# Phase II Trial of a 75-mg/m² Dose of Docetaxel with Prednisone Premedication for Patients with Advanced Non-Small Cell Lung Cancer

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***Background.*** **A prior Phase II study of a 100-mg/m² dose of docetaxel conducted at the Memorial Sloan-Kettering Cancer Center (New York, NY) demonstrated a 38% response rate with grade 3 or 4 neutropenia in 76% of the patients and a grade 2 or greater rash or infusion-related reaction in 41% and 34% of the patients, respectively. The current Phase II study sought to determine the activity of a 75-mg/m² dose of docetaxel to establish whether this lower dose, combined with prednisone, ameliorates toxicity.**

***Methods.*** **Twenty untreated patients with advanced non-small cell lung cancer (NSCLC) received a 1-hour 75-mg/m² dose of docetaxel every 21 days. Fifty milligrams of prednisone were administered twice the day before chemotherapy and once each of the next 3 days. Patients' disease-related symptoms were assessed prospectively using the Lung Cancer Symptom Scale (LCSS).**

***Results.*** **All patients were assessable for response and toxicity. Five patients had a major objective response (25%; 95% confidence interval, 11–50%). The median duration of response was 9.1 months. The projected 1-year survival was 71%. Grade 3 or 4 neutropenia occurred in 70% of the patients. Grade 2 or greater rash and infusion-related reactions decreased to 25% each. Analysis of the LCSS measurements found that six of nine component symptoms improved on Day 22, and all improved when baseline measurements were compared with the best value for each patient during the study.**

***Conclusions.*** **Docetaxel administered at a dose of 75 mg/m² every 21 days shows significant antitumor activity in untreated patients with NSCLC. Neutropenia is comparable with that observed at a 100-mg/m² dose. The number of infusional reactions and rash decreased when docetaxel at this dose was administered with prednisone. Based on response rates observed in trials using a 100-mg/m² dose with similar degrees of neutropenia, a 100-mg/m² dose with steroid pretreatment is recommended future trials. *Cancer* 1995;75:968–72.**

**Key words: docetaxel, NSCLC, taxoid, taxotere.**

Docetaxel is a semisynthetic taxoid prepared from a precursor compound derived from the needles of the European yew, *Taxus baccata*.[1–3] Docetaxel (Taxotere; RP 56976; NSC 628503) and paclitaxel (Taxol) promote microtubule assembly and inhibit depolymerization.[1,4–6] Phase I trials defined the dose-limiting toxicity to be neutropenia and recommended a Phase II 1-hour 100-mg/m/² dose every 3 weeks. Phase II trials using this dose for patients with non-small cell lung cancer (NSCLC) showed response rates of 31–38%[1,7,8] with grade 3 or 4 leukopenia observed in 52–76% of patients. Infusion-related reactions and rash were common, and fluid retention was found in patients who received cumulative doses greater than or equal to 500 mg/m². We undertook this Phase II study of a lower dose of docet-

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axel with prednisone treatment in an attempt to lessen these side effects and maintain efficacy.

## Patients and Methods

### *Patients*

From March to July 1993, 20 patients with pathologically confirmed NSCLC were enrolled. All had unresectable Stage III or IV disease.[9] All patients had a Karnofsky performance status of greater than or equal to 60%. Patients were required to have measurable or evaluable indicator lesions on physical examination, chest roentgenogram, or computed tomography scan.[10–12] Specifically excluded as indicator lesions were effusions, bone metastases, and previously irradiated tumors. No prior chemotherapy was allowed. Patients were not permitted to have received radiation therapy to major bone marrow areas within the 3 weeks before study entry. Requirements for eligibility also included a leukocyte count greater than or equal to $3500/mm^3$, granulocyte count greater than or equal to $2000/mm^3$, platelet count greater than or equal to $100{,}000/mm^3$, bilirubin level less than or equal to 1.5 mg/dL, and creatinine level less than or equal to 2.0 mg/dL or creatinine clearance of greater than or equal to 60 mL/minute. Patients with greater than grade 1 peripheral neuropathy, untreated or clinically evident brain metastases, unstable cardiac disease, or prior malignancy were excluded. Written informed consent was obtained from all patients, and the protocol was approved by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center.

### *Treatment Plan*

Before therapy, all patients had a complete history and physical examination, complete blood count, prothrombin and partial thromboplastin time, electrolytes, glucose, hepatic and renal biochemical tests, urinalysis, chest roentgenogram, and electrocardiogram. A computed tomography scan of the chest including the adrenals was performed within 2 weeks of initiating treatment. Bone and brain scans were obtained if clinically indicated.

Docetaxel was supplied by Rhône-Poulenc Rohrer Central Research (Collegeville, PA) as a concentrated sterile solution with 40 mg/mL (80 mg/2 mL/vial) in polysorbate 80. Before infusion, docetaxel was diluted in 250 mL of 5% dextrose. Docetaxel was administered in a 1-hour 75-$mg/m^2$ intravenous infusion in the Adult Day Hospital of Memorial Sloan-Kettering Cancer Center (New York, NY). During the first and second infusions of docetaxel a physician was present for the initial 10 minutes. Blood pressure and pulse were obtained six times during and 30 minutes after infusion was completed, and patients remained in this area for at least 2 hours after completing docetaxel infusion. All patients received an adapted regimen for preventing allergic reactions to the contrast media; prednisone 100 mg orally was administered before treatment and 50 mg once each on the morning of treatment and the two next days.[13] No other premedications were given routinely. If infusion-related symptoms occurred, the infusion was interrupted and diphenhydramine was administered. On subsequent cycles, those patients then were routinely premedicated with diphenhydramine 25 or 50 mg intravenously and cimetidine 300 mg intravenously.

Docetaxel was administered every 21 days. During the first two cycles of treatment, patients were evaluated weekly for toxicity (Common Toxicity Criteria from the Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD); thereafter, evaluation occurred on treatment days. Disease-related symptoms were assessed by patients' completing the Lung Cancer Symptom Scale[14,15] before receiving docetaxel on each treatment day. Tumor response assessment was made every 3 weeks if the lesions were identified on chest radiographs or on physical examination. Computed tomographic scans were obtained every 6 weeks. Categories of response included complete, partial, improved, no change, and progression.[10–12] Duration of response and survival were measured from the date of the first treatment of docetaxel. All major responses were reviewed by a reference radiologist (R.T.H.) and an external review panel.

## Results

Twenty patients were enrolled, all of whom were assessable for response and toxicity. Patient characteristics are summarized in Table 1. Five major objective responses were documented (25% observed major response rate, 95% confidence interval, 11–50%). Three patients had improvement in evaluable indicator lesions (n = 11), and two patients with measurable lesions (n = 9) attained a partial response. No complete remissions occurred. Maximal responses were documented as late as 6 months after commencing treatment. Response data are summarized in Table 2.

The overall median survival is 9.1+ months. Of the 5 major responders, 2 continued in the study at 11+ and 8+ months, respectively. The projected 1-year survival for all patients was 71%. Seventeen of 20 patients completed the Lung Cancer Symptom Scale[14,15] at baseline and during the trial. Changes in the mean 100-mm visual analogue scale scores measuring disease-related

**Table 1. Pretreatment Patient Characteristics**

| | No. | % |
|---|---|---|
| No. of patients | 20 | — |
| Stage | | |
| IIB | 4 | 25 |
| IV | 16 | 75 |
| Sex | | |
| Men | 10 | 50 |
| Women | 10 | 50 |
| Karnofsky Performance Status | | |
| 80–90% | 14 | 70 |
| 60–70% | 6 | 30 |
| Weight loss ≥6% | 6 | 30 |
| Elevated serum LDH | 10 | 50 |
| Bone metastases | 2 | 10 |
| Median age (yr) | 58 | — |
| Range (yr) | 42–69 | — |
| Cell types | | |
| Adenocarcinoma | 14 | 70 |
| Squamous cell carcinoma | 1 | 5 |
| Large cell carcinoma | 3 | 15 |
| NSCLC, not specified | 2 | 10 |
| Prior treatment | | |
| Surgery | 5 | 25 |
| Radiation | 4 | 20 |

LDH: lactic dehydrogenase; NSCLC: non-small cell lung carcinoma.

symptoms for these 17 patients reported from baseline to Day 22 and from baseline to the best point observed during the study are displayed in Table 3. Numerically, six of the nine component symptoms improved from Days 1–22, and all showed improvement from baseline to the best-observed study point.

All patients were assessable for hematologic toxicity, summarized in Table 4. Fourteen of 20 patients (70%) had grade 3 or 4 neutropenia. Two patients had grade 3 or 4 anemia, and none had thrombocytopenia greater than or equal to 2+. Eight patients (40%) were hospitalized on 12 occasions for neutropenia with or without fever or localizing signs of infection. Overall, 10 patients were hospitalized 19 times while in the study. Six patients required a dose reduction to 55 mg/m$^2$ as a result of admission for grade 3 or 4 neutropenia associated with fever and requiring parenteral antibiotics, and two of these had a further dose reduction to 40 mg/m$^2$ because of a second such hospitalization. One was given prophylactic filgrastim after experiencing grade 3 leukopenia with fever despite two dosage reductions.

Twelve patients experienced 15 infusion-related re-

**Table 2. Response Data**

| | |
|---|---|
| No. of patients | 20 |
| Major responses | 5 |
| Complete resonses (CR) | 0 |
| Partial responses (PR) | 2 |
| Improvement (I) | 3 |
| 95% confidence interval | 11–50 |
| Response duration (mo) | |
| Median | 9.1 |
| Range | 5.0–11.5+ |
| Survival | |
| Median (mo) | 9.1+ |
| One-year projected (%) | 71 |

**Table 3. Measurement of Disease-Related Symptoms Using the Lung Cancer Symptom Scale***

| | Pretreatment to Day 22* | P† | Pretreatment to "best" | P† |
|---|---|---|---|---|
| Hemoptysis | −0.47 | 0.40 | −0.83 | 0.18 |
| Pain | −0.23 | 0.75 | −1.61 | 0.07 |
| Appetite | −0.69 | 0.62 | −1.08 | 0.44 |
| Cough | −1.01 | 0.32 | −2.22 | 0.15 |
| Dyspnea | +0.49 | 0.43 | −0.68 | 0.39 |
| Activity | +0.12 | 0.89 | −1.20 | 0.25 |
| Quality of life | +0.08 | 0.94 | −1.48 | 0.22 |
| Fatigue | −1.01 | 0.22 | −2.22 | 0.02 |
| Lung cancer symptoms | −1.06 | 0.30 | −2.10 | 0.06 |

Values are changes in mean 100 mm visual analogue scale scores.[14,15]

* Each patient's score on a given symptom underwent "square-root transformation" to stabilize variance, followed by calculation of the difference from baseline to Day 22 or "best." The obtained values were then averaged for all patients on a given symptom and represent the displayed results.

† *P* values are derived from paired *t* tests comparing pretreatment values to Day 22 (first tumor assessment) and "best" values recorded for each patient during their time on study. A negative value indicates an improvement in a symptom, whereas a positive value indicates a worsening.

**Table 4. Docetaxel Toxicity**

| | Highest NCI toxicity grade | | | | |
|---|---|---|---|---|---|
| **Toxicity** | *0* | *1* | *2* | *3* | *4* |
| Alopecia | 0 | 59 | 41 | — | — |
| Neutropenia | 5 | 5 | 20 | 30 | 40 |
| Anemia | 5 | 65 | 20 | 5 | 5 |
| Infusion reactions | 40 | 35 | 25 | 0 | 0 |
| Diarrhea | 50 | 45 | 5 | 0 | 0 |
| Rash | 65 | 10 | 25 | 0 | 0 |
| Neurosensory | 65 | 20 | 15 | 0 | 0 |
| Mucositis | 65 | 30 | 5 | 0 | 0 |
| Nausea/vomiting | 75 | 25 | 0 | 0 | 0 |
| Weight gain | 75 | 25 | 0 | 0 | 0 |
| Liver biochemical | 85 | 10 | 5 | 0 | 0 |
| Thrombocytopenia | 90 | 10 | 0 | 0 | 0 |
| Neuromotor | 95 | 0 | 0 | 5 | 0 |

NCI: National Cancer Institute.

Values are percent of patients (n = 20).

actions; all but 1 of these episodes occurred on the first or second cycle. Overall, of 111 administered doses, 9 grade 1 and 6 grade 2 reactions were observed (14% frequency of infusion-related reactions). The most common syndrome consisted of flushing without associated dyspnea, chest tightness, or diaphoresis. Other frequent symptoms included chest and/or throat tightness, blurred vision, and low back or truncal pain. Five episodes required brief interruption of the infusion. Diphenhydramine (25 or 50 mg intravenously) was given. No reaction necessitated hospitalization, and symptoms never recurred after the infusion recommenced.

Seven patients experienced a rash, five of whom were minimally symptomatic (grade 2). Observed changes included scattered maculopapular eruptions and desquamation of the hands and/or feet. No patient required treatment delay, dose reduction, or dermatologic evaluation, and all rashes were self-limited. Grade 1 weight gain accompanied by peripheral edema, with or without pleural effusion, was observed in 5 patients (25%). No grade 2 or greater weight gain was seen, and this constellation of signs was noted almost exclusively in individuals who received higher cumulative doses of docetaxel. Grade 1 weight gain was noted in 3 of 4 individuals receiving cumulative doses greater than 500 mg/m$^2$, but in only 1 of 16 other patients. One patient required diuretics for symptomatic edema.

Other less frequent toxicities are summarized in Table 4 and included alopecia, nausea, vomiting, diarrhea, and liver dysfunction. In two patients, grade 2 sensory neuropathy developed, which was transient in one and allowed for retreatment on schedule, whereas it improved in the other individual after an additional 2-week treatment-free interval. A third patient experienced grade 3 motor and grade 2 sensory neuropathy characterized by proximal muscle weakness and stocking-glove peripheral neuropathy necessitating discontinuation of docetaxel. These symptoms improved to grade 1 over 6 months.

Grade 2 hepatotoxicity was seen in one patient with a history of continuing alcohol abuse but with no stigmata of chronic liver disease and normal liver biochemical tests at study entrance. After receiving four cycles of docetaxel, the patient's albumin level decreased to 3 g/dL, serum glutamic oxaloacetic transaminase increased to 101 U/L (grade 2), and alkaline phosphatase peaked at 433 U/L (grade 2). An abdominal computed tomography and ultrasound revealed ascites and a cirrhotic liver uninvolved by tumor. Ascitic fluid was a cytology-negative transudate. The patient's liver abnormalities normalized over a 2-month period after drug discontinuation and alcohol abstention. Overall, treatment was discontinued in two patients because of toxicity. There were no treatment-related deaths.

## Discussion

Prior Phase II studies with a 100-mg/m$^2$ dose of docetaxel in untreated patients with inoperable non-small cell lung cancer have demonstrated major objective response rates ranging from 31% to 38%[1,7,8] making this one of the most active single agents tested. This study sought to determine the antitumor activity of docetaxel administered at a dose of 75 mg/m$^2$ and whether this lower dose, when combined with prednisone premedication, could lessen the severity and frequency of adverse effects. Because the current study and our prior trial[1] were nonrandomized and contained a relatively small number of patients (29 and 20, respectively), direct statistical comparisons cannot be made. Pretreatment patient characteristics are comparable except that this study contains a greater proportion of patients with a high Karnofsky performance status (14 of 20 vs. 11 of 29 with a Karnofsky performance status of 80% or 90%). This trial again shows docetaxel to be an active agent in untreated patients with NSCLC. A lower observed response rate (25% vs. 38%) is noted, but confidence intervals for true response rates overlap. However, considering the difference in Karnofsky performance status, this lower response rate raises questions as to the equality of the two regimens. Furthermore, similar trends toward higher response rates with a 100-mg/m$^2$ dose of docetaxel, versus a 75-mg/m$^2$ dose, versus a 60-mg/m$^2$ dose have been reported by other investigators of patients with breast cancer and NSCLC.[1,7,8,16,17] Median duration of response (9.1 vs. 5.3 months) and median survival (9.1 + vs. 6.3 months) are superior in the current study, and these differences may be due partly to the relatively small number of patients in each study and to the better performance status of the former group as a whole.

Our prior Phase II study showed docetaxel to be associated with grade 3 or 4 neutropenia in 76%, grade 2 or greater rash in 41%, grade 2 or greater infusion-related reactions in 34%, and weight gain in 24%. As displayed in Table 5, use of this dose of 75 mg/m$^2$ had little impact on the frequency or severity of neutropenia and neurologic toxicity. Hospitalization rates were comparable. However, both rash and infusion-related reactions were less frequent and less severe. This may be related to a normal variation in the studied populations, prednisone use, and/or use of a lower dose of docetaxel in the current study. Other groups have found similarly that use of prednisone partially may obviate infusion-related reactions and rash.[18] Weight gain occurred in 75% of patients receiving cumulative docetaxel doses greater than or equal to 500 mg/m$^2$, the exact frequency noted in our prior study.[1] Thus, corticosteroid usage

**Table 5. Comparison of Docetaxel Toxicities of Two Different Schedules***

| | | NCI toxicity grade | | | | |
|---|---|---|---|---|---|---|
| **Toxicity** | **Trial** | ***0*** | ***1*** | ***2*** | ***3*** | ***4*** |
| Neutropenia | 1 | 0 | 10 | 14 | 28 | 48 |
| | 2 | 5 | 5 | 20 | 30 | 40 |
| Rash | 1 | 41 | 17 | 38 | 3 | 0 |
| | 2 | 65 | 10 | 25 | 0 | 0 |
| Infusion reactions | 1 | 41 | 24 | 24 | 10 | 0 |
| | 2 | 40 | 35 | 25 | 0 | 0 |
| Neurosensory | 1 | 59 | 28 | 10 | 3 | 0 |
| | 2 | 65 | 20 | 15 | 0 | 0 |
| Weight gain | 1 | 76 | 14 | 10 | 0 | 0 |
| | 2 | 75 | 25 | 0 | 0 | 0 |

NCI: National Cancer Institute.

* Trial 1, Docetaxel 100 mg/m$^2$ every 21 days, no premedication, n = 29; Trial 2, Docetaxel 75 mg/m$^2$ every 21 days, prednisone premedication, n = 20.

does not appear to impact on the incidence of fluid retention.

Docetaxel is a promising drug in the treatment of patients with NSCLC, and future trials will focus on combining this agent with cisplatin or ifosfamide (agents with known activity in this disease) in an effort to improve response rates and survival. However, these combinations are likely to be associated with increased toxicity as well, and, thus, the use of docetaxel in the minimal dose required to maintain optimal antitumor activity is desired. Our study suggests that use of docetaxel at a 75-mg/m$^2$ dose does not impact on the incidence of grade 3 or 4 neutropenia and associated hospitalization. Furthermore, peripheral neuropathy, another major concern when considering combination therapy, does not seem to decrease. Based on this and other studies, we recommend a dose of 100 mg/m$^2$ with corticosteroid premedication for future trials. Our symptom assessment was feasible and suggests that docetaxel administration is associated with either a stabilization or improvement of tumor-related symptoms.

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