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Comparison of the pharmacokinetics and efficacy of irinotecan after administration by the intravenous versus intraperitoneal route in mice

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Abstract Irinotecan (CPT-11) is a new drug active in colorectal cancer. A comparison was made of the efficacy and pharmacokinetics of CPT-11 after i.p. versus i.v. administration to mice. We found that i.p. administration of CPT-11 to mice bearing C26 colon cancer was more efficient and less toxic than i.v. administration; a 100-mg i.p. dose induced an increase in life span equivalent to that produced by a 300-mg i.v. dose, and toxic deaths appeared after doses of 400 mg/kg given i.v. and 800 mg/kg given i.p. Pharmacokinetic parameters of CPT-11 and SN-38 were compared after i.v. or i.p. administration in mice bearing P388 leukemia ascites. Peritoneal CPT-11 and SN-38 AUC values were higher after i.p. administration than after i.v. injection. Plasmatic AUC values remained equivalent. Moreover, peritoneal CPT-11 clearance was 10-fold lower after i.p. versus i.v. administration. If the survival and pharmacologic advantage of i.p. CPT-11 in the murine model considered can be translated to a safe and practical mode of therapy in patients and if local toxicity does not prove to be a major adverse effect, then a potentially useful agent could be added to the drugs known to be active when given by the i.p. route for adjuvant therapy in colon cancer.

Key words Pharmacokinetics · Irinotecan

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Introduction

Colorectal cancer is among the most common types of cancer, along with breast and lung cancer. Its prognosis largely depends on the extent of the disease at the time of diagnosis. Whereas Dukes' A and B1 disease leads to a 90% cure probability, the probability of cure for Duke's B2 and C falls to 75% and that for Duke's D disease, to 35% [1–3]. This is probably due to occult or microscopic residual disease at the time of diagnosis. Adjuvant chemotherapy with various 5-fluorouracil (5FU)-based regimens leads to an increase in disease-free survival only for patients with Dukes' stage B2 and C disease [4, 5]. Some clinical studies have suggested that intraperitoneal chemotherapy would be very relevant in the adjuvant setting of colon cancer due to the route of spread of cancer cells: the liver via the portal system, the local suture sites, and the peritoneal surfaces [6]. Irinotecan (CPT-11) is a topoisomerase I inhibitor active in colorectal cancer [7, 8]. It is a prodrug that is converted by a carboxylesterase to its active metabolite, SN-38, which is detoxified by glucuronyl transferases into glucuro-conjugated SN-38 (SN-38-G) [9, 10].

This study was undertaken to determine whether a pharmacologic advantage would be obtained after i.p. administration of CPT-11. For that purpose we compared the activity and toxicity of CPT-11 given by the i.v. or i.p. route to mice bearing C26 colon carcinoma and then studied the pharmacokinetics of CPT-11 and its metabolites SN-38 and SN-38-G after i.p. or i.v. administration to mice.

Materials and methods

Animals

Female BALB/c mice (5 weeks old) were purchased from Iffa Credo (St. Germain sur l'Arbresle, France). They were housed in cages and maintained in a controlled environment, with food and water being provided ad libitum. After a 2-week period of quarantine they were used for experiments.

Tumor lines

For survival studies we used the C26 murine colon tumor. This tumor model was maintained by S.C. transplantation every 10 days. For experiments a tumor piece was digested with trypsin at 0.25% and collagenase at 1,000 UI/ml for 1 h at 37 °C. After filtration on a 70-μm filter (Nunc) the cell viability was determined by trypan blue exclusion and 2×10^6 viable cells were inoculated i.p. For pharmacokinetic experiments we used the murine leukemia cell line P388. The cell line was maintained by serial i.p. transplantation of malignant ascites every week (10^6 cells/mouse).

Drugs

CPT-11 was supplied by Rhône Poulenc Rorer Laboratory (Neuilly sur Seine, France). The drug was diluted in a 0.9% NaCl solution immediately before administration. The injection volume did not exceed 250 μl/mouse for i.v. administration or 500 μl/mouse for i.p. injection.

Survival studies

To assess the antitumor activity we treated mice on days 2, 6, and 10 after i.p. implantation of C26 tumor cells. The total doses ranged from 100 to 500 mg/kg for the i.v. route and from 50 to 1,000 mg/kg for i.p. administration. Five to ten animals per dose were used, although for the two highest doses given i.v., only two animals were treated. Control animals were injected i.p. or i.v. with solution. As their life spans were identical, data obtained from the two control groups were pooled for the survival study. Antitumor activity was determined by the median survival time. Toxic deaths and immediate toxic deaths were defined as deaths occurring at less than 7 days after the end of the treatment and less than 24 h after an injection, respectively. Kaplan-Meier curves of animal survival were used for comparison by a log-rank test of the two routes of administration at each dose level.

Pharmacokinetics studies

Since the C26 tumor model did not produce ascites formation after i.p. inoculation, pharmacokinetic studies were carried out using the P388 murine leukemia cell line, which is implanted i.p. A pharmacokinetic study was performed at 7 days after inoculation, leading to 2–3 ml of ascites formation. CPT-11 was given at a single i.v. or i.p. dose of 66 mg/kg. Six animals per time were killed at 5, 15, and 30 min as well as 1, 2, 4, 8, and 24 h after administration. After centrifugation of blood and ascites, plasma and peritoneal fluid were isolated and frozen at −20 °C until analysis.

Analytic assay

Assays for CPT-11, free SN-38, and total SN-38 were performed by high-performance liquid chromatography (HPLC) according to the method previously described by Rivory and Robert [11], with few modifications, and were validated for mouse plasma and ascites. In brief, plasma and peritoneal exudate (50 μl) were added to camptothecin serving as the internal standard (1 μg/ml) and 0.01 *N* HCl in a final volume of 200 μl. For determination of total SN-38, 25 μl of β-glucuronidase (2,000 U/ml) was also added. In all cases, after the addition of 400 μl of acetonitrile/methanol (50/50) followed by vortexing and centrifugation, supernatant was injected onto a Nucleosil C18 5-μm column (300 × 0.9 mm). The mobile phase comprised (potassium phosphate 66 at m*M* /sodium heptane sulfonate at 2 m*M*, pH 4)/acetonitrile (66/34) run at a flow rate of 1 ml/min. A fluorospectromonitor (RF-535 Shimadzu) was set at an excitation wavelength of 355 nm and an emission wavelength of 515 nm for the determination of CPT-11 and of SN-38 and camptothecin. CPT-11 and SN-38 gave mean retention times of 4.5 and 6.3 min, respectively. Calibration curves were established for each determination by mouse serum containing CPT-11 at 50–5,000 ng/ml, free SN-38 at 25–1,000 ng/ml, and total SN-38 at 25–5,000 ng/ml. The limits of quantification were 50 and 25 ng/ml for CPT-11 and SN-38, respectively. The intraday and within-day coefficients of variation were $< 10\%$ for the three controls (70, 450, and 1,200 ng/ml and 40,320 and 600 ng/ml for CPT-11 and SN-38, respectively).

Pharmacokinetics analysis

AUC values for CPT-11 and for free and conjugated SN-38 were calculated by a trapezoidal method and extrapolated to infinity by division of the last sampling concentration (C24 h) by the last log-linear phase slope (k). The terminal half-life was defined as the ratio between *Ln2* and k: AUC(0→∞) = AUC trapezoidal (0→24 h) + C_{24h}/k. Plasmatic and peritoneal CPT-11 clearance values were calculated as the ratio between the dose and the plasmatic and peritoneal AUC(0→∞) values, respectively.

Results

Antitumor activity of CPT-11 after i.v. and i.p. administration to colon C26-bearing mice

Table 1 summarizes the mean survival times recorded for animals after i.v. and i.p. administration of CPT-11. Control animals died after 13.3 ± 4.2 days. The effect

Table 1 Survival time of mice bearing C26 colon cancer after i.p. and i.v. administration of CPT-11. Toxic deaths and immediate toxic deaths were defined as deaths occurring at less than 7 days after the end of the treatment and less than 24 h after an injection, respectively. The log-rank test was considered significant when $P < 0.05$ (*NS* Not significant)

Dose (mg/kg)	Survival time (mean ± SD, in days)		Log-rank test	Number of toxic deaths (early toxic deaths)/ total number of animals	
	i.v.	i.p.		i.v.	i.p.
Control	13.3 ± 4.2	13.3 ± 4.2			
50	14 ± 4.3	17.4 ± 5.4	NS		
100	15.8 ± 3.3	21.2 ± 3.8	NS		
200	16.1 ± 3.0	26.3 ± 4.9	$P < 0.01$		
300	21.4 ± 2.0	26.6 ± 4.7	NS		
400	12.7 ± 11.2	33.0 ± 5.5	$P < 0.05$	4 (4)/10	
600	0	33.0 ± 5.5		2 (2)/2	
800		8.3 ± 6.9			4 (1)/5
1000		3.2 ± 3.2			5 (5)/5

Table 2 Pharmacokinetic parameters (mean ± SD) recorded for CPT-11 and for free and conjugated SN-38 in plasma and ascites after i.v. administration to mice bearing P388 ascitic leukemia

	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	AUC μg h l^{-1}
Plasma:				
CPT-11	6,571 ± 2,064	0.29 ± 0.10	2.3 ± 0.9	16,348 ± 7,477
Free SN-38	1,125 ± 147	0.53 ± 0.41	6.0 ± 4.0	9,940 ± 2,939
SN-38-G	2,620 ± 644	0.6 ± 0.6	6.6 ± 2.6	15,493 ± 5,126
Ascites:				
CPT-11	3,007 ± 1,150	2.3 ± 1.3	2.8 ± 1.3	12,251 ± 3,361
Free SN-38	2,894 ± 346	1.4 ± 0.66	4.6 ± 2	21,349 ± 5,405
SN-38-G	2,211 ± 870	0.75 ± 0.66	5.1 ± 3.8	15,126 ± 6,117

of CPT-11 was dependent upon the route of administration, since we obtained the same increase in median survival time with 300 mg/kg given i.v. (21.4 ± 2 days) as with 100 mg/kg given i.p. (21.2 ± 3.8 days). A dose-effect relationship was observed after CPT-11 administration via the two dosing routes. The maximal antitumor effect, obtained after i.v. administration of 300 mg/kg, was 21.4 ± 2 days, whereas that obtained after i.p. administration of 400 mg/kg was 33 ± 5.5 days. Early toxic deaths occurred after i.v. injection of 400 mg/kg and i.p. administration of 800 mg/kg. No overt sign of local toxicity was seen. The peritoneum did not look hemorrhagic, and fibrin deposits were not observed.

Pharmacokinetics of CPT-11 and of free and glucuro-conjugated SN-38 after i.v. injection

Pharmacokinetic studies were performed in P388-bearing mice at a total dose of 200 mg/kg, where the highest difference between i.p. and i.v. administration was observed. The plasmatic and peritoneal pharmacokinetic parameters are summarized in Table 2. Figure 1 shows the plasmatic and ascitic concentration-time curves generated for CPT-11, free SN-38, and conjugated SN-38. In plasma and ascites the half-life of CPT-11 is shorter than that of free SN-38 or SN-38-G (Table 2). The maximal concentration of CPT-11 measured in plasma was 2-fold that measured in ascites. By contrast, the SN-38 C_{max} was 2-fold higher in ascites than in plasma. Consequently, although the exposure to SN-38 was higher by a factor of 2 in ascites than in plasma, the CPT-11 AUC value seen in plasma was only 1.3-fold that observed in ascites. Finally, the ascitic and plasmatic AUC values recorded for glucuronated SN-38 were similar. Plasma CPT-11 clearance was 4.9 ± 2.3 l/h.

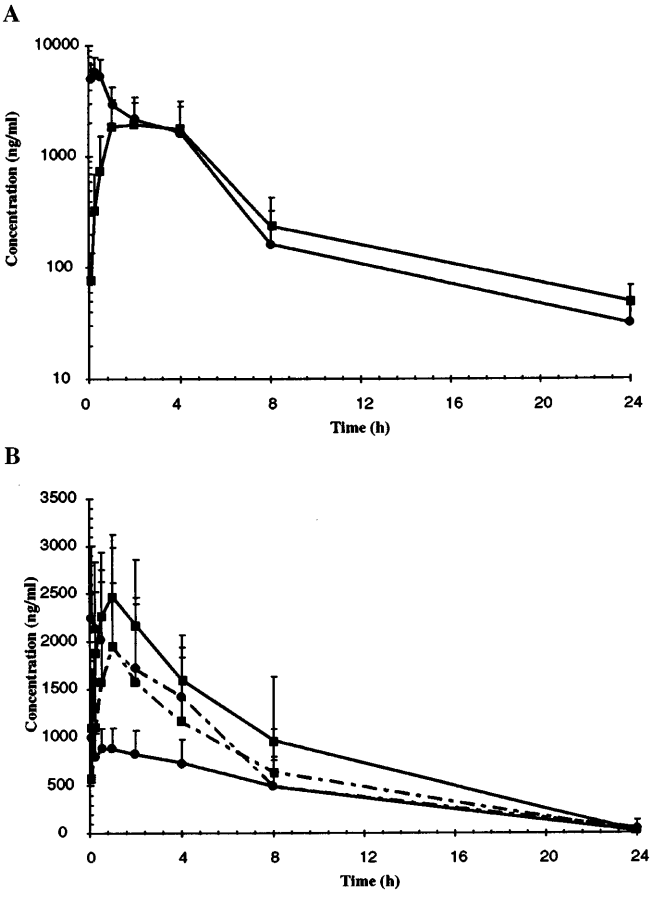

Fig. 1A,B Plasmatic (●) and ascitic (■) concentration-time curves generated for **A** CPT-11 and for **B** free SN-38 (–) and glucuronated SN-38 (–·–) after i.v. administration of CPT-11 to mice bearing P388 ascitic leukemia

Pharmacokinetics of CPT-11 and of free and conjugated SN-38 after i.p. injection

The plasmatic and peritoneal pharmacokinetic parameters are summarized in Table 3. The plasmatic and peritoneal disappearance of CPT-11, free SN-38, and conjugated SN-38 is presented in Figs. 2A and 2B, respectively. The half-lives of SN-38 and SN-38-G in plasma and ascites were identical, whereas the CPT-11 half-life observed in plasma was 3-fold that seen in ascites (6.4 ± 5.5 versus 2.0 ± 0.5 h). Levels of exposure to CPT-11 and SN-38 were 14.5- and 4.2-fold higher in ascites than in plasma, respectively. Ascites and plasma SN-38-G AUC values did not differ significantly.

Comparison of pharmacokinetic parameters after i.v. and i.p. administration

Table 4 summarizes our comparison of the AUC values noted for CPT-11 and for free and conjugated SN-38 following administration by the two dosing routes. The

Table 3 Pharmacokinetic parameters (mean ± SD) recorded for CPT-11 and for free and conjugated SN-38 in plasma and ascites after i.p. administration to mice bearing P388 ascitic leukemia

	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	AUC μg h l^{-1}
Plasma:				
CPT-11	2,143 ± 1,418	0.75 ± 0.67	6.4 ± 5.5	12,588 ± 10,524
Free SN-38	1,298 ± 176	0.8 ± 0.8	6.4 ± 2.2	10,479 ± 2,711
SN-38-G	2,629 ± 988	0.67 ± 0.72	6.1 ± 3.6	17,772 ± 4,357
Ascites:				
CPT-11	76,282 ± 22,218	0.11 ± 0.06	2.0 ± 0.5	182,834 ± 75,687
Free SN-38	3,234 ± 1,074	1.26 ± 1.52	10.8 ± 2.0	44,733 ± 16,288
SN-38-G	3,702 ± 2,091	0.8 ± 1.57	6.3 ± 1.6	24,516 ± 9,838

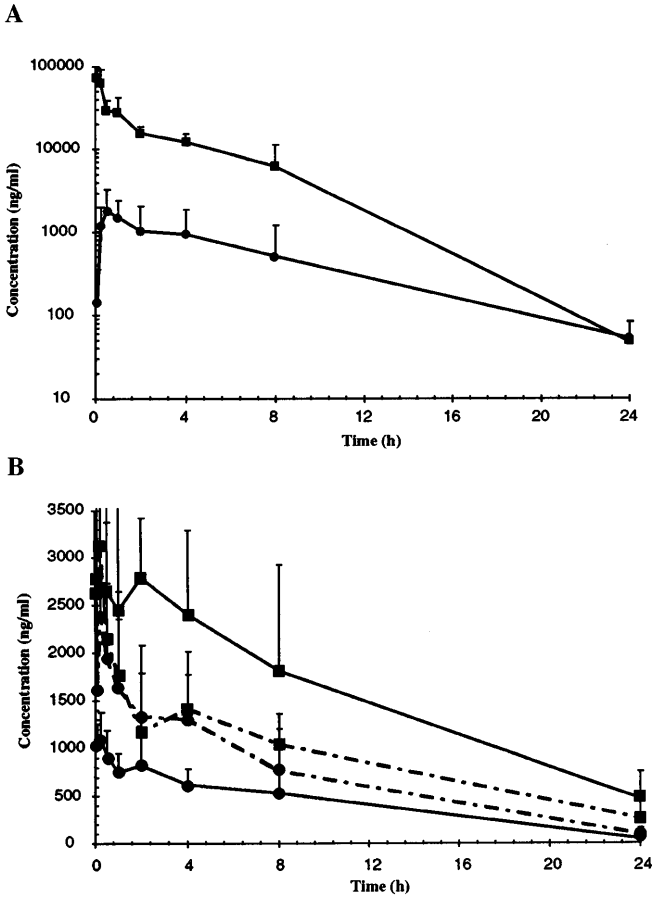

Fig. 2A,B Plasmatic (●) and ascitic (■) concentration-time curves generated for **A** CPT-11 and for **B** free SN-38 (–) and glucuronated SN-38 (–•–) after i.p. administration of CPT-11 to mice bearing P388 ascitic leukemia

peritoneal free SN-38 AUC value was significantly higher after i.p. dosing than after i.v. administration ($P = 0.0065$), whereas the plasmatic free SN-38 AUC values were equivalent. AUC ratios of CPT-11 and free SN-38 were similar. The peritoneal CPT-11 clearance after i.p. administration was 10-fold lower than the plasmatic CPT-11 clearance after i.v. administration.

Discussion

This study compared the antitumor activity, the acute toxicity, and the pharmacokinetics of CPT-11 following i.v. and i.p. administration to mice. For that purpose we used the C26 murine colon carcinoma model previously shown by Corbett et al. [12] to exhibit a very high level of metastatic spread after i.p. implantation in BALB/c mice. Moreover, the liver was the main site of metastasis, with metastases being histologically apparent at the time of death [12]. However, this model spreads locally rather than intra-abdominally via the lymphatic and venous drainage as in the case of human colon cancer. Despite these limitations, the use of this model was relevant for the study of the efficacy of i.p. administration of CPT-11 in both local disease and liver metastases. Unfortunately, the C26 model was not associated with production of ascites, and we had to use a P388 murine leukemia cell line for the pharmacokinetic study. However, it is reasonable to postulate that the tumoral model did not modify the pharmacokinetic profile of CPT-11 and its metabolites.

We found that i.p. administration of CPT-11 was more efficient and less toxic than i.v. administration. A 100-mg i.p. dose induced an increase in life span equivalent to that produced by a 300-mg i.v. dose, and toxic deaths appeared after doses of 400 mg/kg given i.v. and 800 mg/kg given i.p. These differences could be related to pharmacokinetic parameters.

The toxic deaths related to CPT-11 administration occurred immediately or soon after CPT-11 injection and the symptoms suggested a cholinergic syndrome. During clinical trials, such a cholinergic syndrome was described [7, 8]. Our pharmacokinetic study demonstrated that the plasmatic C_{max} value recorded for CPT-11 was 2-fold lower after i.p. dosing than after i.v. injection. It is noteworthy that a 2-fold difference also

Table 4 Comparison of CPT-11, free SN-38, and conjugated SN-38 AUC values (mean ± SD) recorded after i.v. and i.p. administration of CPT-11 in plasma and ascites of mice bearing P388 ascitic leukemia

	Plasma AUC μg h l^{-1}		Ascites AUC μg h l^{-1}	
CPT-11	12,588 ± 10,524	16,348 ± 7,477	182,384 ± 75,687	12,251 ± 3,361
Free SN-38	10,479 ± 2,711	9,940 ± 2,939	44,733 ± 16,288	21,349 ± 5,405
SN-38-G	17,771 ± 4,357	15,493 ± 5,126	24,516 ± 9,838	15,126 ± 6,117

existed in the toxic-death-related doses. As in humans, we can hypothesize that the cholinergic syndrome in mice was related to the CPT-11 C_{max}. Finally, the model considered did not allow us to determine the local toxicity of CPT-11 on the mesothelium.

Our data demonstrate a pharmacologic advantage for i.p. administration of CPT-11, which can be calculated by the ratio of the total body clearance of CPT-11 to its regional exchange. This ratio was about 10. Such a ratio is comparable with those reported for methotrexate [13, 14], cisplatin [15], or teniposide [16], but is lower than those reported for 5FU [17], etoposide [18], or melphalan [19]. However, according to Dedrick [20], i.p. administration of such a drug in a large volume would be expected to maintain a significantly greater concentration in the peritoneal space than in the plasma. Effectively, i.p. administration produced a higher peritoneal CPT-11 and SN-38 AUC values than did i.v. administration. CPT-11 efficacy has been related to SN-38 exposure either in vitro [21, 22] or in vivo [23], and a higher peritoneal SN-38 AUC value could explain the higher antitumor activity. Moreover, after i.p. administration, plasma AUC values recorded for both CPT-11 and SN-38 were on the same order of magnitude as those obtained after i.v. administration. Thus, both CPT-11 and SN-38 respond to the principle of double route defined by Howell [24], which associates higher local concentrations with equivalent systemic exposure.

Moreover, as CPT-11 is metabolized by the liver, the hepatic extraction of CPT-11 could lead to a continuous conversion of CPT-11 to SN-38 in the liver tissue. Considering the mechanism of cytotoxicity of topoisomerase I inhibitors [25], the presence of the replication event seemed to be necessary to obtain cytotoxicity; thus long-term exposure of metastases to SN-38 could be of benefit for the eradication of liver metastases. The existence of a peritoneal conversion of CPT-11 to SN-38 could be due to a peritoneal carboxylesterase activity or to an exudation of plasmatic carboxylesterase through the peritoneal membrane. In vitro studies using mouse and human tissues have shown that CPT-11 may be converted into SN-38 in the liver, lungs, colon, stomach, uterus, pancreas, and several tumor tissues. Maximal esterase activity was generally found in the liver. This activity was high in serum from mice and was very low in humans. Purified liver carboxyesterases from nine species metabolized CPT-11, but the specific activity varied from 1 to 65 orders of magnitude. Thus, CPT-11 transformation may occur in all tissues, with the possibility of in situ formation of the active metabolite [26, 27].

In the adjuvant treatment of colon cancer the major objective of i.p. chemotherapy is to eradicate occult liver metastasis by providing a pharmacokinetic advantage through a higher degree of local exposure associated with an equivalent level of systemic exposure [24]. Another potential advantage of i.p. administration is the absorption of the cytotoxic drug via the lymphatics and the portal vein, which may be beneficial in the prevention or the treatment of hepatic micrometastases [3]. However, no drug has ever been demonstrated to be effective when given i.p. as adjuvant therapy for colorectal cancer. Our results show that CPT-11 does not possess all properties proposed by Speyer [6] in defining the ideal drug for its use, as other drugs tested for i.p. administration. However, it comes close enough to be of some clinical interest. The survival and pharmacological advantage found for i.p. CPT-11 in the murine model considered allows us to plan a phase I clinical trial of CPT-11 i.p. administration in humans. The first dose level of this trial would be low (i.e., 100 mg/m^2) for confirmation of the lack of local toxicity, and the subsequent dose level would be near the recommended i.v. dose (350 mg/m^2).

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