Phase II Trial of Weekly Docetaxel in Second-Line Therapy for Nonsmall Cell Lung Carcinoma

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BACKGROUND. The authors conducted a Phase II study to evaluate the activity and toxicity of weekly docetaxel in second-line therapy for nonsmall cell lung carcinoma (NSCLC).

METHODS. Patients with documented recurrent or refractory NSCLC, previously treated with no more than one chemotherapy regimen, were eligible if they had a performance status (PS) of 0–2, measurable or evaluable disease, and adequate organ function. Patients were treated with docetaxel 36 mg/m^2/week for 6 consecutive weeks, administered intravenously with dexamethasone premedication. Cycles were repeated every 8 weeks.

RESULTS. Thirty-one patients were enrolled. One patient was ineligible because of uncontrolled brain metastases. Hematologic toxicity was minimal. Nonhematologic toxicities were modest except for diarrhea and cumulative fatigue. There were no treatment-related deaths. The overall response rate was 10% (95% confidence interval [CI], 1.6–29%). The median survival time (MST) was 8.0 months. and the 1-year survival rate was 31% (95% CI, 17– 58%). Patients with PS 0–1 had a MST of 11.9 months with 1-year survival of 42%.

CONCLUSIONS. Weekly docetaxel is very well tolerated as second-line therapy for NSCLC. The activity of this regimen appears to be comparable to the standard 3-week schedule. This regimen offers new opportunities for combination regimens, both as first- and second-line therapy for NSCLC. ***Cancer* 2001;92:2158–63.**

KEYWORDS: weekly docetaxel, second-line therapy, nonsmall cell lung carcinoma (NSCLC), quality of life.

Until recently, second-line chemotherapy for advanced nonsmall cell lung carcinoma (NSCLC) was of unproven benefit. Two large randomized trials have now shown a survival advantage and an improvement in quality of life (QOL) for docetaxel in previously treated NSCLC patients. The first trial, by Shepherd et al.,[1] compared docetaxel with best supportive care in patients who received one or more platinum-based combinations. Despite a low objective response rate, there was a significant difference in survival in favor of the docetaxel group (1-year survival of 40% vs. 16%). The second trial, by Fossella et al., compared docetaxel to either vinorelbine or ifosfamide.[2] The results confirmed a significant survival advantage for patients treated with docetaxel at 75 mg/m^2, administered every 3 weeks (1-year survival of 32% vs. 19%). Importantly, both trials also showed an improved QOL for patients treated with docetaxel.[3,4]

However, hematologic toxicity in these studies was substantial. Grade 3–4 neutropenia was observed in 76% of patients in the Canadian trial, including 67% of patients treated with docetaxel 75 mg/m^2. Febrile neutropenia was observed in 1.8% of these patients as op-

posed to 22.4% of those who received 100 mg/m^2. In the U.S. trial, 54% of patients treated with docetaxel 75 mg/m^2 had Grade 3–4 neutropenia, and 8% had febrile neutropenia. These results were not unexpected because the dose-limiting toxicity of docetaxel administered every 3 weeks is indeed myelosuppression.

Therefore, an alternative schedule would be advantageous in this population of previously treated patients. Hainsworth et al. reported a Phase I trial of docetaxel administered on a weekly schedule and recommended a dose of 36 mg/m^2/week for 6 consecutive weeks, repeated every 8 weeks.[5] Myelosuppression was decreased markedly compared with the traditional 3-week schedule. There were no episodes of Grade 4 neutropenia, and Grade 3 neutropenia was infrequent. Anemia and thrombocytopenia were very modest, as were nonhematologic toxicities.

On the basis of the benefits associated with docetaxel in second-line NSCLC, and its relatively benign toxicity profile when used on a weekly schedule, we conducted a Phase II trial to test weekly docetaxel in second-line NSCLC.

MATERIALS AND METHODS

Patient Eligibility

Patients with histologically or cytologically documented NSCLC were eligible if they had recurrent or refractory disease and received one prior chemotherapy regimen. Prior therapy with either paclitaxel or docetaxel, administered on a 3-week schedule, was acceptable. A Cancer and Leukemia Group B (CALGB) performance status (PS) of 0–2 and measurable or evaluable disease were required. Patients with brain metastases were eligible if they were neurologically stable after brain irradiation. Patients who received thoracic radiotherapy were eligible if they had measurable or evaluable disease outside the radiated field. Adequate renal (serum creatinine $<$ 1.5 mg/dL), hepatic (bilirubin $<$ 1.5 times the upper limit of normal), and hematologic (granulocytes $>$ 1500/μL, hemoglobin $>$ 10 g/dl, and platelet count $>$ 100,000/μL) parameters were required. Patients with other nonpulmonary primary tumors surgically resected more than 5 years before study entry, without administration of adjuvant chemotherapy or radiotherapy, were eligible. Patients with an uncontrolled infection, patients with a psychiatric condition that would preclude informed consent, and pregnant women or nursing mothers were excluded. All patients signed a written informed consent form approved by the Mount Sinai Medical Center Institutional Review Board.

Pretreatment evaluation consisted of a complete history and physical examination, posteroanterior and lateral chest X-ray, complete blood cell count, and serum chemistry analysis. Computed tomographic (CT) scans of the chest to the level of the adrenal glands were obtained in all patients. Computed tomography scan of the brain, abdomen, and pelvis, and radionuclide bone scans were performed when clinically indicated. All pretreatment laboratory work was obtained within 14 days of study entry, whereas X-rays or CT scans utilized for tumor measurements were obtained within 28 days of study entry. A complete blood cell count was repeated every week, and the serum chemistry analysis was repeated on Day 1 of each treatment cycle. Relevant studies for tumor measurement were repeated after each 6-week cycle.

Treatment Regimen

Treatment consisted of docetaxel at a dose of 36 mg/m^2/week for 6 consecutive weeks, administered intravenously over 15 minutes. Premedication consisted of 3 doses of dexamethasone 8 mg, given 12 hours before, at the time of chemotherapy administration, and 12 hours later. Further antiemetics were used at the physician's discretion. The use of filgrastim was not allowed. Concomitant radiation therapy was not permitted. Cycles were repeated every 8 weeks. Patients who continued to benefit were permitted to receive additional cycles at the discretion of the attending physician. Chemotherapy was discontinued in patients with progressive disease (PD) or unacceptable toxicity.

Dose modifications based on hematologic toxicity were made as follows: at the start of each cycle, the absolute neutrophil count (ANC) had to be greater than or equal to 1500/mm^3 and the platelet count greater than or equal to 100,000/mm^3. A 20% dose reduction was required if patients developed the following: Grade 4 neutropenia lasting more than 5 days; febrile neutropenia; Grade 4 thrombocytopenia. If on any day of a scheduled treatment, the ANC was less than 1500/mm^3 or the platelet count was less than 100,000/mm^3, treatment was withheld that week, and missed doses were not "made up."

Dose adjustments also were made for nonhematologic toxicities. For Grade 2 diarrhea, treatment was withheld until full recovery, and the dose of docetaxel reduced by 20%. If diarrhea persisted, the dose was further reduced by 20%; and if diarrhea still persisted, the patient was removed from the study. For hepatic dysfunction, doses were adjusted according to bilirubin, alkaline phosphatase, and aspartate aminotransferase levels. For neurologic toxicity of Grade 3–4, patients were removed from the study; for Grade 2, patients were retreated on recovery to a less than Grade 1 toxicity with a dose reduction of 20%. Hypersensitivity reactions were treated according to estab-

lished guidelines. No dose reductions were made for fluid retention. Patients who developed symptomatic edema or other signs of fluid retention were treated with oral diuretics. For other toxicities that exceeded Grade 2 except alopecia, nausea, or vomiting, a 20% dose reduction was required.

Response and Toxicity Criteria

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

Statistical Analysis

The primary objectives of this trial were to define the activity and the toxicity of weekly docetaxel in patients with recurrent or refractory NSCLC. The study had an 80% power, with a level of significance of 0.05, to test the hypothesis that H0: *P* value less than 10% versus *P* value greater than 0.20, where *P* denotes the response rate as defined above. Overall survival and failure free survival were analyzed using the Kaplan–Meier estimation method. Survival was defined as the time between initiation of treatment and death. If death had not occurred, survival time was considered censored at time of last follow-up. Failure free survival was defined as the time between initiation of treatment and failure (i.e., death or disease progression). If failure had not occurred at the time of this analysis, failure free survival was considered censored at the time of last follow-up.

RESULTS

Patient Characteristics

Thirty-one patients were entered between August 1998 and June 2000. One patient was considered ineligible because of uncontrolled brain metastasis. The characteristics of the 30 eligible patients are summarized in Table 1. There were 17 males and 13 females with a median age of 68 (range, 47–84). Twenty-one patients had a PS of 0–1 (70%) and 9 had PS of 2 (30%). Previous chemotherapy consisted of a combination of vinorelbine and gemcitabine in 9 patients (30%), cisplatin or carboplatin with paclitaxel in 10 patients (33%), cisplatin with vinorelbine or gemcitabine in 3 patients (10%), and different single agents or combinations in the remaining patients. Response to first-line therapy is shown in Table 1.

TABLE 1
Patient Characteristics

Characteristic	No. of patients	Percentage
No. of patients	30	
Gender		
Male	17	57
Female	13	43
Age (yrs)		
Median	7.5	
Range	47–84	
Performance status		
0	1	3
1	20	67
2	9	30
Previous chemotherapy		
Cis or Carbo + Paclitaxel	10	33
Cis + Gem or Vin	3	10
Gem + Vin	9	30
Other Combinations	3	10
Single Agents	5	17
Response to prior chemotherapy		
Partial response	10	33
Stable disease	7	23
Progressive disease	12	40

Cis: cisplatin; Carbo: carboplatin; Gem: gemcitabine; Vin: vinorelbine.

Toxicity

All 30 eligible patients, who received a total of 134 treatment doses, were evaluable for toxicity. Median number of cycles per patient was one. The incidence and severity of myelosuppression for all doses are shown in Table 2. Hematologic toxicity was very mild, with only one patient experiencing Grade 4 neutropenia (3%). There were no episodes of febrile neutropenia. There were no episodes of Grade 3–4 anemia, but 17% of patients experienced cumulative Grade 2 anemia. Thrombocytopenia was not encountered.

Nonhematologic toxicities were, in general, well tolerated (Table 2). Nausea, emesis, and mucositis were mild. Diarrhea was moderate to severe in 4 patients (13%), and required dose modifications in all 4 patients. Peripheral neuropathy was rare, with only one Grade 1 episode. Fatigue was pronounced and observed in 33% of patients, mostly at the end of the 6-week cycle, and partially reversible during the treatment break. Fluid retention was noted in 13% of patients. Lacrimation and nail changes were mild, but persistent.

TABLE 2
Hematologic and Nonhematologic Toxicity (All Cycles)

	Toxicity scale grading		
Event	**2 (%)**	**3 (%)**	**4 (%)**
Neutropenia	1 (3)	1 (3)	1 (3)
Anemia	9 (30)	5 (17)	0
Thrombocytopenia	0	0	0
Nausea/vomiting	0	1 (3)	1 (3)
Diarrhea	3 (10)	2 (7)	2 (7)
Mucositis	4 (13)	0	0
Rash	2 (7)	1 (3)	1 (3)
Paresthesia	2 (7)	1 (3)	0
Fluid retention	3 (10)	1 (3)	0
Fatigue	8 (27)	4 (13)	6 (20)
Alopecia	11 (37)	2 (7)	0

TABLE 3
Tumor Response

Best response	No. of patients	Percentage
Complete response	0	0
Partial response[a]	3	10
Stable disease	6	20
Progressive disease	17	57
Unevaluable[b]	3	10

[a] 95% confidence interval: 1.6–29%.

[b] Unevaluable patients are discussed in the text.

Response and Survival

Among the 30 eligible patients, 3 achieved a PR (overall response rate [ORR], 10%; 95% confidence interval [CI], 1.6–29%), 6 had SD (20%), and 17 had PD (57%) after the first cycle (Table 3). Three patients did not complete the first cycle of therapy and were not considered evaluable for response: one moved out-of-state and could not be observed; one developed a nonpathologic hip fracture and did not resume therapy after convalescence, and the third patient withdrew consent and requested to be transferred to another hospital. First-line therapy in the three patients who responded consisted of gemcitabine alone, gemcitabine and vinorelbine, and carboplatin and paclitaxel, respectively. Performance status was a powerful predictor of response: all patients with PS 2 progressed. Prior response to chemotherapy was not predictive of response to docetaxel.

At a median follow-up of 7.1 months, the median survival time (MST) for all patients was 8.0 months (95% CI, 5.6–13.9; Fig. 1). The 1-year actuarial survival was 31% (95% CI, 17–58%). For patients with PS 0–1, the MST and 1-year survival were 11.9 months and 42%, respectively. Failure free survival was 2.5 months for all patients (95% CI, 1.7–5.3), 3.5 months for PS 0–1, and 1.8 months for PS 2 patients.

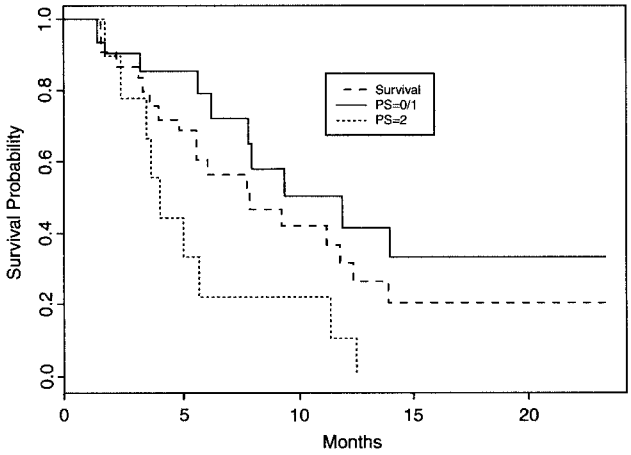

FIGURE 1. The overall survival curve and the survival stratified by performance status (PS) curves are shown.

DISCUSSION

Before docetaxel, the administration of second-line therapy for advanced NSCLC patients was of questionable benefit and did not follow rational or systematic guidelines. Randomized data are now available and indicate a survival benefit as well as an improvement in QOL for docetaxel compared with supportive care or other chemotherapeutic agents, such as vinorelbine or ifosfamide.[1,2] However, the main limitation of docetaxel, when administered on a standard every 3-week schedule, is hematologic toxicity, which can be substantial.

Based on our results, the weekly administration of docetaxel seems to be a well tolerated and convenient regimen. Its main advantage over the traditional schedule is the lack of neutropenia and associated febrile episodes, which may be particularly important for previously treated patients. Anemia was uncommon in our study because of the low number of cycles received by each patient, but it may be observed in patients who receive two or more cycles. Thrombocytopenia was nonexistent and does not appear to be a significant toxicity of this regimen. Thus, the weekly schedule is particularly suitable for those patients who are at high risk for myelotoxic complications from chemotherapy.

An unexpected toxicity in our study was diarrhea, which was severe in some patients. When docetaxel is given every 3 weeks, diarrhea is neither common nor severe, and was rarely observed in the second-line randomized trials discussed above. The reasons for this toxicity, which seems to be schedule-dependent

are not immediately apparent and require further investigation. Cumulative fatigue is also an important toxicity and has been well described with docetaxel, given either every 3 weeks or on a weekly schedule. An alternative schedule of 3 consecutive weeks, with a 1-week break, may diminish the frequency of fatigue and currently is being investigated.

Although the group of patients in our study was relatively small, it appears that efficacy is not compromised on the weekly schedule. Our response rate is comparable to the randomized trials, despite the presence of a high percentage of patients with poor PS in our study. More importantly, our MST also compares favorably to the larger studies. The benefit of docetaxel in second-line therapy, according to our study, was evident only in patients with PS 0–1. Although the same argument can be held for first-line therapy, it remains questionable whether patients with PS 2 should be treated with second-line therapy.

Two other studies evaluated weekly docetaxel in second-line therapy for NSCLC and have been reported in abstract form.[6,7] Serke et al. from Germany treated 26 patients for whom first-line platinum-based chemotherapy with docetaxel at 35 mg/m^2/week for 6 weeks failed.[6] There was minimal hematologic toxicity, and a preliminary response rate of 17% was reported. The second trial from Spain used docetaxel at a dose of 43 mg/m^2/week for 6 weeks.[7] Among 26 evaluable patients, hematologic toxicity was again very mild, but nonhematologic toxicities were more severe because of the higher doses of docetaxel utilized. The ORR was 17.4%. Survival data were not mature for either one of these studies. Based on these preliminary reports, the experience for weekly docetaxel in this setting appears consistent and reproducible.

Weekly docetaxel also has been studied in other solid tumors. Burnstein et al. were one of the first to report on the use of weekly docetaxel in advanced breast carcinoma. The investigators treated 29 patients with weekly docetaxel at 40 mg/m^2/week for 6 weeks.[8] Efficacy was within the range reported for taxanes in previously treated patients with advanced disease. Only 28% of patients had any Grade 3 toxicity, mainly neutropenia and fatigue. Cumulative toxicities (in addition to fatigue) included eye tearing and nail changes, which were mild but persistent. In prostate carcinoma, a disease in which docetaxel is being increasingly utilized, a study of weekly administration showed a PSA response rate of 47% according to standard criteria, with a less than 10% incidence of toxicities.[9] Taken together, these studies, albeit small, indicate similar efficacy of weekly docetaxel compared with the standard 3-week schedule and confirm a different, perhaps preferable, toxicity profile.

There is not much information on the use of weekly docetaxel in the first-line therapy of NSCLC. The most mature Phase II data come from Hainsworth and colleagues, who tested weekly docetaxel in the elderly or in patients who were not determined to be candidates for platinum-based chemotherapy.[10] Thirty-nine patients received docetaxel at 36 mg/m^2/week for a maximum of 4 cycles. Toxicity was mild with essentially no clinically significant myelosuppression. An ORR of 18%, with a median survival of 5 months, was reported for the entire group. The response rate was higher in patients with PS 0–1 (26%) compared with PS 2 (7%), but 1-year survival was the similar between the 2 groups. The authors concluded that weekly docetaxel compares favorably with other therapeutic interventions in elderly patients with advanced NSCLC. Further studies with weekly docetaxel, alone or in combination, in the first-line management of NSCLC currently are being undertaken.

Based on a favorable toxicity profile and similar efficacy, it appears that when used as second-line therapy in NSCLC, the overall therapeutic index of docetaxel is improved with the weekly schedule. Our group currently is testing weekly docetaxel in combination with trastuzumab as second-line therapy for NSCLC patients who overexpress HER-2/*neu*. In addition, combination regimens with weekly docetaxel and the new molecular-targeted agents also are being planned and may further improve treatment efficacy in advanced NSCLC.

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