A Phase II Study of Weekly Paclitaxel in Elderly Patients with Advanced Non-Small Cell Lung Cancer

Panos Fidias, Jeffrey G. Supko, Renato Martins, Anthony Boral, Robert Carey, Michael Grossbard, Geoffrey Shapiro, Patricia Ostler, Joan Lucca, Bruce E. Johnson, Arthur Skarin, and Thomas J. Lynch

ABSTRACT

Purpose: Our aim was to evaluate the efficacy, toxicity, and pharmacokinetic behavior of single-agent paclitaxel given weekly to elderly patients with lung cancer.

Experimental Design: Previously untreated patients with stage IIIB/IV non-small cell lung cancer were eligible for the study if they were at least 70 years of age and had preserved organ function. Paclitaxel was administered over 1 h at a dose of 90 mg/m² for 6 consecutive weeks on an 8-week cycle. The pharmacokinetics of paclitaxel were assessed during the first and sixth week of therapy in a subgroup of eight patients.

Results: A total of 35 patients (median age, 76 years; range, 70–85) were enrolled. The overall response rate was 23%. Median time to failure was 5.2 months, whereas the median survival time was 10.3 months. Survival rates after 1 and 2 years were 45 and 22%, respectively. Grade 3/4 toxicities included neutropenia (5.8%), hyperglycemia (17.6%), neuropathy (5.8%), and infection (8.8%). Two patients died from treatment-related toxicity. There was no significant difference (P = 0.18) between the total body clearance of paclitaxel on the first (17.4 ± 2.9 liters/h/m²) and sixth (15.8 ± 4.1 liters/h/m²) week of therapy.

Conclusion: Paclitaxel administered as a weekly 1-h infusion at a dose of 90 mg/m² is a safe and effective therapy for elderly patients with advanced non-small cell lung cancer. Its pharmacokinetics in elderly patients do not appear to differ from historical data for younger patients, and there was no suggestion of a change in drug clearance after repeated weekly dosing.

INTRODUCTION

Lung cancer is the leading cause of malignancy-related deaths in the United States (1). Over the last decade the role of chemotherapy in the treatment of advanced NSCLC has been clearly defined (2). Nevertheless, the failure to include elderly patients in clinical trials represents a limitation of these studies. A retrospective analysis of insurance claims revealed that only 5.1% of patients above the age of 64 received chemotherapy for advanced lung cancer, whereas this value increased to 18.8% for younger insured patients (3). Elderly patients are not only less likely to receive chemotherapy in the community; they are similarly underrepresented in clinical trials. This was shown very clearly in a recent analysis of clinical trial data from the Southwest Oncology Group (4). Despite the fact that patients older than 65 years of age account for >50% of all lung cancer cases, the median age of the patient populations evaluated in published clinical trials has been much younger, regardless of whether there was a protocol-defined age limit (5–11). Consequently, it is clear that our knowledge of the use of chemotherapy agents in elderly patients is based on a very select group of individuals. This is a real shortcoming because toxicity remains a significant consideration when attempting to treat a larger fraction of older individuals with aggressive combination regimens. Older patients frequently present with more extensive comorbid conditions as well as impaired renal or hepatic function; they therefore may exhibit diminished capacity to eliminate drugs, resulting in unusual sensitivity to standard dosing regimens (12–15). There is a need for protocols aimed specifically at elderly patients, which could allow broader participation and also provide the opportunity to closely study the toxicity and efficacy of chemotherapy in these patients.

The activity of paclitaxel against NSCLC has been demonstrated in several clinical trials. Response rates of 11–38% in previously untreated patients have been reported (16). In vitro experiments and clinical studies have suggested that prolonged exposure to paclitaxel, through either continuous infusion schedules or weekly administration, can lead to enhanced cytotoxicity while maintaining a favorable toxicity profile (17–21). At present, our experience with the use of weekly paclitaxel in previously untreated patients with NSCLC is rather limited, although the results that have been described appear to be very encouraging (22). Furthermore, although the pharmacokinetics

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1 To whom requests for reprints should be addressed, at Massachusetts General Hospital, 100 Blossom Street, Cox 201, Boston, MA 02114. Phone: (617) 726-9298; Fax: (617) 724-1137; E-mail: Pfidias2@Partners.org.

3 The abbreviations used are: NSCLC, non-small cell lung cancer; PS, performance status; SGOT, serum glutamic-oxaloacetic transaminase; ANC, absolute neutrophil count; AUC, area under the curve from time zero to infinity; CL, total plasma clearance.
of paclitaxel have been evaluated extensively when it is given by i.v. infusion over 1, 3, 24, or 96 h, there have been no studies designed to specifically examine the disposition of the drug in an elderly patient population (23).

On the basis of the established activity of paclitaxel against NSCLC, the rationale for prolonged exposure, and the tolerability of the weekly schedule, we decided to study this agent in a group of elderly patients with advanced disease. A dose of 90 mg/m² was chosen based on the available data from Phase I studies with this schedule (21, 24). This report describes the clinical efficacy, safety profile, and pharmacokinetics of paclitaxel when administered to elderly patients with NSCLC according to a weekly schedule.

PATIENTS AND METHODS

Patient Selection. Previously untreated patients were eligible for the study if they were at least 70 years of age and had histologically documented, measurable, or evaluable stage IIIB/IV NSCLC. A baseline PS of 0–3 in the Eastern Oncology Cooperative Group scale was required. The following laboratory parameters had to be met: bilirubin ≤1.5 mg/dl, SGOT equal to or less than two times the upper limit of normal, alkaline phosphatase equal to or less than two times upper limit of normal, serum creatinine ≤2.0 mg/dl, WBC count ≥3,000/µl, and platelet count ≥100,000/µl. Patients with uncontrolled brain metastases or symptomatic neuropathy, or those actively receiving radiation therapy were excluded. The protocol was explained to the patients, and signed informed consent approved by the institutional review board was obtained.

Pretreatment evaluations included a complete physical examination, a complete blood count with differential, and the following serum chemistry tests: electrolytes, blood urea nitrogen, creatinine, glucose, alkaline phosphatase, SGOT, and total and direct bilirubin. All sites of disease were documented by the institutional review board was obtained.

Treatment Plan. Paclitaxel (Taxol®; Bristol-Myers Squibb, Princeton, NJ) was infused i.v. over 1 h at a dose of 90 mg/m² each week for 6 consecutive weeks, followed by a 2-week break. This 8-week period defined a treatment cycle. Premedication consisted of 20 mg dexamethasone, 300 mg cimetidine or 50 mg ranitidine, and 50 mg diphenhydramine given i.v. 30 min prior to the administration of paclitaxel. Patients who did not routinely receive antiemetic prophylaxis with a serotonin antagonist. Treatment continued until tumor progression, development of unacceptable toxicity, attainment of maximum clinical response, or patient withdrawal.

On-Treatment Evaluation. On the day of therapy, patients were evaluated for toxicity assessment. Laboratory monitoring with complete blood count and differential, serum creatinine, blood urea nitrogen, electrolytes, glucose, alkaline phosphatase, SGOT, and total and direct bilirubin was performed on a weekly basis.

If the ANC was ≤500/µl or the platelet count ≤20,000/µl at any point during the cycle, there was a 50% reduction in the paclitaxel dose after recovery of ANC >1,200/µl or platelet count >100,000/µl.

Patients were removed from the study in the event of a severe allergic reaction despite premedication or grade 3/4 neutropenia. Complete tumor assessment was undertaken after the first cycle and at least every two cycles thereafter.

Statistical Methods. Patients who received a single infusion of chemotherapy were considered evaluable for toxicity. Patients who either completed a restaging evaluation or had clinically obvious disease progression in the absence of a formal evaluation were considered evaluable for response, regardless of the amount of chemotherapy received. Results are reported both for the group as a whole and for the subgroup of evaluable patients. Response assessment was based on standard criteria (25). Failure-free survival is reported from the date of registration until the date of documented progression, death from any cause, institution of second-line chemotherapy or radiation, or withdrawal because of toxicity. Overall survival was measured from the date of registration until time of death.

Received dose intensity was expressed in mg/m²/week and was calculated according to the method of Hryniuk and Goodyear (26).

Pharmacokinetic Studies. Sampling to define the plasma concentration-time profile of paclitaxel for the first and sixth weekly doses given during the first cycle of therapy was performed in all patients who consented to participate in the nonobligatory pharmacokinetic component of the study. Blood specimens (7 ml) were drawn from a vein in the arm opposite to that used for dosing into a Vacutainer tube with freeze-dried sodium heparin anticoagulant (Becton Dickinson, Franklin Lakes, NJ) at the following times relative to the start of the drug infusion: 0, 0.5, 0.92, 1.17, 1.5, 2.0, 3.0, 4.0, 6.0, and 24 h. Sample tubes were mixed by inversion and placed on wet ice until centrifuged (2500 × g for 10 min at 4°C) within 15 min, after which the plasma was transferred into a polypropylene cryovial and stored at −70°C until assayed. The beginning and ending times of the drug infusion and sample collection intervals were monitored with a digital timer.

A validated analytical method based on isocratic reversed-phase high performance liquid chromatography with automated column switching and UV detection was used to measure the concentration of paclitaxel in plasma, as described previously (27). Each study sample was independently assayed in duplicate, on different days, together with a series of eight standard solutions of paclitaxel in plasma at concentrations of 5.56–556 ng/ml. Standard curves were analyzed by linear regression using a weighting factor of 1/√x,-md. Values of the parameters describing the best-fit line were used to calculate the paclitaxel concentration in study samples. Results were considered acceptable if the two determinations differed from their average by ≤10%; otherwise, the sample was reassayed. Specimens with an estimated concentration above the upper limit of the standard curve were reassayed in duplicate after appropriate dilution with drug-free plasma. During their application to the present study, the between-day accuracy and precision of the assay were assessed by analyzing the interpolated drug concentrations from 12 standards curves generated over a 6-month period. Grand mean ± SD values of the between-day accuracy and precision were 9.2 ± 4.3% (range, 3.0–15.4%) and 107.3 ± 6.2% (range, 95.4–110.9%), respectively.

Actual sample times were calculated from the beginning of the drug infusion to the midpoint of each sample collection
interval. Individual patient plasma concentration-time curves were analyzed by noncompartmental methods using routines supplied in the WinNonlin Version 1.1 software package (Scientific Consulting, Apex, NC; Ref. 28). The AUC for the plasma profile from time zero to infinity was estimated using the logarithmic-linear trapezoidal algorithm to the last data point, with extrapolation to time infinity using the estimated value of the slope of the terminal logarithmic-linear disposition phase. Mean values of the pharmacokinetic variables were calculated as the geometric mean of the individual patient values (29). SDs for the geometric mean values were estimated by the jackknife method (30). The paired two-tailed t test using log-transformed values of pharmacokinetic variables was used to assess the existence of differences in drug disposition between the first and sixth weekly doses of paclitaxel. P/H110210.05 (two-tailed) was considered significantly different.

RESULTS

Patient Characteristics. A total of 35 patients were enrolled in this study from September 1998 to August 2000. The main demographic characteristics of the cohort are summarized in Table 1. The protocol allowed poor PS patients to be entered; however, only a single patient with a PS of 3 was enrolled. Thirty of 35 patients presented with stage IV disease, whereas the remaining patients were considered incurable by chemoradiation or surgery. Squamous cell histology was observed in only six cases.

Response. Five of 35 patients were not assessable for response. One patient developed a pathological fracture prior to the first cycle of therapy, and his condition declined rapidly after surgery. Two patients died during their first treatment cycle and will be described in detail later. Two additional patients were removed from the study because of toxicity after receiving just two doses of chemotherapy and were never reassessed for response.

Considering all 35 patients enrolled, 8 patients achieved a partial response, whereas no complete responses were observed, yielding an overall response rate of 23% (95% confidence interval, 10–40%). However, when only evaluable patients were included in the analysis, the response rate improved to 27% (95% confidence interval, 12–46%). In addition, stable disease was observed in 13 of 35 patients, whereas 9 patients had progressive disease at the time of their first tumor reassessment (Table 2).

The median time to response was 9.2 weeks (range, 7–15.6 weeks). Patients who did not respond after receiving the first two cycles of therapy failed to show any evidence of a response during continued treatment.

Survival. Survival analysis was performed in June 2001, at which point the median follow-up time for surviving patients was 17.6 months. Only four patients had been followed for less than 1 year. The median time to failure was 5.2 months, with a 1-year failure-free survival of 16% (Fig. 1). At the time of this analysis, 23 patients had died and 12 patients were still alive. The median survival of the 35-patient cohort was 10.3 months, with a 1-year survival of 45% and a 2-year survival of 22% (Fig. 2).

Toxicity. There were two treatment-related deaths during the first cycle of therapy. An 85-year-old patient developed nonneutropenic pneumonia after the third weekly dose. Subsequently, he sustained a myocardial infarction while hospitalized, leading to multisystem organ failure and eventual death. A

| Table 1 Patient characteristics of elderly patients with advanced NSCLC |
|-------------------------|-----------------|-------|
| Characteristic          | n   | %    |
| Patients                | 35  | 100  |
| Age (yr)                |     |      |
| Median                  | 76  | 21.7 |
| Range                   | 70–85| 21   |
| Sex                     |     |      |
| M                       | 24  | 68   |
| F                       | 11  | 32   |
| Stage                   |     |      |
| III                     | 5   | 14   |
| IV                      | 30  | 86   |
| PS                      |     |      |
| 0–1                     | 28  | 80   |
| 2                       | 6   | 17   |
| 3                       | 1   | 3    |
| Histology               |     |      |
| Adenocarcinoma          | 25  | 71   |
| Squamous                | 6   | 17   |
| Large cell              | 3   | 9    |
| NOSa                    | 1   | 3    |

a NOS, not otherwise specified.

| Table 2 Treatment outcome of elderly patients with advanced NSCLC treated with weekly paclitaxel |
|-------------------------|-----------------|-------|
| Characteristic          | Months | %      |
| Response                |        |       |
| All patients (n = 35)   | 23     |       |
| 95% confidence interval | 10–40  |       |
| Evaluable patients (n = 30) | 27  |       |
| 95% confidence interval | 12–46  |       |
| Failure-free survival   |        |       |
| Median                  | 5.2   |       |
| 1 year                  | 16    |       |
| Overall survival        |        |       |
| Median                  | 10.3  |       |
| 1 year                  | 45    |       |
| 2 years                 | 22    |       |

Fig. 1 Failure-free survival of elderly patients with advanced lung cancer treated with weekly paclitaxel.
second patient presented with febrile neutropenia, presumed pneumonia, and rapid atrial fibrillation after three weekly doses of paclitaxel. He was treated with antibiotics and supportive measures, but developed worsening respiratory distress and ultimately expired.

Two of 34 patients (5.8%) experienced grade 4 neutropenia during the entire study, complicating only 0.4% of all administered doses. There were no cases of grade 3 or 4 anemia or thrombocytopenia observed, and there was no evidence of cumulative hematological toxicity. Nonhematological toxicity was typically mild; however, significant neurological events occurred in six patients (Table 3). There were two cases of grade 3 peripheral neuropathy, observed after 17 and 18 weekly doses, respectively. The other neurological events were not clearly related to the study medication. One patient developed a grandmal seizure during his third weekly dose in the setting of hypotension and dehydration. A computed tomography scan of the head was unrevealing, and the possibility of an allergic reaction to paclitaxel could not be excluded. Two more patients developed confusion, possibly related to the use of antihistamines in their premedication regimen, and another patient developed grade 3 depression and anxiety. Hyperglycemia >250 mg/dl related to the use of steroids was evident in 6 of 34 patients but complicated only 9.9% of all cycles delivered. A single patient contributed half of the instances of severe hyperglycemia. One patient experienced grade 3 elevation of his total bilirubin, which was clearly related to tumor progression.

Treatment Delivery. A total of 437 weekly doses of paclitaxel were given to 34 patients. The planned dose intensity specified by the protocol was 67.5 mg/m^2/week. The median number of doses administered was 12 (range, 2–30), and the median time on therapy was 16 weeks. Received dose intensity was 45–73.6 mg/m^2/week, with a median value of 66.2 mg/m^2/week, representing 98% of the planned dose intensity.

**Pharmacokinetics.** Pharmacokinetic studies were performed to evaluate whether drug disposition changed after repeated weekly dosing, to determine the magnitude of intra- and interpatient variability in the pharmacokinetic parameters in this patient population, and to compare the disposition of paclitaxel in elderly patients to historical data for younger patients similarly treated. It was estimated that a cohort of at least 10–12 patients would be required to establish a clinically significant difference in the mean values of a pharmacokinetic parameter, assumed to be 1 SD, between two doses given at different times to the same patients. Because of ethical considerations, patients were not required to participate in the pharmacokinetic studies as a condition for entry into this clinical trial. Among the 35 patients entered into the study, 13 patients consented to pharmacokinetic sampling, and complete sample sets for both the first and last weekly doses of the first cycle of therapy were obtained from 8 patients. Mean values of the pharmacokinetic parameters for both doses of the drug are summarized in Table 4. There were no statistically significant differences in any parameter determined at these two times (Fig. 3). Intrapatient variability calculated as the percentage of difference in the CL values for the two doses in a given patient ranged from 3.5 to 30.0%, about a median of 11.3%. In comparison, interpatient variability, as reflected by the coefficient of variation of the CL values for the entire cohort, was 16.8% for dose 1 and 26.0% for dose 6. Finally, the CL and other pharmacokinetic variables for paclitaxel in this cohort were comparable to values that have been reported for studies involving younger patients treated with similar doses given as a 1-h i.v. infusion (21, 31, 32). Thus, when administered according to the dosage and schedule evaluated in this study, the pharmacokinetics of paclitaxel in elderly patients do not appear to differ from those for younger patients and were unchanged after repeated weekly dosing.

**DISCUSSION**

Using variable definitions of an elderly population, investigators have reported response rates and overall survival statis-
tics in advanced NSCLC similar to those for younger patients (33–35). Interestingly, a retrospective analysis of prognostic factors for long-term survivors of NSCLC treated in Southwest Oncology Group studies showed that the highest proportion of 1-year survivors (26%) was found in patients ≥70 years of age (36). The obvious suggestion from all available information is that age alone should not play a pivotal role in deciding the most appropriate strategy for patients with lung cancer.

However, generalization of these results raises several questions. Whether unintended or by design, patient selection for therapy is commonplace in any clinical trial and in everyday clinical practice. The toxicities associated with chemotherapeutic agents obviously become a paramount concern to physicians treating patients with advancing age. In an Eastern Oncology Cooperative Group randomized study that evaluated the combination of cisplatin/paclitaxel versus cisplatin/etoposide, leukopenia and neuropsychiatric toxicity were significantly more common among the elderly patients, although their overall functional status declined similarly to that of younger patients with time (33). Enhanced sensitivity to chemotherapy among the elderly, especially hematological toxicity, has been observed in other studies as well (13, 15). Consequently, it appears reasonable to perform elderly-specific clinical trials to establish doses that are tolerated by this patient population and to evaluate response. Two studies performed in Italy have demonstrated the feasibility of such an approach for Phase III studies (37, 38).

Single-agent paclitaxel given as a 3-h i.v. infusion every 3–4 weeks in patients with advanced NSCLC has produced response rates of 11–38% and median survival times of 6.7–11 months (16). Because the antiproliferative activity of paclitaxel is cell cycle specific, prolonging exposure to the drug above a threshold concentration should ultimately be more efficacious than short-term exposure to higher drug concentrations. The relevance of this hypothesis has been supported by in vitro experiments with a variety of cell lines and suggested by the results of clinical studies (17–19). Seidman et al. (20) delivered paclitaxel by a 96-h i.v. continuous infusion to breast cancer patients who progressed after shorter taxane infusion and obtained a response rate of 26.9% in 26 assessable patients. Moreover, in a cohort of 13 patients with relapsed ovarian cancer who had failed a standard paclitaxel-containing regimen, administration of paclitaxel on a weekly schedule resulted in four partial responses (21). These findings suggest that prolonging the exposure to paclitaxel might provide added benefits, either through long-term infusion or repeated weekly delivery of low doses by very short infusions. However, similar trials have been less conclusive in lung cancer patients. Socinski et al. (39) observed no objective responses in a group of 13 patients who were refractory to regimens containing platinum compounds or paclitaxel given as a 24-h i.v. infusion when they were given additional treatment with 96-h infusional paclitaxel, although disease stabilization occurred in 23% of the cases. In another study, 41 evaluable patients with progressive disease during or after treatment with carboplatin and paclitaxel received weekly paclitaxel at a dose of 80 mg/m² and had a response rate of 7.3% with a 1-year survival of 18% from the start of second-line therapy (40).

Considerable experience has been gained with the use of weekly paclitaxel at doses of 80–100 mg/m². The incidence of grade 3/4 neutropenia was 2–15%, thrombocytopenia was 0–1%, and neurotoxicity was 8–33% in >200 patients treated in this manner, the large majority of whom had previously received one or more chemotherapy regimens (21, 24, 41, 42). Similarly, we observed limited toxicity with this schedule of administration. It must be noted, however, that two patients died as a result of infectious episodes during chemotherapy, underscoring the occasionally poor tolerance of elderly patients to cytotoxics.

Our interest in evaluating weekly paclitaxel to treat NSCLC in an elderly patient population was based on several factors, including the established single-agent activity of the drug against this disease, the rationale for prolonged exposure, and the limited toxicity associated with this administration schedule in younger patients. The response rate observed in this study was similar to that reported with higher doses of paclitaxel given as a 3-h infusion once every 3 weeks (16). The median survival time and 1-year survival rate were exceptionally good, considering that 86% of our patients had stage IV disease, and were similar to results from Phase II studies with combination chemotherapy (43–47). Phase III studies will be needed to optimally evaluate the role of single-agent paclitaxel in the treatment of advanced NSCLC. At present, Cancer and Leukemia Group B is performing a randomized study to compare the activity of single-agent paclitaxel with its combination with carboplatin, when administered as a 3-h infusion every 3 weeks, in previously untreated patients with advanced lung cancer.

Results and toxicities of studies using weekly taxanes in the treatment of chemotherapy-naive lung cancer patients are compared in Table 5 (22, 48). Akerley et al. (22) performed a Phase II study in 36 patients, using a 3-h infusion of paclitaxel at a dose of 150 mg/m², whereas Hainsworth et al. (48) administered docetaxel at a dose of 36 mg/m²/week to 39 elderly or infirm patients. Hematological and neurological toxicities were more severe for the higher dose of paclitaxel. It was recently reported that only 58% of the intended dose was delivered to lung cancer patients when paclitaxel 175 mg/m² infused over 3 h was given repeatedly on a once-a-week schedule (49).
There was no evidence suggestive of a clinically significant alteration in paclitaxel pharmacokinetics after repeated weekly dosing; however, it is recognized that definitive conclusions cannot be drawn from the number of patients evaluated in this study. The disposition of the drug was found to be very similar to that for younger patients treated with 1-h infusions of comparable doses, as determined in previously reported studies (21, 31, 32). The degree of the intra- and interpatient variability in the clearance of the drug in elderly patients was also found to be similar to the range of values observed in studies involving predominantly younger groups of patients. Therefore, in the absence of significant toxicity, there is no evidence to support an automatic reduction in the dose of paclitaxel based on age alone.

Hematological toxicity has been associated with the duration of systemic exposure to paclitaxel above a threshold concentration in the 50–100 nM range (50). This is clearly demonstrated by a comparison of the 3- and 96-h i.v. infusion schedules. Because of the nonlinear, schedule-dependent pharmacokinetics of paclitaxel, its average AUC for doses of 135–140 mg/m² is 4.8 μg·h/ml when administered over 96 h and 8.1 μg·h/ml when given over 3 h (51, 52). Despite having a lower AUC, the more prolonged infusion schedule sustains plasma concentrations above the 50-nM threshold for a much longer period of time, thereby resulting in more severe hematological toxicity than is observed with the shorter infusion. In this study, we found that for each weekly dose, the plasma concentration of paclitaxel exceeded 50 nM for ~17–20 h without evidence of severe toxicity. Although it is unclear whether the duration of systemic drug exposure is clinically relevant in terms of overall treatment efficacy, our results do suggest that weekly administration of paclitaxel results in prolonged systemic drug exposure, which can be repeated frequently without major side effects. We conclude that single-agent paclitaxel at the dose and schedule evaluated in this study is associated with promising survival and tolerable toxicity, thus representing a viable treatment option for elderly patients with advanced lung cancer.

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