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ORIGINAL ARTICLE

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A phase I, dose-finding study of irinotecan (CPT-11) short i.v. infusion combined with fixed dose of 5-fluorouracil (5-FU) protracted i.v. infusion in adult patients with advanced solid tumours

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Abstract *Purpose*: Irinotecan (CPT-11) and 5-fluorouracil (5-FU) are effective cytotoxic agents in the treatment of solid tumours. Continuous i.v. infusion (CI) of 5-FU is significantly more active and better tolerated than bolus i.v. 5-FU. This phase I pharmacokinetic and clinical study evaluated escalating CPT-11 doses administered every 3 weeks combined with a fixed dose of 5-FU CI over 14 days to find the maximum tolerated dose (MTD) of this combined chemotherapy. *Patients and methods*: Patients with solid tumours showing failure with previous standard treatment or for whom no established curative therapy existed received CPT-11 i.v. over 90 min (six dose levels were evaluated: 150, 175, 200, 250, 300 and 350 mg/m^2) plus a fixed dose of 5-FU CI 250 mg/m^2 per day over 14 days. If the MTD was not reached at CPT-11 level 6, then 5-FU was increased to 300 mg/m^2. In step 2, 5-FU was administered as a true protracted infusion at the recommended dose found during step 1. In step 3, the recommended dose of CPT-11 was divided and administered in a weekly schedule for 4 weeks combined with a fixed dose of 5-FU CI 250 mg/m^2, and then followed by 2–5 weeks rest. *Results*: Neutropenia and diarrhoea were the main toxicities, leading to early termination of infusion in three of six patients in level 7. Therefore, CPT-11 350 mg/m^2 + 5-FU 250 mg/m^2 CI over 14 days was identified as the recommended dose. In step 2, CPT-11 dose had to be reduced to 300 mg/m^2 due to toxicity. The weekly schedule of CPT-11 75 mg/m^2 + 5-FU 250 mg/m^2 CI was feasible with only one patient experiencing severe diarrhoea. No interactions were found in the kinetics parameters of CPT-11 or 5-FU for the different dose levels studied. *Conclusion*: CPT-11 300 mg/m^2 + 5-FU 250 mg/m^2 protracted infusion is the recommended dose for phase II trials, neutropenia and diarrhoea being the dose-limiting toxicities.

Keywords CPT-11 · 5-Fluorouracil · Phase I · Solid tumours · Pharmacokinetic

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Introduction

Irinotecan (CPT-11) and 5-fluorouracil (5-FU) are effective cytotoxic agents in the treatment of solid tumours such as colorectal cancer [1–3], lung cancer [4, 5] and gastric adenocarcinoma [6]. CPT-11 is a semisynthetic derivative of the natural alkaloid camptothecin that is hydrolysed in vivo to SN-38, an active metabolite that exerts its cytotoxic action by inhibiting the nuclear enzyme DNA topoisomerase I. Several phase I clinical trials on CPT-11 monotherapy have been carried out in Europe, United States and Japan, which showed that diarrhoea and neutropenia are the main dose-limiting toxicities (DLT) of the drug regardless of the schedule of administration [7–12]. CPT-11 350 mg/m^2 every 3 weeks has been the most commonly developed schedule in European countries because the highest dose-intensity was reached with this regimen compared with the weekly schedule.

Because colorectal cancer is usually a slow-growing tumour, with few cells actively dividing at the same time, the use of continuous infusion (CI) of 5-FU has been

extensively explored in recent decades. Several phase II studies in patients with advanced colorectal cancer evaluating 300 mg/m^2 per day of 5-FU CI, have shown an overall response rate of 25–50% [13–15]. A meta-analysis of seven phase III trials comparing bolus i.v. 5-FU versus 5-FU CI confirmed a modest but significant improvement in response rate favouring CI [16]. This meta-analysis also showed some differences in the toxicity profile according to the route of administration. Grade 3 or 4 haematological toxicity was uncommon in CI schedules, whereas hand-food syndrome was the most prevalent toxic adverse event. There were no differences in the proportion of other non-haematological toxicities such as diarrhoea, nausea/vomiting or mucositis. According to these findings, a prolonged infusion regimen of 5-FU was therefore chosen as the basis to investigate the optimum dose and schedule of CTP-11 in this combination.

We report here the results of a phase I clinical and pharmacokinetic study of escalating doses of CPT-11 administered every 3 weeks combined with a fixed dose of 5-FU CI over 14 days. The objectives of the study were: (1) to establish the maximum tolerated dose (MTD) of CPT-11 for this schedule, (2) to determine the quantitative and qualitative toxic effects, the DLT and the recommended dose for phase II trials, (3) to define the safety profile of this combination, (4) to investigate if any antitumour activity could be documented, and (5) to determine the pharmacokinetic parameters of CPT-11 and 5-FU and their metabolites.

Patients and methods

The protocol and the patient consent form were reviewed by Independent Ethics Committees at the two centres involved in the study (Hospital Universitario San Carlos and Hospital Universitario 12 de Octubre, in Madrid).

Selection of study population

The inclusion criteria for the present study were: written informed consent, signed and dated; histologically proven advanced solid tumour; adults (18–70 years of age) who had previously failed standard treatment or for whom no established curative therapy existed; life expectancy >3 months; WHO performance status ≤ 2; polymorphonuclear neutrophil count >2000 mm^{-3}, platelets count $>100{,}000$ mm^{-3}, haemoglobin >10 mg/dl; satisfactory renal function: creatinine <125 μmol/l; prothrombin time >0.5 normal time; bilirubin <1.5 times the upper limit of the normal range (UNL) and serum transaminases <3 times UNL or, in the presence of hepatic metastases, bilirubin <1.5 times UNL and serum transaminases <5 times UNL; prior therapy without limitation for the first dose levels and for the final steps near the MTD and recommended dose, a maximum of one previous chemotherapy regimen; a washout period since previous chemotherapy of 4 weeks (6 weeks for previous mitomycin C, nitrosourea or extended-field radiation therapy); absence of previous exposure to topoisomerase I inhibitors; absence of severe concomitant infections, major organ failure, angina pectoris, bowel obstruction or inflammatory intestinal disease and symptomatic brain metastases or carcinomatous leptomeningitis; no prior severe toxicity with the same schedule of 5-FU; and absence of history of other cancer except curatively resected in situ cervical carcinoma or basal/spindle cell carcinoma of the skin. Pregnant woman or patients (male or female) with reproductive potential and no effective contraception were excluded.

Pretreatment and follow-up studies

During the 7 days before registration a complete history, physical examination and determination of performance status were obtained for each patient. Complete blood cell counts were performed at baseline and twice weekly during the treatment period. Biochemistry analyses including renal and hepatic function, serum electrolytes and prothrombin time were obtained at baseline and then weekly. A chest radiograph and an ECG were carried out at baseline and when clinically indicated. Toxic effects were classified according to the National Cancer Institute (NCI) common toxicity criteria and a weekly assessment was required. Tumour response evaluation was recorded by the investigators according to WHO criteria, following the general practice in each centre.

Dosage and drug administration

The study design had three distinct steps:
Step 1 A fixed dose of 5-FU 250 mg/m^2 per day CI was administered over 14 days using an indwelling catheter and a portable infusion device, followed by a 7-day rest period. Any commercially available form of 5-FU licensed and registered in Spain was permitted. CPT-11 was administered i.v. over 90 min on day 1 just before 5-FU infusion, using the following dose escalation scheme: 150, 175, 200, 250, 300, 350 mg/m^2. If the MTD was not reached at level 6, a seventh dose level would be studied with the maximum dose of CPT-11 (350 mg/m^2) and with an increased 5-FU dose (300 mg/m^2). No dose escalation was permitted in any patient. CPT-11 was provided by Rhône-Poulenc-Rorer in the form of ready-to-use vials containing 100 mg of active drug. Three patients were initially enrolled at each level, and they had to receive at least one cycle and be observed for toxicity during a minimum of 2 weeks before escalating to the next dose level. If one of these three patients developed a DLT at one level, at least three more patients had to be treated at the same dose

level. If a DLT occurred, the infusion was to be discontinued immediately, regardless of the duration of the cycle at that time. MTD was considered to have been reached when 50% of patients experienced the same DLT, defined as grade 4 haematological toxicity, febrile neutropenia (fever >38.5°C concomitant with grade 3 or 4 neutropenia), sepsis concomitant to grade 3/4 neutropenia, symptomatic thrombocytopenia, any grade 3 or 4 nonhaematological toxicity at cycle 1 except for alopecia, or early infusion termination before 14 days for any reason other than technical issues, only for the first step and first infusion. The recommended dose was defined as the dose level immediately below the MTD.

Step 2 Patients were treated with the recommended dose of CPT-11 found in the previous step and 5-FU CI was extended to a true protracted CI (3 of 3 weeks without a break). At least three patients were to be treated at the recommended dose of the combination. 5-FU infusion starting either on the same day as CPT-11 or on day 3 to evaluate pharmacological interaction between the two drugs.

Step 3 A fixed dose of 5-FU 250 mg/m^2 CI was combined with the recommended CPT-11 dose on a weekly schedule for 4 weeks, dividing the dose by four, and then followed by 2–5 weeks rest to allow recovery from toxicity, thus assessing the feasibility of a weekly schedule at the recommended dose of the combination.

Pharmacokinetic evaluation

Sampling schedule

Plasma samples for the determination of CPT-11, SN-38 and 5-FU were to be obtained during the first and second steps of this study. Samples were obtained before drug infusion, during infusion at 20, 40, 60 and 90 min, and then at 5 min, 30 min and 1, 2, 4, 8, 12, 24, 36, 48, 96, and 168 h after the end of drug infusion during the first and second steps. During the second step, for those patients who started 5-FU infusion 48 h after the start of CPT11 administration, sampling times were predose, at 40 min and 90 min during infusion of CPT11, and then until 336 h. The times scheduled for the collection of samples for measurement of 5-FU were 48, 96, 168, 240 and 336 h.

Determination of CPT11, SN38 and 5-FU

5-FU and total plasma concentrations of CPT11 and its metabolite SN38 (both carboxylate and lactone forms) were measured by HPLC following previously described methods [17]. In all cases the quantitation limits were established to be 5 ng/ml and intraassay and interassay variabilities were lower than 10%.

Pharmacokinetic and statistical analyses

The pharmacokinetic analysis of CPT-11 was done using a non-compartmental approach. Calculations were performed with Win-Nonlin Professional. The main pharmacokinetic variables evaluated for CPT-11 were AUC_{0-inf}, AUC_{0-last}, Cl, C_{max} and $t_{1/2}$. The main pharmacokinetic variables evaluated for the SN-38 metabolite were AUC_{0-last}, AUC_{0-inf}, C_{max} and $t_{1/2}$. The ratio AUC_{CPT-11}/AUC_{SN-38} was also calculated. Dose linearity and differences in clearance by dose level were evaluated by ANOVA. Data are shown as means $\pm$ SD.

For 5-FU the main parameters calculated were C_{ss}, AUC_{0-24}, AUC_{0-48} and Cl_{ss}. The concentrations of 5-FU during stable infusion showed marked variations in some patients, and therefore the C_{ss} was defined as the median of those concentrations reaching a plateau by visual inspection. Clearance at steady-state (Cl_{ss}) was calculated as the quotient infusion rate by concentration at steady-state (C_{ss}).

Data from 42 patients (44 infusions) were available for pharmacokinetic analysis of CPT-11 and SN-38, and 42 patients were also included in the kinetic analysis of 5-FU.

Results

The characteristics of the 54 patients involved in the study are listed in Table 1. Of these 54 patients, 31 were included in step 1 (dose escalation). In step 2, 17 patients received a fixed dose of 5-FU 250 mg/m^2 per day CI with CPT-11 350 mg/m^2 in 8 or CPT-11 300 mg/m^2 in nine. Six patients were recruited in step 3. Two patients (both in step 3) were considered not eligible, one due to a history of more than one palliative chemotherapy and another due to a history of a second cancer (bowel

Table 1 Patient characteristics ($n=54$)

Age (years)	
Median	57.5
Range	21–71
Male/female	40/14
Performance status	
0–1	50 (92.5%)
2	4 (7.5%)
Tumour types	
Gastrointestinal (total)	35 (64.8%)
Colorectal	27 (50%)
Head and neck	4 (7.4%)
Others	15 (27.8%)
Sites of disease	
Liver	29 (53.7%)
Lung	19 (35.2%)
Abdominal lymph nodes	11 (20.4%)
Others	32 (61.2%)
Prior therapy	
Chemotherapy	48 (88.9%)
Surgery	43 (79.6%)
Radiotherapy	15 (27.8%)
Immunotherapy	3 (5.6%)

lymphosarcoma). A total of 109 cycles were received by patients in step 1 and a total of 92 were given during steps 2 and 3. All treated groups were similar in the median number of cycles received (overall median value of three).

Determination of MTD and recommended dose

Six patients experienced at least one DLT during cycle 1; all of these patients were in the highest dose groups (Table 2). Neutropenia and diarrhoea were the main toxicities, leading to early termination of infusion in three out of six patients at level 7 (CPT-11 350 mg/m^2 + 5-FU 300 mg/m^2 CI over 14 days). Therefore, CPT-11 350 mg/m^2 + 5-FU 250 mg/m^2 CI over 14 days was identified as the recommended dose. Nevertheless, in step 2 of the study, when 5-FU was administered as a true protracted infusion (without any period of rest), four out of eight patients experienced grade 3/4 diarrhoea and neutropenia. In accordance with these findings, CPT-11 300 mg/m^2 + 5-FU 250 mg/m^2 protracted infusion was considered the optimum combination for this schedule. Only one patient in the weekly scheme presented DLT grade 3/4 diarrhoea. A weekly schedule of CPT-11 75 mg/m^2 + 5-FU 250 mg/m^2 protracted infusion for 4 weeks every 6 weeks is feasible, but due to the design of this study it is not possible to recommend this dose for weekly administration.

Haematological toxicity

In step 1, neutropenia appeared in 67.8% of evaluable patients and 50.5% of evaluable cycles. Grade 3/4 neutropenia during the first cycle only occurred with the three highest dose groups (one out of three patients at 300/250, one out of six patients at 350/250 and three out of six patients at 350/300). The median time to nadir in both the first evaluable cycle and all evaluable cycles was 13 days for the neutrophil concentration, and the median time for recovery from grade 3/4 neutropenia to grade 1 was 4 days. During step 2, grade 3/4 neutropenia occurred in four out of eight patients (three of them during the first cycle) at a dose of CPT-11 350 mg/m^2, and six out of nine patients (four of them during the first cycle) at a CPT-11 dose of 300 mg/m^2. The nadir was reached at a median time of 10 days and the median time for recovery from grade 3/4 neutropenia to grade 1 was 6 days. No grade 3/4 neutropenia was found when CPT-11 was administered on a weekly schedule.

Only three cases of grade 3/4 anaemia were reported (two during the first cycle), all of them in the lowest dose groups. There were no cases of grade 3/4 thrombocytopenia in any of the evaluable first cycles in step 1. Only three patients in all evaluable cycles in steps 2 and 3 experienced grade 3/4 thrombocytopenia.

Nonhaematological toxicities

The most frequent nonhaematological adverse events are listed in Table 3. During the first step, 19 patients (61.3%) experienced diarrhoea, 14 of them in the three highest dose groups. Grade 3/4 diarrhoea appeared in one patient at level 5 (300/250) and two patients at level 7 (350/300). During steps 2 and 3, diarrhoea was reported in 20 patients (80.7%) and 51 cycles (55.4%), being grade 3/4 in 47.8% of patients and 16.3% of cycles, respectively. The proportion of cycles with grade 3/4 diarrhoea and the number of cycles in which diarrhoea resulted in hospitalization was much smaller with the weekly schedule than with the 3 weeks administration (14 out of 66 cycles in step 2, and 2 out of 26 cycles in step 3). At the recommended dose, the median time to onset of grade 3/4 diarrhoea was 7 days (range 2–16 days) in the first and following cycles. The median durations of grade 3 and 4 diarrhoea were 8 and 11 days, respectively (range 1–21 days). Apart from diarrhoea, other adverse events including emesis, asthenia, alopecia and cholinergic

Table 3 Nonhaematological adverse events (worst NCI grade) by patient during step 1

Toxicity	Grade 3/4	All
Diarrhoea	3 (9.7%)	19 (61.3%)
Vomiting	2 (6.5%)	17 (54.8%)
Nausea	1 (3.2%)	12 (38.7%)
Asthenia	1 (3.2%)	13 (41.9%)
Cholinergic syndrome	0	11 (35.5%)
Alopecia	0	16 (51.6%)
Mucositis	2 (6.5%)	9 (29.0%)
Neurological symptoms	1 (3.2%)	2 (6.5%)
Cutaneous signs	0	3 (9.7%)

Table 2 Incidence of DLTs during the first cycle of CPT-11 + 5-FU CI over 14 days (step 1, $n = 31$)

DLTs	Dose levels of CPT-11/5-FU (mg/m^2)						
	150/250 ($n = 3$)	175/250 ($n = 4$)	200/250 ($n = 3$)	250/250 ($n = 3$)	300/250 ($n = 6$)	350/250 ($n = 6$)	350/300 ($n = 6$)
Drug-related toxicity leading to early termination of infusion	0	0	0	0	1	0	3
Grade 4 neutropenia	0	0	0	0	1	0	1
Febrile neutropenia	0	0	0	0	0	1	2
Grade 3/4 diarrhoea	0	0	0	0	1	0	2

syndrome were considered to be clinically relevant. Some abnormal values of bilirubin ASAT and ALAT concentrations were observed, all of them mild or moderate. No toxic deaths were reported during this trial.

Efficacy data

Although efficacy was not a primary end-point of the study, 11 out of 47 patients eligible and evaluable for response who had been treated in all three steps achieved an objective response. Overall response rate was 23.4%. Of 27 patients with advanced colorectal cancer as a primary tumour, 22 were evaluable for response. Eight patients (36.4%), all but one previously treated with chemotherapy for advanced disease, achieved an objective partial response. Interestingly, six out of ten patients (60%) with advanced colorectal cancer responded at the recommended doses used in steps 2 and 3. Furthermore, objective responses were recorded in one patient with squamous cell head and neck carcinoma, one patient with a pancreatic primary tumour and a woman diagnosed with uterine carcinoma and pulmonary metastases.

Pharmacokinetic results

Dose linearity was found for AUC_{0-last} ($P < 0.0001$), AUC_{0-inf} ($P < 0.001$) and C_{max} ($P = 0.0234$). No clearance differences were found between the different dose levels, although the number of patients was low and the variability high. No differences were observed between the two 5-FU administration schedules in step 2. Mean clearance for all the patients evaluated was 11.06 ± 4.54 l/h/m^2, and mean terminal plasma half-life was 11.73 ± 6.27 h. Table 4 shows the mean parameters of CPT-11 and SN-38 for the 300 mg and 350 mg doses, where the patients studied provided a more accurate estimation. Figure 1 depicts plasma concentration profiles for CPT-11 and SN-38 in those patients receiving the final recommended dose.For calculation of AUC_{0-24} and AUC_{0-48} of 5-FU, 33 and 28 patients were available, respectively, and 9 of them were available in the group receiving the 300 mg dose level of CPT-11 (see Fig. 2). No apparent differences in C_{ss} or Cl were found for the coadministered dose of CPT-11. The AUCs calculated at 24 h ($n = 33$) and 48 h ($n = 28$) were 2668.6 (1210.7) and 4733.5 (2255.9). The mean C_{ss} and calculated Cl were 114.2 ± 62.7 μg/l and 121.7 ± 70.1 l/h/m^2, respectively.

For some patients a reliable calculation of the time-plasma concentration terminal slope for SN-38 was not possible and therefore AUC_{0-inf} was not calculated.Table 5 shows the mean ratios of SN-38/CPT-11 for AUC_{0-last} and AUC_{0-inf}. Although highly variable, these data agree with those reported in the literature, showing that plasma concentrations of CPT-11 are about 100 times greater than those of SN-38. A significant positive linear relationship was found between CPT-11 and SN-38 for the parameters AUC_{0-last} ($r = 0.48$; $P = 0.0014$) and C_{max} ($r = 0.37$; $P = 0.0174$).

Discussion

5-FU and CPT-11 are among the most active drugs against advanced colorectal cancer. Preclinical studies have shown an additive cytotoxic effect of both drugs, 5-FU and CPT-11, when used in combination [18]. During the last decade, several phase I clinical trials have assessed the feasibility and safety profile of different combinations of CPT-11 and 5-FU (with or without leucovorin) [19–27]. The DLTs reported in these previous trials are summarized in Table 6. Weekly, biweekly and every 3 or 4 weeks CPT-11 schedules have been evaluated, and the recommended doses were 80–125 mg/m^2 for the weekly schedule, 180–200 mg/m^2 for the biweekly schedule and 250–400 mg/m^2 for the every 3 or 4 weeks schedule, depending on the combined 5-FU schedule and whether leucovorin was added or not. 5-FU was administered as intravenous bolus, intermittent high-dose or 4-day CI, and was primarily modulated by leucovorin. In these studies, neutropenia and diarrhoea were found to be the main DLTs, although some differences in the pattern of toxicity were seen depending on the schedule. Hence, myelosuppression was lower with weekly CPT-11, mostly associated with 5-FU CI [20, 21]. In contrast, neutropenia (not diarrhoea) was the DLT of high-dose CPT-11 every 3 or 4 weeks or given with bolus 5-FU plus leucovorin [19, 22,

Table 4 Kinetic parameters of CPT-11 and SN-38 by dose level of CPT-11 administered (*AUC* area under the plasma concentration time curve, C_{max} maximum plasma concentration, t_{max} time to reach C_{max}, *Cl* clearance, $t_{1/2}$ terminal elimination half-life)

Dose level (mg/m^2)	AUC_{0-last} (μg/h l) CPT11/SN38	AUC_{0-inf} (μg/h l) CPT11/SN38	C_{max} (μg/l) CPT11/SN38	t_{max} (h) CPT11/SN38	Cl (l/h/m^2) CPT11	$t_{1/2}$ (h) CPT11/SN38
300						
Number od observations	14/14	14/13	14/14	14/14	14	14/13
Mean	30994.1/359.9	31856.2/631.9	4208.3/73.4	1.5/3.4	11.8	12.0/13.5
SD	16927.1/457.0	17055.4/643.3	1129.2/34.3	0.2/6.4	5.6	7.6/19.8
350						
Number of observations	17/17	17/13	17/17	17/17	17	17/13
Mean	35186.7/417.5	37674.7/550.4	5195.9/98.9	1.7/1.5	10.8	11.6/9.2
SD	12653.3/457.6	14036.8/517.9	1972.3/162.2	0.3/0.6	4.6	6.4/8.3

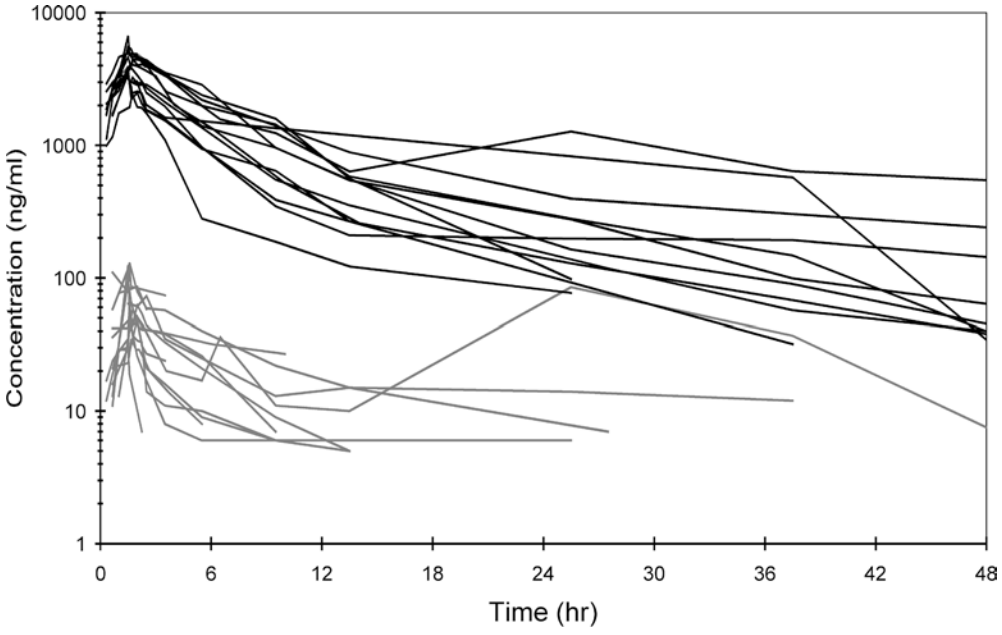

Fig. 1 Semilogarithmic plot of concentration–time profile for those patients receiving the final recommended 300 mg dose level ($n = 14$). CPT-11 concentration are those in the upper range (*dark lines*) while SN-38 are all in the lower part (*light lines*)

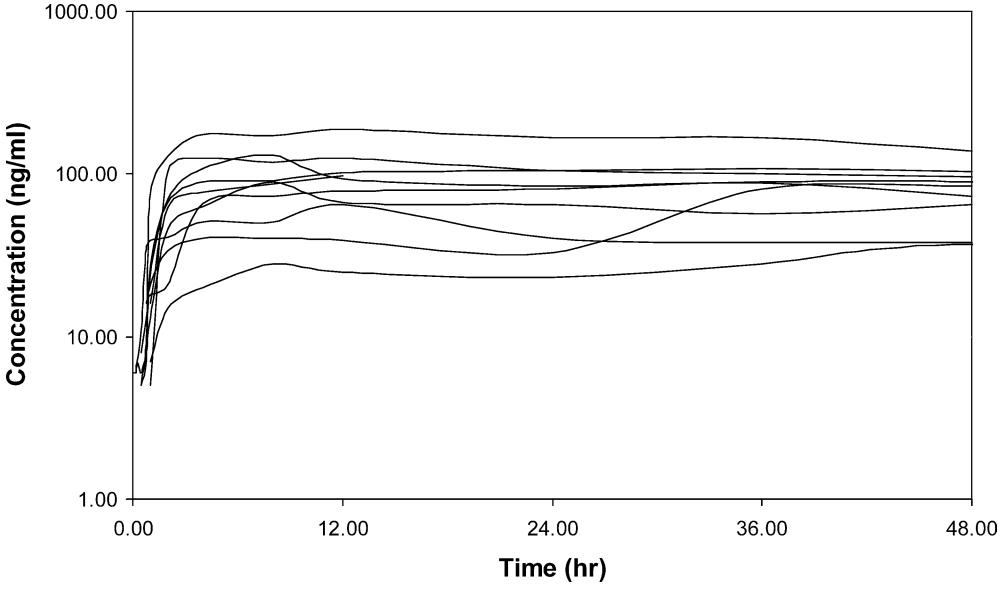

Fig. 2 Semilogarithmic plot of concentration–time profile for 5-FU in patients receiving the final recommended 300 mg dose level of CPT-11 and for whom a full profile could be obtained ($n = 9$)

Table 5 SN38/CPT11 AUC ratios

	AUC_{0-last} ($n = 42$)	AUC_{0-inf} ($n = 38$)
Mean	0.011	0.016
SD	0.010	0.012

23, 26], thus underlining the well-known different pattern of 5-FU toxicity according to the type of infusion.

Saltz et al. [28] reported an acceptable tolerability of their CPT-11 plus bolus 5-FU/LV combination in their phase III trial, but an additional analysis focusing on the toxicity in two phase III trials (N9741, C89803) comparing 5-FU bolus/leucovorin plus CPT-11 versus a regimen of oxaliplatin led to the boards of the North Central Cancer Treatment Group and Leukemia Group B to recommend the suspension of enrolment in these trials due to an unexpectedly high death rate associated with the use of an identical drug combination, and to suggest a better option based in infusional schedules of 5-FU associated with CPT-11 [29]. In the present trial, both neutropenia and diarrhoea were DLTs, but when the recommended-dose of CPT-11 was fractionated weekly for 4 weeks, severe neutropenia was not seen and the incidence of hospitalization due to severe diarrhoea was also lower than with the 3-week schedule.

Our goal was to find a suitable combination of the European gold standard CPT-11 every 3 weeks with a nonhaematologically toxic drug and schedule such as 5-FU protracted infusion. To add more information, we tried to verify whether our recommended dose could be adapted to an American weekly CPT-11 schedule. In our

Table 6 Phase I studies combining irinotecan + 5-FU with or without leucovorin (*B* bolus, *ICI* intermittent CI, *PCI* protracted CI, *LV* leucovorin)

CPT-11 weekly			CPT-11 biweekly			CPT-11 every 3–4 weeks		
Reference	Schedule	DLTs	Reference	Schedule	DLTs	Reference	Schedule	DLTs
19	5-FU B + LV	Neutropenia	22	5-FU B + LV	Neutropenia	24	5-FU ICI + LV	Neutropenia, diarrhoea
20	5-FU ICI + LV	Diarrhoea	23	5-FU B + ICI	Neutropenia, diarrhoea	25	5-FU PCI	Neutropenia, diarrhoea
21	5-FU ICI	Diarrhoea				26	5-FU B	Neutropenia
						27	5-FU B + LV	Neutropenia, diarrhoea
						This trial	5-FU PCI	Neutropenia, diarrhoea

experience, although the weekly schedule was clearly less toxic, as described above, we cannot recommend a specific dose of CPT-11 because the MTD for this combination is still unknown. Only a new phase I trial will help clarify this issue. Apart from neutropenia and diarrhoea, other clinically relevant side effects were emesis, asthenia and mucositis. Although steroids and serotonin antagonist drugs were allowed and routinely given to the patients, about half of the patients suffered from nausea or vomiting during the treatment period but none of them discontinued the treatment due to this adverse event. Most cases of asthenia and mucositis were mild or moderate.

Cytotoxic activity was not a primary objective of this study, but it is worth noting that the overall response rate was 23.4%. Pretreated patients with advanced colorectal cancer represented 50% of the responding population, with an overall response rate of 36.4%, and 60% for patients treated at the recommended doses. Despite the low number of patients involved in the study, the results are better than those achieved in second-line phase II trials with CPT-11 alone [2, 3, 30], or in trials with second-line infusional 5-FU with or without leucovorin [31, 32]. Our overall response rate in pretreated patients is slightly lower than that obtained in two recent phase III trials in nonpretreated patients involving three different schedules of CPT-11 plus 5-FU/leucovorin [28, 33].

Pharmacokinetic data and conclusions

The pharmacokinetic parameters observed for CPT-11 and SN-38 when CPT-11 was administered with 5-FU are similar to those found in previous studies when CPT-11 was administered alone [34]. The relatively low concentration of SN-38 compared to CPT-11 levels (about 100-fold lower) was also consistent with previous findings [34, 35].

A linear increase in plasma concentrations of CPT-11 was observed with increasing doses, although variability was high and a low number of patients were evaluated at lower doses. Moreover, a linear relationship was found between CPT-11 and SN-38 for both AUC and C_{max}. The concentrations and the clearance of 5-FU when combined with CPT-11 agree with those described in the literature when 5-FU is administered alone [36, 37].

In conclusion, the recommended doses for phase II trials are 300 mg/m^2 for CPT-11 every 3 weeks and 250 mg/m^2/daily for protracted infusion of 5-FU. Neutropenia and diarrhoea are the DLTs of this combined schedule.

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