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ORIGINAL ARTICLE

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Phase I study of an oral formulation of irinotecan administered daily for 14 days every 3 weeks in patients with advanced solid tumours

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Abstract A phase I study was conducted with oral irinotecan given daily for 14 days every 3 weeks in 45 patients with solid tumours to establish the maximum tolerated dose (MTD), toxicity, preliminary antitumour response and pharmacokinetics. Irinotecan was administered orally as a powder-filled capsule at doses ranging from 7.5 to 40 mg/m^2 per day. Tumours were predominantly colorectal (30) together with 10 other gastrointestinal, 2 breast, 2 small cell lung and 1 ovarian. All but three patients had received prior chemotherapy. The median number of administered cycles was 3 (range 1–19). Gastrointestinal toxicities (grade 3 nausea, grade 3/4 vomiting and diarrhoea) and one incidence of grade 3 asthenia were dose limiting. There were no grade 3/4 haematological toxicities. The MTD was 30 mg/m^2 per day. There were two documented partial responses, one in a patient with cancer of the small intestine and the other in a patient with colon cancer. Stable disease was seen in 16 patients (35.5%). Peak concentrations of irinotecan and metabolite SN-38 were reached within 2.0–2.4 h. The metabolic ratio of SN-38 AUC to irinotecan AUC was 0.17 ± 0.10 (mean $\pm$ SD). The dose recommended for phase II studies is 30 mg/m^2 per day administered daily for 14 days every 3 weeks.

Keywords Irinotecan · CPT-11 · SN-38 · Oral · Pharmacokinetics · Phase I

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Introduction

The topoisomerase I inhibitor irinotecan (CPT-11, CAMPTO) has demonstrated activity towards a range of solid tumours. It has proven single-agent activity in the first-line and second-line treatment of advanced/metastatic colorectal cancer [1–5] and is now regarded as standard second-line therapy [6, 7]. More recently, irinotecan combined with 5-fluorouracil (5-FU) and leucovorin (LV) has shown a survival advantage over both irinotecan alone and 5-FU/LV when administered first-line to patients with metastatic colorectal cancer, in two phase III trials [8, 9]. Irinotecan in combination with either bolus or infusional 5-FU/LV has now become the reference regimen for the first-line treatment of advanced/metastatic colorectal cancer.

However, recent reports have suggested that the irinotecan/5-FU/LV combination may be more toxic than originally indicated [10, 11]. An FDA safety warning advised dose reductions in the case of severe diarrhoea [12]. These recent reports serve to highlight the importance of drug delivery in determining the therapeutic ratio.

As irinotecan is a cell cycle-specific (S-phase) drug, it has been postulated that prolonged administration could increase antitumour efficacy and diminish toxicity [13]. This has been confirmed in preclinical studies [14–16]. Although administration of irinotecan as a continuous low-dose infusion is feasible [17, 18], protracted intravenous delivery is inconvenient for patients and costly.

There is, therefore, considerable interest in the development of oral drug formulations which provide a convenient and inexpensive route of administration. Another potential benefit of oral delivery is the high level of carboxylesterases, the enzymes required for the conversion of irinotecan to its active metabolite SN-38, in the gastrointestinal tract [19].

It has been found that childhood neuroblastoma xenografts are highly sensitive to orally administered irinotecan [14, 20]. Furthermore, a phase I study of oral irinotecan administered daily for 5 days every 3 weeks to patients with refractory malignancies, resulted in a partial response in one patient with previously treated colorectal cancer [21]. The observed activity and favourable pharmacokinetic characteristics supported further clinical investigation of oral irinotecan using a different schedule. Therefore, this phase I study of oral irinotecan given daily for 14 days every 3 weeks was conducted in patients with metastatic solid tumours. The aim of the study was to determine the maximum tolerated dose (MTD), the recommended phase II dose and the toxicity profile. Any antitumour activity was documented and the plasma pharmacokinetics of irinotecan and its metabolite SN-38 were determined. Due to the established efficacy of irinotecan in the treatment of colorectal cancer, the majority of patients enrolled into the study had metastatic colorectal carcinoma.

Patients and methods

Patient selection

Patients with solid tumours with measurable or assessable disease refractory to standard therapy were eligible. Other eligibility criteria were age >18 years, a World Health Organisation (WHO) performance status ≤ 2 and an estimated life expectancy $\geq$12 weeks. Previous chemotherapy had to have been discontinued for at least 4 weeks before study entry, or for at least 6 weeks in those treated with mitomycin or nitrosourea. Patients had to have adequate haematological function defined as haemoglobin $\geq$10 g/dl, neutrophil count $\geq 2.0\times10^9$ cells/l, platelet count $\geq 150\times10^9$ cells/l; adequate hepatic function defined as serum bilirubin level less than the upper normal limit (UNL), transaminase levels less than three times UNL or less than five times UNL when related to liver metastasis, and adequate renal function defined as a serum creatinine level <1.5 mg/dl. Patients had to be able to swallow normally and had to be willing to comply with the intake of capsules. Exclusion criteria included: leukaemia, a history of treatment with high-dose chemotherapy with progenitor blood cell transplantation or with irinotecan, previous pelvic irradiation, chronic enteropathy (e.g. active inflammatory bowel disease, extensive intestinal resection, or chronic diarrhoea), bowel obstruction or subobstruction, symptomatic brain metastasis or carcinomatous leptomeningitis, concomitant severe infection (including prior documentation of HIV positivity), major organ failure, and evidence of active alcoholism or drug addiction. Pregnant or lactating women were excluded from the study. The study protocol was approved by the Medical Ethics Committee of the hospital, and all patients gave written informed consent.

Toxicity and response evaluation

Baseline evaluation prior to study entry included a complete medical history and physical examination, blood count, biochemical profile, serum tumour markers and tumour evaluation using appropriate radiographic imaging. Complete blood count data were obtained twice weekly during the first cycle and then weekly for subsequent cycles. Biochemical profiles were analysed weekly during the first cycle and then at the start of each cycle. Tumours were measured every 6 weeks by examination with the same radiographic method used at baseline. Response to therapy was assessed according to WHO criteria. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. Patients were instructed to take 4 mg of loperamide initially, and then 2 mg every 2 h (4 mg every 4 h at night) at the first sign of diarrhoea until at least 12 h after the resolution of any diarrhoea-related problem. No prophylactics were provided for diarrhoea. Patients recorded side effects, time of occurrence and intake of (co)medication in a diary. Loperamide was supplied by the sponsor and provided sufficiently on hand by the oncology nurses to patients in case antidiarrhoeal support was required. Additional antidiarrhoeal measures were used at the discretion of the treating physician. Patients were instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhoea.

Prophylactic antiemetics were not allowed on the first day of a treatment-cycle, but could be administered on subsequent days at the discretion of the investigator. The routine prophylactic use of colony-stimulating growth factors was not recommended and not permitted during the first treatment cycle, while during subsequent treatment cycles, its therapeutic use could be considered at the investigator's discretion in patients with serious neutropenic complications.

Drug administration and dose escalation

Irinotecan was supplied as powder-filled capsules (PFC) containing 5 mg or 20 mg of drug (Aventis Pharma, Antony, France) and administered daily for 14 consecutive days followed by 1 week of rest. The starting dose of 7.5 mg/m^2 per day was based on the recommended dose level in a 14-day i.v. schedule study. Dose increments of 2.5 mg/m^2 were to guarantee patients safety and provided convenience in dose calculation in future studies. Dose increments of 10 mg/m^2 per level were applied from 22.5 mg/m^2 until the MTD had been established. The assigned daily oral dose was swallowed

with a glass of water in the morning, at approximately the same time each day. Patients were required to fast for at least 4 h prior to and for 1 h following dosing. A minimum of three patients were treated at each dose level with a minimum 1-week interval between the entry of the first patient and the next two patients. Before escalation to the next dose level, all three patients had to have received at least one treatment cycle and to have been observed for toxicity for a minimum of 1 week.

A dose-limiting toxicity (DLT) was defined as any of the following events during the first treatment cycle: grade 4 neutropenia for longer than 7 days or within the 14 days of treatment, febrile neutropenia, neutropenic infection (grade 4 neutropenia with grade 3/4 or documented infection), grade 4 thrombocytopenia, grade 3/4 diarrhoea despite maximal intensive loperamide support, grade 3 nausea or grade 3/4 vomiting despite maximal oral antiemetic therapy, failure to complete the 14 days of full-dose irinotecan therapy or any NCI-CTC grade 3 or 4 non-haematological toxicity (excluding alopecia). In case of DLT, the treatment was discontinued until recovery to grade 1 or better, and, if clinically indicated, resumed for the subsequent cycle at one dose level lower. If one of the first three patients experienced a DLT at a dose level, three additional patients were enrolled at this dose level. If no DLT was seen in any of the three additional patients, the dose was escalated for the next patient. There were no intrapatient dose escalations. The MTD was defined as the dose at which two of three or two of six patients experienced DLT. The next lower dose level below the MTD was the recommended dose for phase II studies.

Patients could be retreated at a reduced dose level, depending upon the adverse events in their current cycle or due to any adverse events on the first day of the next cycle. Only when an adverse event subsequently was evaluated as not treatment-related, could the dose be re-escalated at the next cycle (only if no toxicities worse than grade 1 were observed, with the exception of alopecia). No dose reductions within a treatment cycle were made. After identification of the MTD, additional patients were included at the same dose level in order to ensure its feasibility. Treatment was continued until evidence of disease progression or unacceptable toxicity occurred, or until patient withdrawal of consent.

Pharmacokinetics

The pharmacokinetics of irinotecan and SN-38 were studied on days 1 and 14 during the first cycle of chemotherapy. Heparinized blood samples (7 ml) were collected before administration, at 15, 30, 60 and 90 min and 2, 3, 4, 6, 8, 10 and 24 h after the first administration (and prior to administration on day 2) and at 48 h after the day-14 drug administration. Samples were chilled on ice, centrifuged and the plasma stored at −20°C until analysis. Irinotecan and SN-38 concentrations were measured in plasma, as total lactone forms, by a reverse-phase HPLC method using fluorescence detection. The limit of quantitation was 1.00 ng/ml for both compounds [22]. For each individual, the maximum plasma concentration (C_{max}) and corresponding time (T_{max}) on days 1 and 14 were generated from the data. The terminal rate constant k was determined by log-linear regression analysis of the terminal phase of the plasma concentration-time curve. The area under the concentration-time curve (AUC) on days 1 and 14 was estimated by the linear-logarithmic trapezoidal method up to the last measured data point (AUC_t) with extrapolation to infinity using k. The metabolic ratio was defined as SN-38 AUC_t/irinotecan AUC_t. Accumulation of irinotecan and SN-38 was defined by the ratio AUC_t day 1/AUC_t day 14. To compare the exposure to irinotecan and SN-38 on day 14 with the data for day 1, a SAS mixed procedure was carried out after logarithmic transformation of the dose-normalized AUC_t and C_{max}. Correlations between dose and AUC_t on day 14 were analysed using the Pearson correlation test (r_p). Statistical analysis was performed with SPSS (version 6.1 for Windows) and SAS (version 6.12).

Results

Patient characteristics and dosing

Between November 1998 and February 2001, 45 patients (20 females, 25 males) with a median age of 56 years (range 25–69 years) and a median performance status of 1 (range 0–2) were enrolled, and their characteristics are presented in Table 1. Of the 45 patients, 42 had received prior chemotherapy and 11 had received prior radiation (to the pelvis in 5 patients and to extra pelvic sites in 6 patients). All patients were assessable for toxicity, and 38 were assessable for response because 1 patient was not properly assessed during the study and 6 patients withdrew from the study due to unacceptable toxicity before the first tumour assessment. The majority of patients (66%) had metastatic colorectal cancer. The median interval from diagnosis to study entry was 14.6 months (range 1.7–70.1 months). The results of the dose escalation are presented in Table 2. The median number of treatment cycles per patient was 3 (range 1–19). A total of 179 cycles were given. No DLTs were observed until dose level 6 (Table 2). DLTs were reported at the following dose levels: 20 mg/m^2 per day, two patients failed to complete their treatment cycle due to vomiting within 2 h of drug intake; 30 mg/m^2 per day, one patient experienced grade 3 asthenia; 35 mg/m^2 per day, two patients experienced grade 3 diarrhoea; 40 mg/m^2 per day, one patient with grade 4 diarrhoea and another with grade 3 nausea, anorexia and asthenia with grade 4 vomiting. Five patients withdrew from the study after experiencing DLT and two required dose reductions. According to the dose escalation rules, the MTD was determined at 30 mg/m^2 per day.

Table 1 Patient characteristics

Characteristic		No. of patients	%
Gender			
Male		25	56
Female		20	44
Age (years)			
Median	56		
Range	25–69		
Performance status			
0		13	29
1		28	62
2		4	9
Prior chemotherapy		42	93
No. of regimens			
Median	1		
Range	0–3		
Prior radiotherapy		11	24
Primary tumour			
Colorectum		30	
Small intestine		2	
Oesophagus/stomach		6	
Pancreas		2	
Lung		2	
Ovaries		1	
Breast		2	

Haematological toxicity

No significant haematological toxicity was observed during this study with oral irinotecan. None of the 45 patients experienced neutropenia greater than grade 2 or thrombocytopenia greater than grade 1 during all treatment cycles. Five patients experienced grade 3 anaemia.

Non-haematological toxicity

Gastrointestinal toxicity, including nausea, vomiting and diarrhoea was found to be dose-limiting. Table 3 lists the frequency and severity of diarrhoea, nausea and vomiting during treatment course 1 and all courses. Grade 3/4 diarrhoea was observed in 7 (15%) of 45 patients and 8 (4%) of 179 cycles. Grade 1/2 diarrhoea occurred in 67 cycles (37%). The median day of onset of diarrhoea (all grades) in cycle 1 was day 10 (range day 1–22) and the median duration was 3 days (range 1–26 days). Grade 3 nausea and grade 3/4 vomiting were observed in three patients (four cycles) and three patients (three cycles), respectively. No cumulative intestinal toxicity was observed. Other treatment-related side effects were asthenia (grade 1/2, 27 patients; grade 3, 2 patients), anorexia (grade 1/2, 13 patients; grade 3, 2 patients), mucositis (grade 1/2, 4 patients), alopecia (grade 1/2, 6 patients). Only one grade 1 cholinergic syndrome occurred during the third cycle in one patient (12.5 mg/m^2 per day). No treatment-related deaths were observed.

Antitumour activity

Two confirmed partial responses were documented: one in a 43-year-old man with cancer of the small intestine treated at the 7.5 mg/m^2 per day dose level (response duration, 6 months) and one in a 61-year-old woman with colon cancer treated at the 17.5 mg/m^2 per day dose level (response duration, 6 months). A total of 16 of 45 treated patients had as best response stable disease (35.5%), with a median duration of 2.8 months (CI 95% 2.6–4.8 months). A 52-year-old man with metastatic colon cancer, previously treated with surgery followed by 5-FU/LV, received 19 cycles of irinotecan (22.5 mg/m^2 per day), and had stable disease for at least 17 months. The median time to progression for the 45 treated patients was 2.1 months (CI 95% 1.28–2.76 months).

Pharmacokinetics

Figure 1 shows a typical pharmacokinetic profile of irinotecan and SN-38 during day 1 at the MTD. Pharmacokinetic parameters for day 14 (steady state)

Table 2 Dose escalation and dose limiting toxicity during first cycle

Dose (mg/m^2/day)	No. of patients (no. of cycles)	Patients with DLT	No. of patients dose-reduced	No. of patients dose-delayed	Dose-intensity (mg/m^2/3 weeks)		
					Planned	Actual[a]	%
7.5	3 (18)	0	0	1	105	114	108
10	3 (7)	0	0	1	140	141	100
12.5	3 (22)	0	1	1	175	162	93
15	3 (7)	0	0	0	210	204	98
17.5	3 (18)	0	0	3	245	225	91
20	6 (19)	2[b]	0	1	280	252	90
22.5	3 (24)	0	0	1	315	321	102
30	14 (48)	1[c]	0	2	420	406	97
35	2 (6)	2[d]	1	1	490	330–447	67–91
40	5 (10)	2[e]	0	2	560	417	74

[a]Actual dose intensity = mean dose value of patients at a certain dose level.
[b]Two patients were unable to complete cycle.
[c]Patient suffered from asthenia.
[d]Two patients had diarrhoea as DLT.
[e]One patient developed diarrhoea; the other had suffered from nausea, vomiting and asthenia.

Table 3 Gastrointestinal toxicity

Dose (mg/m^2/day)	No. of patients	No. of cycles	No. of patients developing toxicity in the first cycle/number of all assessable cycles causing toxicity							
			Diarrhoea			Nausea		Vomiting		
			Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 2	Grade 3	Grade 4
7.5	3	18	1/2	0/1		0/1		–		
10	3	7	–			0/1		–		
12.5	3	22	–			0/2		–		
15	3	7	–			1/2		1/1		
17.5	3	18	1/2			–		–		
20	6	19	–	0/1		1/1	1/1	0/1	1/1	
22.5	3	24	–			0/1		–		
30	15	48	1/3		0/1	1/1		2/2		0/1
35	2	6	0/1	2/3		–	1/2	1/2		
40	5	10	1/1	1/1	1/1	3/3	1/1	1/2		1/1

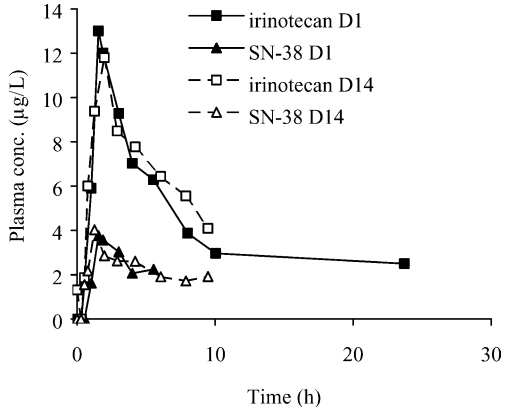

Fig. 1 Typical pharmacokinetic profiles for irinotecan and SN-38 for days 1 and 14. Patients were treated with 30 mg/m^2 irinotecan orally as a powder-filled capsule

were determined for 25 patients (Tables 4 and 5). Extrapolation of the AUC of irinotecan and SN-38 exceeded 20% in most cases and therefore AUC_t values are reported. Absorption was rapid as irinotecan levels were quantifiable within 15–20 min, and maximal concentrations of irinotecan and SN-38 were achieved between 2.0 h and 2.4 h (medium time after administration). Variability was high and the coefficient of variation ranged between 59% and 108% for the AUC of irinotecan and between 52% and 138% for the AUC of SN-38. No accumulation was observed, as no statistically significant differences were found between the day-14 and day-1 values of either AUC_t or C_{max} (Tables 4 and 5). The metabolic ratio (AUC SN-38/AUC irinotecan) during day 1 was 0.17 ± 0.10 (mean $\pm$ SD). The relationships between irinotecan dose and AUC_t for irinotecan and SN-38 are shown in Figs. 2 and 3, respectively. The AUC_t (day 14) of irinotecan was significantly linearly correlated with dose ($r_p = 0.55$, $P = 0.005$). No significant relationship between the AUC_t (day 14) and dose of SN-38 ($r_p = 0.30$, $P = 0.28$) was found. However, the data shown in Fig. 3 tentatively suggest a dose-related increase in SN-38.

Table 4 Pharmacokinetic parameters of irinotecan on day 14 after administration of oral irinotecan. The data presented are means (coefficient of variation %), except T_{max} median (range). (*NS* non-significant)

Dose (mg/m^2/day)	*n*	T_{max} (h)	C_{max} (µg/l)	C_{max} day 14/day 1	AUC_t (µg h/l)	$AUC_{day\ 14/day\ 1}$ (%)
7.5	3	1.5 (0.6–3.9)	3.7 (25)	1.2 (5)	18.1 (72)	104 (7)
10	3	1.8 (1.5–3.5)	6.7 (80)	1.5 (47)	42 (108)	150 (49)
12.5	3	2.1 (2.0–4.4)	8.3 (32)	1.0–1.5[a]	58 (77)	107–325[a]
15	3	2.0 (2.0–2.9)	12.0 (106)	1.3 (130)	66 (113)	157 (127)
17.5	3	2.0 (1.7–3)	11.9 (92)	0.8 (38)	77.6 (68)	132 (81)
20	4[b]	2.1 (1.5–2.9)	18.1 (12)	0.6 (15)[a]	118 (98)	211 (49)
22.5	3	3.1 (0.7–4.0)	10.6 (25)	1.1 (32)	128.9 (59)	195 (75)
30	2[c]	2.0–3.0	6.3–11.8	0.5–1.1	64.5–77.2	66–599
40	1[d]	3.1	26.8	0.6	245	315
P value[e]		(Mixed procedure)		0.392 (NS)		0.151 (NS)

[a] $n = 2$ on day 1
[b] $n = 6$ on day 1
[c] $n = 3$ on day 1
[d] $n = 4$ on day 1
[e] Comparison day 1 vs 14

Table 5 Pharmacokinetic parameters of the active metabolite SN-38 on day 14 after oral administration of irinotecan. The data presented are means (coefficient of variation %), except T_{max} median (range). (*NS* non-significant)

Dose (mg/m^2/day)	*n*	T_{max} (h)	C_{max} (μg/l)	C_{max} day 14/day 1	AUC_t (μg h/l)	$AUC_{day\ 14/day\ 1}$ (%)	Metabolic ratio
7.5	3	1.5 (0.5–2.2)	1.8 (52)	1.2 (33)	4.2 (94)	66–72[a]	0.21 (33)
10	1	1.8	3.0	1.0	8.9	65	0.09
12.5	1	0.55	2.2	1.0	8.6	166	0.08
15	1	2.0	1.4	0.7	0.7	8	0.02
17.5	2	1.5–2.0	2.1–4.0	0.5–1.0	10.1–16.2	65–117	0.12–0.25
20	4[b]	2.2 (1.5–3.1)	1.8 (54)	1.4 (14)	4.6 (138)	40 (85)[a]	0.03 (27)
22.5	3	3.1 (1.7–6.0)	2.1 (23)	1.3 (9)	9.7 (52)	110 (89)	0.10 (18)
30	1	1.3	4.0	0.9	21	167	0.33
40	1[c]	2.0	2.0	0.7	10.1	168	0.04
P value[d]		(Mixed procedure)		0.651 (NS)		0.188 (NS)	

[a] $n = 2$
[b] $n = 6$ on day 1
[c] $n = 4$ on day 1
[d] Comparison day 1 vs 14

Discussion

The preferred schedule for intravenous delivery of irinotecan varies when used as a single agent and in combination chemotherapeutic regimens. Examples are: a 90-min infusion of 350 mg/m^2 given 3-weekly [3], a 90-min infusion of 125 mg/m^2 for 4 weeks every 6 weeks [9], and a 22-h infusion of 180 mg/m^2 given 2-weekly [8]. Despite these differences in scheduling, response rates and toxicity profiles are similar with DLTs being diarrhoea or a combination of diarrhoea and neutropenia [23]. The latter adverse events are both schedule-dependent and noncumulative. The schedule of administration in the present study imitates closely that of an earlier study with a 14-day prolonged intravenous schedule of irinotecan in which the recorded DLTs were nausea, vomiting and diarrhoea [17]. The DLTs for the oral PFC used in the present study (Table 2) were consistent with those already reported in abstract form for oral irinotecan using the same schedule [20]. An alternative oral dosing schedule, daily for 5 days every 3 weeks, produced DLTs of nausea, vomiting, diarrhoea and neutropenia [24, 25]. The recommended dose for phase II studies reported here and elsewhere [20] is 30 mg/m^2 per day when irinotecan is administered daily for 14 days every 3 weeks, and 80 mg/m^2 per day when given daily for 5 days every 3 weeks [25].

Significantly, in the present study, irinotecan administered orally as a PFC was absorbed rapidly from the gastrointestinal tract and peak concentrations of irinotecan and its active metabolite SN-38 were reached within 2.0–2.4 h of administration. Large interpatient variability in the pharmacokinetic parameters was observed at all dose levels. The AUC_t of irinotecan, but not that of SN-38, was linearly correlated with dose (Figs. 2 and 3). However, Fig. 3 tentatively suggests a dose-related increase in SN-38. Dose proportionality was difficult to assess in this study because of the high interpatient variability and the small number of patients at each dose level. In previous studies, using both intravenous and oral irinotecan, the AUC of irinotecan and SN-38 have been found to be positively (linearly) dose-related, although variability between patients was

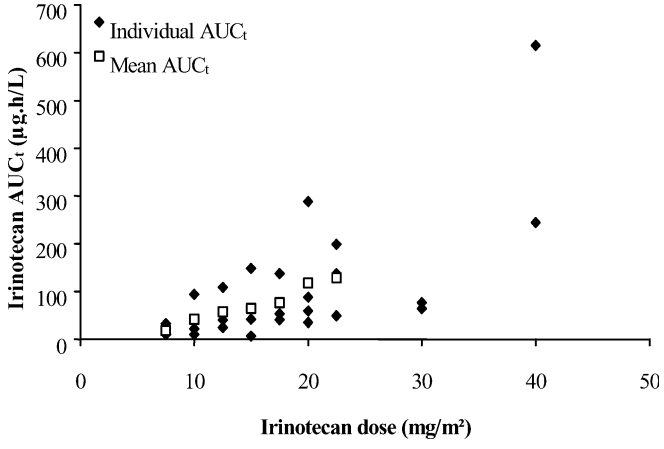

Fig. 2 Individual and mean AUC_t of irinotecan on day 14 after daily oral administration of powder-filled capsules of irinotecan over a period of 14 days

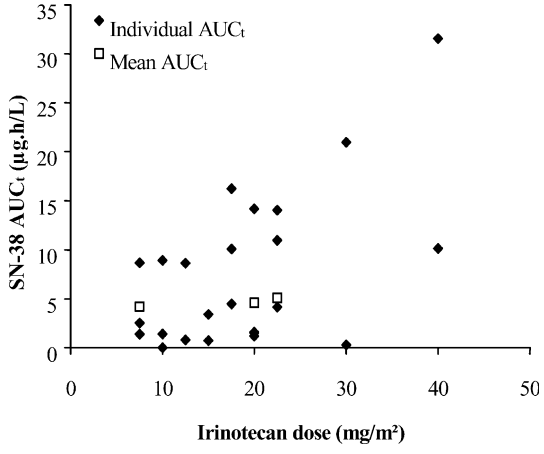

Fig. 3 Individual and mean AUC_t of SN-38 on day 14 after daily oral administration of powder-filled capsules of irinotecan over a period of 14 days

high [26, 27]. The pharmacokinetics of irinotecan are complex and involve metabolic conversions, including the formation of SN-38 by esterases, glucuronidation of SN-38 by UGT1A1, and the production of several oxidation products by CYP3A4 [27]. During a phase I pharmacokinetic study by one of the authors of the present study in patients with liver dysfunction, clearance following intravenous irinotecan administration decreased exponentially with increasing levels of bilirubin and alkaline phosphatase. Unconjugated bilirubin is a substrate for UGT1A1, and increased pretreatment values have been found to correlate with increased irinotecan toxicity and increased AUC of irinotecan and SN-38 [28].

In the present study, the metabolic ratio (SN-38 AUC/irinotecan AUC) was 0.17 ± 0.10 (mean $\pm$ SD), which is higher than the metabolic ratio found after short infusions of irinotecan (ranging between 0.03 and 0.05) but similar to the metabolic ratios previously reported for oral irinotecan [21, 24, 26, 29]. It has been suggested that presystemic conversion of irinotecan to SN-38 by intestinal carboxylesterase in the gastrointestinal tract and the liver is the reason for the increased metabolic ratio [30]. However, an increased metabolic ratio has also been found after a prolonged low-dose intravenous infusion of irinotecan (0.16) [17].

The overall systemic exposure to oral irinotecan over one cycle (3 weeks) at the recommended dose (420 mg/m^2) in the present study was around 10% of the exposure measured after the intravenous administration of 350 mg/m^2 [26]. Whereas, as a result of the increased metabolic ratio, the overall exposure to the active metabolite SN-38 was around 40–60% of the exposure measured after intravenous administration of 350 mg/m^2 irinotecan.

Preliminary antitumour data from the present study suggest that the efficacy of oral irinotecan should not differ from that achieved with intravenous schedules of administration. However, the determination of response rates was only a secondary objective of this study. A response rate of 4.5% was seen and 35.5% of treated patients achieved stable disease. These figures compare favourably with the results from phase II studies using high dose-intensity intravenous infusions of irinotecan given second-line where response rates of 9–17% in metastatic colorectal cancer were observed with the percentage of patients achieving stable disease ranging from 38% to 52% [23]. The response data are also similar to those from a phase I trial of irinotecan administered as a 14-day intravenous infusion [17] and a phase I trial of irinotecan as an intravenous solution administered orally daily for 5 days every 3 weeks in which a partial response was seen in 1 patient (4%) and stable disease in 17 patients (61%) of 28 patients with solid tumours [21]. In other phase I studies of irinotecan as PFC in mixed solid tumours, partial responses were seen in 2 patients (4%) and disease stabilization in 20 patients (43%) of 46 patients receiving irinotecan for 5 days every 3 weeks [24], and stable disease in 10 (53%) of 19 patients receiving irinotecan daily for 14 days every 3 weeks [20].

As different schedules have produced similar response rates [17, 23, 24], the optimal administration schedule for irinotecan remains uncertain. Although the experimental data suggest that protracted low-dose administration should result in increased efficacy [14, 15], it remains to be established whether there will be any schedule dependency with regard to the response rate in humans. The results from the phase II trials using the oral irinotecan formulation will help to clarify this issue. However, the results of the study reported here suggest that there will be no loss of efficacy. Furthermore, oral administration of irinotecan is pharmacologically attractive since it results in a relative increase in the exposure to the active metabolite of irinotecan, SN-38. The latter observation along with the lack of haematological toxicity and a patient preference for oral chemotherapy [31] are encouraging for the future widespread use of the PFC formulation of irinotecan.

In summary, in this phase I trial, oral irinotecan up to a dose of 30 mg/m^2 per day was well tolerated with none of the myelosuppression commonly associated with high dose-intensity intravenous infusions. The DLTs were diarrhoea, nausea and vomiting, and asthenia, and the MTD and dose recommended for phase II studies was 30 mg/m^2 per day.

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