Phase II Study of Patients with Metastatic Nonsmall Cell Carcinoma of the Lung Treated with Paclitaxel by 3-Hour Infusion

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BACKGROUND. Single-agent chemotherapy produces partial responses in the range of 7–27% in patients with Stage IV nonsmall cell lung carcinoma (NSCLC). Cisplatin-based combination regimens have achieved higher response rates but with significant toxicity. Two prior studies employing 24-hour infusions of paclitaxel showed responses of 21% and 24%. The purpose of this Phase II study was to determine the effects of paclitaxel administered by short duration infusions on response rate, toxicity, and quality of life (QOL) in patients with NSCLC.

METHODS. Twenty patients with histologically proven Stage IV NSCLC were enrolled in this study. All were treated on an outpatient basis with standard premedication followed by paclitaxel 200 mg/m^2 infused intravenously over 3 hours. Treatments were repeated every 21 days for a maximum of 6 cycles.

RESULTS. The objective response rate was 6/19 (32%; 95% confidence interval, 13–57%). The median duration of response was 6.0 months (range, 2–13 months). The median survival of the entire group was 6.0 months (range, 2–24+ months), and the 1-year survival rate was 22%. Toxicity was mild, with only one hospitalization required for treatment of catheter-related thrombosis. Nonresponding patients were found to have worsening Functional Assessment of Cancer Therapy (FACT)-G and FACT-L scores. Because this was a small clinical study, it did not demonstrate consistent improvement in FACT-G or FACT-L in responding patients.

CONCLUSIONS. Paclitaxel given as a 3-hour infusion is a well-tolerated, active single agent in the treatment of Stage IV NSCLC, worthy of further study. Baseline QOL scores predicted those more likely to respond to treatment, but changes in QOL status did not correlate well with objective response status. ***Cancer*** **1997; 79:724–9.**
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Lung carcinoma remains the leading cause of death from cancer in the United States. Fifty to sixty percent of patients with nonsmall cell lung carcinoma (NSCLC) have distant metastases at the time of presentation. In addition, disease relapse occurs in many surgically resected patients and in unresectable patients who are treated with radiotherapy.[1] A number of chemotherapeutic agents are active in the treatment of NSCLC, but their activity as single agents ranges from only 7% to 27%. Regimens containing cisplatin have been associated with higher response rates but also with significant toxicity. Patients treated with combination chemotherapy have been reported to have a median survival of only 6–8 months and a 1-year survival rate of only 10–20%.[1,2] More effective agents and treatment regimens that will improve patients' quality of life (QOL) need to be identified.[3]

Standard chemotherapy regimens are associated with significant toxicity.[1,2,4] Patients with metastatic NSCLC are often debilitated, have significant underlying medical illnesses, and may tolerate chemotherapy poorly. Many patients are currently not offered standard chemotherapy because of concerns about toxicity. Phase II chemotherapy studies to date have largely reported the effects on objective response, toxicity, and survival, but few have carefully examined the effects of chemotherapy on the symptoms and the QOL of NSCLC patients.

Paclitaxel is a new antimicrotubule agent that possesses unique mechanisms of cytotoxic action and a broad antineoplastic spectrum. When administered as a 24-hour infusion, the dose-limiting toxicity of paclitaxel is leukopenia. Nonhematologic toxicities that have been observed with shorter infusions include arthralgia, myalgia, alopecia, nausea, stomatitis, neuropathy, transient rash, pruritus, fatigue, liver enzyme elevations, and triglyceride elevation. A hypersensitivity reaction manifesting as anaphylaxis has been observed in rare cases, usually at the beginning of the first infusion.[5]

The M. D. Anderson Cancer Center and the Eastern Cooperative Oncology Group (ECOG) reported that paclitaxel is an active agent in the treatment of patients with metastatic NSCLC.[6,7] During those 2 trials, patients were treated with single agent paclitaxel 200–250 mg/m^2 infused over 24 hours. These studies reported similar response rates of 24% (in 6 of 25 patients) and 21% (in 5 of 24 patients). The 1-year survival rates in these studies were 38–41%. Paclitaxel was described as the ''most active agent evaluated by ECOG in the last ten years.''[7]

Because prognosis is generally poor for metastatic NSCLC regardless of treatment, it is important to monitor the impact of treatment on QOL as well as on the disease process. A few prospective studies have compared chemotherapy with supportive care alone and found a median survival advantage of only a few months.[2] To determine and improve overall benefit, it is crucial to evaluate the impact of treatment on QOL as we study new drugs or combination therapies.

One study prospectively evaluated the specific subjective symptoms in patients receiving paclitaxel in a Phase I clinical trial. The results suggested that the paclitaxel treatment was well tolerated; patients scored their symptom distress as being no different after treatment than prior to treatment.[8] A newer tool, the Functional Assessment of Cancer Therapy (FACT) scale developed by Cella, meets all requirements for use in clinical oncology trials, including ease of administration, brevity, reliability, validity, and responsiveness to clinical change. This tool appears suitable for evaluation of changes in the QOL of patients enrolled in Phase II chemotherapy protocols.[9]

The reported efficacy of single agent paclitaxel administered by 24-hour infusion in 2 Phase II trials prompted us to evaluate shorter infusion paclitaxel in previously untreated American Joint Committee on Cancer (AJCC) Stage IV NSCLC patients. In the treatment of patients with ovarian carcinoma, a 3-hour infusion of paclitaxel was shown to have equivalent response rates and less hematologic toxicity than a 24-hour infusion.[10] The purpose of this Phase II study was to determine the effects of short infusion paclitaxel on response rate, toxicity, and QOL in patients with NSCLC.

MATERIALS AND METHODS

Between July 1993 and July 1995, 20 patients with histologically confirmed Stage IV NSCLC were enrolled in this study. All had either measurable or evaluable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, and gave written informed consent. All patients were required to have a white blood cell count of $\geq$3500/mm^3, a platelet count of $\geq$100,000/mm^3, and bilirubin $\leq$1.5 mg%. Patients with brain metastases, active infection, myocardial infarction during the preceding 6 months, or congestive heart failure were excluded. No patients had received prior chemotherapy.

Patients were evaluated with complete history and physical examination, standard chemistry panel, and appropriate radiologic imaging studies. Patients were followed with measurement of objective tumor parameters at baseline and after 2 and 4 cycles of treatment. Pretreatment patient characteristics are summarized in Table 1.

Paclitaxel 200 mg/m^2 was prepared in glass bottles and administered intravenously, (i.v.), using nitroglycerin administration sets (polyethylene lined PVC tubing), over 3 hours. Premedication, given to prevent potential hypersensitivity reactions, consisted of dexamethasone 20 mg, given orally (12 and 6 hours prior to paclitaxel administration); diphenhydramine 50 mg i.v.; and cimetidine 300 mg i.v. (30 minutes prior to paclitaxel administration).

All patients were treated on an outpatient basis. Blood pressure and heart rate were monitored every 15 minutes during the infusion of paclitaxel. Treatments were repeated every 21 days in the absence of disease progression. A maximum of 6 cycles of treatment were given. A weekly complete blood count and white blood cell differential was obtained for all patients during the study.

Standard ECOG criteria for solid tumor response was used in the evaluation of all cases. Partial response

TABLE 1
Patient Characteristics

Characteristics	No. of patients[a]
Gender	
Male	11
Female	9
Median age, yrs (range)	63 (36–79)
ECOG performance status	
0–1	15
2	5
Histology	
Adenocarcinoma	12
Squamous cell CA	4
Anaplastic CA	4
Prior therapy	
Radiation	7
Surgery	1
Both	3

ECOG: Eastern Cooperative Oncology Group; CA: carcinoma.
[a] Applies to all characteristics except median age.

(PR) was defined as a decrease greater than or equal to 50 percent in the size of indicator lesion (s), lasting for at least 4 weeks without an increase in the size of any area of known malignant disease or the appearance of new areas of disease. Also considered partial response was substantial improvement in nonmeasurable disease confirmed by two investigators. Stable disease required satisfaction of all of the following criteria: no significant change in measurable disease for at least 6 weeks (2 treatment cycles), no increase in size of any known malignant disease, no appearance of new areas of malignant disease, and no significant deterioration in symptoms or performance status (more than 1 score level). Patients were considered to have disease progression when any of the following criteria were met: significant increase in size (>25%) of lesions present at start of therapy, appearance of new malignant disease, or deterioration of ECOG performance status by more than 1 score level.

Duration of response was measured from the date of a patient's enrollment in the study to the date of disease progression. Overall survival was measured from the date of a patient's enrollment in the study to the date of death. The overall survival curve and median survival were determined by the Kaplan–Meier method.[11] Anticipating a response rate of 25%, we planned to accrue 40 patients for the study, allowing the response rate to be determined within standard error of ±10%. However, patient accrual slowed during the second year of the study, and the study was closed after 20 patients were enrolled.

Toxicity was evaluated according to the ECOG Common Toxicity Criteria. Treatment was withheld 1 week for any continuing Grade 3 or 4 toxicity. No dose modifications were employed. No patients received colony stimulating factors.

The FACT-L quality of life questionnaire was administered at the time of study entry and prior to treatment cycles. Patients' QOL was assessed by FACT-G (general questions) and FACT-L (lung-specific questions). The categories assessed in FACT-G subscale scores include physical well-being, social/family well-being, relationship with doctor, emotional well-being, and functional well-being.[4,9]

RESULTS

Twenty patients were enrolled in the study between July 1993 and July 1995. A total of 76 cycles of treatment were given to the 20 patients; the median number of cycles of treatment given to each patient was 3.5 (range, 1–6). All 76 cycles were evaluable for toxicity. One patient's treatment was discontinued after the first cycle because his medical insurance company would not permit a second treatment. He is considered evaluable for toxicity and survival, but not for response or changes in QOL.

The objective response rate was 6/19 (32%; 95% confidence interval, 13–57%). All six responses were partial; five were measurable responses and one was substantial improvement in evaluable disease. The responding patient with evaluable disease had bone and lymphangiitic lung metastases. Following treatment, we observed significant improvement in chest X-ray and pulmonary function, with stable findings on bone scan. The median duration of response for these 6 responding patients was 6 months (range, 2–13 months). Responding sites of disease for the six patients included lung (in six patients), mediastinal nodes (in two), hilar nodes (in two), bone (in two), and pleura (in one). Five patients were found to have stable disease. One patient received one cycle of treatment and is not evaluable for response status. The median freedom from progression for these 12 patients who had partial response, had stable disease, or were not evaluable was 6 months. Eight patients' disease progressed during treatment. The median survival of the entire group was 6.0 months (range, 2–24+ months). One-year actuarial survival is 22%. The actuarial survival curve for all 20 patients is shown in Figure 1. One patient remains alive 24 months after starting treatment.

Treatment was generally well tolerated. Only 1 patient developed Grade 4 granulocytopenia (<500) during 1 of 6 cycles of treatment. Four patients developed Grade 3 granulocytopenia (<1000). In 10 patients the hemoglobin level decreased by 2 g/dL or more. There

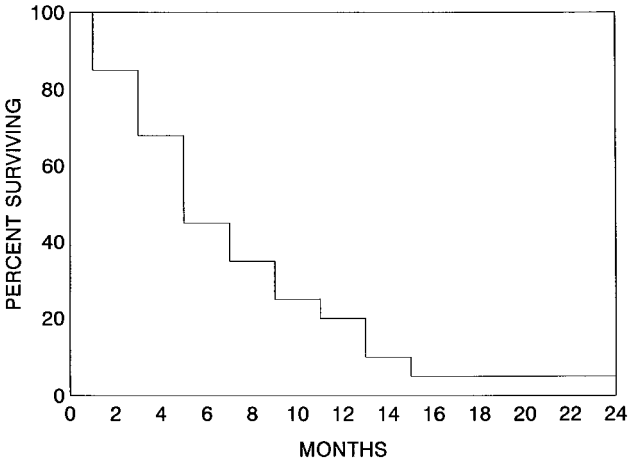

FIGURE 1. Overall survival (the actuarial survival curve) is shown for all 20 patients in the study.

were no instances of Grade 3 or 4 thrombocytopenia. No patient developed significant infection or required transfusion of red blood cells or platelets.

Six patients experienced symptoms of Grade 2–3 sensory neuropathy. In these patients who developed neuropathy, the symptoms appeared to worsen with subsequent treatments. However, treatment delays were only required for one patient because of neurotoxicity. This responding patient stopped treatment after 5 cycles because of Grade 3 sensory neuropathy (severe paresthesia that interfered with walking).

Alopecia was universal. Five patients complained of myalgia; these episodes were treated with brief courses of analgesics and did not interfere with treatment. One patient required hospitalization for the treatment of central venous catheter thrombosis. For the second and subsequent cycles of treatment, 9 cycles (16%) were delayed 1 week because of neuropathy (2), neutropenia (1), and severe fatigue (6). No severe gastrointestinal toxicity was observed.

Seventeen patients completed the baseline FACT-L and FACT-G questionnaires. Eleven patients with stable or responding disease were reassessed after completion of 3 or 4 cycles of therapy. Six progressing patients were evaluated after 2 cycles and then removed from the study. Three patients did not complete either the baseline or the follow-up questionnaire and therefore could not be evaluated for changes in their QOL.

One responding patient showed improvement in FACT-G and another showed improvement in FACT-L, while the remaining four responders had either stable or worsening FACT scores. Of five patients with stable disease, four showed significant improvement in FACT-L, with improvement in cough, shortness of breath, and tightness in the chest reported. Four of the six progressing patients showed worsening of FACT-G and FACT-L, whereas it was noted that the other two had significantly improved FACT-L scores. Table 2 lists the changes noted in lung symptoms recorded on FACT-L questionnaires for all 17 evaluable patients.

TABLE 2
Changes in FACT-L Lung Symptoms with Paclitaxel

Symptoms or observations	No. of Patients		
	Better	Stable	Worse
Shortness of breath	6	8	3
Weight loss	5	8	4
Clear thinking	2	9	6
Coughing	7	8	2
Hair loss	0	5	12
Good appetite	4	7	6
Tightness in chest	4	9	4
Easy breathing	7	8	2

FACT: Functional Assessment of Cancer Therapy.

DISCUSSION

Five other studies have evaluated the efficacy of single-agent paclitaxel in the treatment of patients with NSCLC.[6,7,12,13,14] With paclitaxel 200 mg/m^1 infused over 3 hours, this study resulted in a response rate of 32%, median survival of 6.0 months, and a 1-year survival rate of 22%. In the 2 previous 24-hour infusion studies, response rates of 24% and 21% were similar, but the 1-year survival rates of 38% and 42% seemed higher.[6,7] This apparently higher survival may have been related in part to differences in the patient populations, such as the exclusion of patients with a performance status score of 2 from the ECOG trial.[7] In both 24-hour infusion trials, however, it was found that the incidence of severe leukopenia was significantly greater than observed with shorter infusions.

Studies in ovarian and breast carcinoma showed that shorter infusions resulted in a reduced risk of myelosuppression and that higher doses could be given safely without the need for hospitalization or colony stimulating factors.[10,15] This finding encouraged us and others to evaluate the value of shorter infusions of paclitaxel in the treatment of NSCLC. Three other studies of patients with NSCLC evaluated the efficacy and toxicity of shorter infusions of paclitaxel. Gatzemeier et al.[12] reported a 24% response rate in 50 patients with advanced NSCLC to a dose of 225 mg/m^2 given over 3 hours every 21 days. In results similar to those in our study, hematologic toxicities were mild, and only one patient (2%) developed Grade

3–4 neutropenia. Grade 1–2 polyneuropathy was common in the study by Gatzemeier et al., affecting 56% of patients, but only one (2%) experienced Grade 3 neuropathy.

Hainsworth et al.[13] reported a 25% response rate in 53 assessable patients treated with either 135 or 200 mg/m^2 given as 1-hour infusions. Those patients were randomly assigned to either a single day 1-hour infusion or a 3-day, divided dose schedule with each dose administered by 1-hour infusion. Approximately half the patients studied (30 of 59) had received prior chemotherapy. A higher response rate was observed with the higher dose of paclitaxel used in this study (31% vs. 12%).

We compared response rates among studies that employed 3-hour infusions. Millward et al.[14] reported a 10% response rate with 175 mg/m^2, our study shows a 32% response rate with 200 mg/m^2, and Gatzemeier et al.[12] reported a 24% response rate with 225 mg/m^2. The apparently lower response rate observed by Millward et al. may be related to either a true dose-response effect, or differences in the patient populations, or it may be speculated that different brands of paclitaxel may have different levels of activity.

Within the limitations of a small clinical study, we attempted to correlate objective response status with subjective changes in QOL reported by each patient. When analyzed by response status, patients with disease progression showed worsening FACT scores, but there was no consistent trend when comparing responders and patients with stable disease. However, we did note a relation between response status and baseline FACT-G scores. Patients with higher baseline FACT-G scores were more likely to show partial response, and those with lower baseline FACT-G scores were more likely to have disease progression.

QOL determination indicated that three patients (two responders and one with disease progression) experienced significant improvement in FACT-G score, and seven (one responder, four stable, and two with disease progression) had improved FACT-L symptom scores. Consistently with the results just cited, other investigators have documented symptom palliation and QOL improvement in the absence of objective tumor response to chemotherapy. Ellis et al.[16] and Hardy et al. evaluated symptom relief in 118 Stage IIIB and IV NSCLC patients treated with mitomycin C, vinblastine, and cisplatin. The objective response rate was only 32%. However, complete disappearance or ''good improvement'' in at least 1 tumor symptom was achieved in 69%. For each of the evaluated symptoms (pain, cough, dyspnea, and malaise), a majority of patients noted complete or good symptomatic relief. Median symptomatic response duration was 15 weeks. Median survival was 5 months.[16,17]

Similar discrepancies between treatment response, symptomatic benefit, and QOL changes have also been observed in some breast carcinoma patients treated with paclitaxel. Seidman et al.[18] reported QOL outcomes from a Phase II trial in which paclitaxel plus granulocyte colony stimulating factor was administered to women with metastatic breast carcinoma. Although improved Functional Living Index-Cancer (FLIC) scores were most often noted in responding patients, occasional patients with either stable or progressive disease also improved their scores. Patients with a partial response or stable disease reported minimal changes in psychologic well-being (determined by the Rand General Well-Being instrument) and symptom distress (determined by the Memorial Symptom Assessment Scale-Global Distress Index). Patients with progressive disease generally had declining scores.

Compared with the reports just cited, the QOL results in our study are somewhat disappointing. However, because of the small patient population in our study, the effect of paclitaxel on QOL is not proven. Larger, randomized clinical trials are still required to determine whether paclitaxel treatment favorably or unfavorably affects QOL compared with an alternative treatment regimen.

In conclusion, paclitaxel is an active single agent in the treatment of NSCLC when administered as a 3-hour infusion. It is well tolerated on an outpatient basis. In our study, the effect of treatment on QOL varied. The QOL of most of the responding patients was only slightly affected. Lung-related symptoms, as determined by the FACT-L questionnaire, were found to improve in several patients without objective tumor response. Patients with disease progression generally reported worsening of their overall QOL and lung-related symptoms. Additional studies in NSCLC evaluating combinations of paclitaxel and other agents are warranted. Initial results of the combination of paclitaxel and carboplatin appear promising, with response rates reportedly as high as 62%, and the projected 1-year survival rate 54%.[19]

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