A Phase I and Pharmacokinetic Study of Irinotecan Given as a 7-Day Continuous Infusion in Metastatic Colorectal Cancer Patients Pretreated with 5-Fluorouracil or Raltitrexed

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ABSTRACT

Purpose: The purpose is to determine the plasma pharmacokinetics, the maximum-tolerable dose and to preliminarily evaluate the antitumor activity of irinotecan administered as a 7-day continuous infusion every 21 days in metastatic colorectal cancer patients pretreated with 5-fluorouracil or raltitrexed.

Experimental Design: A total of 13 patients entered the study. Three received irinotecan at 20 mg/m²/day (dose level I), 6 at 25 mg/m²/day (dose level II), and 4 at 22.5 mg/m²/day (dose level III). In 8 patients, plasma levels of irinotecan and its metabolites SN-38 and SN-38 glucuronide (SN-38glu) were measured by high-performance liquid chromatography and main pharmacokinetic parameters, including steady-state concentration, area under the time-concentration curve, and clearance, were calculated and normalized to the dose level of 22.5 mg/m²/day.

Results: Dose-limiting toxicity was grade 3–4 diarrhea, which occurred in 4 of 6 patients at dose level II and in 2 of 4 patients at dose level III. Therefore, we defined 22.5 mg/m²/day the maximum-tolerable dose and 20.0 mg/m²/day the recommended dose for Phase II studies. Hematological toxicity was rare. The pharmacokinetic data provided evidence that continuous infusion increased the metabolism of irinotecan to SN-38 and also results in increased glucuronidation of the active metabolite SN-38 by carboxyl-esterase (CE); SN-38 glucuronide is the rate-limiting enzyme deacetylation of irinotecan to SN-38.

Conclusions: The administration of irinotecan as a 7-day continuous infusion every 21 days is feasible with diarrhea being the dose-limiting toxicity; recommended dose for Phase II studies is 20.0 mg/m²/day. The comparison of the present data with those obtained after a standard 30–90 min. i.v. infusion of irinotecan demonstrates that continuous infusion improves the transformation of irinotecan to SN-38 and also results in increased glucuronidation of the active metabolite. Antitumor activity in pretreated metastatic colorectal cancer patients is encouraging.

INTRODUCTION

Irinotecan (CPT-11), a semisynthetic derivative of the natural alkaloid camptothecin, is a selective inhibitor of topoisomerase I, a nuclear enzyme responsible for relaxation of supercoiled DNA during replication and transcription (1, 2).

Irinotecan has a broad spectrum of activity against solid tumors; in particular, Phase III randomized studies in advanced colorectal cancer demonstrated improved survival with irinotecan compared with best supportive care or 5-fluorouracil (5-FU) continuous infusion in patients pretreated with 5-FU (3, 4) and superior efficacy for the combination of irinotecan/5-FU/leucovorin versus 5-FU/leucovorin in terms of response rate, time to disease progression, and survival in chemotherapy-naïve patients (5, 6).

In vivo irinotecan is enzymatically converted to its active metabolite SN-38 by carboxyl-esterase (CE); SN-38 forms reversible complexes with DNA/topoisomerase I that generates single-strand breaks in the DNA. Then, cell death occurs when the DNA replication fork reaches the SN-38/DNA-topoisomerase I cleavable complexes, resulting in irreversible double-strand breaks. This process may require several hours or days to be completed, and although irinotecan and SN-38 have terminal half-lives of ~6–13 and 12–24 h, respectively, after a short i.v. infusion (7–9), a more prolonged exposure might enhance the formation of lethal strand breaks and cytotoxicity because of the increasing number of cells entering into the S phase of the mitotic cycle (10, 11). Some in vitro and in vivo studies suggest that camptothecin derivatives bind topoisomerase I predominantly in actively transcribed genes (12) and that irinotecan is more effective when administered in prolonged infusion schedules in tumor-bearing mice (13, 14). Furthermore, longer infusions produce lower peak-plasma drug concentration, and this might overcome the rate-limiting enzyme deacetylation of irinotecan to SN-38 (15) allowing a more efficient drug activation. Clinical studies did not confirm the improved activity of irinotecan administered as protracted infusion observed in tumor-bearing mice, but in the clinical setting, this method of...
administration of irinotecan was evaluated only in small Phase I studies, including heavily pretreated patients; therefore, a proper evaluation of antitumor activity of infusional irinotecan is lacking.

Two Phase I and pharmacokinetic trials in adult patients with solid tumors demonstrated that the administration of irinotecan as a prolonged i.v. infusion (96 h and 14 days) is feasible with diarrhea being the dose-limiting toxicity (DLT) and with promising antitumor activity, especially in colorectal cancer patients. Pharmacokinetic analysis showed a greater SN-38/irinotecan area under the time-concentration curve (AUC) ratio (0.24 and 0.16, 96 h versus 14 days, respectively) compared with the values observed after a 30–90 min infusion (approximately 0.03–0.09) suggesting a more extensive metabolism of irinotecan to SN-38 (16, 17). This observation may confirm the hypothesis of rate-limiting conversion of irinotecan to SN-38 and may explain, at least in part, the low dose-intensities achievable with the continuous infusion schedules.

These findings demonstrate that protracted infusion is associated to better irinotecan activation, but the schedules evaluated in previous Phase I studies may be discommoding for the patient and for the health care facilities. To evaluate a more convenient schedule of irinotecan administration, we initiated a Phase I study to define the maximum-tolerable dose (MTD) of irinotecan administered as a 7-day continuous infusion every 21 days, to determine the plasma pharmacokinetics of irinotecan, SN-38 and SN-38 glucuronide (SN-38glu), and to preliminary evaluate the antitumor activity of this treatment in metastatic colorectal cancer patients pretreated with 5-FU or raltitrexed.

PATIENTS AND METHODS

Patients Selection. Main eligibility criteria included: histologically confirmed diagnosis of colorectal adenocarcinoma with metastatic disease, age < 75 years, Eastern Cooperative Oncology Group performance status ≤ 2, measurable disease, leukocyte count ≥ 3500/mm³, neutrophils count ≥ 1500/mm³, platelet count ≥ 100,000/mm³, serum creatinine ≤ 1.3 mg/dl, serum bilirubin ≤ 1.5 mg/dl and aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≤ 2.5 times normal values (≤ 5 times normal values if liver metastases were present), previous palliative chemotherapy with 5-FU+/−LV or raltitrexed. Exclusion criteria were as follows: previous chemotherapy including irinotecan; symptomatic cardiac disease; myocardial infarction during the last 24 months; uncontrolled arrhythmia; active infections; inflammatory bowel disease; and total colectomy. The study was approved by the local Ethics Committee, and patients were informed of the investigational nature of the trial and provided their written informed consent before registration onto the study.

Treatment and Dose Escalation. The starting dose of irinotecan was 20 mg/m²/day given as a 7-day continuous infusion (140 mg/m² cumulative dose) repeated every 3 weeks. This dose represented 40% of the dose intensity achieved with the recommended dose of 350 mg/m² administered as a 30–90 min infusion every 3 weeks and a similar dose intensity achievable with a 14 days continuous infusion (16). The dose was escalated of 5 mg/m²/day in subsequent groups of patients up to determine MTD. Dose escalation was permitted only once patients recruited at the immediately lower dose level had completed at least the first cycle (21 days). At least 3 new patients were recruited for each dose level. Three additional patients (for a total of 6) were treated at a dose level if 1 of the first 3 patients exhibited DLT. The MTD was defined as the dose level associated with the same DLT in at least 2 of 3–6 patients. DLT was defined as any National Cancer Institute-Common Toxicity Criteria grade 3–4 nonhematological toxicity, except for alopecia and vomiting, any grade 4 neutropenia lasting > 5 days, or associated with fever ≥ 38°C and any grade 4 thrombocytopenia occurring at any time during all of the treatment period. After achieving the MTD at 25 mg/m²/day, in consideration of the good tolerability of the starting dose of 20 mg/m²/day, the protocol was amended, and additional patients were treated at the intermediate dose of 22.5 mg/m²/day. Therefore, the following dose levels were evaluated: 20 mg/m²/day for 7 days (dose level I); 25 mg/m²/day for 7 days (dose level II); and 22.5 mg/m²/day for 7 days (dose level III).

Treatment was administered every 3 weeks for a maximum of nine cycles until evidence of disease progression, unacceptable toxicity, or patient refusal. Treatment was delayed in case one or more of the following were present on the day of drug administration: neutrophils < 1,000/mm³; platelets < 100,000/mm³; and persistent diarrhea or stomatitis > grade 1. In case of DLT, treatment was continued, after recovery, at the immediately lower dose level or reduced by 25%. In case of life-threatening toxicities, treatment was discontinued or the dose was reduced by 50%.

Neither antiemetic premedication nor prophylactic treatment with granulocyte colony-stimulating factor was routinely administered. In case of diarrhea, at the time of the first loose stool, patients were instructed to take 4 mg of loperamide followed by 2 mg every 2 h. Patients were allowed to stop taking loperamide 12 h after the last episode of diarrhea. If diarrhea persisted for > 24 h despite loperamide treatment, patients were treated with ciprofloxacin. If diarrhea persisted for > 48 h despite loperamide and ciprofloxacin treatment, patients were hospitalized for i.v. rehydration and treatment with octreotide.

Drug Administration. Irinotecan (Campto; Aventis Pharma, Italy) was supplied in 5-ml vials as a concentrated sterile solution, containing irinotecan 100 mg as the free base and sorbitol, lactic acid, and sterile water for injection. The appropriate volume of irinotecan solution was transferred to a 100-ml pump reservoir. Final dilution to a total volume of 75 ml was made with 0.9% sodium chloride solution. The reservoir was connected to a CADD-PLUS ambulatory infusion pump (Deltec, Inc., St. Paul, MN) and infused for 7 days through an implantable central venous catheter. In these conditions, irinotecan is stable for extended periods of time (18).

Assessability, Toxicity, and Response Criteria. Pre-treatment evaluation included history and physical examination, performance status assessment, complete blood cell with differential and platelet counts, complete blood profile, carcinoembryonic antigen, urinalysis, electrocardiogram, chest X-ray or computed tomography scan, abdominal computed tomography scan and/or magnetic resonance imaging, and any other appropriate diagnostic procedure to evaluate metastatic sites. During treatment, a physical examination was performed every 3 weeks, a complete blood cell count every week, and blood
profile and urine analysis every 3 weeks. Toxicities were monitored weekly and were scored according to standard National Cancer Institute-Common Toxicity Criteria. Responses were assessed and evaluated every 9 weeks according to WHO criteria (19). For the evaluation of liver metastases, an abdominal computed tomography scan or magnetic resonance imaging was required. A chest X-ray and/or an abdominal sonogram or computed tomography scan were repeated at least every 6 months if there was no evidence of lung or abdominal disease, respectively.

**Pharmacokinetics.** Pharmacokinetic analysis of irinotecan and their metabolites, SN-38 and SN-38glu was performed in 8 patients receiving irinotecan at the doses of 20, 22.5, and 25 mg/m²/day for 7 days. Blood was withdrawn from a peripheral catheter placed in a vein of the forearm, baseline, 24, 72, 120, and 168 h (end of infusion) and 30 min, and 1 and 2 h after the end of drug administration. Blood samples were centrifuged and plasma was stored at ~20°C until irinotecan and metabolite concentrations were determined by high-performance liquid chromatography previously described with minor modifications (20). To increase the lower limit of quantitation, 1 ml of plasma was used instead of 100 µl. Plasma irinotecan and SN-38 were extracted from plasma with methanol containing 0.1% HCl 10 N; the samples were centrifuged, and the clear supernatant was evaporated under nitrogen flow at 45°C. The dried pellet was reconstituted in methanol acidified with 0.1% HCl 10 N and eluted through a µBondapack C₁₈ stationary phase (300 × 3.9 mm, 10 µm; Waters, Milford, MA) by KH₂PO₄, 0.1 M/acetonitrile (65:35, v/v) pH 4.0, containing 3 mM sodium heptanesulfonate. The chromatographic system LC Module I Plus (Waters) was equipped with a model 474 scanning fluorescence detector (excitation and emission wavelengths, 375 and 525 nm, respectively). Data analysis was performed by the Millennium 2.1 software (Waters). The SN-38glu plasma concentration was measured as described above after incubation of plasma samples with β-glucuronidase (1000 UI/100 µl of plasma) at 37°C for 2 h before extraction. The difference between peak heights corresponding to SN-38 in β-glucuronidase-treated versus untreated samples corresponded to the plasma levels of SN-38glu.

The high-performance liquid chromatography method used in the present study allowed a reproducible and sensitive measurement of plasma concentration of the drug and its metabolite. Coefficients of variation for irinotecan and SN-38 accounted for 7.8 and 12.5%, respectively, whereas lower limits of quantitation were 1.36 and 0.41 nmol/liter, and the recovery was 87 and 79% for irinotecan and SN-38, respectively.

Individual plasma concentrations of irinotecan, SN-38, and SN-38glu were normalized to the dose of 22.5 mg/m² and the AUC of irinotecan, SN-38, and SN-38glu from 0 to 170 h was calculated by the log-linear trapezoidal method until the last sampling time. Peak plasma concentration (Cmax) was obtained by visual inspection of the concentration versus time profile of irinotecan and metabolites, whereas steady-state concentrations (Css) were calculated as mean values of plasma levels at 72, 120, and 168 h of infusion. Finally, the clearance of irinotecan (Cl) was determined as the infusion rate of the drug divided by itsCss value (16). The relative extent of metabolic conversion (REC) of irinotecan was calculated as AUC_{SN-38}/AUC_{CPT-11}, whereas the drug metabolic ratio was obtained as (AUC_{SN-38}+AUC_{SN-38glu})/AUC_{CPT-11} (16).

Finally, the ratio between the AUC values of SN-38glu and SN-38 was calculated to obtain an indirect estimate of the activity of glucuronidation of the active metabolite SN-38.

**RESULTS**

**Patients and Toxicity.** A total of 13 patients with metastatic colorectal adenocarcinoma entered the study. Patients characteristics are listed in Table 1. All patients completed at least one cycle of chemotherapy and were evaluable for toxicity. Overall, 63 courses of irinotecan therapy were administered with a median of five cycles/patient (range, one to eight cycles). One patient received only one cycle of chemotherapy because of central venous catheter thrombosis, and he was subsequently treated with irinotecan 90-min infusion through a peripheral vein of the forearm, whereas 2 patients received only two courses of irinotecan treatment because of rapidly progressive disease.

The DLT was grade 3–4 delayed diarrhea. At the first dose level (20 mg/m²/day), DLTs were not observed; therefore, subsequent patients (6) were treated at 25.0 mg/m²/day, and 1 case

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<th>Table 1 Patient’s characteristics</th>
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<tr>
<td>n</td>
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<tr>
<td>Patients</td>
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<tr>
<td>Male/Female</td>
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<td>Age, years</td>
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<td>Range</td>
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<td>ECOG refusal status</td>
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<tr>
<td>1</td>
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<tr>
<td>Primary</td>
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<tr>
<td>Rectum</td>
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<tr>
<td>Previous surgery on primary tumor</td>
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<tr>
<td>Number of metastatic sites</td>
</tr>
<tr>
<td>Multiple</td>
</tr>
<tr>
<td>Sites of disease</td>
</tr>
<tr>
<td>Lung</td>
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<tr>
<td>Abdomen</td>
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<tr>
<td>Other</td>
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<tr>
<td>Liver involvement</td>
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<tr>
<td>25–50%</td>
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<tr>
<td>&gt;50%</td>
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<tr>
<td>Previous chemotherapy</td>
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<tr>
<td>5-FU c.i.</td>
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<tr>
<td>5-FU/LV bolus and 5-FU c.i.</td>
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<tr>
<td>Reltitrexed</td>
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<tr>
<td>Previous radiotherapy</td>
</tr>
<tr>
<td>CEA, ng/ml</td>
</tr>
<tr>
<td>Range (4.5–720)</td>
</tr>
<tr>
<td>Courses/patient</td>
</tr>
<tr>
<td>Range</td>
</tr>
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</table>
of grade 4 diarrhea and 3 cases of grade 3 diarrhea occurred. Because of the absence of DLTs at the starting dose level and
the high incidence of grade 3–4 diarrhea at 25.0 mg/m²/day, 3
additional patients were treated at the intermediate dose level
of 22.5 mg/m²/day to better define the MTD of irinotecan. At this
dose level 1 patient experienced grade 3 delayed diarrhea, and
we planned the enrollment of 3 additional patients at the same
dose level, but after the recruitment of the fourth patient, we
observed a second case of grade 3 diarrhea that occurred during
the third cycle. Therefore, we defined 22.5 mg/m²/day the MTD
and 20.0 mg/m²/day the recommended dose for Phase II studies.

Three additional patients initially treated at the irinotecan dose-
level of 25.0 and 22.5 mg/m²/day received, after dose reduction
for diarrhea, irinotecan at 20.0 mg/m²/day. At this dose, irino-
tecan was well tolerated thus confirming that the dose of 20.0
mg/m²/day administered as a 7-day continuous infusion every
21 days has a good toxicity profile and can be recommended for
additional studies. Table 2 summarizes the frequency and se-
verity of DLTs/dose level.

Delayed diarrhea developed 8–14 days after the start of
irinotecan infusion and lasted for a median of 4 days (range,
1–24 days). Diarrhea generally responded to high-dose loper-
amide, but 4 patients (five courses) needed additional treatment
with ciprofloxacin and octreotide. No symptoms of cholinergic
syndrome (early onset diarrhea, flushing, or diaphoresis) were
observed.

Grade 2 and 3 nausea and/or vomiting occurred, respec-
tively, in 3 (23%) and 1 (8%) patients and responded well to
standard antiemetics; on the contrary, grade 1 nausea occurred
in 69% of patients and was scarcely manageable with standard
chemotherapy. Hematological toxicity was rare; one episode of grade
3 neutropenia occurred, whereas no episodes of thrombocyto-
penia were observed, thus, granulocyte colony-stimulating fac-
tor support was never required. Other observed toxicities were
anemia, occurring respectively in 5 (38%) and 3
(23%) patients, and grade 1–2 alopecia in 4 (30%) patients
(Table 3). Nine (14%) cycles were delayed, of at least 1 week
because of unresolved toxicities and 21 (33%) cycles and 7
(54%) patients required dose reductions because of diarrhea.
Four patients were hospitalized because of diarrhea, but no toxic
deaths occurred.

Antitumor Activity. Among the 12 patients evaluable
for activity (1 patient not evaluable because of central venous
catheter thrombosis, and he was subsequently treated with iri-
notecan 90-min infusion through a peripheral vein of the fore-
arm), we observed 3 (25%) partial responses, 2 (17%) minor
responses (minor response was defined as 25–50% reduction in
disease), 4 (33%) disease stabilizations, and 3 (25%) progres-
sions. All responses, except one minor response, were observed
at the dose level of 25.0 mg/m²/day (Table 4). Responses lasted
a median of 6.0 months (range, 2.2–11.0 months).

Pharmacokinetics. Main pharmacokinetic parameters of
irinotecan and its metabolites are reported in Table 5, whereas
the plasma profiles of irinotecan, SN-38, and SN-38glu are
shown in Fig. 1. Pharmacokinetic analysis demonstrated that the
C_{ss} of irinotecan was 42.7 ± 25.2 nmol/liter, whereas those of
SN-38 and SN-38glu were 14.88 ± 3.47 nmol/liter, respectively.
Moreover, the mean ratio of AUC_{CPT-11} and AUC_{CPT-11}(REC) was
0.28 ± 0.03, whereas irinotecan clearance was 45.3 ± 26.7 l/h/m².
Finally, the drug metabolic ratio and the ratio of SN-38/SN-38glu were
0.88 ± 0.07 and 0.46 ± 0.02, respectively.

**DISCUSSION**

Irinotecan administered as a 30–90-min infusion has dem-
strated activity against a variety of solid tumors and has been
approved in the majority of countries worldwide for the first and
second line treatment of advanced colorectal cancer (21). De-
velopment of strategies to enhance the efficacy of this drug is an
important issue. Irinotecan is a S-phase-specific agent, and
given that only a fraction of cancer cells in a solid tumor are
actively synthesizing DNA at any given time, prolonged exposure
could result in enhanced cytotoxicity of these drugs. Pre-
clinical data in human tumor xenografts suggest that the activity
of topoisomerase I inhibitors is highly schedule-dependent and
protracted infusional schedules may be more effective (13, 14,
22, 23). Two Phase I and pharmacokinetic trials in adult patients
with solid tumors demonstrated the feasibility and the activity of

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Dose levels and dose-limiting toxicities (DLTs)</th>
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<tbody>
<tr>
<td>Dose level</td>
<td>Irinotecan dose (mg/m²/day)</td>
</tr>
<tr>
<td>I</td>
<td>20.0</td>
</tr>
<tr>
<td>II</td>
<td>25.0</td>
</tr>
<tr>
<td>III</td>
<td>22.5</td>
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</table>

* Three additional patients initially treated at the II or III dose level of irinotecan received additional treatment at 20.0 mg/m²/day after dose reduction for diarrhea.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Overall maximum toxicity/patient (13 evaluable patients)</th>
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<tr>
<td>Adverse event</td>
<td>1</td>
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<tr>
<td>Diarrhea</td>
<td>n (%)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Cholinergic syndrome</td>
<td>2 (15)</td>
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<tr>
<td>Neutropenia</td>
<td>0</td>
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* Febrile neutropenia: 0.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Objective responses (12 evaluable patients)</th>
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<tbody>
<tr>
<td>Irinotecan dose (mg/m²/day)</td>
<td>Overall</td>
</tr>
<tr>
<td>Response (WHO)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Complete</td>
<td>0</td>
</tr>
<tr>
<td>Partial</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Minor</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Stable</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>Progression</td>
<td>3 (25%)</td>
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irinotecan administered as an i.v. infusion of 96 h or 14 days, with main DLTs being diarrhea, nausea/vomiting, and thrombocytopenia. An interesting finding in these studies was the markedly increased systemic exposure to SN-38, relative to the exposure to irinotecan, achieved with a protracted infusion schedule. Indeed, it was observed that a higher SN-38/irinotecan AUC ratio (0.24 and 0.16 for 96 h and 14 days, respectively) compared with the values observed after a 30 or 90-min infusion (~0.03–0.09), thus suggesting an extensive metabolism of irinotecan to SN-38 (14, 16, 17). These observations suggested that human carboxyl-esterase enzyme could be saturable, hence, the decrease in infusion rate could be associated to an augmented production of SN-38 (16).

Data from the present study revealed a higher than a 4-fold increase in the REC with a 7-day continuous infusion versus the REC in patients treated at approximately the same cumulative dose of irinotecan (150 mg/m²) administered as a 60-min i.v. infusion (0.28 versus 0.073, respectively; Ref. 20). The increase in REC was mainly because of the increment in SN-38 AUC rather than to the reduction of irinotecan AUC. Indeed, the plasma concentration of the active metabolite at the end of infusion was less than one-third with respect to the maximal plasma concentration calculated after a 60-min infusion of irinotecan 150 mg/m². It is conceivable that lower peak concentrations of SN-38 could also surmount problems related to saturable metabolic steps (i.e., glucuronidation) or to excretion processes (i.e., those regulated by cMOAT or P-gp) involved in drug elimination, hence reducing systemic toxicity (16). Indeed, the slow rate of drug infusion facilitated irinotecan conversion into SN-38 and increased drug elimination, as demonstrated by the increase in REC and total body clearance of irinotecan (Cl) with respect to previous studies (20). Interestingly, the comparison of the present results with those reported by Takimoto et al. (16) suggests that the increase in the rate of infusion and drug dose is associated with a decrease in the metabolic ratio (AUC_{SN-38} + AUC_{SN-38glu})/AUC_{CPT-11} and REC and increase in SN-38/SN-38glu AUC ratio. Table 6 reports the SN-38 AUC measured with short and prolonged infusion regimens and shows that SN-38 AUC value after a 90-min infusion of irinotecan 150 mg/m² was lower than that obtained after the administration of irinotecan 22.5 mg/m²/day for 7 consecutive days (275 ± 69 versus 1920 ± 300 hxsol/liter, respectively).

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**Table 6** Area under the time-concentration curve (AUC) of SN-38 after administration of irinotecan by short or prolonged infusions

<table>
<thead>
<tr>
<th>Dose regimen</th>
<th>Dose intensity (mg/m²/week)</th>
<th>SN-38 AUC (nmol/liter x h)</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Irinotecan administered as prolonged i.v. infusion</td>
<td></td>
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<tr>
<td>22.5 mg/m²/day × 7 day every 3 wk</td>
<td>52.5</td>
<td>1920 ± 300&quot;</td>
<td>16</td>
</tr>
<tr>
<td>12.5 mg/m²/day × 14 day every 3 wk</td>
<td>58.5</td>
<td>2500 ± 1200&quot;</td>
<td>15</td>
</tr>
<tr>
<td>12.5 mg/m²/day × 4 day × 2 wk every 3 wk</td>
<td>33.3</td>
<td>769 ± 368&quot;</td>
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<tr>
<td>Irinotecan administered as 1-h i.v. infusion</td>
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<tr>
<td>150 mg/m² every 3 wk</td>
<td>50</td>
<td>275 ± 69&quot;</td>
<td>19</td>
</tr>
<tr>
<td>300 mg/m² every 3 wk</td>
<td>100</td>
<td>484 ± 132&quot;</td>
<td>19</td>
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" Mean ± SD.  
* Mean ± SE.
despite the dose intensity being nearly equivalent (150 versus 157.5 mg/m² every 3 weeks, respectively); hence, to obtain the same AUC value of SN-38, the dose of irinotecan that could be administered would be too high and tolerated poorly.

With regard to treatment toxicity, we found that the administration of irinotecan as a 7-day continuous infusion every 21 days is feasible with diarrhea being the DLT. The MTD is 22.5 mg/m²/day, and the recommended dose for additional evaluation is 20 mg/m²/day. The toxicity profile of this prolonged infusion schedule seems to be different from that usually reported with short i.v. infusions; in particular, we observed a higher incidence of delayed diarrhea, but severe myelosuppression was uncommon, and cholinergic syndrome was absent. In the present study, we did not observe significant correlations between irinotecan or SN-38 pharmacokinetics and toxicity. With regard to antitumor activity, it was encouraging in 5-FU or raltitrexed-pretreated metastatic colorectal cancer patients.

In the present study, it has been observed an increase in REC value with respect to that calculated after a 4-day continuous infusion or after shorter durations (i.e., 60 or 90 min). This result supports an augmented conversion of irinotecan into SN-38, whereas the 7-day infusion is consistent with a prolonged inhibition of topoisomerase-I enzyme. It is not clear the impact of such metabolic alterations on clinical activity of irinotecan, but an important finding of all studies using infusion of irinotecan is the different toxicity profile observed with minimal hematological toxicity. This could make more feasible the combination of irinotecan with myelosuppressive drugs such as cisplatin or taxanes, and the irinotecan/cisplatin or irinotecan/taxanes combination are actives regimens in several tumors such as lung cancer and gastric cancer.

In conclusion, prolonged administration seems to be a promising method of delivering irinotecan. Although total administered doses were ~50–60% lower than those administered with a standard 30–90 min infusion, biological activity was seen in terms of both toxicity and antitumor effect. The lack of severe myelosuppression on this infusion schedule may offer an opportunity to combine irinotecan with more myelosuppressive chemotherapeutic agents. Severe diarrhea is the most important toxicity observed in this study, and new strategies to decrease its incidence are needed. Preliminary results of Govindarajan et al. [24, 25] indicate a reduced incidence of gastrointestinal toxic effects of irinotecan by the concomitant use of thalidomide, and we are conducting a clinical and pharmacokinetic trial to confirm these findings. The optimization of such combinations requires careful evaluation in future trials.

ACKNOWLEDGMENTS

We thank Michele Andreuccetti for data analysis and technical assistance.

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Clinical Cancer Research

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