (95% CI, 24–59%) (Fig 1). The failure free survival for all patients was 4.4 months (95% CI, 3.4–5.6 months). The median survival for patients with a performance status of 2 was 3.9 months, whereas the median survival for patients with a performance status of 0–1 was 11.7 months ($P = 0.0008$). There was no difference in survival between males and females or between patients with Stage IV or recurrent disease and those with Stage III disease.

DISCUSSION

Several new chemotherapeutic agents have been introduced into clinical practice in the last few years,

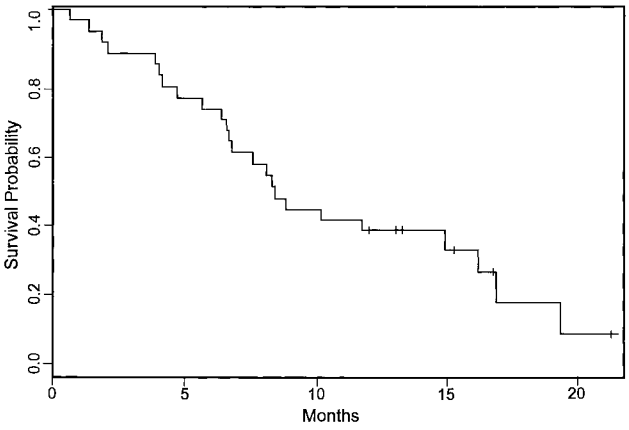

FIGURE 1. The overall survival curve is shown for the patients in this study.

and most have been utilized in the treatment of advanced NSCLC patients. Among these agents, vinorelbine and gemcitabine have generated a great deal of interest. They each demonstrated reproducible single-agent activity and were associated with promising median and 1-year survival rates when tested in several Phase II trials. More importantly, both vinorelbine and gemcitabine, when used in combination with cisplatin, have produced improved survival rates compared with more traditional regimens in large Phase III randomized trials. In a multicenter European trial, LeChevalier et al.[5] reported improved survival for patients treated with cisplatin and vinorelbine compared with cisplatin and vinblastine or vinorelbine alone. In the U.S., Wozniak et al. reported for the Southwest Oncology Group a trial of cisplatin and vinorelbine versus cisplatin alone, and demonstrated improved survival for patients treated with the combination.[6] More recently, Sandler et al. randomized patients to cisplatin and gemcitabine versus cisplatin alone and demonstrated an improved median survival for patients who received the combination.[7] These trials led to the independent approval of vinorelbine and gemcitabine for use in the treatment of patients with advanced NSCLC.

However, in contrast to the relatively benign and well-tolerated toxicities of each of these agents when used alone, their use in combination with cisplatin is usually associated with more pronounced toxicity. For example, the incidence of Grade 3/4 neutropenia in the U.S. study of cisplatin and vinorelbine was 81%.[6] Likewise, cisplatin and gemcitabine have a much higher incidence of hematologic toxicity than gemcitabine alone, with approximately 50% of patients experiencing Grade 3/4 thrombocytopenia.[7] Further, the nonhematologic toxicities associated with cisplatin can also be severe. Attempts to combine vinorelbine or gemcitabine with carboplatin[9,10] have been hampered by significant neutropenia and/or thrombocytopenia, which in some of the piloted regimens required growth factor support.

The schedule and doses chosen for our Phase II study were based on one of a few Phase I trials available at the time our protocol was initiated.[11–14] The French schedule used escalating doses of gemcitabine and vinorelbine given on Days 1 and 8 every 21 days[11] in an attempt to avoid the hematologic nadirs expected to occur on Day 15 of the treatment cycle. Indeed, hematologic toxicity in this schedule was minimal and the doses chosen for our trial were based on their escalation chart. Other Phase I combinations of gemcitabine and vinorelbine administered both drugs on Days 1, 8, and 15 every 28 days.[12–14] In the San Antonio trial, both neutropenia and thrombocytopenia were prohibitive in the first six patients and the schedule was subsequently modified to a biweekly schedule with less toxicity.[12] In two other trials using the Days 1, 8, and 15 schedule, dose escalation was possible, but hematologic toxicity seemed more pronounced. These schedules have yet to be formally tested in Phase II trials of advanced NSCLC.

Our objective response rate of 25% fell within the expected range in comparison with other new platinum-based regimens tested in Phase II trials of advanced NSCLC. Johnson et al. reported a 27% response rate in a Phase II trial of carbolatin and paclitaxel (given over 24 hours) in 51 patients with advanced NSCLC.[15] These results are in general agreement with several other Phase II trials of this combination.[16] Treat et al. reported on the combination of cisplatin and tirapazamine in 44 patients with advanced NSCLC and observed a response rate of 23%.[17] Furthermore, our response rate is also comparable to cisplatin plus vinorelbine and cisplatin plus gemcitabine, as described in the Phase III trials above, although comparisons between pilot Phase II trials and multicenter randomized trials need to be interpreted cautiously. However, and more importantly, the median survial time (MST) of 8.3 months and the 1-year survival rate of 38% in our trial are at least comparable to other established regimens and are very encouraging in the context of advanced NSCLC. This is particularly true for patients with performance stages 0–1, who had a 48% 1-year survival rate.

The toxicity of this regimen was modest and easily managed, particularly when examined in the context of a patient population that included a large percentage of elderly patients (44% were age 70 years or older), as well as patients with brain metastases (13%), and patients with performance status of 2 (22%). These patients do not usually tolerate platinum-based regimens well and are at a greater risk for severe

complications. In our trial, with the exception of one treatment-related fatality, which was fulminant and unpredictable, the toxicities described seem to be truly representative of what can be expected in an older, unselected, community-based population. This observation has important implications for the choice of a chemotherapy regimen in elderly patients. The ELVIS ("Elderly Lung Cancer Vinorelbine Italian Study") trial compared vinorelbine as a single agent versus best supportive care and reported improved survival and quality of life for patients treated with vinorelbine.[18] A subsequent study comparing vinorelbine alone, gemcitabine alone, and the combination of gemcitabine and vinorelbine is currently in progress, and the results will help determine the best management strategy for this group of patients.

A trial by Lorusso et al., reported in preliminary form, also tested the combination of gemcitabine and vinorelbine in the treatment of patients with advanced NSCLC.[19] The investigators used the same schedule and similar doses used in our trial. Fifty-two patients with Stage IIIB and IV NSCLC (28 and 24 patients, respectively) received gemcitabine at 1200 mg/m^2 and vinorelbine at 30 mg/m^2 on Days 1 and 8 every 21 days. The response rate was 36% and the median survival time 9.0 months. A clinical benefit response (improvement in performance status, weight gain, and pain reduction) was observed in 56% of patients. Although the higher number of Stage IIIB patients probably accounts for the difference in response rate compared with our trial, the fact that these two nearly identical studies achieved similar survival results confirm the feasibility and viability of this new regimen in the treatment of advanced NSCLC patients.

In conclusion, the combination of gemcitabine and vinorelbine is an active and well tolerated regimen for patients with advanced NSCLC. Studies comparing this combination with more standard combinations and other new regimens are ongoing. Until results of randomized trials are available, we have demonstrated that gemcitabine and vinorelbine can be safely used in the treatment of patients with advanced NSCLC and may be particuarly suitable for patients who cannot tolerate more toxic platinum-based regimens.

REFERENCES

1. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1998. *CA Cancer J Clin* 1998;48:6–48.
2. Ihde DC. Chemotherapy of lung cancer. *N Engl J Med* 1992; 327:1434–41.
3. 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 randomized clinical trials. *Br J Med* 1995;311:899–909.
4. Ramanathan RK, Belani CP. Chemotherapy for advanced non-small cell lung cancer: past, present, and future. *Semin Oncol* 1997;24:440–54.
5. LeChevalier T, Brisgand D, Douillard J-Y, Alberola V, Monnier A, Riviere 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;12:360–7.
6. Wozniak AJ, Crowley JJ, Balcerzak SP, Weiss GR, Laufman LR, Baker LH, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small cell lung cancer: a SouthWest Oncology Group study. – 1998;16:2459–65.
7. Sandler A, Nemunaitis J, Dehnam C, Cormier Y, von Pawel J, Niyikiza C, et al. Phase III study of cisplatin with or without gemcitabine in patients with advanced non-small cell lung cancer [abstract 1747]. *Proc Am Soc Clin Oncol* 1998;17:454a.
8. Rosell R, Tonato M, Sandler A. The activity of gemcitabine plus cisplatin in randomized trials in untreated patients with advanced non-small cell lung cancer. *Semin Oncol* 1998;25(Suppl 9):27–34.
9. Garst J, Crawford J, O'Rourke M, Herndon J, Traxler L, Burman S, et al. Vinorelbine and carboplatin for the treatment of patients with advanced non-small cell lung cancer: a phase II response, toxicity, and survival study [abstract 1223]. *Proc Am Soc Clin Oncol* 1996;15:404.
10. Ng EW, Sandler AB, Einhorn LH. A Phase II study of carboplatin plus gemcitabine in non-small cell lung cancer [abstract 1801]. *Proc Am Soc Clin Oncol* 1998;17:468a.
11. Rodier JM, Chouaki N, Schlumberger M, Ducreux M, Ruffie P, Rongier AM, et al. Gemcitabine and vinorelbine in solid tumors: preliminary results of a phase I study [abstract 881]. *Proc Am Soc Clin Oncol* 1997;16:249a.
12. Stephenson J, Aylesworth C, Johnson T, Atkins M, Rinaldi D, Burris H, et al. A phase I study of gemcitabine plus vinorelbine on an every other week schedule [abstract 970]. *Proc Am Soc Clin Oncol* 1998;17:253a.
13. Krajnik G, Mohn-Staudner A, Marhold F, Malayeri R, Zochbauer, Kummer F, et al. Vinorelbine/gemcitabine in advanced non-small cell lung cancer: a phase I trial [abstract 722]. *Proc Am Soc Clin Oncol* 1997;16:206a.
14. Herbst R, Dang N, Lynch C, Teicher B, Strauss G, Elias A, et al. Phase I study of combination weekly gemcitabine and vinorelbine in patients with lung cancer [abstract 1877]. *Proc Am Soc Clin Oncol* 1998;17:488a.
15. Johnson DH, Paul DM, Hande KR, DeVore RF. Paclitaxel and carboplatin in advanced non-small cell lung cancer: a phase II trial. *J Clin Oncol* 1996;14:2054–60.
16. Bunn PA. Defining the role of paclitaxel in lung cancer: summary of recent studies and implications for future directions. *Semin Oncol* 1997;24(Suppl 12):153–62.
17. Treat J, Johnson E, Langer C, Belani C, Haynes B, Greenberg R, et al. Tirapazamine with cisplatin in patients with advanced non-small cell lung cancer: a phase II study. *J Clin Oncol* 1998;16:3524–7.
18. The Elderly Lung Cancer Vinorelbine Italian Study Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small cell lung cancer. *J Natl Cancer Inst* 1999; 91:66–72.
19. Lorusso V, Mancarella S, Carpagnano F, Di Rienzo G, Cisternino L, Napoli G, et al. Gemcitabine plus vinorelbine in patients with stage IIIB–IV NSCLC: a phase II study [abstract 1808]. *Proc Am Soc Clin Oncol* 1998;17:470a.