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CPT-11 (Irinotecan) and 5-Fluorouracil: a Promising Combination for Therapy of Colorectal Cancer

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CPT-11 (Campto®, irinotecan) is a new topoisomerase I inhibitor and one of very few new cytotoxic agents to demonstrate clinical activity in colorectal cancer since the introduction of 5-fluorouracil (5-FU) into clinical practice almost 40 years ago. Because of the unique mechanism of action of CPT-11, its proven activity in colorectal cancer, and its lack of cross-resistance with 5-FU, the combination of CPT-11 with 5-FU is a logical approach to attempt to improve on the results obtained with CPT-11 or 5-FU-based treatments alone. Various administration schedules of CPT-11/5-FU combinations have been investigated in phase I studies in Japan, the U.S. and Europe. Preliminary results indicate that concurrent administration of substantial doses of CPT-11, 5-FU and folinic acid is feasible in terms of safety. Preliminary analysis of controlled pharmacokinetic data suggests that 5-FU has no substantial effect on the metabolism of CPT-11 to its active metabolite SN-38. Major objective responses and other indicators of clinical activity have been observed with the combination in both chemotherapy-naive and pretreated patients with colorectal cancer. Studies are ongoing to define fully optimum dosage schedules of CPT-11/5-FU combinations, and some of these schedules will soon enter phase II and III clinical trials. It is hoped that such a combination will prove to be an important advance in the treatment of colorectal cancer. Copyright © 1996 Elsevier Science Ltd

Key words: CPT-11, 5-FU, colorectal cancer

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INTRODUCTION

THE EFFICACY of CPT-11 (Campto®, irinotecan) in metastatic colorectal cancer has been demonstrated in both chemotherapy-naive patients and in those who are refractory to 5-fluorouracil (5-FU) [1–5]. Furthermore, CPT-11 and 5-FU have different mechanisms of action and do not appear to exhibit cross-resistance [6, 7]. It is possible, therefore, that a combination of CPT-11 and 5-FU will have significant activity in the treatment of advanced colorectal cancer. However, because of the similar adverse event profiles of the two drugs, toxicity is a potential concern with the combination. The dose-limiting toxicities for CPT-11 are delayed diarrhoea and neutropenia [6]; with 5-FU, particularly when it is co-administered with folinic acid, the most important adverse effects are diarrhoea, neutropenia and mucositis [7, 8].

Various administration schedules of CPT-11/5-FU combinations have been or are currently being investigated in phase I trials. The objectives of these studies are to define the optimal starting dose of each agent and the dose-limiting toxicities for the combination, and to evaluate the effects of 5-FU on the pharmacokinetics of CPT-11.

Available results of phase I studies are summarised in Table 1 [9–13] and presented below, in chronological order.

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THE JAPANESE EXPERIENCE

In two Japanese studies involving a total of 56 patients with metastatic colorectal cancer, CPT-11 was given in escalating doses as a 90-min intravenous infusion, in combination with a 5- to 7-day continuous infusion of 5-FU, either as a simultaneous schedule administered every 3–4 weeks or as a sequential schedule repeated every 45 weeks.

Simultaneous administration of CPT-11 and 5-FU

In the first study, CPT-11 and 5-FU were administered simultaneously. CPT-11 was given in doses of 50–250 mg/m^2 as a 90-min intravenous infusion (day 1) immediately followed by a 7-day continuous infusion of 5-FU (400 mg/m^2/day) (Figure 1) [10, 14]. 36 patients

Table 1. Summary of phase I studies of CPT-11 in combination with 5-FU

Study design; country (reference)	Doses (mg/m^2) and administration: CPT-11	5-FU	Other	Schedule	Results
Metastatic colorectal cancer; chemotherapy-naive Historical control (CPT-11 alone) Japan [9, 10]	50–250, 90-min infusion, d1 (dose escalation in increments of 25)	400/day CI, d1–d7 (fixed dose)	$5HT_3$ antagonist prior to CPT-11 doses ≥175	sim. q3-4w	MTD CPT-11 250 mg/m^2 4/36 PR (ORR: 11.1%) AUC (SN-38): combination< CPT-11 alone
Metastatic colorectal cancer; chemotherapy-naive Non-comparative Ongoing study Japan (Y. Shimada, personal communication)	100–175 90-min inf, d1 + d15 (dose escalation in increments of 25)	600/day CI d3–d7 (fixed dose)	–	seq. q4-5w	MTD of CPT-11 not reached (at 150 mg/m^2) 5/19 PR (ORR: 26.3%)
Metastatic colorectal cancer; 20/24 pretreated with 5-FU U.S.A. [11]	(i) 100, 90-min infusion (fixed dose) (ii) 100–125–150, 90 min infusion (dose escalation)	(i) 210–425 i.v. bolus (dose escalation) (ii) 500, i.v. bolus (fixed dose)	FA 20 (i.v. bolus FA 20 (i.v. bolus)	All drugs weekly for 4w, then 2w break;	No substantial differences in AUC (CPT-11 or SN-38) for CPT-11 with or without 5-FU/FA MTD CPT-11 125, 5-FU 500, FA 20 4/19 PR
Solid tumours (colorectal 21/29); second or third-line, refractory Crossover Ongoing study France [12]	200–350 30-min infusion, d1 or d6 (dose escalation in increments of 15%)	375 i.v. bolus d2–d6 or d1–d5 (fixed dose)	–	q4w; CPT-11 given 1d before or 1d after 5-FU	No difference in CPT-11 or SN-38 clearance for CPT-11 given before or after 5-FU MTD not reached at CPT-11 300/5-FU 375

AUC, area under the plasma concentration–time curve; CI, continuous infusion; FA, folinic acid; 5-FU, 5-fluorouracil; $5HT_3$ antagonist, granisetron; i.v., intravenous; MTD, maximum tolerated dose; ORR, overall response rate in evaluable patients; PR, partial response; pts, patients; q3-4w, every 3–4 weeks; seq, sequential administration of drugs; sim, simultaneous administration of drugs; SN-38, active metabolite of CPT-11; w, weeks.

with metastatic colorectal cancer were enrolled, the majority of whom had received previous chemotherapy with 5-FU or cisplatin. The dose of CPT-11 was increased in increments of 25 mg/m^2, and granisetron was administered prior to doses ≥ 175 mg/m^2 to prevent nausea and vomiting. This regimen was repeated every 3–4 weeks until grade 3 non-haematological or grade 4 haematological toxicity was observed.

When given in combination with this continuous infusion of 5-FU, the maximum tolerated dose (MTD) of CPT-11 was 250 mg/m^2, the same as the Japanese MTD of CPT-11 when administered as a single agent. Neutropenia and diarrhoea were the dose-limiting toxicities. Four partial responses were achieved, at dose levels of 100, 150, 200 and 225 mg/m^2, respectively (overall response rate 11.1%) [10]. The pharmacokinetics of CPT-11, its active metabolite SN-38, and 5-FU were analysed in 12 patients in this study; 3 or these patients were treated with CPT-11 100 mg/m^2, 3 with 125 mg/m^2 and 6 with 150 mg/m^2. These pharmacokinetic data were compared with historical data from lung cancer patients treated with CPT-11 (100 mg/m^2) alone [9].

The area under the plasma concentration–time curve (AUC) of SN-38, an active metabolite of CPT-11, was sig-

Japanese study [9, 10]
Design: non-comparative; pharmacokinetic data were compared with historical data (from lung cancer patients given CPT-11 alone)
CPT-11: 30-min intravenous infusion
5-FU: 7-day continuous infusion

Day of cycle:	1 2 3 4 5 6 7 8 9–14	15–21	Cycles repeated every 3–4 weeks
Cycle 1: CPT-11	✓ – – – – – – – –	–	
5-FU/FA	– ——————→ –	–	

American study [11]
Design: crossover–alternating 6-week cycles; ↔ = 24-h pharmacokinetic sampling
CPT-11: 90-min intravenous infusion
5-FU/folinic acid: intravenous bolus injections

Day of cycle:	1 2	8	15	22	29–35	36–42
Cycle 2: CPT-11	✓ – – – – – – ✓	– – – – – – ✓	– – – – – – ✓		–	–
5-FU/FA	– ✓ – – – – – ✓	– – – – – – ✓	– – – – – – ✓		–	–
	↔	↔				
Day of cycle:	1 2	8	15	22	29–35	36–42
Cycle 1: 5-FU/FA	✓ – – – – – – ✓	– – – – – – ✓	– – – – – – ✓		–	–
CPT-11	✓ – – – – – – ✓	– – – – – – ✓	– – – – – – ✓		–	–
	↔					

European study [13]
Design: crossover–alternating 4-week cycles
CPT-11: 30-min intravenous infusion
5-FU: intravenous bolus injections

Day of cycle:	1 2 3 4 5 6 7 8–14	15–21	22–28	1 2 3 4 5 6 7 8–14, etc ...
Cycle 1: CPT-11	✓ – – – – – – –	–	–	Cycle 2: – – – – – ✓ – –
5-FU	– ✓ ✓ ✓ ✓ ✓ – –	–	–	✓ ✓ ✓ ✓ ✓ – –

Figure 1. Comparison of administration schedules used in phase I studies of CPT-11/5-FU combinations in patients with advanced colorectal cancer.

nificantly lower in patients treated with the CPT-11/5-FU combination than in those who had received CPT-11 to SN-38 by carboxylesterase may have been inhibited during co-administration of 5-FU. Conversely, the pharmacokinetics of 5-FU did not appear to be influenced by concomitant administration of CPT-11.

The results of this pharmacokinetic analysis, however, should be interpreted with caution. Firstly, there was considerable interpatient variation in the values of the pharmacokinetic parameters of CPT-11 and SN-38 observed within the present study [14]. More importantly, the results for the comparison were derived from two entirely separate patient populations with different cancers and who received different CPT-11 regimens.

Sequential administration of CPT-11 and 5-FU

In a second, non-comparative, ongoing study of chemotherapy-naive patients with histologically-confirmed metastatic colorectal cancer, the combination regimen was modified from a simultaneous to a sequential schedule to avoid the pharmacokinetic interaction suggested in the earlier study. In that study, CPT-11 disappeared from the plasma within 48 h of administration; therefore, in the subsequent trial, following administration of CPT-11 on day 1, 5-FU was delayed until day 3 of the treatment cycle. The continuous infusion of 5-FU was shortened to 5 days to improve patient compliance, and the equivalent daily dose was increased to 600 mg/m^2. The four planned doses of CPT-11 were 100, 125, 150 and 175 mg/m^2, given as a 90-min infusion. The dose intensity of CPT-11 was increased compared with the earlier study, by administering it every 2 weeks, on days 1 and 15 of the treatment cycle. This cycle was repeated every 4 to 5 weeks.

Preliminary results are available for CPT-11 dose levels up to 150 mg/m^2 (level 3). 20 patients have been enrolled to date, of whom 19 are assessable. Neutropenia was manageable at these first three dosage levels; only 1 patient experienced grade 4 neutropenia (125 mg/m^2 dose level). The incidence of diarrhoea during the first course of treatment was also low; only 1 patient experienced grade 4 diarrhoea (125 mg/m^2 dose level) and this resolved completely.

Although antitumour response was not a primary endpoint, a total of five partial responses (four at 126 mg/m^2 and one at 150 mg/m^2) were observed in assessable patients giving an overall response rate of 26.3% (95% confidence interval (CI) 6.5–46.1%). The final results of this study are currently being prepared for publication (Y. Shimada, personal communication).

THE AMERICAN EXPERIENCE

Several studies of CPT-11-based combination therapy are in progress in the U.S. (L. Saltz, personal communication). We shall present the experience of the Memorial Sloan-Kettering Cancer Center (New York) [11]. The combination used at this centre was based on the schedule of CPT-11 which has been most widely investigated in the

U.S.—a single 90-min infusion given once weekly for 4 weeks followed by a 2-week break. This was combined with a modified 5-FU regimen in which folinic acid was co-administered with once-weekly bolus injections of 5-FU.

The objective of the study was to determine the MTD of 5-FU given, with fixed doses of CPT-11 and folinic acid. CPT-11 was given at a dose of 100 mg/m^2 over 90 min (a 20% reduction from the usual starting dose of 125 mg/m^2). 5-FU was given in escalating doses starting at 210 mg/m^2. When a dose of 500 mg/m^2 of 5-FU was reached, the 5-FU dose was fixed at this level, and thereafter doses of CPT-11 were increased from 100 mg/m^2 in increments of 25 mg/m^2. Throughout the study, folinic acid was given at a fixed dose of 20 mg/m^2 by intravenous bolus injection. The low dose of folinic acid was selected to minimise the occurrence of diarrhoea. All drugs were given weekly for 4 weeks, followed by a 2-week break.

As noted earlier in this manuscript, data from the Japanese group had suggested that there might be an interaction with 5-FU that inhibited the conversion of CPT-11 to its active metabolite, SN-38 [9, 10]. This was felt to be an important issue to explore in the American study, which was designed to investigate this interaction (see Figure 1). On day 1 patients received CPT-11 only, and 24-hour sampling was performed for pharmacokinetic analysis. At the end of the 24-h period (day 2), patients received folinic acid and 5-FU. The following week (day 8), patients received all 3 drugs together, and 24-h pharmacokinetic sampling was repeated. At the beginning of the second 6-week cycle, the order of drug administration was reversed—folinic acid and 5-FU were given first (on day 1), followed by CPT-11. Each patient, therefore, served as his/her own control for the comparisons of pharmacokinetics of CPT-11 given with or without, and before or after 5-FU/folinic acid.

Eligible patients were not allowed to have had more than two prior chemotherapy regimens, prior pelvic radiotherapy, prior treatment with mitomycin, nitrosoureas or carboplatin, or prior severe dose-limiting 5-FU toxicity.

The complete report of this trial is in press at the time of writing [11]. Preliminary results, which were presented in abstract form earlier this year [12, 15], are summarised below.

Optimum dosage schedule of CPT-11/5-FU/folinic acid

To date, 27 patients (17 males, 10 females) have been enrolled in this trial [12]. Of the 24 patients with colon cancer, 20 had received at least one prior 5-FU-based regimen. Reduction in white blood cell count were not dose-limiting, although the absolute neutrophil count was dose-limiting in 1 of the 6 patients who received the highest of these doses of 5-FU. The other 5 patients tolerated a 5-FU dose level of 426 mg/m^2 without difficulty. The 5-FU dose was, therefore, increased to 500 mg/m^2 and fixed at this level for the subsequent CPT-11 dose/escalations. During this second part of the study, dose-limiting granulocytopenia was observed in 2 of the 3 patients who received CPT-11 at a dose of 150 mg/m^2. This dose level was, therefore, deemed to exceed the MTD.

Importantly, no dose-limiting diarrhoea was observed in any of the 27 patients studied thus far during this study at

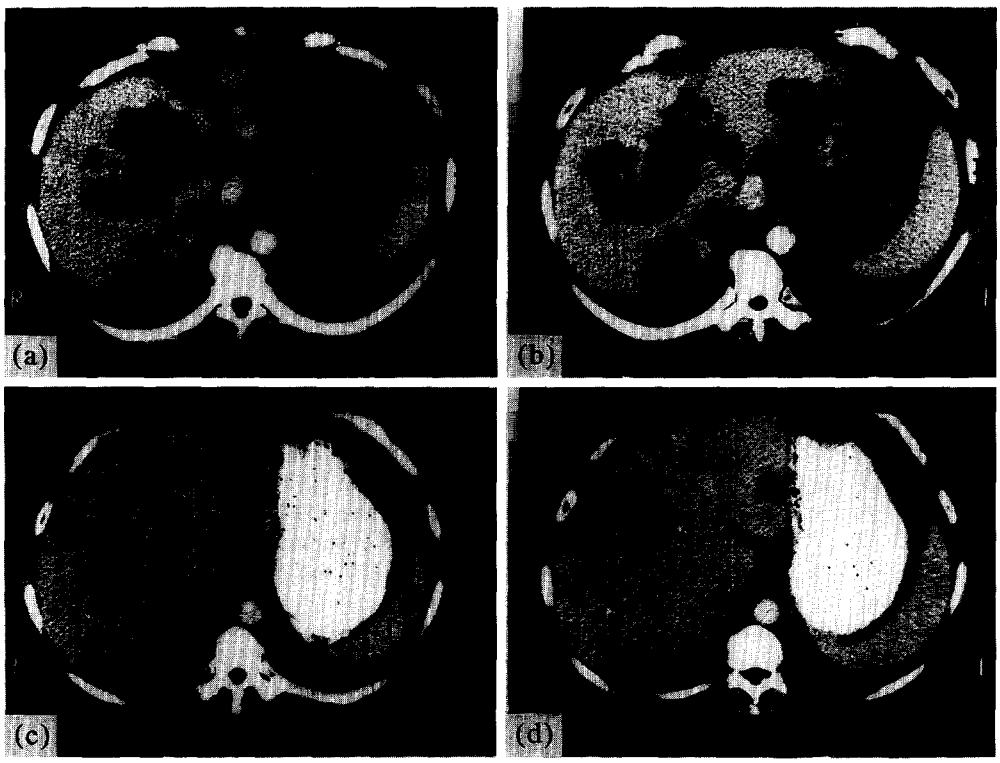

Figure 2. CT scans demonstrating major objective response to CPT-11 and leucovorin. The patient had colon cancer metastatic to the liver. (a) and (b) are from the CT scan taken after tumour progression following 1 year of 5-FU and high-dose leucovorin. (c) and (d) are from the patient's CT scan taken approximately 12 weeks later, after receiving treatment with CPT-11, 5-FU and leucovorin weekly for 4 weeks, followed by a 2-week break.

any CPT-11 dosage. This was attributed to the close adherence to the recommended loperamide schedule. Loperamide therapy was initiated at the first sign of diarrhoea. Patient education and careful monitoring of signs and symptoms of delayed diarrhoea also played an important role in minimising this potentially dose-limiting event.

Based on these encouraging safety results, the recommended doses for further investigation of this combination in phase II and III trials are anticipated to be CPT-11 125 mg/m^2, 5-FU 500 mg/m^2 and folinic acid 20 mg/m^2 weekly for 4 weeks, followed by a 2-week break.

Lack of pharmacokinetic interaction between CPT-11 and 5-FU

Preliminary pharmacokinetic data for the first 21 patients show that the AUCs of CPT-11 and its active metabolite SN-38 are unaffected by administration of CPT-11 with or without, or before or after 5-FU/folinic acid. Similarly, there was no substantial difference between these schedules in any of the other pharmacokinetic parameters measured (e.g. peak plasma concentration, elimination half-life) for either CPT-11 or SN-38. These early results strongly suggest that 5-FU does not interfere with the enzymatic conversion of CPT-11 to SN-38.

Antitumour activity

Although the primary objectives of this phase I trial were to define the optimum dosages of each of the drugs and to investigate any pharmacokinetic interaction between them, a number of objective tumour responses were observed. Of 19 patients with measurable colorectal cancer, 3 of 16 who had received prior 5-FU-based therapy achieved a partial response, as did 1 of 3 chemotherapy-naive patients. CT evidence of major antitumour activity is demonstrated in Figure 2. This dramatic response was obtained after 12 weeks of treatment with CPT-11, leucovorin and 5-FU in a patient whose metastatic colorectal cancer had progressed after 1 year of weekly high-dose leucovorin and 5-FU. In addition to objective tumour regression, other indicators of antitumour activity were observed, including substantial reductions in carcinoembryonic antigen (CEA) levels, reduced requirement for analgesia, and improvements in Karnofsky performance status.

THE EUROPEAN EXPERIENCE

The dosage schedule of CPT-11 given as a single agent in European studies was 350 mg/m^2 every 3 weeks. This schedule was the basis of the combination regimen investigated in a phase I study performed at the Salpêtrière Hospital in Paris. The objective of this ongoing study is to define the MTD of CPT-11 when given with a fixed dosage of 5-FU (administered as an intravenous bolus daily for 5 consecutive days every 4 weeks), and the optimal dosage and sequence of the combination for phase II studies [12]. Again, another important objective was to assess the effects of 5-FU on the pharmacokinetics of CPT-11. For this reason, as in the U.S. study, a crossover design was used (see Figure 1).

CPT-11 was administered as a 30-min intravenous infusion in escalating doses from 200 to 350 mg/m^2. For each patient, CPT-11 was given either 1 day before or 1 day after a 5-day course of daily injections of 5-FU (planned dose 500 mg/m^2), in alternate 4-week cycles. Thus, each patient served as his/her own control. Although probably unrelated to drug treatment, 1 of 2 patients who received 5-FU 500 mg/m^2 and the lowest dose of CPT-11 died; the schedule was therefore modified to include a reduced 5-FU fixed dose of 375 mg/m^2.

No major toxicity with CPT-11/5-FU combination therapy

Early results of this ongoing study have been presented previously by Grossin and associates [13]. To date, 29 patients have been enrolled, of whom 21 had colorectal cancer, 5 had other tumours of the gastrointestinal (GI) tract and 3 had non-GI tumours. Most patients were heavily pretreated with radiotherapy and/or chemotherapy. A median of two previous lines of chemotherapy had been received. Results are available for CPT-11 dose levels up to 300 mg/m^2.

Neutropenia was manageable and was not dose-limiting at CPT-11 doses up to 300 mg/m^2. WHO grade 3 or 4 neutropenia was experienced by 2 of 7 patients treated with CPT-11/5-FU 230/375 mg/m^2 and 2 of 5 patients at the 300/375 mg/m^2 dose level.

Delayed diarrhoea occurred in only a small proportion of patients. At the highest dose level (CPT-11 200 mg/m^2; 5-FU 375 mg/m^2), only 1 of 5 patients developed severe delayed diarrhoea (NCI-CTC grade 3 or 4). Although most patients experienced the recognised cholinergic-like syndrome of acute diarrhoea, this resolved within a few hours and was not a major problem. After a total of 89 treatment cycles, there were no reports of severe nausea and vomiting, or mucositis. Grade 3 or 4 fever was associated with only two cycles (CPT-11 doses 260 and 300 mg/m^2). Severe anaemia (grade 3 or 4) was observed in a total of seven cycles at both low- and high-dose levels, but this may have been attributable, at least in part, to previous chemotherapy.

Thus, in this ongoing study, the MTD has not yet been reached, and the use of a higher dose level of CPT-11 (350 mg/m^2—the recommended dose of the single agent) with 5-FU 375 mg/m^2 is currently being investigated. Furthermore, the low frequency of mucositis observed in this study indicates that a higher dose of 5-FU may be tolerable, and investigations of CPT-11 350 mg/m^2 with 5-FU >375 mg/m^2 are also currently underway.

Pharmacokinetic results

Pharmacokinetic analysis for this study was performed by G. Bastian at the SOMPS Institute. Data from 10 patients in whom CPT-11 was given before 5-FU in cycle 1 and after 5-FU in cycle 2 showed that there was no notable difference in CPT-11 clearance between the two cycles (24.07 versus 24.23 l/h), and the plasma concentration–time curves during the two cycles were superimposable for both CPT-11 and SN-38 (Figure 3).

DISCUSSION

Phase II studies of CPT-11 monotherapy in colorectal cancer have produced objective response rates of 15–32% in chemotherapy-naive patients [1–3] and 18–27% in pretreated patients [1, 3–5], most with clinical evidence of resistance to 5-FU. These results indicate that CPT-11 is an important new cytotoxic agent for the treatment of colorectal cancer. Until now, 5-FU has been the only effective

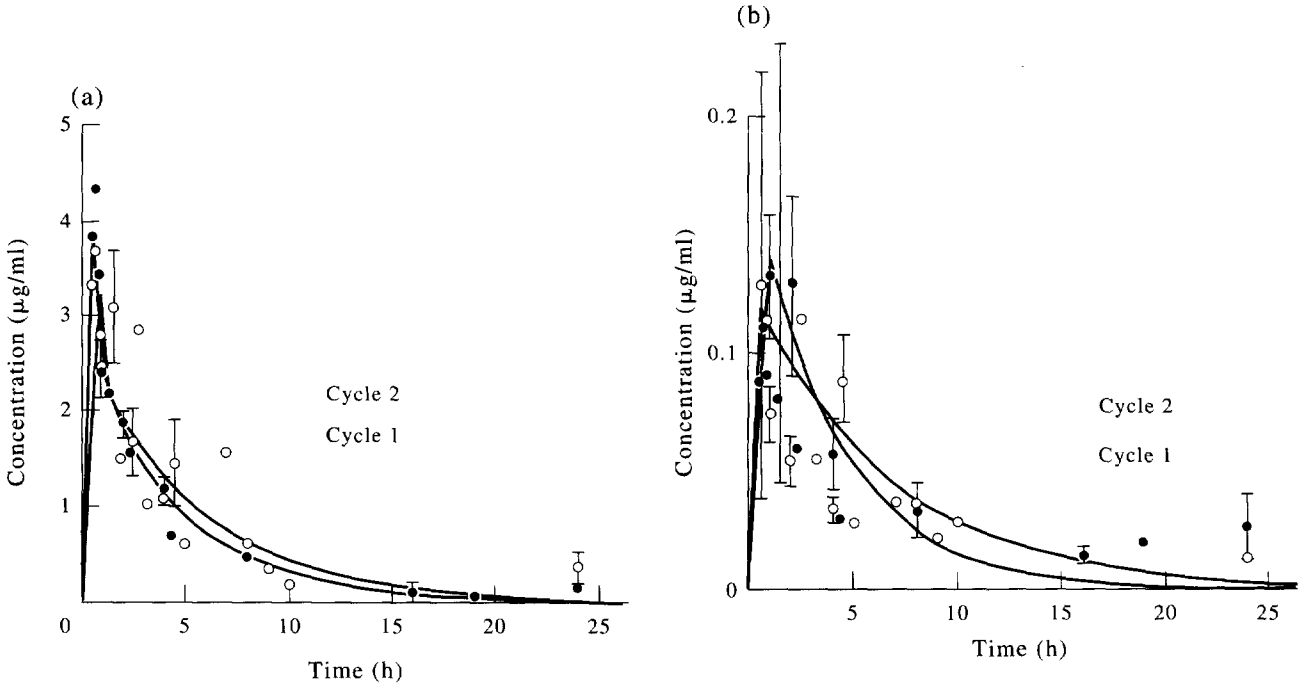

Figure 3. Mean plasma concentration–time curves for (a) CPT-11 and (b) SN-38 in 10 patients treated with CPT-11 followed by 5-FU/folinic acid (C → F; cycle 1) and 5-FU/folinic acid followed by CPT-11 (F → C; cycle 2).

drug available for the treatment of colorectal cancer during almost 40 years since its introduction into clinical practice.

In addition to the impressive efficacy of CPT-11 monotherapy demonstrated in phase II studies in patients with colorectal cancer, the rationale for its combination with 5-FU stems from the knowledge that the two compounds exert their antitumour effects through quite different mechanisms of action. The fluoropyrimidine 5-FU exerts its cytotoxic effect by inhibiting thymidylate synthase (TS) activity. This results in depletion of deoxythymidine triphosphate, an essential precursor for DNA synthesis. Although various other mechanisms of action have also been implicated, the enhanced activity of 5-FU in combination with folinic acid suggests that inhibition of TS is central to the clinical activity of 5-FU [7]. A number of different mechanisms of resistance to 5-FU have been identified in experimental and clinical studies. Although the relative frequency with which each of these mechanisms is responsible for 5-FU resistance in humans is uncertain, it is known that increased TS expression occurs in cells exposed to 5-FU, and that this process allows cells to develop resistance rapidly to the effects of 5-FU [7].

CPT-11 exerts its cytotoxic effect by an entirely different mechanism of action. It is a specific inhibitor of DNA topoisomerase I, an important enzyme in the cell replication process. CPT-11 converts topoisomerase I into a DNA-damaging agent which ultimately causes cell death as a result of irreversible arrest of DNA replication [16–18]. Cells containing high levels of topoisomerase I, notably colorectal cancer cells [19, 20], are likely to be particularly susceptible to the actions of CPT-11 [21].

CPT-11 has demonstrated a broad spectrum of antitumour activity both *in vitro* and *in vivo*, even in tumours considered to be relatively drug-resistant, such as colorectal cancer. CPT-11 is metabolised in the liver to its active metabolite 7-ethyl-10-hydroxy-camptothecin (SN-38) [22]. Indeed, SN-38 exhibits 160- to 2000-fold greater activity than CPT-11 *in vitro*. The *in vitro* antitumour activity of CPT-11 has been shown to be higher than that of anticancer agents such as doxorubicin, 5-FU and cisplatin in some cell lines [23]. Furthermore, CPT-11 has demonstrated sustained *in vivo* activity against tumours expressing the multidrug resistance (MDR) phenotype [24]. Synergistic activity has been demonstrated when CPT-11 is combined with other anticancer agents, including doxorubicin and cisplatin [24].

Thus, the impressive preclinical and clinical results obtained with CPT-11, together with its unique mechanism of action and lack of cross-resistance with other cytotoxic agents provide a clear rationale for the investigation of CPT-11-based combinations, including those involving 5-FU.

Various combination regimens of CPT-11 and 5-FU have been investigated in phase I studies in Japan, the U.S. and Europe. In Japan, when given as a single dose in combination with a 7-day continuous infusion of 5-FU 400 mg/m^2/day, in 3- to 4-week cycles, the maximum tolerated dose (MTD) of CPT-11 was 250 mg/m^2 [10], the same as that of CPT-11 when given as a single agent in the Japanese study. In an ongoing study in which CPT-11 is given 2 days prior to a 5-day infusion of 5-FU 600 mg/m^2/day, the MTD had not been reached at a dose level of 150 mg/m^2 every 2 weeks; indeed, no severe toxicities were observed up to this dose level.

In the U.S. study [11], when combined with weekly injections of 5-FU 500 mg/m^2, dose-escalation of CPT-11 to

150 mg/m^2 once weekly was associated with dose-limiting neutropenia. Here, the MTD for CPT-11 in this combination regimen was defined as 125 mg/m^2, the usual dosage for single-agent phase II trials in the U.S.

These results indicate that, despite concerns of overlapping toxicities, substantial doses of CPT-11 and 5-FU can be administered concurrently.

In the French study [13], the MTD has not yet been reached at a dose level of CPT-11 200 mg/m^2, plus 5-FU 375 mg/m^2 daily for 5 days given in 4-week cycles [13]. No unexpected toxicity has been observed during this study and the dose intensity of the combination is already higher than that of any single agent. A combination of 5-FU 375 mg/m^2 plus CPT-11 350 mg/m^2, the recommended dose for single-agent CPT-11 therapy in Europe, is currently being investigated.

While the results of early studies in Japan suggested that 5-FU might interfere with the metabolites of CPT-11 to its more active metabolite SN-38 [9, 14], this has been refuted in later, well controlled studies. In the Japanese study, co-administration of 5-FU with CPT-11 resulted in a significantly lower mean AUC for SN-38 compared with that observed following administration of CPT-11 alone [9]. It is important to note, however, that there was considerable interpatient variation in the values of pharmacokinetic parameters of CPT-11 and SN-38 in this study [14]. Furthermore, since an historical group of patients with lung cancer was used as a source of comparative pharmacokinetic data for CPT-11 monotherapy, these results should be interpreted with caution. The use of a crossover design in subsequent U.S. and European studies eliminates interference from confounding factors, since each patient acted as his/her own control. In neither of these studies was there evidence of a substantial pharmacokinetic interaction, regardless of whether CPT-11 was given before, after or simultaneously with 5-FU.

Although antitumour response was not a primary endpoint in these dose-finding studies, objective responses and other indicators of clinical efficacy, including improvement in performance status and a reduced requirement for analgesia, were noted.

Based on these encouraging results, the combination regimens will be taken into further clinical development. Ongoing and planned studies will continue to assess the efficacy of CPT-11 with 5-FU. The main objective of the clinical development of CPT-11 in colorectal cancer is to determine the best combination in terms of efficacy and safety. Once this is established, phase II and III studies will compare the efficacy and safety of CPT-11/5-FU combinations with modified regimens of 5-FU such as continuous infusion or 5-FU/folinic acid combinations, with a particular objective to assess potential benefits in survival and quality of life. Future studies should also investigate combinations of CPT-11 with other promising new agents such as raltitrexed (ZD1694, a thymidylate synthase inhibitor) and oxaliplatin.

In conclusion, the preliminary results obtained with CPT-11/5-FU combinations in phase I studies indicate that concurrent administration of substantial doses of CPT-11, 5-FU and folinic acid is feasible in terms of safety, and clinically-relevant dose intensity is achievable for each compound. Preliminary analysis of available controlled pharmacokinetic data appears to demonstrate that 5-FU has no substantial effect on the metabolism of CPT-11 to SN-38 [11]. Major objective responses and other indicators of clinical activity have been observed. Given the acceptable safety profile and encouraging preliminary response data achieved when CPT-11 is administered with 5-FU, it is hoped that this combination will prove to be an important advance in the treatment of colorectal cancer.

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