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Dose escalation and pharmacokinetic study of irinotecan in combination with paclitaxel in patients with advanced cancer

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Abstract *Purpose*: Based on preclinical data demonstrating synergy between camptothecin analogues and taxanes, we determined the maximum tolerated dose (MTD) of irinotecan that could be given in combination with a fixed dose of paclitaxel of 75 mg/m^2, when both drugs were delivered on a weekly schedule. The pharmacokinetics of this combination were explored to determine whether the sequence of administration affected the elimination of irinotecan. *Methods*: For the first cycle patients with advanced cancer were treated with irinotecan given as a 90-min infusion followed immediately by paclitaxel given at a dose of 75 mg/m^2 over 1 h. The sequence of drug administration was reversed in subsequent cycles for most patients. Chemotherapy was given weekly for 4 weeks, followed by a 2-week rest. In selected patients, plasma concentrations of irinotecan were determined by high-performance liquid chromatography during the first 24 h of cycle 1 and after the first dose of cycle 2 to determine whether the order of drug administration affected the elimination of irinotecan, or the toxicologic effects of the chemotherapy. *Results*: A total of 53 cycles were delivered to 21 patients. Reversible neutropenia was dose-limiting. Suppression of the other blood cell elements was modest. There was one partial response in a man with a previously treated cholangiocarcinoma that lasted 26 weeks. Prolonged stabilization of disease (6 months or more) was observed in five of the patients (24%). At the recommended dose of irinotecan (50 mg/m^2), transfusions of red cells and platelets were not required. The sequence of drug administration produced no significant differences in the pharmacokinetic parameters of irinotecan or SN-38, which were similar to the values reported when irinotecan is administered alone. The most prominent nonhematologic toxicities were mild diarrhea and fatigue. *Conclusions*: The recommended dose of irinotecan on this schedule is 50 mg/m^2. The sequence of drug administration affects neither the elimination of irinotecan nor the chemotherapy-related toxicity. This combination is well tolerated and causes minimal clinical side effects.

Key words Irinotecan · Paclitaxel · Combination therapy · Pharmacokinetics

Introduction

The camptothecins and the taxanes are two relatively new classes of plant alkaloid chemotherapy agents. Each has a unique mechanism of action and a broad spectrum of antineoplastic activity. Camptothecin inhibits topoisomerase I, an enzyme that is involved in the cleavage and reannealing of single-strand DNA during replication and transcription. The cytotoxicity induced by camptothecin is highly cell-cycle dependent [15, 24], with cells in S phase being 100- to 1000-fold more sensitive than cells in other phases of the cell cycle [22]. Irinotecan, 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11), is a semisynthetic derivative of camptothecin. Irinotecan has demonstrated activity in a variety of tumors, with single-agent response rates ranging from 30% to 46% in lymphomas and carcinomas of the lung, colorectum, and cervix [3].

Paclitaxel binds preferentially to microtubules and impairs microtubular disassembly. This results in the inhibition of the essential dynamic processes of the microtubule network [33]. As a result, there is a transitory

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accumulation of cells in the G_2/M phase of the cell cycle [25]. Paclitaxel was initially tested on a schedule consisting of a 24-h infusion, repeated every 3–4 weeks. Recently, it has been shown that a 1-h infusion given weekly can produce higher drug dose intensity and has promising activity in number of different diseases [2, 11, 21]. For example, Klaassen et al. have performed a dose-finding study in which paclitaxel was given for six consecutive weeks, followed by a 2-week rest [21]. In a heavily pretreated population, they found only mild-to-moderate toxicities when paclitaxel was administered at a dose of 90 mg/m^2. The dose intensity of paclitaxel achieved with this schedule compared favorably with the dose intensity attained when paclitaxel is given over 3 h every 3 weeks [21].

Preclinical studies that have evaluated combinations of a camptothecin with a taxane have produced conflicting results. Although an antagonistic effect has been identified in a few studies [8, 19], in several others an additive or synergistic interaction has been demonstrated [5, 7, 27, 31]. In most of these studies, there was simultaneous exposure to the cytotoxic agents. However, Madden et al. have noted that the sequence of treatment is important [27]. They have found that treatment with a taxane followed by a camptothecin is synergistic, while reversing the order of drug treatment or treating the cells with the taxane and the camptothecin simultaneously results in no more than additive effects [27].

Accordingly, we designed a dose-escalation study to determine the maximum dose of irinotecan that could be given with paclitaxel when both drugs were delivered on a weekly schedule. The dose of paclitaxel was fixed at 75 mg/m^2, a dose which gave comparable dose intensity to that achieved on a once every 3-week schedule and produced plasma concentrations comparable to the concentrations which were synergistic in the models reported by Madden et al. [27]. In this study, we also evaluated whether the order of drug administration affected the pharmacokinetics of irinotecan or the clinical toxicity associated with this drug regimen.

Materials and methods

Eligibility

Patients with biopsy-proven solid tumors for which no effective therapy existed were eligible to participate in this study. Prior therapy was permissible provided the patient had not been treated with a regimen containing irinotecan or paclitaxel, or been given irradiation to ≥20% of the bone marrow. All patients were more than 18 years of age, nonpregnant, had an ECOG performance status ≤2, and had measurable or evaluable disease. Adequate end-organ function was defined as an absolute neutrophil count ≥1500/μl, and platelets ≥100,000/μl, total bilirubin ≤2.0 mg/dl, SGOT not more than three times the normal limit or SGOT more than five times the normal limit if the liver was involved with tumor, and a creatinine clearance ≥70 ml/min. Patients with central nervous system (CNS) metastases were eligible provided the CNS disease had remained stable for at least 4 weeks following completion of surgery and/or radiation therapy and the patient did not require anticonvulsant medications. Pregnant and lactating patients were excluded. Patients with serious intercurrent medical illness, active infection, or patients who had not fully recovered from the effects of previous treatment were also excluded. Informed, written consent was obtained according to Federal and institutional guidelines.

Dosages and drug administration

Irinotecan was given as a 90-min infusion at a starting dose of 50 mg/m^2. The dose was escalated in successive groups of patients according to a modified Fibonacci design. Paclitaxel was administered at a fixed dose of 75 mg/m^2 by intravenous infusion over 60 min. In the first 9 patients, irinotecan was given first and the paclitaxel infused immediately after completion of the irinotecan. In the 12 patients subsequently treated, the sequence of administration was changed on the second and subsequent cycles (paclitaxel was given first over 60 min followed immediately by the 90-min irinotecan infusion) in order to study the sequence dependence of chemotherapy administration. In selected patients, pharmacokinetic studies were carried out during the first day of cycles 1 and 2. Treatment was repeated for four consecutive weeks followed by a 2-week rest period. This constituted one cycle of treatment.

Dose-limiting toxicity (DLT) was determined during the first cycle of treatment and was defined as an absolute neutrophil count (ANC) $< 500/\mu l$ and fever (a temperature of 38.5 °C, or the occurrence of three temperatures of 38 °C or more within a 24-h period, taken at least 4 h apart, during the period of granulocytopenia), a platelet count $< 50{,}000/\mu l$, any nonhematologic toxicity (with the exception of alopecia) of three or more, or any toxicity which delayed treatment for more than 2 weeks. A minimum of three patients were treated at each dose level. When DLT occurred in any patient, up to six patients were enrolled at that dose. The maximum tolerated dose (MTD) was defined as one dose level below the dose that induced DLT in at least two of a maximum of six total patients.

Dose reductions by one dose level were permitted for DLT or for treatment delays due to unresolved toxicities. Chemotherapy was administered provided that there was adequate hematologic reserve (ANC ≥1500/μl and platelet ≥100,000/μl), there was no mucositis or diarrhea, and with the exception of alopecia, there was no other nonhematologic toxicity of more than grade 1. Treatment criteria were similar for each week during a cycle and at the start of a new cycle. If treatment was not given on weeks 2 or 3, then the chemotherapy was delayed for 1 week and the cycle extended to a total of 7 weeks. If retreatment on week 4 of a cycle was not feasible due to toxicity, then the cycle was abbreviated and the next cycle started 2 weeks later. If persistent chemotherapy-related toxicity prevented retreatment within 3 weeks of the planned date, the patient was removed from the study.

Patients were premedicated with prednisone 60 mg orally approximately 12 and 6 h before paclitaxel. In addition, 50 mg of diphenhydramine and 300 mg of cimetidine were administered 30 to 60 min before paclitaxel. The chemotherapy drugs were obtained commercially and the doses calculated according to the patient's actual body weight. Antiemetic therapy consisted of 10 μg/kg of granisetron with 10 mg of dexamethasone administered intravenously 30 min before the start of chemotherapy on each treatment day. The antiemetics were repeated every 8 h as needed to control nausea.

Plasma concentrations of irinotecan and its major metabolite, SN-38, were determined in selected patients during the first course of cycles 1 and 2 to determine whether paclitaxel administration before or after irinotecan would affect the pharmacokinetic parameters. The analysis was conducted for total irinotecan rather than separately for the lactone and carboxy forms. The samples were collected in heparinized tubes before drug administration, at 30, 60, 90 min during the infusion of irinotecan and 0.5, 1.5, 3.5 and 6 h after the end of the infusion. Samples were immediately processed with 250 μl plasma added to 500 μl internal standard

solution in polystyrene tubes. The internal standard solution consisted of camptothecin 50 μg/ml in acetonitrile acidified with glacial acetic acid, 4.0 ml in 100 ml. The samples were vortexed for 30 s, placed into a water bath at 40 °C for 15 min, cooled to room temperature and then mixed with 900 μl of a 25 m*M* triethylamine buffer (pH 4.2). The supernatant was transferred to 1.5-ml Eppendorf tubes, centrifuged for 4 min at 13,000 *g* in a microfuge and an aliquot of the clear supernatant analyzed by high-performance liquid chromatography (HPLC).

Chromatographic separation was conducted on a Microsorb C18 (4.6 × 250 mm, 5 μm particle size) reverse-phase HPLC column eluted with 72:28 (v/v) 25 m*M* TEA/acetonitrile buffer at 1 ml/min utilizing a fluorescence detector with λ_{ex} 372 nm and λ_{em} 535 nm (Pharmacia & Upjohn). Maximum plasma concentration, terminal half-life and AUC were determined by noncompartmental analysis of the data utilizing PC-NONLIN software (Scientific Consulting, Lexington, Ky.) and standard pharmacokinetic equations. The coefficients of variation for the intraday reproducibility were 9% and 7% for concentrations of 50 and 200 n*M* respectively. The interday coefficient of variation derived from five calibration curves over a 5-week period was 11%. The limit of detection was 20 n*M* for irinotecan and 2.5 n*M* for SN-38. The AUC values were extrapolated to infinity.

On-study examinations and criteria for assessment of response and toxicity

A history, physical examination, complete blood count, electrolytes, BUN, creatinine, liver function tests (aspartate aminotransferase, lactate dehydrogenase, total and direct bilirubin, alkaline phosphatase), serum calcium and phosphate, amylase, uric acid, total protein, albumin, prothrombin time, urinalysis, pregnancy test (if indicated), electrocardiogram, chest radiograph, and computed tomography scans if appropriate for staging the disease were preformed prior to the start of treatment. A 24-h urine collection for creatinine clearance was obtained in patients more than 65 years old. A physical examination and toxicity assessment were repeated weekly. Toxicity was graded according to the National Cancer Institute common toxicity criteria. A complete blood count with differential and liver and renal function tests were obtained weekly during the first 12 weeks of treatment. After the first 12 weeks, complete blood counts and physical examinations were obtained weekly, and the renal and liver function tests were repeated at least every 3 weeks. A chemistry profile was repeated before every treatment cycle. Formal tumor measurements were obtained after every two cycles of chemotherapy. Survival was estimated using the Kaplan-Meier method.

Results

Patient characteristics are shown in Table 1. The majority of patients (57%) had lung, pancreatic or hepatocellular cancer. Most patients (66%) had received no prior chemotherapy and were relatively asymptomatic. Stabilization of disease lasting 3 or more months was observed in 17 patients. Stable disease lasted 6 or more months in 5 of these 17 patients, and in this group there was one patient each with cancer of the pancreas, lung, gallbladder, appendix, and esophagus. A patient with a metastatic cholangiocarcinoma whose disease was resistant to 5-fluorouracil (5-FU) and was progressing rapidly prior to treatment on this study attained a partial response, with a 75% reduction in multiple liver metastases, which lasted 26 weeks. Six cycles of irinotecan and paclitaxel were delivered to this patient.

Table 1 Patient characteristics

Enrolled	21
Sex	
Male	15
Female	6
Age (years)	
Median	54
Range	53–69
Performance status	
0	12
1	9
Tumor histology	
Pancreas	4
Hepatocellular	3
Lung	4
Esophagus	2
Gallbladder	2
Other[a]	6
Prior therapy	
Chemotherapy	3
Chemotherapy and radiation	4
Radiation	1
None	13

[a] One patient each had cancer of the parotid, colorectum, duodenum, appendix, biliary tract, and an unknown primary

The median survival was 22 weeks. Eight of the patients were alive and four were still receiving treatment at the time of writing. The patient who had a partial response survived 52 weeks.

Dose delivery and adjustments

Two patients were treated at the second dose level of irinotecan (65 mg/m^2) and both developed DLT. The first patient required a 2-week treatment delay due to prolonged neutropenia and five packed red-cell transfusions for grade 3 anemia. This patient was subsequently reduced to the first dose level (50 mg/m^2). The second patient was reduced to the first dose level due to neutropenia and thrombocytopenia. All of the other patients on the study were enrolled at the first dose level. One of these patients was reduced to 37.5 mg/m^2 of irinotecan during the third week of the first cycle because of grade 2 diarrhea. This patient was removed from the study while receiving a second cycle because of disease progression.

A total of 53 cycles of chemotherapy were delivered. The average number of cycles per patient was three (range one to nine). Of the 50 cycles administered at 50 mg/m^2 of irinotecan, 13 (26%) were delivered as planned. Delays due to neutropenia occurred at week 3 in 14 cycles and at week 4 in 13 cycles. Diarrhea developing at week 4 resulted in delays in five cycles. Additional delays were the result of intercurrent illness and complications of the disease. The mean actual dose intensity/planned dose intensity in those patients who completed one cycle of chemotherapy was 86%.

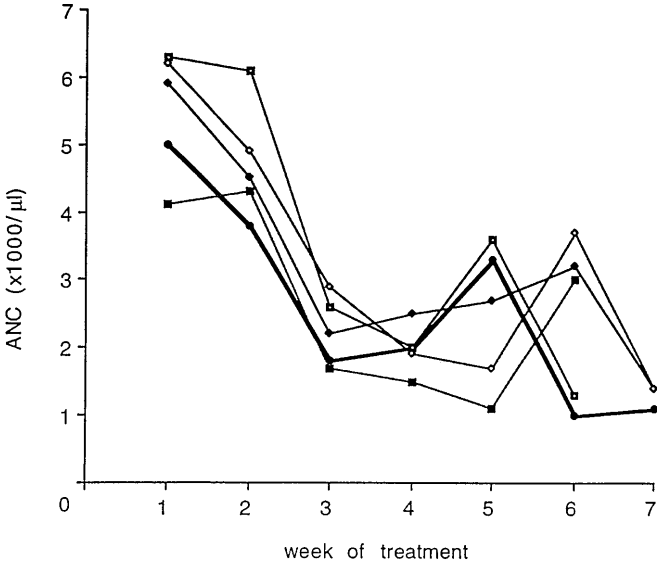

Fig. 1 Hematologic toxicity by treatment week. The median neutrophil nadir for each week of treatment for the first five cycles of treatment. Each line reflects a treatment cycle and each point is the median neutrophil count on that week of treatment. Some cycles extend to 7 weeks because of treatment delays during the cycle. The plot for the first cycle is indicated by a heavier line. Data represent all 50 cycles administered at an irinotecan dose of 50 mg/m^2

Hematologic toxicity

Overall, this regimen was well tolerated and toxicity was non-cumulative (Fig. 1). For the 50 cycles in which the dose of irinotecan was 50 mg/m^2, the median nadir ANC was 1,100/μl (range 300–7700/μl). Two patients had to he hospitalized due to neutropenic fever. One of the two patients who experienced neutropenic fever did so on both the first cycle and the third treatment cycle despite treatment delays. Suppression of the other marrow elements was modest. The median nadir platelet count was 187,000/μl (range 104,000–453,000/μl). No transfusions were required and no patient required a dose modification due to prolonged myelosuppression.

Nonhematologic toxicities

Diarrhea, fatigue and neuropathy were the most prominent nonhematologic toxicities (Table 2). Diarrhea with an early onset (up to 24 h after irinotecan delivery) occurred in just one patient and was mild. Diarrhea generally began 2–4 days after chemotherapy (median time to onset was 4 days), rarely lasted more than 48 h, and was more prominent during weeks 3 and 4. Intensive management with high-dose loperamide was never required. Mild fatigue was reported by 14 patients, and in many cases was unrelated to myelosuppression. Mild neuropathy occurred in 22% of the patients, and in one patient, it progressed to a grade 2 toxicity during the sixth cycle. Facial flushing was observed in two patients during the first cycle. A non-pruritic rash of the chest wall and upper limbs was observed in one patient during cycle 2 and in a second patient during cycle 5. Two patients were hospitalized for treatment of deep vein thrombosis. Other serious adverse events requiring hospitalization that occurred in one patient each were pulmonary embolism, renal calculi, pleural effusion and seizure. These complications were not thought to be related to the chemotherapy. One patient developed a Mallory-Weiss tear as a result of severe chemotherapy-related vomiting.

Table 2 Common nonhematologic toxicities (data from all 50 cycles for a 50 mg/m^2 dose of irinotecan)

	Toxicity grade			
	1	2	3	4
Nausea	8	1	2	0
Vomiting	6	0	0	1
Diarrhea	13	3	1	0
Fatigue	14	2	1	0
Neuropathy	4	1	0	0

Pharmacokinetic studies

Pharmacokinetic parameters were obtained from the first day of cycles 1 and 2 in 11 and 6 patients, respec-

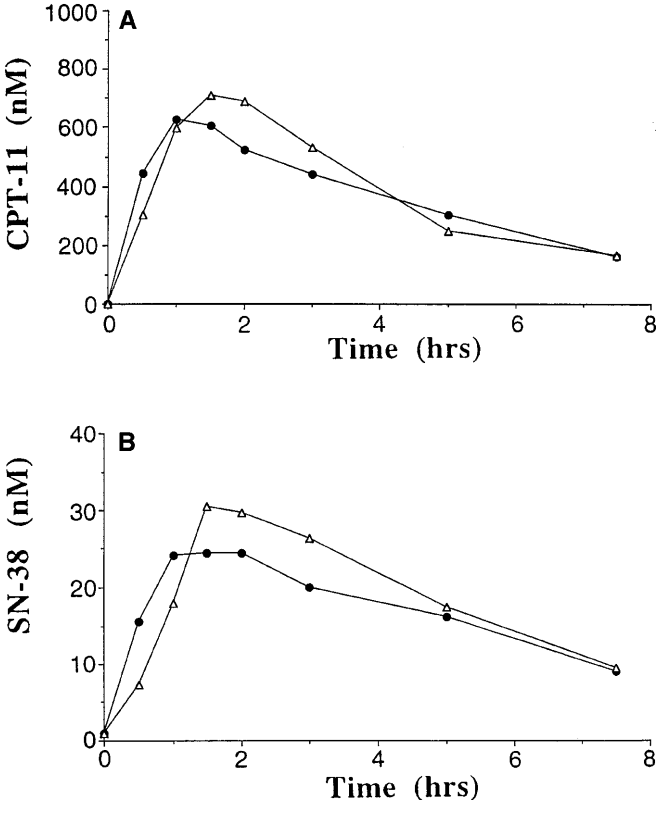

Fig. 2A,B Plasma elimination curves for irinotecan (**A**) and SN-38 (**B**). Data are shown for cycle 1 (●) and cycle 2 (△) and represent the mean values for the patients sampled

Table 3 Pharmacokinetic parameters (analysis was conducted on 11 patients during cycle 1 and on 6 patients during cycle 2). The values shown are means ± SD

Pharmacokinetic parameter	Irinotecan-taxol		Taxol-irinotecan	
	Irinotecan	SN-38	Irinotecan	SN-38
C_{max} (ng/ml)	368 ± 103	14.3 ± 5.8	415 ± 175	17.8 ± 6.2
$T_{1/2}$ (h)	3.3 ± 1.2	4.2 ± 1.8	2.7 ± 1.0	3.5 ± 1.1
AUC (ng · h/ml)	2096 ± 858	110 ± 29	2035 ± 745	112 ± 37
V_d (l/m^2)[a]	123 ± 41	–	106 ± 27	–
Cl (l/h/m^2)[b]	25.7 ± 7.2	–	27.6 ± 5.1	–

[a] Volume of distribution at steady-state
[b] Total systemic clearance

tively, who received treatment with irinotecan at a dose of 50 mg/m^2. The plasma elimination curves for irinotecan and SN-38 are shown in Fig. 2. The mean values for C_{max}, AUC, terminal half life and volume of distribution at the steady-state were comparable between the cycles, suggesting there were no sequence-dependent effects (Table 3). Comparison of paired analysis of mean neutrophil and platelet nadirs showed no difference with the sequence of administration ($P \geq 0.25$).

Discussion

A drug regimen combining a camptothecin and a taxane on a weekly schedule is attractive for several reasons. Both of these classes of agents have been shown to have a broad spectrum of clinical activity which is dependent on the schedule of administration. In addition, the mechanism of action and the nonhematologic toxicity profiles for the camptothecins and taxanes are different. Finally, most [5, 7, 27, 31], but not all [8, 19], of the preclinical studies have identified an additive or synergistic interaction between the taxanes and camptothecins. In the majority of the preclinical studies, a simultaneous exposure to the drug combination was evaluated. However, Madden et al. have noted that the sequence of treatment is important [27]. They found that a 90-min exposure to a sublethal concentration of paclitaxel produces a tenfold reduction in the concentration of camptothecin required to reduce cellular proliferation by 50% [27]. Reversing the order of drug treatment or treating the cells with the taxane and the camptothecin simultaneously results in a loss of this synergy. A sequence dependence has been noted in vitro when camptothecins have been combined with other chemotherapy drugs [4, 13, 17, 18, 26].

The extent to which these in vitro sequence-dependent effects can be extrapolated to the complex environment in vivo when designing a combination drug regimen remains unclear. However, modeling of a 1-h infusion at a dose of 80 mg/m^2 suggests that plasma concentrations of paclitaxel in excess of 50 n*M* are maintained for over 22 h (M. Egorin, personal communication), suggesting that low-level exposure to the taxane prior to irinotecan may have been achieved with this dose and schedule. In addition, this combination has shown promising activity in a dose-finding study of paclitaxel followed by irinotecan, with both given weekly for 3 weeks followed by a 1-week rest in patients with small-cell lung cancer [36].

The primary toxicity of irinotecan in most studies has been myelosuppression, particularly neutropenia. Nonhematologic toxicities include fatigue and gastrointestinal side effects, particularly diarrhea [10, 39]. When irinotecan is given on a weekly schedule, serious diarrhea occurs in 25–35% of the patients [40]. Abigerges et al. have found that the incidence of severe, irinotecan-induced diarrhea can be decreased by using an aggressive regimen of loperamide. Using this regimen, the MTD of irinotecan can be increased by 70% [1]. In the present study aggressive management of irinotecan-induced diarrhea was not necessary. This was probably due to the relatively low dose of irinotecan utilized in our regimen.

Paclitaxel was initially tested on a schedule consisting of a 24-h infusion, repeated every 3–4 weeks. Subsequently, it was demonstrated that reducing the infusion time to 3 h resulted in less myelosuppression with equivalent clinical activity. More recently, it has been shown that a 1-h infusion given weekly can produce a higher paclitaxel dose intensity than a once-every-3-week schedule and has promising activity in a number of different diseases [2, 11, 21]. In a heavily pretreated population, Klaassen et al. have found only mild-to-moderate toxicities when paclitaxel is administered at doses of 90 mg/m^2 for six consecutive weeks followed by a 2-week rest [21]. In a less heavily pretreated population, Akerly et al. were able to deliver 175 mg/m^2 for 6 of 8 weeks, thus attaining a dose intensity approximately threefold higher than can be generally given on a once-every-3-week schedule [2]. Although neutropenia was dose-limiting during cycle 1 of this study, peripheral neuropathy was increasingly prominent in subsequent cycles, and as a result, dose reductions were necessary in one-third of patients treated at the recommended MTD. As a result of using a lower dose of paclitaxel, we saw limited neurotoxicity at a dose intensity comparable to schedules using a once-every-3-week schedule.

A frequent observation in the development of combination drug regimens that include a camptothecin is the requirement of a significant reduction in the dose of one or more of the drugs compared to the dose feasible when the drugs are given as single agents. In our study, we also found that the combination of irinotecan with

paclitaxel resulted in a significant compromise in the dose intensity compared with the doses that are feasible when these drugs are given as single agents. The actual dose intensity of irinotecan delivered in our study was 29 mg/m^2 per week, whereas in the three U.S. registration trials it ranged from 56 to 62 mg/m^2 per week. A greater delivered dose intensity has been observed in studies that have evaluated the combination of paclitaxel and topotecan, albeit at the cost of greater toxicity than we observed in our study [23]. Promising activity in small-cell lung cancer has resulted in the continued evaluation of the combination of topotecan and paclitaxel using lower better-tolerated doses. It is of interest that in contrast to most drug combinations, combinations which include 5-FU and irinotecan can be given with a dose-intensity that approximates the MTD when these drugs are given separately [37]. The apparent attenuation of host tissue toxicity with this combination does not appear to compromise the antitumor activity of these agents, and is being addressed in ongoing clinical studies [38].

Sequence-dependent effects when paclitaxel is used in combination regimens have been demonstrated in a number of clinical trials. Toxicity is increased when cisplatin is delivered before paclitaxel, in part because of reduced renal clearance of paclitaxel with this sequence [34]. Infusion of paclitaxel before either cyclophosphamide or doxorubicin also results in increased toxicity [14, 20]. The sequence-dependent effects in each of these cases occurs when paclitaxel is given by 24- or 72-h infusion. Sequence-dependent hematologic toxicity is not seen when a 3-h infusion of paclitaxel is delivered with doxorubicin, although the incidence of congestive heart failure is increased with this regimen compared to schedules in which the paclitaxel is infused over 24 h [12]. O'Reilly et al. have evaluated the sequence-dependent effects of topotecan in combination with a 24-h infusion of paclitaxel and have found that the pharmacokinetics and toxicologic effects are comparable [30]. Paclitaxel concentrations were not measured in our study and a sequence-dependent effect on its pharmacokinetics cannot be excluded.

The metabolism of irinotecan is complex and requires de-esterification of the parental compound to active metabolites, primarily SN-38, in the liver. Previous studies have identified significant interpatient variability in pharmacokinetic parameters. The plasma half-life has been found to be in the range 2.8 h to 14.2 h for irinotecan and 5.9 h to 13.8 h for SN-38 in different studies [1, 29, 35]. The concentration-time data has been fitted to a two- or three-compartment model. For example, Forni et al. have described a triexponential model with the α, β, and γ half-lives of 6.7 min, 2 h, and 9.3 h, respectively [9]. It is feasible, therefore, that limiting our plasma sampling to 6 h following the chemotherapy infusion may have failed to identify a modification in the terminal half-life of either irinotecan or SN-38. These sampling points were based on the pharmacokinetic parameters reported by Negoro et al. [29], indicating that, following a dose of 50 mg/m^2 of irinotecan, the terminal half-life of SN-38 is 6 h, facilitating management in an outpatient setting.

In studies of the effects of another chemotherapy drug on the plasma elimination of irinotecan, an alteration in the pharmacokinetic parameters of irinotecan has been identified in some cases. Saltz et al. have demonstrated modest changes in the conversion of irinotecan to SN-38 which were dependent on the sequence of drug administration for a regimen which included 5-FU, leucovorin, and irinotecan, but this pharmacologic interaction was not clinically significant [37]. In combination with cisplatin, a modest increase in the dose of irinotecan from 80 to 90 mg/m^2 (12.5%) has been shown to result in a 57% increase in the SN-38 AUC [28]. In a previous study it has been shown that in this dose range the SN-38 AUC tends to increase in proportion to the dose of irinotecan, suggesting that cisplatin alters the pharmacokinetics of irinotecan [29]. In contrast, in a limited number of patients we found no indication that there was a sequence-dependent effect on the metabolism of irinotecan when given with paclitaxel.

The pharmacokinetic parameters for both sequences of administration in this study are in agreement with other reported values for irinotecan given alone [6, 16]. For example, at a similar dose of irinotecan (50 mg/m^2), Negoro et al. have found peak plasma concentrations (C_{max}) of 610 ± 30 and 220 ± 80 ng/ml, AUCs of 2970 ± 1140 and 117 ± 30 ng·h/ml, and half-lives of 2.4 ± 1.6 and 6.0 ± 1.9 h for irinotecan and SN-38, respectively [29]. The plasma clearance (Cl) observed in that study was 21.5 ± 6.2 l/h per m^2, which was also similar to our findings. Although the concentrations of the active lactone form of irinotecan and SN-38 and the pharmacokinetics of paclitaxel were not determined in this study, we feel it is unlikely that a clinically significant sequence-dependent effect for these parameters was present because we observed no differences in toxicity between the two sequences. This is in agreement with the results of a pharmacokinetic study of irinotecan and its metabolites in which irinotecan was administered immediately following a 3-h infusion of paclitaxel. The clearance of irinotecan and the ratio of irinotecan to SN-38 in the plasma were found to be similar to the reported values for irinotecan given alone [32].

In summary, this drug regimen proved to be well tolerated, and was devoid of the significant gastrointestinal or neurologic toxicities observed when irinotecan and paclitaxel are used at the maximum single-agent dose on a weekly schedule. Preservation of a reasonable dose-intensity in this drug combination was feasible, at least for paclitaxel, compared to the dose delivered on a once-every-3-week schedule. In this limited population, no differences in the side effects were observed in patients who had the sequence of drug administration reversed, nor was there a difference noted in the pharmacokinetics of irinotecan, suggesting that the sequence of administration was not critical, and that the 1-h infusion of paclitaxel in this study was adequate to

sensitize cells to subsequent treatment with a camptothecin, based on in vitro modeling. With one documented partial response and the prolonged disease stabilization observed in another 24% of the patients in this population with resistant cancers, we feel that this regimen is worthy of further testing in selected patient populations, which might include lung cancer and hepatobiliary malignancies.

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