Prospective Randomized Trial of Docetaxel Versus Best Supportive Care in Patients With Non–Small-Cell Lung Cancer Previously Treated With Platinum-Based Chemotherapy

By Frances A. Shepherd, Janet Dancey, Rodryg Ramlau, Karin Mattson, Richard Gralla, Mark O'Rourke, Nathan Levitan, Laurent Gressot, Mark Vincent, Ronald Burkes, Susan Coughlin, Yong Kim, and Jocelyne Berille

Purpose: **To evaluate whether treatment with single-agent docetaxel would result in longer survival than would best supportive care in patients with non–small-cell lung cancer who had previously been treated with platinum-based chemotherapy. Secondary end points included assessment of response (docetaxel arm only), toxicity, and quality of life.**

Patients and Methods: **Patients with performance statuses of 0 to 2 and stage IIIB/IV non–small-cell lung cancer with either measurable or evaluable lesions were eligible for entry onto the study if they had undergone one or more platinum-based chemotherapy regimens and if they had adequate hematology and biochemistry parameters. They were excluded if they had symptomatic brain metastases or if they had previously been treated with paclitaxel. Patients were stratified by performance status and best response to cisplatin chemotherapy and were then randomized to treatment with docetaxel 100 mg/m^2 (49 patients) or 75 mg/m^2 (55 patients) or best supportive care. Patients in both arms were assessed every 3 weeks.**

Results: **One hundred four patients (103 of whom were eligible for entry onto the study) were well balanced for prognostic factors. Of 84 patients with measurable lesions, six (7.1%) achieved partial responses (three patients at each dose level). Time to progression was longer for docetaxel patients than for best supportive care patients (10.6 *v* 6.7 weeks, respectively; $P < .001$), as was median survival (7.0 *v* 4.6 months; log-rank test, $P = .047$). The difference was more significant for docetaxel 75 mg/m^2 patients, compared with corresponding best supportive care patients (7.5 *v* 4.6 months; log-rank test, $P = .010$; 1-year survival, 37% *v* 11%; χ^2 test, $P = .003$). Febrile neutropenia occurred in 11 patients treated with docetaxel 100 mg/m^2, three of whom died, and in one patient treated with docetaxel 75 mg/m^2. Grade 3 or 4 nonhematologic toxicity, with the exception of diarrhea, occurred at a similar rate in both the docetaxel and best supportive care groups.**

Conclusion: **Treatment with docetaxel is associated with significant prolongation of survival, and at a dose of 75 mg/m^2, the benefits of docetaxel therapy outweigh the risks.**

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THE RESULTS OF A large meta-analysis of 52 randomized clinical trials showed conclusively that the administration of chemotherapy offers a significant, but modest, survival advantage for all stages of non–small-cell lung cancer (NSCLC).[1] In early-stage disease, postoperative cisplatin-based adjuvant chemotherapy is associated with a hazards ratio of 0.87, which is equivalent to an absolute survival benefit of 5% at 5 years. For patients with more advanced tumors, the hazards ratio for chemotherapy is 0.73, with a 10% absolute improvement in survival at 1 year over supportive care alone. These results are all the more compelling because none of the studies in the meta-analysis used the newer and more active chemotherapy drugs that have become available in the last decade. Currently, randomized trials using the most active regimens for advanced NSCLC have shown consistent overall response rates of approximately 30% to 40% and 1-year survival rates of 35% to 40%.[2] This represents a clear advance over the 10% 1-year survival rate that can be expected with supportive care alone.

As chemotherapy gains wider acceptance for the treatment of earlier stages of NSCLC, particularly in the neoadjuvant setting, the practicing oncologist will be faced with a growing population of high performance status patients who have relapsed after their first-line chemotherapy. The role of second-line chemotherapy after initial treatment with a platinum-based regimen remains largely undefined. Most studies undertaken to date have been small phase II trials; drug dosages and schedules have varied

From the University of Toronto, Toronto, and London Regional Cancer Centre, London, Ontario, Canada; Regional Hospital of Lung Disease and Tuberculosis, Poznan, Poland; Helsinki University, Helsinki, Finland; Alton Ochsner Medical Foundation, New Orleans, LA; Greenville Memorial Medical Center, Greenville, SC; University Hospitals of Cleveland, Cleveland, OH; Veterans Affairs Medical Center, Houston, TX; and Rhône-Poulenc Rorer, Collegeville, PA, and Paris, France.

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Address correspondence to Frances A. Shepherd, MD, Princess Margaret Hospital, 610 University Ave, Ste 5-104, Toronto, Ontario M5G 2M9, Canada; email fshepherd@torhosp.toronto.on.ca.

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considerably, and results have been reported incompletely.[3] In a recent review of second-line chemotherapy for NSCLC, Fossella et al[3] reported disappointing results for the treatment of this patient population. In almost half the studies, no responses were seen, and in most of the others, the overall response rate was less than 15%. Median and 1-year survival rates were seldom reported.

Docetaxel is one of the few agents that have been evaluated extensively in the second-line setting. Seven phase II trials of single-agent docetaxel in platinum-treated patients with NSCLC have been reported.[4-11] A total of 312 patients in these seven studies were treated with docetaxel 100 mg/m^2 every 3 weeks. Overall response rates ranged from 14% to 24%. Median survival was uniformly greater than 7 months, and, when reported, 1-year survival rates ranged from 25%[6] to 44%.[5]

The promising results seen in these phase II studies of single-agent docetaxel led to the initiation of two large randomized trials of this agent for patients previously treated with cisplatin-based combination chemotherapy. We report here the results of one of these studies in which docetaxel treatment was compared with best supportive care (BSC).

PATIENTS AND METHODS

To be eligible for study, all patients must have received prior treatment with a platinum-containing (cisplatin or carboplatin) chemotherapy regimen. They may have received more than one chemotherapy regimen but could not have been treated previously with taxanes, including paclitaxel. All patients were required to have histologic or cytologic proof of unresectable locally advanced or metastatic NSCLC. Because response was only a secondary end point of this study, patients with both measurable and evaluable indicator lesions were eligible. Each patient was required to have a performance status of 2 or lower on the Eastern Cooperation Oncology Group (ECOG) scale, adequate hematologic parameters (WBC count $\geq 3.5 \times 10^9$/L, absolute neutrophil count $\geq 2.0 \times 10^9$/L, platelet count $\geq 100{,}000 \times 10^9$/L), serum creatinine level of 2.0 mg/dL or lower, total bilirubin level less than or equal to the institutional upper limit of normal (ULN), and hepatic enzyme levels of 1.5 times the ULN or lower (with the exception of alkaline phosphatase, which could be up to five times the ULN). Patients were excluded if they had symptomatic or uncontrolled brain metastases or peripheral neuropathy greater than National Cancer Institute grade 2. Patients were still considered eligible if they had received prior radiation therapy, provided that 25% or less of their total bone marrow had been irradiated, but had to wait 30 days before entry onto the study. They were also required to wait 21 days before entry onto the study after being treated with any chemotherapy, immunotherapy, or biologic systemic anticancer therapy (42 days for mitomycin and nitrosoureas). All patients provided signed, written, informed consent.

Investigation and Treatment

Within 7 days of entry onto the study, all patients underwent a complete medical history and physical examination, including a full neurologic examination and documentation of ECOG performance status. Patients also underwent complete hematologic and biochemical testing and had an ECG and baseline chest x-ray performed. Within 3 weeks before the initiation of therapy, clinically indicated scans, including computed tomographic scans of the brain, thorax, and upper abdomen (or abdominal ultrasound) and radionuclide bone scans were performed.

All patients were required to complete quality-of-life (QOL) questionnaires before undergoing therapy. The Lung Cancer Symptom Scale was used in North America, and the European Organization for the Research and Treatment of Cancer quality-of-life questionnaire for lung cancer was used in Europe. Sixteen patients in North America and 25 patients in Europe completed both questionnaires.

Eligible patients were stratified on the basis of their ECOG performance status (0-1 *v* 2) and on their best response to prior platinum-based therapy (progression *v* no change, partial response, or complete response).

Patients randomized to the docetaxel arm were premedicated with oral dexamethasone 8 mg bid for 5 days (10 doses) starting 24 hours before each infusion of docetaxel. In the second half of the study, this regimen was reduced to a total of five doses. Docetaxel 100 mg/m^2 as a 1-hour intravenous infusion was administered every 21 days for the first half of the study. When interim safety-data monitoring identified a significantly higher toxic death rate in the chemotherapy arm of the study, the protocol was amended and the docetaxel dose was reduced to 75 mg/m^2 given intravenously over 1 hour every 3 weeks for the second half of the trial.

For patients who developed grade 4 neutropenia that lasted more than 7 days or that was associated with a temperature of more than 38°C, a 25% permanent dose reduction was required. Patients with grade 4 thrombocytopenia were re-treated with a 25% dose reduction after recovery. The dose was also reduced by 25% for grade 4 vomiting that could not be controlled by antiemetic drugs or for grade 3 or higher diarrhea. Treatment was discontinued in cases of grade 3 neuropathy.

Patients randomized to the BSC arm were treated with whichever therapy was judged to be appropriate by the treating physician. This treatment could have included treatment with antibiotics, analgesic drugs, transfusions, and palliative radiotherapy.

Patients in both arms of the study were evaluated every 3 weeks. At each follow-up visit, they underwent a complete medical history and physical examination, with documentation of weight and ECOG performance status. Vital signs were recorded and toxicities were evaluated. QOL questionnaires were also completed every 3 weeks. A chest x-ray was performed every 3 weeks, and scans were repeated every 6 weeks to document response or disease progression.

In the chemotherapy arm, treatment was continued until disease progression or unacceptable toxicity developed. In the BSC arm, patients continued to be evaluated as described above every 3 weeks for the first 18 weeks and then every 6 weeks.

Objective tumor response and duration of response were assessed only in the docetaxel arm. Standard World Health Organization response criteria were applied, and all responses had to be confirmed in 28 days or more after the initial documentation of response. Survival was calculated from the date of randomization until the date of death. Survival time was censored for loss of contact or initiation of antitumor therapy, including subsequent chemotherapy, immunotherapy, or surgery. Time to disease progression was assessed from the date of randomization until the date of disease progression. Time to disease progression was also censored at the last tumor assessment if there was no documentation of progression. Response duration was calculated from the date of randomization until the date of documentation of disease progression.

Table 1. Baseline Patient Characteristics

Characteristic	Docetaxel						Best Supportive Care	
	Overall		75 mg/m^2		100 mg/m^2			
	No.	%	No.	%	No.	%	No.	%
Total no. of patients	104		55		49		100	
Sex								
Male	72	69.2	35	63.6	37	75.5	65	65.0
Female	32	30.8	20	36.4	12	24.5	35	35.0
Age, years								
Median	61		61		61		61	
Range	37-76		37-73		39-76		28-77	
Stage								
IIIA/B	24	23.1	15	27.3	9	18.4	19	19.0
IV	80	76.9	40	72.7	40	81.6	81	81.0
Performance status								
0	17	16.3	13	23.6	4	8.2	22	22.0
1	62	59.6	28	50.9	34	69.4	53	53.0
2	25	24.0	14	25.5	11	22.4	25	25.0
No. of prior regimens								
1	77	74.0	44	80.0	33	67.3	76	76.0
2	15	14.4	7	12.7	8	16.3	15	15.0
≥ 3	12	11.5	4	7.3	8	16.3	9	9.0
Best response to cisplatin								
PR/CR	35	33.7	14	25.5	21	42.9	37	37.0
NC	50	48.1	31	56.4	19	38.8	43	43.0
PD	19	18.3	10	18.2	9	18.4	20	20.0

Abbreviations: NC, no change; PD, progressive disease.

Statistical Considerations

The primary end point of the study was survival. The sample size was chosen on the basis of a log-rank test used to compare the two randomized groups. Comparisons of survival for the two halves of the study were made between the patients treated at docetaxel doses of either 100 mg/m^2 or 75 mg/m^2 and the corresponding BSC patients in that part of the trial. Secondary end points included objective tumor response and duration of response, as well as changes in QOL determined on the basis of the QOL instruments, changes in performance status and weight, and changes in analgesic use.

A sample size of 100 patients per group was estimated on the basis of a projected median survival of 7 months in the docetaxel group and 4 months in the BSC group and on the basis of the log-rank test with an alpha level of 5% (two-sided) and a power of 90% to compare the groups. The sample size was not estimated for an analysis intended to compare results within the four strata, as defined by performance status and response to prior therapy.

RESULTS

The study opened in November 1994 and closed in December 1998. Thirty-six centers participated in the trial: 16 from the United States, 10 from Canada, three from Finland, two each from the United Kingdom and Poland, and one each from Hungary and Puerto Rico.

The baseline patient demographics are listed in Table 1. One hundred patients were randomized to the BSC arm and 104 to the docetaxel arm (49 at 100 mg/m^2, 55 at 75 mg/m^2). One patient in each arm had an unconfirmed diagnosis of NSCLC. The two arms were well balanced with respect to sex, performance status, tumor stage, number of prior chemotherapy regimens, and best response to prior platinum-based chemotherapy.

Response and Survival

Response and survival data are listed in Table 2. As permitted by the protocol, 19 of the patients randomized to the docetaxel arm had only evaluable, nonmeasurable disease. Of the remaining patients, six (7.1%) achieved partial remission. This included three patients treated at each of the two docetaxel levels. The overall response rate, on the basis of an intent-to-treat analysis including patients with both measurable and evaluable lesions, was 5.8%. Of the six responders, three had responded to their prior chemotherapy treatment, and the other three had achieved stable disease. No patient who responded to docetaxel had progressed while receiving platinum-based chemotherapy. Two of the responders had docetaxel therapy as more than a second-line treatment (one had received it as third-line treatment, and the other, fourth-line). The time interval from the last chemotherapy treatment varied from 1 to 21 months among the responders. Performance status was a good predictor, because the performance status of all six responders was 0

Table 2. Summary of Response and Survival

Parameter	Docetaxel						Best Supportive Care
	Overall		75 mg/m^2		100 mg/m^2		
	No.	%	No.	%	No.	%	
Total no. of patients	103*		55		48*		100
Response*							
CR	—		—		—		—
PR (ITT)	6	5.8	3	5.5	3	6.3	
PR†	6	7.1†	3	7.1†	3	7.1†	—
SD	44	42.7	26	47.3	18	37.5	—
PD	34	33.0	18	32.7	16	33.3	—
NE	19	18.4	8	14.5	11	22.9	—
					—		—
Duration of response, weeks							
Median	26.1		26.1		23.9		
Range	23.7-31.0+		25.0-26.9		23.7-31.0+		
Survival							
Median, months	7.0		7.5		5.9		4.6
Range							
1-Year, %	29		37		19		19

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; NE, not evaluable.

*One patient in the docetaxel 100 mg/m^2 group was excluded from the intent-to-treat population (ITT) because of unconfirmed NSCLC.

†Based on 84 patients with measurable lesions.

(one responder) or 1 (five responders). Disease stage was not as predictive of response, with four stage III responders and two stage IV responders. The median duration of response was 26.1 weeks (range, 23.7 to 31.0+ weeks). Time to progression was significantly longer for docetaxel-treated patients overall (10.6 weeks *v* 6.7 weeks; $P = .001$), and this effect was seen in patients treated at both dose levels (docetaxel 100 mg/m^2, $P = .037$; docetaxel 75 mg/m^2, $P = .004$).

A comparison of survival for the entire chemotherapy and BSC groups is shown graphically in Fig 1. The median duration of survival for the chemotherapy arm was 7.0 months (95% confidence interval, 5.5 to 9.0 months) and was 4.6 months (95% confidence interval, 3.7 to 6.0 months) for the BSC group (log-rank $P = .047$). The 1-year survival rates for chemotherapy and BSC were 29% and 19%, respectively.

In Figs 2A and 2B, survival is compared separately for patients who were treated with docetaxel 100 mg/m^2 and docetaxel 75 mg/m^2, compared with the corresponding BSC patients of the two phases of the trial. No difference in survival was seen between the docetaxel 100 mg/m^2 and BSC arms ($P = .780$). However, survival in patients treated with docetaxel 75 mg/m^2 was significantly better than in those treated with BSC (log-rank test, $P = .01$). The median survival time of the docetaxel patients was 7.5 months, compared with only 4.6 months for the BSC patients, and 1-year survival rates in the two groups were 37% and 12%, respectively (χ^2 test, $P = .003$). In the docetaxel 75 mg/m^2 part of the study, nine patients received chemotherapy after docetaxel treatment (three in the docetaxel arm and six in the BSC arm). The difference in survival in favor of docetaxel remained significant even when these patients were included in the analysis (log-rank, $P = .039$).

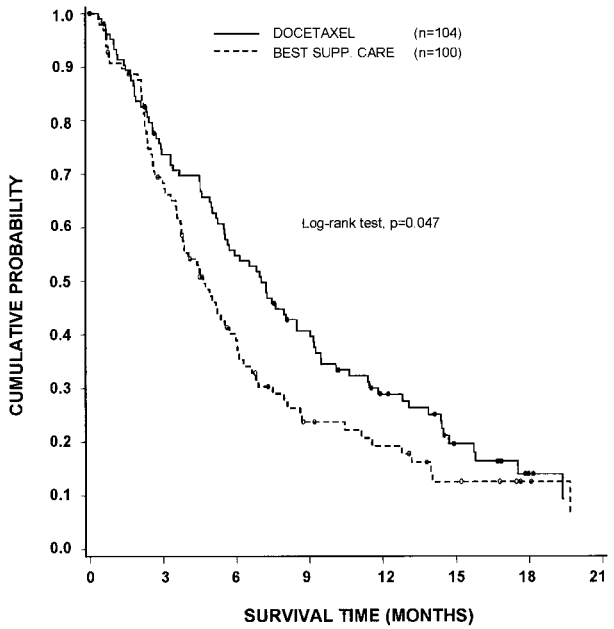

Fig 1. A comparison of survival of all patients treated with docetaxel and all BSC patients.

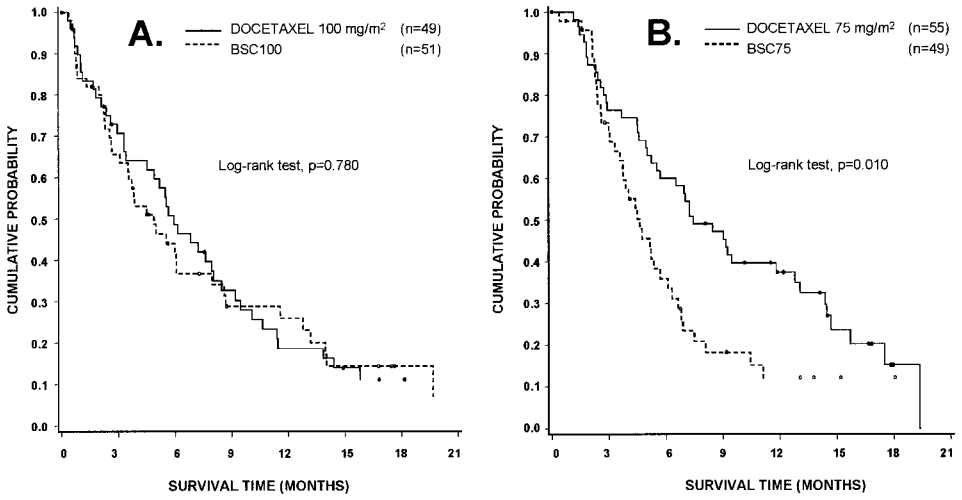

Fig 2. A comparison of survival of (A) patients treated with docetaxel 100 mg/m^2 and corresponding BSC patients and (B) patients treated with docetaxel 75 mg/m^2 and corresponding BSC patients.

Cox modeling was undertaken to determine the impact of several prognostic variables on survival. After adjustment for the significant variables of performance status, tumor stage, number of organs involved, number of prior chemotherapy regimens, and total baseline score on the Lung Cancer Symptom Scale, treatment with docetaxel 75 mg/m^2 was found to have a significant impact on survival (hazards ratio, 0.484; $P = .004$).

Toxicity

Six patients died within 30 days of receiving chemotherapy, five in the high-dose and one in the low-dose docetaxel arm, because of causes other than progressive disease. Three patients suffered fatal febrile neutropenia after treatment with docetaxel 100 mg/m^2. Two patients, one at each docetaxel level, developed pneumonia while they were not neutropenic. Whether a period of neutropenia before the onset of the pneumonia predisposed these patients to the development of infection remains speculative and unconfirmed. The sixth patient died at home of an unknown cause 8 days after treatment with docetaxel 100 mg/m^2.

The report of five possibly treatment-related deaths in the first 49 patients on the chemotherapy arm of the study led to a data and safety monitoring committee meeting to review the protocol and to make recommendations for change. Three deaths were clearly related to chemotherapy-induced neutropenia, and for the remaining two, a definite relationship to chemotherapy could not be established. Furthermore, no common prognostic factor, such as age or performance status, could be identified to account for this unusual number of toxic deaths. In view of these results, the protocol was amended to reduce the initial planned dose of docetaxel to 75 mg/m^2 for the remainder of the trial.

In the docetaxel arm, a total of 451 treatment cycles was administered. For the 49 patients treated at the 100-mg/m^2 dose, the median number of cycles was only two (range, 1 to 17), and only 68% of cycles could be delivered at the initial planned dose. The 55 patients treated with docetaxel 75 mg/m^2 received a median of four treatment cycles. At both doses, treatment could be delivered every 3 weeks in approximately 90% of cycles.

For the patients who received chemotherapy, hematologic toxicities are listed in Table 3. Grade 3 or 4 neutropenia occurred in 86% and 67% of patients treated with docetaxel 100 mg/m^2 and 75 mg/m^2, respectively. Eleven patients (22.4%) developed febrile neutropenia (three fatal cases) at the higher dose, compared with only one patient (1.8%) at the lower dose (no fatal cases). Grade 3 or 4 thrombocytopenia occurred in less than 1% of all chemotherapy cycles, and there were no episodes of clinical bleeding in either chemotherapy group. Grade 3 or 4 anemia occurred in 11 patients (10.6%): eight treated with docetaxel 100 mg/m^2 and three treated with 75 mg/m^2. Interestingly, 10.6% of the BSC patients reported grade 3 or 4 anemia as well.

A summary of nonhematologic toxicities is listed in Table 4 for all patients, including those in the BSC arm. It is important to note that "toxicities" were seen in all treatment groups, which serves to emphasize the point that treatment-emergent symptoms may be disease-related rather than treatment-related in this population of patients with advanced cancer. For example, severe asthenia was seen most frequently (28%) in the BSC group. Neurosensory change occurred in every treatment arm and was most common (3%) in the BSC arm, compared with 2% in each of the two docetaxel groups. Nausea and vomiting were

Table 3. Summary of Severe (grade 3/4) Hematologic Toxicity for Patients Treated With Docetaxel*

	Docetaxel					
	Overall		75 mg/m^2		100 mg/m^2	
Toxicity	No.	%	No.	%	No.	%
Total no. of patients	104		55		49	
Anemia	11	10.6	3	5.5	8	16.3
Neutropenia	79	76.0	37	67.3	42	85.7
Thrombocytopenia	1	1.0	0		1	2.0
Febrile neutropenia	12	11.5	1	1.8	11	22.4
Septic deaths	3	2.9	0		3	6.1

*Incidence of grade 3/4 toxicity per patient.

equally distributed across the groups, but diarrhea occurred only in the chemotherapy patients. Mild to moderate fluid retention (always $\leq$ grade 2) was seen in seven patients (12.7%) treated with docetaxel 75 mg/m^2, five patients (10.2%) treated with docetaxel 100 mg/m^2, and four BSC patients (7.8%). Infection occurred at some time in 34% of chemotherapy patients but was also documented in 21% of BSC patients, even in the absence of chemotherapy-induced neutropenia as a precipitating cause.

Clinical Benefit

In addition to response and survival, QOL and other clinical benefit parameters were measured. QOL data will be reported in detail in another article. However, all QOL parameters favored docetaxel-treated patients, and the differences were significantly different for the pain and fatigue scales ($P = .006$ and .06, respectively). There was less worsening of performance status from baseline to last assessment on study for docetaxel patients. The mean change was 0.56 for docetaxel patients, compared with 0.80 for BSC patients ($P = .11$). Only 7% of docetaxel patients experienced more than 10% weight loss from baseline weight, compared with 15% of BSC patients ($P = .07$).

As listed in Table 5, the use of all tumor-related medications was significantly less common in docetaxel-treated patients, compared with BSC patients ($P = .02$). Fewer docetaxel patients (32%) than BSC patients (49%) required morphine or morphine-equivalent medications for pain ($P = .01$). Nonmorphine analgesic use was also less frequent in docetaxel patients (39% *v* 55%; $P = .03$). Finally, 30% of docetaxel patients, compared with 49% of BSC patients, received medications for tumor-related indications other than pain ($P < .01$). Radiotherapy (at least one treatment during study treatment or follow-up) was required by fewer docetaxel patients (26% of docetaxel patients *v* 37% of BSC patients; $P = .09$).

Table 4. Summary of Nonhematologic Toxicity

	Docetaxel 75 mg/m^2 (n = 55)*				Docetaxel 100 mg/m^2 (n = 49)*				Best Supportive Care (n = 100)*			
	All grades		Grade 3/4		All grades		Grade 3/4		All grades		Grade 3/4	
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Asthenia	30	54.5	10	18.2	30	61.2	11	22.4	47	47.0	28	28.0
Cardiac	5	9.1	1	1.8	8	16.3	2	4.1	8	8.0	1	1.0
Diarrhea	20	36.4	1	1.8	15	30.6	2	4.1	5	5.0	0	
Fever, no infection	34	61.8	0		18	36.7	0		7	7.0	0	
Fluid retention	7	12.7	0		5	10.2	0		4	7.8	0	
Hypertension	2	3.6	0		0		0		0		0	
Hypotension	2	3.6	0		6	12.2	3	6.1	2	2	1	1
Infection	17	30.9	3	5.5	18	36.7	7	14.3	21	21.0	5	5.0
Nausea	20	36.4	2	3.6	17	34.7	1	2.0	26	26.0	5	5.0
Neuromotor	8	14.5	1	1.8	8	16.3	2	4.1	8	8.0	3	3.0
Neurosensory	11	20	1	1.8	13	26.5	1	2.0	10	10.0	3	3.0
Pulmonary	21	38.2	11	20.0	26	53.1	18	36.7	50	50.0	30	30.0
Stomatitis	14	25.5	1	1.8	13	26.5	2	4.1	4	4	0	
Vomiting	13	23.6	2	3.6	13	26.5	1	2.0	22	22.0	1	1.0

*Total number of patients.

Table 5. Summary of Tumor-Related Treatment Other Than Chemotherapy

	Docetaxel (%)	Best Supportive Care (%)	*P*
Any medication	62	77	.02
Morphine for pain	32	49	.01
Nonmorphine analgesics for pain	39	55	.03
Medications for indications other than pain	30	49	< .01
Radiation	26	37	.09

DISCUSSION

Because the benefits of first-line chemotherapy for advanced NSCLC are modest at best, the administration of second-line treatment deserves careful scrutiny. This is particularly true because more and more patients are receiving combined-modality therapy that includes chemotherapy for early-stage lung cancer, and they may be candidates for second-line treatment at the time of disease progression or relapse. Until recently, the literature on the treatment of advanced NSCLC with second-line chemotherapy consisted only of phase I and II trials. In an overview of treatment for recurrent NSCLC, Fossella et al[3] emphasized some of the difficulties with these studies. Most were small, consisting of fewer than 30 patients. Frequently the details of prior treatment were not included in the report, nor was the performance status of the patients. Although all studies reported response rates, very few provided median survival or 1-year survival rates. The agents most frequently evaluated in phase II studies include the vinca alkaloids vindesine and the newer agent vinorelbine, the taxanes paclitaxel and docetaxel, and, more recently, gemcitabine.

Variable and conflicting results have been reported in studies of second-line vinorelbine therapy. In two trials in which vinorelbine 25 mg/m^2[12] or 20 mg/m2[13] was administered weekly, no responses were seen. However, in a small 10-patient trial of vinorelbine 30 mg/m2 per week, a 20% response rate was reported by Sandoro et al.[14]

Numerous studies with paclitaxel also produced conflicting results, perhaps in part because of variability in both the dose and administration time of paclitaxel.[3] No responses were seen in a small study in which paclitaxel 140 mg/m^2 was administered over 96 hours.[15] In another trial in which paclitaxel 200 to 250 mg/m^2 was given over 24 hours, only two (14%) confirmed partial responses were observed, with two further responses that lasted less than 4 weeks.[16] In two trials in which varying doses of paclitaxel were given over 1 hour, only one (2.5%) of 40 patients responded in one study,[17] but there were 26 responses (23%) in the second.[18]

Gemcitabine has also demonstrated activity in the second-line setting. Rossi et al[19] observed partial responses in six (20%) of 30 patients treated with gemcitabine 1,000 mg/m^2 weekly for 3 weeks. It is interesting that responses were also seen in two patients who had brain metastases and in two whose disease had progressed during cisplatin therapy.

Docetaxel has been studied more extensively than any other agent for the second-line treatment of NSCLC. In seven phase II trials, in which more than 300 patients were treated, response rates ranging from 14% to 24% were consistently reported.[3-11] In most of these studies, the docetaxel dose was 100 mg/m^2 intravenously over 1 hour every 3 weeks.

These promising phase II trial results led to two randomized studies of second-line docetaxel in patients previously treated with cisplatin-based chemotherapy. In one study (the TAX 320 trial), patients were randomized to receive docetaxel 100 mg/m^2, docetaxel 75 mg/m^2, or either vinorelbine 30 mg/m^2 weekly for 3 weeks given every 4 weeks or ifosfamide 2 g/m^2 daily for 3 days every 4 weeks, as chosen by each investigator.[20] In this study, patients could have received prior taxane therapy. Despite this, an advantage was demonstrated for treatment with docetaxel. Overall response rates of 11.9% and 7.5% were obtained for docetaxel at doses of 100 mg/m^2 and 75 mg/m^2, respectively, compared with only 1% for patients treated with either vinorelbine or ifosfamide. The best survival was seen in the docetaxel 75-mg/m^2 arm, in which 32% of patients were alive at 1 year, compared with 21% and 19% in the other two arms (χ^2 test $P = .025$).

The study reported here is the first to shed any light on the true role of second-line chemotherapy in the treatment of advanced NSCLC in that patients were randomized either to chemotherapy with docetaxel or to BSC. The overall response rate of 7% in our trial was less than that reported in any of the phase II studies of docetaxel but was similar to the results of the TAX 320 trial. This somewhat disappointing result may have been due to selection of a poorer group of patients with more advanced tumors. Approximately 80% of patients had stage IV disease; 25% were of ECOG performance status 2, and 25% had received two or more prior chemotherapy regimens. It is possible that only in this unfavorable population were investigators willing to run the risk of a 50% chance of no chemotherapy treatment.

Despite the low overall response rate, however, treatment with docetaxel was associated with significant prolongation of survival. Prolongation of median survival was seen with both doses of docetaxel, but the most marked improvement was associated with docetaxel 75 mg/m^2. The actual 1-year survival rate for patients treated at this dose was 37%. These

results are similar to those obtained with first-line combination regimens.

In this study, the 100-mg/m^2 dose was associated with five reports of toxic deaths early in the trial. Three were thought to be related to docetaxel, and for the other two patients, an association with docetaxel treatment could not be ruled out. Excessive toxicity also contributed to diminished dose delivery. The median number of cycles delivered was only two, and this, combined with the 10% early death rate, may account for the lack of survival benefit seen at the 100-mg/m^2 dose. When the docetaxel dose was reduced to 75 mg/m^2 in the second half of the trial, dose delivery improved, with a median of four cycles given; the rate of febrile neutropenia fell from 22% to 2%, and there were no toxic deaths.

This high rate of toxic deaths was not seen in the 100 mg/m^2 arm of the TAX 320 study,[16] nor in any of the other phase II studies, all of which used a 100-mg/m^2 dose. In the phase II trial from the M.D. Anderson Cancer Center, grade 4 neutropenia occurred in 85% of patients. This resulted in fever that required intravenous antibiotics in 16% of patients, but there was only one toxic death. In the multicenter trial reported by Gandara et al,[6] the febrile neutropenia rate was similar, at 14%, but treatment-related death was not seen in 80 patients. Robinet et al[8] also reported a 19% febrile neutropenia rate (11% by cycle) but no toxic deaths. We do not have a clear explanation as to why our patients experienced such a high toxic death rate at a dose of 100 mg/m^2. These patients were not elderly nor in a poor prognostic group, and this degree of toxicity could not have been predicted before treatment for any of them.

Salminen et al[21] also reported a high degree of toxicity in heavily pretreated breast cancer patients who were given docetaxel 100 mg/m^2. Although none of their patients experienced a toxic death, almost half experienced treatment interruption because of toxicity. Salminen et al recommend a starting dose of 75 mg/m^2 in the second- and third-line treatment settings.

Nonhematologic toxicity was modest at both docetaxel doses. Grade 3 or 4 nausea and vomiting, diarrhea, and fluid retention were reported in less than 5% of patients and were never dose-limiting. It is of particular interest to note that the highest rates of neurosensory toxicity (3%) and asthenia (28%) occurred in patients on the BSC arm.

Clinical benefit in our study could be demonstrated by end points other than response and survival rates. A significant positive effect of docetaxel was evident in the analyses of both narcotic and nonnarcotic pain medication usage and in the need for radiation therapy. These observations are in keeping with those of Ellis et al,[22] who showed that tumor-related symptoms could improve in as many as two thirds of patients, even though overall response rates may be as low as 25% to 30%.

In summary, this is the first trial to document that in good-performance patients with NSCLC, a trial of second-line chemotherapy is justified after first-line treatment with a platinum-based regimen. Treatment with docetaxel is associated with significant prolongation of survival and significant improvements in disease-related symptoms. At a dose of 75 mg/m^2, the benefits of docetaxel therapy outweigh the risks.

APPENDIX
Investigators

The following investigators contributed patients to this multicenter trial: Canada—Ronald Burkes, MD, Mount Sinai Hospital, Toronto, Ontario; Richard Gregg, MD, Kingston Regional Cancer Centre, Kingston, Ontario; Frances Shepherd, MD, Princess Margaret Hospital, Toronto, Ontario; Ronald Feld, MD, Princess Margaret Hospital, Toronto, Ontario; Vera Hirsch, MD, Montreal General Hospital, Montreal, Quebec; Jamie Skillings, MD, Nova Scotia Cancer Centre, Halifax, Nova Scotia; Karen Gelmon, MD, British Columbia Cancer Agency, Vancouver, British Columbia; Francis Laberge, MD, Hopital Laval, Sainte-Foy, Quebec; Shou-Ching Tang, MD, General Hospital, St. John's, Newfoundland; Mark Vincent, MD, London Regional Cancer Centre, London, Ontario; Finland—Karin Mattson, MD, Helsinki University, Helsinki; Markku Pekonen, MD, Savonlinna Central Hospital, Savonlinna; Matti Salmo, MD, Vaasa Centre Hospital, Vaasa; Poland—Jacek Jassem, MD, Institute of Radiology, Gadansk; Rodryg Ramlau, MD, Regional Hospital of Lung Disease and Tuberculosis, Poznan; Hungary—Mel Kraszko, MD, Mellkasi Betegsegek Korhaza, Deszk; Puerto Rico— Luis Baez Diaz, MD, San Juan Municipal Hospital, San Juan; Sweden—Bent Bergman, MD, Avdelningen for Lungmedicim, Goteborg; United Kingdom—Robin Rudd, MD, St. Bartholomew Hospital, London, England; Allen Lamont, MD, Southend General Hospital, Essex, England; and United States—Howard Burris III, MD, Cancer Therapy and Research Center, San Antonio, TX; Alex Chang, MD, Genesee Hospital, Rochester, NY; Tracey Dobbs, MD, Baptist Regional Cancer Center, Knoxville, TN; Robert Figlin, MD, UCLA Medical Center, Los Angeles, CA; Richard Gralla, MD, Alton Ochsner Medical Foundation, New Orleans, LA; F. Anthony Greco, MD, Sarah Cannon Cancer Center, Nashville, TN; Laurent Gressot, MD, Veteran's Affairs Medical Center, Houston, TX; Basil Kasimis, MD, VA New Jersey Healthcare, East Orange, NJ; Thomas Ladd, MD, University of Illinois at Chicago, Chicago, IL; Nathan Levitan, MD, University Hospitals of Cleveland, Cleveland, OH; Gershon Locker, MD, Evanston Hospital, Evanston, IL; Thomas Lynch, MD, Massachusetts General Hospital, Boston, MA; Vicki Morrison, MD, Veterans Affairs Medical Center, Minneapolis, MN; Mark O'Rourke, MD, Cancer Treatment Center, Greenville, SC; Lee Schwartzberg, MD, WestClinic, Memphis, TN; and Arnold Wax, MD, Las Vegas, NV.

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CORRESPONDENCE

Docetaxel as Second-Line Chemotherapy for Non–Small-Cell Lung Cancer

To the Editor: In the recently published study[1] carried out in patients with non–small-cell lung cancer previously treated with platinum-based chemotherapy, the authors' conclusion is questionable for the following reasons.

Enrollment. The study was carried out in 35 centers enrolling a total of 204 patients in a 4-year period. Therefore, each center enrolled a mean number of only one to two patients per year. Were these patients consecutively enrolled onto the trial? As the participating centers have presumably a lot of experience in the treatment of non–small-cell lung cancer patients, it is likely that a selection bias occurred in the enrollment of these patients. In any case, an explanation of why such a small number of patients participated in the study should be given to allow the results to be considered transferable to all patients with non–small-cell lung cancer refractory to first-line cisplatin-based chemotherapy.

Sample size and statistical significance levels. When a significantly larger number of deaths, probably related to chemotherapy, were found in the 100-mg/m^2 docetaxel arm with respect to the best supportive care arm (five *v* zero, ie, $>$ 10% of patients died due to adverse events), the dose was decreased to 75 mg/m^2. Two unplanned comparisons of survival were reported: 100 mg/m^2 and 75 mg/m^2 versus the corresponding controls, named, respectively, the first and second parts of the study. In the first part of the study, no difference was detected; in the second part, the median survival observed in the chemotherapy arm was significantly higher than that observed in the best supportive care arm. In our opinion, because of the low number of patients (55 *v* 49), and the shortcomings of the enrollment of patients onto the trial, the conclusion that "treatment with docetaxel is associated with significant prolongation of survival, and at a dose of 75 mg/m^2, the benefits of docetaxel therapy outweigh the risk" is not acceptable (by the way, the power of the log-rank test used for these two separate, unplanned comparisons was not reported). Many of the reported differences between the two treatment groups did not reach statistical significance, and therefore they could be due to chance. Moreover, it is not mentioned which statistical tests were used to make the comparisons (ie, in comparing the mean decrease of performance status, were parametric or nonparametric tests used?).

Heterogeneity. The therapies of the best supportive care arm were not standardized, and this could produce a relevant noise in evaluating clinical benefit and quality of life. In particular, the use of corticosteroids, which can have an important influence on the pain and fatigue symptoms, was more frequent in the docetaxel arms. In fact, patients randomized to the docetaxel arm were premedicated with oral dexamethasone 8 mg bid for 5 days (10 doses) starting 24 hours before each 21-day infusion of docetaxel (in the second part of the study, this regimen was reduced to a total of five doses).

Adverse events. The possibility of death due to adverse events, fevers, neutropenia, stomatitis, and diarrhea, more frequently observed in the chemotherapy group, should be explicitly mentioned in future informed consent forms. How is it possible that all dimensions of quality of life were better in the chemotherapy group than in the best supportive care group?

In conclusion, due to the shortcomings of the study, its results can be considered, at most, as encouraging for the planning of a trial in which supportive care is more standardized.

Fausto Roila
Policlinico Hospital
Perugia, Italy

Albano Del Favero
Institute of Internal Medicine and Oncological Sciences, University
Perugia, Italy

Enzo Ballatori
University of L'Aquila
L'Aquila, Italy

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In Reply: Drs Roila, Del Favero, and Ballatori have raised several questions concerning the results of the TAX 317 trial of docetaxel versus best supportive care for the treatment of patients with non–small-cell lung cancer (NSCLC) previously treated with cisplatin-based chemotherapy.[1] They first questioned whether there might have been patient selection bias in the participating centers because 35 centers were required to accrue 204 patients over a 4-year period. I think that the difficulty with accrual was largely due to the design of the study, which included a best supportive care (BSC) arm in the trial, rather than selection bias. In the United States, where the trial opened initially, neither patients nor physicians were willing to participate in a study in which there was a 50% chance of not receiving chemotherapy. This resulted in very slow accrual and the need to expand the trial to Canadian and European centers. This explanation is supported by the observation that the TAX 320 trial,[2] in which docetaxel at doses of 75 mg/m^2 and 100 mg/m^2 was compared with vinorelbine or ifosfamide without a BSC arm, opened *after* the TAX 317 study yet completed its accrual of over 360 patients more than a year *before* TAX 317 finished. Second, patients who had received paclitaxel treatment were excluded from our study, which further hampered accrual in the United States, where first-line paclitaxel and carboplatin therapy is the most frequently used regimen for NSCLC. This problem was circumvented once again by the addition of Canadian and European centers to the trial. Finally, it should be noted that 30% of the patients on the study came from the center of the principal investigator. In that center, all patients who met the eligibility criteria were approached to participate in the trial without any selection bias. The only patients who were not enrolled were those who refused to participate, and for the most part, those patients did not wish to have further chemotherapy.

The sample size of 100 patients per group was estimated on the basis of a projected median survival of 4 months for BSC patients and 7 months for docetaxel-treated patients on the basis of the log-rank test with an alpha level of 5% (two-sided) and a power of 90% to compare the groups. In fact, at the time of the updated survival analysis, which

was undertaken in October 1999, the survival of the 104 docetaxel-treated patients was exactly as projected (7 months), as was that of the BSC patients (4.6 months), and these differences were statistically significant (log-rank, $P = .047$). This was the primary analysis planned at the initiation of the trial. Because of the toxicity seen at the 100-mg docetaxel dose in the TAX 317 trial, it was thought that 75 mg/m^2 would be a more appropriate dose in the setting of second-line treatment for NSCLC. For this reason, the study protocol was amended to reduce the dose of docetaxel from 100 to 75 mg/m^2 at the midpoint of patient enrollment. Thus, two further unplanned analyses of the data were undertaken. First the survival of patients treated with docetaxel 75 mg/m^2 was compared with that of the corresponding BSC patients from the second half of the trial, and a significant survival advantage was seen for the docetaxel-treated patients, despite the small number of patients in this analysis (log-rank, $P = .010$). Second, the impact of docetaxel 75 mg/m^2 treatment was assessed along with other important prognostic variables using Cox modeling, and once again, treatment with docetaxel 75 mg/m^2 was found to have a significant impact on survival (hazards ratio, 0.484; $P = .004$). We agree that a sample size of 104 patients would ordinarily be inadequate to determine that docetaxel is superior to BSC in this patient population. However, the power of the test becomes irrelevant once a significant difference is observed: The observed median survivals of 9 months and 4.6 months for docetaxel and BSC, respectively, are greater than the initially predicted 7 months and 4 months, on which the initial sample size estimation was based. Furthermore, the findings of TAX 317 are confirmed by similar results in the TAX 320 trial. In that study, patients treated with docetaxel 75 mg/m^2 had a 1-year survival rate (32%) that was similar to that of the TAX 317 trial and significantly better than that for treatment with either vinorelbine or ifosfamide (χ^2, $P = .025$). Given the data from the two trials, we believe that our conclusion that docetaxel 75 mg/m^2 is safe and effective second-line treatment for NSCLC is indeed valid.

The reviewers have suggested that BSC should have been standardized, but they do not state how this might be done. We believe that it would be absolutely impossible to do this in view of the variability of symptoms that might develop in patients with progressive NSCLC. Radiation would be offered for painful bone metastases or brain metastases, whereas pleural drainage with possible sclerosing procedures would be offered to patients with increasing effusion. These are a few examples of the protean nature of this malignancy, and they serve to point out the difficulties that would be encountered if one tried to standardize BSC in a protocol. Furthermore, we do not even believe that it would be ethical to prohibit third-line chemotherapy. We would like to emphasize, however, that only nine of the 104 patients in the second half of the TAX 317 trial received off-protocol chemotherapy at the time of disease progression. The difference in survival remained significant even when these patients were included in the survival analysis (log-rank, $P = .037$).

The reviewers also suggest that the benefits seen in quality of life may have been due to corticosteroid therapy. Patients in the docetaxel arm received dexamethasone for only 2.5 days of the 21-day cycle, and most of the quality-of-life assessments were completed after two oral doses at most of the total five (or eight before the amendment) dexamethasone doses. We believe that it is unlikely that this brief time on corticosteroids would have had a significant or lasting effect on global quality of life. Similarly, we do not think that it could affect the total need for pain medications throughout the entire cycle or reduce the need for palliative radiotherapy. We would like to point out that *all* dimensions of quality of life were not better in the chemotherapy group, as many remained the same or were equal on both arms of the study. A full report of quality-of-life assessment in the two second-line trials is planned.

The reviewers recommend another trial of second-line therapy with standardization of a BSC arm. We doubt that it will be possible to mount such a trial. We have discussed the difficulties of recruiting to our trial and of defining BSC above. However, the main reason that another BSC trial is unlikely to be conducted lies in the extreme difficulty of performing such a study. We believe that the time for BSC trials has now passed and that in view of the positive results of the TAX 317 and 320 trials, investigators would question the ethics of a no-chemotherapy arm for patients with a good performance status. Docetaxel 75 mg/m^2 should now be considered the gold standard for the second-line treatment of NSCLC, and new treatments or treatment strategies should be compared with this standard.

Frances A. Shepherd
University of Toronto
Toronto, Ontario, Canada

Luz Hammershaimb
Aventis Pharmaceuticals Inc
Collegeville, PA

Yong S. Kim
Aventis Pharmaceuticals Inc
Bridgewater, NJ

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Correspondence Re: "Doc, Shouldn't We Be Getting Some Tests?"

To the Editor: The article "Doc, Shouldn't We Be Getting Some Tests?"[1] was read with great interest. I have generally been using these guidelines in my practice for many years, but recently have been reconsidering. Although technically correct, the article leaves out certain issues that are worthy of discussion.

The first issue is the value of the office visit. Although follow-up mammograms may find an occasional curable breast cancer, the patient need not see the oncologist to get a follow-up mammogram. The primary care physician can do the routine care for other health concerns. Data of which I am aware show that routine oncology office visits prolong survival. Therefore, if we are to be consistent, we should not have patients come back for routine office visits, and we should revert to the type of episodic emergency oncology care that we have been decrying for years. The second issue is the value of these tests for some of the patients, even if the median survival does not improve. There are data showing that patients with isolated hepatic recurrences can have their survival improved by timely surgery.[2] Let us further take the case of a woman with an estrogen receptor–positive tumor treated previously only with lumpectomy and radiation therapy who develops a significant rise in the CA 27.29 marker. It makes sense to consider

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ORIGINAL REPORT

Randomized Phase III Trial of Pemetrexed Versus Docetaxel in Patients With Non–Small-Cell Lung Cancer Previously Treated With Chemotherapy

Nasser Hanna, Frances A. Shepherd, Frank V. Fossella, Jose R. Pereira, Filippo De Marinis, Joachim von Pawel, Ulrich Gatzemeier, Thomas Chang Yao Tsao, Miklos Pless, Thomas Muller, Hong-Liang Lim, Christopher Desch, Klara Szondy, Radj Gervais, Shaharyar, Christian Manegold, Sofia Paul, Paolo Paoletti, Lawrence Einhorn, and Paul A. Bunn Jr.

From Indiana University and the Hoosier Oncology Group; Eli Lilly and Company, Indianapolis, IN; The University of Texas M.D. Anderson Cancer Center, Houston, TX; University of Colorado Cancer Center, Denver, CO; Virginia Cancer Institute, Richmond, VA; Princess Margaret Hospital and the University of Toronto, Toronto, Ontario, Canada; Instituto Arnaldo Vieira de Carvalho, Sao Paolo, Brazil; San Camillo-Forlanini Hospitals, Rome, Italy; Chang Gung Memorial Hospital, Taoyuan, Taiwan; University Hospital Basel, Petersgraben Switzerland; Fachklinik München, Gauting; Hospital Grosshansdorf, Grosshansdorf; Krankenhaus Hofheim Am Taunus, Hofheim; Thoraxklinik-Heidelberg, Heidelberg, Germany; National University Hospital, Singapore; Semmelweis Medical University Diosarok, Budapest, Hungary; Centre Francois Baclesse, Caen, France; Mayo Hospital, Lahore, Pakistan.

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Nasser Hanna, MD, Indiana University, 535 Barnhill Dr, Room 473, Indianapolis, IN 46202; e-mail: nhanna@iupui.edu.

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ABSTRACT

Purpose
To compare the efficacy and toxicity of pemetrexed versus docetaxel in patients with advanced non–small-cell lung cancer (NSCLC) previously treated with chemotherapy.

Patients and Methods
Eligible patients had a performance status 0 to 2, previous treatment with one prior chemotherapy regimen for advanced NSCLC, and adequate organ function. Patients received pemetrexed 500 mg/m^2 intravenously (IV) day 1 with vitamin B_{12}, folic acid, and dexamethasone or docetaxel 75 mg/m^2 IV day 1 with dexamethasone every 21 days. The primary end point was overall survival.

Results
Five hundred seventy-one patients were randomly assigned. Overall response rates were 9.1% and 8.8% (analysis of variance $P = .105$) for pemetrexed and docetaxel, respectively. Median progression-free survival was 2.9 months for each arm, and median survival time was 8.3 versus 7.9 months (P = not significant) for pemetrexed and docetaxel, respectively. The 1-year survival rate for each arm was 29.7%. Patients receiving docetaxel were more likely to have grade 3 or 4 neutropenia (40.2% *v* 5.3%; $P < .001$), febrile neutropenia (12.7% *v* 1.9%; $P < .001$), neutropenia with infections (3.3% *v* 0.0%; $P = .004$), hospitalizations for neutropenic fever (13.4% *v* 1.5%; $P < .001$), hospitalizations due to other drug related adverse events (10.5% *v* 6.4%; $P = .092$), use of granulocyte colony-stimulating factor support (19.2% *v* 2.6%, $P < .001$) and all grade alopecia (37.7% *v* 6.4%; $P < .001$) compared with patients receiving pemetrexed.

Conclusion
Treatment with pemetrexed resulted in clinically equivalent efficacy outcomes, but with significantly fewer side effects compared with docetaxel in the second-line treatment of patients with advanced NSCLC and should be considered a standard treatment option for second-line NSCLC when available.

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INTRODUCTION

Lung cancer is the most common cancer in the world today (12.3% of all new cases), with an estimated 1.2 million new cases and 1.1 million deaths (17.8% of all cancer deaths) worldwide in 2000.[1] Non–small-cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer. For chemotherapy-naïve patients with a good performance status (PS) and stage IIIb (with pleural effusion) or IV disease, platinum-based chemotherapy offers a modest survival advantage over best supportive care (BSC) alone.[2-4]

Docetaxel (Taxotere; Aventis Pharmaceuticals, Bridgewater, NJ) is currently the only US Food and Drug Administration and European Agency for the Evaluation of Medical Products–approved chemotherapy agent for the second-line treatment of advanced NSCLC. The approval was based on phase III studies by Shepherd et al[5] and Fossella et al.[6] For patients with a good PS at the

time of disease progression following first-line chemotherapy, docetaxel, despite a low response rate, is associated with a 10% to 20% prolongation of 1-year survival and an improved quality of life when compared with ifosfamide, vinorelbine, or BSC alone.[5,6] In view of these modest results, new agents with single-agent activity are greatly needed for this patient population.

Pemetrexed (Alimta, Eli Lilly and Company, Indianapolis, IN) is a novel, multitargeted antifolate chemotherapy agent that is active in multiple tumor types including NSCLC.[7-10] Its primary mechanism of action is to inhibit the enzyme thymidylate synthase, resulting in decreased thymidine necessary for pyrimidine synthesis. Pemetrexed also inhibits dihydrofolate reductase and glycinamide ribonucleotide formyl transferase, the latter of which is a folate-dependent enzyme involved in purine synthesis. Phase II studies of pemetrexed in previously untreated patients with NSCLC have demonstrated single agent response rates of 17% to 23%.[7,8] A phase II study of pemetrexed in patients with advanced NSCLC, who had progressed during or within 3 months of completing first-line chemotherapy, demonstrated a response rate of 8.9% and median survival time of 5.7 months.[9]

Folate and vitamin B_{12} nutritional status affects the toxicity of pemetrexed, including rates of neutropenic fever. Treatment with pemetrexed without vitamin supplementation results in a significantly higher incidence of hematologic and nonhematologic toxicity.[10-12] Therefore, supplementation with folic acid at 350-1,000 μg orally daily and vitamin B_{12} 1,000 μg IM every 9 weeks is essential to control the toxicity of pemetrexed. Bunn et al reported that in a multistudy single-agent database of 246 patients treated with pemetrexed, 5.0% versus 0% had drug-related deaths, 32.0% versus 2.6% had grade 4 neutropenia, and 37.0% versus 6.4% had any grade 4 hematologic or grade 3 or 4 nonhematologic toxicity, without and with vitamin supplementation, respectively.[12] Based on the similar efficacy observed between pemetrexed and docetaxel in separate trials and the expected lower toxicity rates with pemetrexed, a multinational phase III study comparing these two agents in the second-line treatment of NSCLC was undertaken.

PATIENTS AND METHODS

Patients with histologic or cytologic confirmation of NSCLC with stage III or IV disease not amenable to curative therapy were assessed for eligibility. Eligible patients met the following criteria: treatment with only one prior chemotherapy regimen for advanced disease (one additional prior regimen was allowed for neoadjuvant, adjuvant, or neoadjuvant plus adjuvant therapy); measurable or evaluable disease; an Eastern Cooperative Oncology Group (ECOG) PS of 0 to 2; and adequate bone marrow, renal, and hepatic function. Patients with prior docetaxel or pemetrexed treatment, Common Toxicity Criteria (CTC) $\geq$ grade 3 peripheral neuropathy, an inability to interrupt nonsteroidal anti-inflammatory drugs, uncontrolled pleural effusions, symptomatic or uncontrolled brain metastases, or significant weight loss ($\geq$ 10% body weight in the preceding 6 weeks) were ineligible. The protocol was approved through institutional ethics review boards, and all patients provided written informed consent before treatment.

Treatment Plan

Eligible patients were randomly assigned to receive either pemetrexed or docetaxel. Patient randomization was stratified for PS (0 or 1 *v* 2), prior platinum or paclitaxel use, number of prior chemotherapy regimens (1 or 2), time since last chemotherapy ($<$ 3 *v* $\geq$ 3 months), best response to last chemotherapy (objective tumor response/stable disease versus progressive disease/unknown), stage (III *v* IV), baseline plasma homocysteine level ($<$12 μmol/L *v* $\geq$ 12 μmol/L), and center. Patients received either 500 mg/m^2 pemetrexed as a 10-minute intravenous infusion or 75 mg/m^2 docetaxel as a 1-hour intravenous infusion on day 1 of a 21-day cycle. Cycles were repeated until disease progression, unacceptable toxicity, or until the patient or the investigator requested therapy discontinuation. Patients on the pemetrexed arm were instructed to take folic acid 350-1,000 μg (or an equivalent) orally daily beginning approximately 1 to 2 weeks before the first dose of pemetrexed and continuing daily until 3 weeks after the last dose of pemetrexed. A 1,000 μg vitamin B_{12} injection was administered intramuscularly approximately 1 to 2 weeks before the first dose of pemetrexed and was repeated approximately every 9 weeks until after discontinuation. Folic acid and vitamin B_{12} were given because of their ability to reduce toxicities without affecting the efficacy of pemetrexed.[11] Patients on the pemetrexed arm were instructed to take dexamethasone (4 mg orally twice daily the day before, the day of, and the day after pemetrexed) as a prophylactic measure against skin rash. Patients on the docetaxel arm were instructed to take dexamethasone (8 mg orally twice daily the day before, the day of, and the day after docetaxel), but were not required to take vitamin supplementation. A maximum of two dose reductions were allowed based on nadir counts or clinically significant nonhematologic toxicities and dose delays up to 42 days from day 1 of the current cycle were permitted for recovery from adverse events. Granulocyte colony-stimulating factor support was allowed to treat a neutropenic event or as prophylaxis in a patient who had experienced a neutropenic event with a previous cycle.

The baseline assessment included a history and physical examination, complete blood count, comprehensive blood chemistries, calculated creatinine clearance, vitamin metabolite panel, chest x-ray and computed tomorgraphy scan of the chest and the upper abdomen. Bone scans and brain imaging were performed only if clinically indicated. The Lung Cancer Symptom Scale (LCSS) was administered at baseline and weekly during the study. The observer LCSS was administered at baseline and at the end of each cycle.[13] Toxicity evaluations were based on the National Cancer Institute CTC, version 2. Hematologic laboratory values and folic acid compliance (pemetrexed arm only) were evaluated weekly. Chemistry laboratory values were evaluated following days one and eight of each cycle. Tumor measurements were assessed after every two cycles.

Statistical Analysis

The primary objective of the study was to compare overall survival between the two treatment groups on an intent-to-treat basis. Secondary objectives were to compare toxicities (including use of concomitant supportive measures), objective response rates

(RR), progression-free survival (PFS), time to progressive disease (TPD), time to treatment failure (TTF), time to response, duration of response, and quality-of-life measurements (using the LCSS) between the treatment groups.

Unless otherwise noted, all tests of hypotheses were conducted at the $\alpha = 0.05$ level, with a 95% CI. Cox proportional hazard models were used to compare the overall survival time and other time-to-event end points between the treatment arms; Kaplan-Meier estimates were used to assess the median time-to-event parameters, except for time-to-response using analysis of variance. The study was designed to have an 81% chance of demonstrating noninferiority for survival time (defined as pemetrexed arm $\leq$ 10% worse than docetaxel arm) for pemetrexed when compared to docetaxel using the true hazard ratio (HR) to be 0.83. This translated to an upper bound of the 95% CI less than 1.11 for the HR of pemetrexed over docetaxel. In addition, the hypothesis that pemetrexed retained $\geq$ 50% of the survival benefit of docetaxel over BSC using data from the randomized comparative trial of docetaxel versus BSC by Shepherd et al[5] was prospectively planned (percent retention method).[14] In the trial reported by Shepherd et al, the HR of docetaxel over BSC was estimated to be 0.56 (95% CI, 0.35 to 0.88). Setting the percentage of historical benefit at 50% and maintaining an approximate one-sided 2.5% type I error, an upper 95% CI bound of less than 1.21 for the HR of pemetrexed over docetaxel was required to establish the noninferiority of pemetrexed.

Tumor response was compared using the Fisher's exact test with 95% CI calculated using the method of Leemis and Trivedi.[15] A Cox proportional multiple regression (CMR) model was developed with an interactive stepwise regression to identify the potential factors as predictors of survival independent of therapy. A final model was fitted on the survival, including therapy in the model to estimate the treatment effect adjusting for these factors. The incidence of CTC toxicities, adverse events, concomitant medications used, and hospitalizations were analyzed using Fisher's exact test. Distribution of changes from baseline in the average symptom burden index (ASBI) of the patient LCSS, and individual symptoms of the observer LCSS, were compared with the Mental-Haenszel χ^2 test.[16]

The overall survival time was defined as the time from the date of randomization to date of death due to any cause. Patients who were alive on the date of last follow-up were censored on that date. PFS was the time from randomization until documented progression or death from any cause and was censored at the date of the last follow-up visit for patients who were still alive and who had not progressed. TPD was defined as the time from the date of randomization to the first date of documented disease progression and was censored at the date of death for patients who died without documented disease progression or the date of the last follow-up visit for patients who were still alive and who had not progressed. TTF was defined as the time from randomization to the date of progression of disease, discontinuation of treatment, or death due to any cause and was censored at the date of the last follow-up visit for patients who did not discontinue, who were still alive, and who did not have disease progression. Tumor response was assessed using the Southwest Oncology Group criteria[17] and required confirmation at least 4 weeks after initial response (Complete response [CR] defined as complete disappearance of all measurable and evaluable disease; partial response [PR] defined as $\geq$ 50% decrease in the sum of products of perpendicular diameters of all measurable lesions; progressive disease [PD] defined as 50% increase in the sum of products of all measurable lesions, or worsening of evaluable disease, or appearance of any new lesions; and stable disease [SD] defined as not qualifying for CR, PR, or PD). Duration of tumor response was defined as the time from the date of the first objective status assessment of CR or PR until the first date of documented disease progression or death due to any cause and was censored at the date of the last follow-up visit for tumor responders who were still alive and who had not progressed. Duration of clinical benefit (CR/PR/SD) was defined as the time from the date of randomization to the first date of documented disease progression or death due to any cause for patients who had a best overall tumor response better than progressive disease and was censored at the date of the last follow-up visit for those patients who were still alive and had not progressed.

For each patient, LCSS scores were rated as improved, stable, or worsened based on comparison with baseline. The average symptom burden index (ASBI) was the average of the six symptom-specific questions regarding anorexia, fatigue, cough, dyspnea, hemoptysis, and pain.[13] Meaningful change for the ASBI was defined as at least half of the SD of the baseline ASBI for all patients that was maintained for at least 4 consecutive weeks.[18] Meaningful change for observer LCSS scales was defined as at least a one-point change on the five-point scale that was maintained for at least two cycles. Changes in LCSS scores that could not be confirmed were classified as unknown.

RESULTS

From March 2001 through February 2002, 571 patients were randomly assigned to receive either pemetrexed or docetaxel. Two hundred sixty-five of 283 patients randomly assigned to pemetrexed received at least one cycle of therapy (18 patients received no treatment due to: failure to meet inclusion criteria [n = 7], death from disease [n = 5], other adverse events [n = 3], personal conflict [n = 2], or protocol violation [n = 1]). Two hundred seventy-six of 288 patients randomly assigned to docetaxel received at least one cycle of therapy (12 patients received no treatment due to failure to meet inclusion criteria [n = 2], death from disease or other cause [n = 2], personal conflict [n = 5], loss to follow-up [n = 3].) At the time of analysis, 409 (71.6%) of 571 patients had died. The median follow-up for all patients was 7.5 months, and the clinical data were collected up to January 30, 2003. The baseline patient and disease characteristics are listed in Table 1.

The two arms were well balanced for all demographic and stratification factors. All 571 randomly assigned patients were assessable for survival, and 538 of 541 patients (n = 265 for pemetrexed, 276 for docetaxel) who received therapy were assessable for response. One pemetrexed and two docetaxel patients were randomly assigned and received at least one cycle of therapy but did not meet the protocol required criteria for response evaluation.

Treatment Administered

The median number of cycles of chemotherapy administered was four in each group, with a range of one to 20 and

Table 1. Baseline Patient and Disease Characteristics

Characteristic	% of Patients: Pemetrexed Group (n = 283)	% of Patients: Docetaxel Group (n = 288)
Sex		
Male	68.6	75.3
Female	31.4	24.7
Age, years		
Median	59	57
Range	22-81	28-87
Performance status		
0 or 1	88.6	87.6
2	11.4	12.4
Stage IV	74.9	74.7
Prior Platinum	92.6	89.9
CR/PR to prior platinum	34.7	37.5
Prior paclitaxel	25.8	27.8
CR/PR to prior paclitaxel	39.7	35.0
Best response, any prior chemotherapy		
CR/PR	35.7	36.5
SD	37.5	32.3
PD/unknown or not evaluable	26.9	31.3
Time since last chemotherapy		
< 3 months	50.4	48.1
Histology		
Adenocarcinoma	54.4	49.3
Squamous cell carcinoma	27.6	32.3
Homocysteine levels		
< 12 μmol/L	71.4	68.9
Prior radiation	44.2	45.5

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

one to14 for patients receiving pemetrexed and docetaxel, respectively. Patients received 96.6% and 94.4% of the planned dose-intensity of pemetrexed and docetaxel, respectively (P = not significant).

Efficacy

There was no significant difference in overall RR (9.1% *v* 8.8%) or SD rates (45.8% *v* 46.4%) between the pemetrexed and docetaxel arms, respectively. The RR to second-line treatment in patients with a CR or PR, SD, and PD to first-line therapy was 11.1%, 10.2%, and 4.6%, respectively, and the SD rate to second-line treatment in patients with a CR or PR, SD, and PD to first-line therapy was 47.0%, 50.0%, and 40.3% respectively.

Paclitaxel sensitivity and resistance in first-line treatment did not predict for a difference in response between pemetrexed and docetaxel in second-line treatment (P = not significant). Patients who achieved a CR or PR with first-line paclitaxel (n = 54) had a 7.1% versus 3.9% RR to pemetrexed and docetaxel, respectively (SD rates were 32.1% *v* 30.8%). Patients with SD following first-line paclitaxel (n = 55) had an RR of 3.8% versus 6.9% for pemetrexed and docetaxel, respectively (SD rates were 50.0% *v* 51.7%) and patients with PD (or unknown response) with first-line paclitaxel (n = 44) had an RR of 5.3% versus 4.0% for pemetrexed and docetaxel, respectively (SD rates 42.1% *v* 48.0%).

There were no significant differences in PFS (Fig 1, Table 2), TPD and TTF (Table 2). There was also no significant difference in median time to response, median duration of response, and median duration of clinical benefit (Table 2). On an intent-to-treat basis, the median survival time for pemetrexed was 8.3 months versus 7.9 for docetaxel (HR, 0.99; 95% CI, 0.82 to 1.2; noninferiority $P = .226$; Fig 2). Using the percent retention method, the estimate of the percentage of survival benefit (of docetaxel over BSC) retained by pemetrexed was 102% with the lower 95% CI bound of 52% and was statistically significant ($P = .047$). The 1-year overall survival rate for each arm was 29.7%.

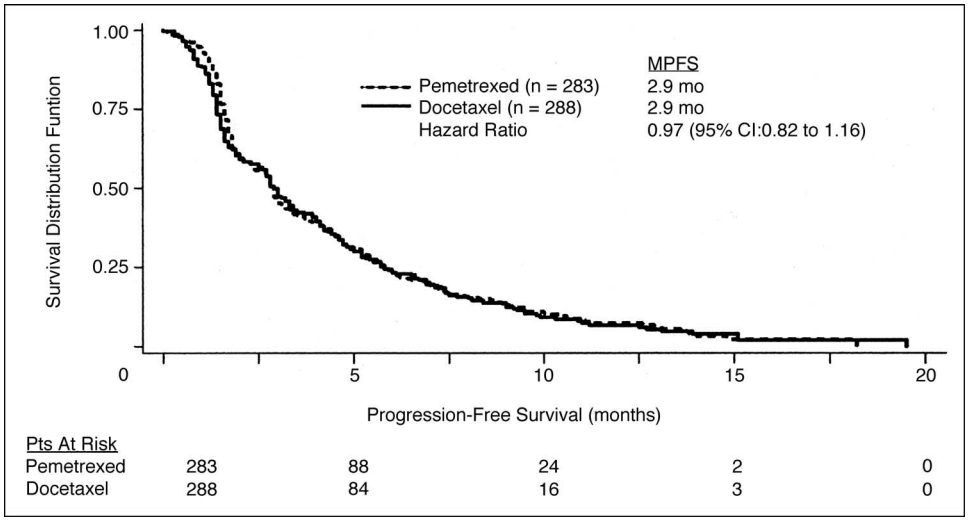

Fig 1. Median progression-free survival (MPFS). Pts, patients. Mo, months.

Table 2. Summary of Time-To Event-Variables (ITT)

Variable	Pemetrexed Group* (n = 283)	Docetaxel Group (n = 288)	HR	95% CI	*P*
Progression-free survival			0.97	0.82 to 1.16	.759‡
Median, months†	2.9	2.9			
Range, months	0-18.2	0-19.5			
Patients censored, %	6.4	10.4			
Time-to-progression			0.97	0.80 to 1.17	.721‡
Median, months†	3.4	3.5			
Range, months	0.5-18.2	0.3-19.5			
Patients censored, %	24.7	27.8			
Time-to-treatment failure			0.84	0.71 to 0.997	.046‡
Median, months†	2.3	2.1			
Range, months†	0.0-18.2	0.0-13.1			
Patients censored, %	1.4	1.7			
Duration of response			0.77	0.40 to 1.47	.427‡
Median, months†	4.6	5.3			
Range, months†	2.1-15.3	1.7-11.7			
Patients censored, %	25.0	16.7			
Duration of clinical benefit			0.91	0.71 to 1.16	.450‡
Median, months†	5.4	5.2			
Range, months†	1.2-18.2	1.5-14.6			
Patients censored, %	10.3	13.9			
Time-to-response			NA	NA	.105§
Median, months	1.7	2.9			
Range, months	1.2-4.3	1.4-7.8			

Abbreviations: ITT, intent-to-treat; HR, hazard ratio; NA, not assessable.
*Pemetrexed (n = 282) in time-to-treatment failure analysis.
†Median time-to-event value calculated using Kaplan-Meier method.
‡Comparison of hazard ratio between treatment arms using the Cox Proportional Hazard model.
§Analysis of variance *P* value.

Approximately 41.9% of all randomly assigned patients (46.6% and 37.2% of patients on the pemetrexed and docetaxel arms, respectively) received additional anticancer drug therapy after going off-study. Approximately 31.8% of patients randomly assigned to the pemetrexed arm eventually received docetaxel off-protocol. The median survival was 9.5 months for this group and 11.2 months for patients on the docetaxel treatment arm that received any other poststudy chemotherapy. Only 1.8% of all patients received gefitinib (Iressa; AstraZeneca UK Limited, Cheshire, UK) poststudy.

Multiple Regression Analysis

CMR analysis was performed on 532 patients to identify additional factors that affected survival and to estimate

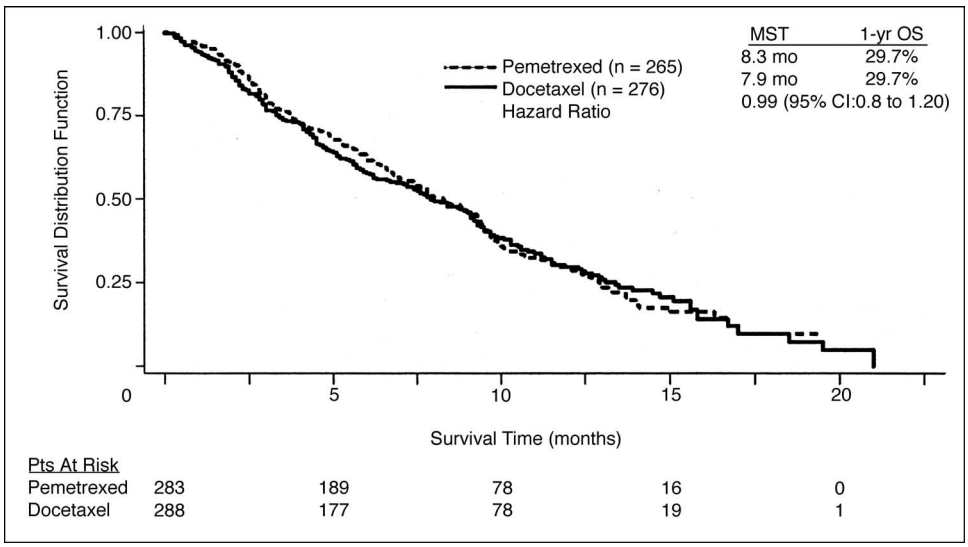

Fig 2. Median survival time (MST). Mo, months; yr, year; Pts, patients.

Table 3. Cox Model Subgroup Analysis of Variables Associated With Improved Survival

Variable	Pemetrexed Survival (months)	Docetaxel Survival (months)	P*
Performance status			
0 or 1	9.4	9.1	.996
2	3.6	2.2	.264
Stage			
III	9.3	10.3	.948
IV	7.9	7.2	.896
Time since last chemotherapy			
< 3 months	7.0	6.2	.670
≥ 3 months	9.3	9.2	.588
Effect of treatment adjusted for prognostic factors	—	—	.051†

*Comparison between treatment arms using Cox Proportional Hazard model.
†Effect of treatment adjusted for prognostic factors *P* value is based on non-inferiority model.

the treatment effect adjusting for these factors. The CMR analysis showed that pemetrexed and docetaxel achieved similar survival after adjusting for all baseline factors. The factors significantly associated with increased survival were: PS 0 or 1 (HR, 0.25; 95% CI, 0.19 to 0.34; $P < .001$), stage III disease (HR, 0.77; 95% CI, 0.60 to 0.97; $P = .026$), and longer time since last chemotherapy (HR, 0.74; 95% CI, 0.60-0.97; $P = .004$). Similar survival was seen between treatment groups after adjusting for each of these factors (HR, 0.93; 95% CI, 0.76-1.13; noninferiority $P = .051$; Table 3).

Quality of Life Analysis

Overall, 474 patients (pemetrexed, n = 227; docetaxel, n = 247) were assessable for the ASBI analysis of the patient LCSS. There was no significant difference in the distribution of numbers of patients reporting changes in the ASBI between the two arms of the study (Table 4). Overall, 472 patients (pemetrexed, n = 239; docetaxel, n = 233) were evaluable for observer LCSS analysis. Patients on both arms were rated with similar rates of improvement or stabilization of anorexia (55.6% *v* 60.9%), fatigue (54.8% *v* 56.7%), cough (63.6% *v* 64.4%), dyspnea (63.6% *v* 59.9%), hemoptysis (70.3% *v* 73.2%) and pain (64.0% *v* 62.1%).

Table 4. Rates of Change in Average Symptom Burden Index of the Patient Lung Cancer Symptom Scale

	% of Pemetrexed (n = 227) Patients	% of Docetaxel (n = 247) Patients	P*
Improved	21.2	21.5	
Worsened	33.0	27.9	.1447
Stable	29.5	24.7	
Unknown	16.3	25.9	

NOTE. The Average Symptom Burden Index is the average of the six symptom-specific questions from the patient Lung Cancer Symptom Scale regarding anorexia, fatigue, cough, dyspnea, hemoptysis, and pain.
*Mantel-Haenszel χ^2 test was used to evaluate any treatment differences over all categories (improved, worsened, stable, unknown).

Toxicity

All treated patients (n = 541) were assessable for toxicity. Hematological toxicity and hospitalizations, growth factor and transfusion needs are summarized in Tables 5 and 6 and nonhematologic toxicity is summarized in Table 7. Treatment-related deaths were attributed to docetaxel and pemetrexed in 5 and 3 patients, respectively. Patients receiving docetaxel experienced significantly higher rates of neutropenia, neutropenic fever, infections and hospitalization due to neutropenic events compared to patients receiving pemetrexed. In addition, more patients on the docetaxel arm required hospitalization due to other drug-related adverse events (excluding neutropenic complications) compared to those on the pemetrexed arm (10.5% versus 6.4%, $P = .092$). In addition, the use of granulocyte colony-stimulating factors (G-CSFs) was substantially increased for patients receiving docetaxel when compared to pemetrexed. Only 4 patients in the docetaxel arm and 1 patient in the pemetrexed arm received G-CSF as prophylaxis without a prior event of neutropenia. The remaining patients used G-CSF during treatment of neutropenia (n = 49 in the docetaxel arm; n = 5 in the pemetrexed arm) or as prophylaxis for subsequent cycles following an episode of neutropenia. There were no statistically significant differences in the

Table 5. Grade 3 and 4 Hematologic Toxicities

	% of Pemetrexed Patients (n = 265)	% of Docetaxel Patients (n = 276)	P*
Neutropenia	5.3	40.2	< .001
Febrile Neutropenia	1.9	12.7	< .001
Neutropenia with infection	0.0	3.3	.004
Anemia	4.2	4.3	.99
Thrombocytopenia	1.9	0.4	.116

NOTE. Toxicities graded using the National Cancer Institute Common Toxicity Criteria version 2.
*Fisher's exact test.

Table 6. Hospitalizations and Supportive Care

	% of Pemetrexed Patients (n = 265)	% of Docetaxel Patients (n = 276)	P*
≥ 1 hospitalization for neutropenic fever†	1.5	13.4	< .001
≥ 1 hospitalization for any other drug-related adverse event	6.4	10.5	.092
G-CSF/GM-CSF	2.6	19.2	< .001
Erythropoietin	6.8	10.1	.169
RBC transfusions	16.6	11.6	.1078

Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.
*Fisher's exact test.
†Pemetrexed treated patients were hospitalized for neutropenic fever a total of 29 days; docetaxel treated patients were hospitalized for neutropenic fever a total of 195 days.

incidences of thrombocytopenia, anemia, RBC transfusions, or use of erythropoietin between the treatment groups. There was a significantly higher rate of alopecia for patients receiving docetaxel and a slightly greater incidence of rise in ALT for patients receiving pemetrexed.

DISCUSSION

This is the largest phase III study ever reported for the second-line treatment of advanced NSCLC. In our study, response and clinical benefit rates (CR/PR/SD) were similar in patients receiving either pemetrexed or docetaxel. Patients who had a clinical benefit with first-line chemotherapy were more likely to have clinical benefit with second-line therapy on this trial. Patients with stage III disease (*v* stage IV disease), PS 0 or 1 (*v* 2), or were ≥ 3 months (*v* < 3 months) since last their chemotherapy benefited more with second-line chemotherapy on this trial. All efficacy end points, including overall survival time (median 8.3 versus 7.9 months) and 1-year percent survival (29.7%), were clinically comparable between treatment arms.

The patients receiving docetaxel in the current study performed as well as (or in some categories better than) the patients receiving docetaxel on the phase III studies reported by Shepherd et al[5] and Fossella et al.[6] The RR to docetaxel at 75 mg/m^2 on all three studies was 6.7% to 8.8% and the SD rate was 36% to 46%. The median survival time for docetaxel was 5.7 months in the Fossella et al study, 7.5 months in the Shepherd et al study, and 7.9 months in this study.

The design and patient characteristics of this trial have similarities, but also important distinctions from the trials previously reported by Shepherd et al and Fossella et al. Each study evaluated patients who had previously received chemotherapy for advanced NSCLC, required an ECOG PS 0 to 2, and excluded patients with symptomatic brain metastases. However, only the current study limited patients to one prior chemotherapy regimen for advanced disease (25% to 35% of patients on the other trials had received > one prior regimen for metastatic disease), did not require prior platinum (although 95% of patients had received platinum) and excluded patients with uncontrolled pleural effusions and significant weight loss. The study by

Table 7. Nonhematologic Toxicities

	Pemetrexed (n = 265)		Docetaxel (n = 276)		
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	P*
Fatigue	34.0	5.3	35.9	5.4	.99
Nausea	30.9	2.6	16.7	1.8	.57
Vomiting	16.2	1.5	12.0	1.1	.72
Pulmonary	0.8	0.0	2.1	1.4	NA†
Neurosensory	4.9	0.0	15.9	1.1	NA†
Stomatitis	14.7	1.1	17.4	1.1	.99
Alopecia	6.4	—	37.7	—	< .001
Diarrhea	12.8	0.4	24.3	2.5	.069
Rash	14.0	0.8	6.2	0.7	1.00
Weight loss	1.1	0.0	1.8	0.0	NA
Edema	4.5	0.0	8.3	0.0	NA
ALT	7.9	1.9	1.4	0.0	.028

Abbreviation: NA, not applicable.
*Fisher's exact test used; comparison is between grade 3 and 4 toxicities except for alopecia.
†*P* value not calculated due to small number of patients (< 4 when arms combined) experiencing grade 3 or 4 toxicity.

Shepherd et al did not allow prior paclitaxel, while 42% of patients (on the 75 mg/m^2 arm of docetaxel) had received paclitaxel on the Fossella et al study as did 25% in this study. Prior treatment with paclitaxel did not seem to reduce efficacy to any of the agents under study in either of the trials. PS 2 patients made up approximately 24% and 18% of those treated with docetaxel in the Shepherd et al and Fossella et al studies. Approximately 12% on each arm in this study had a PS of 2. Otherwise, the patient characteristics were similar on all three studies (sex, age, stage, % with PD to first-line therapy). Patients on this study and the Fossella et al study did not routinely receive G-CSF as prophylaxis, unless the patient had already experienced a neutropenic event with a previous cycle, but rather only as treatment for toxicity. Therefore, the high rates of use of G-CSF on the docetaxel arm of the current study cannot be attributed to the routine use of G-CSF for prophylaxis.

Although there was clinically equivalent efficacy demonstrated between the two agents in this study, there were several clinically and statistically significant differences in their toxicity profiles. There were higher rates of neutropenia (with and without complications) and more frequent use of G-CSF for patients on the docetaxel arm when compared to the pemetrexed arm. The rate of grade 3 or 4 neutropenia due to docetaxel in our study was 40.2%, which is significantly lower than the rates of neutropenia reported with the 75 mg/m^2 docetaxel arms of the studies by Shepherd et al (67.3%) and Fossella et al ($>$ 54%). The rate of neutropenic fever due to docetaxel in our study was 12.7%, which is also comparable to that observed in the combined docetaxel arms in the Shepherd et al (11.5%) and Fossella et al studies (10%). When considering only the 75 mg/m^2 arms of those studies, however, the rate of neutropenic fever was lower in the Shepherd et al study (1.8%) and Fossella et al study (8%) when compared with our study, despite a significantly higher percentage of patients at risk. Pemetrexed treated patients experienced significantly fewer hospitalizations for neutropenic fever. Rates of infection with docetaxel were also comparable between the three studies (approximately 3% in the combined docetaxel arms). The higher rate of neutropenic complications with docetaxel in this study is not related to the duration of treatment given (median 3 to 4 cycles on each study), patient characteristics—the Shepherd et al study had more PS 2 patients, and they were more heavily pretreated with chemotherapy in that 25% were receiving docetaxel as third-line or greater— or use of prophylactic G-CSF without a preceding neutropenic event. In addition, the rates of other hematologic toxicities (anemia and thrombocytopenia) were comparable among the three studies.

In this study, patients treated with pemetrexed had a significantly lower rate of alopecia ($P < .001$) and a trend toward lower rates of grade 3 or 4 diarrhea ($P = .069$) compared with patients receiving docetaxel. An increase in ALT was the only toxicity that was higher in the pemetrexed arm ($P = .028$). Overall, the rates of improvement or stabilization of baseline symptoms were similar between the two arms ($P = .145$).

In conclusion, treatment with pemetrexed demonstrated clinically equivalent efficacy with a significantly improved safety profile compared with those receiving docetaxel in the second-line setting for advanced NSCLC in this study. Based on these results, treatment with pemetrexed should be considered a standard treatment option for second-line NSCLC.

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Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Owns stock (not including shares held through a public mutual fund): Paolo Paoletti, Eli Lilly; Frances A. Shepherd, Eli Lilly. Acted as a consultant within the last 2 years: Nasser Hanna, Eli Lilly, Aventis; Ulrich Gatzemeier, Eli Lilly; Paul A. Bunn Jr., Eli Lilly; Miklos Pless, Eli Lilly; Christian Manegold, Eli Lilly; Frank V. Fossella, Eli Lilly, Aventis; Frances A. Sheperd, Eli Lilly, Aventis. Performed contract work within the last 2 years: Paul A. Bunn Jr., Eli Lilly; Frances A. Sheperd, Eli Lilly. Received more than $2,000 a year from a company for either of the last 2 years: Nasser Hanna, Eli Lilly, Aventis; Ulrich Gatzemeier, Eli Lilly; Paul A. Bunn Jr., Eli Lilly; Christian Manegold, Eli Lilly; Frank V. Fossella, Eli Lilly, Aventis; Frances A. Sheperd, Eli Lilly, Aventis.

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