A phase I and pharmacokinetic study of irinotecan in patients with hepatic or renal dysfunction or with prior pelvic radiation: CALGB 9863


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Background: To ascertain if hepatic or renal dysfunction or prior pelvic radiation (XRT) leads to increased toxicity at a given dose of irinotecan and to characterize the pharmacokinetics of irinotecan and its major metabolites in patients with hepatic or renal dysfunction.

Patients and methods: Adults with tumors appropriate for irinotecan therapy and who had abnormal liver or renal function tests or had prior radiation to the pelvis were eligible. Patients were assigned to one of four treatment cohorts: I, aspartate aminotransferase (AST) ≥3× upper limit of normal and direct bilirubin <1.0 mg/dl; II, direct bilirubin 1.0–7.0 mg/dl; III, creatinine 1.6–5.0 mg/dl with normal liver function; IV, prior pelvic XRT with normal liver and renal function. Starting with reduced doses of either 145 or 225 mg/m², irinotecan was administered every 3 weeks to at least three patients within each cohort. Irinotecan and its metabolites in the blood were measured in all patients.

Results: Thirty-five patients were evaluable for toxicity. No dose-limiting toxicity was seen in cohort I, although only three patients were treated and at a dose of 225 mg/m². Patients with elevations of direct bilirubin had dose-limiting toxicities, even though the starting dose was 145 mg/m². These same patients appeared to have comparable exposure to the active metabolite SN-38 as normal patients treated with full-dose irinotecan. Patients with elevations of creatinine or with prior pelvic radiotherapy did not appear to have increased risk of toxicity at the doses explored in this study.

Conclusions: Patients with elevated bilirubin treated with irinotecan have an increased risk of toxicity and a dose reduction is recommended. Patients with elevated AST, creatinine or prior pelvic radiation do not appear to have increased sensitivity to irinotecan, but the data are not adequate to support a specific dosing recommendation.

Key words: hepatic dysfunction, irinotecan, pharmacokinetics

Introduction

Irinotecan (CPT-11; 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxy camptothecin) is a semisynthetic derivative of the natural alkaloid camptothecin. It is a prodrug that belongs to the class of antineoplastic agents called topoisomerase I inhibitors. In vivo, irinotecan is converted by carboxylesterases to its most active cytotoxic metabolite, 7-ethyl-10-hydroxy-camptothecin (SN-38), which exerts its cytotoxicity by generating intermediate forms of drug-stabilized covalent DNA–topoisomerase-I complexes.

Irinotecan has been studied as a single agent in many different cancers, including those of the gastrointestinal tract and lung. It has been explored in a variety of schedules, ranging from weekly to every 3 weeks. It first became indicated as a second-line treatment for patients with advanced colorectal cancer [1, 2]. It has also been tested in combination therapies, and is part of the three drug combination with 5-fluorouracil and folinic acid that is now considered one of the front-line treatment options for patients with advanced colorectal cancer [3, 4].

The dose-limiting toxicities of irinotecan are diarrhea and myelosuppression. Diarrhea appears to be due to intraluminal exposure to SN-38, although it is controversial as to the importance of biliary excretion of SN-38 versus intraluminal formation by beta glucuronidases [5]. Aggressive early intervention with loperamide has been encouraged to try to reduce the severity of toxicity [6]. Further experience with irinotecan in combination with
5-fluorouracil and leucovorin has renewed concerns about the risk of toxicity with this agent [7]. A possible correlation between baseline unconjugated bilirubin levels and severe diarrhea and neutropenia was observed in two patients with Gilbert’s syndrome [8], but the importance of elevations of the conjugated (direct) bilirubin fraction is not certain. In addition, the biliary index (a hypothetical surrogate for biliary SN-38 excretion) has been demonstrated to correlate with the severity of diarrhea on the weekly schedule [9, 10].

These observations raise concerns for the dosing of irinotecan, since many patients with metastatic colorectal or other gastrointestinal cancers will have extensive liver metastases and subsequent liver dysfunction. The Cancer and Leukemia Group B (CALGB) has previously published prospective studies of paclitaxel [11] and gemcitabine [12] in similar patient populations to assess the need for dose adjustments. Also, patients with rectal or cervical cancer may well have received whole pelvis radiation treatment, which would not be expected to alter the pharmacokinetics of a drug but could alter the toxicity profile.

Irinotecan is an effective agent that is likely to be used in all of the above settings. As a single agent, it is often used on a 3 weekly schedule. Therefore, the CALGB undertook this study to determine the toxicity and pharmacokinetics and to identify appropriate doses of irinotecan for patients with varying degrees of hepatic or renal dysfunction or prior pelvic radiation therapy.

Patients and methods

Patient eligibility

Adult patients with biopsy-proven solid tumors or lymphomas that were refractory to standard therapy or for which no standard therapy existed were eligible for this study. Other eligibility criteria included: CALGB performance status 0–2; life expectancy ≥2 months; ≥4 weeks from prior systemic chemotherapy; major surgery or radiation therapy; 6 weeks from mitomycin C or melphalan; ≥3 months from suramin treatment. Granulocyte count ≥1500/µl, platelet count ≥100 000/µl and albumin ≥2.5 g/dl were also required. The protocol was approved by each participating institution’s Institutional Review Board and by the National Cancer Institute and CALGB. Written informed consent to undergo therapy and pharmacokinetic studies was obtained from all patients.

Eligibility of patients with hepatic or renal dysfunction was determined by laboratory values. Patients were required to have a level of aspartate aminotransferase (AST) ≥3× the upper limit of normal (ULN) with normal bilirubin and serum creatinine; direct bilirubin 1.0–7.0 mg/dl with any level of AST; or normal liver function tests with serum creatinine 1.6–5.0 mg/dl. Patients with external biliary drainage catheters, whose initial liver function tests met these criteria, could be included in the study in the cohort reflecting those pretreating abnormalities even if the liver function tests normalized after the procedure, although no such patients were enrolled on this study. Patients with prior pelvic irradiation met all other eligibility criteria and had levels of AST <3× ULN, creatinine <1.6 mg/dl and direct bilirubin <1.0 mg/dl.

Exclusion criteria were as follows: prior treatment with irinotecan or nitrosoureas; known untreated brain metastases; uncontrolled or severe cardiac disease; and the use of concomitant medications affecting hepatic or renal function, including non-steroidal anti-inflammatory agents, antiseizure medications and steroids (except as antiemetics for chemotherapy).

Study design

The following eight institutions within the CALGB enrolled patients: the University of Chicago, Walter Reed Army Medical Center, University of Iowa, North Shore University Hospital, University of California at San Francisco, Roswell Park Cancer Institute, Georgetown University and the Ohio State University. Conference calls were held every other week. During these calls, toxicity data were reviewed by all participating investigators and decisions were made on dose escalations or reductions within cohorts.

Patients were categorized into one of four cohorts as follows: I, direct bilirubin <1.0 mg/dl, AST ≥3× ULN and serum creatinine <1.6 mg/dl; II, direct bilirubin 1.0–7.0 mg/dl with any level of AST and serum creatinine <1.6 mg/dl; III, serum creatinine 1.6–5.0 mg/dl with AST <3× ULN and direct bilirubin <1.0 mg/dl (these hepatic and renal function abnormalities were documented within 3 days prior to initiating therapy); IV, prior pelvic irradiation with AST <3× ULN, direct bilirubin <1.0 mg/dl and serum creatinine <1.6 mg/dl. No dosage escalation was permitted for an individual patient.

The starting dose for patients in cohorts I, III and IV was 225 mg/m² by 90-min infusion every 3 weeks. One cycle consisted of two treatments. Three patients were accrued to each dose level. If none of these three patients experienced a dose-limiting toxicity (DLT), the dose was to be increased in a subsequent group of three patients to 280 mg/m². If one of the first three patients experienced DLT, three more patients were to be accrued to that dose level. If none of these additional three patients experienced DLT, then the dose was to be escalated to 280 mg/m². If one of the additional three patients experienced DLT, then either an additional cohort of patients could be added or escalation terminated. If two or more of the second group of three patients experienced DLT, then accrual was stopped. If two of the first three patients experienced DLT, then an additional three patients could be accrued at that dose level, but dose escalation could take place only if none of the additional cohort experienced DLT. The last planned dose escalation was to 350 mg/m². If three or more of six patients experienced DLT at the 225 mg/m² dose, then a dose of 180 mg/m² was to be explored. Parameters for dose escalation or decrease were similar for patients in cohort II, although the initial dose was 145 mg/m² and a decremental dose of 115 mg/m² was explored due to toxicities. Patients who experienced a DLT, but appeared to be receiving benefit from the irinotecan were allowed to receive repeat treatment at the next lower dose level.

No standard premedication was recommended, although antiemetics and steroids were allowed. Prophylactic atropine was not prescribed but could be used at the discretion of the treating physician. All concomitant medications were to be recorded.

A complete blood count and platelet count were obtained two times a week during the treatment course. Liver function tests and renal function were assessed weekly. A weekly history and physical examination were also performed.

The CALGB Common Toxicity Criteria were used in this study. DLT was defined as follows: any grade 4 non-hematologic toxicity other than fever, infection or as noted below; grade 3 nausea, vomiting, diarrhea or anorexia despite optimal supportive care; grade 3 stomatitis or esophagitis/dysphagia lasting ≥7 days despite optimal supportive care; grade 4 neutropenia complicated by fever ≥38°C; grade 4 hemorrhage or thrombocytopenia; failure to recover neutrophils (≥1500/µl) or platelets (≥100 000/µl) by day 28. Dose-limiting hepatic toxicity was defined as follows: cohorts I and II, elevations of AST or alkaline phosphatase ≥2.5× baseline or bilirubin ≥1.5× baseline; cohorts III and IV, AST or alkaline phosphatase ≥5× ULN or bilirubin ≥2.5× ULN. Dose-limiting renal toxicity was defined as follows: cohorts I, II and IV, creatinine ≥2× ULN; cohort III, creatinine ≥2.5× baseline. No colony stimulating factors were allowed in this study unless a life-threatening event occurred.

When possible, patients with measurable disease were assessed for response at the end of every two cycles of treatment. Partial response was defined as a reduction of ≥50% in the sum of the products of the perpendicular
analyzed by high-performance liquid chromatography as described previously [13]. Samples were frozen and stored at –80°C until analysis. All samples were analyzed by high-performance liquid chromatography as described previously [9] except for changes in the percentage of acetonitrile in mobile phase from 30 to 35% and the reconstitution of samples in the mobile phase rather than in acidified methanol.

**Pharmacokinetic sample acquisition and handling**

Blood samples were obtained from patients before initiation of the 90-min irinotecan infusion, at 15 min and 30 min into the infusion, at the end of the infusion, and then at 10, 20, 30, 45, 60, 90 min and 2, 4, 6, 24 and 72 h after completion of the infusion. At each time point, 7 ml of blood were drawn into heparinized tubes and stored on ice until centrifuged at 1258 g for ~10 min at room temperature. The resulting plasma was removed and placed into a 17 × 100 mm polypropylene, snap-cap tube which was appropriately labeled. Samples were frozen and stored at –80°C until analysis. All samples were analyzed by high-performance liquid chromatography as described previously [9] except for changes in the percentage of acetonitrile in mobile phase from 30 to 35% and the reconstitution of samples in the mobile phase rather than in acidified methanol.

**Pharmacokinetic analysis**

Pharmacokinetic parameter estimates for irinotecan and its metabolites, SN-38, aminopentoic acid camptothecin (APC) and SN-38 glucuronide (SN38G) were obtained by posterior Bayesian estimation using an established model [13] and historical priors obtained from phase I studies of intravenous irinotecan in patients with solid tumors [9, 14, 15] using NONMEM (version V) [16]. Briefly, a seven-compartment model was used to describe the disposition of irinotecan and its metabolites in which the disposition of each of the metabolites was dependent upon the disposition of the parent compound (Figure 1). Formation and elimination of the metabolites were modeled as first-order processes and formation of each of the metabolites was determined to be rate-limiting.

Pharmacokinetic parameters estimated using the model were the inter-compartment and elimination rate constants (denoted K in Figure 1) and the apparent volumes of the compartments. Irinotecan clearance (CL) was estimated as the product of the elimination rate constant for irinotecan (K10) and the volume of the central compartment (V1). As the fraction of the irinotecan dose metabolized to SN-38 (Fmsn) and APC (Fmapc) and the fraction of SN-38 metabolized to SN38G (Fmsng) were not known, metabolite clearances are reported as the clearance divided by the fraction metabolized: CL/Fmsn, CL/Fmapc, CL/Fmsng. Similarly, volume of the central compartment for each of the metabolites is reported as VSN/Fmsn, VAP/Fmapc and VSN38G/Fmsng, respectively. Area under the plasma concentration versus time curve (AUC) for irinotecan was calculated by dividing dose by CL (or dose divided by CL divided by fraction metabolized for metabolites) as a measure of each subject’s exposure to parent drug and metabolites.

Individual pharmacokinetic parameter estimates for cohorts II, III and IV were compared using the Kruskal–Wallis rank sum test. A P value of <0.05 was considered significant. Cohort I data were excluded from the statistical analysis because the small number of subjects and large variability in pharmacokinetic parameter estimates in this group prevented meaningful statistical analysis.

**Results**

Between June 1998 and April 2001, 35 patients were enrolled in this study. Of these, all were evaluable for toxicity assessment. The characteristics of the 35 patients treated are listed in Table 1. Seventeen males and 18 females were evaluable in this study. Twenty-nine patients had received prior chemotherapy. Metastatic gastrointestinal cancer was the underlying disease in 13 patients, eight of the patients had primary liver cancer and nine patients had genitourinary cancers. The CALGB performance status was 0–1 in all but five patients. No patient was receiving medications that are known to interfere with or alter hepatic function.

The baseline laboratory parameters of the patients are shown in Table 2. In the patients with hepatic dysfunction, the range of AST was 134–394 U/l, and direct bilirubin concentrations ranged from 0.7 to 5.5 mg/dl. The range of serum creatinine in patients with renal dysfunction was from 1.6 to 3.5 mg/dl, and the blood urea nitrogen concentrations ranged from 16 to 50 mg/dl. (Calculated creatinine clearance, incorporating patient age and weight into the formula, showed correlation between serum creatinine in all patients in this cohort.)

The distribution of patients and treatment per cohort, dose and infusion schedule are detailed in Table 3. Seven patients encountered a DLT during the first cycle; five of the seven had had prior chemotherapy and two prior radiotherapy (Table 4). The most common DLT was neutropenia, seen in four patients, which manifested as nadir counts rather than protracted neutropenia. In cohort II, two of the DLTs were neutropenia in patients with baseline direct bilirubins of 4.5 and 1.5 mg/dl, respectively, and the other DLT was worsening liver function in a patient with a baseline direct bilirubin of 1.4 mg/ dl. The two patients with DLT in
the renal dysfunction cohort had grade 4 diarrhea and neutropenia with calculated creatinine clearances of 36 and 32 ml/min, respectively. No patient who had a DLT was re-dosed with irinotecan.

One patient with hepatocellular carcinoma in cohort II achieved a partial response, defined as a >50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions.

Pharmacokinetics

Pharmacokinetic studies were performed on 34 courses of irinotecan administered to 35 patients. All patients were studied on their first dose of irinotecan. Patients in cohort I were studied only at a dose of 225 mg/m² (three patients). Patients in cohort II were studied at doses of 115 (seven patients) and 145 (five patients) mg/m². Patients in cohort III were studied only at a dose of 225 mg/m² (eight patients). Patients in cohort IV were studied at doses of 225 mg/m² (nine patients) and 280 mg/m² (two patients).

Distributions of individual clearance estimates among cohort groups are shown in Figure 2 and average values are reported in Table 5. There were no significant differences in the pharmacokinetic parameter estimates for irinotecan nor its metabolites between patients with renal impairment and those with prior radiotherapy. In comparison, patients in cohort II (serum direct bilirubin level >1 mg/dl) had significant, clinically relevant decreases in irinotecan clearance, SN-38 clearance/fraction metabolized (CL/Fmsn) (Figure 2) and SN-38 volume of the central compartment/fraction metabolized (VSN1/Fmsn) (Table 5).

Irinotecan CL was estimated to be reduced by 35% in cohort II compared with cohorts III and IV, and both CL/Fmsn and...


\[ V_{SN1/Fmsn} \text{ for SN-38 were estimated to be reduced by 58%, suggesting an increase in the fraction of irinotecan metabolized to SN-38. Average estimates of } CL/Fmsng \text{ for SN38G and } CL/Fmapc \text{ for APC were also decreased in cohort II compared to cohorts III and IV; however, large variability within the cohort groups prevented detection of significant differences in the fraction of the parent compound metabolized among cohorts (Figure 2).}

Predicted exposure to irinotecan and its metabolites for a standardized dose of 145 mg/m\(^2\) irinotecan are shown in Figure 3. Despite the fact that patients in cohort II received 35–49% lower doses of irinotecan compared with the other cohorts, systemic exposure (area under the curve) was similar across the cohorts.

**Discussion**

The dosing of chemotherapeutic agents in patients with organ dysfunction has long been an empiric exercise. Because new agents are generally tested in, and restricted to usage in, patients with normal organ function, decisions on the dosing of patients with organ dysfunction are often based on the anecdotal observations made during the period of early drug development and knowledge of metabolic pathways. Prospective studies have refined this method of dosing of some drugs, including carboplatin [17], etoposide [18], paclitaxel [11] and gemcitabine [12].

Our initial goal was to define specific dose recommendations for single-agent irinotecan for patients fitting the definition of each cohort. Given the heterogeneity of the patient population and the small sample sizes, we cannot determine precise dosing recommendations. Based on our data, we cannot determine how patients with elevated transaminases but normal bilirubin and creatinine should be dosed with irinotecan. Patients with elevated direct bilirubin should be treated with irinotecan at reduced doses. The dosing of irinotecan in patients with renal dysfunction is not clarified by this study, since no patient with a serum creatinine >3.5 mg/dl was included and the doses explored in this study are below the standard recommended doses. Patients with prior pelvic radiation may best be treated at reduced doses of irinotecan, although a specific recommendation cannot be made based on these data.

There were no episodes of dose-limiting diarrhea in patients with an increased direct bilirubin. This is consistent with the hypothesis that biliary excretion of SN-38 is responsible for the diarrhea, since patients with an increased direct bilirubin have cholestasis and impaired excretion of bilirubin and xenobiotics. The findings of the current study demonstrate that patients with baseline elevations in direct bilirubin, but not transaminases, experienced greater relative exposures to both irinotecan and SN-38 due to reduced irinotecan clearance and an increased fraction of irinotecan metabolized, presumably by CYP3A4. The clinical relevance of these perturbations is that such patients, despite reduced dosing of irinotecan, had drug and metabolite exposures similar to patients with decreased renal function or with normal renal and hepatic function and prior radiation therapy to the pelvis, as shown in Figure 3. These findings are similar to those of Raymond et al. [19], who has demonstrated that baseline total bilirubin levels may be used to determine dosing parameters for patients with hepatic dysfunction.

The application of these data to standard usage of irinotecan, which may be on a weekly schedule and usually involves combination with other chemotherapeutics, is problematic. In particular,
its co-administration with agents that may affect hepatic metabolic pathways needs to be carefully studied before entering clinical practice. Also, this study employed conventional dosing by body-surface area, which may not be appropriate for irinotecan [20] and which makes the data more difficult to interpret.

The results of this study are a reminder that the data generated in early phase I or II trials are not generalizable to patients with organ dysfunction. New agents need to be studied extensively to understand their pharmacokinetics and pharmacodynamics in such patients and to establish guidelines for their dosing in a variety of clinical settings and in combination with other drugs. In keeping with this philosophy, a study of OSI-774 in patients with organ dysfunction or prior radiotherapy is now underway within the CALGB.

Acknowledgements

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Table 5. Average parameter estimates

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Values reported for cohort 1 represent parameter estimates for each of two individuals.

*P <0.05 compared to groups 3 and 4.

CL, irinotecan clearance; CL/Fmsn, CL/Fmapc and CL/Fmsng, clearance divided by the fraction metabolized; Fmsn, fraction of the irinotecan dose metabolized to SN-38; Fmapc, fraction of the irinotecan dose metabolized to APC; Fmsng, fraction of SN-38 metabolized to SN38G; K_{el1}, elimination rate constant for irinotecan; V_{II}, volume of the central compartment; V_{SN1}/Fmsn, V_{A1}/Fmapc and V_{SG1}/Fmsng, volume of the central compartment for each of the metabolites.


Figure 3. Predicted area under the curve for irinotecan and its metabolites following an intravenous infusion of 145 mg/m² irinotecan administered over 90 min.