Phase I Pharmacokinetic, Food Effect, and Pharmacogenetic Study of Oral Irinotecan Given as Semisolid Matrix Capsules in Patients with Solid Tumors

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ABSTRACT

Purpose: **To characterize the maximum-tolerated dose, recommended dose, dose-limiting toxicities (DLT), pharmacokinetic profile, and food effect of orally administered irinotecan formulated as new semisolid matrix capsules.**

Experimental Design: **Irinotecan was given orally in fasted patients once daily for 5 consecutive days and repeated every 3 weeks. Patients were randomly assigned to take the drug along with a high-fat, high-calorie breakfast for the administration at day 1 of the first or second cycle. Dosages tested were 70 and 80 mg/m^2/day.**

***Results*:** **Twenty-five patients received 101 cycles of therapy (median two cycles, range 1-15). During the first cycle, grade 3 delayed diarrhea and grade 3 fever were the DLTs at the dosage of 80 mg/m^2/day in three out of five patients. Hematologic and nonhematologic toxicities were mild to moderate. Exposure to the active metabolite SN-38 was relatively high compared with i.v. infusion, but no relevant accumulation was observed. Food had no significant effect on irinotecan pharmacokinetics. One confirmed partial remission and 10 disease stabilizations were observed in previously treated patients. No association was found between the UGT1A1*28 genotype and the risk of severe irinotecan-induced toxicity.**

Conclusions: **For oral irinotecan, a dose of 70 mg/m^2/day for 5 consecutive days every 3 weeks is recommended for further studies. Delayed diarrhea was the main DLT, similar to that observed with intravenously administered irinotecan. This study confirms that oral administration of irinotecan is feasible and may have favorable pharmacokinetic characteristics.**

INTRODUCTION

In clinical studies, irinotecan has shown single-agent activity against a spectrum of solid tumors (1), in particular, colorectal cancer (2–9). In two phase III studies, the combination of irinotecan with either bolus or infusional 5-fluorouracil plus folinic acid regimens for the first-line treatment of advanced and metastatic colorectal cancer was significantly superior over the corresponding control regimen in terms of response rate, time to progression and overall survival (10, 11). As a result, irinotecan has been approved for clinical use in advanced colorectal cancer given as an i.v. infusion, both as first-line therapy in combination with 5-fluorouracil and as salvage treatment in refractory disease (1).

Irinotecan requires bioactivation to form its biologically active metabolite SN-38 (12), which is subsequently detoxified to SN-38 glucuronide by the polymorphic enzyme UDP glucuronosyltransferase 1A1 (UGT1A1; refs. 13–15). In addition, irinotecan is metabolized by cytochrome *P*450 isoenzymes, CYP3A4 and CYP3A5, to form the metabolites APC and NPC (16, 17). Furthermore, the elimination pathways of irinotecan and SN-38 are partially mediated by membrane-localized, energy-dependent outward drug pumps, belonging to the superfamily of ATP-binding cassette (ABC) transporters, like MDR1 P-glycoprotein (ABCB1; refs. 18, 19).

We did this phase I study to evaluate the oral administration of irinotecan formulated as new semisolid matrix capsules in patients with refractory solid tumors. The objectives of this trial were (*a*) to determine the maximum-tolerated dose (MTD) and dose-limiting toxicities (DLT) of irinotecan when administered once daily for 5 consecutive days every 3 weeks, (*b*) to characterize the pharmacokinetics of irinotecan and its metabolite, SN-38, (*c*) to correlate the observed irinotecan-associated toxicity with genetic polymorphisms in genes involved in the pharmacokinetics of irinotecan, (*d*) to analyze the effect of food on the bioavailability, and (*e*) to evaluate preliminary antitumor activity.

MATERIALS AND METHODS

Eligibility Criteria. Patients with a histologically confirmed diagnosis of a malignant solid tumor refractory to

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conventional chemotherapy or for whom no effective therapy existed were eligible. Other eligibility criteria were similar to those described previously (20). Specific exclusion criteria included prior treatment with irinotecan, concomitant treatment with CYP3A4 inhibitors or inducers (wash-out period of at least 7 days since last intake), symptomatic brain metastases or leptomeningeal involvement, active inflammatory bowel disease, bowel (sub-)obstruction, chronic diarrhea, known chronic malabsorption or total colectomy, or other major abdominal surgery that might result in substantial alteration in transit or absorption of oral medication. The Institutional Ethical Boards approved the study protocol, and all patients gave written informed consent.

Treatment and Dose-Escalation. Irinotecan was supplied as semisolid matrix capsules, containing 5, 20, or 50 mg of the active drug substance, and these were stored at room temperature. The capsules also contained lecithin and lauroyl macrogolglycerides as inactive ingredients and a yellowish waxy mass. The drug was supplied by Aventis Pharma (Antony, France) in 30 mL bottles, containing 20 capsules of the 50 mg dosage form and 40 capsules of the 5 and 20 mg dosage form. Capsules were taken once a day in the morning for 5 consecutive days with about 180 mL of water after an overnight fasting for at least 4 hours before the daily oral dose and 1 hour following dosing, except for the first dose of the 5-day treatment as described below. Compliance with the scheduled treatment was assessed at the end of each cycle by counting the used and returned capsules of irinotecan.

Prophylactic antiemetics (either metoclopramide or a serotonin 5-hydroxytryptamine-3 receptor antagonist) were allowed 1 hour before irinotecan dosing and up to two additional times daily if necessary during all cycles of treatment, except for the first dose of the 5-day treatment of the first two cycles.

For irinotecan-induced delayed type diarrhea, high-dose loperamide therapy was administered orally consisting of a starting dose of 4 mg at the first episode of diarrhea, followed by 2 mg every 2 hours for at least 12 hours. The patient was allowed to stop loperamide only after a 12-hour diarrhea-free interval. If the diarrhea persisted for >48 hours despite the recommended loperamide treatment, a 7-day prophylactic oral antibiotic therapy (ciprofloxacine, 500 mg b.i.d.) was added in subsequent cycles.

The effect of food on the pharmacokinetics of irinotecan and metabolite SN-38 was assessed on the first day of the first two cycles. Patients were randomly assigned to take the study drug on day 1 of the first cycle in the fed state, and then in the fasted state on day 1 of the second cycle, or in the inverse sequence. The fed state included a Food and Drug Administration–standardized high-fat, high-calorie breakfast, containing ~20% of proteins, 60% of lipids, and 20% of carbohydrate (~1,000 kcal; ref. 21). In the fed condition for the first dose of the 5-day treatment of either cycle 1 or 2, capsules were taken within 5 minutes after completion of the breakfast, which was to be ingested within 30 minutes.

The starting dose of irinotecan, 70 mg/m^2 given once daily for 5 consecutive days, was based on a previous phase I study with a different formulation involving powder-filled capsules of irinotecan (22). Preclinical data indicated that the new formulation exhibited a similar absolute bioavailability of irinotecan. Hence, the starting dose was 10 mg/m^2/day below the MTD (80 mg/m^2/day) of the previous study. Further dose-escalations were based on the prior dose level toxicity. If no significant toxicity was observed at the previous dose level, the dose was escalated to the next higher dose level with 10 mg/m^2/day increments. A treatment cycle was defined as the 5 consecutive days of irinotecan administration plus the necessary time for the patient to recover from any toxicities. Cycles were to be repeated every 21 days. A minimum of three patients was to be treated at each dose level, with a minimum 1-week interval between the entry of the first patient and the entry of the subsequent two patients at any given dose level. Before escalation to the next dose levels, all three patients had to have received at least one treatment cycle. If one of three patients experienced DLT, three additional patients were entered at that dose level. The MTD was defined as one dose level below the dose that induced DLTs in two out of six patients during the first cycle. DLT was defined by the National Cancer Institute Common Toxicity Criteria (version 2.0) as grade 4 neutropenia lasting for ≥5 days, neutropenic fever (defined as grade 4 neutropenia with fever ≥38.5°C), neutropenic infection (defined as grades 3 to 4 neutropenia with ≥ grade 3 infection or documented infection), thrombocytopenia $<25 \times 10^9$ cells/L, ≥ grade 3 diarrhea, despite maximal loperamide support, ≥ grade 2 nausea or vomiting, failing maximal oral antiemetic therapy, or vomiting leading to discontinuation of the study drug intake ≥3 days, other ≥ grade 3 nonhematologic toxicities (except alopecia), and treatment delay due to toxicities attributed to the study drug for >2 weeks (23). Intrapatient dose-escalation was not allowed. The treatment was resumed when the neutrophil count had recovered to $\geq 1.5 \times 10^9$ cells/L, the platelet count to $\geq 100 \times 10^9$ cells/L, diarrhea was grade 0, and any other treatment-related toxicities were ≤ grade 1. Once the MTD was confirmed, at least 10 additional patients were to be enrolled at this dose level to ensure that this dose was feasible for phase II/III studies.

Treatment Assessment. Prior to therapy, a complete medical history was taken and a physical examination and clinical chemistry evaluation was done. Weekly evaluations included history, physical examination, and toxicity assessment. Complete blood cell counts were obtained twice weekly throughout cycle 1 and weekly thereafter, serum biochemistry was determined on days 8 and 15 of cycle 1 and weekly thereafter until recovery, at every subsequent cycle, it was determined once every 3 weeks. Response evaluation was done after every two cycles and assessed according to Response Evaluation Criteria in Solid Tumors (24). Patients were treated for at least two cycles of therapy unless disease progression or unacceptable toxicity was encountered.

Pharmacologic Analysis. For pharmacokinetic analysis, blood samples were taken immediately prior to drug administration, and at 0.5, 1.0, 1.5, 2, 3, 4, 6, 10, 18, and 24 hours after administration on days 1 and 5 of cycle 1, and on day 1 of cycle 2. Urine was collected prior to drug administration, and at time intervals: 0 to 10 and 10 to 24 hours after administration on days 1 and 5 of cycle 1, and day 1 of cycle 2. The concentrations of irinotecan and SN-38 in plasma and urine were quantified by a validated assay based on liquid chromatography with fluorescence detection. The lower limits of quantitation were 1 ng/mL in plasma for both compounds

and 100 and 25 ng/mL in urine for irinotecan and SN-38, respectively, using 50 μL aliquots.

Pharmacokinetic parameters were calculated by standard noncompartmental methods using WinNonlin software version 3.3 (Pharsight, Mountain View, CA), using standard equations. Nonpredicted accumulation was calculated as the ratio of area under the plasma concentration-time curve (AUC)-over-one-dosing-interval (24 hours) on day 5 over AUC-extrapolated-to-infinity on day 1.

Pharmacogenetic Data Analysis. Genomic DNA was extracted from 200 μL plasma using a total nucleic acid extraction kit on a MagnaPure LC (Roche, Mannheim, Germany). Variations in the ABCB1 (nucleotide 3435 C > T; ref. 25), CYP3A4 (CYP3A4*3, CYP3A4*17, and CYP3A4*18), CYP3A5 (CYP3A5*3) genes were analyzed by PCR-RFLP as previously reported (26, 27). For UGT1A1*28, a 35-cycle PCR (1 minute at 94°C, 1 minute at 60°C, and 1 minute at 72°C) was done using primers 5′-FAM-AAG TGA ACT CCC TGC TAC CT-3′ and 5′-AAA GTG AAC TCC CTG CTA CC-3′. The number of TA repeats in the 253-bp PCR product was determined using capillary electrophoresis on an ABI 310 (Applied Biosystems, Foster City; ref. 14, 15). Genetic polymorphisms were correlated with pharmacokinetic parameters obtained in fasted condition cycles in 23 patients.

Statistical Analysis. Pharmacokinetic parameters from the various treatment groups were compared statistically using SAS version 8.2 (SAS Institute, Inc., Cary, NC). To compare the pharmacokinetic parameters with the genetic polymorphisms a Kruskal-Wallis test (SPSS version 10.1, Paris, France) was used or a nonparametrical trend analysis (Stata version 7.0, Stata Corp., College Station, TX; ref. 15). All test results with a $P < 0.05$ were regarded as statistically significant.

RESULTS

Patient Characteristics. A total of 25 patients (10 male and 15 female), with a median age of 53 years (range, 31-76 years) were enrolled into the study (Table 1). All patients were eligible, treated and evaluable for toxicity and DLT. All patients, except four, had received prior chemotherapy and/or radiotherapy. A total of 101 cycles of treatment were given. Dose levels studied were 70 and 80 mg/m^2/day daily-times-five every 3 weeks. Twenty-one patients were assessable for response: three patients, who were not assessable for response, withdrew from the study before the first scheduled tumor reassessment, and one patient had a response which was not properly assessed. A total of 16 patients were evaluable for the food effect, whereas 9 patients were not evaluable for the food effect because of vomiting within 1 hour after the meal.

Dose-Limiting Toxicity. At the starting dose of 70 mg/m^2/day, three patients were treated. Because no DLT was observed, the next dose level of 80 mg/m^2/day was explored. After determination of a DLT consisting of grade 3 delayed diarrhea in one out of three patients, this cohort was expanded (Table 2). One additional patient at this dose level experienced grade 3 fever, regarded as a DLT because no infection was documented and other causes were not found. Subsequently, the dose of 70 mg/m^2/day was further explored with three additional patients. None of these three patients experienced DLT. Therefore, the recommended dose for phase II trials was set at 70 mg/m^2/day for 5 consecutive days every 3 weeks, and 14 additional patients were enrolled at this dose to fully assess feasibility and the food effect. One of these patients experienced DLT (i.e., grade 3 fatigue and grade 3 anorexia).

Hematologic Toxicity and Nonhematologic Toxicity. Hematologic and nonhematologic toxicities were mild to moderate (Tables 3 and 4, respectively). The majority of patients (68%) developed grade 1 or 2 anemia. The nonhematologic toxicities consisted mainly of nausea, vomiting, diarrhea, stomatitis, anorexia, and asthenia. Most patients (76%) experienced grade 1 to 2 nausea, and 13 out of 25 patients (52%) experienced grade 1 to 2 vomiting at both dose levels. Prophylactic antiemetics, either metoclopramide or serotonin antagonists, were used to manage nausea and vomiting. Because almost every patient experienced vomiting during the feasibility step (dose level, 70 mg/m^2/day), the use of oral 5-HT3-blockers was recommended from the first intake of oral irinotecan capsules. Grade 3 delayed diarrhea was observed in five (20%) patients at the 70 and 80 mg/m^2/day dosages, although this was not considered to be DLTs in three patients due to suboptimal supportive treatment with loperamide. Grades 1 to 2 diarrhea was noted in all other patients and was easily manageable with loperamide support, and if necessary, with use of ciproxin. Grade 1 and 2 anorexia was noted in seven (28%) patients, mostly at a dose level of 70 mg/m^2/day. Grade 3 anorexia was observed in

Table 1 Patient characteristics

Characteristic	No. of Patients
Total	25
Assessment	
For DLT	25
For food effect	16
For efficacy	21
No. of cycles per patient	
Median	2
Range	1-15
Gender, male/female	10:15
Age (y)	
Median	53
Range	31-76
WHO performance status	
0	7
1	17
2	1
Previous therapy	
Chemotherapy only	21
≤2 Prior regimens	13
≥3 Prior regimens	8
Radiotherapy only	1
Both	8
None	4
Tumor types	
Lung	3
Melanoma	5
Gastrointestinal tract, including:	6
esophageal, duodenal, colorectal	1 each
Gastric	3
Gynecologic	2
Unknown primary tumor	2
Genitourinary	1
Miscellaneous	6

Table 2 Dose-escalation scheme and DLT

Dose level (mg/m²/d)	No. of patients: *n*	With one dose reduced	With one cycle delayed	No. of cycles	Patients with DLT: First cycle	All cycles	DLT events at first cycle
70	20	2*	2	89	1 of 20	3 of 20	Grade 3 asthenia and grade 3 anorexia (n = 1)
80	5	2†	2	12	2 of 5	2 of 5	Grade 3 diarrhea (n = 1); and grade 3 fever (n = 1)
Total	25	4	4	101			

*Dose reduction from 70 to 60 mg/m²/day.
†Dose reduction from 80 to 70 mg/m²/day.

one patient at a dose level of 80 mg/m²/day of the subsequent cycle, which coincided with inadequate antiemetic treatment with severe nausea and vomiting. Grade 1 to 2 asthenia was observed in 11 (44%) patients at both dose levels. Four patients experienced mild alopecia (grade 1) and one patient had moderate alopecia (grade 2). Finally, a mild cholinergic syndrome was observed in two patients (one in cycle 1 and the other in cycle 2). No patient received prophylactic atropine for this adverse event.

Pharmacokinetics. After oral administration, irinotecan and SN-38 achieved peak plasma concentrations within 2 to 4 hours (Table 5). The mean AUC accumulation ratio on day 5 versus day 1 for irinotecan was 117% (90% confidence interval, 86-160%; P = 0.40), suggesting no accumulation of the parent drug. For SN-38, this ratio was 85% (90% confidence interval, 61-119%; P = 0.43). For the entire population, the mean AUC ratio of SN-38-to-irinotecan was ~13%. This metabolic ratio was dose-independent, and substantially higher than the ratio of about 3% measured after i.v. administration (28). This indicates extensive presystemic biotransformation of irinotecan (i.e., in the gastrointestinal tract and/or during first-pass extraction). As expected, the 24-hour urinary excretion of both irinotecan and SN-38 was low, and accounted for <3% and 1% of the dose, respectively. The mean AUC ratio for fed-to-fasting in the 16 evaluable patients was 1.13 for irinotecan (95% confidence intervals, 0.86-1.48; P = 0.44) and 1.17 for SN-38 (95% confidence intervals, 0.88-1.55; P = 0.36), indicating no change in absorption of irinotecan even after a high-fat meal. The use of other oral comedication was recorded for each patient, and no noticeable interactions were noted (data not shown).

Pharmacogenetics. Five single nucleotide polymorphisms and one dinucleotide repeat were analyzed in four genes of putative relevance for the irinotecan absorption and disposition. One patient had an extra TA repeat in both alleles [$(TA)_7TAA$] of the UGT1A1 gene promoter (UGT1A1*28), whereas another patient had one TA repeat less in one of both alleles (TA_5/TA_6). The genotype frequency for TA_6/TA_6 (n = 13) and TA_6/TA_7 (n = 8) were comparable with previously reported estimates in European Caucasians (29). Although the dose-normalized peak concentration of SN-38 in the fasted condition was significantly affected by UGT1A1*28 genotype (P = 0.026), this was not associated with increased toxicity (i.e., severe diarrhea and/or neutropenia) in patients carrying the variant allele (data not shown). No statistically significant associations with SN-38 pharmacokinetic parameters were observed in a total of 23 patients with variant alleles in CYP3A5*3 and ABCB1 3435\C > T (P > 0.23). The $AUC_{0\text{-}24h}$ of irinotecan of the CYP3A4*1/*3 heterozygous individual was comparable with the $AUC_{0\text{-}24h}$ of irinotecan of CYP3A4*3 wild-type carriers, 379 versus 582.92 (SD ± 302.06) ng/h/mL, respectively. No CYP3A4*17 (i.e., associated with impaired CYP3A4 activity) nor CYP3A4*18 (i.e., associated with enhanced CYP3A4 activity) individuals were identified (30).

Efficacy. A 69-year-old male with metastatic colorectal cancer achieved a confirmed partial response lasting 4 months. A total of 10 patients had disease stabilization for 6 (n = 5), 12 (n = 2), 18 (n = 2), and 24 weeks (n = 1). Ten patients had progressive disease after two cycles of chemotherapy and one patient had early progressive disease.

DISCUSSION

The present phase I study indicates that oral irinotecan, formulated as a semisolid matrix capsules, administered daily for 5 consecutive days every 3 weeks, is feasible and safe. The principal DLT of this oral regimen was nonhematologic and consisted of delayed diarrhea and fever observed at a dose level of 80 mg/m²/day. The pattern of delayed diarrhea is similar to that associated with i.v. administration of irinotecan and could be relieved with loperamide (31). It has been suggested that the

Table 3 Hematologic toxicity (worst grade per patient)

Dose level (mg/m²/d)	No. of patients	No. of cycles	Anemia: Grades 1	2	3-4	Leukocytopenia: Grades 1	2	3	34	Neutropenia: Grades 1	2	3	4	Thrombocytopenia: Grades 1	2	3-4
70	20	89	7	6	0	1	2	0	0	1	0	1*	0	0	0	0
80	5	12	0	2	0	1	1	0	0	0	2	0	0	0	1	0

*Not considered a DLT at subsequent cycle according to protocol definitions.

Table 4 Nonhematologic toxicity (worst grade per patient)

			Diarrhea			Nausea			Vomiting			Stomatitis			Anorexia			Asthenia		
			Grades																	
Dose level (mg/m²/d)	No. of patients	No. of cycles	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
70	20	89	11	7	2*†	12	5‡	0	7	3‡	0	1	0	0	4	2	1*	5	4	2§
80	5	12	1	1	3*‖	1	1‡	3‡	1	2‡	2‡	0	1	0	1	0	1¶	1	3	0

*Considered a DLT at first cycle in one patient.
†Not considered a DLT at first cycle in one patient due to insufficient supportive treatment with loperamide.
‡Not considered a DLT at first or subsequent cycles due to insufficient supportive treatment with antiemetics.
§Considered DLTs at first and subsequent cycle.
‖Not considered DLTs at first and subsequent cycles in two patients due to insufficient supportive treatment with loperamide.
¶Not considered a DLT at subsequent cycle.

delayed diarrhea after irinotecan administration results from the direct effect of SN-38 on the intestinal mucosa (31). At a daily dose of 80 mg/m^2/day, two of five patients experienced grade 3 diarrhea and grade 3 fever, which, according to the predefined criteria for the MTD, precluded further dose-escalation. Hematologic toxicity was mild to moderate and did not result in DLT in the first cycle. The recommended dose is 70 mg/m^2/day for 5 consecutive days every 3 weeks, and this dose level was tested for feasibility and food effect. Nonhematologic toxicities attributed to oral irinotecan treatment, including vomiting, stomatitis, anorexia, asthenia, alopecia, and symptoms associated with mild cholinergic syndrome, were similar to historical experience with i.v. irinotecan (1).

Substantial interpatient variability in pharmacokinetics of irinotecan and SN-38 was observed in our study, which is in agreement with other phase I studies of oral irinotecan (20, 22, 32–35), and can be linked to the complex pharmacology of the drug. After absorption of oral irinotecan, both the parent drug and SN-38 achieved peak plasma concentrations within 2 to 4 hours of administration of the drug. There was no statistically significant accumulation of SN-38 or irinotecan, and there was no statistically significant influence of food on the pharmacokinetics of irinotecan and SN-38. The Food and Drug Administration–defined standard diet used in this investigation is an extreme of the normal conventional daily diets most people would take, suggesting that normal daily diets would have no expected effects on the pharmacokinetics of irinotecan given orally. It is noteworthy, however, that small changes in the pharmacokinetic profile may have been missed simply due to a biased sample estimate.

Furthermore, we found that the metabolic ratio, defined as the AUC of SN-38-to-irinotecan was higher with oral administration compared with i.v. administration of irinotecan (13% versus 3%; ref. 28), suggesting extensive presystemic metabolism of irinotecan. This is consistent with the high expression levels of irinotecan-converting carboxylesterases in the gastrointestinal tract and liver (36). Presystemic metabolism of irinotecan was also observed in the other phase I studies with irinotecan administered either as a solution with CranGrape juice (20), as powder-filled capsules (22, 32–34), or as semisolid matrix capsules (35). The results of the six phase I

Table 5 Mean ± SD (CV%) pharmacokinetic parameters of irinotecan and SN-38

		Irinotecan			SN-38		
		Cycle 1		Cycle 2	Cycle 1		Cycle 2
Parameters	No. of patients	Day 1	Day 5	Day 1	Day 1	Day 5	Day 1
Dose (70 mg/m²/d)							
C_{max} (ng/mL)	20*	81.3 ± 38.3 (47)	136 ± 88 (65)	101 ± 86 (86)	10.7 ± 6.0 (56)	10.0 ± 6.2 (62)	9.3 ± 4.9 (53)
Median T_{max}, h (range)		3 (1-6)	2 (0.5-6)	3 (1-6)	3 (1-6)	1.5 (1.5-3)	3 (1.5-4)
$AUC_{(0\text{-}24h)}$ (ng/h/mL)		601 ± 241 (40)	1,029 ± 814 (79)	689 ± 493 (72)	69.8 ± 52.0 (75)	77.8 ± 53.5 (69)	66.3 ± 49.3 (74)
AUC (ng/h/mL)		735 ± 400 (54)	1,181 ± 940 (80)	758 ± 542 (71)	89.6 ± 55.9 (62)†	81.1 ± 50.5 (62)†	93.9 ± 68.1 (73)
$T_{1/2}$ (h)		8.1 ± 4.0 (50)	8.3 ± 2.1 (25)	6.8 ± 1.7 (25)	10.6 ± 13.3 (125)†	16.8 ± 21.6 (128)†	11.6 ± 11.8 (102)
Metabolic ratio		—	—	—	0.14 ± 0.08 (57)	0.08 ± 0.04 (46)	0.20 ± 0.22 (113)
Dose (80 mg/m²/d)							
C_{max} (ng/mL)	5‡	86 ± 48.0 (56)	116 ± 61 (53)	78.0 ± 79.3 (102)	6.3 ± 3.4 (53)	6.2 ± 2.2 (36)	5.8 ± 3.7 (64)
Median T_{max}, h (range)		3 (0.5-6)	2 (2-4)	4 (3-6)	3 (2-3)	3 (1.5-6)	3 (2-4)
$AUC_{(0\text{-}24h)}$ (ng/h/mL)		656 ± 223 (34)	864 ± 562 (65)	718 ± 560 (78)	46.2 ± 29.2 (63)	49.8 ± 31.4 (63)	41.2 ± 38.1 (92)
AUC (ng/h/mL)		794 ± 335 (42)	1,003 ± 652 (65)	792 ± 600 (76)	88.7 ± 78.9 (89)	54.4 ± 25.5 (47)§	70.6 ± 31.1 (44)§
$T_{1/2}$ (h)		8.7 ± 3.6 (41)	9.0 ± 1.4 (16)	6.9 ± 0.7 (10)	18.2 ± 20.2 (111)	8.9 ± 8.7 (97)§	5.2 ± 1.8 (34)§
Metabolic ratio		—	—	—	0.11 ± 0.09 (80)	0.08 ± 0.08 (101)	0.07 ± 0.01 (17)

NOTE. $AUC_{0\text{-}24h}$ corresponding to $AUC_{0\text{-}t}$ on day 1 at cycle 1 and cycle 2.
Abbreviations: C_{max}, peak plasma concentration; T_{max}, time to C_{max}; $T_{1/2}$, half-life of terminal phase.
*PK parameters were calculated in 16 out of 20 patients on day 1 at cycle 2.
†$T_{1/2}$ and AUC were calculated in 19 patients.
‡PK parameters were calculated in three out of five patients on day 1 at cycle 2.
§$T_{1/2}$ and AUC were calculated in four patients; metabolic ratio is defined as the AUC ratio of SN-38-to-irinotecan.

studies of orally administered irinotecan are summarized in Table 6.

In contrast with our study, the preliminary results of another phase I study of oral irinotecan formulated as semisolid matrix capsules revealed an MTD of 60 mg/m^2/day daily-times-five every 3 weeks (35). A mean (± SD) bioavailability of orally administered irinotecan of 25 ± 23% was found. Furthermore, the AUC of the active metabolite SN-38 following oral administration of irinotecan was 50% of the value from an equivalent i.v. dose, implicating presystemic metabolism of irinotecan as well (35). In addition, over a 5-day dosing interval, orally administered irinotecan produced substantially less systemic exposure to parent drug compared with i.v. treatment on the weekly times-four every 6 weeks schedule, whereas maintaining comparable exposure to SN-38, suggesting that the oral route could be associated with less irinotecan-related toxicity (35).

In a phase I study of irinotecan given as a 5 day continuous infusion in 36 patients, the recommended dose was 30 mg/m^2/day, with diarrhea as DLT at a dose of 40 mg/m^2/day (37). Large variations in clearance and half-lives of irinotecan at the different dose levels (range 5-40 mg/m^2/day) were documented (37), and in this study, the calculated mean metabolic ratio was only 3% to 7%. In another phase I study of irinotecan given as a continuous low-dose infusion for 14 days, the recommended dose was 10 mg/m^2/day times-14 every 3 weeks (38). Diarrhea was a cumulative toxicity if doses were repeated at doses >10 mg/m^2/day or for >17 days (38). The dose intensity of this schedule was ~40% of the dose intensity obtained with 90 minutes i.v. infusion of irinotecan (350 mg/m^2 once every 3 weeks). The mean metabolic ratio was 16% and was constant over the dose range tested. In comparison with the short infusion of irinotecan, it was shown that prolonged exposure to low doses of irinotecan resulted in more efficient conversion of irinotecan in SN-38 (38). Furthermore, the study showed that there was no saturation of the carboxylesterase or UGT enzyme systems during the 14 to 21 days of infusion of irinotecan at the doses tested (38), in contrast with *in vivo* experiments, which showed nonlinear pharmacokinetics of irinotecan as a result of decreased metabolic clearance reflected by carboxylesterase saturation (39, 40).

As mentioned earlier, the cytotoxicity of topoisomerase I inhibitors is made more apparent by exposure time- rather than concentration-dependent factors (41). Schedule dependency as a result of the cell cycle specificity of the topoisomerase I inhibitors is more dependent on pharmacodynamics rather than pharmacokinetics (38). The present study revealed that at the recommended dose, the cumulative AUC of irinotecan is 69% of that after continuous low-dose (10 mg/m^2/day) infusion of irinotecan for 14 days (38), and about 25% of that after 350 mg/m^2 every 3 weeks (42), or 145 mg/m^2 weekly for 4 weeks every 6 weeks (43). However, for SN-38, the mean cumulative AUC was ~70% of both the slow infusion and single high-dose infusion schedules and 50% of that in the weekly regimen. It therefore seems that both slow infusion and oral administration result in more efficient conversion of irinotecan into SN-38, which is reflected in the higher metabolic ratios observed with these schedules.

In our study, no correlation was noted between irinotecan-associated toxicity and the UGT1A1*28 genotype, in contrast to previous observations (15, 44). However, these data need to be interpreted with caution, because the limited number of patients in this study may obscure such relationships. Nevertheless, there was a statistically significant trend (P = 0.026) showing that a smaller number of dinucleotide repeats in the promoter correlate to reduced peak concentrations of SN-38, and therefore to higher levels of activity of UGT in accordance with a previous study (45). Furthermore, no statistic significance between the genetic polymorphisms of CYP3A5*3 and ABCB1 3435 C > T and SN-38 pharmacokinetic parameters (P > 0.23) were found, in accordance with the results of a previous study on i.v. irinotecan metabolism and genetic polymorphisms (28).

This study confirms that oral administration of irinotecan, formulated as semisolid matrix capsules, is safe and feasible and may have improved pharmacokinetic characteristics with food having no statistically significant effect on drug absorption. Sustained drug exposure could be achieved in the formulation without the disadvantages of i.v. delivery and thus with greater convenience for patients. A phase II study of this oral formulation of irinotecan in patients with metastatic breast cancer has been scheduled.

Table 6 Phase I studies with orally administered irinotecan

Oral substance	Schedule (dose range)	No. of patients	DLT events	Recommended dose	Reference
Solution of IV irinotecan mixed in CranGrape juice	Once daily × 5 q3w (20-100 mg/m^2/d)	28	Grade 4 diarrhea	Patients < 65 y, 66 mg/m^2/d × 5 q3w; patients = 65 y, 50 mg/m^2/d × 5 q3w	(20)
Powder-filled capsules	Once daily × 5 q3w (30-90 mg/m^2/d)	46	Neutropenic infection, grade 3 diarrhea, grade 4 vomiting	80 mg/m^2/d × 5 q3w	(22)
Powder-filled capsules	Once daily × 5 q3w (30-60 mg/m^2/d)	19	Grade 3 nausea, vomiting, grade 3 diarrhea, febrile neutropenia	50 mg/m^2/d × 5 q3w	(32)
Powder-filled capsules	Once daily × 14 q3w (7.5-40 mg/m^2/d)	34	Grade 4 diarrhea, grade 3 vomiting	30 mg/m^2/d × 14 q3w	(33)
Powder-filled capsules	Once daily × 14 q3w (7.5-40 mg/m^2/d)	19	Grade 3-4 vomiting, grade 3 diarrhea	30 mg/m^2/d × 14 q3w	(34)
Semisolid matrix capsules	Once daily × 5 q3w (50-70 mg/m^2/d)	43	Grade 3-4 diarrhea, grade 4 neutropenia	60 mg/m^2/d × 5 q3w	(35)

Abbreviations: q, every; w, weeks.

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