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ORIGINAL ARTICLE

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Phase I clinical and pharmacokinetic trial of docetaxel and irinotecan administered on a weekly schedule

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Abstract *Background*: Docetaxel and irinotecan are synergistic agents with a broad spectrum of activity but overlapping myelosuppression. The study was designed to maintain dose intensity while limiting myelosuppression. The objectives of this study were to determine the maximal tolerated dose (MTD) of the combination of docetaxel and irinotecan administered weekly for four consecutive weeks every 42 days, to describe toxicities of this regimen, and to perform a pharmacokinetic analysis to evaluate changes in drug disposition as a function of dose as well as repeated dosing. *Methods*: Adult patients with advanced solid tumors were treated with docetaxel followed by irinotecan. Doses of 30/50, 35/50, 35/66, 30/57, 30/65, 30/80 mg/m^2, respectively, were studied. Pharmacokinetics of docetaxel, irinotecan and SN-38 in plasma were determined on days 1 and 22 by a high-performance liquid chromatography (HPLC) assay. *Results*: A total of 35 patients were treated. The MTD was docetaxel 30 mg/m^2 plus irinotecan 65 mg/m^2. Diarrhea was the dose-limiting toxicity; myelosuppression and other non-hematological toxicities were uncommon and mild. There were no significant differences in pharmacokinetic parameters between day 1 and day 22 ($n = 20$). Five objective responses (breast, stomach and unknown primary) were observed among 30 evaluable patients. In addition, eight patients achieved stable disease. *Conclusions*: The combination of weekly docetaxel and irinotecan is a well tolerated regimen and should be explored in phase II trials. This schedule maintains dose intensity and has limited myelosuppression.

Keywords Phase I · Clinical trial · Pharmacokinetics · Docetaxel · Irinotecan

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Introduction

Docetaxel (Taxotere; Aventis Pharmaceuticals, Bridgewater, N.J.), a semisynthetic derivative of 10-deacetylbaccatin III, is the second taxoid introduced to clinical practice [10]. It has shown significant activity in a variety of solid tumors such as breast, lung, prostate, and ovary. The recommended monotherapy dosage of docetaxel is 60–100 mg/m^2 administered intravenously every 3 weeks, where the dose-limiting toxicity (DLT) is myelosuppression [14, 17]. The results of a large randomized trial indicate that docetaxel may exhibit a dose-dependent antitumor response [29].

The toxicity profile of docetaxel is modified when the drug is administered weekly. Several studies have demonstrated that docetaxel can safely be administered this way at 35–40 mg/m^2, where the DLTs include fatigue and asthenia while myelosuppression is limited [8, 19, 22, 23]. A lack of other significant non-hematological toxicities was observed.

Irinotecan (Camptosar; Pharmacia Corporation, Peapack, N.J.) is a semisynthetic derivative of camptothecin with greater in vitro and in vivo activity, but with less-severe and more predictable toxicity [33]. Irinotecan, an inhibitor of topoisomerase I (Topo-I), is metabolized to SN-38, which is a significantly more potent inhibitor of Topo-I activity. Irinotecan has demonstrated significant antitumor activity in colon and lung cancer [16, 32]. Preliminary data suggest that it has antitumor activity

against gastric, pancreatic, and gynecological cancers [7, 18, 24, 34]. Phase I studies have identified two recommended regimens: 125 mg/m^2 administered on a weekly schedule (for 4 weeks repeated every 6 weeks) or 350 mg/m^2 every 3 weeks. Diarrhea and myelosuppression constitute the DLTs on both schedules [1, 14].

Preclinical data suggest synergistic properties for the combination of docetaxel and irinotecan [4, 5]. Based on this, as well as their broad clinical activity, it seemed reasonable to evaluate this combination in clinical trials. In an effort to reduce the frequency and intensity of docetaxel-induced myelosuppression, while maximizing dosage intensity, we decided to conduct a phase I study and administer both agents on a 4-week-on 2-week-off regimen. The principal objective was to determine the maximal tolerated dose (MTD) and to describe the toxicity profile associated with this regimen. A secondary objective was to obtain additional experience with the use of a single dose of dexamethasone to prevent docetaxel-induced edema. Pharmacokinetic parameters of both irinotecan and docetaxel were evaluated over the dosage levels to determine changes in drug disposition. The pharmacokinetic impact of multiweek dosing of docetaxel and irinotecan was also evaluated in this study.

Materials and methods

Patient selection

Patients eligible for this study required histological evidence of advanced cancer for which prior therapy had failed or for which there was no effective therapy available. Other eligibility criteria included: age ≥18 years; Southwest Oncology Group (SWOG) performance status 0–2; recovery from acute toxicities of chemotherapy, radiation or surgery; adequate bone marrow (absolute neutrophil count, ANC, ≥1500 cells/mm^3, platelet count ≥100,000 cells/mm^3) and liver function tests [bilirubin not more than the upper limit of normal (ULN) and transaminases not more than 2.5 times the ULN if alkaline phosphatase was not more than the ULN or alkaline phosphatase not more than four times the ULN if transaminases were not more than the ULN). Patients with moderate (grade 2 or worse) peripheral neuropathy were excluded from study entry. All patients signed written informed consent before study entry. The protocol was approved by the Institutional Review Board of the University of Southern California.

Dosage and administration

Docetaxel (Taxotere) was supplied by Rhone Poulenc Rorer (RPR, now Aventis Pharmaceuticals) in a 15-ml clear-glass vial containing 2 ml of a 40 mg/ml docetaxel solution in polysorbate 80. A reconstitution diluent vial containing 6 ml of a 13% w/w solution of ethanol in water was also supplied to allow preparation of 8 ml of the premixed solution containing 10 mg/ml of docetaxel. The drug was administered through non-PVC-lined administration sets. The volume of the infusion solution was adjusted so that a concentration of 0.9 mg/ml of docetaxel was not exceeded.

Irinotecan (Camptosar) was supplied by Pharmacia & Upjohn (Kalamazoo, Mich., now Pfizer) in amber vials. Two vial sizes were supplied: 2.0 ml vials containing 40 mg or 5.0 ml vials containing 100 mg irinotecan. Irinotecan was diluted with either 5% dextrose or 0.9% sodium chloride to a total volume of 500 ml.

Intravenous chemotherapy was sequentially administered, with docetaxel infused first as a 30-min infusion, followed immediately by irinotecan over 90 min. Six dose levels of docetaxel/irinotecan were studied: 30/50, 35/50, 35/66, 30/57, 30/65 and 30/80 mg/m^2, respectively. Patients were treated for four consecutive weeks followed by 2 weeks off treatment (each 6-week interval represented one cycle) and were premedicated with 4 mg intravenous dexamethasone prior to the administration of docetaxel. Antiemetic prophylaxis consisted of a serotonin receptor antagonist. Routine use of prophylactic hematopoietic growth factors was not allowed.

Study design and rules for dose escalation

DLT was defined as any grade 3 or 4 non-hematological toxicity (except for nausea, vomiting, fatigue and alopecia), grade 4 thrombocytopenia, or grade 4 neutropenia lasting more than 5 days, or associated with fever. DLT was based on the first cycle of treatment. Toxicities were graded according to the National Cancer Institute (NCI) common toxicity criteria, version 2.0. All patients who completed one cycle of therapy or experienced DLT were evaluable for toxicity. Patients not evaluable for toxicity or who did not comply with established guidelines for the treatment of irinotecan-induced diarrhea were replaced.

MTD was defined as the highest dose tested in which fewer than 33% of patients experienced DLT attributable to the study drugs, when at least six patients were treated at that dosage and were evaluable for toxicity.

At least three patients were treated at each new dose level. If none of three patients experienced DLT, the next three patients were to be treated at the next dose level. If DLT attributable to the study drug(s) was experienced in exactly one of three patients, then three additional patients (for a total of six) were treated at that dose level. If no additional DLT was observed at the expanded dose level, the dose was escalated. Escalation was terminated as soon as two or more patients experience any DLT attributable to the study drugs, at a given dose level. All patients who had not experienced any DLT had to be observed for a minimum of 6 weeks

after the first treatment dose before the dose level was escalated. There was no dose escalation within a patient.

Pretreatment and follow-up studies

Complete history and physical examination, complete blood cell counts (CBC), serum electrolytes and chemistries, and toxicity evaluation were performed at baseline and before each treatment cycle. CBCs were performed weekly while patients were on-study. Tumor measurements were performed at baseline and repeated every 6 weeks to evaluate tumor response. A complete response (CR) was defined as disappearance of all measurable and evaluable disease, a partial response (PR) as $>50\%$ reduction in the sum of the products of perpendicular diameters of all measurable lesions. Progressive disease (PD) was defined as $>25\%$ increase in the sum of the products of the perpendicular diameters of all measurable lesions or clear worsening of evaluable disease or appearance of any new lesion. Stable disease was documented when the criteria for CR, PR or PD were not met. All objective responses were required to last for at least 4 weeks to be declared as confirmed responses.

Dose modification

Toxicities were evaluated according to the NCI common toxicity criteria, revised version 2.0. With the exception of diarrhea, dose reductions were based on toxicities present on each treatment day. Treatment was held in the presence of an ANC <1000 cells/mm^3, or a platelet count $<50{,}000$ cells/mm^3; treatment was restarted after recovery. The dose of both agents was reduced by 25% if the ANC was 500–999 cells/mm^3 or platelets 25,000–49,999 cells/mm^3, and by 50% if the ANC was less then 500 cells/mm^3 or platelets less then 25,000 cells/mm^3. Chemotherapy was reduced by 25% in the event of grade 2 diarrhea and was held until recovery to grades 0/1 for grades 3/4 diarrhea. Subsequent doses of both agents were reduced by 25% for grade 3 and 50% for grade 4. Treatment was also held for grades 2 and 3 peripheral neuropathy. Subsequent doses of docetaxel were reduced by 25% and 50%, respectively, with no dose reductions of irinotecan. Treatment was held for a bilirubin above the ULN or alkaline phosphatase or AST more than five times the ULN. Subsequent doses were reduced by 25%.

Acute diarrhea or abdominal cramping that occurred during or within 1 h of receiving irinotecan was managed with atropine 0.25–1.0 mg intravenously. Patients were instructed to take 4 mg of loperamide at the earliest signs of poorly formed or loose stool or the occurrence of one or two more bowel movements than usual in 1 day. This was followed by 2 mg every 2 h until diarrhea-free for at least 12 h. Patients who did not adhere to this regimen were replaced, and their toxicities were not included in DLT determinations.

Pharmacokinetic analysis

To assess the pharmacokinetics of docetaxel and irinotecan and its active metabolite, SN-38, serial blood samples were collected into 10.0-ml heparinized (green-topped) tubes at the following times: $t=0$ (immediately prior to the start of docetaxel infusion) and at 30 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 h after the start of docetaxel infusion. The 1-h specimen was obtained at the completion of the docetaxel infusion and immediately prior to the start of the irinotecan infusion. The blood samples were centrifuged immediately at 2000 *g* and the plasma transferred into polypropylene vials and stored at -70°C until analyzed for docetaxel, irinotecan, and SN-38. Plasma samples were analyzed for docetaxel, irinotecan, and SN-38 using validated HPLC methods.

For the docetaxel analysis, 0.5 ml plasma was mixed with 50 μl paclitaxel (as internal standard) and 100 μl acetonitrile. The mixture was then shaken vigorously for 5 min. To the mixture was added 0.2 g Na_2SO_4, and the mixture was then shaken for another 5 min and centrifuged at 2000 *g* for 10 min. The top layer, containing acetonitrile solution, was transferred into another glass tube and evaporated to dryness. The residue was reconstituted into 150 μl mobile phase, and the entire solution centrifuged. The supernatant (50 μl) was injected into Perkin-Elmer 410 HPLC system that was fitted with an Alltech Econosphere C18 (5 μm) 250×4.6 mm separation column. The samples were eluted using a mobile phase consisting of 25 m *M* sodium dihydrogen phosphate (57%) and acetonitrile (43%, v/v). The flow rate was set at 1.5 ml/min, and the eluents were monitored using a UV detector set at 227 nm.

Irinotecan was analyzed using the following procedures. Plasma (0.5 ml) was mixed with 50 μl of internal standard solution and 0.8 ml 0.01 *N* HCl and centrifuged. The mixture was then passed through a 100 mg cartridge containing C2 resin. The C2 cartridge was preconditioned using one volume of methanol and one volume of water. The mixture samples were then applied onto the column and washed with one volume of water. The sample was eluted using 1 ml acidified methanol (100 μl HCl in 100 ml methanol). The eluent was evaporated to dryness using a steady stream of dried air at 40°C. The residue was reconstituted into 150 μl mobile phase, and the entire sample was centrifuged at 13,000 rpm for 5 min. An aliquot of 50 μl was injected into a Perkin-Elmer 410 quaternary pump fitted to a Beckman Ultrasphere C18 5 μm 250×4.6 mm column and an all-guard cartridge. The samples were eluted with 50 m *M* sodium phosphate, 5 m *M* 1-pentanesulfonic acid in 28% acetonitrile, where the pH of the solution was adjusted to a pH 3.0 using H_3PO_4. The flow rate was set at 1.0 ml/min, and the eluents were monitored using a fluorescence spectrophotometer with excitation wavelength of 380 nm and emission wavelength of 550 nm.

Blood specimens were collected and pharmacokinetics determined on days 1 and 22 of cycle 1 at each dose level studied. A three-compartment model using MAP Bayesian estimation in ADAPT II was used to analyze irinotecan pharmacokinetics [12]. A three-compartment linear model were fitted to irinotecan and SN-38 plasma concentration-time data and population priors as described by Ma et al. [27]. Individual parameters estimated included the volume of the central compartment (V_1), peripheral compartment (V_2), and SN-38 volume (V_3). The intercompartment rate constants (K_{12} and K_{21}), elimination rate constants for irinotecan and SN-38 from the central compartment were designated as K_{10} and K_{30}, respectively. Using standard equations, systemic clearance ($CL_{irinotecan}$ and CL_{SN-38}) and elimination half-life ($t_{1/2}$) of irinotecan and SN-38 were calculated using the log trapezoidal method.

Results

Patients

A total of 35 patients were accrued between October 1998 and September 2001. Patient characteristics are presented in Table 1. A total of 78 cycles were administered to 30 evaluable patients with a median number of 2 cycles (range 1–7). Five patients were not evaluable: one patient had a performance status of 3 at baseline, and four additional patients were removed early due to clinical progression (Table 2).

Table 1 Patient characteristics

		No. of patients
Total no. of patients		35
Sex		
Male		24
Female		11
Age (years)		
Median	54	
Range	20–73	
Performance status (SWOG)		
0		2
1		24
2		8
3		1
Race		
Hispanic		21
Caucasian		7
Asian		4
African–American		1
Other		2
Prior therapy		
Chemotherapy		25
Radiation		8
Tumor site		
Stomach		15
Esophagus		5
Non-small-cell lung		4
Liver		2
Sarcoma		2
Other[a]		7

[a]Breast, unknown primary, gallbladder, uterus, testis, melanoma and rectum (one each)

Table 2 Dose-escalation scheme

Dose level	Dose (mg/m^2) days 1, 8, 15, 22		No of patients
	Docetaxel	Irinotecan	
I	30	50	6
II	35	50	5
III	35	66	2
IV	30	57	7
V	30	65	7
VI	30	80	8

Toxicities

Grades 3 and 4 toxicities observed on cycle 1 are presented in Table 3. Toxicities observed during all cycles (all grades) are presented in Table 4. Overall, the most common toxicities encountered were fatigue, diarrhea, nausea and vomiting. Most patients (75%) reported fatigue while on treatment, but only 17% had more than grade 2. The majority of patients (65%) experienced diarrhea. Overall, grades 2–4 diarrhea were observed in 40%. The majority of patients (65%) experienced nausea and/or vomiting. Myelosuppression was uncommon and mild. Neutropenia occurred in fewer then one-third of patients (31%), was grade 3 or 4 in only three patients (11%), and was associated with fever once. There were no reports of thrombocytopenia. Only one patient developed significant edema. However, this patient had significant ascites at baseline, low albumin and poor nutritional status, so the edema was attributed to her underlying disease. Seven additional patients developed grades 1/2 edema. No serious hypersensitivity reactions were reported.

Dose-limiting toxicities

One episode of DLT (neuropathy) was observed at level I (docetaxel 30 mg/m^2 and irinotecan 50 mg/m^2), but was found to be secondary to spinal cord compression. One of three patients entered at level II (docetaxel 35 mg/m^2 and irinotecan 50 mg/m^2) developed grade 4 diarrhea. The level was expanded by two patients who both developed grade 4 diarrhea. One of them did not adhere to the guidelines for management of irinotecan-induced diarrhea and was replaced. At that time, two patients had already been accrued to dose level III (docetaxel 35 mg/m^2 and irinotecan 66 mg/m^2): one developed grade 3 diarrhea and grade 3 infection (non-neutropenic), and the other developed grade 3 neutropenia. Because patients at dose levels II and III (docetaxel 35 mg/m^2) developed significant diarrhea, the protocol was

Table 3 Episodes of grade 3/4 toxicities during cycle 1

Toxicity	Dose level					
	I	II	III	IV	V	VI
Leukopenia	1			1		1
Neutropenia	1		1	1		
Diarrhea		2	1	2	1	2
Nausea/vomiting	1	1		2		
Fatigue	1	1		2		1
Edema					1	
Hyperglycemia						1
Peripheral neuropathy	1					

amended and it was decided to determine the MTD of irinotecan when administered with a fixed dose of 30 mg/m^2 of weekly docetaxel. Dose level IV became then docetaxel 30 mg/m^2 and irinotecan 57 mg/m^2. Because of concerns for developing diarrhea, subsequent levels escalated the irinotecan dose by 15–25% instead of the traditional 33%.

At dose level IV one of the first three patients accrued developed grade 3 diarrhea. However, this patient was non-compliant with the diarrhea management guidelines and was replaced. The replacement patient also developed grade 3 diarrhea. Therefore the dose level was expanded and three more patients were accrued. One of these patients had stomach cancer, extensive carcinomatosis and significant ascites and developed grade 3 edema that was considered to be disease-related. No additional DLTs were observed. At dose level V (docetaxel 30 mg/m^2 and irinotecan 65 mg/m^2), one patient developed grade 3 diarrhea, and the dose level was expanded without additional DLTs. Eight patients were accrued to dose level VI (docetaxel 30 mg/m^2 and irinotecan 80 mg/m^2). Two patients with stomach cancer were not evaluable due to early clinical progression: one patient developed disseminated intravascular coagulation, and the other developed a bowel obstruction and line sepsis. Two evaluable patients developed DLTs at this level: one grade 3 diarrhea, and the other grade 3 diarrhea and grade 4 neutropenia. The MTD was determined to be docetaxel 30 mg/m^2 plus irinotecan 65 mg/m^2 on a 4-week-on, 2-week-off schedule.

Table 4 Most common toxicities per patient (all dose levels)

Toxicity	All grades		Grade 3/4	
	No. of patients	% of patients	No. of patients	% of patients
Leukopenia	8	22	3	8.5
Neutropenia	11	31	4	11
Diarrhea	24	68	9	35
Nausea/vomiting	26	74	7	20
Fatigue	27	77	6	17
Infection	7	20	3	8.5
Edema	7	20	1	3
Myalgia/arthralgia	14	40	0	0
Anorexia	11	31	2	6

Tumor response

Five objective responses were observed among 30 evaluable patients, for a response rate of 20%. PRs were observed at dose levels I, II, IV, V and VI. One patient with breast cancer and lung metastasis achieved a CR lasting 11 months. Three PRs were observed in patients with stomach cancer. An additional response was observed in a female patient with extensive carcinomatosis of unknown primary, with a suspected stomach cancer (linitis plastica). In addition, eight patients achieved SD. SD was observed at all dose levels except level IV.

The relatively large number of patients with stomach cancer provided the opportunity to analyze the antitumor activity in this group in more detail. Of the 12 evaluable patients with stomach cancer, 7 had received prior chemotherapy. A 23% response rate was observed; in addition, 5 patients had stable disease. The median time to progression was 2.75 months (range 1.25–10.75 months), and median overall survival 7 months (range 1.25–24 months).

Pharmacokinetics of docetaxel and irinotecan

The pharmacokinetics of docetaxel and irinotecan were evaluated in 20 patients, of whom 15 were evaluated on both day 1 and day 22 to determine whether the pharmacokinetics altered. Non-compartmental pharmacokinetic analyses of docetaxel and irinotecan are reviewed in Tables 5 and 6. There were no significant differences in pharmacokinetic parameters between doses given on day 1 and day 22. In addition, no irinotecan accumulation was observed in this study where average $AUC_{irinotecan1}$ and $AUC_{irinotecan2}$ were 5.1 ± 2.7 and 4.3 ± 3.4 μg h/ml, respectively. Similarly there was no accumulation of SN-38 seen on days 1 and 22 of irinotecan administration.

In one portion of this study, irinotecan was dose-escalated, while docetaxel was kept at 30 mg/m^2. The plasma levels of docetaxel and irinotecan were both analyzed. The AUC and C_{max} were proportional to dose, suggesting that docetaxel and irinotecan demonstrate linear pharmacokinetics in this dosage range. There was no significant variation between the various dosages of irinotecan, which is consistent with the $t_{1/2}$ reported in the packet information that ranges from 5.8 to 11.7 h (for 125 and 340 mg/m^2, respectively) [31].

Discussion

The combination of docetaxel and irinotecan is an interesting regimen as both drugs are synergistic and have a broad spectrum of clinical activity. Three phase I clinical trials have been published and differ from our study in that in all of them docetaxel was administered every 3 weeks [2, 11, 28]. In two of these studies both drugs were administered every 3 weeks. Myelosuppres-

Table 5 Non-compartmental analysis: AUC and half-life of docetaxel, irinotecan and SN-38

Docetaxel/irinotecan (mg/m^2)	No. of points	AUC (ng h/ml)			Half-life (h)	
		Docetaxel	Irinotecan	SN-38	Irinotecan	SN-38
30/50	3	1983 ± 1512	2972 ± 891	159 ± 153	10.2 ± 4.4	10.4 ± 3.8
35/66	2	1142 ± 1056	3633 ± 754	57 ± 23	7.5 ± 2.7	10.7 ± 5.1
30/57	5	1398 ± 1032	3998 ± 590	115 ± 35	5.9 ± 1.5	10.2 ± 4.2
30/65	3	902 ± 135	3558 ± 146	84 ± 49	5.1 ± 2.2	12.8 ± 1.4
30/80	7	2713 ± 1682	7844 ± 3003	196 ± 162	7.2 ± 2.4	8.4 ± 4.1
Total	20					

sion was the most common DLT and grades 3 and 4 diarrhea was observed in 7.5–27% of patients. In the study by Adjei et al. [2], irinotecan preceded docetaxel while the opposite schedule was used by Couteau et al. [11]. Both studies identified a similar MTD for docetaxel, but a significantly different MTD for irinotecan (160 vs 275 mg/m^2, respectively). It is difficult to explain this finding. One possible explanation is because of differences in patient characteristics. This hypothesis is supported by the observation that the patients in the study by Couteau et al. were younger (median age of 54 vs 60 years) and more patients had a performance status of 0 (22% vs 45%). A second hypothesis is that the sequence of drug administration may have altered the pharmacokinetics of one of the agents. However, no significant differences can be appreciated in the pharmacokinetics of docetaxel between the two studies. Unfortunately, Adjei et al. did not determine the pharmacokinetics of irinotecan or SN-38.

In the third phase I trial of this combination, irinotecan was administered on days 1, 8 and 15 while docetaxel was given on day 2 on a 4-week cycle [28]. Neutropenia and diarrhea were again the most common serious toxicities. In this study a lower MTD for docetaxel was established compared to the other two studies (50 vs 60–65 mg/m^2). Similarly, the dose intensity for irinotecan appeared also to be lower (37.5 vs 53.3 and 91.6 mg/m^2 per week). The pharmacokinetics of docetaxel, irinotecan and SN-38 were evaluated in this trial. Although no appreciable differences could be observed in the pharmacokinetics of docetaxel, an increased AUC of SN-38 was found as compared to other studies. Our study does not support the notion that docetaxel increases the AUC of SN-38. Rather the ratio of SN-38 to irinotecan concentrations was similar to values found in the prescribing information [31].

To further define the disposition of irinotecan, we performed a compartmental analysis of irinotecan and SN-38 (Table 6). We used a three compartmental model to analyze the disposition of irinotecan and found that the $CL_{irinotecan}$ was lower than that reported by Murren et al. [30]. We also observed an increase in $t_{1/2\beta}$ as compared to Murren et al. [30]. Despite these differences, the $AUC_{SN\text{-}38}$ values appear to be similar across the dosage levels. Similarly, the central compartment volume (V_1) is similar to those reported in adults but larger than those reported in children [1, 13, 21, 27, 31]. In our study, pharmacokinetics on day 1 and day 22 were compared at various doses. There was no significant difference between day 1 and day 22, but at the highest dosage of irinotecan one patient experienced high pharmacokinetic variability during those 2 days and was excluded from analysis. This patient had an unusually low albumin level even at study entry.

Encouraging early clinical activity has been observed in all studies evaluating the combination of docetaxel and irinotecan. These studies have established that docetaxel and irinotecan can safely be administered on a 3–4-week cycle. However, myelosuppression and diarrhea are common and serious toxicities using these schedules. In one study, the pharmacodynamic relationship between AUC of irinotecan and SN-38 glucuronate (SN-38G) was correlated with the severity of diarrhea [35]. Although we did not determine the level of SN-38G, the levels of its precursor, SN-38, and irinotecan were lower than predicted for severe diarrhea. This may explain why

Table 6 Compartmental analysis of irinotecan on day 1 and day 22

	50 mg/m^2		57 and 65 mg/m^2		80 mg/m^2	
	Day 1	Day 22	Day 1	Day 22	Day 1	Day 22
V_1 (l/m^2)	134.40 ± 13.5	144.8 ± 30.34	72.1 ± 18.6	97.7 ± 20.8	39.2 ± 3.1	44.9 ± 14.7
V_2 (l/m^2)	257.90 ± 83.8	329.3 ± 227.5	97.6 ± 83.2	133.1 ± 117.2	35.8 ± 9.9	64.1 ± 34.1
V_3 (l/m^2)	79.9 ± 0.3	58.9 ± 9.9	51.9 ± 30.8	43.6 ± 18.6	13.2 ± 12.7	3.0 ± 0.9
$CL_{irinotecan}$ ($l/h/m^2$)	8.2 ± 3.2	10.4 ± 2.7	10.4 ± 1.6	14.8 ± 4.8	14.3 ± 7.6	11.2 ± 5.8
CLp dist	52.7 ± 5.5	35.2 ± 4.2	30.9 ± 27.8	32.6 ± 20.2	33.5 ± 2.2	45.1 ± 20.3
$AUC_{irinotecan}$ (ng h/ml)	6,677 ± 2,211	5,000 ± 1,136	5,960 ± 1,297	4,602 ± 1,504	16,181 ± 23,351	9,661 ± 7,074
$t_{1/2\beta}$ (h)	6.4 ± 2.3	5.0 ± 0.4	3.0 ± 0.8	3.03 ± 1.1	3.3 ± 4.8	2.1 ± 1.3
$CL_{metabolism}$	10.3 ± 4.7	9.9 ± 2.2	5.9 ± 2.6	6.71 ± 1.90	1.4 ± 1.7	0.3 ± 0.1
$CL_{SN\text{-}38}$ ($l/h/m^2$)	168.8 ± 119.9	119.1 ± 230.8	209.86 ± 203.6	308.1 ± 243.1	81.4 ± 113.8	12.8 ± 12.8

the degree of diarrhea as an adverse event in our study was less than when higher doses of irinotecan are employed [35].

It is well established that the DLT of docetaxel administered every 3 weeks is myelosuppression. Clinical trials have shown that docetaxel administered on a weekly schedule is associated with significantly less myelosuppression. Therefore, as expected, in our study myelosuppression was less intense than in the trials discussed above. However, the dose intensity of docetaxel in our study was higher, while the dose intensity of irinotecan was comparable.

Overall, we found this regimen to be well tolerated. Hematological toxicity was mild and uncommon. Diarrhea was the most common and serious toxicity. Many of the patients enrolled in this study had baseline nausea due to carcinomatosis which may have limited their ability to follow the strict loperamide-based diarrhea prophylaxis therapy.

Two other groups have evaluated the weekly administration of docetaxel and irinotecan. Similar to the recommendations from this study, Bleickardt et al. recommended a dose of docetaxel 35 mg/m^2 and irinotecan 60 mg/m^2 [6]. Using this schedule, myelosuppression was modest, and diarrhea represented the DLT. On the other hand, Font et al. reported significant myelosuppression when irinotecan was administered at a dose of 70 mg/m^2 in combination with docetaxel 30 mg/m^2 [15]. Therefore, they recommended a dose of irinotecan 70 mg/m^2 and docetaxel 25 mg/m^2 for phase II clinical trials.

A secondary objective of our trial was to obtain additional experience using a single dose of steroids to prevent docetaxel-induced edema. It has been reported that in the absence of dexamethasone, 81% of patients will develop significant edema, causing 30% to discontinue therapy. The addition of a 5-day course of dexamethasone will decrease the incidence of edema to 43% of patients (6% severe) with only 1.6% requiring treatment discontinuation [9]. More recently it has been reported that a 3-day course of steroids is still useful to prevent the development of edema [3]. Lück et al. [26] reported that a single dose of steroid appeared to be adequate to prevent the formation of significant edema; our findings support this. However, patients in our study remained on therapy for a relatively short period and it has been observed that the development of edema is a cumulative toxicity. Nonetheless, edema was uncommon in the ten patients who received three or more cycles of treatment (18 weeks).

Our study confirms that the combination of docetaxel and irinotecan is a well-tolerated regimen and should be explored in phase II trials. The recommended dose for phase II clinical trials is docetaxel 30 mg/m^2 and Irinotecan 65 mg/m^2. The results of our study support weekly dosing as a strategy to limit myelosuppression while maintaining dose intensity. Phase II clinical trials suggest that dosing both agents every 3 weeks is associated with significant toxicity [20, 25].

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