Altered Pharmacokinetics and Metabolism of CPT-11 in Liver Dysfunction: A Need for Guidelines

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ABSTRACT

Metabolic conversion of CPT-11 is a major route of elimination of this new topoisomerase 1 inhibitor. Presently, recommendations for dose adjustments of CPT-11 in patients with liver dysfunction are lacking. We describe the case of a patient with metastatic colon cancer with liver dysfunction treated with CPT-11 at two different dose levels (100 mg/m^2 and 30 mg/m^2, single dose, administered as a 90-min i.v. infusion). The lactones and carboxylates of CPT-11 and SN-38 were determined by high-performance liquid chromatography. SN-38 glucuronide was determined after deglucuronidation. The procedures allowed intrapatient comparison of pharmacokinetics and metabolism of the drug. Severe side effects were encountered, which could be explained by the reduced clearance of CPT-11 and its metabolites. These included neutropenic fever with culture-proven septicemia, thrombocytopenia, somnolence, diarrhea, and signs and symptoms of transient hepatic failure. Our findings offer important data for the further development of guidelines for dose reduction of CPT-11 in patients with liver dysfunction.

INTRODUCTION

CPT-11 (irinotecan), an inhibitor of the nuclear enzyme topoisomerase 1, is a relatively new antineoplastic agent, which is active in metastatic colorectal cancer (1–3). In two recently published reports of randomized trials, CPT-11 appeared to be superior to supportive care (4) and continuous infusions of 5-FU[2] (5) in patients with metastatic colorectal cancer after failure to 5-FU. SN-38 is believed to be the active metabolite of CPT-11 and is formed by the enzyme carboxylesterase (6). Hepatic metabolism by glucuronidation and subsequent biliary excretion is the most important route of elimination of SN-38 (7–9). Experience with CPT-11 treatment in patients with impaired liver function is still very limited. Normal liver and kidney function were required in Phase I and II studies, with CPT-11 performed thus far. However, it is to be expected that the clearance of CPT-11 and its metabolites will be delayed in patients with impaired hepatic function, which often occurs in patients with metastatic colorectal cancer. Indeed, it was concluded from the pharmacokinetic data of 107 patients entered on Phase I trials that a negative correlation exists between the level of serum bilirubin and γ-glutamyltransferase and the total body clearance of CPT-11 (10). Recently, we treated a patient with extensive liver metastases from colorectal cancer and abnormal liver function with a reduced dose of CPT-11. In this patient, we have been able to study CPT-11 pharmacokinetics extensively at two different dose levels of the drug and to relate these data to the observed side effects.

PATIENT AND METHODS

Case History. A 56-year-old female developed a carcinoma of the sigmoid in July 1992 for which she underwent a sigmoid resection. At the time of diagnosis, she already had liver metastases, and during laparotomy, an arterial access device (Port-A-Cath) was implanted allowing hepatic arterial infusion chemotherapy. This treatment was initiated in January 1993 with continuous infusion of 5-FU during 6 days, every 3 weeks. Due to tumor occlusion of the right branch of the portal vein, atrophy of the right liver lobe occurred. This went along with complete disappearance of the metastases in this lobe. In April 1994, she developed thrombosis of the hepatic artery, confirmed by sonography and scintigraphy, which was related to the presence of the Port-A-Cath. Thus, from then on, the liver was only supplied by the left branch of the portal vein. This resulted in further atrophy of the right lobe of the liver while the left lobe of the liver showed reactive hypertrophy. Due to the occlusion of the hepatic artery, 5-FU hepatic artery infusion needed to be discontinued. In June 1995, it was decided to perform another laparotomy aiming at resection of the remaining metastatic disease in the liver. During surgery, a metastasis in the left liver lobe was resected, and also, the largest part of the remnants of the right liver lobe were removed. However, for technical reasons, it was impossible to resect all metastatic tissue at the latter site. A vaccine was prepared, according to the methodology recently described, from the tumor cells for autologous-specific immunotherapy (11). She received four intracutaneous administrations of the vaccine. Thereafter, she was

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[2] The abbreviations used are: 5-FU, 5-fluorouracil; γ-GT, γ-glutamyl transferase; ASAT, aspartate-aminotransferase-transaminase; ALAT, alanine-aminotransferase-transaminase; LDH, lactate dehydrogenase; AF, alkaline phosphatase; TBAP, tetrabutylammonium dihydrogenphosphate; NLF, normal liver function; AUC, area under the curve.

further treated with weekly i.v. administrations of 5-FU in combination with folinic acid. This combined regimen was given in the context of a pilot study of autologous-specific immunotherapy with 5-FU plus folinic acid. In October 1997, the disease had clearly progressed while at that time the patient also developed obstructive jaundice based on occlusion of the extrahepatic bile ducts by lymph node metastases. A stent was placed in the bile duct by endoscopic retrograde cholangiopancreatiography, resulting in a decrease of the serum bilirubin from 304 μmol/liter to 13 μmol/liter (normal < 20). On the patient's request, 5-FU/folinic acid treatment was switched to oral UFT (tegafur + uracil), allowing her to continue a busy traveling schedule. However, under this treatment, the disease slowly progressed with a gradual rise in serum carcinoembryonic antigen. In April 1998, left supraclavicular lymph node metastases were detected. In June 1998, the patient developed progressive jaundice, chills, and fever. The bile duct stent was replaced; however, serum bilirubin failed to drop to normal levels and stabilized for several weeks at 40 μmol/liter. At that time it was felt that the only reasonable further chemotherapy consisted of CPT-11. Dose adjustment was judged to be required in the face of the impaired liver function. The potential risks and benefits of treatment with CPT-11 were extensively discussed with the patient, and she provided informed consent for the therapy and the investigation of the pharmacokinetics. This approach was approved by the ethics committee of the hospital. Although standard treatment would imply a triweekly dose of 350 mg/m^2, it was decided to administer CPT-11 at the dose of 100 mg/m^2 given as a 90-min i.v. infusion. This occurred on July 21, 1998. As concomitant medication, the patient only used paracetamol four times daily, 500 mg, and diclofenac three times daily, 50 mg. Blood samples were drawn before, during, and after the infusion for the pharmacokinetics. Liver functions on the day before treatment were as follows: bilirubin, 77 μmol/liter (89% conjugated; normal < 20), γ-GT, 474 units/liter (normal < 30), ASAT, 60 units/liter (normal < 30), ALAT, 35 units/liter (normal < 35), LDH, 426 units/liter (normal < 250), and AF, 880 units/liter (normal < 90).

Sampling. Blood samples for pharmacokinetics (in the first cycle at the dose of 100 mg/m^2) were drawn before the infusion, just before the end of the infusion, and 10 min, 30 min, 1 h, 2 h, 4 h, 8 h, 24 h, 72 h, 7 days, 8 days, and 9 days after the infusion. In the second and third cycle at a dose of 30 mg/m^2, blood samples were taken immediately before the infusion, at the end of the infusion, and daily thereafter. Blood samples were drawn in cooled heparinized tubes, immediately placed on ice, and centrifuged at 4°C at 4000 rpm for 5 min, after which the plasma was pipetted from the blood cells and frozen at −80°C until analysis.

Sample Treatment and Analysis. Samples were treated and analyzed for the lactones and carboxylates of CPT-11 and SN-38 along the lines of existing procedures (12). Briefly, a 200-μl sample was mixed with 300 μl of ice-cold acetonitrile:methanol (1:1, v/v) and centrifuged for 1 min at 9000 rpm at 1°C. To 250 μl of supernatant, 750 μl of a fresh and ice-cold solution of 50 mM ammonium acetate and 5 mM TBAP (pH 6.60) was added. After vortexing briefly, the sample was placed in the autosampler at 4°C for analysis.

SN-38 glucuronide was also quantified according to a procedure of Rivory *et al.* (13). To 200 μl of plasma, a solution of 800 units β-glucuronidase in 40 μl of water was added. After incubation for 2 h at 37°C, 300 μl of acetonitrile:methanol (1:1, v/v) was added. The sample was vortexed briefly and centrifuged for 2 min at 9000 rpm. To 250 μl of the supernatant, 10 μl of 2 M HCl was added, and the sample was incubated for 5 min at ambient temperature. To this mixture, 750 μl of a solution containing 50 mM ammonium acetate and 5 mM TBAP (pH 6.60) was added. After vortexing briefly, the sample was centrifuged for 2 min at 9000 rpm and placed in the autosampler at 4°C for analysis.

Plasma standards were prepared daily by adding 50 μl of a freshly prepared standard solution in a buffer containing 50 mM ammonium acetate and 5 mM TBAP (pH 6.60) to 450 μl of ice-cold plasma. After vortexing briefly, these standards were ready for use. The plasma concentrations of all components (lactone and carboxylate of both CPT-11 and SN-38) ranged from 1.0 to 300 nM.

The samples were analyzed by high-performance liquid chromatography using a C18 column (5 μm; 150 × 3.2 mm) using buffer [50 mM ammonium acetate, 5 mM TBAP (pH 6.60)]:acetonitrile:methanol (60:12.4:20, v/v/v) as the mobile phase at a flow rate of 0.6 ml/min. The analytes were detected with a fluorescence detector (λ_{ex} = 370 nm; λ_{em} = 515 nm). The data were processed with a Chromeleon data system. The SN-38 glucuronide concentration was calculated by subtracting the concentrations of SN-38 lactone and SN-38 carboxylate from the total SN-38 lactone concentration obtained after the glucuronidase treatment.

Pharmacokinetic Analysis. Using the computer program WINNONLIN1.5 (Scientific Consulting Inc., Cary, NC), the final half-lives were calculated from the final linear part of the semilogarithmic concentration-time curves, the AUC^{∞} by means of the trapezoidal rule, and the calculated final half-life using a weighting factor 1/c. The clearance was calculated by D/AUC^{∞} according to standard noncompartmental methods (14). Additional variables were calculated using metabolic ratio = $AUC^{\infty}_{SN\text{-}38}/(AUC^{\infty}_{CPT\text{-}11} + AUC^{\infty}_{SN\text{-}38})$, and biliary index = $AUC^{\infty}_{CPT\text{-}11} \times AUC^{\infty}_{SN\text{-}38}/AUC^{\infty}_{SN\text{-}38G}$.

RESULTS

Toxicities. During the infusion of 100 mg/m^2 and the first days thereafter, there were no serious problems. However, on day 4, she was admitted in critical condition with high fever (temperature, 38.8°C) and somnolence. The hemogram was severely abnormal with a hemoglobin of 4.4 mmol/liter (N = 7.5–10), platelets, 5 × 10^9/liter (N = 150–400), and WBC count, 2.2 × 10^9/liter (N = 3–10), further decreasing to 0.5 two days later with a neutrophil count of 0.32 × 10^9/liter. Preexisting liver abnormalities further deteriorated: blood determinations revealed a bilirubin of 88 μmol/liter, which increased in the days thereafter to a maximum value of 228 μmol/liter, and γ-GT dropped to 284 units/liter; however, ASAT and ALAT levels had increased to 332 units/liter and 103 units/liter, respectively, whereas LDH increased to 1081 units/liter and AF was lower at 554 units/liter. Hepatic failure was further substantiated by increasing serum ammonia levels to a maximum of 97 μmol/liter (n < 50). In addition, serum creatinine had risen to

190 μmol/liter (N < 120), accompanied by hyperkalemia (6.4 mmol/liter). Also, serum albumin was low with 18 g/liter (N = 34–50), whereas the plasmatic hemostasis was abnormal with an International Normalized Ratio prothrombin time of 1.30. Blood cultures were positive for *Escherichia coli*, *Klebsiella* pneumonia, and *Clostridium perfringens*. The patient was treated by hydration, antibiotics, resonium enemas, granulocyte colony-stimulating factor, and RBC and platelet transfusions. In the days thereafter, her condition gradually improved, although 8 days after the administration of CPT-11, she developed mild delayed diarrhea lasting for 5 days, which required treatment with loperamide. Two weeks after this first cycle, liver function tests revealed: bilirubin, 90 μmol/liter, γ-GT, 180 units/liter, ASAT, 26 units/liter, ALAT, 14 units/liter, LDH, 220 units/liter, and AF, 334 units/liter, while the serum ammonia as well as the renal function had normalized. Interestingly, the treatment resulted in a partial remission with an 80% volume reduction of the diameter of the supraclavicular lymph node and a reduction of the liver size while the serum carcinoembryonic antigen dropped rapidly from 48380 μg/liter to 5600 μg/liter. After close deliberations, it was decided to offer the patient a second course of CPT-11, but based on the pharmacokinetic profile (see pharmacokinetics), the dose was reduced to 30 mg/m^2. The first cycle at this dose level was tolerated well. Although a minor increase in transaminase values recurred, the bilirubin remained stable with values varying between 70 and 100 μmol/liter. Myelosuppression did not recur either. One week thereafter, a second cycle of CPT-11 at a dose of 30 mg/m^2 was administered. This time, however, somnolence recurred and lasted for 3 days. This went along with a transient increase of serum ammonia to 189 μmol/liter while serum ASAT and ALAT transiently rose to 141 and 101 units/liter, respectively. In addition, leukopenia (WBC, 1.3 × 10 g/liter) recurred, although thrombocytopenia did not. After clinical recovery, the patient was then discharged from the hospital with the plan, if the clinical condition would allow it, to continue CPT-11 at a still lower dose. However, her condition gradually deteriorated, and eventually she died on September 28, 1998, 70 days after the first treatment with CPT-11. A postmortem examination was performed. This revealed that the disease had metastasized extensively to the liver, lymph nodes, lungs, kidneys, right adrenal gland, right ovary, and skin. Remarkably, there was an extensive grade of necrosis in the metastases. Therefore, it was hypothesized that this was likely to have contributed to the death of the patient.

Pharmacokinetics. The concentrations of CPT-11 and its metabolites measured before and after the three 90-min infusions are given in Table 1. The values of the main pharmacokinetic parameters are summarized in Table 2 and compared to the data known from the literature (Table 3) after 90-min infusions of CPT-11.

During the first cycle, peak plasma concentrations of CPT-11 and SN-38 were within the range of reported values (15, 16). The peak concentration of SN-38G was obtained at 8 h after infusion and remained at this level for about 2 days. Compared to patients with NLF, the clearance of CPT-11 was severely reduced, which resulted in a clearly increased final half-life and consequently in an increased AUC^{∞}. Likewise, the final half-life and AUC of SN-38 were increased and in particular those of SN-38G. As a consequence, the biliary index was high, 3346 ng·h/ml. The metabolic ratio of 14.7% was also higher than the range measured in the patients of Rothenberg *et al.* (15), *i.e.*, 2.8–12.1% (mean, 7.4%).

Table 1. Concentrations of CPT-11 and its metabolites after three i.v. infusions of 90 min [a]

	Concentration (nM) CPT-11		Concentration (nM) SN-38		
Time (h)	Lactone	Carbox	Lactone	Carbox	SN-38 glu
Cycle 1					
−0.1	0.0	0.0	0.0	0.0	0.0
1.5	1338.2	1214.7	22.6	20.6	206.9
1.6	708.8	956.4	23.4	20.4	219.7
1.7	603.7	1025.7	22.1	21.0	241.1
2.0	574.6	1182.1	22.5	23.4	243.5
2.5	468.1	1139.6	22.0	22.8	291.7
3.5	365.1	1129.0	15.7	22.2	344.5
5.5	292.5	970.9	12.9	16.1	369.7
9.6	239.6	801.3	11.0	14.7	414.6
25.5	87.3	287.3	8.5	10.6	321.8
50.0	43.2	137.1	6.6	11.5	330.3
74.0	24.9	75.2	5.5	10.9	282.5
148.0	5.8	17.2	4.2	9.1	100.6
167.6	5.0	13.3	3.5	8.7	97.5
191.4	n.d.	4.6	n.d.[b]	5.9	79.1
412.9	n.d.	n.d.	n.d.	n.d.	5.9
435.1	n.d.	n.d.	n.d.	n.d.	6.1
506.6	n.d.	n.d.	n.d.	n.d.	4.2
Cycle 2					
1.5	202.2	296.0	12.1	20.2	77.5
9.2	71.0	180.8	4.1	12.4	193.1
24.8	24.6	64.7	n.d.	4.9	173.4
47.7	10.8	30.5	3.2	3.7	149.9
73.2	4.6	12.3	n.d.	n.d.	72.6
124.2	n.d.	n.d.	n.d.	n.d.	24.6
163.9	n.d.	n.d.	n.d.	n.d.	15.1
Cycle 3					
1.5	268.5	298.7	17.9	17.6	96.8
24.2	20.8	61.3	3.1	5.5	165.2
46.3	6.6	24.4	2.7	4.1	95.4
70.7	n.d.	13.0	n.d.	3.3	66.8
118.7	n.d.	3.9	n.d.	n.d.	44.4

[a] In cycles 1, 2, and 3, the patient received CPT-11 at a dose of 100, 30, and 30 mg/m^2, respectively. After 96 h and 120 h, and between 144 and 168 h, transfusion of 1050 ml of red cells was given.
[b] n.d., signals below lower limit of quantification of 3 nM.

The pharmacokinetic results obtained after the second and third cycles were comparable. Taking into account the reduced dose (30 mg/m^2) in comparison to cycle 1 (100 mg/m^2), it is obvious that for CPT-11 maximal concentrations (C_{max}), half-life ($t_{1/2}$), and AUCs were relatively less elevated than the corresponding values after the first cycle, whereas the clearance was somewhat less reduced. For SN-38, C_{max} and AUCs were relatively more elevated than the corresponding values after the first cycle, whereas $t_{1/2}$ was reduced. This resulted in metabolic ratios of 11.7% and 10.1% for cycles 2 and 3, respectively. The values of the pharmacokinetic parameters for SN-38 glucuronides were in accordance with the ratio of the doses used for cycles 2 and 3 in comparison with cycle 1. The sustained high concentrations of SN-38G observed during the first cycle were re-

Table 2 Pharmacokinetic parameters of CPT-11 and its metabolites after three 90-min infusions[a]

	CPT-11			SN-38			SN-38
	Lactone	Carboxylate	Total	Lactone	Carboxylate	Total	Glucuronides
Cycle 1							
C_{max} (nM)	1338.2	1214.7	2552.9	23.4	23.4	45.9	414.6
t_{max} (h)	1.5	2.0	1.5	1.6	2.0	2.0	9.6
$t_{1/2}$ (h)	33.4	32.6	32.8	134.7	434.9	232.8	63.7
Cl (liter/h/m^2)	16.2		4.2				
AUC^{∞} (nM · h)	10316	29835	40150	1849	7655	6933	49915
AUC_{120h} (nM · h)	9255	26580	35840	851	1375	2227	33790
Cycle 2							
C_{max} (nM)	202.2	296.0	498.2	12.1	20.2	32.3	193.1
t_{max} (h)	1.5	nm[b]	1.5	1.5	nm	1.5	9.3
$t_{1/2}$ (h)	20.2	20.0	20.1	107.7	56.6	73.7	43.0
Cl (liter/h/m^2)	19.9		6.1				
AUC^{∞} (nM · h)	2508	5703	8227	703	665	1089	14313
AUC_{120h} (nM · h)	2508	5703	8227	703	665	1089	12520
Cycle 3							
C_{max} (nM)	268.5	298.7	567.2	17.9	17.6	35.5	165.2
t_{max} (h)	1.5	nm	1.5	1.5	nm	1.5	nm
$t_{1/2}$ (h)	13.3	27.5	25.7	110.8	64.4	31.5	81.5
Cl (liter/h/m^2)	18.3		6.0				
AUC^{∞} (nM · h)	2719	5384	8306	695	742	901	15680
AUC_{120h} (nM · h)	2719	5345	8183	695	742	901	10610

[a] In cycles 1, 2, and 3, the patient received CPT-11 at a dose of 100, 30, and 30 mg/m^2, respectively.
[b] nm, not reliably measurable.

Table 3 Reference values for pharmacokinetic parameters of CPT-11 and its metabolites after an i.v. infusion of 100 mg/m^2 in 90 min

	CPT-11		SN-38		SN-38
	Lactone	Total	Lactone	Total	SN-38 Glucuronides
Rothenberg *et al.*[a]					
C_{max} (nM)	1154 (916–1283)	2141 (1733–2516)	38.2 (10.5–66.5)	86.1 (29.5–118.8)	
$t_{1/2}$ (h)	7.3 (3.9–12.3)	11.5 (5.5–19.3)	13.4 (7.6–19.1)	17.0 (11.8–23.3)	
Cl (liter/h/m^2)	45.5 (40.7–54.1)	14.7 (13.7–15.5)			
AUC^{∞} (nM · h)	3722 (3083–4100)	11377 (10783–12150)	536 (364–709)	924 (317–1486)	
Gupta *et al.*[b]					
Cl (liter/h/m^2)		20.3 ± 4.4			
AUC^{∞} (nM · h)		9338 ± 1612		256 ± 70	693 ± 597

[a] Mean values (range) of four patients receiving 100 mg/m^2 as a 90-min i.v. infusion and sampled during 50 h.
[b] Mean values (± SD) of three patients receiving 100 mg/m^2 as a 90-min i.v. infusion and samped during 24 h.

corded over a shorter time period after the second cycle and even disappeared during the third cycle. Due to the shorter half-lives, compounds were detectable in plasma for a shorter time during cycles 2 and 3 than during cycle 1. As a consequence, the biliary index was drastically reduced to 376 and 286 ng·h/ml for cycles 2 and 3, respectively.

DISCUSSION

This study, based on an intrapatient comparison of pharmacokinetics and metabolism, shows a major impact of liver dysfunction on clinical pharmacokinetics and toxicity of CPT-11 and its metabolites. Great caution is mandatory in the case of CPT-11 administration in patients with impaired liver function. Considering the high incidence of liver metastases in colorectal cancer, this observation is of great practical value. Our study calls for a detailed study to investigate the pharmacology of CPT-11 in patients with a spectrum of liver function abnormalities. This should result in guidelines for dose adjustments of CPT-11 in this category of patients. An interesting question arising from the present study is whether CPT-11 or its metabolites are hepatotoxic on their own. If one looks at the levels of bilirubin, transaminases, and ammonia in our patient, a transient, incremental deterioration of these parameters was seen after CPT-11 administration. However, it cannot be excluded that the clinical picture of septicemia might have contributed to some extent to the transient deterioration of the hepatic function.

In our patient, C_{max}, half life ($t_{1/2}$) values of CPT-11 and SN-38 were within the range of those found by Rothenberg *et al.* (15) during the first cycle, indicating that distribution of CPT-11 and early conversion into SN-38 were comparable to patients with NLF (Table 3). However, the AUCs of CPT-11 and its metabolites were elevated compared with those of patients with NLF (15, 16) because of the prolonged half-life resulting from their impaired clearance. The increase of the metabolic ratio may even be caused by an increased metabolism of CPT-11 into SN-38. Thus, these effects resulted in an increased tissue expo-

sure to both the parent drug and its metabolites, leading to enhanced toxicity.

Following 100 mg/m^2 of CPT-11, sustained high concentrations of SN-38 and SN-38G were obtained at 24 h. Comparison of these levels with the steady state levels, 96, 11.2, and 37 nM for total CPT-11, SN-38, and SN-38G, respectively, recorded by us[3] during continuous 5-day i.v. infusion at MTD (25 mg/m^2/day) led to the conclusion that the maximum dose to be administered to our patient at re-exposure to the drug should not exceed 30 mg/m^2. As a consequence, the CPT-11 dose was reduced 3.3-fold (from 100 to 30 mg/m^2), which resulted in a 3.8–4.1-fold decrease in the CPT-11 lactone AUC and a 2.6–2.7-fold decrease in the SN-38 lactone AUC. This would appear to be a near dose-proportional decrease in CPT-11 and SN-38 exposure. These reduced AUCs did not lead to a further impairment of the liver function.

After the dose of 30 mg/m^2, the patient tolerated the drug well. After this dose, the AUC^{∞}s of CPT-11 and SN-38 were within the range found by Rothenberg *et al.* (15) in patients with NLF receiving 100 mg/m^2. However, the AUC^{∞} of SN-38G was still much higher than that found by Gupta *et al.* (16), indicating that prolonged presence of elevated levels of SN-38G does not contribute to the toxicity of CPT-11. This is in agreement with a recent observation in patients with Gilbert's syndrome, deficient in hepatic UDP glucuronosyl transferases, and impaired SN-38 glucuronidation, who experienced severe side effects following CPT-11 administration (17).

Preliminary information on the subject of CPT-11 pharmacokinetics is available from an abstract that was presented recently (18). Most of the 20 patients in this study had relatively mild elevations of serum bilirubin (<50 μmol/liter). However, it was clear from the presented data that even in patients with these mild bilirubin elevations, systemic exposure to CPT-11 and SN-38 was largely increased. It is expected that with the growing experience in larger numbers of patients, guidelines for patients with disturbed liver function will be defined. Prospective clinical studies on this subject are also ongoing in the United States.

In conclusion, CPT-11 pharmacokinetics are highly dependent on liver function. Changes in metabolism and elimination will greatly affect toxicity. Because many patients with metastatic colorectal cancer have liver metastases, quite often in combination with significant liver function impairment, detailed studies addressing this subject are highly warranted.

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