Phase II Trial of Paclitaxel by 96-Hour Continuous Infusion in Combination with Cisplatin for Patients with Advanced Non-Small Cell Lung Cancer

O. S. Breathnach, M. S. Georgiadis, B. S. Schuler, P. Pizzella, V. Llorens, V. Kasturi, S. M. Steinberg, K. O’Neil, C. H. Takimoto, and Bruce E. Johnson

INTRODUCTION

Our purpose was to determine the antitumor efficacy and safety profile of the combination of paclitaxel administered by 96-h continuous i.v. infusion followed by bolus cisplatin in patients with untreated advanced non-small cell lung cancer (NSCLC). Fifty-eight patients with untreated advanced or recurrent NSCLC were enrolled between October 1995 and December 1998. The median patient age was 60 years (age range, 34–75 years). Twenty-four patients were female. The majority of patients (n = 52) had an Eastern Cooperative Oncology Group performance status of 0/1. Twelve patients had stage IIIIB NSCLC, 43 had stage IV disease, and 3 had recurrent disease after prior resection. Seven patients had received cranial irradiation for brain metastases, and 5 patients had received bone irradiation before enrollment. Patients were treated with paclitaxel (120 mg/m²/96 h) by continuous i.v. infusion followed by cisplatin (80 mg/m²) on day 5. Therapy was administered every 3 weeks as tolerated until disease progression or a maximum of six cycles. A total of 264 cycles of therapy were administered. Twenty-nine patients received all six cycles. Forty-six patients had measurable disease, with 20 patients achieving a partial response, and no complete responses were seen (overall response rate, 43%; 95% confidence interval, 29–60%). The median progression-free survival was 5.5 months. At a median potential follow-up of 27.2 months, the median survival for all 58 enrolled patients was 8.5 months, and the actuarial 1-year survival was 37% (95% confidence interval, 25.9–50.5%). This is the most extensive evaluation of prolonged continuous infusional paclitaxel in patients with advanced-stage cancer. In contrast to predictions from in vitro cytotoxicity models, the regimen does not appear to be obviously superior to shorter infusion times in the clinical setting. Additional trials of this regimen in patients with NSCLC are therefore of low priority.

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1 To whom requests for reprints should be addressed, at Lowe Center for Thoracic Oncology, The Dana Farber Cancer Institute, Dana 1234, 44 Binney Street, Boston, MA 02115. Phone: (617) 632-5301; Fax: (617) 632-5786.
Phase I trial and because doses could only be escalated by one-third by adding G-CSF, we selected the MTD in the absence of colony-stimulating growth factors for the current trial.

PATIENTS AND METHODS

Patients. Patients who were more than 18 years of age with a histologically or cytologically proven diagnosis of NSCLC and who had either measurable or evaluable disease were candidates for this trial. Eligible patients had either stage IIB or IV disease or recurrent metastatic cancer after resection of stage III disease. Patients with stage IIB disease who were ineligible for our combined modality clinical trial (sequential chemotherapy and radiation therapy) as assessed by our radiation oncology department because of the extent of their disease or the presence of pleural effusions, were eligible. No patients had received prior chemotherapy or chest irradiation. Patients with intracranial metastases were eligible after completion of whole-brain irradiation therapy, provided they had improvement or stabilization of their neurological deficits and did not require whole-brain irradiation therapy, provided they had improvement with intracranial metastases were eligible after completion of whole-brain irradiation therapy, provided they had improvement or stabilization of their neurological deficits and did not require ongoing corticosteroid therapy. Prior palliative radiation therapy to painful bone metastases was permitted, provided any resultant hematological toxicity had resolved. Other eligibility criteria included an ECOG PS of 0 – 2, an ANC of $\geq 1.5 \text{ mg/dl}$, and a serum bilirubin concentration of $\leq 1.5 \text{ mg/dl}$. Patients with symptomatic heart disease, cardiac arrhythmias other than controlled atrial fibrillation, or myocardial infarction within the preceding 3 months were ineligible. Written informed consent was obtained from all patients. The protocol was approved by the Investigational Review Boards of the NCI and the National Naval Medical Center.

Patient Evaluation. Initial evaluation included a history and physical examination. All patients had the following series: (a) complete blood cell count with differential, serum electrolytes, liver function tests, blood urea nitrogen and creatinine, and urinalysis; (b) electrocardiogram; (c) chest radiograph and CT scan of the chest and upper abdomen; and (d) fiberoptic bronchoscopy airway survey. Patients with symptoms suggestive of metastatic bone disease had radionucleotide bone scans. Patients with neurological symptoms or signs had CT of the brain performed.

Evaluations during the course of therapy included biweekly complete blood cell count with differential, serum electrolytes, liver function tests, blood urea nitrogen, and serum creatinine. Toxicity was assessed at the completion of each cycle and graded according to the NCI CTC by our research nurse and by the principal investigator (23). A history, physical examination, and chest radiograph were performed before each treatment cycle. CT of the chest evaluations was performed after every two cycles of therapy or performed more frequently if progressive disease was suspected. Additional imaging studies, such as bone scans or CT of the brain, were performed to evaluate areas of clinically suspected new or progressive disease. All radiology films of each patient were reviewed, and tumor sizes were measured by the one radiologist (P. P.) in the absence of clinical details.

Treatment Plan. Paclitaxel and cisplatin were administered as described previously in the Phase I trial (22). Patients were treated with paclitaxel at 30 mg/m^2/day for 4 days (120 mg/m^2/96 h) and treated with 80 mg/m^2 of cisplatin on day 5, on completion of the paclitaxel infusion. Only cycle one of the chemotherapy was administered in the in-patient setting. During the first cycle, serum samples were drawn for pharmacokinetic evaluations at time 0 and 48, 72, and 96 h after initiation of the paclitaxel infusion. A portacath device was also inserted during this admission to facilitate the administration of subsequent cycles of chemotherapy as outpatient therapy. Cycles were repeated every 3 weeks as long as the ANC was $> 1500/\mu l$, the platelet count was $> 100 \times 10^3/\mu l$, and all nonhematological toxicity had improved to a NCI CTC of $\leq 1$ before commencing the next cycle. Patients were treated with up to six cycles of paclitaxel and cisplatin.

Dose delays for up to 2 weeks were permitted to allow for recovery from toxicity. If the dose was delayed for more than 2 weeks, further treatment was modified. A 20% reduction in the paclitaxel dose was made if there was documented asymptomatic grade 4 neutropenia (ANC $< 500/\mu l$) lasting $> 5$ days, an episode of febrile neutropenia, or a platelet nadir of $\approx 25 \times 10^3/\mu l$ or if the ANC at day 36 of the cycle was 1000 – 1499/\mu l, and the platelet count was $\approx 100 \times 10^3/\mu l$. A 40% reduction in the paclitaxel dose was initiated if the ANC value was 500 – 999/\mu l and platelet count was $\approx 100 \times 10^3/\mu l$. The patient was taken off study if the ANC value was $< 500/\mu l$ and the platelet count was $< 100 \times 10^3/\mu l$ at day 36 of the respective cycle. Patients had to meet both the ANC and platelet criteria described above.

Cisplatin dose adjustments were based on renal toxicity. If the peak serum creatinine during the cycle had more than doubled since the start of the previous cycle and was between 2.0 and 3.0 mg/dl, the patient’s dose of cisplatin was decreased to 60 mg/m^2. If the patient was already receiving cisplatin at 60 mg/m^2 or if the renal toxicity was greater than that outlined above, cisplatin was discontinued, and the patient was treated with paclitaxel alone. A combination of dexamethasone and ondansetron was used for antiemetic control. These were administered empirically before cisplatin therapy and administered p.o. for 4 days thereafter to prevent chemotherapy-induced delayed emesis.

Study Design. The study was conducted using a two-stage optimal design for Phase II (24). For this design, it was assumed that a response rate of 30% would be undesirably low in view of the results from several other studies of combination therapy in this disease ($P_0 = 0.30$) and that a 50% response rate would be a desirable outcome because this rate had been achieved in a preliminary fashion in the prior Phase I trial of this combination schedule ($P_1 = 0.50$). Using these design parameters, the first stage of the study was to initially enroll 22 patients with measurable disease and to stop accrual if 7 or fewer of these 22 patients responded (PR or complete response). Under the null hypothesis (for 30% response rate), the probability of early termination was 67%. If 8 or more of the 22 patients responded, then the accrual was to continue until 46 patients with measurable disease could be evaluated. If 8 – 17 of these 46 patients had a response, this was not considered sufficiently interesting for further evaluation in later trials, whereas a clinical response in 18 or more of the 46 patients with
measurable disease would merit further investigation in a later trial.

**Treatment Response and Statistical Evaluation.** Patients with bidimensionally measurable tumor masses were assessable for objective response. The criteria for tumor responses to therapy were defined in accordance with the WHO criteria (25). Toxicity profiles reported by patients or elicited on physical examination at the end of each cycle were graded according to the NCI CTC and recorded by the same research nurse (B. S. S.) throughout the study (23).

Because of the two-stage design of this study, the 95% CI for the overall response rate was constructed using a method that reflects the study design (26). Time to progression and survival time were calculated from the on-study date until the date that progression was first noted, death, or last follow-up, as appropriate. The Kaplan-Meier method was used to estimate the probability of survival or progression-free survival as a function of time, and the Mantel-Haenszel procedure was used to determine the significance of the difference between pairs of Kaplan-Meier curves (27, 28). All Ps are two-sided and denoted by \( P \). Duration of response was measured from the date of best response to the date of progression or death, whichever was first. Patients who had yet to progress or die had their progression and survival times censored as of June 25, 1999.

**Pharmacokinetic Analysis.** Blood samples were collected and processed for paclitaxel pharmacokinetics as outlined in the Phase I trial (22). A total of 140 samples were obtained from 36 patients. Although samples on the other patients were collected, they were not available for analysis. The average steady-state paclitaxel plasma concentration (\( C_{ss} \)) for each patient was calculated as the mean of the measured paclitaxel plasma level for each sample collected per patient. The clearance of paclitaxel was calculated using the following formula: clearance = infusion rate/\( C_{ss} \).

### RESULTS

**Patient Population.** Between October 1995 and December 1998, 58 patients were accrued onto this study. Six patients were still alive as of June 25, 1999. Demographic and clinical characteristics of all of the patients are listed in Table 1. Seventy-four percent \((n = 43)\) of patients had stage IV disease. Sixteen patients had evidence of metastatic disease to bones at the time of presentation. Five of these patients received radiation to painful bony metastases for symptomatic relief before enrollment on this trial. Ten patients had liver involvement. Six patients had metastases to the adrenal glands. The seven patients with brain metastases received cranial irradiation before enrollment on the trial. They had stable neurological disease after radiation therapy in the absence of corticosteroid therapy. Bilateral pulmonary involvement was seen in eight patients, and cervical adenopathy was seen in three patients. Forty-six patients had measurable disease.

**Drug Dosages.** The median number of completed cycles of chemotherapy was six (range, two to six cycles). Twenty-nine patients received all six cycles. Six patients received five cycles, and five patients received four cycles. Eight patients received three cycles, and eight patients received two cycles. Dose reductions in paclitaxel were required in 20 patients. The dose reductions in paclitaxel were secondary to delayed hematological recovery in six patients, febrile neutropenia (fever of 100.5°F in the setting of an ANC of <500/µL) in seven patients, and prolonged grade IV neutropenia in the remaining seven patients. The dose of cisplatin was reduced in 12 patients. Dose reductions in cisplatin were performed because of allergic reactions \((n = 2; \text{cycle 5 and 6)}, \text{induced renal impairment (n = 3), sepsis (n = 2), emesis despite H}_3\text{-receptor antagonist and steroid antiemetic prophylaxis (n = 2), hearing loss (n = 2), and patient request (n = 1). Seventy-seven cycles (29%) in 39 patients (70%) were delayed. The median duration of delay between delayed cycles was 7 days. This delay was to allow full hematological recovery. The dose intensity per cycle achieved was 103 mg/m²/96 h for paclitaxel (86% of intended) and 66 mg/m² for cisplatin [82% of intended (29)].

**Pharmacokinetic/Pharmacodynamic Studies.** Pharmacokinetic studies were performed by high-performance liquid chromatography during the first cycle of paclitaxel in 36 patients. Steady state \((C_{ss})\) concentrations were calculated as described in the Phase I trial (22). The average of the calculated average plasma paclitaxel concentrations \((C_{ss, avg})\) per patient was 0.075 µmol (range, 0.021–0.166 µmol). The \(C_{ss}\) was not statistically significantly related to either greatest toxicity experienced or response rates (all \( P > 0.10 \)).

**Toxicity Profile.** Fifty-six of the enrolled patients received at least two cycles of chemotherapy. Three patients developed hypersensitivity reactions within minutes of initial paclitaxel exposure, despite the standard premedication to prevent this occurrence. Two of these patients opted to come off study and were treated with alternate agents. The other patient...
was successfully retreated after further premedication with dexamethasone, diphenhydramine, and H2-receptor antagonist. All three patients are included in the intent-to-treat survival analysis, but the two patients who did not receive further paclitaxel are excluded from further toxicity reports.

Treatment-related toxicities are summarized in Tables 2 and 3. Nine patients had grade IV neutropenia for 5 days or more, with eight episodes of febrile neutropenia in seven patients. Twelve patients were transfused with 48 units of packed RBCs. Eight patients received a transfusion on more than one cycle. No patients received epoetin. No platelet transfusions were required.

Fatigue and nausea were the most commonly reported nonhematological side effects. Modest fatigue (grade I/II) occurred in 40 patients (71%) soon after chemotherapy and lasted for up to 1 week. Nausea was well controlled in most patients, with only 7% of patients reporting grade III/IV nausea. Approximately half of the patients did not experience emesis. All patients had received empiric prophylactic antiemetic therapy with dexamethasone and H2-receptor antagonists. Both patients who reported auditory impairment, necessitating a decrease in their dose of cisplatin, had a preexisting impairment. There were no treatment-related deaths.

Response Rates. Of 58 patients, 56 patients were assessable for disease response. Forty-six patients had bidimensionally measurable disease for evaluation of objective response rates. Of those with measurable disease, 20 (43%) patients had a PR (95% CI, 29–60%), 24 patients had stable disease, and 2 patients had progressive disease. There were no patients with complete responses. Ten patients had evaluable disease. Of these, six patients showed responsive disease, two patients had stable disease, and two patients showed disease progression. Thus, 26 of 56 patients (46%) with measurable or evaluable disease had a response to therapy. The two patients who had hypersensitivity reactions to paclitaxel and came off study are not included in the evaluation of response rate because they were treated with other agents; one patient was treated with gemcitabine and one was treated with vinorelbine at other medical facilities.

Survival Assessment. The median time to progression for all 58 patients was 5.5 months. The 1-year progression-free survival rate was 8.2% (95% CI, 3.3–18.9%). The median response duration in the 26 patients with either an objective PR or responsive evaluable disease was 4.8 months. All 58 patients were assessable for survival, with a median potential follow-up of 27.2 months. The median survival time was 8.5 months. The actuarial 1-year survival was 37% (95% CI, 25.9–50.5%; Fig. 1). At the time of analysis, 52 patients had died; 2 of the remaining 6 patients had not yet developed progression of their disease. All deaths but one were due to progressive disease. The sole exception was a patient who died of a pulmonary embolus

### Table 2  Hematological toxicity for all 56 treated patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>WBC</td>
<td>5 (9)</td>
<td>11 (20)</td>
<td>20 (36)</td>
<td>13 (23)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>ANC</td>
<td>4 (7)</td>
<td>6 (11)</td>
<td>9 (16)</td>
<td>9 (16)</td>
<td>28 (50)</td>
</tr>
<tr>
<td>Platelets</td>
<td>18 (32)</td>
<td>28 (50)</td>
<td>7 (12)</td>
<td>3 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1 (2)</td>
<td>18 (32)</td>
<td>24 (43)</td>
<td>9 (16)</td>
<td>4 (7)</td>
</tr>
</tbody>
</table>

*Ten cycles in nine patients were complicated with grade 4 neutropenia for 5 days or more. Eight episodes of febrile neutropenia were documented in seven patients.*

### Table 3  Nonhematological toxicity for all cycles

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>0 (%)</th>
<th>1 (%)</th>
<th>2 (%)</th>
<th>3 (%)</th>
<th>4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>8 (14)</td>
<td>11 (20)</td>
<td>33 (59)</td>
<td>4 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27 (48)</td>
<td>10 (18)</td>
<td>16 (29)</td>
<td>3 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28 (50)</td>
<td>12 (21)</td>
<td>11 (20)</td>
<td>3 (5)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>45 (80)</td>
<td>4 (7)</td>
<td>5 (9)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Neurosensory</td>
<td>43 (76)</td>
<td>6 (11)</td>
<td>6 (11)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neuroauditory</td>
<td>46 (82)</td>
<td>0 (0)</td>
<td>9 (16)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neuromotor</td>
<td>55 (98)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Renal</td>
<td>53 (94)</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>55 (98)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (25)</td>
<td>5 (9)</td>
<td>35 (62)</td>
<td>2 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Paclitaxel HSR$^a$</td>
<td>55 (98)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cisplatin HSR$^b$</td>
<td>54 (96)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*$^a$HSR, hypersensitivity reaction. Two additional patients had HSRs (grade 1 and grade 3, respectively) within minutes of starting the first cycle of paclitaxel and opted to come off protocol.

*$^b$Two patients had HSRs (grade 2 and grade 3) occurring in cycle 5 and 6, respectively.
in the absence of progressive disease 6 weeks after starting treatment.

Analysis of potential prognostic factors demonstrated that only ECOG PS appeared to be at least moderately well associated with progression-free survival ($P = 0.079$) or overall survival ($P = 0.0036$). There was also a slight trend toward improved survival among patients with bronchioloalveolar carcinoma ($P = 0.15$). Neither age nor stage of disease (IIIB, IV, or recurrent disease) had any association with either progression-free survival or overall survival. No statistically significant association was identified between patients with brain metastases and other patients with stage IV disease in terms of survival.

**DISCUSSION**

*In vitro* cytotoxicity studies show that prolonged exposure of tumor cells to paclitaxel produces significantly higher rates of tumor cell growth inhibition. This result has been shown for lung, breast, pancreas, and ovarian cancer cell lines (11–13). Thus, it was hypothesized that in the clinical setting, prolonged continuous infusional paclitaxel would produce an improved therapeutic result. Data from prolonged infusional therapy with 5-fluorouracil in patients with recurrent colorectal carcinoma, showing renewed responses in patients who had failed bolus 5-fluorouracil schedules, also heightened expectations (30).

Prior Phase II clinical trials evaluating 96-h infusional paclitaxel in patients with advanced-stage cancer are summarized in Table 4 (15–21, 31). The present study represents the most extensive evaluation of the regimen including not only the greatest number of patients per trial but also pharmacokinetic data. In seven of these eight trials, the patients received paclitaxel alone as the second-line therapy; all patients had failed other chemotherapy agents or conventional schedules of paclitaxel chemotherapy. With response rates of 30% and 48% achieved in patients with relapsed metastatic breast cancer, the authors concluded that further evaluation of the regimen was warranted (15, 16). No responses were achieved in patients with metastatic NSCLC or ovarian cancer, and the regimen was not recommended as a second-line therapy (17, 18). One previous study had evaluated the role of 96-h infusional therapy as a first line therapy in advanced-stage disease (21). The study included only 12 patients with metastatic colon cancer enrolled over a 2-year period. None of the patients achieved an objective response, and 10 of the 12 patients developed progressive disease.

In view of the encouraging results of our Phase I trial, in association with our *in vitro* data on prolonged paclitaxel exposure, we decided to assess 96-h prolonged infusional paclitaxel followed by bolus cisplatin in chemotherapy-naïve patients with advanced NSCLC (22). The regimen was well tolerated. Hematological and nonhematological toxicities resemble those experienced previously by patients with lung cancer on our Phase I trial (22).

In contrast to predictions from *in vitro* cytotoxicity models, the 96-h prolonged infusional schedule of paclitaxel does not appear to be superior, either in response rate or survival, to shorter infusion times in the clinical setting in patients with advanced-stage NSCLC. The confirmed objective response rate in our study was 43%. This response rate is similar to results reported by other groups (range of response rate, 27–44%) using shorter infusion times (1-, 3-, and 24-h schedules) with various schedules (weekly to every 3 weeks) of paclitaxel, with or without a platinum agent (7–10, 32–34). The actuarial 1-year survival of 37.4%, like the response rate, is similar to the results of other schedules of paclitaxel as a first-line therapeutic regimen in patients with advanced-stage NSCLC (7–10, 32–34).

Although there may be initial concern that the MTD from our Phase I trial in the absence of G-CSF was selected for the Phase II study, data from other authors have not shown improved results with dose escalation with G-CSF support in patients with advanced lung cancer treated with paclitaxel-platinum combinations (8, 10).

Anticancer activity has been demonstrated *in vitro* with plasma paclitaxel levels as low as 0.05 μmol (35). These plasma levels are attainable *in vivo* in humans. The average steady-state plasma concentration in the patients in this study was 0.075 μmol (range, 0.021–0.166 μmol). Three of the prior Phase II studies with 96-h prolonged infusional paclitaxel performed pharmacokinetic evaluations (15, 17, 20). They compared the steady-state plasma concentration ($C_{ss}$) of paclitaxel during cycle 1 to toxicity and response rates. They found a proportional relationship between paclitaxel dose and $C_{ss}$, with greater toxicity experienced with a higher $C_{ss}$. No significant association was apparent between the paclitaxel $C_{ss}$ of responders and nonresponders. Other authors, comparing 3-h and 24-h paclitaxel infusions, have shown that the duration of plasma paclitaxel concentration above 0.05 μmol/liter predicts for neutropenia (36). Pharmacokinetic evaluation of average steady-state plasma concentrations in patients treated on a Phase III trial comparing two doses of paclitaxel (24-h infusion) in combination with cisplatin showed overall survival in patients with advanced NSCLC demonstrated that the average paclitaxel steady-state plasma concentration ($C_{ss,avg}$) was not a determinant of response, progression-free survival, or survival in patients with NSCLC (10, 37). In our study, we found no significant association between the paclitaxel $C_{ss,avg}$ and toxicity grade, duration of grade IV neutropenia, or best objective response.

We have shown that prolonged infusional paclitaxel therapy in combination with bolus cisplatin therapy is an effective therapy in advanced-stage disease (21). The study included only 12 patients with metastatic colon cancer enrolled over a 2-year period. None of the patients achieved an objective response, and 10 of the 12 patients developed progressive disease.
therapy that can be administered safely in the outpatient setting. Despite achieving the response criteria for proceeding beyond the first stage of accrual and considering the therapy sufficiently active to warrant further investigation based on the final results in 46 patients, the overall response rate and survival of the patients treated with this regimen were not as great as anticipated from our Phase I trial. The response rates and overall survival achieved are similar to other schedules of paclitaxel or other new agents. The optimal schedule for paclitaxel remains to be defined. Shorter infusion schedules of 1–3 h are more convenient for patients and staff and appear to have equal therapeutic efficacy. Because our results are no better than those achieved with shorter infusions, we conclude that further evaluation of 96-h prolonged infusional paclitaxel as a first-line therapy for patients with NSCLC should be regarded as a low priority.

REFERENCES

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