Anti-Cancer Drugs 1998, 9, pp. 611–619

Clinical report

Phase I trial of a 96 h paclitaxel infusion with filgrastim support in refractory solid tumor patients

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A phase I study of a 96 h paclitaxel infusion with filgrastim support was performed to determine the toxicity, maximum-tolerated dose (MTD) and pharmacokinetics in patients with refractory solid tumors. In this phase I trial, the initial paclitaxel dose was 140 mg/m^2/96 h followed by filgrastim (5 μg/kg/day s.c.) beginning 24 h after the paclitaxel and continued until granulocyte recovery. Cycles were repeated every 21 days. Patients with refractory solid tumors were eligible; however, only one previous chemotherapy regimen was allowed. The dose of paclitaxel was escalated by 20 mg/m^2/96 h in subsequent cohorts until dose-limiting toxicity (DLT) occurred. Pharmacokinetic analysis was performed by quantitating paclitaxel concentrations at baseline, 24, 48, 72 and 96 h after the start of the paclitaxel infusion. Twenty-one patients were entered into this trial of which 19 were evaluable. A total of 52 treatment cycles were administered. DLT was seen in two of four patients at 200 mg/m^2/96 h, and consisted of diarrhea, mucositis and granulocytopenic infection. The MTD of the 96 h paclitaxel infusion was 180 mg/m^2 with filgrastim support. Mucosal and granulocyte toxicity were correlated with steady-state paclitaxel concentrations (C_{ss}) greater than 0.100 μmol/l. In the presence of liver function test 1.5 times or lower than normal, metastatic liver disease did not alter paclitaxel C_{ss}. Objective responses were observed in non-small cell lung cancer, small cell lung cancer and melanoma. The recommended phase II dose of paclitaxel infused over 96 h with filgrastim support is 180 mg/m^2. Paclitaxel C_{ss} correlate with mucosal and granulocyte toxicity. In the presence of normal enzymatic function, metastatic liver disease does not affect paclitaxel clearance. [© 1998 Lippincott Williams & Wilkins.]

Key words: Continuous infusion, paclitaxel, phase I study.

Introduction

Paclitaxel is a natural product initially isolated from the bark of the western yew tree, *Taxus brevifolia*.[1] It is the first of a new class of antineoplastic agents that exerts their effect by enhancing tubulin polymerization. In mammalian cells, paclitaxel exposure promotes the assembly of microtubules and interferes with their depolymerization resulting in mitotic arrest of dividing cells.[2,3] Clinically, paclitaxel has been studied extensively and has been shown to have a broad spectrum of antitumor activity. It is active in breast cancer, ovarian cancer, lung cancer, head and neck cancer, and melanoma as well as other tumor types.[4] Phase III trials in both ovarian and non-small cell lung cancer (NSCLC) have shown survival advantages in favor of paclitaxel-containing regimens.[5,6]

The optimal dose and schedule of paclitaxel in most solid tumors has not yet been defined. Paclitaxel has been administered by a number of infusion schedules including 1, 3, 24, 96, 120 or 164 h infusions with demonstrated clinical activity in all settings.[7–12] Preclinical data suggest that the cytotoxicity of paclitaxel may be enhanced by prolonged exposure. *In vitro*, 4-fold less resistance developed in multidrug-resistant MCF-7 human breast cancer cells exposed to paclitaxel for 24 h as compared to 3 h.[13] In lung cancer cell lines, prolonged exposure resulted in enhanced cytotoxicity compared to short exposure.[14] This preclinical data appears to predict clinical activity. Seidman *et al.*[15] demonstrated a 27% response to 96 h paclitaxel infusions in a population of metastatic breast cancer patients refractory to short taxane infusions.

The maximum-tolerated dose (MTD) of paclitaxel given as a 96 h infusion has been defined in a phase I/

Supported in part by a grant (RR00046) from the General Clinical Research Centers program of the Division of Research Resources, National Insititutes of Health, and by grants from Amgen and Bristol-Myers Squibb Oncology.

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II study by Wilson *et al.*[10] In that study, the MTD was 140 mg/m^2/96 h in patients without liver metastases and 105 mg/m^2/96 h in patients with liver metastases. The dose-limiting toxicity (DLT) was mucositis and myelosuppression. In the phase II portion of that study, the investigators demonstrated that filgrastim significantly reduced the incidence of grade 4 granulocytopenia and allowed a 17% increase in the dose intensity of paclitaxel compared with those patients not receiving filgrastim.

Filgrastim has been shown to reduce both myelosuppression and mucositis in bladder cancer patients underoing treatment with methotrexate, vinblastine, adriamycin and cisplatin (M-VAC).[16] Both of these toxicities are dose-limiting when using a 96 h paclitaxel infusion alone.[10] Since the 96 h infusion schedule has been shown to be clinically active and the optimal dose has not yet been defined, we designed a phase I trial to define the MTD, DLT and pharmacokinetics of a 96 h paclitaxel infusion with filgrastim.

Patients and methods

Patients

From March 1996 to September 1997, 21 patients with refractory solid tumors were entered into this phase I trial. Patients were eligible if they were refractory to standard first-line therapy or had a solid tumor for which there was no accepted standard first-line therapy. All patients were required to have a tissue diagnosis of malignancy and only one prior treatment regimen was allowed. Patients could have either measurable or evaluable disease. Entry criteria for this study also included: performance status 0 or 1 (ECOG), age 18 or higher, absolute neutrophil count (ANC) $\geq$ 1500/ml, platelets $\geq$ 100 000/ml, hemoglobin above 9.9 g/dl, creatinine less than twice institutional normal, bilirubin less than 1.5 mg/dl, AST and ALT less than 1.5 times institutional normal, alkaline phosphatase less than twice institutional normal, and at least 4 weeks from any prior cytotoxic chemotherapy or radiation therapy. Patients were ineligible if they had significant co-morbid conditions (including pregnancy) or a psychiatric illness that prevented informed consent. All patients were informed of the investigational nature of the trial and gave informed consent. This trial was approved by the Protocol Review Committee of the Lineberger Comprehensive Cancer Center (LCCC) and the Institutional Review Board of the University of North Carolina School of Medicine, and labeled LCCC 9601.

Patient evaluations and response toxicity assessments

A complete medical history and physical examination were performed as an initial evaluation. This initial evaluation included a complete blood count (CBC) including platelet count, and differential and serum chemistry panel including creatinine, and liver function tests. Patient radiographs were reviewed to assure measureable or evaluable disease.

During treatment, the CBC was monitored biweekly and the serum chemistry panel was monitored prior to each cycle of treatment. Response assessment was formally done every two cycles of treatment. Standard response criteria were applied.[17] Complete response (CR) was defined as the disappearance of all clinical evidence of disease and disease-related symptoms for 4 weeks or longer. Partial response (PR) was defined as a 50% reduction in the sum of the products of bidimensionally measured diameters of all measurable lesions without the appearance of new lesions for 4 weeks or longer. Stable disease was defined as no change or 25% or less increase in the sum of the products of bidimensionally measured diameters of all measurable lesions. Progressive disease (PD) was defined as the appearance of new lesions or an increase of 25% or greater in the sum of the products of bidimensionally measured diameters of all measurable lesions. Whenever PD was documented, treatment on this trial was stopped. In the case of multiple lesions, the largest and most representative lesions (up to five lesions) were used to assess response.

Toxicity was assessed with each cycle of treatment. The CALGB Expanded Toxicity Criteria was used for toxicity grading. DLT was defined as any grade 3–4 non-hematologic toxicity (with the exception of infection grading which had to be grade 4), grade 4 granulocytopenia or thrombocytopenia lasting more than 7 days, or failure to recover granulocytes > 1500/μl or platelets > 100 000/μl by day 35 of the cycle. DLT was assessed during cycle 1. The MTD of the 96 h paclitaxel infusion given with filgrastim was defined as the dose level immediately below that which caused DLT in one-third or more patients in any cohort. If patients experienced DLT but were responding to treatment, continued treatment with 96 h paclitaxel infusion was allowed at the next lowest dose level.

Treatment plan

Paclitaxel (Taxol; Bristol-Myers Squibb Oncology, Princeton, NJ) was administered as a 96 h continuous infusion. A 24 h supply of paclitaxel was diluted in

500 ml of 0.9% sodium chloride or 5% dextrose injection in an evacuated glass container (Baxter, Chicago, IL) to a final concentration of 0.3–1.2 mg/ml. The 96 h infusion was completed with four successive 24 h aliquots of paclitaxel. The paclitaxel solution was infused through a non-PVC lined fluid path with a 0.2 μm in-line filter (#9986; IMED, San Diego, CA).

Patients were pre-medicated 30 min prior to paclitaxel with dexamethasone 20 mg i.v., ranitidine 50 mg i.v. and diphendydramine 50 mg i.v. The initial dose of paclitaxel was 140 mg/m^2/96 h. Subsequent cohorts (three patients per cohort) were escalated in 20 mg/m^2/96 h increments. Granulocyte-colony stimulating factor [(G-CSF) Filgrastim; Amgen, Thousand Oaks, CA] was administered 24 h after completion of the paclitaxel infusion at 5 μg/kg/day s.c. and continued until WBC $\geq$ 10 000/mm^3.

Patients required either a central venous device or a peripherally inserted central catheter (PICC) for the paclitaxel infusion. All patients received their paclitaxel infusions in the Clinical Research Center at the University of North Carolina to allow adequate sampling for the pharmacokinetic portion of the study. A maximum of six cycles of treatment were planned.

Pharmacokinetics

Blood samples for determination of paclitaxel concentrations and pharmacokinetic analysis were drawn at baseline, 24, 48, 72 and 96 h after the start of the paclitaxel infusion. Blood samples were drawn with each cycle when possible. A total of 225 samples were collected from 20 patients (46 total pharmacokinetic cycles). Plasma was immediately separated by centrifugation at 1500 r.p.m. for 12 min at 4°C and stored in polypropylene tubes at −20°C until analysis.

The steady-state plasma concentration of paclitaxel (C_{ss}) was calculated for each cycle in a patient by one of two different methods. The 24 h time point was omitted in all patients because C_{ss} had not been reached. In 38 of 46 pharmacokinetic cycles, the C_{ss} was calculated as the mean of the 48, 72 and 96 h time points. In eight of 46 pharmacokinetic cycles, the C_{ss} was assumed to be the 96 h time point because these patients had a sustained increase in concentration (greater than 10%) across the sampling times; these profiles were expected given that some patients have a long terminal elimination phase for paclitaxel.

Paclitaxel plasma concentrations were quantitated by reverse-phase HPLC according to modifications of a previously published assay.[18] The internal standard was cephalomannine (NSC 318735). A stock solution (100 μg/ml) of paclitaxel (Aldrich, Milwaukee, WI) was prepared in ethanol and stored at −20°C. Ten microliters of cephalomannine (100 μg/ml) was added to 0.8 ml of standard or sample. The solutions were vortexed, centrifuged and applied to a 100 mg C_{18} solid-phase extraction column (Applied Separations, Allentown, PA) that had been preconditioned with 2 × 1 ml of acetonitrile and then 2 × 1 ml of distilled water. After applying the sample or standard to the column, the columns were washed with 3 × 1 ml of distilled water and eluted with 2 × 1 ml of acetonitrile. The eluent was dried in a TurboVap® evaporator (Zymark, Hopkinton, MA). The dried extract was reconstituted with 150 μl of 45% acetonitrile in distilled water and 100 μl was injected into the HPLC system.

The HPLC system consisted of a Hypersyl C_{18} 5 μm, 100 × 4.6 mm column (Phenomenex, Torrance, CA) and a RP18 7u 15 × 3.2 guard column (Alltech, Deerfield, IL). The guard column was changed after injection of 32–46 samples. Samples were chromatographed isocratically with 45% acetonitrile in distilled water at a flow rate of 1 ml/min and the eluate was monitored at 227 nm with a Shimadzu 6PD-6AV UV-Vis spectrophotometric detector. The retention times for cephalomannine and paclitaxel were 6.7 and 8.2 min, respectively. After all samples were injected, the column was washed for 1 h with 100% acetonitrile followed by a 1 h wash with 45% acetonitrile in distilled water. Paclitaxel standard curves were linear ($r^2 > 0.99$ in all cases) and concentrations ranged from 0.028 to 0.234 μmol/l (24–200 ng/ml). Paclitaxel plasma concentrations were quantitated by linear regression of the peak height ratio (paclitaxel/cephalomannine) compared to paclitaxel standards prepared in normal healthy volunteer plasma. Three paclitaxel quality controls (0.0351, 0.105 and 0.234 μmol/l) were run at the beginning and end of each HPLC run. The intra-assay coefficient of variation (CV%) was below 10%; the inter-assay CV% was below 14%. The limit of detection was 24 ng/ml (0.028 μmol/ml).

Statistical analysis

The primary objective of the trial was to define the MTD of a 96 h paclitaxel infusion with filgrastim support. A standard phase I trial design was used with three to six patients treated at each dose level. The MTD of the 96 h paclitaxel infusion with filgrastim support was that dose level immediately below the dose level that resulted in DLT in more than one-third of patients.

The association between paclitaxel dose and clearance as well as dose and paclitaxel steady-state concentration was examined by the Spearman correlation. The Kruskal-Walis test was used to assess the association between metastatic liver disease and paclitaxel clearance and to evaluate relationships between paclitaxel C_{ss} and grade of mucositis and neutropenia. The proportion of patients with $C_{ss} > 0.100$ μmol/l with greater than grade 2 mucositis and grade 4 neutropenia was compared to patients with less than grade 2 mucositis and less than grade 4 neutropenia using Fischer's Exact test.

Results

Patients

Between March 1996 and September 1997, 21 patients were accrued into this study. Table 1 shows the demographic and clinical characteristics of the patients. Two patients were non-evaluable. One patient had a port-a-cath placed on the initial day of treatment and approximately 72 h into the paclitaxel infusion developed an infection at the port-a-cath site. Because this event was iatrogenic, the patient was felt to be non-evaluable for toxicity. The second patient underwent a thoracentesis 3 days before treatment that was complicated by a small apical pneumothorax. A follow-up chest X-ray suggested resolution. Twelve hours into the paclitaxel infusion the patient developed chest pain and dyspnea. A chest X-ray revealed an expanded pneumothorax requiring tube thoracostomy. The paclitaxel infusion was discontinued and the patient was deemed non-evaluable. Therefore, 19 patients were evaluable for toxicity. Of these, 13 had received one prior chemotherapeutic regimen; however, none had received prior paclitaxel. Seven patients had one previous course of radiotherapy. All patients had an ECOG performance status of 0 or 1. The median age was 55 years (range 23-67).

Treatment, delivery and toxicity

Table 2 summarizes the treatment delivery of all 19 evaluable patients. A total of 52 courses of treatment were administered. No hypersensitivity reactions were seen in any of the 52 courses. The median number of cycles per patient was 2 (range 1-6). Nine of the 19 patients (47%) completed only one or two cycles of treatment due to progressive disease. Eighty-six percent of cycles were completed without dose reduction. The duration of filgrastim treatment did not differ between the dose levels (Table 2).

The hematologic toxicity of the 96 h paclitaxel infusion is shown in Table 3. None of the patients experienced dose-limiting hematologic toxicity as described in Patients and methods. Grade 4 granulocytopenia increased with increasing dose (33% dose at level 1 and 2, 50% at dose level 3, and 75% at dose level 4); however, it was of similar duration at all dose levels. As noted, filgrastim duration was similar at all

Table 1. Patient characteristics

Total no. of patients	21
Total no. of patients evaluable	19[a]
Sex	
male	12
female	7
Age (years)	
median	55
range	23–67
Prior combination chemotherapy	
none	6
one prior regimen	13
Tumor types	
non-small cell lung	5
small cell	5 (4 lung, 1 cervix)
renal	2
melanoma	2
esophageal	2
hepatoma	2
head/neck	1

[a]The following numbers characterize the evaluable patients only.

Table 2. Summary of treatment delivery

Dose level	Dose (mg/m^2/ 96 h)	No. of patients treated	Total no. of courses	Mean no. of courses (range)	Mean no. of courses at full dose	Mean no. of days of (range)
1	140	3	8	2 (1–5)	8	8 (4–10)
2	160	6	14	2 (1–6)	13	10 (4–12)
3	180	6	17	2 (1–6)	12	8 (6–9)
4	200	4	13	4 (1–6)	12	8 (6–10)

Table 3. Hematologic toxicity (n=19)

Dose level	No. of patients	Parameter	Maximal grade			
			0/1	2	3	4
1	3	WBC	2	0	1	0
		ANC	2	0	0	1
		HGB	2	0	1	0
		PLT	3	0	0	0
2	6	WBC	2	0	2	2
		ANC	2	1	1	2
		HGB	3	2	1	0
		PLT	5	1	0	0
3	6	WBC	0	1	1	4
		ANC	0	2	1	3
		HGB	0	4	2	0
		PLT	4	2	0	0
4	4	WBC	0	1	0	3
		ANC	0	1	0	3
		HGB	1	2	1	0
		PLT	3	1	0	0

dose levels. All patients had resolution of myelosuppression before day 21 and none of the patients required a delay in the administration of a subsequent cycle because of prolonged or cumulative cytopenias. In fact, none of the patients had grade 4 neutropenia lasting more than 7 days. No grade 3 or 4 thrombocytopenia was seen. Grade 3 anemia occurred in five of 19 patients (26%). Five patients (26%) required transfusion of packed red blood cells. Hospitalization for fever in the setting of grade 4 granulocytopenia increased with increasing dose [two of 22 cycles (9%) at dose levels 1 and 2 versus 11 of 30 cycles (36%) at dose levels 3 and 4].

Non-hematologic toxicity (grade 3 and 4) is shown in Table 4. Mucositis, diarrhea and infection were the only high grade non-hematologic toxicities observed. Grade 1 and 2 toxicities consisted of nausea/vomiting (37%), myalgia/arthralgia (5%), diarrhea (16%), mucositis (32%) and alopecia (68%). Neuropathy was not seen at any dose level.

DLT occurred in two of four patients at 200 ng/m^2/96 h, thereby defining the MTD of a 96 h paclitaxel infusion with filgrastim support as 180 mg/m^2.

Therapeutic response

As noted above, nine of 19 patients (47%) received only one or two cycles of treatment as progressive disease was documented. Three patients had objective responses. One patient with small cell carcinoma of the lung (SCLC), who initially had limited stage disease treated with cisplatin, etoposide and thoracic radiation

Table 4. Non-hematological toxicity (grade 3/4)

Dose level	No. of patients	Parameter	Maximal grade	
			3	4
1	3	–	0	0
2	6	infection	0	1
3	6	mucositis	1	0
4	4	mucositis	1	0
		diarrhea	1	0
		infection	0	1

therapy, and who relapsed in the liver had a partial response (PR) after two cycles lasting approximatley 6 weeks. One patient with non-small cell lung cancer (NSCLC) previously untreated had a PR after two cycles but subsequently progressed after four cycles. One patient with previously untreated metastatic melanoma had a complete response (CR) in s.c. metastases after six cycles of treatment and remained in CR for 5 months after cessation of treatment. Two patients with hepatoma experienced stable disease for 2 and 5 cycles of treatment. The one patient having stable disease for two cycles had a greater than 50% decrease in the α-fetoprotein level, however, did not receive further treatment becasue of DLT. Three patients (esophageal, SCLC and NSCLC) had disease stabilization for six, six and four cycles, respectively. Two patients did not have an assessment of their response after experiencing DLT.

Pharmacokinetics

Paclitaxel pharmacokinetics were determined from blood samples of 19 patients in 46 cycles (Table 5). Twelve patients had paclitaxel concentration data from more than one cycle. Plasma paclitaxel concentrations did not change within a patient between cycles (same dose level). There was no evidence of dose-dependent clearance over the dose ranges studied (p=0.39). Paclitaxel C_{ss} increased proportionately with dose (p=0.0016). Five patients (one non-evaluable) had paclitaxel concentration data from more than one dose level. These patients had dose reductions due to toxicity; each patient exhibited a corresponding decrease in paclitaxel after dose reduction. Paclitaxel concentration data were collected over three dose levels in one patient; there was no evidence of dose-dependent clearance in this subject. Not all patients reached steady-state by 24-48 h; this concentration data was handled as described in Patients and methods. Paclitaxel clearance in patients with meta-

Table 5. Paclitaxel pharmacokinetics

Dose (mg/m^2)	No. of patients	No. of pharmacokinetic cycles	C_{ss} (μmol/l)[a]	SD	CL (l/h/m^2)[b]	SD
140	6	12	0.0631	0.0162	28.8	10.6
160	8	10	0.0735	0.0213	28.1	6.23
180	7	13	0.0787	0.0193	28.5	7.01
200	4	11	0.105	0.011	24.2	2.31

[a]If a patient had more than one pharmacokinetic cycle, the mean C_{ss} of the cycles was used.
[b]Mean steady-state paclitaxel concentration; C_{ss} increased with dose (p=0.0016).
[c]Mean paclitaxel clearance; CL did not change with dose (p=0.39).
SD, Standard deviation.

Table 6. Paclitaxel clearance in metastatic liver disease

Liver disease[a]	No. of patients	Paclitaxel clearance[a] (l/h/m^2)	SD
++	5	24.4	4.6
+	3[b]	30.1	6.9
0	12	28.6	7.7

[a]See text for definition.
[b]Mean paclitaxel clearance (p=0.36).
[c]Patient 5 was non-evaluable for toxicity; pharmacokinetic data was used.
SD, standard deviation.

static liver disease was compared with patients with no liver involvement as judged by CT scans. As noted in the eligibility criteria, all patients had bilirubin levels below 1.5 mg/dl, AST and ALT below 1.5 times normal, and alkaline phosphatase below 2 times normal. Liver involvement was determined by CT and graded as follows: extensive (++=>2 cm masses or diffuse involvement), moderate (+=$\leqslant$2 cm masses) and none (0=no liver involvement). There were no significant differences in paclitaxel clearance values in patients with varying liver involvement (p=0.36).

Paclitaxel steady-state concentrations were significantly correlated with mucositis of grade 2 or higher and neutropenia of grade 4 (Table 6). In patients with paclitaxel $C_{ss} \geqslant 0.100$ μmol/l, five of six patients developed mucositis of grade 2 or higher and six of six patients had grade 4 neutropenia. In comparison, in patients with paclitaxel $C_{ss} < 0.100$ μmol/l, one of 13 patients developed mucositis of grade 2 or higher ($p < 0.003$) and three of 13 patients exhibited grade 4 neutropenia ($p < 0.003$). All patients experiencing a DLT had a paclitaxel $C_{ss} > 0.100$ μmol/l. The mean paclitaxel C_{ss} in patient cycles with grade 2 or higher mucositis (0.104 μmol/l) was significantly greater ($p < 0.003$) than in patient cycles with less than grade 2 mucositis (0.0723 μmol/l). Patient cycles with grade 4 neutropenia had a significantly higher ($p < 0.005$) mean paclitaxel C_{ss} (0.0911 μmol/l) than patient cycles with grade 3 or less neutropenia (0.0708 μmol/l).

Discussion

The optimal infusion schedule of paclitaxel remains uncertain. Experimental evidence suggests that prolonged exposure to low concentrations of paclitaxel is more cytotoxic than shorter, higher-dose exposure.[13,19] A previous phase I/II trial by Wilson *et al.*[10] defined the MTD of 96 h paclitaxel infusions as 140 mg/m^2; principal DLTs were mucositis and myelosuppression. The addition of filgrastim following a 96 h paclitaxel infusion allows dose escalation to the MTD of 180 mg/m^2 with the DLTs of diarrhea, mucositis and neutropenic infections. The toxicity patterns for paclitaxel differ based on the infusion schedule. In our study, no peripheral neuropathy and only a 5% incidence of arthralgia/myalgia was observed. These two toxicities are dose limiting when using the 3 and 1 h infusion schedules.[7,8] Wilson *et al.*[10] also reported infrequent and mild peripheral neuropathy and arthralgia/myalgia as well as diarrhea when paclitaxel doses in the 120-140 mg/m^2 range were infused over 96 h. Similarly, Seidman *et al.*[15] reported grade 1 or 2 diarrhea in 43%, grade 2 or 3 neuropathy in 8% and grade 2 or 3 arthralgia/myalgia in 16% of 26 previously taxane-treated breast cancer patients receiving a 96 h paclitaxel infusion of 120-140 mg/m^2. The toxicity pattern of a 96 h paclitaxel infusion, although different than shorter infusions, appears acceptable within the dose ranges discussed above.

Previous pharmacologic studies of 96 h paclitaxel infusions have suggested impaired clearance of paclitaxel in patients with hepatic dysfunction. Wilson *et al.*[10] showed an association between the presence of

metastatic liver disease, as detected by CT scans and elevated liver function tests, and decreased paclitaxel clearance. In that study, elevated AST levels (defined as 1.5 or higher times normal) correlated with the presence of liver metastases. Given the decrease in paclitaxel clearance and subsequent higher C_{ss} which correlated with increased toxicity, they have recommended a lower starting dose of paclitaxel (105 mg/m^2/96 h) in patients with evidence of extensive liver involvement by CT scan (defined as greater than 2 cm masses or diffuse involvement) or a 1.5-fold or higher elevation of AST. Our study could not address the issue of AST elevation because we excluded patients with AST elevation 1.5 or higher times normal. However, using the same criteria as Wilson *et al.*,[10] we did not find a correlation between CT-detected liver involvement and decreased paclitaxel clearance in the setting of an AST 1.5 or lower times normal (Table 6). Fetell *et al.*[20] recently reported a trial which further supports the correlation between hepatic enzyme function and paclitaxel clearance. In that study, a difference in the MTD of a 96 h paclitaxel infusion was observed between glioblastoma patients receiving or not receiving enzyme-inducing antiepileptic drugs (EIAEDs). These drugs are known to be potent inducers of the hepatic cytochrome (P450) enzyme system. In patients not receiving EIAEDs, the MTD of a 96 h paclitaxel infusion was 140 mg/m^2 while the dose could be escalated to 200 mg/m^2 in patients receiving EIAEDs. Paclitaxel C_{ss} for patients receiving EIAEDs was approximately 50% lower than patients not receiving EIAEDs at a paclitaxel dose of 140 mg/m^2/96 h.

Both mucosal and granulocyte toxicity have been correlated with paclitaxel C_{ss}. In the study by Wilson *et al.*[10] paclitaxel C_{ss} levels above 0.07 μmol/l were correlated with grade 4 neutropenia and grade 3 or higher mucosal toxicity. Seidman *et al.*[15] reported higher paclitaxel C_{ss} in patients experiencing grade 4 neutropenia (0.068 μmol/l) compared to patients with grade 3 or lower neutropenia (0.039 mmol/l). They also reported an association between paclitaxel C_{ss} and elevated hepatic transaminases. In our study, we have found a similar relationship between paclitaxel C_{ss} and mucosal and granulocyte toxicity. However, we were able to achieve paclitaxel C_{ss} of 0.0723 and 0.0708 μmol/l with acceptable mucosal and granulocyte toxicity (Table 7) with the addition of filgrastim following 96 h paclitaxel infusion. Significant granulocyte and mucosal toxicity was observed when paclitaxel C_{ss} was 0.100 μmol/l or higher.

Several phase I studies of prolonged infusion paclitaxel have been reported (Table 8). As can be seen, infusions have ranged from 96 to 164 h. The MTD was 140 mg/m^2/96 h in the two studies where paclitaxel was administered alone. With the more prolonged infusion schedules of 120 and 164 h, slightly higher total doses (150–160 mg/m^2) may be achieved; however, daily doses tend to be lower (35 mg/m^2 on the 96 h schedule versus 22.8–30 mg/m^2 on the longer infusions). Both filgrastim and the use of EIAEDs allow higher total daily doses to be administered (45–50 mg/m^2 over 96 h). The toxicity is strikingly consistent across studies and consists mainly of mucositis and myelosuppression.

The role of 96 h paclitaxel infusions has not been clearly defined. This schedule has been shown to be clinically active in doxorubicin-refractory and short-taxane refractory metastatic breast cancer patients.[15] This data served as the basis for a multi-center phase III study led by the MD Anderson Cancer Center and supported by the National Cancer Institute (T93-0165) comparing 3 versus 96 h paclitaxel infusions in this population. In contrast, 96 h paclitaxel infusions have

Table 7. Paclitaxel plasma concentrations and neutropenia/mucositis

Toxicity grade	C_{ss}[a] (μmol/l)	SD	p[b]	No. of patients $C_{ss} > 0.1$	No. of patients $C_{ss} < 0.1$	p[c]
Mucositis						
0–1	0.0723	0.0180	<0.003	1	12	<0.003
2–4	0.104	0.0151		5	1	
Neutropenia						
0–3	0.0708	0.0185	<0.005	0	10	<0.004
4	0.0911	0.022		6	3	

[a]From 46 cycles.
[b]p value: Kruskal–Walis test.
[c]p value: Fisher's Exact test.
SD, standard deviation.

Table 8. Phase I studies of prolonged infusions of paclitaxel

Author	No. of evaluable patients	Infusion schedule (h)	MTD	Maximum dose/ day (mg/m^2)	DLT
Spriggs[11]	20	120	150 mg/m^2/120 h	30	stomatitis neutropenia
Wilson[10]	12	96	140 mg/m^2/96 h	35	mucositis neutropenia
Skubitz[12]	29	164	160 mg/m^2/164 h	22.8	mucositis neutropenia
Fetell[20]	24	96	140 mg/m^2/96 h (EIAED−)	35	febrile neutropenia
			200 mg/m^2/96 h (EIAED+)	50	
Soulie[21]	13	164	140 mg/m^2/164 h	20	neutropenia
Socinski[a]	19	96	180 mg/m^{2}96 h with filgrastim	45	mucositis diarrhea febrile neutropenia

[a]Present study.

not shown objective activity in refractory ovarian[22] or NSCLC.[23] In combination with other agents, 96 h paclitaxel infusions have shown promising activity in hormone-refractory prostate and NSCLC. Hudes *et al.*[24] reported a phase II trial of a 96 h paclitaxel infusion plus oral estramustine phosphate in hormone-refractory prostate cancer. Objective measurable responses were observed in four of nine patients and 17 of 32 (53%) assessable patients with bone limited disease had a 50% or greater decline in pretreatment prostate-specific antigen. Georgiadis *et al.*[25] reported a 55% response rate in NSCLC with the combination of cisplatin and a 96 h paclitaxel infusion. In the phase I trials outlined in Table 8, objective responses were observed in melanoma, NSCLC, sarcoma, renal cell carcinoma and small cell lung cancer.

In conclusion, this study defines the MTD of a 96 h paclitaxel infusion with filgrastim support as 180 mg/m^2. The significant toxicities of this regimen correlate with plasma paclitaxel C_{ss}. DLTs include mucositis, diarrhea and neutropenic infectious complications. Although we routinely premedicated our patients with dexamethasone, ranitidine and diphenhydramine as have others,[20,24] several investigators[10,15] have shown this is not necessary when using prolonged infusions of paclitaxel. In those trials, hypersensitivity reactions were not seen despite deleting the standard pretreatment regimens necessary during the use of short paclitaxel infusion. Because of the pharmacokinetic portion of the study, patients in the present study were hospitalized in the Clinical Research Center of the University of North Carolina, but we[23] and others have shown that prolonged paclitaxel infusions can be done safely in the outpatient setting. Given preclinical data, toxicity profile and clinical activity as noted above, further investigation of this schedule and dose of paclitaxel seems warranted in selected tumor types.

References

1. Wani MC, Taylor HL, Wall ME, *et al.* Plant antitumor agents VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. *J Am Chem Soc* 1971; **93**: 2352-7.
2. Schiff PB, Fant J, Horwitz SB. Promotion of microtubule assembly *in vitro* by Taxol. *Nature* 1979; **277**: 665-7.
3. Schiff PB, Howitz SB. Taxol stabilizes microtubules in mouse fibroblast cell. *Proc Natl Acad Sci USA* 1980; **77**: 1561-5.
4. Rowinsky EK, Donehower RC. Paclitaxel (Taxol). *N Engl J Med* 1995; **15**: 1004-14.
5. McGuire WP, Hoskins WJ, Brady MF, *et al.* Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996; **334**: 1-8.
6. Bonomi P, Kim K, Kugler J, Johnson D. Comparison of survival for stage IIIB versus stage IV non-small cell lung cancer (NSCLC) patients treated with etoposide-cisplatin versus Taxol-cisplatin: an Eastern Cooperative Group (ECOG) trial. *Proc Am Soc Clin Oncol* 1997; **16**: 454a.
7. Hainsworth J, Greco A. Paclitaxel administered by 1-hour infusion—preliminary results of a phase I/II trial comparing two schedules. *Cancer* 1994; **74**: 1377-82.
8. Seidman AD, Tierstan A, Hudis C, *et al.* Phase II trial of paclitaxel by 3 hour infusion as initial and salvage chemotherapy for metastatic breast cancer. *J Clin Oncol* 1995; **13**: 2575-81.
9. Chang AY, Kim K, Glick J, *et al.* Phase II study of Taxol, merbarone, and piroxantrone in stage IV non-small cell lung cancer: the Eastern Cooperative Oncology Group results. *J Natl Cancer Inst* 1993; **95**: 388-94.

10. Wilson WH, Berg S, Byant G, *et al.* Paclitaxel in doxorubicin-refractory or mitoxantrone-refractory breast cancer: a phase II trial of 96 hour infusion. *J Clin Oncol* 1994; **2**: 1621–9.
11. Spriggs DR, Tondini C. Taxol administered as a 120 hour infusion. *Invest New Drugs* 1992; **10**: 275–8.
12. Skubitz KM. A phase I study of ambulatory continuous infusion paclitaxel. *Anti-Cancer Drugs* 1997; **8**: 823–8.
13. Zhan A, Kang YK, Regis J, *et al.* Taxol resistance: *in vitro* and *in vivo* studies in breast cancer and lymphoma. *Proc Am Ass Cancer Res* 1993; **34**: 215.
14. Georgiadis MS, Russell E, Johnson BE. Prolonging the exposure of human lung cancer cell lines to paclitaxel improves the cytotoxicity. *Proc Am Ass Cancer Res* 1994; **35**: 341.
15. Seidman AD, Hochhauser D, Gollub M, *et al.* Ninety-six-hour paclitaxel infusion after progression during short taxane exposure: a phase II pharmacokinetic and pharmacodynamic study in metastatic breast cancer. *J Clin Oncol* 1996; **14**: 1877–84.
16. Gabrilove JL, Jakubowski A, Scher H, *et al.* Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. *N Engl J Med* 1988; **319**: 1414–22.
17. Miller AB, Hoogstraten B, Staquent M, *et al.* Reporting results of cancer treatment. *Cancer* 1981; **47**: 207–14.
18. Jamis-Dow CA, Klecker RW, Sarosy G, *et al.* Steady-state plasma concentrations and effects of taxol for a 250 mg/m^2 dose in combination with granulocyte-colony stimulating factor in patients with ovarian cancer. *Cancer Chemother Pharmacol* 1993; **33**: 48–52.
19. Spencer CM, Faulds D. Paclitaxel. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of cancer. *Drugs* 1994; **48**: 794–847.
20. Fetell MR, Grossman SA, Fisher JD, *et al.* Preirradiation paclitaxel in glioblastoma multiforme: efficacy, pharmacology, and drug interactions. *J Clin Oncol* 1997; **15**: 3121–8.
21. Soulie' P, Trandafir L, Taamma A, *et al.* Schedule-dependent paclitaxel tolerance/activity: data from a 7 day infusion phase I study with pharmacokinetics in paclitaxel refractory ovarian cancer. *Anti-Cancer Drugs* 1997; **8**: 763–6.
22. Markman M, Rose P, Kennedy A, *et al.* A Phase II study of 96 hour paclitaxel (P) as salvage therapy in ovarian carcinoma (OC). *Proc Am Soc Clin Oncol* 1996; **5**: 283.
23. Socinski MA, Steagall A, Gillenwater H. Second Line chemotherapy with 96 hour paclitaxel in refractory non-small cell lung cancer: report of a phase II trial. *Cancer Invest* 1998; in press.
24. Hudes GR, Nathan F, Khater C, *et al.* Phase II trial of 96-hour paclitaxel plus and estramustine phosphate or metastatic hormone-refractory prostate cancer. *J Clin Oncol* 1997; **15**: 3156–63.

(Received 5 May 1998; accepted 5 May 1998)