Weekly Docetaxel with Either Gemcitabine or Vinorelbine as Second-Line Treatment in Patients with Advanced Nonsmall Cell Lung Carcinoma

Phase II Trials of the Minnie Pearl Cancer Research Network

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BACKGROUND. The current study was conducted to evaluate the feasibility, toxicity, and efficacy of weekly docetaxel when paired with either gemcitabine or vinorelbine as the second-line treatment of patients with advanced nonsmall cell lung carcinoma.

METHODS. Patients with progressive nonsmall cell lung carcinoma after one previous chemotherapeutic regimen, an Eastern Cooperative Oncology Group performance status of 0–2, and measurable lesions were eligible for treatment in these Phase II trials. Patients who had not received gemcitabine previously were treated with docetaxel, 30 mg/m^2, and gemcitabine, 800 mg/m^2, both of which were administered intravenously (i.v.) on Days 1, 8, and 15 of a 28-day cycle. If the patients had received gemcitabine as part of first-line therapy, they were treated with docetaxel, 30 mg/m^2, and vinorelbine, 20 mg/m^2 i.v., on Days 1, 8, and 15 of a 28-day cycle. Patients were reevaluated after two courses of treatment, and responding patients continued treatment for six courses or until disease progression.

RESULTS. Forty patients were treated with a combination of docetaxel and gemcitabine, and 23 patients received docetaxel and vinorelbine. The docetaxel/gemcitabine combination was reasonably well tolerated, with moderate myelosuppression and a few nonhematologic toxicities reported. The objective response rate was 10%, with a 1-year survival rate of 20%. The docetaxel/vinorelbine combination was found to be poorly tolerated, with Grade 3/4 leukopenia reported in 71% of patients and neutropenic fever reported in 70% of patients despite frequent dose reductions and omission of the Day 15 doses. Enrollment onto this regimen was stopped prematurely due to toxicity, and after no major responses were observed in the first 20 evaluable patients.

CONCLUSIONS. The combination of weekly docetaxel/gemcitabine appears to be feasible and relatively well tolerated as second-line treatment in patients with advanced nonsmall cell lung carcinoma, whereas a weekly combination of docetaxel and vinorelbine did not appear to be tolerable at the doses and schedule used in the current study. Neither regimen showed a level of activity that suggested any advantage compared with the results obtained with single-agent docetaxel in this setting. ***Cancer* 2001;92:2391–8.** *© 2001 American Cancer Society.*

KEYWORDS: docetaxel, gemcitabine, vinorelbine, second-line treatment, nonsmall cell lung carcinoma, Phase II trial.

The recent introduction of several new antineoplastic agents has improved first-line therapy for patients with advanced nonsmall cell lung carcinoma. A number of different regimens containing one or more new agents, usually in combination with a platinum agent,

have improved response rates and survival when compared with previous cisplatin-based combination regimens.[1–4] In addition, the decreased toxicity associated with the use of the new regimens has resulted in their applicability to a broader spectrum of lung carcinoma patients.

With the increased efficacy and favorable toxicity profile of first-line regimens, a larger number of patients with advanced nonsmall cell lung carcinoma remain with a relatively good performance status, and subsequently are candidates for second-line treatment. To our knowledge, until recently, traditional antineoplastic agents lacked efficacy in patients who previously had received cisplatin-based regimens. However, docetaxel and gemcitabine both showed activity as second-line agents in early Phase II trials.[5,6] Docetaxel now has been studied extensively in the second-line treatment of patients with nonsmall cell lung carcinoma. In two large randomized trials, docetaxel produced survival advantages compared with either best supportive care or treatment with vinorelbine or ifosfamide.[7,8]

The use of docetaxel in a weekly schedule appears to minimize myelosuppression and has been associated with mild to moderate nonhematologic toxicity.[9] This schedule of administration has shown excellent activity in patients with breast carcinoma, prostate carcinoma, and nonsmall cell lung carcinoma.[10–13] In a group of 39 elderly patients with advanced nonsmall cell lung carcinoma, we demonstrated a 19% response rate and a 1-year survival rate of 28% with weekly docetaxel (36 mg/m^2/week).[13] In the Phase II trial reported in the current study, we evaluated a combination of weekly docetaxel with weekly gemcitabine as the second-line therapy for patients with nonsmall cell lung carcinoma. For those patients who already had received gemcitabine as first-line therapy, we substituted weekly vinorelbine for gemcitabine and evaluated the docetaxel/vinorelbine combination. In the current study, we describe the results of these Phase II trials.

MATERIALS AND METHODS

Between December 1998 and January 2000, a total of 64 patients were enrolled in this Phase II trial and received a combination of either docetaxel and gemcitabine or docetaxel and vinorelbine. This trial was conducted in the Minnie Pearl Cancer Research Network, a multicenter, community-based collaborative group. All patients were required to have biopsy-proven nonsmall cell lung carcinoma that was either metastatic or locally progressive after treatment with one previous chemotherapy regimen. Previous taxane therapy was acceptable, provided a weekly schedule had not been employed. Patients were permitted to have received $\leq$ 2 previous courses of radiation therapy, with $<$ 25% of total bone marrow-bearing bone encompassed by the radiation fields. Patients with central nervous system involvement (brain or meninges) at the time of disease recurrence or progression were ineligible. The single exception to this was a patient who previously had been treated for brain metastases with radiation therapy or surgical excision and who had no residual neurologic symptoms or evidence of residual metastases detected on computed tomography (CT) or magnetic resonance imaging scan at the time of systemic tumor recurrence. Additional eligibility criteria included measurable or evaluable disease; Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; a leukocyte count $\geq$ 3000/μL; a platelet count $\geq$ 100,000/μL; bilirubin $\leq$ 1.5mg/dL; and serum creatinine $\leq$ 1.5 mg/dL. Written informed consent was required from all patients prior to enrollment in the trial. This clinical trial was approved by the Institutional Review Board at Centennial Medical Center, as well as the review boards at all participating network sites.

Prior to the initiation of therapy, all patients underwent routine laboratory evaluation, chest radiography, and CT scan of the head, chest, and abdomen. Additional radiologic evaluation was performed if clinically indicated. Unidimensional or bidimensional measurements were recorded for all patients.

All patients entering this Phase II trial received weekly docetaxel/gemcitabine unless they previously had received gemcitabine as part of their first-line therapy. Patients who previously had received gemcitabine were treated with the docetaxel/vinorelbine combination. All patients received docetaxel, 30 mg/m^2, by 30-minute to 60-minute intravenous (i.v.) infusion on Days 1, 8, and 15 of each 28-day cycle. Gemcitabine, 800 mg/m^2, was administered i.v. over 30 minutes on Days 1, 8, and 15, immediately preceding the docetaxel infusion. If patients had received previous gemcitabine, vinorelbine (20 mg/m^2 i.v.) was administered on Days 1, 8, and 15, immediately preceding docetaxel. Premedications for docetaxel included dexamethasone, 8 mg, administered orally on the evening before treatment, again at the time of treatment, and 12 hours after treatment with docetaxel.

Complete blood counts were measured prior to each dose of treatment, and dose modifications were made on the basis of myelosuppression. The prescribed dose modifications were identical for both regimens. If the leukocyte count was $>$ 3000/μL and the platelet count was $>$ 100,000/μL, full doses of both

agents were administered. If the leukocyte count was 2000–3000/μL or the platelet count was 75,000–100,000/μL, a 75% dose of either gemcitabine or vinorelbine was administered with a full dose of docetaxel. If the leukocyte count was $<$ 2000/μL or the platelet count was $<$ 75,000/μL, both drugs were omitted and the patient was reevaluated on the day of the next scheduled treatment. Treatment was resumed when blood counts rose to a leukocyte count of $>$ 3000/μL and a platelet count of $>$ 100,000/μL. When a treatment dose was omitted, the length of the treatment cycle was not extended to "make up" the dose; rather, the courses of treatment remained at 28 days and the dose simply was omitted. Patients who required hospitalization for the treatment of neutropenia and fever received 75% doses of gemcitabine or vinorelbine during subsequent cycles but continued to receive full doses of weekly docetaxel. The use of cytokines after episodes of neutropenia was left to the discretion of the treating physician; however, the use of cytokines could not substitute for the prescribed dose reductions. Patients developing NCI Common Toxicity Criteria Grade 3 or 4 nonhematologic toxicity (other than nausea, emesis, or alopecia) had treatment withheld until the toxicity reversed to $\leq$ Grade 2; treatment then was resumed using 75% doses of the offending agent(s).

Patients were evaluated for response after 2 courses of treatment (8 weeks). All abnormal pretreatment radiologic studies were repeated. Patients with stable disease or an objective response continued therapy, and treatment was discontinued if patients exhibited progressive disease. A maximum of 6 courses of treatment (6 months) was recommended for patients with continued response or stable disease; however, patients with a good response who tolerated therapy well could have the treatment duration extended at the discretion of the treating physician.

Response categories were assigned using standard definitions. A complete response required the disappearance of all clinical and radiologic evidence of tumor for a minimum of 4 weeks. A partial response required a $\geq$ 50% decrease in tumor size (sum of the products of the measured lesions) for at least 4 weeks with no new lesions appearing and with nonmeasurable lesions remaining stable or regressing. Stable disease was defined as a response that was less than a partial response (i.e., a $<$ 50% decrease in the sum of products of the measured lesions) or progression that was less than that defined as progressive disease. Progressive disease was defined as an increase of at least 25% in the product of measured lesions or the appearance of new lesions.

This Phase II trial initially was intended to accrue 80 evaluable patients, with the expectation that approximately 40 patients would receive the docetaxel/gemcitabine combination and 40 patients would receive the docetaxel/vinorelbine combination. With each regimen, the toxicity and efficacy was evaluated briefly after 20 patients were treated. At this time, a decision was made to continue to the planned patient accrual target if at least two patients had achieved objective responses.

All patients who received at least two courses of therapy were considered to be evaluable for response. In addition, patients experiencing a rapid decline due to disease progression prior to the completion of two courses were considered to be nonresponders. The duration of response was calculated from the day of the first documentation of response to the date of documented disease progression. Time to progression was calculated from the first day of treatment to the date of documented disease progression. Survival was calculated from the first day of treatment until the date of death. All patients were included in the survival analyses. Survival curves were calculated according the method of Kaplan and Meier.[14] All patients who received one dose of treatment were included in the toxicity analysis.

A total of 64 patients were entered this trial, and the characteristics of the 63 eligible patients are summarized in Table 1. One patient who received the docetaxel/vinorelbine combination later was found to be ineligible because no previous treatment had been administered, and this patient was excluded from further analyses. Of the remaining 63 patients, 40 were treated with weekly docetaxel/gemcitabine and 23 patients received weekly docetaxel/vinorelbine. Full accrual to the docetaxel/vinorelbine arm was not completed, based on efficacy and toxicity analysis of the first 17 evaluable patients. The majority of patients (81%) had a good ECOG performance status (0 or 1). Twenty-seven patients (43%) had received previous chemotherapy alone, whereas 36 patients (57%) had received combined modality therapy (chemotherapy/radiotherapy) as their initial treatment. Overall, 51 patients (81%) had received previous chemotherapy with both a platinum agent and a taxane. Thirty-five of 63 patients (56%) entered this trial within 6 months of completing their previous therapy. Twenty-five of 48 evaluable patients (52%) had achieved an objective response to first-line treatment, whereas 23 patients (48%) had not responded to previous therapy.

RESULTS

Docetaxel/Gemcitabine

Thirty-one of 40 patients (78%) received at least 2 courses of therapy with weekly docetaxel and gemcit-

TABLE 1
Patient Characteristics

Characteristic	No. of patients (%)	
	Docetaxel/ gemcitabine (n = 40)	Docetaxel/ vinorelbine (n = 23)
Median age (yrs) (range)	60 (41–78)	62 (32–80)
Gender		
Male/female	29/11	17/6
ECOG performance status		
0	8 (20%)	6 (26%)
1	27 (68%)	10 (43%)
2	5 (12%)	7 (31%)
Previous therapy		
Chemotherapy alone	22 (55%)	5 (22%)
Paclitaxel/carboplatin	18	3
Paclitaxel/carboplatin/vinorelbine	2	0
Other (1 each)	2	2
Chemotherapy plus radiation therapy	18 (45%)	18 (78%)
Paclitaxel/carboplatin	10	12
Paclitaxel/carboplatin/vinorelbine	2	0
Paclitaxel/carboplatin/gemcitabine	0	2
Carboplatin/etoposide	2	0
Other (1 each)	4	4
Best response to previous therapy		
Complete response	6 (15%)	5 (22%)
Partial response	14 (35%)	5 (22%)
No response	20 (50%)	13 (66%)
Interval since previous therapy (mos)		
< 6	21 (53%)	14 (61%)
≥ 6	19 (47%)	9 (39%)
Site of treatment		
Sarah Cannon Cancer Center	23 (58%)	14 (61%)
Network sites	17 (42%)	9 (39%)

ECOG: Eastern Cooperative Oncology Group.

abine and were evaluated for response. Three additional patients did not complete two courses of treatment due to rapid tumor progression; these patients were removed from study and were considered to be nonresponders. The remaining six patients withdrew from treatment because of intercurrent illness (four patients) and unacceptable toxicity (two patients).

The median number of courses of docetaxel/gemcitabine was two (range, one to six courses). The majority of patients who did not complete the planned 6 courses of treatment were removed from the study due to progressive disease (67%). Patients with stable disease or those who had achieved an objective response at the time of first reevaluation received a median of four courses (range, two to six courses). Of the 31 patients who completed the first 2 courses, 18 patients (58%) received 100% of the planned treatment doses. For these 31 patients, the percent of planned drug administered during the first 2 courses was as follows: docetaxel, 84% and gemcitabine, 75%. The Day 15 dose of chemotherapy was omitted most frequently; 48% of patients received the planned docetaxel dose on Day 15, and 29% of patients received the planned gemcitabine dose.

Efficacy

Three of 31 evaluable patients (10%) achieved a partial response to treatment with weekly docetaxel and gemcitabine. Two of the three objective responses occurred in patients who had not responded to previous treatment. Fifteen additional patients (48%) achieved either a minor response or stable disease at the time of first reevaluation. The median duration of the response was 5 months (range, 3–6 months). Patients with stable disease or a minor response had a median time to disease progression of 6 months (range, 1–22+ months).

The actuarial survival for the 40 patients who received the docetaxel/gemcitabine combination is shown in Figure 1. The median survival for the entire group of patients was 6 months, with an actual 1-year survival rate of 20%.

Toxicity

The toxicity of the weekly docetaxel/gemcitabine regimen is summarized in Table 2. In general, the regimen was well tolerated with myelosuppression being the most common treatment-related toxicity. Grade 3/4 leukopenia and thrombocytopenia each were observed in 15% and 13% of patients, respectively. There were three hospitalizations for the treatment of neutropenia and fever, and no patient required a platelet transfusion. Cytokines (granulocyte–colony-stimulating factor [G-CSF] or granulocyte-macrophage–colony-stimulating factor [GM-CSF]) were administered to 18 patients (45%) at some point during therapy at the discretion of the treating physician. There were no treatment-related deaths reported.

The most common Grade 3/4 nonhematologic toxicity was fatigue, which occurred in 13 patients (33%). Other severe nonhematologic toxicities were uncommon (Table 2).

Docetaxel/Vinorelbine

Twenty-three patients were treated with the docetaxel/vinorelbine combination; 17 patients (74%) received at least 2 courses of weekly docetaxel/vinorelbine and were evaluated for response. Three patients were unable to complete two courses due to rapid tumor progression and were categorized as nonresponders. Three additional patients were removed from treatment early because of treatment-related

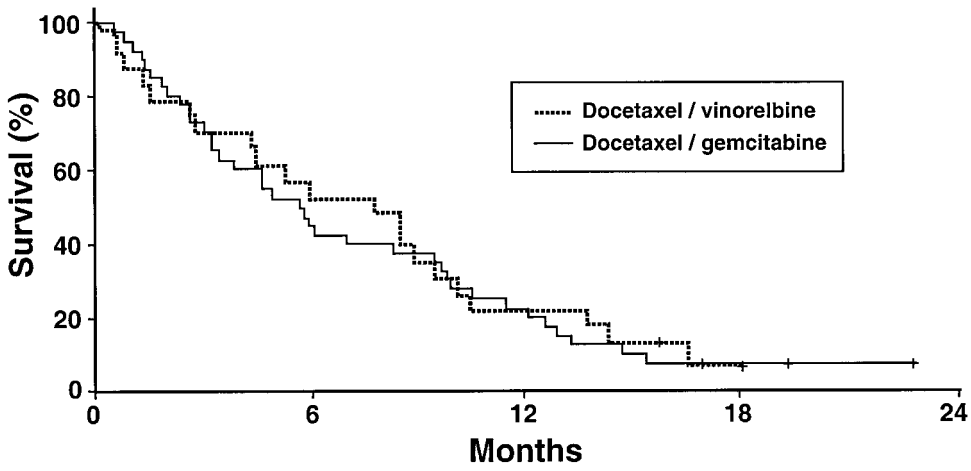

FIGURE 1. Actuarial survival curves for patients treated with weekly docetaxel/gemcitabine and docetaxel/vinorelbine. The median survivals (6 months and 8 months, respectively) and 1-year survivals (20% and 22%, respectively) were similar for the 2 groups.

TABLE 2
Weekly Docetaxel/Gemcitabine: Treatment-Related Grade 3/4 Toxicity (40 Patients/116 Courses)

	No. of patients (%)		No. of courses (%)	
Toxicity	**Grade 3**	**4**	**3**	**4**
Hematologic				
Leukopenia	6 (15%)	0	6 (5%)	0
Thrombocytopenia	5 (13%)	0	8 (7%)	0
			No. of patients (%)	
Myelosuppression-related complications				
Neutropenia/fever			3 (8%)	
Bleeding			0	
Platelet transfusion			0	
RBC transfusion			5 (13%)	
Cytokines used			18 (45%)	
Treatment-related death			0	
Nonhematologic				
Fatigue			13 (33%)	
Nausea/emesis			4 (10%)	
Skin toxicity (rash)			2 (5%)	
Peripheral edema			1 (3%)	
Peripheral neuropathy			1 (3%)	
Diarrhea			1 (3%)	
Thrombophlebitis			1 (3%)	

RBC: red blood cells.

death (sepsis) (one patient) and intercurrent illness (two patients).

During the first 2 courses, the percentage of planned drug administered was as follows: docetaxel, 75% and vinorelbine, 69%. The percentage of planned treatment dose administered on each of the 3 treatment days was as follows: Day 1, 94%; Day 8, 76%; and Day 15, 18%.

Efficacy

There were no objective responses noted in the 20 evaluable patients in the current trial. Eight patients (40%) had achieved stable disease at the time of the first reevaluation. The median time to disease progression for the 8 patients with stable disease was 5 months (range, 1–8 months). The median survival for the entire group was 8 months, with an actual 1-year survival rate of 22%. There was no significant difference in the survival of the patients treated with the docetaxel/gemcitabine combination compared with those treated with the docetaxel/vinorelbine combination (Fig. 1).

Toxicity

Neutropenia was the most common Grade 3/4 treatment-related toxicity reported with the weekly docetaxel/vinorelbine regimen, occurring in 17 of 23 patients (74%) (Table 3). Severe thrombocytopenia was not reported to occur in any patient, and only 2 patients (9%) developed anemia that required a red blood cell transfusion. Sixteen patients (70%) required hospitalization for the treatment of neutropenia and fever, and there was 1 apparent treatment-related death due to neutropenia and sepsis.

Severe nonhematologic toxicity was uncommon with the weekly docetaxel/vinorelbine regimen (Table 3).

Because of the high rate of severe myelosuppression and the inability to administer the planned doses, coupled with the lack of major responses observed in the first 23 patients treated, accrual to the docetaxel/vinorelbine treatment arm was discontinued.

DISCUSSION

Until recently, patients with progressive nonsmall cell lung carcinoma after first-line chemotherapy were not considered to be candidates for further treatment, due

TABLE 3
Weekly Docetaxel/Vinorelbine: Treatment-Related Grade 3/4 Toxicity (23 Patients/55 Courses)

	No. of patients (%)		No. of courses (%)	
Toxicity	**Grade 3**	**4**	**3**	**4**
Hematologic				
Leukopenia	13 (57%)	4 (17%)	25 (45%)	5 (9%)
Thrombocytopenia	0	0	0	0

	No. of patients (%)
Myelosuppression-related complications	
Neutropenia/fever	16 (70%)
Bleeding	0
Platelet transfusion	0
RBC transfusion	2 (9%)
Cytokines used	13 (57%)
Treatment-related death	1 (4%)
Nonhematologic	
Fatigue	1 (4%)
Nausea/emesis	1 (4%)
Peripheral neuropathy	1 (4%)
Dysphagia	1 (4%)

RBC: red blood cell.

to the lack of demonstrated single-agent efficacy in this setting. In addition, patients often were poor candidates for such treatment because of their poor performance status and the toxicity of the previous chemotherapy. Recently, docetaxel has proven efficacious in the second-line treatment of nonsmall cell lung carcinoma, and currently is considered to be the standard treatment in this group of patients. In a large randomized trial, docetaxel (75 mg/m^2, administered every 3 weeks) was proven to be superior to treatment with either vinorelbine or ifosfamide in patients who had received 1 previous chemotherapy regimen for advanced nonsmall cell lung carcinoma.[8] In this randomized trial, the 1-year survival rate for patients receiving docetaxel (75 mg/m^2) was 32%, versus 19% for those patients receiving other treatments. In a second randomized trial, single-agent docetaxel proved superior to best supportive care as second-line therapy.[7] In this second trial, treatment with docetaxel produced a 1-year survival rate of 37% in a group of 55 patients who previously had received cisplatin-based regimens without previous taxane therapy. More recently, docetaxel administered on a weekly schedule to patients with previously treated advanced nonsmall cell lung carcinoma also demonstrated substantial activity.[15–17] Although to our knowledge reported trials are relatively small, response rates have been reported to range from 12–27% using weekly docetaxel doses ranging from 35–43 mg/m^2. These results, taken together with other weekly data regarding docetaxel, suggest that weekly docetaxel therapy has efficacy similar to the more myelosuppressive, every-3-week dosing schedules.

In the current Phase II trials, we attempted to improve the efficacy of single-agent docetaxel in the second-line treatment of patients with advanced nonsmall cell lung carcinoma by adding weekly agents–gemcitabine and vinorelbine. Both these agents are active in the first-line treatment of nonsmall cell lung carcinoma, and gemcitabine also has demonstrated variable levels of second-line activity.[6,18–21] At the time we designed these Phase II trials, information regarding the efficacy of vinorelbine in the second-line setting was not available; since that time, results from clinical trials suggest a low level of single-agent activity and no survival benefit for vinorelbine in the second-line setting.[8] In the current trials, we lowered the weekly dose of docetaxel to 30 mg/m^2 to include treatment with the second agent. The large majority of patients treated in these trials previously had received both paclitaxel and platinum as components of first-line therapy.

The combination of docetaxel and gemcitabine proved feasible in this patient population. Myelosuppression was moderate, although reduction or omission of the Day 15 dose (particularly gemcitabine) was relatively frequent and 45% of the patients received cytokines (G-CSF or GM-CSF) at some time during their treatment course. However, the efficacy of this treatment was somewhat disappointing, with only 3 of 31 patients (10%) achieving a major response and an actual 1-year survival rate of 20% reported for the entire treatment group.

The combination of docetaxel and vinorelbine has demonstrated efficacy as first-line treatment of patients with advanced nonsmall cell lung carcinoma. An intensive regimen, using docetaxel (60 mg/m^2) and vinorelbine (45 mg/m^2) every 2 weeks with cytokine support, produced a high response rate (54%) but with substantial toxicity.[22,23] Crawford et al. recently reported the preliminary results of a weekly docetaxel/vinorelbine regimen in previously treated patients with nonsmall cell lung carcinoma; the maximum tolerated doses (without cytokines) were docetaxel, 25 mg/m^2 and vinorelbine, 20 mg/m^2, both administered on Days 1, 8, and 15 of a 28-day cycle.[24] The response rate was not reported; however, the 1-year survival in a group of 36 patients was 39%.

In contrast, the very similar combination of weekly docetaxel/vinorelbine used in the current study was not well tolerated by patients receiving second-line treatment. Toxicity in the first 23 patients treated included a 74% rate of Grade 3/4 leukopenia and 16 of 23 patients required treatment for neutro-

penia and fever. The majority of patients (57%) received cytokines during treatment; in spite of this, the planned Day 15 doses were administered in only 18% of courses. In the 20 evaluable patients, no major responses were observed, although the median survival (8 months) and the 1-year survival rate (22%) were identical to the survival statistics noted with our second-line docetaxel/gemcitabine regimen. However, rather than modifying the regimen by decreasing the doses of docetaxel and vinorelbine further, it was believed that premature closure of this regimen was appropriate.

The results of treatment with these combination regimens do not suggest any improvement in efficacy compared with previous results with single-agent docetaxel. Although comparison of treatment results from nonrandomized trials is difficult for a variety of reasons, the survival results in these trials appeared to be somewhat inferior to previously published single-agent results from large multicenter trials. Therefore, we would not recommend the further development of these combination regimens as second-line therapy for patients with advanced nonsmall cell lung carcinoma. The weekly administration of clinically useful doses of docetaxel and vinorelbine most likely will be difficult in any patient population, and the use of this regimen will almost certainly require the routine administration of cytokines.

At the current time, single-agent docetaxel remains the treatment of choice for the second-line treatment of patients with advanced nonsmall cell lung carcinoma. It appears somewhat unlikely that combination regimens containing currently available agents will result in substantial incremental gains in this clinical setting. In our previous experience in this patient population, the combination of gemcitabine and vinorelbine, although well tolerated, also produced a relatively low response rate of 18% with a 1-year survival rate of 20%.[25] Even in the first-line treatment setting, the precise incremental benefit of combination regimens versus treatment with the newer drugs as single agents is undefined. In a recently reported randomized trial, Gridelli et al. found no significant differences in efficacy when single-agent treatment with vinorelbine or gemcitabine was compared with the vinorelbine/gemcitabine combination in the first-line treatment of elderly patients with nonsmall cell lung carcinoma.[26] Results from randomized trials comparing other single agents (paclitaxel, gemcitabine) with standard platinum-containing, two-drug combinations are pending. Further efforts in the second-line treatment of patients with nonsmall cell lung carcinoma should involve the pairing of docetaxel and other standard agents with novel agents such as the tyrosine kinase inhibitors or anti-angiogenesis agents.

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