Cancer Chemother Pharmacol (2006) 58: 165–172
DOI 10.1007/s00280-005-0138-9

ORIGINAL ARTICLE

**Henry C. Pitot · Alex A. Adjei · Joel M. Reid
Jeff A. Sloan · Pamela J. Atherton · Joseph Rubin
Steven R. Alberts · Barbara A. Duncan · Louis Denis
Larry J. Schaaf · Donghua Yin · Amarnath Sharma
Patrick McGovren · Langdon L. Miller
Charles Erlichman**

A phase I and pharmacokinetic study of a powder-filled capsule formulation of oral irinotecan (CPT-11) given daily for 5 days every 3 weeks in patients with advanced solid tumors

Received: 29 June 2005 / Accepted: 10 October 2005 / Published online: 19 November 2005

Abstract Purpose: Intravenous (i.v.) irinotecan is a cytotoxic topoisomerase I inhibitor with broad clinical activity in metastatic colorectal cancer and other tumors. The development of an oral formulation of irinotecan could enhance convenience and lessen the expense of palliative irinotecan delivery. This phase I study evaluated the dose-limiting toxicities (DLT), maximum tolerated dose (MTD), and pharmacokinetics (PK) of irinotecan given as a powder-filled capsule (PFC) daily for 5 days every 3 weeks. Patients and methods: Patients with advanced solid tumors received escalating doses of oral irinotecan daily for 5 days every 3 weeks. Plasma samples were collected following the first and fifth doses of irinotecan during Cycle 1 to determine the PK of irinotecan and its major circulating metabolites: SN-38, SN-38G, and APC. Results: 20 patients (median age 61.5 years, range 40–75; M/F 12/8; ECOG PS 0 = 5, 1 = 11, 2 = 4) received oral irinotecan at dose levels of 30 ($n = 3$), 40 ($n = 3$), 50 ($n = 6$), and 60 ($n = 8$) mg/m^2/day. Of the eight patients enrolled at 60 mg/m^2, three patients experienced DLT (≥ grade 3) consisting of nausea (three patients), vomiting (three patients), diarrhea (two patients), and febrile neutropenia (two patients) for which all the three patients required hospitalization. Treatment of six patients at the 50-mg/m^2 dose level resulted in no DLT. Other toxicities observed include abdominal pain, alopecia, anorexia, and asthenia. After oral administration, irinotecan was rapidly absorbed into systemic circulation and converted to the active metabolite SN-38. Increasing dose levels resulted in a dose-dependent increase in mean exposure parameters (Cmax and AUC) of irinotecan and metabolites. Systemic exposure parameters (Cmax and AUC_{0-24}) of irinotecan and SN-38 were comparable between days 1 and 5. The extent of conversion from irinotecan to SN-38 was approximately threefold higher after the oral administration compared to that previously observed after i.v. administration. The exposure parameters of irinotecan or SN-38 are of limited value in predicting severity of Cycle 1 toxicities in the twofold dose range evaluated. Conclusion: Daily oral administration of irinotecan as the PFC formulation for 5 days every 3 weeks can safely deliver protracted exposure to SN-38, with the MTD of 50 mg/m^2/d.

Keywords Oral irinotecan · Pharmacokinetics · Advanced solid tumors · Phase I

Supported in part by Pharmacia and National Cancer Institute Grants U01-CA69912, M01-RR00585, and CA15083-26

H. C. Pitot (✉) · A. A. Adjei · J. Rubin · S. R. Alberts
C. Erlichman
Division of Medical Oncology, Mayo Clinic College of Medicine,
200 First Street SW, Rochester MN 55905, USA
E-mail: pitot.henry@mayo.edu
Tel.: +1-507-2844718
Fax: +1-507-5380823

J. M. Reid
Division of Oncology Research, Mayo Clinic College of Medicine,
Rochester MN 55905, USA

J. A. Sloan · P. J. Atherton
Section of Biostatistics, Mayo Clinic College of Medicine,
Rochester MN 55905, USA

L. J. Schaaf · P. McGovren · L. L. Miller
Pharmacia, Peapack, NJ, USA

B. A. Duncan · L. Denis · D. Yin · A. Sharma
Pfizer Inc, New London, CT, USA

Introduction

Camptothecin is a plant alkaloid obtained from the Chinese tree *Camptotheca acuminata*. Camptothecin and its derivatives are potent inhibitors of topoisomerase I (topo-1) [1]. Irinotecan hydrochloride (irinotecan;

Camptosar®) is a semi-synthetic derivative of camptothecin that has broad clinical activity. Intravenous (i.v.) administration of irinotecan with 5-fluorouracil and leucovorin is considered one of the standard therapies for stage IV colorectal carcinoma [2, 3]. The development of an oral form of irinotecan has the obvious merits of enhancing convenience and of reducing expense of drug delivery in this palliative setting. A previous clinical trial was performed to test an orally administered formulation of i.v. irinotecan mixed with a CranGrape® drink [4]. Irinotecan doses were given once per day for five consecutive days, and treatment courses were repeated every 21 days. The toxicity profile of the i.v. formulation given orally was generally comparable to that observed in patients receiving i.v. therapy. These toxicities included gastrointestinal side effects (nausea, vomiting, and diarrhea) and myelosuppression—primarily neutropenia. Dose-limiting toxicities (DLTs) of delayed diarrhea and neutropenia were noted at 50 mg/m^2/day in patients ≥65 years old and at 66 mg/m^2/day in patients <65 years old. Irinotecan has been formulated as a powder-filled capsule (PFC). Initial preclinical studies demonstrated that the variability in irinotecan bioavailability with the PFC formulation seemed less than that observed when the i.v. irinotecan solution was administered orally. Based on these data, a starting dose of 30 mg/m^2/day for 5 days [60% of the maximum tolerated dose (MTD) for patients ≥65 years old] was selected for the current trial.

We performed a phase I study to determine MTD and DLT of irinotecan when administered orally in a PFC formulation once per day for 5 consecutive days every 3 weeks. We also characterized the pharmacokinetics (PK) of irinotecan and its metabolites SN-38, SN-38 glucuronide (SN-38G) and APC, and sought evidence of antineoplastic activity of irinotecan with this formulation.

Material and methods

Patients

All patients participating in this study had histologic confirmation of a nonlymphoid, nonleukemic malignancy for which there was no known standard therapy that was either curative or capable of extending life expectancy. Additional eligibility criteria at study entry consisted of: Eastern Cooperative Oncology Group performance status ≤ 2, age ≥18 years, absolute neutrophil count ≥2,000/mm^3, platelet count ≥150,000/mm^3, hemoglobin level ≥9.0 gm/dl, serum creatinine within the institutional limits of normal, direct bilirubin within the institutional limits of normal, aspartate aminotransferase (SGOT) ≤ 3.0 times the institutional upper limit of normal (may be ≤ 5.0 times if liver involved with tumor), oral intake ≥1,200 calories/day, and predicted life expectancy >12 weeks. Written informed consent was obtained from all patients prior to the study entry. The study was approved by the Mayo Foundation Institutional Review Board.

Patient exclusion criteria included: prior chemo or biological therapies within 4 weeks of study entry; any prior mitomycin C or nitrosourea chemotherapy; prior high-dose chemotherapy and progenitor cell transplant; prior radiation therapy to $>10\%$ of the bone marrow; active inflammatory bowel disease, significant bowel obstruction, chronic malabsorption or other major abdominal surgery resulting in alteration in transit or absorption of oral medication; ingestion of antacids, H2 antagonists, proton pump inhibitors, sucralfate, or anticonvulsants within the previous week; pregnancy or lactation; unwillingness to practice adequate contraception by men or women of child-bearing age; uncontrolled hypertension or cardiac arrhythmia; unstable angina; symptomatic congestive heart failure; myocardial infarction within the previous 6 months; central nervous system metastases or leptomeningeal disease; known HIV positivity or AIDS-related illness; active infections; or other severe nonmalignant systemic diseases which, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

Study design

Irinotecan hydrochloride trihydrate (irinotecan) was supplied and formulated by Pharmacia (Peapack, NJ, USA) as a PFC. The capsules contained 5, 20 or 50 mg of active irinotecan drug, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate as excipients. The capsules were administered once daily for 5 consecutive days with treatment repeated every 3 weeks. Irinotecan was administered in the morning with water and patients fasted for at least 4 h before and for 1 h after dosing. The starting dose of irinotecan was 30 mg/m^2/day for 5 days every 3 weeks with planned dose escalation to 40, 50, 60, 70, 80, and 90 mg/m^2 dose levels. A standard ''cohorts of three'' phase I clinical design was employed in this trial [5].

Prestudy evaluations included: a complete history and physical exam including height, weight, performance score, and tumor measurement; complete blood count; serum chemistries; chest X-ray; urinalysis; electrocardiogram; serum tumor markers; indicator lesion imaging (MRI, CT scan, or ultrasound); and a serum pregnancy test in women of child-bearing potential. All patients underwent an interim history and physical examination prior to each subsequent cycle of therapy. Complete blood counts were performed twice weekly during cycle 1 and then weekly for subsequent cycles. Serum chemistry tests were performed weekly during the interval between treatments. The first cycle of therapy for each patient was administered as an inpatient at the Mayo General Clinical Research Center to expedite PK sampling, and subsequent cycles were administered as an outpatient.

Definitions of DLT included: grade 4 neutropenia for ≥5 days, neutropenic fever or infection, grade 4 thrombocytopenia, grade ≥3 diarrhea, nausea or vomiting despite maximal antidiarrheal or antiemetic support, ≥ grade 3 nonhematologic toxicity attributed to irinotecan therapy, failure to complete the first 5 days of irinotecan therapy due to drug-related toxicities, or failure to recover from toxicities (≤ grade 1) to be eligible for retreatment with irinotecan within 36 days of the start of Cycle 1.

Toxicities were evaluated using National Cancer Institute Common Toxicity Criteria (NCI CTC). The DLTs were evaluated for the first cycle only. The MTD was defined as the dose level which, at most, one of six patients experienced DLT and the next higher dose level produced DLT in at least two of six patients. Once DLT was observed in two of six patients at a given dose level, three more patients were treated at the previous dose level to better characterize the MTD.

Prophylaxis for nausea and vomiting consisted of prochlorperazine 5–10 mg orally 3–4 times per day. With persistent nausea or vomiting, ondansetron 8 mg orally up to 1 h before irinotecan dosing and up to two additional doses daily could be prescribed. Loperamide was given for any signs of diarrhea during the treatment with oral irinotecan. Patients were instructed to take 4 mg at the first sign of loose stool, then 2 mg every 2 h around the clock until diarrhea-free for at least 12 h. Patients were allowed to take 4 mg every 4 h at night. Other supportive care consisted of oral or sublingual hycosamine for symptoms of early cholinergic syndrome.

Sample collection

Serial blood samples of 7 mL were collected for PK analysis immediately before (time 0), and 15, 30, 60, 90 min and 2, 3, 4, 6, 8, 10, and 24 h after the first and fifth doses. An additional blood sample was collected at 48 h after the fifth dose. Blood specimens were drawn from a peripheral vein into heparinized tubes and immediately cooled in an ice water slurry. After centrifugation, plasma was transferred to plastic tubes, frozen, and stored at $\leq -30°C$ until analysis.

Assay methods

Plasma samples were assayed for irinotecan, SN-38, total SN-38, and APC concentrations using validated, sensitive and specific isocratic high-performance liquid chromatography (HPLC) methods [6]. The lower limits of quantitation (LLOQ) were 1.28, 0.48, 0.37, and 0.96 ng/mL for irinotecan, SN-38, total SN-38, and APC, respectively. The inter-day coefficient of variation (CV%) was less than 11% for all four analytes. The assay precision, expressed as CV% of the estimated concentrations of quality control samples, was less than 10% over the linear concentration range for each of the analytes.

Calculation of PK parameters

Irinotecan doses were converted to anhydrous-free base equivalents in the PK analysis. Plasma concentration–time data of irinotecan, SN-38, SN-38G, and APC were analyzed by noncompartmental methods [7] using WinNonlin V.3.2 (Pharsight®, Mountain View, CA, USA). As a measure of the extent of irinotecan metabolism to SN-38, the relative extent of conversion (REC) was calculated as the ratio of SN-38 AUC and irinotecan AUC. The relative extent of SN-38 metabolism to SN-38G (relative extent of glucuronidation, REG) was calculated as the ratio of SN-38G AUC and SN-38 AUC. The relative extent of conversion from irinotecan to APC (relative extent of oxidation, REO) was defined as the ratio of APC AUC and irinotecan AUC. For the calculation of REC, REG and REO, AUC0–∞ values from the first dose and AUC0–24 values from the fifth dose were used. REC and REG values obtained in this trial are compared to those derived from a prior phase II, single-agent, i.v. irinotecan trial in metastatic colorectal cancer patients who had failed prior 5-fluorouracil (FU)-containing regimens [18]. REO values obtained in this trial are compared to those from a ^{14}C-labeled irinotecan study in 8 solid-tumor patients with "adequate" organ function [6]. The mass-based AUC values (ng*h/mL) were used in calculation of the AUC ratios for the present and prior studies.

Statistical analysis

The safety, toxicity, and PK data were analyzed primarily in a descriptive fashion. The number and severity of toxic incidents indicated the level of tolerance for oral irinotecan in the treatment of advanced cancer. Hematological toxicity measures of neutropenia, leukopenia, and thrombocytopenia were assessed using the continuous variables as outcomes measures (primarily nadir and percentage change from baseline values) as well as categorization via NCI CTC standard toxicity grading. Nonhematological toxicities were evaluated via the ordinal NCI CTC standard toxicity grading only. Frequency distributions and other descriptive measures formed the basis of the analysis of these variables.

Results

A total of 21 patients consented to study participation. One patient did not receive treatment due to small bowel obstruction. Patient characteristics for the 20 patients receiving oral irinotecan are shown in Table 1. A total of 82 assessable cycles of irinotecan were administered over 4 different dose levels (Table 2). The median number of

Table 1 Patient characteristics ($n = 20$)

Number of patients treated	20
Gender (M/F)	12/8
Median age (range)	61.5 years (40–75)
ECOG performance status	
0	5
1	11
2	4
Tumor type	
Colorectal	7
Upper gastrointestinal	3
Lung	3
Pancreas	2
Unknown	2
Other (appendix, melanoma, hepatocellular)	1 each
Prior therapy	
Chemotherapy	17
#Regimens (1/2)	13/4
Surgery	14
Radiation therapy	5
Other (hormone, immuno)	1 each

Table 2 Dose levels

Dose (mg/m^2)	No. of patients	No. of cycles
30	3	19
40	3	10
50	6	16
60	8	37

treatment cycles was 3.5 (range: 1–13) and the median duration of treatment was 10.9 weeks (range: 2.7–42.3).

Toxicity

Dose-limiting toxicity was observed in three patients at 60-mg/m^2 dose level. One patient (a 62-year-old male) with advanced esophageal adenocarcinoma experienced grade 3 nausea, diarrhea, and vomiting. The patient was also unable to recover from the toxicities in time for retreatment. A second patient (59-year-old male) with advanced appendiceal adenocarcinoma and peritoneal metastases had an episode of neutropenic fever along with grade 3 nausea and grade 2 diarrhea. The third patient (a 72-year-old female) at the 60-mg/m^2 level had advanced colon carcinoma and also experienced a neutropenic sepsis, grade 3 nausea, vomiting, and grade 2 diarrhea and dehydration. Because of the severity of the side effects, the patient declined further oral irinotecan treatment. All three patients required hospitalization during their first cycle of protocol treatment. Treatment of a total of six patients at the 50-mg/m^2 dose level yielded no cycle 1 DLTs. Hematological toxicity for all dose levels and patients is shown in Table 3. There were no episodes of grade 3 or 4 thrombocytopenia.

The principle nonhematological toxicities were gastrointestinal (Fig. 1). The majority of patients experienced some amount of diarrhea, nausea, and/or vomiting during the protocol treatment. Though abdominal pain was a prominent adverse event in this trial, typical symptoms of early cholinergic syndrome (lacrimation, diaphoresis, flushing, or abdominal cramping) were mild in most patients. Patients were observed for 24 h after the first and fifth doses of oral irinotecan in the first cycle for cholinergic symptoms. Eleven patients (55%) reported at least 1 cholinergic symptom; nine (45%) reported the symptoms during the first day and seven (35%) reported symptoms on day 5. Most patients reported the symptoms as mild; however, two patients experienced severe symptoms on day 5, one experienced severe flushing and sweating, and another reported severe ''other'' symptoms. Both patients were treated at the 60-mg/m^2/day dose level. Other nonhematological toxicities related to treatment that were not dose limiting included alopecia, anorexia, fatigue, and stomatitis.

There were no responses (complete or partial) observed in this study. The median time to progression for 12 patients who were recorded as stable disease was 3.3 months (range 1.5–9.8). Four patients, two with advanced colorectal and one each with lung and pancreas, had stable disease from 4.7 to 9.8 months.

Pharmacokinetics

Pharmacokinetics were characterized for 20 patients who received oral irinotecan in doses ranging from 30 to 60 mg/m^2/d. Figure 2 shows mean plasma concentration–time profiles of irinotecan, SN-38, SN-38G, and APC after the first dose of 50 mg/m^2 irinotecan. Following oral administration, irinotecan was rapidly absorbed into systemic circulation and converted to the

Table 3 Cycle 1 hematologic toxicity

Dose level (mg/m^2)	No. of patients	Leukocyte nadir CTC grade			Neutrophil nadir CTC grade			Platelet nadir CTC grade		
		1/2	3	4	1/2	3	4	1/2	3	4
30	3	1	0	0	1	0	0	1	0	0
40	3	1	1	0	0	1	0	0	0	0
50	6	0	0	0	0	0	0	0	0	0
60	8	3	1	1	3	0	2	1	0	0

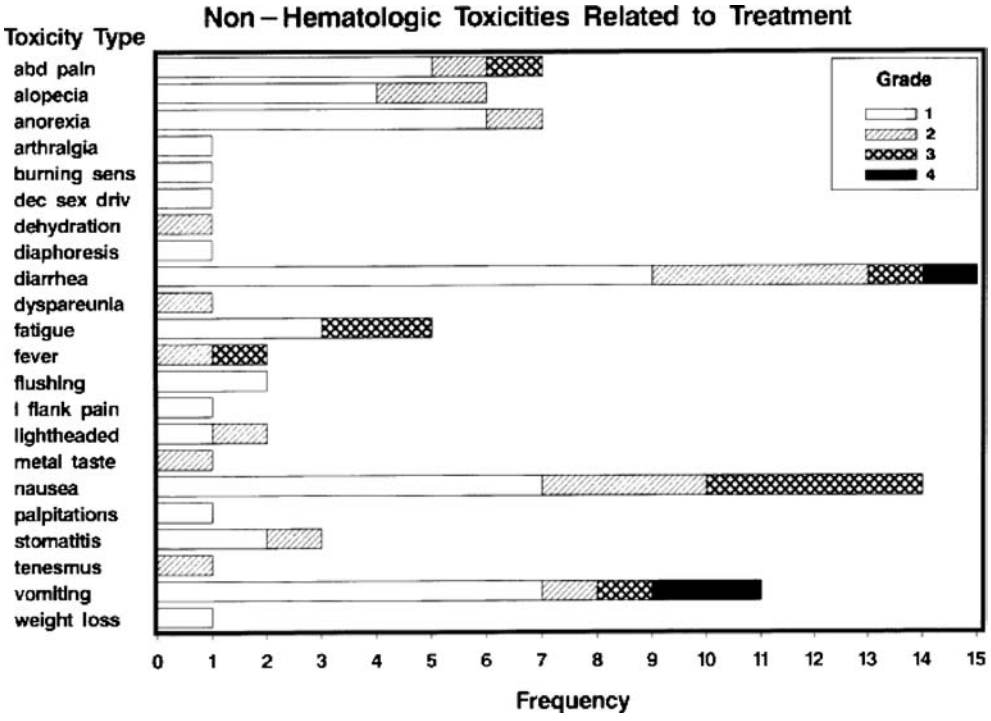

Fig. 1 Nonhematologic toxicities related to treatment

active metabolite, SN-38, as well as the other two metabolites, SN-38G and APC. The mean peak plasma concentrations (Cmax) of irinotecan and its metabolites were achieved within 6 h after dosing. Thereafter, plasma concentrations of irinotecan and the metabolites declined gradually and were still quantifiable at 24 h after dosing for all dose levels.

Table 4 summarizes PK parameters of irinotecan and the metabolites at the four dose levels evaluated. The mean Cmax and AUC of irinotecan and each of the metabolites increased with dose. There was a substantial overlap in exposure among the four dose levels, mainly due to the considerable interpatient variability and a narrow dose range evaluated. $T_{1/2}$ values of irinotecan and the metabolites were comparable among the four different dose levels, and were prolonged on day 5 compared to day 1. Both the Cmax and AUC_{0-24} were comparable between the first and the fifth doses for irinotecan and SN-38, indicating a nominal degree of drug accumulation following multiple dosing. The AUC ratios (REC, REG, and REO) were generally similar among dose groups. Apparent oral clearance (Cl/F) expressed in units of L/h was not associated with body surface area (Pearson correlation coefficient <0.02, $P>0.9$).

Figure 3 compares the AUC ratios following oral administration of irinotecan in this study to those obtained after i.v. dosing of irinotecan in previous studies. The most notable difference is observed for REC, where the mean REC for oral dosing is about threefold higher than for i.v. dosing (0.14 ± 0.07 for po vs. 0.033 ± 0.028 for i.v.). This result demonstrates that irinotecan is more efficiently converted to the active metabolite, SN-38, after oral administration. The mean REO is slightly higher after oral dosing (0.55 ± 0.31 for po vs. 0.33 ± 0.28 for i.v.), but the REG values are not different between the two administration routes.

The correlation between systemic exposures and toxicities of irinotecan was explored using the Cmax and AUC_{0-24} of irinotecan and SN-38 after the fifth dose and the severity of Cycle 1 toxicities. The association between exposure parameters of irinotecan or SN-38 and the severity of Cycle 1 neutropenia or diarrhea was weak (Spearman correlation coefficient

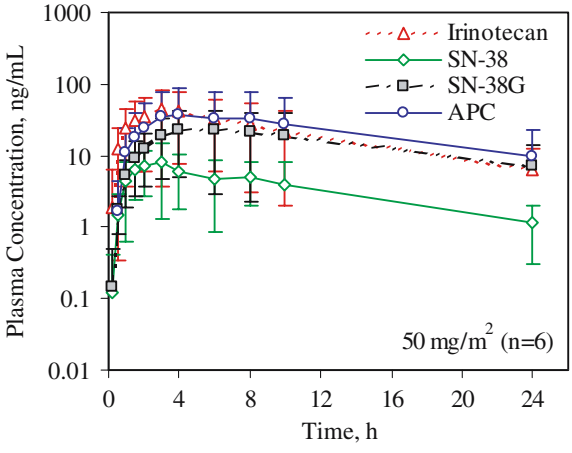

Fig. 2 Plasma concentration–time profiles of irinotecan and its metabolites in cancer patients following the first dose of irinotecan administered orally as a PFC formulation at 50 mg/m^2. *Curves with error bars* indicate mean ± SD

Table 4 Mean* (± SD) PK paramaters of irinotecan and its metabolites in cancer patients following oral administration of irinotecan as a PFC formulation

Treatment period		First dose (day 1)				Fifth dose (day 5)			
Dose (mg/m^2)		30	40	50	60	30	40	50	60
N		3	3	6	8	3	3	6	8
Irinotecan	Cmax (ng/mL)	14.2 ± 5.7	51.6 ± 50.9	47.4 ± 39.7	68.3 ± 48.8	25.0 ± 21.9	48.2 ± 52.6	67.2 ± 55.0	91.0 ± 46.1
	Tmax (h)	3.3 ± 0.6	3.3 ± 0.6	3.5 ± 1.4	3.7 ± 1.6	3.0 ± 0	3.3 ± 0.6	2.4 ± 0.7	4.1 ± 1.9
	AUC_{0-24} (ng h/mL)	111 ± 50	408 ± 408	486 ± 421	607 ± 508	208 ± 198	581 ± 693	581 ± 449	1020 ± 739
	$AUC_{0-\infty}$ (ng h/mL)	122 ± 63	472 ± 490	652 ± 480	690 ± 551	233 ± 228	742 ± 932	763 ± 571	1360 ± 906
	$t_{1/2}$ (h)	6.1 ± 3.4	7.3 ± 1.4	7.4 ± 0.4	7.8 ± 1.4	6.8 ± 2.4	8.7 ± 2.6	12.3 ± 1.8	12.6 ± 1.6
SN-38	Cmax (ng/mL)	2.9 ± 1.2	3.4 ± 2.7	8.9 ± 6.2	6.8 ± 4.7	2.8 ± 1.6	2.7 ± 1.5	6.3 ± 3.0	10.0 ± 5.3
	Tmax (h)	4.0 ± 2.0	4.3 ± 1.5	5.3 ± 2.3	3.6 ± 2.7	4.0 ± 1.7	4.0 ± 1.7	2.2 ± 0.7	4.9 ± 3.4
	AUC_{0-24} (ng h/mL)	25.0 ± 9.2	28.6 ± 13.4	82.3 ± 61.4	73.4 ± 53.1	27.6 ± 15.9	33.0 ± 22.8	65.1 ± 27.0	123 ± 82
	$AUC_{0-\infty}$ (ng h)	13.3, 41.4	59.0 (*n* = 1)	110 ± 85	124 ± 113	18.0 (*n* = 1)	29.7 (*n* = 1)	141 ± 15	274 ± 138
	$t_{1/2}$ (h)	2.4, 11.4	12.4 (*n* = 1)	7.3 ± 2.1	10.5 ± 1.2	4.0 (*n* = 1)	11.3 (*n* = 1)	20.1 ± 4.4	15.2 ± 0.4
SN-38G	Cmax (ng/mL)	9.7 ± 6.9	18.6 ± 20.7	24.9 ± 19.4	18.2 ± 8.9	11.6 ± 8.3	22.2 ± 22.4	23.6 ± 17.2	23.0 ± 7.8
	Tmax (h)	5.3 ± 1.1	4.0 ± 0	4.8 ± 2.8	4.4 ± 1.5	3.7 ± 0.6	5.0 ± 1.7	4.0 ± 1.1	4.7 ± 2.8
	AUC_{0-24} (ng h/mL)	100 ± 67	213 ± 244	350 ± 318	214 ± 116	141 ± 129	317 ± 420	313 ± 251	334 ± 180
	$AUC_{0-\infty}$ (ng h/mL)	54.3, 204	268 ± 311	310 ± 273	286 ± 180	196 ± 193	515 ± 731	622 ± 429	621 ± 391
	$t_{1/2}$ (h)	7.4, 8.6	9.2 ± 0.6	9.3 ± 1.9	9.3 ± 1.8	12.0 ± 3.5	12.2 ± 5.9	22.2 ± 4.5	17.8 ± 4.9
APC	Cmax (ng/mL)	4.7 ± 1.5	16.8 ± 20.3	40.9 ± 48.8	18.0 ± 7.8	9.9 ± 10.5	15.8 ± 15.2	34.0 ± 40.4	26.9 ± 16.7
	Tmax (h)	4.7 ± 1.1	3.7 ± 0.6	5.2 ± 2.2	5.4 ± 2.2	3.0 ± 0.0	3.7 ± 0.6	4.3 ± 1.4	5.9 ± 3.4
	AUC_{0-24} (ng h/mL)	53.7 ± 23.3	176 ± 210	527 ± 692	215 ± 100	119 ± 142	228 ± 269	414 ± 392	375 ± 210
	$AUC_{0-\infty}$ (ng h/mL)	89.2 (*n* = 1)	506 (*n* = 1)	833 ± 1044	257 ± 128	29.8, 325	116, 755	674 ± 485	541 ± 279
	$t_{1/2}$ (h)	7.8 (n = 1)	8.9 (n = 1)	7.5 ± 1.6	7.0 ± 1.0	4.3, 7.5	6.6, 12.6	13.0 ± 1.9	12.8 ± 5.3
AUC ratios **	REC (SN-38/irinotecan)	0.27 (*n* = 2)	0.06 (*n* = 1)	0.17 ± 0.04	0.11 ± 0.03	0.18 ± 0.10	0.09 ± 0.04	0.14 ± 0.06	0.13 ± 0.06
	REG (SN-38G/SN-38)	4.09, 4.93	10.6 (*n* = 1)	5.71 ± 0.73	2.53, 6.37	4.52 ± 1.58	7.14 ± 5.77	4.64 ± 2.81	3.51 ± 2.02
	REO (APC/irinotecan)	0.58 (*n* = 1)	0.49 (*n* = 1)	1.01 ± 0.48	0.41 ± 0.24	0.49 ± 0.15	0.40 ± 0.18	0.65 ± 0.22	0.44 ± 0.26

*Individual PK parameters are listed if $N < 3$. **$AUC_{0-\infty}$ ratios were reported for the first dose and AUC_{0-24} ratios were reported for the fifth dose

= 0.4943, $P = 0.037$) in the twofold dose range evaluated. Although patients experienced toxicities that had relatively high plasma exposure of irinotecan and SN-38 among this population, high exposure of irinotecan and SN-38 did not necessarily lead to toxicities in all patients.

Discussion

Use of irinotecan in metastatic colorectal cancer has evolved over the last decade from phase I testing to comparative phase III clinical trials leading to the ap-

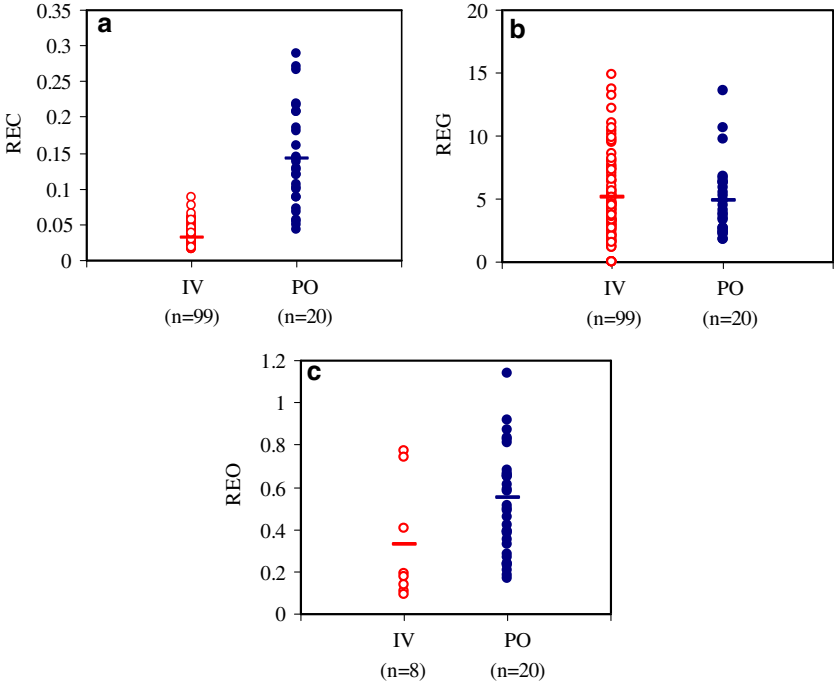

Fig. 3 Comparison of the relative extent of conversion (estimated as REC, REG, and REO ratios) after intravenous (i.v.) and oral (po) administration of irinotecan to cancer patients. As described in Material and methods, REC, REG, and REO were the AUC ratios of SN-38 to irinotecan, SN-38G to SN-38, and APC to irinotecan, respectively. The i.v. data were from previous trials in cancer patients [6, 18]. For po, $AUC_{0-\infty}$ ratios of the first dose and AUC_{0-24} ratios of the fifth dose from patients receiving 30, 40, 50, and 60 mg/m^2 of irinotecan as the PFC formulation were combined. The *solid lines* indicate the mean values

proval by the Food and Drug Administration for both first- and second-line indications [2, 3, 8, 9]. The use of oral chemotherapy has potential practical and economic advantages over i.v. administration. A study evaluating patient preferences concluded that patients prefer oral chemotherapy so long as they can be assured that efficacy was not compromised [10]. Another trial compared use of i.v. 5-fluorouracil/leucovorin with oral UFT/leucovorin and found that over eight out of ten patients preferred oral therapy [11]. Reasons sited for the oral chemotherapy preference included less toxicity, ability to take the medication at home and use of pill over injection.

This phase I study reports a single-center study of oral irinotecan given as a PFC formulation administered for 5 consecutive days every 3 weeks. The majority of patients enrolled in this trial had advanced gastrointestinal cancers, with the most common being the colorectal cancer. The DLTs encountered at the 60 mg/m^2/day dose level included nausea, vomiting, diarrhea, and neutropenic fever/sepsis. These are similar to the DLTs reported in phase I studies using i.v. irinotecan [8, 12, 13].

Pharmacokinetics results of this study show that irinotecan was rapidly absorbed into systemic circulation after oral dosing and converted to the active metabolite SN-38. Similar to that previously observed for i.v. [13–16] and oral [4] dosing, there was substantial inter-patient variability in plasma exposures of irinotecan and SN-38 following oral administration. The terminal $t_{1/2}$ values of irinotecan and the metabolites after oral dosing were similar to those observed after i.v. dosing in previous clinical studies [4, 13–16]. Consistent with the relatively moderate $t_{1/2}$ values, the accumulation of irinotecan and the metabolites was minimal after consecutive daily dosing for 5 days. The absence of a relationship between clearance and body surface area suggests that irinotecan can be administered orally to adults without correction for body surface area. However, further studies using this approach would be required to establish a dose given the large interpatient variability observed in this trial.

The extent of conversion from irinotecan to SN-38, as indicated by the REC value, was approximately threefold higher after oral administration compared to i.v. dosing. The first pass metabolism following oral administration likely contributed to the high REC, since the gastrointestinal wall and the liver are known to express carboxyesterase at very high levels. On the other hand, the higher REC following oral dosing indicated that the carboxyesterase-mediated hydrolysis of irinotecan to SN-38 is a rate-limiting process during irinotecan disposition.

We evaluated the relationships between irinotecan and SN-38 PK parameters and Cycle-1 toxicities but this analysis was limited by several factors including the small number of patients in each cohort, the limited number of dose levels and observed toxicities, and the relatively large interpatient variability with the oral therapy. In contrast with results from studies of i.v. irinotecan [14, 17], the relationship observed between the plasma exposure of irinotecan or SN-38 and toxicities was weak in the twofold dose range evaluated. Based on these results, it is difficult to predict the occurrence and severity of toxicities based on plasma irinotecan or SN-38 exposure at the MTD.

The recommended phase II dose of PFC oral irinotecan for this trial is 50 mg/m^2/day for 5 consecutive days every 3 weeks. Gastrointestinal and myelosuppressive DLTs continue to be problematic for this oral formulation of irinotecan. A new formulation of oral irinotecan is currently in clinical trials with plans to combine the drug with capecitabine in phase I and subsequent phase II trials for patients with advanced colorectal carcinoma.

Acknowledgements The authors wish to thank Ms. Brenda Hippert and Ms. Melanie Kasner for excellent data management, Ms. Michelle Daiss for protocol development coordination, Ms. Jill Piens for coordination of the pharmacokinetic studies, Oncology Nurses on Mayo Clinic and General Clinical Research Center, and all the patients who took part in this trial. The clinical specimens were assayed by AvTech (Kalamazoo, MI, USA).

References

1. Pommier Y, Tanizawa A, Kohn KW (1994) Mechanisms of topoisomerase I inihibition by anticancer drugs. In: Liu LF (ed) Advances in pharmacology. Academic, New York, pp 73–92
2. Saltz LB, Cox JV, Blanke C et al (2000) Irinotecan plus fluorouracil and leucovorin for metestatic colorectal cancer: irinotecan study group. New Engl J Med 343:905–914
3. Douillard JY, Cunningham D, Roth AD et al (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomized trial. Lancet 355:1041–1047
4. Drengler RL, Kuhn JG, Schaaf LJ et al (1999) Phase I and pharmacokinetic trial of oral irinotecan administered daily for 5 days every 3 weeks in patients with solid tumors. J Clin Oncol 17:685–696
5. Simon RM, Friedlin B, Rubinstein LV et al (1997) Accelerated titration designs for Phase I clinical trials in oncology. J Natl Cancer Inst 89:1138–1147
6. Slatter JG, Schaaf LJ, Sams JP et al (2000) Pharmacokinetics, metabolism, and excretion of irinotecan (irinotecan) following intravenous infusion of [(14)C]irinotecan in cancer patients. Drug Metab Dispos 28:423–433
7. Gibaldi M, Perrier D (1982) Non-compartmental analysis based on statistical moment therapy. In: Gibaldi M, Perrier D (eds) Pharmacokinetics, 2nd edn. Marcel Dekker, New York, pp 409–417
8. Rothenberg ML, Kuhn JG, Burris HA et al (1993) Phase I and pharmacokinetic trial of weekly irinotecan. J Clin Oncol 11:2194–2204
9. Rougier P, van Cutsem E, Bajetta E et al (1998) Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 352:1407–1412
10. Liu G, Franssen E, Fithc MI et al (1997) Patient preferences for oral versus intravenous palliative chemotherapy. J Clin Oncol 15:110–115
11. Borner MM, Schoffski P, de Wit R et al (2002) Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a randomised crossover trial in advanced colorectal cancer. Eur J Cancer 38:349–358
12. Rowinsky EK, Grochow LB, Ettinger DS et al (1994) Phase I and pharmacological study of the novel topoisomerase I inhibitor 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyl-oxycamptothecin (irinotecan) administered as a ninety-minute infusion every three weeks. Cancer Res 54:427–436

13. Abigerges D, Chabot GG, Armand JP et al (1995) Phase I and pharmacologic studies of the camptothecin analog irinotecan administered every 3 weeks in cancer patients. J Clin Oncol 13:210–221
14. Chabot GG, Abigerges D, Catimel G et al (1995) Population pharmacokinetics and pharmacodynamics of irinotecan (irinotecan) and active metabolite SN-38 during phase I trials. Ann Oncol 6:141–151
15. Rivory LP, Riou JF, Haaz M-CH et al (1996) Identification and properties of a major metabolite of irinotecan (irinotecan) isolated from the plasma of patients. Cancer Res 56:3689–3695
16. Pitot HC, Goldberg RM, Reid JM et al (2000) Phase I dose finding and pharmacokinetic trial of irinotecan hydrochloride (CPT-11) using a once-every-three-dosing schedule for patients with advanced solid tumor malignancy. Clin Cancer Res 6:2236–2244
17. Gupta E, Lestingi TM, Mick R et al (1994) Metabolic fate of irinotecan in humans: correlation of glucuronidation with diarrhea. Cancer Res 54:3723–3725
18. Schaaf L, Ichhpurani N, Elfring G et al (1997) Influence of age on the pharmacokinetics of irinotecan (CPT-11) and its metabolites, SN-38 and SN-38 glucuronide (SN-38G) in patients with previously treated colorectal cancer (abstract). Proc Am Soc Clin Oncol 16:202a