Phase 1 and Pharmacokinetic Study of Intravenous Irinotecan in Refractory Solid Tumor Patients with Hepatic Dysfunction


Abstract

Purpose: To determine the recommended starting doses and pharmacokinetics of irinotecan in cancer patients with impaired liver function treated on a weekly schedule.

Experimental Design: Patients with solid tumors who had impaired liver function were enrolled into four groups based on baseline serum total bilirubin and aspartate aminotransferase (AST)/alanine aminotransferase (ALT): Group 1 (n = 19): total bilirubin 1.5 to 3.0 × institutional upper limit of normal (IULN) and ALT/AST ≤ 5.0 × IULN; Group 2 (n = 7): total bilirubin 3.1 to 5.0 × IULN and ALT/AST ≤ 5.0 × IULN; Group 3 (n = 6): total bilirubin ≤ 1.5 × IULN and ALT/AST 5.1 to 20.0 × IULN; Group 4 (n = 10): total bilirubin 1.5 to 3.0 × IULN and ALT/AST 5.1 to 20.0 × IULN. Irinotecan was given as a 90-minute i.v. infusion weekly for the first 4 weeks in each 6-week cycle at starting doses which escalated from 40 to as much as 75 mg/m². After the first treatment, doses were adjusted based on individual patient toxicities. Starting doses for patients with hepatic dysfunction were derived from the maximum tolerated doses noted in the four hepatic dysfunction groups.

Results: Forty-two patients were treated. Among the most frequent adverse events were neutropenia (41%, grades 3/4), diarrhea (15%, grades 3/4), nausea (10%, grade 3), and vomiting (5%, grades 3/4). Two patients died from drug-induced neutropenic sepsis. Two patients had objective tumor responses (complete response, liver metastases from unknown primary; partial response, colon cancer). Hepatic dysfunction reduced irinotecan clearance while increasing relative exposure to the active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38). SN-38 exposures in patients receiving doses of 40 to 75 mg/m² were comparable to exposures in patients with normal liver function treated with a starting dose of 125 mg/m².

Conclusions: Irinotecan starting doses that seem to be safe for hepatically impaired patients treated with the weekly schedule are 60, 50, 60, and 40 mg/m² for groups 1 to 4, respectively. At these starting doses, exposure to SN-38 and the adverse event profile are similar to that observed in patients with normal liver function and antitumor activity can be observed.

The broad-spectrum, cytotoxic drug irinotecan (CPT-11; Camptosar irinotecan hydrochloride injection) is a semisynthetic, water-soluble derivative of the plant product, camptothecin. Irinotecan is a prodrug that is metabolized by carboxylesterases to the potent topoisomerase I inhibitor, SN-38 (7-ethyl-10-hydroxycamptothecin), which seems to be primarily responsible for the antitumor effects of irinotecan (1). The clinical pharmacology and anticancer applications of irinotecan have been the subject of several recent reviews (2–6).

Based on the results of several phase 3 survival trials (7–11), irinotecan administered i.v. has been approved for first- and...
second-line chemotherapy of metastatic colorectal cancer. Irinotecan has shown activity in phase 2 trials against several other malignancies of gastrointestinal origin (pancreatic, esophageal, and gastric carcinomas) as well as small cell and non–small cell lung cancers, cervical and breast cancers, and glioblastoma (12–19).

Irinotecan’s most clinically relevant toxicities are diarrhea, nausea, vomiting, and neutropenia (7, 9). I.v. administration may also be associated with cholinergic symptoms (miosis, rhinitis, salivation, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis) due to the anticholinesterase activity of irinotecan (20, 21).

The liver plays a major role in the disposition of irinotecan. Cytochrome P450 3A (CYP3A)-mediated oxidative metabolism of irinotecan to the biologically inactive metabolites APC (7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carboxylxycamptothecin or the aminopentanoiccarboxylic acid metabolite of irinotecan) and NPC (7-ethyl-10-[4-(1-piperidino)-1-amino]-carboxylxycamptothecin) occurs in the liver. Hydrolysis of irinotecan to the active metabolite SN-38 by human carboxylesterase-2 (hCE-2) also takes place primarily in the liver. The active metabolite SN-38 is further metabolized by UDP-glucuronosyltransferase (UGT)-catalyzed glucuronidation to SN-38 glucuronide (SN-38G), primarily by the hepatic UGT1A1 isoform. SN-38 and SN-38G are also excreted in bile and the latter metabolite may be back-converted to SN-38 in the gastrointestinal lumen by β-glucuronidase of bacterial origin. In addition, carboxylesterase activity expressed in the intestine seems to mediate direct conversion of luminal irinotecan to SN-38 (22–24). Irinotecan and its metabolites are also subject to biliary and/or intestinal excretion. In a radiolabeled study of irinotecan in patients with solid tumors, fecal excretion accounted for 63.7 ± 6.8% of the dose (32.3% as unchanged parent drug, 8.2% as SN-38, 8.3% as APC, 0.3% as SN-38G, and 1.4% as NPC; ref. 25).

A high proportion of patients with colorectal cancer either present with or develop liver metastases (26) that have the potential to alter the normal hepatic metabolism and excretion mechanisms of irinotecan and SN-38 (27). Case reports describing severe toxicity and major alterations in irinotecan pharmacokinetics in cancer patients with hepatic or hepatorenal dysfunction (28–30) stimulated a clinical trial which defined appropriate doses for and characterized the pharmacokinetics of irinotecan and its metabolites in hepatically impaired patients treated on the once-every-3-weeks schedule (31). Another study characterized the tolerability and pharmacokinetics of irinotecan administered on the every-3-weeks schedule to patients with solid tumors with hepatic or renal dysfunction or prior pelvic radiation (32).

The objectives of the present trial were to define the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and pharmacokinetics in liver-impaired patients treated with the other commonly employed irinotecan treatment schedule, weekly treatment for the first 4 weeks of 6-week cycles given at a starting dose of 125 mg/m².

**Materials and Methods**

**Study design and patient eligibility**

Enrollment was open to patients of either gender. Inclusion criteria included histologic documentation of a malignant solid tumor refractory to standard forms of therapy or for which there was no known curative therapy, age ≥18 years, Southwest Oncology Group performance status of 0 to 3, predicted life expectancy of at least 12 weeks, no radiotherapy for cancer within 4 weeks prior to study entry, and resolution of all side effects of any prior therapy. Exclusion criteria included prior treatment with irinotecan and evidence of hepatic encephalopathy. Hepatically impaired patients with solid tumors were enrolled into four groups based on baseline serum total bilirubin and aspartate aminotransferase (AST)/alanine aminotransferase (ALT; Table 1). Serum total bilirubin and transaminase levels were used because they represent objective and readily measurable laboratory variables. In addition, serum total bilirubin adequately reflects the mixed (direct and indirect) hyperbilirubinemia that is a characteristic of chronic cholestasis frequently associated with hepatic metastases from colorectal cancer (33, 34).

DLT was defined as any of the following events occurring during cycle 1: grade 4 thrombocytopenia of any duration, any other grade 4 hematologic toxicity lasting for 5 days, grade 4 vomiting or diarrhea that occurred despite supportive measures, elevation to grade ≥3 of bilirubin or ALT/AST which were >3 × baseline but not attributable to progressive disease, any other grade 3 nonhematologic toxicity with the exception of alopecia, or febrile neutropenia. Investigators completed a special case report form documenting each instance of DLT.

The MTD was based on the tolerability observed during cycle 1. Three patients were initially to be enrolled into groups 1 and 3 until the starting dose was determined to be safe. Thereafter, patients could be entered into groups 2 and 4 as well as into groups 1 and 3. Escalations were planned in groups of three patients, with an additional three patients to be added at the first indication of DLT. The MTD was the highest dose at which fewer than one-third of patients experienced DLT.

**Treatment**

Irinotecan was administered i.v. in 500 mL of 5% dextrose for 90 minutes, weekly for the first 4 weeks of each 6-week cycle. Treatment was continued until any of the following conditions were met: progressive disease, unacceptable toxicity, patient’s refusal to continue treatment, intercurrent non–cancer-related illness that prevented continuation of therapy, or complete remission. After the initial treatment, doses were adjusted using specific rules to accommodate individual patient tolerance. Supportive care included atropine for the treatment of cholinergic symptoms, loperamide for the treatment of diarrhea, and standard antiemetic agents for the prophylaxis and treatment of nausea and vomiting.

**Clinical evaluations**

Safety was evaluated by physical examination, toxicity assessments, and laboratory determinations done pretreatment, weekly throughout the study, and at study completion. Medical events and laboratory abnormalities were graded using the National Cancer Institute Common Toxicity Criteria, version 1.

The extent of disease was assessed every other cycle by physical examination and with the same radiographic method used to detect lesions at study entry. Complete remission was defined as the

<table>
<thead>
<tr>
<th>Table 1. Hepatic dysfunction groups</th>
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<tr>
<td><strong>Group</strong></td>
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<tr>
<td>3</td>
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<td>4</td>
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</tbody>
</table>
disappearance of all clinically detectable malignant disease for at least 4 weeks or, for patients with bone metastases, a normalization of radiographs or complete sclerotic healing of lytic metastases in association with a normal bone scan. Partial remission was defined as ≥50% reduction in the sum of the products of perpendicular diameters of all measurable lesions for at least 4 weeks. Responses that did not qualify as complete response, partial response, or progression were classified as stable disease. Progressive disease was defined as an increase of ≥25% in the sum of the products of measurable lesions over the smallest sum observed (or over baseline, if no decrease had occurred), a reappearance of any lesion that had disappeared, or the appearance of any new lesion or site. All patients with a complete remission or partial remission were to have a confirmatory evaluation at least 4 weeks later and reevaluations every other cycle thereafter.

Pharmacokinetic evaluations

Sample collection. Serial 5-mL blood samples were collected via venipuncture or indwelling i.v. cannula following the first and third doses of cycle 1 at the following times: predose, 45 minutes after the start of the infusion, just prior to the end of the 90-minute infusion, and 5, 15, 30, 60, 90 minutes and 2, 3, 4, 6, 8, 24, 48, and 72 hours after the end of the infusion. Plasma was separated from whole blood within 30 minutes after collection and stored at −20°C. A baseline (pretreatment) urine sample was collected as well as all urine in divided collection intervals: 0 to 6, 6 to 8, 8 to 24, 24 to 48, and 48 to 72 hours following the start of the infusion of the first dose.

Bioanalytic methods. Plasma and urine specimens were assayed for total concentrations (lactone + carbonyxylate species) of irinotecan, SN-38, APC, and total SN-38 (SN-38 + SN-38G after β-glucuronidase treatment) using validated, sensitive, and specific isocratic high-pressure liquid chromatographic methods with fluorescence detection (35).

Pharmacokinetic analysis. Doses of irinotecan were expressed as anhydrous free-base equivalents. Plasma-concentration data were analyzed by noncompartmental methods (36) using Kinetic 2000, version 3.1 (InnaPhase Corp., Philadelphia, PA). Metabolic ratios for the various irinotecan metabolites were calculated as defined by Rivory et al. (37): the relative extent of metabolism of irinotecan to SN-38 was estimated as the ratio of SN-38 area under the plasma concentration versus time curve (AUC0-∞) to irinotecan AUC0-∞, the relative extent of oxidation of irinotecan to APC as the ratio of APC AUC0-∞ to irinotecan AUC0-∞, and the relative extent of glucuronidation of SN-38 as the ratio of SN-38G AUC0-∞ to SN-38 AUC0-∞. Renal clearance (CLR) was calculated as CLR = AE/AUC0-∞, where AE is the cumulative amount of irinotecan excreted over the entire 72 hours, post-dose collection interval.

Although irinotecan starting doses ranged from 50 to 75, 60 to 75, and 40 to 50 mg/m², in groups 1, 3, and 4, respectively, the pharmacokinetic variables of irinotecan and the metabolites (SN-38, SN-38G, and APC) were not differentiable by irinotecan dose levels within each of these hepatic dysfunction groups (data not presented). Therefore, data from all dose levels within each group were combined in the pharmacokinetic analysis.

Comparison of pharmacokinetics in heptatically impaired and heptatically normal patients. Pharmacokinetic variables obtained in this trial are compared with those derived from a prior phase 2, single-agent, i.v. irinotecan trial in metastatic colorectal cancer patients who had experienced failure of prior 5-fluorouracil–containing regimens (M-6475-0037; study 0037; ref. 38). Patients in study 0037 were required per protocol to have a total serum bilirubin of ≤2.0 mg/dl, regardless of liver tumor involvement, as well as AST ≤3.0 × institutional upper limit of normal (IU/L; or ≤5.0 × IU/L, if the liver was involved). ALT values were not captured in study 0037. Bioanalytic methods for pharmacokinetics in study 0037 were identical to those in this trial and the same bioanalytic laboratory assayed all samples from both trials.

APC pharmacokinetic variables obtained in this trial are compared with those from a 14C-labeled irinotecan study (M-6475-0062; study 0062) in eight patients with solid tumors with essentially normal organ function (25).

Results

Patient characteristics. Forty-three patients were enrolled and 42 were treated from April 1996 to March 2002: 19 patients in group 1, 7 in group 2, 6 in group 3, and 10 in group 4. Patient demographics are shown in Table 2. The median patient age was 62 years with a range of 38 to 81 years. Approximately two-thirds of the patients were male, and most were White (83%). Thirty-one patients (74%) had a Southwest Oncology Group performance status of 1 or 2 at baseline, the remainder had a performance status of 0. Patient distribution by cancer type was: 11 (26%) patients with liver cancer; 7 (17%) with colorectal cancer; 6 (14%) with pancreatic cancer; 5 (12%) with cholangiocarcinoma; 3 (7%) with lung cancer (one non–small cell lung cancers and two nonspecified type); 10 (24%) with other cancers. The median time from initial diagnosis of metastatic disease to the first administration of study medication was 5.4 weeks (range, 0.1–81.7 weeks). Of the 42 treated patients, 36 (86%) had measurable disease. Most patients had lesions in the liver (88%). Twenty-nine patients (69%) had undergone prior therapy (surgery and/or radiotherapy/systemic therapy).

Dose escalation and assessment of first-cycle MTD and DLTs. The protocol specified that six patients in each hepatic function category were to be enrolled at the MTD to confirm that the incidence of DLTs was <33%. However, fewer than six patients were enrolled in groups 2 to 4 due to the unavailability of patients with the protocol-specified characteristics. In these cases, the MTD was determined as the dose level at which fewer than 33% of patients experienced DLT, regardless of the total number of patients accrued.

The starting dose for groups 1 and 3 was 75 mg/m². However, only one of four patients in the first cohort of group 1 completed all four doses in cycle 1 without safety issues. Because the three patients treated with a starting dose of 75 mg/m² in other hepatic dysfunction groups (including two patients in group 3 and one patient who was misclassified into group 1 but who actually belonged in group 4) did not complete all four doses of the first cycle, the starting dose for groups 1 and 3 was decreased to 60 mg/m². None of the first six patients in group 1 treated with a starting dose of 60 mg/m² experienced a DLT, leading to re-escalation to 75 mg/m². Two of the three patients subsequently treated with a dose of 75 mg/m² experienced DLT (drug-related tumor lysis syndrome associated with renal failure as well as grade 4 diarrhoea), establishing the MTD at 60 mg/m² for group 1. No DLTs were observed in four more patients treated at 60 mg/m².

One of the first two patients in group 3 treated with 75 mg/m² had a DLT of grade 3 neutropenic fever. Following reduction of the starting dose to 60 mg/m², the first patient experienced grade 4 neutropenia that lasted >5 days. None of the three additional patients treated in this cohort experienced a cycle 1 DLT. The recommended starting dose for group 3 was therefore defined as 60 mg/m².

Five patients in group 2 treated with a starting dose of 50 mg/m² were evaluable for DLT. One of these patients
experienced grade 3 dehydration secondary to drug-related nausea, vomiting, and diarrhea. The recommended starting dose for group 2 was therefore defined as 50 mg/m².

Of the first three patients in group 4 treated with 50 mg/m², one had a DLT of grade 4 thrombocytopenia and the cohort was expanded. One of the three additional patients had a DLT of grade 4 diarrhea. Because the MTD had been exceeded, the dose was reduced to 40 mg/m². None of the three patients in this cohort experienced a DLT, establishing 40 mg/m² as the MTD for group 4. One patient who was actually in group 4 had been misclassified into group 1 and was treated with a starting dose of 75 mg/m². This patient did not have a DLT.

**Overall treatment administration.** Among the 42 treated patients, 89 cycles and 533 weeks of treatment were given. Treatment was delivered for a median of 1.0 cycle (range, 1.0-10.0 cycles). The median absolute dose intensities for patients in groups 1 to 4 and all patients were 30.3, 20.8, 37.1, 27.0, and 30.0 mg/m²/wk, respectively (median relative dose intensities of 72%, 63%, 93%, 80%, and 75%). The median duration of therapy was one cycle. The main reason for study withdrawal was progressive disease (23 of 42 patients) across all groups.

**Safety.** Administration of irinotecan in this patient population at starting doses of 40 to 75 mg/m² was relatively safe. Among the most frequent adverse events were gastrointestinal events of diarrhea (62%), nausea (55%), and vomiting (43%). The rates of grade 3 to 4 diarrhea were 5% and 10%, respectively. Grade 3 nausea occurred in 10% of patients. Grades 3 to 4 vomiting occurred in one patient each.

Hematologic toxicities included anemia (86%), leukopenia (64%), and neutropenia (52%). The most frequent clinically significant grades 3 to 4 hematologic toxicity was neutropenia. Incidence rates of grades 3 to 4 neutropenia were 29% and 12%, respectively; 14% of patients had grade 3 anemia, no grade 4 anemia was reported.

Although all patients had an elevated bilirubin, ALT, and AST levels at study entry, these values increased by >20% for at least one evaluation in 71%, 24%, and 40%, respectively, of patients with an on-treatment laboratory assessment. Increases were most often attributable to progressive disease.

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**Table 2. Patient demographics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1, n = 19 (%)</th>
<th>Group 2, n = 7 (%)</th>
<th>Group 3, n = 6 (%)</th>
<th>Group 4, n = 10 (%)</th>
<th>All, n = 42 (%)</th>
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<td>5 (50.0)</td>
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<td>&lt;65</td>
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<td>≥65</td>
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<td>2 (33.3)</td>
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<td>16 (38.1)</td>
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<td>Mean (SD)</td>
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<td>61.7 (10.2)</td>
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<td>Median (min, max)</td>
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<td>Gall bladder</td>
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<td>—</td>
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<td>1 (2.4)</td>
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<tr>
<td>Lung</td>
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<td>1 (16.7)</td>
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<td>Bladder</td>
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<td>Esophagus</td>
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<td>Stomach</td>
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<td>3 (50.0)</td>
<td>5 (50.0)</td>
<td>21 (50.0)</td>
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</table>
One patient discontinued therapy due to neutropenic sepsis, which was considered a drug-related adverse event. For two patients, the cause of death was attributed to study medication; both patients died of neutropenic sepsis. One group 2 patient with a prior history of pelvic radiation received one cycle of irinotecan treatment at 60 mg/m². A group 4 patient who was performance status 2 at study entry received two cycles of irinotecan at a starting dose of 50 mg/m², with one dose reduction. Both patients were heavily pretreated, having received six prior regimens of chemotherapy.

**Efficacy.** Among the 36 patients with measurable disease, two patients had an objective tumor response. One patient, who had liver metastases from an unknown primary tumor, had a complete remission after three cycles of therapy. The second patient, who had colon cancer, had a partial remission at cycle 2 that was maintained for 5 months. Six patients with measurable disease and three patients with nonmeasurable lesions had stable disease as their best response. Nineteen patients had progressive disease as their tumor outcome, and 12 patients were not evaluable. Median time-to-tumor progression was 11.0, 10.3, 16.0, and 8.5 weeks for groups 1 to 4, respectively, and was 10.9 weeks for all patients.

**Pharmacokinetics.** Figure 1 shows the mean plasma concentration-time profiles of irinotecan and its metabolites for each of the four groups following the 90-minute i.v. infusion of irinotecan on day 1 of cycle 1. In all groups, irinotecan concentrations reached a maximum at the end of the infusion and, thereafter, declined biexponentially. All three metabolites were detected soon after the start of irinotecan infusion. The disposition profiles of irinotecan and the metabolites seemed to be similar in shape among the four groups.

Table 3 summarizes the pharmacokinetic variables of irinotecan, SN-38, SN-38G, and APC in the four groups following the infusion of irinotecan on day 1 of cycle 1. For context, pharmacokinetic variables determined in cancer patients with relatively normal hepatic function from studies 0037 (38) or 0062 (25) are also included in the table. Data from these two studies were selected for comparison because the bioanalytic methods were identical to those used in this trial and the same bioanalytic laboratory assayed all samples from all three trials.

Compared with the reference starting dose (125 mg/m²) in patients with normal hepatic function, reductions in starting dose by 40% to 68% based on the degree of liver dysfunction led to comparable systemic exposure of SN-38, SN-38G, and APC (Table 3). However, the mean exposure (AUC0-24) of irinotecan in these groups seemed to be lower than that in the reference group (Table 3) and was also lower than would be expected on a dose-adjusted basis (i.e., lower than expected...
Table 3. Pharmacokinetic variables (mean ± SD) in cycle 1, week 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Reference*</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
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<td>50-75</td>
<td>75</td>
<td>40-75</td>
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<td>CL (L/h/m²)</td>
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<td>7</td>
<td>6</td>
<td>10</td>
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<td>SN-38</td>
<td>2.04 ± 0.69</td>
<td>1.89 ± 0.97</td>
<td>1.67 ± 0.20</td>
<td>1.87 ± 0.57</td>
<td>2.28 ± 0.57</td>
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<tr>
<td>AUCmax (ng/mL)</td>
<td>27.8 ± 11.6</td>
<td>28.3 ± 8.27</td>
<td>28.0 ± 14.3</td>
<td>28.4 ± 16.2</td>
<td>29.4 ± 10.5</td>
</tr>
<tr>
<td>AUC0-24 (ng/mL)</td>
<td>267 ± 115</td>
<td>241 ± 90.3</td>
<td>254 ± 135</td>
<td>182 ± 56.7</td>
<td>330 ± 148</td>
</tr>
<tr>
<td>Dose-normalized AUCmax (ng/mL)</td>
<td>27.8 ± 11.6</td>
<td>55.9 ± 18.0</td>
<td>70.0 ± 35.9</td>
<td>56.0 ± 35.1</td>
<td>75.3 ± 26.0</td>
</tr>
<tr>
<td>Dose-normalized AUC0-24 (ng/mL)</td>
<td>267 ± 115</td>
<td>473 ± 182</td>
<td>634 ± 339</td>
<td>355 ± 125</td>
<td>846 ± 369</td>
</tr>
<tr>
<td>CLn (L/h/m²)</td>
<td>0.033 ± 0.013</td>
<td>0.051 ± 0.013</td>
<td>0.059 ± 0.022</td>
<td>0.046 ± 0.016</td>
<td>0.077 ± 0.04</td>
</tr>
<tr>
<td>Vss (L/m²)</td>
<td>138 ± 60.9</td>
<td>107 ± 42</td>
<td>109 ± 39.4</td>
<td>89.5 ± 21.4</td>
<td>84.8 ± 22.1</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>6.07 ± 1.19</td>
<td>14.7 ± 2.81</td>
<td>19.1 ± 3.97</td>
<td>11.6 ± 3.02</td>
<td>19.0 ± 4.06</td>
</tr>
</tbody>
</table>

**Reference** APC plasma pharmacokinetic variables are from study 0062 (n = 8).

Based on the lower doses administered to the hepatic dysfunction patients. Irinotecan mean CL was reduced to the greatest degree (~70%) in group 4 and reduced by ~30% to 55% in other groups (Table 3) in comparison with the reference group. Irinotecan CLn was also lower in the four hepatic dysfunction groups, but CLn of the metabolites remained largely unchanged. Overall, urinary excretion of unchanged irinotecan and its metabolites (SN-38, SN-38G, and APC) was low and consistent with previous results in patients with normal hepatic function (25).

As indicated in Table 3, irinotecan steady-state volume of distribution (Vss) did not vary among hepatic dysfunction groups but may have been somewhat lower than in the comparator group. In the reference group, t1/2 values were in the order of irinotecan < SN-38 = SN-38G < APC. However, this order was changed in all hepatic dysfunction groups to
irinotecan \( \approx \text{APC} \prec \text{SN-38} \prec \text{SN-38G} \), indicating that the \( t_{1/2} \) values of irinotecan, SN-38, and SN-38G were prolonged in patients with hepatic dysfunction (~3-fold for groups 2 and 4; 2-fold for group 1, and <2-fold for group 3); however, the \( t_{1/2} \) of APC was not changed. The observed increase in irinotecan \( t_{1/2} \) was mainly due to the reduction in irinotecan CL because \( V_{ss} \) remained unchanged.

With regard to the AUC ratios, SN-38 AUC/irinotecan AUC values seemed to be higher in hepatic dysfunction groups compared with the reference group and are in the order of group 4 > group 2 > group 1 > group 3, although there was overlap among the groups. The SN-38G/SN-38 AUC ratio and the APC/irinotecan AUC ratio were not substantially different between the reference and hepatic dysfunction groups (Table 3).

Because total bilirubin and hepatic transaminase concentrations were used to categorize the patients, the degree of change in irinotecan and SN-38 AUC values normalized to 125 mg/m\(^2\) as a function of bilirubin and transaminases was evaluated. Figure 2 illustrates a clear trend of proportional increases in dose-normalized irinotecan and SN-38 AUC values with increasing total bilirubin, whereas both AUC values increased to an apparent plateau with increasing AST. In general, a high serum total bilirubin concentration seemed to be a reasonably good predictor of lower irinotecan CL (i.e., increased dose-normalized AUC\(_{0-\infty}\)) as well as of reduced irinotecan MTD. For example, groups 2 and 4, which included patients with higher total bilirubin, were also the groups in which a greater reduction in irinotecan CL and lower MTD was observed. Group 3, whose patients had total bilirubin values that were close to or within the reference range (<1.5× IULN), displayed a less pronounced change in irinotecan CL.

Pharmacokinetic sampling was carried out following the first and third doses of cycle 1. In most patients, exposures to irinotecan and SN-38 in these two periods were similar. However, there were some patients who displayed considerable within-patient variability, with either an increase or a decrease in week 3 exposures. There was no clear trend in changes in irinotecan or SN-38 exposure between week 1 and week 3 (data not presented) although changes in liver function assessments were associated with changes in drug exposure in some patients.

**Discussion**

Hepatic metabolism and biliary excretion are the major pathways for clearance of irinotecan and its active metabolite, SN-38, from the systemic circulation. Previously reported case studies have suggested that liver dysfunction could lead to
decreases in clearance of irinotecan and SN-38, exposing patients to greater risk of toxicity (28–30). A trial using the once-every-3-week schedule showed that the pharmacokinetics of irinotecan was altered in cancer patients with hepatic dysfunction, and that dose reduction was necessary in patients with bilirubin values >1.5 × IULN (31). More recently Venook et al. (32) showed that three of five patients with direct bilirubin of 1.0 to 7.0 mg/dL experienced DLTs at 145 mg/m² on the every-3-week schedule and that SN-38 exposures at 145 mg/m² were comparable to those at 300 mg/m² in patients with relatively normal hepatic function. The present trial showed that patients with hepatic impairment treated weekly for the first 4 weeks in 6-week cycles also require a modified irinotecan starting dose based on the degree of hepatic dysfunction. In agreement with previous reports, this trial also confirmed that hepatic dysfunction decreases irinotecan CL and increases relative SN-38 exposure, providing a pharmacologic rationale for the lower starting dose in liver-impaired patients.

The results of this trial provide some guidance for irinotecan starting doses in cancer patients with liver dysfunction treated on the weekly schedule based on both bilirubin and transaminase concentrations. Transaminase concentrations were not used in the previously reported once-every-3-week trial as one of the criteria to define the degree of hepatic dysfunction; however, there were indications that transaminase concentrations also correlated with irinotecan clearance (31). With the weekly schedule evaluated in the present study, it seemed that a substantial reduction in the starting dose of 125 mg/m² was necessary in all of the hepatic dysfunction groups. As expected, the determined MTDs (60 mg/m² for groups 1 and 3, 50 mg/m² for group 2, and 40 mg/m² for group 4) and the magnitude of alternations in irinotecan pharmacokinetics (in general, group 4 > group 2 ≥ group 1 > group 3) correlated with the degree of liver dysfunction. Patients with group 4 characteristics of liver impairment (highly elevated serum total bilirubin and transaminase concentrations) were the most susceptible to irinotecan toxicities, had the lowest MTD, and exhibited the greatest alteration in irinotecan pharmacokinetics; this group had the largest reduction in irinotecan clearance and the highest dose-normalized SN-38 AUC among the four groups evaluated.

Group 1 patients in this trial and group 3 patients in the every-3-weeks trial of Raymond et al. (31) had equivalent baseline total bilirubin values of 1.5 to 3.0 × IULN. We note that starting doses deemed to be safe for patients with this degree of hyperbilirubinemia were comparable across equivalent intervals for the two schedules (two cycles = 6 weeks for the every-3-week schedule and one cycle = 6 weeks for the weekly × 4 every-6-weeks schedule): 200 mg/m²/cycle × 2 = 400 mg/m², single dose every-3-weeks (400 = 57% of normal starting dose of 350 mg/m²/two cycles = 700 mg/m²) compared with 60 mg/m²/wk, weekly × 4 every-6-weeks (240 = 48% of normal starting dose of 500 mg/m²/one cycle).

UGT1A1 is responsible for the homeostasis of bilirubin and the glucuronidation of a wide selection of drugs, including irinotecan, and xenobiotics. Results from several recently published trials indicate that patients who are homozygous for the UGT1A1*28 polymorphism are at greater risk for irinotecan-induced grades 3 or 4 neutropenia or diarrhea (39, 40). Although the effect of the UGT1A1 genotype was not investigated in the present study, prescribers should take this factor into consideration when deciding on an irinotecan starting dose for liver-impaired patients who are known to be UGT1A1*28 homozygous.

The pharmacokinetic results from this study showed that although the exposure of irinotecan and SN-38 followed the same trend of change in each group, the mean ratio of SN-38 AUC to irinotecan AUC seemed to increase with the severity of hepatic dysfunction. The relative increase in dose-normalized AUC was greater for SN-38 than for irinotecan in each hepatic dysfunction group. Therefore, it seems that hepatic dysfunction has a greater effect on the disposition of SN-38 than on irinotecan; this is most noticeable in patients with group 4 characteristics. Moreover, it seems that the major liver enzymes involved in irinotecan metabolic pathways (specifically, carboxylesterase, CYP3A4, and UGT1A1) remained functional, to some extent, with various degrees of liver dysfunction; this is supported by unchanged SN-38G/SN-38 AUC and APC/irinotecan AUC ratios and increased SN-38/irinotecan values. These results suggest that biliary excretion of irinotecan and its metabolites was likely the primary elimination process affected, which is consistent with previously published results (31).

Between groups of patients with the same transaminase concentration range (group 1 versus group 2 and group 3 versus group 4), a lower MTD was observed in the group with the higher serum total bilirubin. This observation confirms the value of elevated bilirubin in predicting susceptibility to irinotecan toxicities over the dose range tested in patients with hepatic dysfunction. A recently published study of single-agent irinotecan in colorectal cancer patients with relatively normal hepatic function found a modest association between baseline bilirubin and the severity of irinotecan-induced neutropenia (41). In both the present and previous studies in patients with hepatic dysfunction (31), an exponential decrease in irinotecan clearance and an increase in relative SN-38 exposure (based on dose-normalized AUC values) were associated with an increase in bilirubin. Both SN-38 and bilirubin are cleared from the circulation via UGT1A1-mediated glucuronidation followed by biliary excretion. Elevated bilirubin reflects deficient biliary excretion and/or metabolism in the impaired liver. Although direct proof is lacking in the clinical setting, it has also been proposed that elevated bilirubin may also compete with SN-38 for UGT1A1-mediated glucuronidation (42).

The transaminases (particularly AST) also showed a certain degree of correlation with irinotecan clearance and the relative SN-38 exposure. In hepatic dysfunction groups with similar total bilirubin range, groups with higher transaminase concentrations seemed to be associated with lower MTDs (group 4 versus groups 1 and 2). These observations indicate that transaminases may also have certain added value to bilirubin in predicting susceptibility to irinotecan toxicities in patients with hepatic dysfunction. However, higher transaminase concentrations in group 3 compared with those in groups 1 and 2 did not lead to a lower MTD for this group, suggesting that transaminases alone may not be as important as bilirubin as a predictor of irinotecan toxicity.

Patients with hepatic dysfunction often require drug dose modifications based on the severity of their impairment. Currently, hepatic dysfunction is often assessed using the Child-Pugh criteria, the use of which is advocated by the Food and Drug Administration (43). The Child-Pugh approach,
originally developed for patients with end-stage liver disease, has five components—total bilirubin, albumin, prothrombin time, ascites, and encephalopathy. In contrast, the National Cancer Institute Organ Dysfunction Working Group recommends a classification based on total bilirubin and AST. A recent comparison showed that the National Cancer Institute Organ Dysfunction Working Group index, using total bilirubin and AST, provided a simple and objective way of assessing hepatic dysfunction that could be applied in outpatient clinics and clinical trials for chemotherapy dose modification (44). Although the current trial also used total bilirubin and AST, the precise definitions of hepatic dysfunction categories are different in this trial compared with National Cancer Institute Organ Dysfunction Working Group criteria. However, the results of this trial are consistent with the major finding of a comparative assessment of Child-Pugh and National Cancer Institute Organ Dysfunction Working Group criteria, i.e., that total bilirubin should be the predominant factor in classifying the severity of hepatic dysfunction in cancer patients.

In summary, the present trial showed increases in exposure to irinotecan and SN-38 necessitating lower irinotecan starting doses in patients with hepatic dysfunction treated with the weekly irinotecan schedule. Irinotecan starting doses that seem to be safe for this patient population ranged from 40 to 60 mg/m<sup>2</sup>, depending on the degree of hepatic dysfunction as measured by total bilirubin and transaminase concentrations. Within this irinotecan starting dose range, the drug-related toxicity profile observed in liver-impaired patients was similar to that observed in cancer patients with relatively normal liver function receiving the standard starting dose of 125 mg/m<sup>2</sup>. The data also show that irinotecan given at these reduced starting doses can have antitumor activity in patients with compromised liver function.

Acknowledgments

We thank S.K. Gaylor and M.P. Eli of Pfizer and the General Clinical Research Center, Vanderbilt University Medical Center (NIH grant RR00099) for their contributions to the pharmacokinetic component of the study.

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