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Phase I and pharmacokinetic study of docetaxel, irinotecan, and celecoxib in patients with advanced non-small cell lung cancer*

Athanassios Argiris[1], Victoria Kut[1], Lynn Luong[2] and Michael J. Avram[2]
[1]*Division of Hematology-Oncology, Department of Medicine;* [2]*Department of Anesthesiology and Mary Beth Donnelley Clinical Pharmacology Core Facility, Northwestern University Feinberg School of Medicine and the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL*

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Summary

Purpose: We studied the toxicities, potential pharmacokinetic interactions, and preliminary antitumor activity of the combination of docetaxel and irinotecan with celecoxib, a selective cyclooxygenase-2 inhibitor. *Patients and methods*: Eligible patients had advanced non-small lung cancer (NSCLC) with measurable disease, good performance status, and adequate end organ function. Docetaxel and irinotecan were administered intravenously on days 1 and 8, every 21 days, and their doses were escalated on successive patient cohorts at three dose levels: 30/50, 30/60, and 35/60 (doses in mg/m^2). Celecoxib was administered at a starting dose of 400 mg orally twice daily without interruption, beginning on day 2 of cycle 1. Pharmacokinetic studies were performed on day 1 of cycle 1 and day 1 of cycle 2. *Results*: Seventeen patients with advanced NSCLC were enrolled and collectively received 78 cycles of therapy. Diarrhea was the most common toxicity; it was noted in 13 patients (76%). Dose-limiting toxicities occurred at dose level 1 (myocardial infarction in a patient with multiple coronary artery disease risk factors) and dose level 3 (grade 4 neutropenia with fatal urosepsis). Other major toxicities were: grade 3 neutropenia (2 patients); grade 3/4 diarrhea (3/1); grade 3 nausea (2); grade 2 rash (1); and grade 3 pneumonitis (1). The maximum tolerated dose was at dose level 3, i.e., docetaxel 35 mg/m^2 and irinotecan 60 mg/m^2 on days 1 and 8, plus celecoxib 400 mg twice daily, repeated every 21 days. Five of 15 evaluable patients achieved an objective response. The pharmacokinetics of docetaxel were not altered by celecoxib. However, we observed an 18% increase in the average elimination clearance of irinotecan coincident with the addition of celecoxib. *Conclusions*: The addition of celecoxib to docetaxel and irinotecan was generally well tolerated but unpredictable fatal toxicity occurred. Diarrhea was the most common toxicity. Antitumor activity was promising. The alteration of irinotecan pharmacokinetic parameters observed may not be clinically relevant.

Introduction

Lung cancer is usually diagnosed at advanced stages when the curative potential is very limited. Although chemotherapy has been conclusively shown to improve the survival of patients with advanced non-small cell lung cancer (NSCLC), the absolute survival benefit remains small; treatment results have not improved beyond what is achieved with 2-drug combinations [1]. State-of-the-art treatment for advanced NSCLC with contemporary chemotherapy combinations achieves response rates of 15–35%, median survival of 8–10 months, and 1-year survival of 30–40%. Platinum-based combinations have been the mainstay of lung cancer chemotherapy, whereas non-platinum-based combinations have also been studied extensively in recent years [2, 3]. The taxanes (paclitaxel and docetaxel) and irinotecan have shown significant antitumor activity in lung cancer with response rates of 10–30% when used as single agents in chemotherapy naïve patients [4].

Irinotecan (CPT-11) is a water-soluble analogue of camptothecin that inhibits topoisomerase I, a key enzyme that alters the tertiary structure of DNA during replication

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and transcription [5]. Irinotecan is metabolized by carboxylesterase, primarily in the liver, to SN-38, which has cytotoxic activity that is 100 to 1000-fold more than that of irinotecan. The dose-limiting toxicities of irinotecan are neutropenia and diarrhea. Docetaxel is a semisynthetic taxane, derivative of 10-deacetylbaccatin III, a precursor extracted from the needles of the European yew, taxus baccata. It acts as a mitotic spindle poison by promoting microtubule assembly but inhibits tubulin depolymerization and disrupts cell division. Docetaxel is metabolized by the CYP3A4 isoenzyme. Most clinical trials have used a docetaxel dose of 75–100 mg/m^2 given every 3 weeks [6]. The dose-limiting toxicity (DLT) with this schedule of administration was neutropenia. Alternative schedules of administration have been shown to modify the toxicity profile of the taxanes, and possibly alter their mechanism of action. Laboratory data have demonstrated that the taxanes have antiangiogenic properties at doses much lower than the ones required for cytotoxicity [7]. Administration of docetaxel on a weekly basis has been shown to be well-tolerated, with a reduction in the incidence of severe neutropenia and maintenance of therapeutic efficacy [8–10].

Given the single agent activity of irinotecan and docetaxel in NSCLC, these agents have been studied in combination in phase I and II trials in NSCLC. Their combination is supported by preclinical data that have demonstrated an additive or synergistic effect between the camptothecins and the taxanes, which may be schedule-dependent [11, 12]. A phase I trial by Bleickardt et al. investigated the administration of both drugs on a weekly schedule [13]. Diarrhea was the predominant dose-limiting toxicity but, unlike the every 3 weeks schedule, neutropenia was modest. The recommended phase II doses were docetaxel 35 mg/m^2 and irinotecan 60 mg/m^2 given on days 1 and 8 of a 21-day schedule. A Japanese randomized phase II study demonstrated that the combination of irinotecan (60 mg/m^2 on day 1 and 8) and docetaxel (60 mg/m^2 on day 1), repeated every 3 weeks, has similar efficacy to an irinotecan/cisplatin combination regimen [14]. Nausea and vomiting were reduced with the docetaxel-based regimen, but diarrhea was more pronounced. This study showed that the combination of irinotecan and docetaxel is at least as active as a cisplatin-based regimen and that it warrants further investigation in NSCLC.

In an attempt to improve further treatment results, molecularly targeted agents have been added to combination chemotherapy regimens. A class of agents that has been investigated for its anticancer potential is the non-steroidal antiinflammatory drugs (NSAIDs), especially the more selective cyclooxygenase-2 (COX-2) inhibitors such as celecoxib and rofecoxib [15]. NSAIDs inhibit cyclooxygenase, an enzyme that catalyzes the rate-limiting step in the arachidonic acid-prostanoid synthetic pathway. Increased prostaglandin levels have been detected in multiple epithelial cancers [16]. Prostaglandins, especially of E-series, have long been known to promote tumorigenesis by stimulating angiogenesis and inhibiting immune surveillance [17, 18]. Lung cancer tumors, especially well or moderately differentiated adenocarcinomas, frequently express high levels of COX-2. Multiple studies have shown that 70% or more of adenocarcinomas are positive for COX-2 by immunohistochemical methods [19–22]. In addition, early clinical data suggest that COX-2 expression may be of prognostic significance in stage I NSCLC [21, 23].

COX-2 inhibitors have demonstrated antiproliferative properties and have been shown to enhance the cytotoxicity of chemotherapy, including irinotecan and SN-38 (the active metabolite of irinotecan), cisplatin, etoposide, and docetaxel, in preclinical models [24–26]. The addition of a selective COX-2 inhibitor to a taxane-containing regimen is of particular interest since laboratory data suggest that a taxane may induce the expression of PGE-2 and COX-2 in a carcinoma cell line [27]. Celecoxib, at a dose of 400 mg twice daily orally, has been approved by the U.S. Food and Drug Administration for the prevention of adenoma formation and subsequent carcinogenesis in patients with familial adenomatous polyposis. The mechanism of action of celecoxib is not fully understood, but it appears to be related to induction of apoptosis or an antiangiogenesis effect [15]. Thus, celecoxib is a promising biologic agent that warrants evaluation in the treatment of patients with non-small cell lung cancer. We therefore designed a phase I and pharmacokinetic study of the triple combination of irinotecan, docetaxel, and celecoxib in advanced NSCLC.

Patients and methods

Patient selection

Patients were required to have recurrent or metastatic NSCLC and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2. Patients could have received up to two prior chemotherapy regimens for recurrent or metastatic disease but not containing irinotecan or docetaxel. Prior biological therapies (e.g., antibodies or kinase inhibitors) were permitted. All patients had to be at least 18 years of age and were required to provide informed consent. The study protocol was reviewed and approved by the Institutional Review Board of Northwestern University. Patients with brain metastases were not eligible. Patients with any coexisting medical condition that would preclude full compliance with study were excluded. Subjects were required to practice adequate contraception or abstinence, and pregnant or lactating females were excluded. Patients had to have fully

recovered from the effects of any prior surgery, chemotherapy, or radiation therapy and were required to have adequate end organ function. Patients with pre-existing neuropathy more than grade 1 were excluded. No concurrent use of antiepileptics, cyclosporine A, or fluconazole was permitted. Patients who had been diagnosed or treated for peptic ulcer disease or gastritis/esophagitis within 60 days prior to study entry were excluded as were patients with a history of hypersensitivity to COX-2 inhibitors, NSAIDs, salicylates, sulfonamides, or drugs formulated with polysorbate 80. The use of NSAIDs at any dose at a frequency of $\geq$3 times/week for a cumulative period of more than 2 weeks during 30 days prior to study entry was not allowed. Also, the prior use of corticosteroids was restricted to a cumulative period of less than 2 weeks over the previous 3 months. Finally, patients also had to be willing to abstain from use of all NSAIDs and COX-2 inhibitors for the duration of the study.

Treatment plan and dose modifications

Docetaxel was administered intravenously over one hour. Patients received dexamethasone, 8 mg orally, 12 h before and 12 h after docetaxel infusion, and also received 10 mg of dexamethasone intravenously along with standard antiemetics, 60 min prior to the infusion. After the completion of the docetaxel infusion, irinotecan was administered intravenously over 30 min. Celecoxib was administered twice daily orally with food starting on the second day of cycle 1 and continued without interruption. Irinotecan and docetaxel were administered on days 1 and 8 of a 21-day schedule. The doses of docetaxel and irinotecan were calculated using the patient's actual weight on day 1 of each cycle. Treatment continued until progression of disease or intolerable toxicities.

On day 1 of each cycle, irinotecan and docetaxel were administered provided the ANC was higher than 1200/μL, platelet count was above 100,000/μL, there was complete resolution of stomatitis, and there was no toxicity (other than alopecia and anemia) > grade 1. Treatment was omitted if these conditions were not met and the patients were reassessed until the toxicity resolved and retreated after a week had elapsed. On day 8 of the cycle, treatment was continued if the ANC was higher than 1000/μL, platelet count was above 75,000/μL and there was no toxicity (except alopecia and anemia) > grade 1, and stomatitis had completely resolved to grade 0. Treatment was held if a patient's total bilirubin was $>1 \times$ ULN, the alkaline phosphatase was $>5 \times$ ULN, or the AST was $>5 \times$ ULN and if there was no recovery within 3 weeks, the patient was taken off study. Irinotecan and docetaxel were reduced by 20%, if patients developed grade 4 neutropenia or neutropenic fever, grade 4 thrombocytopenia, or more than grade 2 (i.e., grade 3–4) non-hematologic toxicity (with the exception of alopecia), including grade 3 or 4 diarrhea despite the appropriate management of diarrhea. The dose of docetaxel was reduced by 20% for grade 2 neuropathy and treatment was discontinued if patient developed grade 3 or 4 neuropathy. No further dose reductions of either docetaxel or irinotecan were allowed. Patients who developed grade 4 (life-threatening) hypersensitivity reactions were removed from study. Celecoxib was decreased to 200 mg orally twice a day if grade 3 or 4 toxicity or other celecoxib-related toxicity persisted >10 days from the last dose of chemotherapy. The patient was taken off celecoxib if toxicity did not decrease to grade 0 or 1 within 3 weeks from the last dose of chemotherapy.

DLT definition and dose escalation design

Toxicity was graded according to modified version of the National Cancer Institute-Common Toxicity Criteria, version 2.0. The dose-limiting toxicity was defined as any of the following: 1. grade 4 vomiting or diarrhea despite appropriate antiemetic or antidiarrheal therapy; 2. any grade 3 or 4 non-hematologic toxicity; 3. an ANC $<$ 500/μl associated with a temperature of 100.5°F or higher; 4. grade 4 thrombocytopenia; or 5. treatment delay of >3 weeks as a result of drug toxicity. Initially, DLT was defined during the first 3 cycles (9 weeks) of therapy in order to include potential relatively late effects of therapy. However, after enrollment at level 1 was completed the protocol was amended so that DLT was defined during the first cycle only.

Doses were escalated in cohorts of 3 patients, starting with level 1, on 3 major dose levels (see Table 1). The

Table 1 Dose levels

		Dose levels					
	Days of cycle	1	1A	2	2A	3	3A
Celecoxib (mg)	Twice daily, 1–21*	400	200	400	200	400	200
Irinotecan (mg/m^2)	1 and 8	50	50	60	60	60	60
Docetaxel (mg/m^2)	1 and 8	30	30	30	30	35	35

*2–21 for cycle 1 only. A cycle is 21 days.

starting dose level was at dose level 1. Three patients were entered on each dose level. If no DLT developed, patients were entered on the next dose level. If 1 patient developed DLT, then 3 additional patients were entered on the same dose level. If at any dose level >1/6 patients developed DLT, then up to 6 patients were treated with a lower dose of celecoxib 200 mg twice daily (i.e. levels 1A, 2A, 3A). The recommended phase II dose was defined as the highest dose level that produced a maximum of 0/3 or 1/6 DLTs.

Pretreatment assessment and follow-up studies

Patient evaluation included history and physical examination, determination of ECOG PS and body surface area, complete blood counts with differential (CBC), electrolytes, and biochemistry studies prior to each treatment cycle. CBC was done on day 8 of the cycle as well. History and physical examination, complete blood counts with differential, electrolytes, and biochemistry studies were performed weekly during the first cycle of treatment. Baseline tumor assessments that included computed tomography (CT) scans in all cases were obtained within 4 weeks of treatment initiation and repeated every third cycle (9 weeks) while on treatment. Solid tumor response criteria (RECIST) were used to evaluate responses [28].

Pharmacokinetic analysis

Pharmacokinetic studies were performed on the first day of cycle 1 and cycle 2. Subjects were admitted overnight to the General Clinical Research Center of Northwestern University to receive treatment for day 1 of both cycles 1 and 2. The purpose of these studies was to characterize the kinetics of docetaxel and irinotecan in patients before and after beginning daily celecoxib treatment. The sampling schedule was predicated on a one-hour docetaxel infusion beginning at time t_0 followed immediately by a half-hour irinotecan infusion. Blood samples were drawn at 15 min intervals during the infusion of each drug, at 15 min intervals following termination of the irinotecan infusion to one hour, and at hourly intervals thereafter until 12 h after the termination of the irinotecan infusion. After centrifugation, plasma was separated and stored at -80°C until processed for plasma drug concentration analysis.

After sample preparation, plasma docetaxel concentrations were determined by reverse-phase high performance liquid chromatography with tandem mass spectrometric detection (LC/MS/MS). Following addition of the internal standard paclitaxel to 200 μl of plasma, paclitaxel and docetaxel were isolated by solid-phase extraction using Sep-Pac Vac 1 ml 100 mg cyanopropyl columns (Waters Corporation, Milford, MA) using a slight modification of the method of Garg et al. [29] Following gradient elution from a Synergi 4 μ Max-RP 50 $\times$ 2 mm column (Phenomenex, Torrence, CA) and detection by negative ion turbo spray MS/MS (API 3000, MDS Sciex, Concord, ON, Canada), docetaxel concentrations were quantitated using the internal standard area ratio method. The method was linear over a plasma standard concentration range of 0.5–500 ng/ml with coefficients of variation and bias of less than 10% throughout the entire standard range.

Total plasma irinotecan and SN-38 concentrations were measured by LC/MS/MS after sample preparation by solid-phase extraction because there is no advantage to monitoring the lactone and carboxylate forms separately [30]. Following addition of the internal standard camptothecin to 200 μl of plasma, irinotecan, SN-38, and camptothecin were isolated by solid-phase extraction using 1.5 ml 100 mg C18 columns (Burdick & Jackson, Muskegon, MI) using a slight modification of the method of Barilero et al. [31]. Following gradient elution from a Targa 3 μ C_{18} 50 $\times$ 2.1 mm column (Higgins Analytical, Mountain View, CA) and detection by positive ion turbo spray MS/MS, irinotecan and SN-38 concentrations were quantitated using the internal standard area ratio method. The method was linear over a plasma standard concentration range of 0.5–500 ng/ml with coefficients of variation of 10% or less and bias of less than 10% throughout the entire standard range.

Three-compartment pharmacokinetic models with zero order drug input were fit to venous plasma docetaxel and irinotecan concentration versus time data using a relative error model with SAAM II (version 1.2, SAAM Institute, Seattle, WA) implemented on a Pentium®-based personal computer. The SAAM II objective function was the extended least-squares maximum likelihood function using data weighted with the inverse of the model-based variance of the data at the various times [32]. Systematic deviations of observed data from the calculated values were sought using the one-tailed one-sample runs test, with $P < 0.05$, corrected for multiple applications of the runs test, as the criterion for rejection of the null hypothesis. Model misspecification was sought by visual inspection of the measured and predicted marker concentrations *versus* time relationships. The pharmacokinetics of the irinotecan metabolite SN-38 were described by the time to maximum observed concentration (t_{max}), the maximum observed concentration (C_{max}), and the area under the plasma SN-38 concentration versus time relationship for the 12.5 h over which the concentrations were measured ($AUC_{0 \rightarrow 12.5\ h}$). Times to maximal concentrations and maximum concentrations were obtained by inspection of the data. The areas under the plasma metabolite concentration histories were estimated using Table Curve 2D version 5 (SPSS, Chicago, IL). All data

are summarized as mean and standard deviation. Pharmacokinetic parameters obtained in the two cycles were compared using the paired *t*-test if the data were normally distributed and with the Wilcoxon signed-rank test if they were not. Correlations between irinotecan elimination clearance and SN-38 C_{max} and $AUC_{0\rightarrow 12.5\ h}$ were sought using standard least squares linear regression. The criterion for rejection of the null hypothesis was a two-tailed $P < 0.05$.

Results

Patient characteristics

Seventeen patients, 11 males and 6 females, with advanced NSCLC were enrolled in the study between July 2002 and December 2003 (see Table 2). Their median age was 58 years; 8 patients had PS 0 and 9 had PS 1. The vast majority of patients had adenocarcinoma ($N = 13$). Five patients had received prior chemotherapy and 1 had received prior biological therapy (gefitinib). Eight patients were treated on dose level 1, 3 patients on dose level 2, and 6 patients on dose level 3. No celecoxib dose reductions or modifications were required. The patient cohort enrolled on the first dose level was expanded to 8 patients due to the occurrence of a DLT and because 2 patients were not evaluated for toxicity for the required 3 cycles of therapy; one patient withdrew from study after 2 cycles and the other had evidence of disease progression after 2 cycles.

Table 2 Patient characteristics

Total number of patients	17
Sex	
Male	11
Female	6
Race	
Caucasians	14
African-American	3
Age, years	
Median	58
Range	42–79
ECOG performance status	
0	8
1	9
Stage at enrollment	
IV	9
Recurrent	8
Histology	
Adenocarcinoma	13
Squamous cell	2
Bronchioloalveolar	1
NOS	1
Prior treatment	
Chemotherapy	5
Radiotherapy	5
Biologic therapy	1
No. of cycles delivered	
Level 1	30
Level 2	26
Level 3	22

A total of 78 3-week cycles of irinotecan, docetaxel, and celecoxib were administered. The median number of chemotherapy cycles delivered was 4 (range, 1–15). Two patients received only one cycle of chemotherapy and then removed from study due to the development DLT. An additional patient developed grade 3 pneumonitis after the fourth cycle of therapy and withdrew from study as well. Of 15 patients who received more than one cycle of therapy, 4 patients required dose reduction secondary to grade 3 diarrhea (1 on dose level 1, one on dose level 2, and 2 on dose level 3). There were treatment delays of up to 2 weeks in 6 patients (3 of whom also required dose reduction) for the following reasons: grade 2 fatigue and grade 3 dyspnea (1), unrelated foot drop (1), grade 1 pneumonitis with grade 2 dyspnea (1), grade 2 stomatitis (1), and grade 3 diarrhea (2).

Toxicity

All 17 patients were assessable for toxicity. Two patients developed DLTs. One patient treated on dose level 1 suffered a myocardial infarction within 24 h after receiving therapy on day 8 of the first cycle. A causal association to treatment was possible, so this was deemed a DLT. This patient had a history of stroke, diabetes mellitus, and hypertension, and, therefore, had significant risk factors for coronary artery disease. A second patient, a 79-year old female, treated on dose level 3, developed grade 4 diarrhea and grade 4 neutropenia, without fever, associated with urosepsis that proved fatal. This patient's docetaxel and irinotecan pharmacokinetic parameters were similar to those of the rest of the patients.

The most common hematological toxicity was anemia with 3 patients developing grade 3 anemia, one patient at dose level 1 and 2 patients at dose level 3 (Tables 3 and 4). Serious neutropenia and thrombocytopenia were rare; 3 patients experienced grade 3/4 neutropenia at dose level 3 and one patient had grade 3 thrombocytopenia at dose level 3.

Non-hematologic toxicities across all dose levels are displayed in Table 3, while grade 3/4 non-hematologic toxicities by dose level are displayed in Table 5. Diarrhea was the most common non-hematologic toxicity;

Table 3 Toxicities in all dose levels ($N = 17$)

	Grade				
Toxicity	0	1	2	3	4
Anemia	6	2	6	3	0
Neutropenia	12	0	2	2	1
Thrombocytopenia	13	0	3	1	0
Diarrhea	4	5	3	4	1
Stomatitis	15	1	1	0	0
Nausea	8	4	3	2	0
Vomiting	11	2	3	1	–
Anorexia	11	5	1	0	0
Fatigue	7	4	4	2	0
Pneumonitis	15	1	0	1	0
Alopecia	8	5	4	–	–
Rash	16	0	1	0	0

Table 4 Grade 3/4 hematologic toxicities by dose level

		Toxicity		
	No. of patients	Anemia	Neutropenia	Thrombocytopenia
Level 1	8	1/0	0	0
Level 2	3	0	0	0
Level 3	6	2/0	2/1	1/0
All levels	17	3/0	2/1	1/0

13 patients (76%) developed diarrhea of any grade; 4 patients had grade 3 diarrhea and 1 patient who developed urosepsis with hypotension and also noted to have diarrhea was considered to have grade 4 diarrhea (see Table 3). In general, patients adhered to the recommended high-dose loperamide regimen for the management of diarrhea. Of note is that the onset of serious diarrhea was often delayed, suggesting cumulative toxicity: 3 of the 5 patients who developed grade >2 diarrhea did so after receiving their third cycle of therapy. Other delayed toxicities were the following: stomatitis grade 2 after the 4th cycle in one patient and grade 3 pneumonitis after the 4th cycle in another patient. Also, one patient who received 15 cycles of therapy developed grade 2 nail changes. There was no significant treatment-related neuropathy noted on study. A patient developed mild foot drop during therapy that was thought to be due to preexisting spinal stenosis and unrelated to cancer progression or therapy. Moreover, 4 patients who did not have evidence of pneumonitis reported dyspnea, which was felt to be disease-related in all cases. One patient developed Candida esophagitis, documented by upper endoscopy during treatment that required hospitalization. Finally, a total of 4 patients developed deep venous thrombosis and/or pulmonary embolism while on study.

Antitumor efficacy

Fifteen patients were assessable for response. Two patients could not be evaluated because they were taken off study after cycle 1 due to toxicity. Best response was partial response in 5 patients (33%), stable disease in 6 (40%), and progression in 4 (27%). Four of the objective responses were observed in the 10 evaluable chemotherapy naïve patients and 1 in the 5 evaluable previously chemotherapy treated patients. A patient who had been treated previously with first-line gefitinib for advanced bronchioalveolar carcinoma without objective or symptomatic response had stable disease associated with marked symptom improvement with cessation of bronchorrhea on study treatment. Thirteen patients have died, 12 due to disease progression and one due to toxicity. The median time to progression was 4.2 months. The median overall survival was 7.5 months and the 1-year survival rate was 41%.

Pharmacokinetics results

The pharmacokinetic parameters for both cycles of docetaxel and irinotecan administration are listed in Table 6. As suggested by the virtual superimposition of the plasma concentration histories for the two cycles of both of these drugs, the pharmacokinetics of the drugs differed minimally between cycles. The only significant difference in pharmacokinetic parameters found was an 18% increase

Table 5 Grade 3/4 non-hematologic toxicities by dose level

		Toxicity							
	No. of patients	DLT	Diarrhea	Stomatitis	Nausea	Vomiting	Anorexia	Fatigue	Pneumonitis
Level 1	8	1	1/0	0	1/0	0	0	0	0
Level 2	3	0	1/0	0	0	0	0	0	0
Level 3	6	1	2/1	0	1/0	1/0	0	2/0	1/0
All levels	17	2	4/1	0	2/0	1/0	0	2/0	1/0

Table 6 Pharmacokinetic parameters of Docetaxel and Irinotecan Administered by Sequential Infusion

	Docetaxel Cycle 1	Docetaxel Cycle 2	*P* value	Irinotecan Cycle 1	Irinotecan Cycle 2	*P* value
No. of patients	11	11	–	11	11	–
Age, years						
Mean	57.2	57.2	–	57.2	57.2	–
Standard deviation	8.8	8.8		8.8	8.8	
Body surface area, m^2						
Mean	1.80	1.80	–	1.80	1.80	–
Standard deviation	0.13	0.13		0.13	0.13	
Central volume, V_C, L/m^2						
Mean	2.2	2.6	0.22	16.1	18.2	0.63
Standard deviation	1.2	1.2		9.9	19.4	
Fast volume, V_F, L/m^2						
Mean	2.6	3.5	0.19	45.4	44.4	0.88
Standard deviation	1.6	2.9		19.2	14.1	
Slow volume, V_S, L/m^2						
Mean	79.0	75.5	0.61	103.6	121.5	0.30
Standard deviation	21.7	24.4		49.0	54.1	
Steady state volume, V_{SS}, L/m^2						
Mean	84.0	81.6	0.73	165.1	184.0	0.28
Standard deviation	22.6	25.5		58.4	73.0	
Fast clearance, Cl_F, $L/h/m^2$						
Mean	3.7	4.3	0.15	91.1	108.2	0.46
Standard deviation	2.1	2.4		51.3	40.5	
Slow clearance, Cl_S, $L/h/m^2$						
Mean	8.9	7.7	0.19	11.5	12.8	0.47
Standard deviation	4.1	2.6		6.2	4.1	
Elimination clearance, Cl_E, $L/h/m^2$						
Mean	29.9	29.4	0.81	16.9	19.9	0.02
Standard deviation	9.9	7.5		5.7	7.0	
Elimination half-life, $t_{1/2\beta}$, hr						
Mean	8.7	8.4	0.20	7.5	7.5	0.98
Standard deviation	3.2	1.5		2.4	2.2	

in the average elimination clearance of irinotecan observed in cycle 2. SN-38 pharmacokinetic parameters are listed in Table 7. The time to peak SN-38 concentrations was on average approximately one hour after beginning the 30 min irinotecan infusion in both cycles. Although peak SN-38 concentrations were on average 17.5% less in cycle 2 than in cycle 1, this difference did not reach statistical significance. The average SN-38 AUC observed in cycle 2 was 21.8% less than that of cycle 1, and was, therefore, significantly different from that of cycle 1.

There were significant correlations between irinotecan elimination clearance and both maximum SN-38 concentration and SN-38 AUC (Figures 1 and 2, respectively). The correlations predicted a more than 50% decrease in SN-38 C_{max} with a trebling of irinotecan elimination clearance (Figure 1; $C_{max} = -0.712 * Cl_E + 35.017$; $R^2 = 0.366$, $P = 0.003$) and a nearly 60% decrease in SN-38 AUC with a trebling of irinotecan elimination clearance (Figure 2; $AUC_{0 \rightarrow 12.5\ h} = -3.782 * Cl_E + 166.139$; $R^2 = 0.502$, $P < 0.001$).

Discussion

The combination of irinotecan and docetaxel has been tested in a number of phase I clinical trials [13, 33–35] as well as in a phase II randomized study in NSCLC conducted in Japan [14] and other phase II trials in NSCLC [36, 37] and other solid tumors [38]. The design of our

Table 7 Pharmacokinetic parameters of SN-38 resulting from a 30 min irinotecan infusion

	Cycle 1	Cycle 2	*P*
Number of patients	11	11	–
Age, yr			
Mean	57.2	57.2	–
Standard deviation	8.8	8.8	
Body surface area, m^2			
Mean	1.80	1.80	–
Standard deviation	0.13	0.13	
Irinotecan dose, mg/m^2			
Mean	54.2	54.1	0.95
Standard deviation	7.0	5.4	
Time to maximum conc., t_{max}, h			
Mean	0.91	0.93	0.84
Standard deviation	0.32	0.16	
Maximum concentration, C_{max}, ng/ml			
Mean	24.0	19.8	0.05
Standard deviation	9.4	4.7	
Area under the curve from 0–12.5 h, $AUC_{0\rightarrow 12.5\ h}$, (ng•h/mL)			
Mean	107.9	85.3	0.01
Standard deviation	40.2	24.1	

study was based on the observations by Bleickardt et al. [13] who recommended for phase II study docetaxel 35 mg/m^2 and irinotecan 60 mg/m^2 on days 1 and 8 of a 21–day schedule. In the present study, we were able to add celecoxib 400 mg twice daily without the development of prohibitive toxicity. Diarrhea was the predominant toxicity, whereas the hematologic toxicity profile was, in general, mild or moderate. However, the toxicities we observed when irinotecan and docetaxel were used in combination with celecoxib appear more pronounced

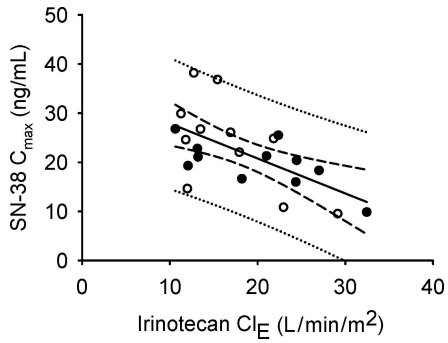

Figure 1. The relationship between peak SN-38 concentrations (C_{max}) and irinotecan elimination clearance in patients during cycle 1 (open circles) and cycle 2 (closed circles). The solid line represents the least squares linear regression line while the dashed lines represent its 95% confidence interval and the dotted line represents the 95% confidence lines for the data.

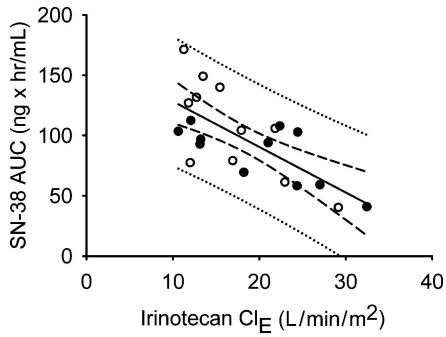

Figure 2. The relationship between the area under the SN-38 concentration versus time relationship from the beginning of the infusion until 12.5 h later ($AUC_{0\rightarrow 12.5\ h}$) and irinotecan elimination clearance in patients during cycle 1 (open circles) and cycle 2 (closed circles). The solid line represents the least squares linear regression line while the dashed lines represent its 95% confidence interval and the dotted line represents the 95% confidence lines for the data.

than the ones reported for comparable doses/schedules of irinotecan and docetaxel given alone in the study by Bleickardt et al. [13] The decrease in the AUC of SN-38 in Cycle 2 and the concomitant administration of irinotecan and celecoxib in that same cycle would have led to the expectation of an amelioration of diarrhea in the present study [26]. Nevertheless, diarrhea was commonly seen and was often severe in our patients. An increase in hematologic toxicities by the addition of celecoxib to chemotherapy was reported in a phase II randomized trial by Keresztes et al. [39]. In our study, an elderly patient developed grade 4 neutropenia that led to septic death. A difference in irinotecan or docetaxel pharmacokinetics compared to concurrent controls was not appreciable in this case and an idiosyncratic reaction was possible.

Contrary to more favorable experience in Japan [14], the activity of the combination of irinotecan and docetaxel in NSCLC seen in two recent phase II trials conducted in the U.S. was relatively low [36, 37]. It is hypothesized that the addition of a COX-2 inhibitor, as suggested by preclinical models [25, 26], will enhance the antitumor activity of chemotherapy. Johnson et al. demonstrated the biologic effect after treatment with celecoxib by showing decreased levels of PGE-M, the major urinary metabolite of PGE-2, in the urine and decreased levels of PGE-2 within the tumor [40]. A phase II trial of induction therapy in resectable NSCLC investigated the addition of celecoxib to carboplatin and paclitaxel with promising results [41]. However, a phase II randomized 2 by 2 design study did not show encouraging efficacy when celecoxib was added to the chemotherapy doublets irinotecan/docetaxel or irinotecan/gemcitabine in the second-line treatment of advanced NSCLC [39]. In the study reported here, in a small number of patients, the response rate and survival results with the triple combination of irinotecan, docetaxel, and celecoxib were promising.

Docetaxel and irinotecan do not seem to interact at a pharmacokinetic level [33–35]. However, there are no published data on the celecoxib effect on the pharmacokinetics of docetaxel or irinotecan. The docetaxel and irinotecan pharmacokinetics of both cycles of the present study (Table 6) are similar and consistent with pharmacokinetics reported previously [42–46]. The time to peak SN-38 concentrations is approximately one hour after commencing a 30 min infusion [30], as observed in the present study (Table 7). The decreases in SN-38 C_{max} and $AUC_{0\rightarrow 12.5\ h}$ in cycle 2 appear to be related to the increased clearance of irinotecan (Figures 1 and 2). The negative correlation between irinotecan elimination clearance and both the peak SN-38 concentrations and the area under the SN-38 concentration versus time relationships (Figures 1 and 2) may reflect increased metabolism of irinotecan to metabolites other than SN-38 with increased irinotecan elimination clearance or parallel changes in the elimination clearance of both irinotecan and its active metabolite. Data from the present study cannot address these possibilities.

The mechanism of the small increase in the elimination clearance of irinotecan during cycle 2 of the present study is unclear. A plausible explanation is that it relates to celecoxib. Celecoxib is metabolized primarily by CYP2C9, and to a lesser extent by CYP3A4, [47] and inhibits the metabolism of some drugs by CYP2D6 [48] but has not been reported to induce the metabolism of carboxylesterase or CYP3A4 substrates such as irinotecan or UDP-glucoronyl transferase substrates like SN-38. Another possibility is that repeated dosing of irinotecan affected its pharmacokinetics. However, Chabot and colleagues clearly demonstrated that the pharmacokinetics of both irinotecan and SN-38 were unaffected by repeated dosing of irinotecan [30]. Alternatively, it is possible that repeated dosing of docetaxel affected the pharmacokinetics of irinotecan. However, unlike its structurally related taxane paclitaxel, docetaxel does not induce CYP3A4 [49]. Finally, given the susceptibility of docetaxel to modulation of CYP3A4 activity [50], the fact that docetaxel elimination clearance is unchanged in the two cycles of this study militates against induction of CYP3A4 as an explanation of the increased clearance of irinotecan. Thus, the mechanism of the alteration of irinotecan pharmacokinetics we observed is obscure.

In conclusion, the addition of celecoxib to weekly irinotecan and docetaxel is feasible and associated with an acceptable toxicity profile and promising antitumor activity in NSCLC. Although the higher dose level in our study was not considered as maximum tolerated dose based on study definitions, we observed considerable toxicities at that dose level that we believe preclude the consideration of further dose escalation. Therefore, the recommended phase II doses are docetaxel 35 mg/m^2 and irinotecan 60 mg/m^2 on days 1 and 8, every 21 days, plus celecoxib 400 mg twice daily. The observed increase in the elimination clearance of irinotecan and decrease in the AUC of SN-38 in cycle 2 of the present study, although statistically significant, may not be sufficiently large to be of clinical significance.

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