Continuous Administration of Irinotecan by Hepatic Arterial Infusion: A Phase I and Pharmacokinetic Study

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ABSTRACT

Purpose: The main advantage of administering chemotherapy by means of hepatic arterial infusion (HAI) is the achievement of a high concentration of the drug in the liver. Irinotecan (CPT-11) is an active agent for the treatment of advanced colorectal cancer and other tumor types, which frequently metastasize in the liver. We performed a Phase I and pharmacokinetic study to investigate CPT-11 by hepatic arterial administration in patients with liver metastases.

Patients and Methods: Patients with liver metastases received CPT-11 at doses ranging from 15 to 25 mg/m2/day for 5 days every 3 weeks by continuous HAI. All of the patients also received one cycle CPT-11 i.v. Primary end points of the study were to define the maximum tolerated dose (MTD) of hepatic arterial CPT-11 and to study its pharmacokinetics.

Results: Twenty patients were included. The MTD was 25 mg/m2/day and the dose-limiting toxicities were neutropenia and diarrhea. The metabolic ratio was significantly increased with HAI compared with i.v. administration (P = 0.015). The steady-state concentrations of total CPT-11 and CPT-11 carboxylate and lactone were all lower than those during i.v. infusion (P = 0.008, 0.013, and 0.004, respectively), whereas the levels of total SN-38, and SN-38 carboxylate, lactone, and glucuronide were similar. The total body clearance of CPT-11 was significantly higher with HAI (P = 0.008).

Conclusions: The MTD of CPT-11 given by hepatic 5-day continuous infusion was 25 mg/m2/day. HAI of CPT-11 resulted in a higher metabolic ratio because of increased elimination of CPT-11. We recommend 20 mg/m2/day for additional Phase II studies.

INTRODUCTION

About 35–60% of patients with colorectal cancer develop liver metastases, and, in 30–40% of patients, the liver is the only metastatic site (1, 2). The presence of hepatic metastases has a major impact on survival with reported 1- and 3-year survival rates in untreated patients of 31 and 2.6%, respectively (3). When surgery is not feasible, besides systemic chemotherapy, hepatic arterial chemotherapy can be considered if only the liver is involved. Hepatic metastases derive their blood supply mainly from the hepatic artery, whereas the portal circulation supplies the normal liver tissue (4). HAI results in increased local drug concentrations. Furthermore, if the drug is eliminated by hepatic extraction, the hepatic arterial administration will yield lower systemic concentrations, and, hence, less toxicity may be expected than by i.v. administration (5–7).

Most experience of hepatic arterial chemotherapy has been in patients with liver metastases of colorectal cancer, with the fluoropyrimidines fluorodeoxyuridine (FUDR) and 5-fluorouracil (5-FU). Although response rates were significantly higher for hepatic arterial treatment compared with i.v. treatment in randomized studies, no evident prolongation of survival was observed even when meta-analyses were performed (8, 9). Therefore, hepatic arterial chemotherapy is not used for the routine treatment of colorectal cancer metastatic to the liver.

The recent introduction of the camptothecin analogue CPT-11 (Irinotecan), a topoisomerase I inhibitor, has been an important breakthrough in the treatment of colorectal cancer. The main mechanism of action of camptothecins is stabilization of the DNA-topoisomerase I complex on processing of the replication fork, causing single- and double-strand DNA breaks, thereby inhibiting transcription and DNA replication that ultimately result in cell death (10, 11). Irinotecan is active in first- and second-line treatment of advanced colorectal cancer with response rates of 10–20% (12–15). The two schedules of CPT-11 most often used in Phase II and III trials in colorectal cancer are i.v. bolus administration at a dose of 350 mg/m2 every 3 weeks, and 125 mg/m2 once a week for 4 weeks followed by a 2-week rest. Protracted infusion of CPT-11 may result in an enhanced antitumor effect for a number of reasons. The effects of CPT-11 are cell-cycle specific, and more frequent or prolonged dosing will expose more cells in the S phase (16).

3 The abbreviations used are: HAI, hepatic arterial/artery infusion; i.a., intra-arterial (infusion); MTD, maximum tolerated dose; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; SN-38G, SN-38 glucuronide; ACN, acetonitrile; TBAP, tetrabutyl ammonium phosphate.
Furthermore, the DNA-topoisomerase I complex is readily reversible, and prolonged exposure might result in prolonged stabilization resulting in higher cytotoxicity (17); and lower peak plasma concentrations will prevent saturation of carboxylesterases, and, therefore, drug activation, conversion of CPT-11 to the active metabolite SN 38, may become more efficient. Phase I studies of protracted i.v. CPT-11 administration have been performed. The recommended doses for additional Phase II studies were 30 mg/m²/day, for 5 days every 3 weeks (18), 10 mg/m²/day for 14 days every 3 weeks (19), and 10 mg/m²/day for 4 days in 2 of every 3 weeks (20). Diarrhea was the most important dose-limiting toxicity in all three of the schedules.

In this study, we wanted to define the toxicities of CPT-11 and to identify the MTD of CPT-11 when delivered as a 5-day continuous infusion through the hepatic artery. We also compared the pharmacokinetics and pharmacodynamics of CPT-11 when delivered by i.a. and i.v. administration. Because in the study of Ohe et al. on continuous 5-day i.v. infusion, substantial toxicity was observed at a dose-level of 25 mg/m²/day, we decided to start at the lower dose level of 15 mg/m²/day.

PATIENTS AND METHODS

Eligibility Criteria

Patients were eligible if they had a histologically or cyto logically documented solid tumor metastatic to the liver not amenable to surgery. The presence of minimal extrahepatic sites of disease was allowed only if the bulk of the disease was in the liver. The performance status had to be ≤2 (WHO criteria), the life expectancy ≥3 months, and the age ≥70 years. The anatomy of the liver arterial supply was assessed by angiography, and it had to allow placement of a catheter into the hepatic artery for adequate liver perfusion. Other criteria for eligibility were: a WBC count ≥4 × 10⁹/liter; a platelet count ≥100 × 10⁹/liter; serum transaminases ≤2 times the upper limit of normal, a prothrombin time ≤1.2 times the upper limit of normal, serum bilirubin ≤20 μM, and serum creatinine ≤110 μM or a creatinine clearance ≥60 ml/min. No more than two prior chemotherapy regimens were allowed, and the last chemotherapy or prior radiotherapy had to be discontinued at least 4 weeks before study entry, or 6 weeks for nitrosoureas and mitomycin C.

Exclusion criteria were: prior treatment with topoisomerase I inhibitors; a history of inflammatory bowel disease or extensive intestinal resection; central nervous system metastases; uncontroll ed infection; and a history of other cancer except adequately treated in situ carcinoma of the cervix or basal or squamous cell carcinoma of the skin. The study protocol was approved by the Medical Ethical Committee of the Academic Hospital Vrije Universiteit (Amsterdam, the Netherlands), and all of the patients gave written informed consent before study entry.

Dose Escalation

CPT-11 was administered as a 5-day continuous infusion every 3 weeks. The starting dose was 15 mg/m²/day. The first course was administered alternatively by HAI and the second course by i.v. infusion or vice versa. From the third course on, CPT-11 was always given by HAI. Dose levels planned were 15 mg/m²/day, 25 mg/m²/day, 35 mg/m²/day, and additional incremental steps of 10 mg/m²/day. At least three patients had to be treated at each dose level. No intrapatient dose escalation was performed; and when one grade 4, or two grade 3 drug-related toxicities occurred (excluding alopecia, nausea, and vomiting), three additional patients were to be entered at that dose level. The MTD was defined as ≥3 of 6 patients developing grade-4 hematological toxicity or ≥grade-3 nonhematological toxicity.

When the MTD for hepatic arterial CPT-11 was established, dose escalation was terminated. In case the i.v. MTD was identified before that of HAI, further escalation of hepatic arterial CPT-11 was planned. In cases of grade-3 or -4 nonhematological toxicity (other than nausea, vomiting, or alopecia), grade-4 neutropenia, or grade-3 febrile neutropenia, the dose was reduced by 25% in subsequent cycles. If a patient developed grade-3 or -4 nonhematological toxicity or grade-4 neutropenia, despite two successive dose reductions, the patient went off study. Other reasons for treatment termination were progressive disease, hematological or nonhematological toxicity persisting for more than 5 weeks, or patient refusal.

Drug Administration

HAI was given either by percutaneous catheterization of the femoral artery or by an arterial port-a-cath (Deltec, SIMS Deltec Inc., St. Paul, MN). The arterial port-a-cath was placed at laparotomy; the tip of the catheter was inserted in the ligated gastroduodenal artery, and cholecystectomy was performed to prevent chemical cholecystitis. Irinotecan (Campto; RhonePoulenc Rorer, Anthony, France) was supplied in 5-ml vials with sterile solution, containing 100 mg of CPT-11. The appropriate volume of CPT-11 was added to an infusion bag containing 1000 ml of 0.9% NaCl or 5% dextrose for patients treated with cather and bedside pump or was diluted to 250 ml for patients treated with port-a-cath and portable pump. For bedside pumps the infusion rate was 1000 ml/day and for the portable pump 41 ml/day. During the first two cycles, all of the patients received CPT-11 by bedside pump diluted in 1000 ml and were hospitalized. For i.v. administration, CPT-11 was also added to an infusion bag containing 1000 ml of 0.9% NaCl or 5% dextrose and delivered via bedside pump.

Concomitant Medications

Patients received no prophylactic antiemetic therapy before the first cycle. If severe nausea or vomiting occurred, patients received metoclopramide or ondansetron in subsequent cycles. Prophylactic anti diarrheal medication was also not given, and patients were instructed to take loperamide immediately at the onset of the first loose stools at a dose of 4 mg, followed by 2 mg every 2 h until the diarrhea subsided for at least 12 h. If diarrhea persisted for more than 24 h despite loperamide, oral ciprofloxacin was administered for 7 days, and if necessary, treatment with octreotide s.c. was started. Patients with persistent diarrhea for more than 48 h or patients who experienced concomitant vomiting or fever were hospitalized and received i.v. fluids and i.v. antibiotics.

Toxicity and Response Evaluation

Pretreatment evaluation included complete history and physical examination, full blood cell count, blood chemistry tests including creatinine, alkaline phosphatase, γ-glutamyl-
transferrase, ASAT, ALAT, bilirubin, and prothrombin time. These tests were repeated before every course. Electrocardiogram, chest X-ray, and an abdominal computerized tomography (CT) scan were performed before the first course and every other course thereafter. On day 3 of the CPT-11 infusion, serum bilirubin, ASAT, and ALAT were also repeated, and hematology, bilirubin, ASAT, and ALAT were evaluated weekly during treatment. Tumor measurements were performed every other cycle, and responses were evaluated according to the WHO criteria (21). All of the toxicities were scored according to National Cancer Institute Common Toxicity Criteria (22).

**Pharmacokinetics**

**Sampling.** Blood sampling was performed during the first infusion of both the hepatic arterial and the i.v. administrations, to determine the plasma concentrations of CPT-11, SN-38, and SN-38G. Blood samples (8 ml) were collected in cooled heparinized tubes before treatment, 1, 3, 6, 12, 24 h and 2, 3, 4, 5, 5.5, 6, 6.5, and 7 days after the start of the CPT-11 infusion. Blood samples were placed on ice immediately after collection, and then centrifuged at 2000 × g for 3 min at 4°C. Plasma was stored in 500-μl aliquots in five polypropylene Eppendorf tubes at −80°C until analysis.

**Instrumentation.** At the time of analysis, plasma samples were thawed and briefly vortexed just before sample treatment. Calibration and quality control samples were prepared by spiking blank heparinized plasma and were treated in the same way as patient samples. The concentrations of CPT-11 and SN-38 lactone and carboxylate were determined by high-performance liquid chromatography (HPLC). The system consisted of a Triathlon autosampler, an automatic Valco injection valve, and a GT103 degasser serving two columns connected in parallel (Phenomenex Prodigy ODS2, 5 μm, 150 × 3.2 mm) in a Mistral column thermostat and each provided with a guard column (10GLC 4-ODS-1, 10 × 4 mm), a Gynkovet 300 solvent delivery system, a pulse damper, and a Jasco fluorescence detector. The instrumentation was supplied by Separations, H.I. Ambacht, the Netherlands, and the columns, by Bester, Amstelveen, the Netherlands. The data from both detectors were collected and processed by a Dell Dimension XPS 166 computer (Dell, Amsterdam, the Netherlands) using the chromatographic software Chromeloean (Separations).

**Analysis of CPT-11 and SN-38 Carboxylate and Lactone.** Each analysis was performed in duplicate. Two hundred μl of plasma were added to 300 μl of methanol/acetonitrile (ACN) (50:50%) in a polypropylene micro-test tube (1.5-ml, Eppendorf) to precipitate the plasma proteins. After centrifugation, 250 μl of supernatant were transferred to another micro-test tube containing 750 μl of 50 mM NH4Ac/5 mM tetraethylammonium phosphate (TBAP) (pH 6.60) and vortexed. The micro-test tubes were placed in a cooled (4°C) autosampler and 50 μl of the sample were injected onto each column. CPT-11 carboxylate and lactone were analyzed by the column provided with a mobile phase (0.6 ml/min) consisting of TBAP (5 mM) in NH4Ac (50 mM) buffer/methanol/ACN (60/14/20, v/v/v) and the fluorescence detector set at λex = 385 nm and λem = 530 nm.

**SN-38G Analysis.** Samples were analyzed in duplicate. Two hundred μl of plasma were added to a micro-test tube containing 665 units β-glucuronidase (40 μl) and incubated for 2 h at 37°C to convert SN-38G into SN-38. The plasma proteins were precipitated by adding 300 μl of methanol/ACN (50:50), briefly vortexing, and centrifugation. Ten μl of 2 mM HCl were added to 250 μl to convert SN-38 carboxylate into SN-38 lactone. After 10 min of incubation at 37°C, 750 μl of 50 mM NH4Ac/5 mM TBAP (pH 9.4) were added. The mixture was vortexed and placed in a cooled (4°C) autosampler. Fifty μl of each sample was injected onto both columns. The total concentration of SN-38 lactone represents the sum of the concentrations of SN-38 carboxylate, SN-38 lactone, and SN-38G. By subtracting the concentrations of SN-38 carboxylate and lactone the concentration of SN-38 lactone could be determined. The determination of total CPT-11 was used as a control.

**Characteristics of the Assays.** The lower limit of quantification (LLQ) was 0.5 nM for CPT-11 carboxylate and lactone and 1.0 nM for SN-38 carboxylate and lactone. The within-day precision was smaller than 4.4, 3.3, 4.8, 2.1, and 5.6% for CPT-11 carboxylate, CPT-11 lactone, SN-38 carboxylate, SN-38 lactone, and SN38G, respectively. The between-day precision was smaller than 7.2, 8.5, 9.9, 7.8, and 15.1% for CPT-11 carboxylate, CPT-11 lactone, SN-38 carboxylate, SN-38 lactone, and SN38G, respectively.

**Calculations.** Steady-state concentrations were determined by calculating the mean of the concentrations measured on days 1, 2, 3, 4, and 5. These steady-state concentrations were used to calculate the following parameters:

\[
\text{Metabolic ratio} = \frac{\text{SN-38 carboxyl} + \text{SN-38 lactone}}{\text{CPT-11 carboxyl} + \text{CPT-11 lactone}} \times 100% \quad (A)
\]

\[
\text{CPT-11-lactone ratio} = \frac{\text{CPT-11 lactone}}{\text{CPT-11 carboxyl} + \text{CPT-11 lactone}} \times 100% \quad (B)
\]

\[
\text{SN-38-lactone ratio} = \frac{\text{SN-38 lactone}}{\text{SN-38 carboxyl} + \text{SN-38 lactone}} \times 100% \quad (C)
\]

\[
\text{SN-38G ratio} = \frac{\text{SN-38G}}{\text{SN-38 carboxyl} + \text{SN-38 lactone}} \times 100% \quad (D)
\]

\[
\text{Biliary index (BI)} = \text{CPT-11 total} \times \frac{\text{SN-38 total}}{\text{SN-38G}} \quad (E)
\]

\[
\text{CPT-11 total body clearance (Cl}_{\text{TB}} = \frac{\text{Infusion rate}}{\text{CPT-11 total}} \quad (F)
\]

\[
\text{First-pass hepatic clearance (Cl}_{\text{Fh}} = \text{Cl}_{\text{TB,i.a.}} - \text{Cl}_{\text{TB,i.v.}} \quad (G)
\]
 Statistical Analysis. Statistical analysis was performed using the SPSS software (Version 7.5 for Windows; SPSS, Inc., Chicago, IL). Pearson’s correlation coefficient ($r$) was used for the relationship between dose and the steady-state concentrations of CPT-11 and its metabolites. To compare the parameters of HAI with those of i.v. infusion, Student’s t test for paired samples was used. The level of significance was set at 0.05. All tests for significance were two-tailed.

RESULTS

 Twenty patients were entered in the study; patient characteristics are listed in Table 1. Besides liver metastases, 10 patients also had extrahepatic sites of disease. The total number of courses of CPT-11 given was 66 (median number per patient, 3; range, 1–12), the total number of i.v. courses was 17; the total number of hepatic arterial courses was 49. Three patients received only one i.v. course and three patients only one hepatic arterial course. Fourteen patients received two or more courses and had both hepatic arterial and i.v. treatment. Reasons for treatment termination were: progressive disease in 10 patients, failure to cannulate the hepatic artery or hepatic artery thrombosis in 3 patients, and patient refusal in 2. In one patient, treatment was discontinued because of grade IV diarrhea and neutropenia complicated by a septic shock. Surgery for ileus caused by adhesions in one patient also resulted in study termination for that patient. Clinical deterioration of the general condition occurred in two patients. In one patient, treatment was interrupted after four cycles with stable disease because additional benefit from treatment was not expected.

Toxicity

 All of the patients were assessable for toxicity. Diarrhea and neutropenia were dose limiting at dose level II (25 mg/m$^2$/day). Of the four patients included at dose level I (15 mg/m$^2$/day), one patient received only i.v. treatment because of failure to cannulate the hepatic artery, and three patients received both i.v. and hepatic arterial treatment. Besides grade 3 diarrhea during HAI in one patient, no other serious toxicities were observed. Seven patients were treated at dose level II (25 mg/m$^2$/day), of whom one had only one hepatic arterial course and six received both hepatic arterial and i.v. infusion. Of the seven patients who received hepatic arterial treatment, one had a 25% dose reduction because a dose-limiting toxicity occurred after the first i.v. course. Of the six patients who received i.v. treatment, one had a 25% dose reduction because a dose-limiting toxicity occurred after the first HAI. Dose-limiting toxicity was observed in three patients during hepatic arterial treatment and in three patients during i.v. treatment. All of the dose-limiting toxicities were observed during the first course, irrespective of the mode of administration. Of the six patients who received hepatic arterial treatment at this dose level, one had grade 4 neutropenia, one developed grade 4 neutropenia and grade 4 diarrhea, and one had grade 3 diarrhea and grade 3 nausea and vomiting. One of the five patients who received i.v. infusion at this level had grade 3 vomiting and grade 4 neutropenia complicated by septic shock, one patient developed grade 3 diarrhea and grade 3 nausea and vomiting, and one patient had grade 3 diarrhea and grade 3 mucositis. Because of the striking rise in toxicity observed at dose level II, we decided to treat another group of patients at the intermediate dose of 20 mg/m$^2$/day (dose level III). At this dose level only two of nine patients developed grade 3 or 4 toxicity.

The dose-limiting toxicities were diarrhea and neutropenia. Thirty-eight of all courses were complicated by diarrhea, which was grade 3 or 4 in eight patients, and eight courses were complicated by neutropenia, which was grade 3 or 4 in four patients. Two patients with grade 3 or 4 diarrhea also experienced grade 4 neutropenia, and six experienced grade 1 or 2 neutropenia. All of the patients with grade 3 or 4 diarrhea were hospitalized. The median time to the first onset of diarrhea was 8 days (range, 4–10 days) and the median duration was 8 days (range, 4–16). Abdominal cramps were observed in 21 of 66 cycles and were grade 3 or 4 in two patients. Anorexia was seen after 14 of 66 treatment courses and was severe in one patient. Asthenia was observed only at the highest two dose levels in 10 courses but was never severe. Cutaneous toxicity, consisting of a fine papular exanthema, was observed in two patients treated at dose level I and at one patient at dose level II.

Tumor Response

 Eleven patients were evaluable for response. Nine patients were not evaluable for the following reasons: six received only one cycle (three because of clinically rapid progressive disease, two because they refused further treatment, and one because of the inability to catheterize the hepatic artery); three patients received two or more cycles but had inadequate evaluation. Three of 11 evaluable patients had a partial response, 6 had stable disease, and 2 patients had progressive disease. Two responding patients had colorectal cancer (of nine evaluable colorectal cancer patients), and one patient had biliary tract cancer. The responding patients were treated at dose levels I and II.

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>No. of patients</th>
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<tbody>
<tr>
<td>No. entered</td>
</tr>
<tr>
<td>No. assessable for toxicity</td>
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<tr>
<td>No. evaluable for response</td>
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<tr>
<td>Age, yr, median (range)</td>
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<tr>
<td>Gender, male/female</td>
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<tr>
<td>Performance status (WHO), 0/1/2</td>
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<tr>
<td>Primary tumor: Colorectal</td>
</tr>
<tr>
<td>Pancreas</td>
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<tr>
<td>Other*</td>
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<tr>
<td>Prior chemotherapy regimen: 5-Fluorouracil-based</td>
</tr>
<tr>
<td>Other*</td>
</tr>
</tbody>
</table>

* Biliary duct, 1; liver, 1; leiomyosarcoma testis, 1; unknown primary, 1.

* One patient received three regimens.

* One patient each: doxorubicin; ifosfamide and taxotere; etoposide, vincristine, doxorubicin, ifosfamide, actinomycin D (EVAIA); cisplatin and gemcitabine; and carboplatin.
Pharmacokinetics

CPT-11 pharmacokinetics was obtained on 18 patients: 3 patients at dose level I (15 mg/m²/day), 7 patients at dose level II (25 mg/m²/day), and 8 patients at dose level III (20 mg/m²/day). In 12 patients, blood samples could be obtained during both i.v. and i.a. infusion (dose level I: 3 patients; dose level II: 3 patients; and dose level III: 6 patients), in 2 patients, blood samples were collected only during i.a. infusion (dose level II), and in 4 patients only during i.v. infusion (dose level II: 2 patients; dose level III: 2 patients). Fig. 1 shows the concentration-time curves in a representative patient receiving 20 mg/m²/day as a HAI. Comparable concentrations were obtained when given i.v.

Table 2 Mean steady-state concentrations (±SD) of CPT-11 and its metabolites (nm) during 5-day i.v. and i.a. continuous infusions

<table>
<thead>
<tr>
<th>Dose of CPT-11</th>
<th>No. of patients</th>
<th>CPT-11 total</th>
<th>CPT-11 carb</th>
<th>CPT-11 lact</th>
<th>SN-38 total</th>
<th>SN-38 carb</th>
<th>SN-38 lact</th>
<th>SN-38G</th>
</tr>
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<tr>
<td>i.v. infusion</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>15 mg/m²/day</td>
<td>3</td>
<td>64.6 (24.4)</td>
<td>41.3 (14.9)</td>
<td>23.3 (9.5)</td>
<td>6.8 (3.9)</td>
<td>2.0 (0.9)</td>
<td>4.9 (3.1)</td>
<td>25.3 (16.4)</td>
</tr>
<tr>
<td>20 mg/m²/day</td>
<td>8</td>
<td>83.7 (25.6)</td>
<td>57.3 (17.2)</td>
<td>26.4 (9.2)</td>
<td>10.6 (3.5)</td>
<td>3.7 (1.2)</td>
<td>6.9 (2.3)</td>
<td>29.6 (17.3)</td>
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<tr>
<td>25 mg/m²/day</td>
<td>4</td>
<td>130.0 (67.6)</td>
<td>88.8 (48.8)</td>
<td>41.2 (18.9)</td>
<td>11.2 (4.0)</td>
<td>4.0 (1.9)</td>
<td>7.2 (2.5)</td>
<td>27.7 (13.3)</td>
</tr>
<tr>
<td>HAI</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mg/m²/day</td>
<td>3</td>
<td>59.2 (23.2)</td>
<td>39.4 (14.4)</td>
<td>19.8 (8.9)</td>
<td>7.3 (3.8)</td>
<td>2.5 (1.0)</td>
<td>4.8 (2.7)</td>
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<tr>
<td>20 mg/m²/day</td>
<td>6</td>
<td>62.7 (18.3)</td>
<td>43.7 (11.6)</td>
<td>19.0 (7.0)</td>
<td>10.0 (2.3)</td>
<td>3.4 (1.0)</td>
<td>6.7 (1.3)</td>
<td>29.8 (21.5)</td>
</tr>
<tr>
<td>25 mg/m²/day</td>
<td>5</td>
<td>90.1 (42.4)</td>
<td>61.1 (30.3)</td>
<td>29.0 (12.5)</td>
<td>14.2 (6.1)</td>
<td>4.2 (1.6)</td>
<td>10.0 (4.8)</td>
<td>42.8 (22.6)</td>
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</tbody>
</table>

*carb, carboxylate; lact, lactone.

Pharmacokinetics

CPT-11 pharmacokinetics was obtained on 18 patients: 3 patients at dose level I (15 mg/m²/day), 7 patients at dose level II (25 mg/m²/day), and 8 patients at dose level III (20 mg/m²/day). In 12 patients, blood samples could be obtained during both i.v. and i.a. infusion (dose level I: 3 patients; dose level II: 3 patients; and dose level III: 6 patients), in 2 patients, blood samples were collected only during i.a. infusion (dose level II), and in 4 patients only during i.v. infusion (dose level II: 2 patients; dose level III: 2 patients). Fig. 1 shows the concentration-time curves in a representative patient receiving 20 mg/m²/day as a HAI. Comparable concentrations over time were obtained when CPT-11 was given i.v. The mean steady-state concentrations of CPT-11 and its metabolites per dose level are summarized in Table 2, and the mean calculated ratios for all patients are depicted in Table 3. Because the ratios are independent of the dose, it was possible to calculate mean values for all of the ratios of all of the dose levels. A large interpatient variation in the concentrations of CPT-11 and its metabolites was observed at every dose level after both i.v. and HAI. Steady-state levels were reached within 24 h after starting the infusion for each compound. At treatment interruption after 5 days, the plasma levels of all of the compounds dropped biphasically.

i.v. Infusion. After i.v. infusion, the steady-state concentrations of CPT-11, CPT-11 lactone, and CPT-11 carboxylate increased linearly with the dose (r, 0.536, P = 0.032; r, 0.491, P = 0.053; r, 0.548, P = 0.028, respectively). The steady-state concentrations of SN-38, SN-38 lactone, and SN-38 carboxylate did not significantly increase with the dose (r, 0.395, P = 0.129; r, 0.331, P = 0.211; r, 0.452, P = 0.079, respectively). The steady-state concentration of SN-38 was significantly correlated with the steady-state concentration of CPT-11 (r, 0.739, P = 0.001). Steady-state concentrations of SN-38 and the metabolic ratio were not significantly correlated (r, 0.368, P = 0.161). The total body clearance of CPT-11 showed a large interpatient variability. Its mean value was 8.7 ± 2.4 liter/h/m². The biliary index was not related to the dose of CPT-11 nor to the grade of diarrhea (Fig. 2).

HAI. After i.a. infusion, the steady-state concentrations of CPT-11, CPT-11 lactone, CPT-11 carboxylate, and SN-38 carboxylate did not significantly increase with the dose (r, 0.415, P = 0.141; r, 0.393, P = 0.165; r, 0.418, P = 0.137; r,
The first pass hepatic clearance was 2.7/liter/h/m² significantly lower during i.a. infusion than during i.v. infusion of total CPT-11, CPT-11 lactone, and CPT-11 carboxylate were and arterial infusion of CPT-11, the steady-state concentrations patients for whom pharmacokinetics was available for both i.v. and arterial infusion of CPT-11, the steady-state concentrations. This was not the case during HAI of CPT-11. The metabolic ratio was significantly higher during HAI than during i.v. infusion (P = 0.015). There was no significant difference between the CPT ratio and the SN-38 ratio for i.v. and HAI. The SN-38-glucuronide ratio for i.v. infusion was significantly lower than for HAI of the drug (P = 0.023). The total body clearance of CPT-11 during HAI was significantly higher than during i.v. administration (P = 0.008). This difference is expressed as the first pass hepatic clearance (Table 3).

**DISCUSSION**

The present trial is the first Phase I and pharmacokinetic study of HAI of CPT-11 in patients with liver metastases. Neutropenia and diarrhea were the dose-limiting toxicities and the MTD was observed at 25 mg/m²/day for both hepatic arterial and i.v. infusion. No major difference was observed in toxicities after i.v. or HAI. The dose level of 20 mg/m²/day for 5 days every 3 weeks, on which 9 patients were treated, seemed feasible and safe, and this dose can be recommend for continuous HAI of CPT-11 in Phase II studies.

In our study, to avoid the potential bias of prior CPT-11 infusion, the sequence of i.v. and HAI was alternated in consecutive patients. The major pharmacokinetic results and calculated parameters of our study are compared in Table 4 with the results of other pharmacokinetic studies of short and prolonged infusions of CPT-11. In our study, the metabolic ratio, a measure for the conversion of CPT-11 into SN-38, was 16.5% during HAI and 12.6% during i.v. infusion (dose level, 20 mg/m²/day). This is higher than the metabolic ratio after short infusions (23) and in line with the metabolic ratio found in other studies during prolonged infusions (18, 19, 20, 23). The finding of an increased

### Table 3  Mean (± SD) metabolic ratios, biliary index (B.I.), and clearances [total body clearance (Cl<sub>TB</sub>, liter/h/m²) and first-pass hepatic clearance (Cl<sub>H</sub>, liter/h/m²)] of CPT-11 and its metabolites during i.v. and i.a. 5-day continuous infusions (calculations based on steady-state levels)

<table>
<thead>
<tr>
<th>Dose of CPT-11</th>
<th>No. of patients</th>
<th>Metabolic ratio</th>
<th>CPT-11 ratio</th>
<th>SN-38 ratio</th>
<th>SN-38G ratio</th>
<th>B.I.</th>
<th>CPT-11 Cl&lt;sub&gt;TB&lt;/sub&gt;</th>
<th>CPT-11 Cl&lt;sub&gt;H&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg/m²/day</td>
<td>3</td>
<td>10.4 (3.6)</td>
<td>35.7 (2.5)</td>
<td>70.1 (4.1)</td>
<td>248.9 (180.4)</td>
<td>21.3 (12.6)</td>
<td>9.2 (2.9)</td>
<td></td>
</tr>
<tr>
<td>20 mg/m²/day</td>
<td>8</td>
<td>12.6 (2.3)</td>
<td>31.4 (3.8)</td>
<td>65.1 (2.8)</td>
<td>187.2 (112.7)</td>
<td>36.2 (21.4)</td>
<td>9.4 (1.8)</td>
<td></td>
</tr>
<tr>
<td>25 mg/m²/day</td>
<td>4</td>
<td>9.2 (2.8)</td>
<td>32.2 (2.5)</td>
<td>65.0 (7.5)</td>
<td>152.0 (54.7)</td>
<td>63.5 (7.2)</td>
<td>7.8 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>15</td>
<td>11.3 (3.0)</td>
<td>32.5 (3.5)</td>
<td>66.1 (4.8)</td>
<td>190.4 (117.4)</td>
<td>40.7 (35.3)</td>
<td>8.7 (2.4)</td>
<td></td>
</tr>
<tr>
<td>15 mg/m²/day</td>
<td>3</td>
<td>13.0 (6.6)</td>
<td>32.9 (2.5)</td>
<td>64.1 (4.0)</td>
<td>585 (588.9)</td>
<td>16.9 (11.0)</td>
<td>10.3 (3.8)</td>
<td></td>
</tr>
<tr>
<td>20 mg/m²/day</td>
<td>6</td>
<td>16.5 (4.0)</td>
<td>29.9 (3.6)</td>
<td>67.1 (3.3)</td>
<td>297.3 (197.0)</td>
<td>30.8 (20.2)</td>
<td>11.5 (3.3)</td>
<td></td>
</tr>
<tr>
<td>25 mg/m²/day</td>
<td>5</td>
<td>17.9 (11.1)</td>
<td>32.9 (3.0)</td>
<td>69.1 (6.4)</td>
<td>318.3 (46.1)</td>
<td>20.2 (9.9)</td>
<td>11.8 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>14</td>
<td>16.2 (7.3)</td>
<td>31.6 (3.3)</td>
<td>67.1 (4.8)</td>
<td>374.5 (311.9)</td>
<td>24.7 (16.4)</td>
<td>11.3 (3.9)</td>
<td>2.7 (3.0)</td>
</tr>
</tbody>
</table>

Fig. 2  Relationship between the biliary index and diarrhea observed in patients who received i.v. and hepatic arterial CPT-11.

The steady-state concentrations of SN-38 and SN-38 lactone showed a significant linear correlation with the dose (r, 0.566, P = 0.035; r, 0.570, P = 0.033, respectively). The concentration of SN-38 was not significantly correlated with the concentration of CPT-11 (r, 0.519, P = 0.035; r, 0.584, P = 0.028). The total body clearance of CPT-11 showed large variability between patients at each dose level. Its mean value was 11.3 ± 3.9 liter/h/m². The total body clearance was independent of the dose infused. The first pass hepatic clearance was 2.7 ± 3.0 liter/h/m² and was significantly correlated with the dose infused (r, 0.614, P = 0.034). There was no significant correlation between the biliary index and the degree of diarrhea (Fig. 2).

**Intrapatent Comparison of i.v. and HAI.** In the 12 patients for whom pharmacokinetics was available for both i.v. and arterial infusion of CPT-11, the steady-state concentrations of total CPT-11, CPT-11 lactone, and CPT-11 carboxylate were significantly lower during i.a. infusion than during i.v. infusion (P = 0.008, P = 0.004, and P = 0.013, respectively). Although there was a tendency for higher SN-38 levels during HAI, no significant differences were observed between the steady-state levels of total SN-38, SN-38 lactone, SN-38 carboxylate, and SN-38G during HAI and i.v. administration. The dose of CPT-11 and the steady-state concentrations of CPT-11 and SN-38 were significantly correlated after i.v. infusion. Furthermore, SN-38 steady-state concentrations were significantly correlated with CPT-11 steady-state concentrations. This was not the case during HAI of CPT-11. The metabolic ratio was significantly higher during HAI than during i.v. infusion (P = 0.015). There was no significant difference between the CPT ratio and the SN-38 ratio for i.v. and HAI. The SN-38-glucuronide ratio for i.v. infusion was significantly lower than for HAI of the drug (P = 0.023). The total body clearance of CPT-11 during HAI was significantly higher than during i.v. administration (P = 0.008). This difference is expressed as the first pass hepatic clearance (Table 3).

The present trial is the first Phase I and pharmacokinetic study of HAI of CPT-11 in patients with liver metastases. Neutropenia and diarrhea were the dose-limiting toxicities and the MTD was observed at 25 mg/m²/day for both hepatic arterial and i.v. infusion. No major difference was observed in toxicities after i.v. or HAI. The dose level of 20 mg/m²/day for 5 days every 3 weeks, on which 9 patients were treated, seemed feasible and safe, and this dose can be recommend for continuous HAI of CPT-11 in Phase II studies.
conversion of CPT-11 into SN-38, as an expected result of more effective activation by carboxylesterases, may explain the much lower dose intensity of CPT-11 that can be reached by prolonged infusions compared with short infusions (17, 24). In preclinical models, the activity of CPT-11 is highly schedule dependent, and protracted intermittent dosing enhanced activity and reduced toxicity of the drug (25–27). On the other hand, continuous inhibition of topoisomerase I may result in down-regulation of this enzyme, which is a possible mechanism of acquired CPT-11 resistance. Therefore, protracted intermittent short infusions of CPT-11 may be the preferred schedule for optimal exploitation of carboxylesterases and for overcoming topoisomerase I down-regulation. This is supported by the results of animal experiments in which protracted intermittent dose schedules were more effective despite lower total dosages administered (25, 26).

In our study, major differences between HAI and i.v. infusion were the relatively lower plasma steady-state levels of CPT-11 (lactone plus carboxylate) and the corresponding higher total body clearance of CPT-11 with HAI. The steady-state plasma levels of the various forms of SN-38 (lactone, carboxylate, and glucuronide) were equal or higher after HAI than after i.v. infusion. The metabolic ratio observed after HAI was, therefore, significantly higher than that after i.v. infusion \((P = 0.015)\). From these data, it can be concluded that the conversion of CPT-11 is increased with arterial infusion, and this is probably because of the high content of carboxylesterase and other enzymes in the liver. Studies in mice showed a 3-fold increase in the metabolic ratio after oral CPT-11 administration as compared with i.v. infusion, indicating a first pass hepatic metabolism after oral administration (28), which, as with HAI, was attributed to a high carboxyl esterase content of the liver. HAI may achieve a high local drug concentration and reduced systemic exposure, with the potential for increased local response and reduced systemic toxicity. However, conditions needed to obtain this effect are hepatic extraction/elimination and a short systemic half-life of the drug. Our results showed a higher clearance of CPT-11 after HAI than after i.v. infusion. The difference between the two was attributed to the first-pass hepatic clearance of CPT-11 after HAI \((C_{\text{ft}})\), 1–6 liter/h/m² depending on the dose infused). However, we did not find a significant difference in the concentration of SN-38 after i.v. or i.a. infusion. Furthermore, the side effects and their severity that were recorded in our study were similar after i.v. and HAI. Although HAI resulted in a higher local delivery of CPT-11, it is not known whether the SN-38 concentrations were also higher in tumor cells.

In conclusion, continuous HAI of CPT-11 resulted in a higher metabolic ratio than did continuous i.v. infusion as reflected by a significantly increased metabolic ratio. Despite a first-pass hepatic clearance of CPT-11 after HAI, there was no clinically significant lower systemic exposure to SN-38. Moreover, no significant benefit in side effects was achieved by HAI administration. To answer the question as to whether increased local CPT-11 concentrations are sufficient to achieve better tumor response, Phase II studies are needed.

REFERENCES

8. Harmant, A., Rotstein, L. E., and Langer, B. Regional versus systemic chemotherapy in the treatment of colorectal carcinoma meta-

### Table 4 Mean values (± SD) of the pharmacokinetic variables of CPT-11 and its metabolites from the present study and comparison with literature data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Present study</th>
<th>Ohe et al. (18)</th>
<th>Herben et al. (19)</th>
<th>Takimoto et al. (20)</th>
<th>Canal et al. (23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level</td>
<td>20 mg/m²/day</td>
<td>30 mg/m²/day</td>
<td>10 mg/m²/day</td>
<td>10 mg/m²/day</td>
<td>350 mg/m²/day</td>
</tr>
<tr>
<td>i.v. c.i. 6 5 days every 3 wk</td>
<td>20 mg/m²/day</td>
<td>i.v. 5-day c.i.</td>
<td>i.v. 14-day c.i.</td>
<td>i.v. 4-day c.i.</td>
<td>30 min i.v.</td>
</tr>
<tr>
<td>i.a. infusion</td>
<td>6</td>
<td>7</td>
<td>16 (±2)</td>
<td>24 (±8)</td>
<td>26</td>
</tr>
<tr>
<td>No. of patients</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Dose density, mg/m²/wk</td>
<td>33</td>
<td>50</td>
<td>43</td>
<td>26</td>
<td>116</td>
</tr>
<tr>
<td>CPT-11 metabolic ratio</td>
<td>16.5 (±4.0)</td>
<td>12.6 (±2.3)</td>
<td>16 (±2)</td>
<td>16 (±2)</td>
<td>33 (±9)</td>
</tr>
<tr>
<td>CPT-11 ratio</td>
<td>29.9 (±3.6)</td>
<td>31.4 (±3.8)</td>
<td>33 (±9)</td>
<td>33 (±9)</td>
<td></td>
</tr>
<tr>
<td>SN-38 ratio</td>
<td>67.1 (±3.3)</td>
<td>65.1 (±2.8)</td>
<td>63 (±6)</td>
<td>63 (±6)</td>
<td></td>
</tr>
<tr>
<td>SN-38G ratio</td>
<td>297.3 (±197.0)</td>
<td>187.2 (±112.7)</td>
<td>410 (±200)</td>
<td>410 (±200)</td>
<td></td>
</tr>
<tr>
<td>CL&lt;sub&gt;TBN&lt;/sub&gt;, liter/h/m²</td>
<td>11.5 (±3.3)</td>
<td>9.4 (±1.8)</td>
<td>55&lt;sup&gt;b&lt;/sup&gt; (±58.4)</td>
<td>19.9 (±8.4)</td>
<td>646 (±561)</td>
</tr>
<tr>
<td>CL&lt;sub&gt;ft&lt;/sub&gt;, first pass, liter/h/m²</td>
<td>2.0 (±1.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.I., ml</td>
<td>30.8 (±20.2)</td>
<td>36.2 (±21.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>c.i., continuous infusion; <sup>b</sup> CL<sub>TBN</sub>, total body clearance; CL<sub>ft</sub>, hepatic clearance.