Phase I and Pharmacologic Study of a 3-Hour Infusion of Paclitaxel followed by Cisplatinum and 5-Fluorouracil in Patients with Advanced Solid Tumors

Kapil N. Bhalla,[1] Gondi N. Kumar, U. Kristina Walle, Ana Maria Ibrado, Tahir Javed, Robert K. Stuart, Carolyn Reed, Susan G. Arbuck, and Thomas Walle

Division of Clinical and Translational Research, University of Miami, Sylvester Comprehensive Cancer Center, Miami, Florida 33136 [K. N. B., A. M. I.]; Department of Pharmacology [G. N. K., U. K. W., T. W.], Division of Hematology/Oncology [T. J., R. K. S.], and Department of Surgery [C. R.], Medical University of South Carolina, Charleston, South Carolina 29425; and National Cancer Institute, NIH, Rockville, Maryland 20852 [S. G. A.]

ABSTRACT

A Phase I and pharmacological study of paclitaxel administered as an outpatient, 3-h i.v. infusion just before a 5-day regimen of daily cisplatinum (CP) and a continuous infusion of 5-fluorouracil (5-FU) was performed in patients with advanced solid tumors. A secondary objective was to determine the objective response rate to this regimen. Forty-two patients were enrolled and were evaluable for toxicities. Eighteen patients were previously untreated, whereas the rest had received prior treatment with radiation (J. H. Schiller *et al.*, J. Clin. Oncol., *12:* 241–248, 1994), chemotherapy (M. J. Kennedy *et al.*, Clin. Cancer Res., *4:* 349–356, 1998), or both modalities (J. H. Schiller *et al.*, J. Clin. Oncol., *12:* 241–248, 1994). The paclitaxel dose was escalated from 100–135-170–200-225 to 250 mg/m^2, whereas i.v. 5-FU and CP doses were fixed at 1.0 g/m^2/day continuous infusion and 20 mg/m^2/day, respectively, daily for 5 days. Granulocyte colony-stimulating factor (G-CSF; 5 μg/kg/day) was administered s.c. from day 6, routinely after 250 mg/m^2 dose of paclitaxel or after a lower dose of paclitaxel if ANC <500/μl or febrile neutropenia was observed. Patients were treated every 28 days. Plasma and urine samples were collected to determine the pharmacokinetics of paclitaxel. In previously untreated patients, the maximally tolerated dose of paclitaxel in the drug regimen was determined to be 170 mg/m^2 without and 250 mg/m^2 with G-CSF support. At the higher dose level, mucositis and thrombocytopenia were dose-limiting. In previously treated patients, these toxicities were observed at all dose levels of paclitaxel ≥135 mg/m^2. With increasing doses of paclitaxel, a disproportionate increase in the peak concentrations, as well as the area under plasma concentration time-curve, was seen. This nonlinearity was due to saturable total body clearance and volume of distribution of paclitaxel ($P < 0.001$). The apparent plasma elimination half-life was unaffected by the dose of paclitaxel. CP and 5-FU had no apparent effect on the metabolism of paclitaxel. Among 32 patients evaluable for response, 22 demonstrated an objective response, including five complete remissions. Therefore, a regimen of 3-h infusion of 250 mg/m^2 paclitaxel before CP and FU is tolerable with G-CSF (as above) support in previously untreated patients. The regimen also seems to be highly active against breast and esophageal cancers.

INTRODUCTION

Paclitaxel has a broad spectrum of antitumor activity, including significant clinical activity against ovarian, breast, lung, and esophageal cancers (1–4). As compared with a 24-h infusion, a 3-h infusion of paclitaxel has reduced hematological toxicity without apparent compromise of its clinical efficacy (5). Phase I clinical studies have demonstrated that even in previously treated patients, short (3 h) outpatient infusions of up to 250 mg/m^2 of paclitaxel can be safely administered with G-CSF[2] support (6–8). Because of its high level of activity as a single agent, paclitaxel-based combinations with other chemotherapeutic agents (*e.g.*, CP, doxorubicin, CPA, carboplatin, and others) have been evaluated in Phase I/II studies (9–13). These trials have demonstrated that after the administration of paclitaxel with CPA, CP, or doxorubicin, the severity of toxicity may be sequence-dependent (10–12). For example, host-toxicity is worse when paclitaxel is administered before CPA or doxorubicin, or after CP (9–11). Nevertheless, high levels of activity against epithelial cancers have been noted (1–4). Recent studies have suggested that in locally advanced, but resectable, esophageal cancer preoperative radiation plus CP and 5-FU yields high pCRs and may improve the overall survival of the patients (14, 15). Paclitaxel alone or a combination of daily CP and 5-FU administered as an infusion for 5 days has also been documented to have significant efficacy against the upper aerodigestive tract

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[1] To whom requests for reprints should be addressed, at Division of Clinical and Translational Research, Sylvester Comprehensive Cancer Center University of Miami School of Medicine, 1550 NW 10th Avenue, (M710), Miami, FL 33136. Phone: (305) 243-5907; Fax: (305) 243-5885; E-mail: kbhalla@med.miami.edu.

[2] The abbreviations used are: G-CSF, granulocyte colony-stimulating factor; CP, cisplatinum; CPA, cyclophosphamide; CR, complete remission; pCR, pathological CR; 5-FU, 5-fluorouracil; AUC, plasma concentration-time curve; DLT, dose-limiting toxicity; PR, partial response; Vd_{ss}, volume of distribution; NCI, National Cancer Institute; AUMC, area under the first moment of the AUC; ANC, absolute neutrophil count.

cancers (2, 3, 16). Limited courses of effective chemotherapy incorporating paclitaxel with CP and 5-FU administered before chemoradiotherapy may be attractive as a preoperative treatment of resectable esophageal cancer, which has the potential to improve the pCR rate and survival of patients with resectable esophageal cancer. Therefore, a strong rationale existed to investigate the safe dose and activity of paclitaxel in combination with CP and 5-FU.

Previous studies have indicated that paclitaxel is metabolized to its major metabolite 6α-hydroxyl paclitaxel, a process catalyzed by the liver-microsomal cytochrome P450 3A enzyme subfamily, with a possible contribution from the 2C family (17–19). The pharmacokinetics of paclitaxel is mainly dependent on extra-renal mechanisms that include both metabolism and biliary elimination (20). The Vd_{ss} is approximately twice the total body volume, and the half-life is ~2–5 h (20). Recent studies have indicated saturable clearance and Vd_{ss} for paclitaxel with a disproportionate increase in its AUC with dose (21–23). Gianni *et al.* (23) have also highlighted the nonlinear pharmacokinetics of paclitaxel. Similar observations were made by Schiller *et al.* (7), although a limited number of dose levels were used in this study. Therefore, a clearer picture of the influence of dose on paclitaxel disposition needed to be developed from data obtained from multiple doses of paclitaxel over a wide range of dose levels. Therefore, the major goals of this Phase I and pharmacological study of paclitaxel in combination with CP and 5-FU with or without G-CSF support were: (*a*) to determine the dose of paclitaxel that could be administered with tolerable toxicity before a 5-day i.v. treatment with daily CP and continuous infusion of 5-FU in minimally pretreated and untreated solid tumors; and (*b*) to further evaluate the metabolism of paclitaxel and the dose dependency of its distribution in this clinical setting.

PATIENTS AND METHODS

Patient Eligibility. All patients were required to have histologically confirmed cancers for which therapies with greater potential efficacy than paclitaxel, CP, and 5-FU were not available. Eligibility criteria included: (*a*) age ≥18 years; (*b*) Eastern Cooperative Oncology Group performance score ≤2 (ambulatory and capable of self-care); (*c*) nonpregnant and life expectancy >2 months; (*d*) no prior surgery within 2 weeks and no chemotherapy and/or radiotherapy within 4 weeks (≥6 weeks from nitrosourea and mitomycin therapy); (*e*) adequate hemopoietic (ANC >1800/μl and platelets ≥100,000/μl), hepatic (total bilirubin level ≤1.5 mg/dl, aspartate aminotransferase, and alanine aminotransferase twice normal or greater), and renal (creatinine ≤1.5 mg/dl or creatinine clearance ≥60 ml/min) functions; (*f*) absence of moderate symptoms or objective evidence of peripheral neuropathy; (*g*) absence of recent or active cardiac disease and evidence of conduction system abnormality, or evidence of taking medications known to affect the conduction system; and (*h*) no other concurrent medical problem that would preclude planned chemotherapy. One of the objectives of this Phase I study was to determine the optimum dose of paclitaxel in combination with CP and 5-FU for a subsequent Phase II trial of only two courses of this drug combination for previously untreated resectable esophageal cancers. Therefore, those patients were excluded who had received >2 regimens of prior chemotherapy or received large field irradiation to bone marrow-bearing areas. All patients gave informed written consent before enrollment.

Dosage. The starting dose of paclitaxel was 100 mg/m^2 administered as a 3-h infusion before a 5-day treatment with 20 mg/m^2/day of CP given as a short i.v. infusion, along with 500 ml of normal saline (total dose 100 mg/m^2), and 1000 mg/m^2/day of continuous i.v. infusion of 5-FU (total dose 5 g/m^2) during each cycle of chemotherapy. After a 5-day course of the combination chemotherapy, if grade 4 granulocytopenia was observed (ANC ≤ 500/μl or febrile neutropenia), 5 μg/kg/day of G-CSF was administered s.c. from the 6th day of the subsequent course of the combination chemotherapy incorporating the same dose of paclitaxel. Daily G-CSF was continued until the ANC was ≥1800/μl for 2 consecutive days. Groups of at least three patients were enrolled at escalating doses of 100, 135, 170, 200, 225, and 250 mg/m^2 paclitaxel according to a standard Phase I design. Dose escalation was continued until a potential DLT was encountered in the first two cycles of chemotherapy. DLT was defined as at least one of the following: ANC <500/μl, febrile neutropenia, platelet count <25,000/μl, failure to recover counts in time for the next cycle of chemotherapy to be administered on time, and/or grade 3 or greater nonhematological toxicity. Once a DLT was reached, a total of at least six patients were enrolled at that dose level of paclitaxel. A maximally tolerated dose was defined as one dose level below the dose that induced DLTs in at least two of six patients. If grade 4 granulocytopenia was the DLT responsible for defining an maximally tolerated dose, a higher dose level of paclitaxel with G-CSF support was to be evaluated in the next cohort of patients. Because of the emerging evidence that a paclitaxel dose of >250/mg/m^2 in combination with CP produced dose-limiting neuromuscular toxicity, the paclitaxel dose in the combination was not escalated above 250/mg/m^2 (11). At this dose level, all patients received G-CSF support. Although intrapatient dose escalations were not allowed, dose modifications for paclitaxel were made for patients who experienced ANC <500/μl or for febrile neutropenia, despite the use of G-CSF support in the next cycle of chemotherapy. The paclitaxel dose was reduced by 25% in the next cycle of chemotherapy after abatement of all toxicity if grade 4 thrombocytopenia or bleeding or reversible grade 3 nonhematological toxicity was observed. Paclitaxel was discontinued for grade 2 or greater allergic reactions. In patients with responsive or stable tumors, chemotherapy was continued until either disease progression occurred or DLT was documented despite dose reduction of paclitaxel.

Drug Administration. Paclitaxel was supplied by the Division of Cancer Treatment of the NCI (Bethesda, MD) and was reconstituted according to NCI guidelines, as well as those of the manufacturer. It was administered in nonpolyvinylchloride containers with micropore filters. Patients were premedicated with 20 mg of dexamethasone p.o. 12 and 6 h before paclitaxel and 50 mg of i.v. diphenhydramine and 300 mg of i.v. cimetidine 30 min before paclitaxel. CP was supplied in 10- and 50-mg vials and reconstituted with sterile water to a 1 mg/ml solution. G-CSF (Amgen, Inc., Thousand Oaks, CA) was supplied as a sterile buffered protein solution at a concentration of 0.3 mg/ml. 5-FU for injection was supplied in vials containing

Table 1 Patient characteristics

Total patients (M/F)	42 (22/20)
Median age (range)	51 (19–72)
Performance status (ECOG)[a]	
Grade 0–23	
Grade 1–18	
Grade 2–1	
Primary tumor	
Breast 11	
NSCLC 8	
Head and neck Ca 6	
Esophagus 10	
Colorectal 2	
Melanoma 1	
Pancreas 2	
SCLC 2	
Prior therapy	
None	18
Chemotherapy alone	10
Radiotherapy alone	7
Chemotherapy and radiotherapy	7

[a] ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

500 mg/10 ml of solution. Standard practice guidelines were followed in the use of antiemetics and i.v. hydration to prevent early or delayed nausea and dehydration during chemotherapy.

Pretreatment and Follow-up Evaluations. Before enrollment, all patients underwent a complete history, physical examination, and documentation of performance score. Blood was sampled for a complete blood count, electrolytes, and renal and liver functions, whereas urine was sampled for urinalysis. An electrocardiogram was mandatory. Required radiographs included a baseline chest X-ray and computed tomography of the chest and abdomen according to the location of the macroscopic disease. A complete blood count and differential WBC count were obtained three times weekly until ANC $\geq$1800 on two successive determinations after the ANC nadir. Physical examination was performed before every cycle. Toxicities were evaluated according to the NCI common toxicity criteria (24). Formal tumor measurements by radiographs or computed tomography were performed after every two courses, and patients were able to continue treatment in the absence of progressive disease. Although the patients were not required to have bidimensionally measurable disease, if present it was defined as tumor masses that could be evaluated by radiograph, computed tomography, or physical examination in which two perpendicular dimensions could be defined and followed serially. The criteria for response were those reported by Miller *et al.* (25). A complete response was scored if there was disappearance of all evidence of tumor for at least 4 weeks. A partial response was defined as a >50% reduction in the sum of the products of the longest perpendicular diameters of the indicator lesions for a period of at least 4 weeks. A minor response was scored if a decrease in the parameter was <50%.

Sample Collection and Paclitaxel Analysis. Blood samples were collected during each patient's first paclitaxel treatment cycle in heparinized vacutainers before and at 1 h, 2 h, and 2 h, 55 min after the start of the paclitaxel infusion, as well as 0.25, 0.5, 1, 2, 4, 8, 12, and 24 h after the end of the infusion.

Table 2 Toxicities

Taxol (mg/m^2)	Patients/cycles	Patients (grade-number of patients)			G-CSF administration	Mucositis	Diarrhea	N/V	Neuro
		HB[a]	PLT	ANC					
250	12/31	12 (IV-1, III-5, II-6)	5 (IV-2, III-1, II-2)	8 (IV-1, III-4, II-1, I-2)	12	7 (IV-1, III-3, II-3)	9 (III-2, II-4, I-3)	7 (II-5, I-2)	6 (II-3, I-3)
225	6/20	4 (III-2, II-2)	2 (IV-1, III-1)	3 (IV-1, III-1, II-1, I-2)	3	5 (III-1, II-2, I-2)	3 (I-3)	3 (II-2, I-1)	2 (II-1, I-1)
200	7/23	4 (IV-2, III-2)	5 (IV-2, II-2, I-1)	7 (IV-2, III-3, I-2)	2	7 (III-2, II-5)	6 (II-6)	7 (III-1, II-2, I-4)	2 (II-1, I-1)
170	7/24	2 (III-1, II-1)	3 (IV-1, III-1, I-1)	6 (IV-2, III-1, II-3)	2	5 (IV-2, II-2, I-1)	2 (II-1, I-1)	7 (III-1, II-4, I-2)	2 (II-1, I-2)
135	7/22	5 (IV-1, III-2, II-2)	6 (IV-2, III-1, II-1, I-2)	7 (IV-2, III-3, I-1)	2	4 (IV-1, III-1, I-2)	4 (III-1, II-2, I-1)	6 (II-3, I-3)	1 (I-1)
100	3/9	3 (III-1, II-2)	2 (I-2)	3 (III-1, II-2)	0	2 (II-1, I-1)	1 (I-1)	3 (II-1, I-2)	None

[a] HB, hemoglobin; PLT, platelets; N/V, nausea/vomiting; Neuro, peripheral neuropathy.

Table 3 Pharmacokinetic parameters after a 3-h infusion of paclitaxel in 34 cancer patients[a]

Dose (mg/m^2)	*n*	C_{max}[b] (μM)	*AUC* (μM·h)	$T_{1/2}$ (h)	*CL* (liter/h/m^2)	*MRT* (h)	Vd_{SS} (liter/m^2)
100	3	2.0 ± 0.3	7.0 ± 0.8	4.0 ± 0.7	17.1 ± 2.3	4.9 ± 0.7	58.3 ± 14.4
135	6	4.8 ± 0.7	12.2 ± 1.8	3.3 ± 0.2	14.4 ± 1.7	3.9 ± 0.2	33.6 ± 4.1
170	6	5.8 ± 0.6	15.7 ± 1.4	3.0 ± 0.2	13.3 ± 1.0	3.8 ± 0.3	29.4 ± 3.7
200	7	8.7 ± 1.0	23.2 ± 2.0	3.6 ± 0.3	10.5 ± 1.3	4.0 ± 0.2	26.6 ± 4.0
225	6	12.3 ± 1.1	30.8 ± 2.8	3.7 ± 0.3	9.1 ± 1.0	4.3 ± 0.2	24.7 ± 3.4
250	6	14.3 ± 1.9	38.6 ± 5.5	2.8 ± 0.3	8.3 ± 1.1	3.9 ± 0.2	20.2 ± 4.1

[a] Mean values ± SE.
[b] C_{max}, the maximum (paclitaxel concentrations); $T_{1/2}$, half-life in hours; *CL*, total body clearance; *MRT*, mean residence time.

Plasma was separated by centrifugation and stored frozen until analysis. Plasma (2 ml) was extracted with 10 ml of methyl *t*-butyl ether, which was evaporated to dryness and reconstituted in 200 μl of mobile phase before high-performance liquid chromatography analysis. Standard curves with known amounts of paclitaxel were constructed each day by injecting known amounts of paclitaxel (Calbiochem, La Jolla, CA). The high-performance liquid chromatography system consisted of a Waters injector, pump, and UV detector with a 229-nm filter. The column was a Curosil-G 6 μm, 250 × 3.2 mm inside diameter (Phenomenex, Torrance, CA), the mobile phase was 44% acetonitrile in water, and the flow rate 0.6 ml/min. Used as an internal standard, the retention time for paclitaxel was 14 min, and the detection limit corresponded to ~25 ng/ml of plasma.

Pharmacokinetics of Paclitaxel. The terminal half-life was calculated by linear regression analysis and confirmed with two-compartment modeling of the postinfusion data (PCNONLIN; Ref. 26). For each patient, the *AUC* was calculated by the trapezoidal rule and extrapolated to infinity by linear regression. Total body clearance was calculated as dose/AUC. Mean residence time was calculated from *AUMC*/*AUC*, where *AUMC* is the area under the first moment of the concentration-time curve. The Vd_{ss} at steady state was calculated by a noncompartmental method based on statistical moment theory, adjusting for the duration of the infusion (27):

$$Vd_{SS} = \frac{\text{Dose} \cdot AUMC}{AUC^2} - \frac{\text{Dose} \cdot \text{Infusion time}}{2 \cdot AUC}$$

Metabolism of Paclitaxel in Human Liver Microsomes. The possible inhibitory effect of CP and 5-FU (up to 300 μM each) on the metabolism of paclitaxel to its main metabolite, 6α-hydroxytaxol (17, 18), was studied as described previously (19). Inhibition of the metabolism of paclitaxel by ethinyl estradiol and midazolam, two well-established cytochrome P-450 3A substrates (28, 29), was used as a positive control (19).

Plasma Binding of Paclitaxel. The effect of therapeutic concentrations of CP (10 μg/ml) and 5-FU (200 ng/ml) on the plasma binding of Taxol was studied as described previously (30).

RESULTS

Patients. Forty-two patients were enrolled in the study, and 129 courses of paclitaxel-based chemotherapy were administered. Patient characteristics are listed in Table 1. A large majority of patients had a performance score of 0 or 1 and a histologically confirmed diagnosis of esophagus, lung, head and neck, or breast cancers. Eighteen patients (42%) had not received prior chemotherapy and/or radiotherapy. Median number of courses administered per patient was three and ranged from one to eight.

Toxicities. There were no deaths related to treatment toxicities. Table 2 lists the number of patients enrolled, the number of cycles of chemotherapy administered at each dose level of paclitaxel, and all occurrences of toxicities. The dose of paclitaxel was escalated if DLTs were not encountered at the lower dose level of paclitaxel in the first two cycles of treatment (≥2 of 6 patients). Neutropenia was the principle hematological toxicity. If only grade 4 or febrile neutropenia was observed in the first two cycles at the lower dose level of paclitaxel in <2 of 6 patients, its dose was escalated in the next cohort of patients. Grade 4 or febrile neutropenia requiring G-CSF administration was observed at all dose levels ≥135 mg/m^2. In previously treated patients, even with G-CSF support, the dose of paclitaxel could only be escalated up to 225 mg/m^2. At this and lower dose levels, grade 4 granulocytopenia, thrombocytopenia, and anemia, as well as grade 3 mucositis, were observed. In contrast, in previously untreated patients, the paclitaxel dose could be escalated to 170 mg/m^2 without G-CSF support and to 250 mg/m^2 with G-CSF support, and two cycles of the combination could be given with acceptable toxicity. Because the purpose of this Phase I study was to determine the Phase II dose of paclitaxel that could be administered with G-CSF support in combination with CP and 5-FU for two cycles as preoperative chemotherapy in resectable esophageal cancer, six additional previously untreated patients with this disease were enrolled at the 250 mg/m^2 dose level of paclitaxel. Grade 4 hematological toxicity was observed: neutropenia and anemia, each in 1 of 12 (8.3%) patients, whereas thrombocytopenia was detected in 2 of 12 (16.6%) patients. One of these two patients experienced it in the third cycle of chemotherapy. Three patients (25%) were hospitalized: one for granulocytopenic febrile episode and two with mucositis and diarrhea and/or thrombocytopenia. At this dose level, grade 3 or higher mucositis and diarrhea were observed in 4 of 12 (33.3%) and 2 of 12 (16.6%) patients, respectively. In two patients, these occurred after the third or fourth courses of the regimen. Commonly used palliative measures directed at these toxicities were effective, and, in all situations, these lasted <4 days. Despite the combined use of CP and paclitaxel, the neuromuscular toxicities were grade 2 or lower in 6 of 12 patients at the highest dose level of paclitaxel. These were characterized as peripheral neuropathy and/or myalgias. These toxicities were generally noted after three or more cycles of the

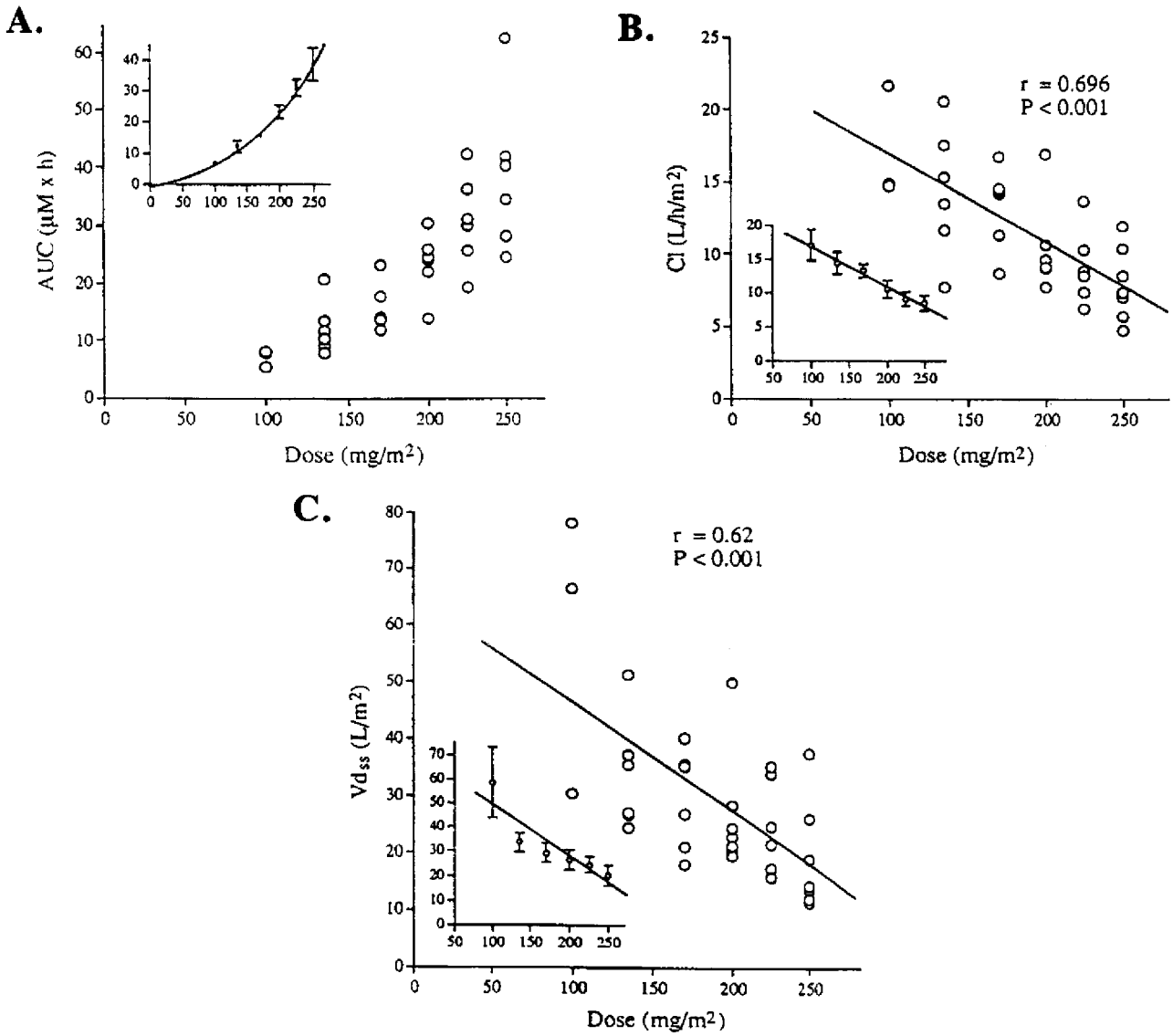

Fig. 1 *A*, effect of dose on the AUC for paclitaxel in 34 cancer patients. *Inset* shows mean values for each dose level. *B*, effect of dose on total body clearance of paclitaxel in 34 cancer patients. *Inset* shows mean values for each dose level. *C*, effect of dose on apparent Vd_{ss} at steady state of paclitaxel in 34 cancer patients. *Inset*, mean values for each dose level.

combination chemotherapy. Sensory symptoms of numbness, burning, paraesthesia, and dysesthesia were predominant, and these generally progressed with an additional cycle of chemotherapy. Symptoms and signs of peripheral neuropathy did not abate after the discontinuation of the chemotherapy.

Pharmacology. The postinfusion AUCs for paclitaxel could be described by a two-compartment model, as reported previously (20). However, underestimation of the concentrations during and immediately after infusion indicated the presence of saturable disposition processes. Noncompartmental analysis produced the pharmacokinetic data shown in Table 3 for the 34 patients studied. A disproportionate increase in the peak concentrations as well as in the AUC values (Fig. 1*A*) with increasing doses was seen. In fact, the AUC values increased exponentially with the paclitaxel dose. The clearance decreased from 17.1 liters/h/m^2 at a dose of 100 mg/m^2 to 8.3 liters/h/m^2 at 250 mg/m^2, and the Vd_{ss} decreased from 58.3 liters/m^2 to 20.2 liters/m^2 at the same dose levels. This occurred without any associated change in the estimated apparent elimination half-life or mean residence time. The dependency of both clearance and Vd_{ss} on paclitaxel dose is more clearly displayed in Fig. 1, *B* and *C*, for the individual patients, as well as for the mean values (*inset*). A highly significant linear relationship was seen for both parameters ($P < 0.001$).

As the present study included administration of both CP and 5-FU starting ~1 h after the end of the paclitaxel infusion, an interaction with paclitaxel metabolism could conceivably occur for the postinfusion elimination (31). This was tested

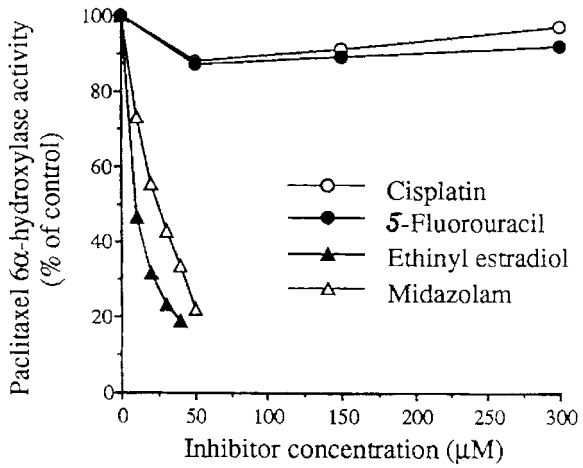

Fig. 2 Effect of CP and 5-FU on paclitaxel 6α-hydroxylation by human liver microsomes. Ethinyl estradiol and midazolam represent positive controls.

using human liver microsomes. As can be seen in Fig. 2, there was no effect of either drug on the formation of the main human metabolite of paclitaxel (*i.e.*, 6α-hydroxytaxol; Refs. 17 and 18), although the concentrations tested were quite high. In the same experiment, potent inhibition by the cytochrome P450 3A substrates ethinyl estradiol and midazolam was observed, similar to a previous study (19). CP and 5-FU were also without effect on the very high plasma binding of paclitaxel (30).

Responses. Thirty-two patients were evaluable for response. There were 5 CRs and 17 PRs, for an overall response rate of 68% (Table 4). CRs were observed at the dose levels of 170, 200, and 250 mg/m^2, whereas PRs were observed at all dose levels of paclitaxel. A dose-response relationship for paclitaxel was not evident. Two of the CRs were observed in patients with breast cancer, whereas the remaining CRs were all in patients with resectable, distal one-third esophageal cancer. The latter three were pCRs, with no evidence of residual microscopic disease in the resected esophagus (Table 4). The pCRs were observed both in epidermoid and adenocarcinoma of esophagus. Except for the two patients with colorectal cancer and the one patient with pancreatic cancer, PRs or CRs were observed in all types of cancers (Table 4). Most of the responses in breast cancer were in soft tissues, lymph nodes, or lung. The regimen clearly exhibited a high degree of activity in the upper aerodigestive tract and breast cancer.

DISCUSSION

In this study, we have presented the findings of a Phase I and pharmacological study of a combination of 3-h infusion of paclitaxel, followed by daily CP plus continuous infusion 5-FU for 5 days. Our data indicate that in previously untreated patients (chemo- and radiotherapy naive), two cycles of this regimen containing 250 mg/m^2 paclitaxel could be safely administered before CP and FU, followed by G-CSF support. Previous studies had demonstrated that paclitaxel alone, as well as a combination of CP and 5-FU, has significant clinical activity against upper aerodigestive tract cancers. Therefore, the present study was conducted to specifically define the dose levels of paclitaxel that could be subsequently investigated in Phase II studies, either administered for two cycles with G-CSF support preoperatively in resectable esophageal cancers or as chemotherapy alone (for more than two cycles) in advanced esophageal cancers.

It is noteworthy that due to the occurrence of grade 4 toxicities, the dose of paclitaxel in the combination without G-CSF support would not have been raised above 170 mg/m^2 in those patients who had received prior chemotherapy and/or radiation therapy. However, because dose escalations of paclitaxel were permissible in the next cohort of patients if DLTs were not observed in the first two cycles of chemotherapy in the previously treated patients, it was feasible to escalate the dose of paclitaxel to 170 mg/m^2 without G-CSF and 225 mg/m^2 with G-CSF support (Table 2). Further dose escalations to 250 mg/m^2 were only safe with G-CSF support in previously untreated patients. In general, at all dose levels of paclitaxel, both hematological and nonhematological toxicities were more severe in the 24 of 42 patients who had previously received chemotherapy, radiotherapy, or both. When administered to previously untreated patients, 250 mg/m^2 paclitaxel proved feasible with G-CSF support. However, the 25% hospitalization rate and 33% grade 3 mucositis suggest that careful monitoring and caution has to be exercised if this dose of paclitaxel is administered preoperatively to patients with esophageal cancer. At the 250 mg/m^2 dose level of paclitaxel with G-CSF support, although significant toxicities (grade 3 nonhematological and grade 4 hematological) were still observed, these mostly occurred in the third or fourth cycle of the chemotherapeutic regimen. Our results also indicate that dose escalations of paclitaxel to 250 mg/m^2 are feasible before CP and 5-FU in up to two cycles of the regimen without exerting prohibitive neurotoxicity. A grade 2 sensory peripheral neuropathy was observed in 3 of 12 (25%) of patients, but this was observed in those who received three or more cycles of the chemotherapeutic regimen. Incapacitating fatigue was not noted in any of the patients receiving less than three cycles of chemotherapy. These observations are also consistent with the study by Wasserheit *et al.* (32), who observed cumulative neuropathy as the major DLT only after multiple cycles of paclitaxel, followed by CP, had been administered. However, in contrast to the present study, in their report, paclitaxel was administered as a 24-h infusion before CP. It should be noted that with any number of cycles, the anticipated neurological toxicity with paclitaxel as a single agent is likely to be less than paclitaxel in combination with CP or other neurotoxic anticancer agents. In our patients with resectable esophageal cancers, administration of this regimen for two cycles preoperatively did not create unusual complications during or after esophagectomy. In addition, although during the present study routine cardiac monitoring was not used, unusual arrhythmias or ischemic cardiac events that would have interrupted chemotherapy were not observed. Further Phase II experience has also been gained with 175 mg/m^2 paclitaxel in combination with CP and 5-FU, where these were administered to chemotherapy naive patients with advanced unresectable or metastatic esophageal cancer (16). In this trial, despite a reduction in the dose of 5-FU to 750 mg/m^2/day, dose alterations, mostly of 5-FU, were necessitated in 15% of the cycles of chemotherapy. G-CSF was ultimately required in 36% of the patients. Grade 3 and grade 4 nonhemato-

Table 4 Responses on the Taxol/CP/5-FU regimen

Cancer types	Responses/evaluable patient/ total no. of patients	Sites of response
Breast	6 (2 CRs)/8/11	Chest wall, lymph nodes, lung
Head and neck cancer	2/3/6	Neck lymph node mass
NSCLC[a]	3/6/8	Liver and hilar adenopathy, lung
Esophagus	8 (3 CRs)/8/9	Epidermoid, adenocarcinomas
Colorectal	0/2/2	
Pancreas	0/1/2	
Melanoma	1/2/2	Lung metastasis
SCLC	2/2/2	Head of pancreas mass
Total	22 (5 CRs)/32/42	

[a] NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

logical toxicities included profound generalized fatigue (35%), stomatitis (24%), nausea and vomiting (17%), diarrhea (14%), and a sensory peripheral neuropathy (18%). Given this degree of toxicity, the optimal dose of paclitaxel in this combination intended for usage for more than two cycles remains to be established. In the present study, the combination of paclitaxel with CP and 5-FU demonstrated significant antitumor activity, especially against esophageal, breast, head and neck, and lung cancers. Although a dose-response relationship for paclitaxel was not obvious, especially if PRs are considered, it is noteworthy that of the five CRs, three were observed at the highest dose level of paclitaxel when administered to previously untreated patients with resectable esophageal cancer. In the Phase II study of this drug combination, although it included lower doses of paclitaxel and 5-FU, high response rates were observed against both epidermoid and adenocarcinoma of esophagus (16).

This present study clearly demonstrates a dose dependency in paclitaxel disposition. Thus, both the total body clearance and the apparent Vd_{ss} demonstrated a >50% decrease at a dose of 250 mg/m^2, compared with 100 mg/m^2. The opposing effect of these two processes on drug elimination leaves the plasma half-life dose independent. These data strongly support previous observations in 30 pediatric patients (21) and in 30 adults (23). Although the present study also involved the administration of CP and 5-FU, there was no indication of any drug interactions. First, these drugs were not administered until at least 1 h after paclitaxel infusion. Second, neither CP nor 5-FU had any direct effect on the formation of the major metabolite of paclitaxel, 6α-hydroxytaxol, a process catalyzed by the cytochrome P-450 3A subfamily (19), with a possible contribution from the 2C family (33). Third, the AUC values in this study at the 135 and 250 mg/m^2 dose levels were virtually identical to those of Gianni *et al.* (23) in a protocol that did not involve CP or 5-FU.

In pharmacokinetics, dose dependence, in general, has recently been reviewed (34). The saturable clearance of paclitaxel most likely involves hepatic metabolism with some contribution from renal and biliary elimination. As shown in human liver microsomes (19), the K_m value for 6α-hydroxylation of paclitaxel is close to the clinical concentration range. This, however, varies between patients and should be addressed by analysis of individual patient data in future studies. Saturation of metabolic clearance after i.v. administration of drugs in humans is uncommon but has been well described for the anticonvulsant drug, phenytoin (35), and also for the *Vinca* alkaloid, vincristine (36). Whereas a dose-dependent increase in extravascular binding or apparent Vd_{ss}, resulting from saturable plasma binding, is quite common (34), the opposite phenomenon (*i.e.*, a dose-dependent decrease in extravascular binding) is unusual. This observation is supported by our recent findings of extensive accumulation of paclitaxel in platelets as a potential model of less accessible cellular binding sites (37). This uptake process becomes saturated within the clinical concentration range for paclitaxel and may involve binding to microtubules (37). The interindividual variability in paclitaxel disposition at any dose level was similar, about 3-fold, for the clearance and the apparent Vd_{ss}. Further analysis of the disposition of paclitaxel in individual patients with respect to the findings in this study, as well as in the studies of Gianni *et al.* (23) and Sonnichsen *et al.* (21), should be of great importance for our ability to better understand the role of the various biological factors that may influence paclitaxel disposition and actions (*e.g.*, sex, age, and race), the potential polymorphism of paclitaxel metabolism, and effects of other drugs.

In summary, the combination of paclitaxel with CP and 5-FU when administered with G-CSF support for two cycles may be a relatively tolerable and highly effective preoperative chemotherapy in resectable, previously untreated esophageal cancer. Although compared with surgery alone preoperative chemotherapy with CP and 5-FU has not been shown to improve survival (38), a safe inclusion of paclitaxel in this regimen, sequentially followed by an established chemoradiotherapy regimen, is an attractive preoperative strategy that needs to be investigated in resectable esophageal cancer.

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