INTRODUCTION

The nuclear enzyme topoisomerase I has been recently recognized as the subcellular target for CPT and its analogues. Although CPT demonstrated activity in diverse tumor types in preclinical studies as well as in limited phase I and II trials in the 1960s (reviewed in Ref. 1), there was a lack of enthusiasm for developing CPT and CPT analogues at that time. In retrospect, this could be attributed to the lack of recognition that CPT possessed a novel mechanism of antineoplastic action, as well as severe and unpredictable nonhematological toxicities, particularly hemorrhagic cystitis and enteritis, which occurred in clinical trials that evaluated the open-ring sodium salt of CPT due to the aqueous insolubility of the closed-ring CPT lactone (1-7). Approximately two decades after the completion of clinical evaluations, the sodium salt of CPT was demonstrated to be a poor inhibitor of topoisomerase I and significantly less active than the closed-ring lactone (8). It is currently believed that the antitumor activity and toxicities noted with the open-ring CPT salt were due to conversion to the lactone in tumors and normal tissues, especially in acidic environments which favor the formation of the lactone (reviewed in Refs. 1 and 8-10). Because high doses of sodium CPT were used in these studies to compensate for the lower potency of the hydroxy acid salt compared with the CPT lactone, it is likely that high concentrations of the active lactone were formed in the acidic milieu of the bladder and stomach.

After the novel mechanism of action and chemistry of CPT were elucidated, structure-activity studies were performed to define features of the molecule that are essential for cytotoxicity and to produce CPT derivatives with increased aqueous solubility under physiological conditions (8, 9, 11). Among the derivatives identified, CPT-11 (Fig. 1A), which was developed at the Yakult Central Institute for Microbiological Research (Tokyo, Japan), was found to be more active than CPT against diverse types of murine and human tumors as well as against pleiotropic drug-resistant tumors in vitro and in vivo (12-20). Unlike CPT and topotecan, another water soluble CPT analogue undergoing broad clinical evaluations (reviewed in Refs. 1 and 21), CPT-11 has little inherent amidotumor activity in vitro. Instead, CPT-11 is a prodrug that undergoes deesterification to SN-38 (Fig. 1B) which has 100-1000-fold more topoisomerase I-inhibitory activity than CPT-11 in vivo and probably a slower plasma elimination rate than the parent compound (22-24). Similar to both CPT and topotecan, the active lactone forms of both CPT-11 and SN-38 exist in a pH-dependent equilibrium with their respective less potent open-ring hydroxy acid species. More basic pHs, including physiological pH, favor the formation of the hydroxy acid forms (1, 9, 10).

ABSTRACT

7-Ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy Ncamptothecin (CPT-11; Irinotecan), a semisynthetic analogue of camptothecin (CPT) with broad preclinical antitumor activity, has demonstrated impressive activity in phase II trials in Japan in advanced small and non-small cell lung, colorectal, cervical, and ovarian carcinomas, as well as in refractory lymphomas and leukemias. In this phase I and pharmacological study, 90-min infusions of CPT-11 were administered every 3 weeks at doses ranging from 100 to 345 mg/m^2 to patients with solid malignancies. Acute, severe, and refractory vomiting, diarrhea, and/or abdominal cramps associated with flushing, warmth, and diaphoresis occurred in the immediate posttreatment period at the 240-mg/m^2 dose level in several patients who were not treated with premedications. The characteristics and temporal nature of these toxicities, the prompt resolution of symptoms following treatment with diphenhydramine, and the successful use of a premedication regimen consisting of ondansetron and diphenhydramine in preventing these acute effects suggest that vasoactive substances are involved in the mediation of these acute toxicities. With the routine use of these premedications, there was no single toxicity type that limited the escalation of CPT-11 doses. Instead, a constellation of severe hematological and gastrointestinal effects precluded the repetitive administration of CPT-11 at doses above 240 mg/m^2, the maximum tolerated dose and recommended phase II dose on this schedule. Major responses were observed in patients with advanced colorectal, cervical, and renal cancers. The disposition of total CPT-11 in plasma was fit by a biexponential kinetic model with renal elimination accounting for 37 ± 4% (SE) of total drug disposition. The C_max for the active metabolite of CPT-11, 7-ethyl-10-hydroxycamptothecin (SN-38), was achieved at 2.2 ± 0.1 h after treatment, and mean residence times for both CPT-11 and SN-38 were long, 9.1 and 10.0 h, respectively. Compared with topotecan, another CPT analogue under development, a larger proportion of total drug exposure was accounted for by the active lactone (closed-ring) forms of CPT-11 and SN-38; areas under the time-versus-concentration curve for their respective lactone were 44 and 50% of areas under the time-versus-concentration curve for total CPT-11 and SN-38. Although intermittent dosing schedules appear to be superior to single dosing schedules for CPT and some CPT analogues in preclinical tumor models, the maintenance of biologically relevant concentrations of SN-38 for relatively long durations may negate the potential pharmacological benefits of intermittent and continuous administration schedules for CPT-11. The clinical activity observed with CPT-11 on the single dosing schedule and the lack of severe diarrhea after repetitive dosing at the maximum tolerated dose, which has been problematic on intermittent schedules, suggest that the single dosing schedule should be evaluated further in the phase II setting and in the development of combination chemotherapy regimens, particularly those containing both CPT-11 and 5-fluorouracil in which diarrhea is a significant concern.
To date, phase I and II trials of CPT-11 have been performed primarily in Japan. Significant antitumor activity has been reported in advanced small and non-small cell lung, colorectal, cervical, and ovarian carcinomas, as well as in refractory lymphomas and leukemias (reviewed in Refs. 1 and 24–30). Although the development of CPT-11 for solid malignancies has focused primarily on intermittent administration schedules, specifically as a 90-min infusion given weekly, an optimal administration schedule has not yet been defined. In addition, the principal toxicity of CPT-11 has been reported to be related to the specific schedule of administration. While diarrhea has been reported to be the principal toxicity of CPT-11 when it is administered on a weekly schedule, myelosuppression has been reported to predominate when CPT-11 is administered as a single 90-min infusion every 3 weeks (reviewed in Refs. 1, 24, and 31). However, even at the recommended phase II dose for CPT-11 on the weekly schedule, 100 mg/m², gastrointestinal and hematological toxicities have occurred frequently, and severe diarrhea has occurred in up to 21% of patients participating in phase II trials (25–27).

This study was performed to assess the feasibility of administering CPT-11 as a single 90-min infusion every 3 weeks. The principal objectives of the study were to: (a) determine the MTD of CPT-11 on this schedule; (b) recommend a dose for subsequent phase II trials; (c) characterize the toxicities associated with this schedule of administration; (d) seek additional evidence for antitumor activity; and (e) describe the pharmacological behavior of CPT-11 administered on this schedule, including the pharmacological behavior of both the lactone and open-ring forms of CPT-11 and SN-38.

MATERIALS AND METHODS

Eligibility. Only patients with histologically documented solid tumors for which no therapies with greater potential benefit than CPT-11 existed were candidates for this study. Eligibility criteria included (a) age ≥ 18 years; (b) an Eastern Cooperative Oncology Group performance status ≤ 2 (ambulatory and capable of self-care); (c) a predicted life expectancy of 12 months; (d) no major surgery, radiation therapy, or chemotherapy within 28 days of entering onto protocol; (e) no prior chemotherapy included mitomycin C or a nitrosourea; (f) adequate hematopoietic (WBC ≥ 3500/µl; platelets ≥ 100,000/µl; hemoglobin ≥ 9.5 g/dl); hepatic (total bilirubin ≤ 2 mg/dl; aspartate aminotransferase ≤ 105 IU/liter) and renal (creatinine ≤ 2 mg/dl or creatinine clearance ≥ 60 ml/min) functions; (f) serum electrolytes within 10% of normal institutional values and serum glucose < 200 mg/dl; (g) no other medical problems of sufficient severity to prevent full compliance with the study; and (h) a negative CPT-11 prick test in which small drops of both CPT-11 (20 mg/ml) and saline solutions were placed 2 cm apart on the volar surface of the forearm followed by the low-angle insertion of a needle through each drop. Fifteen min after the needles were withdrawn, the largest and smallest diameters of the wheal and or erythema were measured and a mean diameter was recorded. The prick test was scored as positive if the injection of CPT-11 induced a wheal ≥ 4 mm or erythema ≥ 15 mm and/or 2-fold greater than that induced by the saline solution.

Patients were defined as heavily pretreated with respect to hematopoietic tolerance if they had received large-field radiation to ≥ 20% of bone marrow-bearing areas such as pelvis or spine, greater than 6 courses of chemotherapy containing an alkylating agent or greater than 2 courses of a nitrosourea or mitomycin C, or widespread metastases to bones or bone marrow. All patients gave informed written consent according to federal and institutional guidelines.

Dosage. The starting dose of CPT-11 was 100 mg/m² administered as an infusion over 90 min every 3 weeks. This dose was selected because it had been associated with no or mild toxicities and was sufficiently lower than the MTD established in a previous phase I study in Japan (31). Since the starting dose exceeded the conventional starting dose based on standard animal toxicological end points (32), subsequent dose escalations were performed according to the following conservative scheme: 150, 200, 240, 290, and 345 mg/m². At least two new patients were treated at each escalated dose level. As the MTD was approached and potential DLT was observed, at least six naive patients were entered. The MTD was defined as one dose level below the dose that induced DLT in greater than one-third of all new patients (at least two of a maximum of six new patients). DLT was defined as one of the following: (a) ANC < 500/µl for > 5 days or associated with fever requiring parental antibiotics; (b) platelets < 50,000/µl; and/or (c) nonhematological toxicity ≥ National Cancer Institute grade 3 (grade 4 for vomiting or diarrhea) (33). Initially, dose escalations in the same patient were not permitted; however, the protocol was revised to permit dose escalations in patients treated with starting doses ≥ 150 mg/m² if at least two courses had been administered at the starting dose level without DLT and if two new patients had already been treated at the next highest dose. Dose reductions by one or two dose levels were permitted for DLT.

Drug Administration. CPT-11 was supplied by Yakult Honsha Co., Ltd. (Tokyo, Japan) and Daiichi Pharmaceutical Co., Ltd. (Tokyo, Japan) in 2- and 5-ml vials containing 20 mg/ml of CPT-11 dissolved in sterile water, 4.5% (w/v) sorbitol, 0.09% (w/v) lactic acid, and sodium hydride to adjust the pH to 3–4. The therapeutic dosage was subsequently diluted in 500 ml of 5% dextrose solution and then administered as an i.v. infusion over 90 min. The initial course of CPT-11 was administered on the inpatient units of the Johns Hopkins Oncology Center while all other treatments were given in the outpatient clinic. Vital signs, including temperature, pulse, blood pressure, and respiratory rate, were recorded during the first course according to the following schedule: pretreatment; every 15 min during the infusion; every 30 min after the infusion for 2 h; and then every 6 h for 24 h posttreatment.

After the first two patients treated with CPT-11 at the 240-mg/m² dose level experienced severe nausea, vomiting, and abdominal cramps, a standard pretreatment medication regimen, consisting of ondansetron, 0.15 mg/kg i.v. pretreatment and every 4 h for two doses, and diphenhydramine, 50 mg i.v. pretreatment, was administered to subsequent patients to reduce severe gastrointestinal effects.

Pretreatment and Follow-up Studies. Histories, physical examinations, and routine laboratory studies were performed at baseline and at least weekly. Routine laboratory studies included a complete blood count, differential WBC, electrolytes, blood urea nitrogen, creatinine, glucose, total protein, albumin, calcium, phosphate, uric acid, alkaline phosphatase, total and direct bilirubin, adenosineaminotransferase, aspartateaminotransferase, amylase, prothrombin and partial thromboplastin times, stool test for occult blood, and urinalysis. An electrocardiogram was also performed prior to each course. Complete blood counts and differential WBC were obtained every other day if the ANC was ≤ 500/µl. Toxicities were evaluated according to the National Cancer Institute common toxicity criteria (33). Formal tumor measurements were performed after every two courses and patients were able to continue treatment if they did not develop progressive disease. A complete response was scored if there was disappearance of all active disease on two measurements separated by a minimum of 4 weeks, a PR required greater than a 50% decrease in the sum of the product of the bidimensional measurements of all measurable lesions documented by two measurements separated by at least 4 weeks, and a MR was scored if a decrease in this parameter was ≥ 25% and ≤ 50%.

Pharmacological Studies. Blood samples in heparinized tubes were collected during the first course before the infusion, then 15 and 45 min during the infusion, and at the end of infusion. Samples were collected and stored at −70°C until analysis. The plasma concentration of total and free CPT-11 was measured on a commercial high-performance liquid chromatography system. The following parameters of drug exposure were assessed: areas under the plasma concentration-time curve from time zero to infinity, AUC (0–∞); areas under the plasma concentration-time curve from time zero to 4 h, AUC (0–4 h); maximum plasma concentration, Cmax; and time to Cmax, Tmax. The PK parameters were calculated using the GraphPad Software. The other results were not statistically significant.
centrifuged at 1000 × g at 5°C for 10 min immediately after sample collection and 1 ml of plasma was then added to 6 ml of cold methanol for quantitation of CPT-11 and SN-38. Both mixtures were vortexed for 10 s, centrifuged at 1000 × g for 10 min, and either immediately analyzed or stored at −70°C. Parallel stability studies for topotecan have demonstrated that both lactone and hydroxy acid species are stable for more than 1.5 years when extracted and stored in this manner. For chromatographic analysis and quantitation of CPT-11 concentrations in plasma, 50-μl aliquots of the methanol extract along with 450 μl of methanol (1:9 dilution) were added to paired autosials. To quantitate SN-38, undiluted methanol extracts were injected directly on the HPLC column. To quantitate total CPT-11 and SN-38, 20 μl of a 20% phosphoric acid solution were added to one vial of each of the two sets to convert SN-38, undiluted methanol extracts were injected directly on the HPLC column after appropriate dilution and acidification.

For quantitation of the CPT-11 and SN-38 lactones, separation of the samples was accomplished by reverse-phase HPLC. The HPLC system consisted of a Waters Model 6000 pump (Waters, Milford, MA), an ISS-100 autosampler (Perkin Elmer, Rockville, MD), and a LS40 Perkin Elmer fluorescence detector. Analyses of CPT-11 and SN-38 were performed separately. Fifty-μl samples were injected onto a C18 column, 250 × 4.6 mm (inside diameter), 5 μm TSK-GEL (Toso Haas, Philadelphia, PA), with a C18 Bondapak Guard-Pak (Waters, Milford, MA) precolumn. For CPT-11, the mobile phase consisted of 55/45 (v/v) methanol/potassium phosphate-heptanesulfonic acid buffer (0.5 mM potassium phosphate solution containing 3 mM heptanesulfonic acid) mixture. The pH of the buffer was adjusted to 4.0 with phosphoric acid. The flow rate was maintained at 1.0 ml/min and the column effluent was monitored fluorometrically with excitation and emission wavelengths set at 370 and 430 nm, respectively. For SN-38, the mobile phase consisted of a 65/35 (v/v) water/acetonitrile mixture. The flow rate was 1.0 ml/min and the column effluent was monitored fluorometrically with excitation and emission wavelengths set at 380 and 520 nm, respectively. Peak areas were integrated from chromatographic data acquired by a PE Nelson 900 intelligent interphase (Cupertino, CA). The converted digital data were acquired on a Dell 486SX personal computer (Dell, Austin, TX) and were analyzed using the PE Nelson 2600 Chromatography Data System. Drug concentrations were determined from linear regression equations derived from calibration curves prepared with standards between 50 and 400 nmol/liter. Under these conditions, the retention times for the CPT-11 and SN-38 lactones were 8.5 and 7.5 min, respectively, while the open-ring forms were eluted in the solvent front with a retention time of approximately 30 s. Acidification of one of the paired samples converted the open-ring forms of both CPT-11 and SN-38 to the lactone enabling quantitation of total CPT-11 and SN-38. To quantitate the concentrations of the hydroxy acid forms of CPT-11 and SN-38, the lactone concentrations of CPT-11 and SN-38 in the unacidified samples were subtracted from the total drug concentrations measured in the acidified samples.

Individual plasma clearance curves were fit using a biexponential linear mammalian model of drug distribution and administration after visual inspection of the raw data and curves. Concentration data were weighted by 1/concentration. Pharmacokinetic modeling and parameter estimation was performed using the nonlinear regression program PC NONLIN (Statistical Consultants, Lexington, KY). Pharmacokinetic parameters were calculated from the estimated parameters \( t_{1/2a} \), \( t_{1/2b} \), \( V_a \), \( V_m \), AUC, and clearance. Nonparametric parameter estimates were also calculated. AUCs for CPT-11 and SN-38 and their respective lactones were calculated using a combination of the linear and logarithmic trapezoidal rule (35). Areas under segments with increasing or constant concentrations were calculated using the linear rule

\[
AUC = \frac{(C_1 + C_2)(t_2 - t_1)}{2}
\]

while segments with decreasing concentrations were calculated using the logarithmic rule

\[
AUC = \frac{(C_1 - C_2)(t_2 - t_1)}{\ln C_1 - \ln C_2}
\]

where \( C_1 \) and \( C_2 \) are the concentrations at the endpoints, \( t_1 \) and \( t_2 \) are the times at the endpoints, and \( t_{1/2} \) is the terminal (\( k_t \) terminal) half-life.

\[
AUMC = \frac{[\text{Dose}][\text{AUC}]^2}{[\text{Dose}][\text{AUC}]^2}
\]

for CPT-11 and SN-38, the lactone concentrations of CPT-11 and SN-38 in the unacidified samples were subtracted from the total drug concentrations measured in the acidified samples.

The AUC from the last measured concentration to infinity and the \( t_{1/2} \) elim were calculated using the estimate of the terminal exponential term (\( A_{\text{terminal}} \)) which was estimated by linear regression using the last 5 to 6 concentrations sampled. For total CPT-11, these AUC estimates were highly correlated with those generated by kinetic analysis. AUMC was calculated in a similar manner. Nonparametric parameters were then calculated as

\[
\text{MRT} = \frac{\text{AUMC}}{\text{AUC}}
\]

\[
\text{Clearance} = \frac{\text{Dose}}{\text{AUC}}
\]

\[
V_d = \frac{[\text{Dose}][\text{AUC}^2]}{[\text{T}][k_T][\text{AUC}^2]}
\]

where \( T \) is infusion time and \( k_T \) is the infusion rate.

Correlations between kinetic parameter values and categorical toxicity data were calculated using Spearman's rank-order correlation statistic. The pharmacodynamics of each species of CPT-11 and SN-38 were also explored using scatterplots of dose or AUC versus the percentage decrease in ANC as defined as

\[
\% \text{ of change in ANC} = \frac{\text{Maximum effect (AUC)} - \text{AUC}_{\text{new}}}{\text{AUC}_{\text{max}}} \times 100\%
\]

Nonlinear least square regression using PC NONLIN was used to estimate \( k_T \) which describes the shape of the curve, and AUCmax, the AUC that results in 50% of the maximal effect (e.g., 100% reduction in ANC).

RESULTS

Thirty-two patients received 144 total courses of CPT-11 through six dose levels (Table 1). Two courses were not fully evaluable; one patient died due to progressive pseudomyxoma peritonei on day 12 of his first course of CPT-11 at 290 mg/m² and a second patient was noncompliant with follow-up evaluations during his third course at 240 mg/m². The median number of courses administered per patient was 3 and ranged from 1 to 21 (1 course, 5 patients; 2 courses, 9 patients; 3 courses, three patients; four courses, three patients; 5 courses, 4 patients; 6 courses, 4 patients; 11 courses, 1 patient; 12 courses, 2 patients; and 21 courses, 1 patient). Two patients were treated at two dose levels, including one patient who was dose escalated due to negligible toxicity and another patient who was dose reduced due to profound toxicity. In addition, two patients required two successive dose reductions and were treated at three dose levels. Patient characteristics are displayed in Table 2. Thirty-one of 32 patients had an Eastern Cooperative Oncology Group performance status of either 0 or 1. Thirty patients had previously received cyto-

\[
\text{Table 1: CPT-11 dose escalations}
\]

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>No. of patients treated</th>
<th>No. of courses/Total (fully evaluable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>3</td>
<td>0/0</td>
</tr>
<tr>
<td>150</td>
<td>3</td>
<td>1/0</td>
</tr>
<tr>
<td>200</td>
<td>3</td>
<td>0/2</td>
</tr>
<tr>
<td>240</td>
<td>11</td>
<td>2/0</td>
</tr>
<tr>
<td>290</td>
<td>9</td>
<td>1/10</td>
</tr>
<tr>
<td>345</td>
<td>3</td>
<td>0/0</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>144 (142)</td>
</tr>
</tbody>
</table>
toxic therapies. Nineteen and 13 patients, respectively, were considered minimally and heavily pretreated.

**Toxicity**

**Dose-limiting Toxicity.** A constellation of severe hematological and nonhematological toxicities, including severe abdominal cramps, diarrhea, nausea, vomiting, and anorexia, as well as prolonged severe neutropenia, were observed consistently at CPT-11 doses of 290 and 345 mg/m² and subsequently defined 240 mg/m² as the MTD and recommended phase II dose for CPT-11 administered as a 90-min infusion every 3 weeks. Table 3 depicts the numbers of dose-limiting hematological and nonhematological events per patient (new and all patients) and per course (first and all courses) at each dose level. These toxicities were not mutually exclusive and individuals commonly experienced more than one dose-limiting event, often during the same course. For example, 11 total dose-limiting events were experienced by 5 of 10 patients during 7 of 19 courses at the 290-mg/m² dose level, while 4 dose-limiting events were experienced by 2 of 3 patients during 3 of 8 courses at 345 mg/m². At the dose recommended for subsequent phase II studies, 240 mg/m², 4 of 13 patients experienced various dose-limiting events; however, these events were noted during only 6 of 72 courses (8.3%).

**Gastrointestinal Toxicity.** Gastrointestinal toxicities, consisting of nausea, vomiting, anorexia, diarrhea, and abdominal cramps, were the principal nonhematological toxicities of CPT-11 on this administration schedule. Nausea, vomiting, and anorexia either occurred immediately and resolved during the pretreatment period or occurred later during the first week following treatment. In some individuals, especially those treated at CPT-11 doses above 240 mg/m², anorexia occasionally lasted 2–3 weeks and often resulted in significant loss of body weight (5–10% of pretreatment weight) and declining performance status. With respect to diarrhea and abdominal cramps, two general patterns were also noted. Some patients experienced acute diarrhea and abdominal cramps beginning in the perinfusional period or within 2 to 6 h posttreatment. These symptoms were often accompanied by complaints of warmth, diaphoresis, and flushing. In contrast, other subjects developed diarrhea later in their course, 2 to 7 days after treatment. Symptoms generally responded, albeit never completely, to conservative measures such as treatment with loperamide and diphenoxylate. In most patients, diarrhea resolved before day 21; however, several subjects developed severe, chronic, and cumulative diarrhea that worsened with each successive course. In two such patients, severe, protracted diarrhea improved considerably after treatment with octreotide, 50 mg s.c. twice daily; however, the agent was discontinued in one individual due to the exacerbation of abdominal cramps.

The frequency and severity of these gastrointestinal effects, as well as their contribution to defining 240 mg/m² as the MTD and recommended phase II dose, are depicted in Tables 3 and 4. Although most patients experienced at least one of these toxicities at CPT-11 doses below 240 mg/m², these effects were usually mild to moderate in severity and required neither symptomatic treatment nor the administration of premedications during subsequent courses. However, a premedication regimen, consisting of diphenhydramine, 50 mg i.v. pretreatment, and ondansetron, 0.15 mg/kg i.v. pretreatment and every 4 h for 2 doses, was administered subsequently to all patients after two subjects developed severe, acute gastrointestinal complaints during their first courses of CPT-11 at the 240-mg/m² dose level. These

### Table 2 Patient characteristics (N = 32)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of courses (fully evaluable)</td>
<td>144 (142)</td>
</tr>
<tr>
<td>Median no. of courses/patient (range)</td>
<td>3 (1-21)</td>
</tr>
<tr>
<td>Median age, yr (range)</td>
<td>49 (21-75)</td>
</tr>
<tr>
<td>ECOG* performance status</td>
<td></td>
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<tr>
<td>0</td>
<td>15</td>
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<tr>
<td>1</td>
<td>16</td>
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<td>2</td>
<td>1</td>
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<td>Previous therapy</td>
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<td>15</td>
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<tr>
<td>Chemotherapy and radiotherapy</td>
<td>12</td>
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<tr>
<td>Chemotherapy and immunotherapy</td>
<td>2</td>
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<tr>
<td>Radiotherapy only</td>
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</tr>
<tr>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>Tumor site</td>
<td></td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>13</td>
</tr>
<tr>
<td>Lung (non-small cell)</td>
<td>7</td>
</tr>
<tr>
<td>Cervix</td>
<td>4</td>
</tr>
<tr>
<td>Uterus (squamous cell)</td>
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</tr>
<tr>
<td>Uterus (sarcoma)</td>
<td>1</td>
</tr>
<tr>
<td>Breast</td>
<td>1</td>
</tr>
<tr>
<td>Stomach</td>
<td>1</td>
</tr>
<tr>
<td>Pseudomyxoma peritonei</td>
<td>1</td>
</tr>
<tr>
<td>Kidney</td>
<td>1</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1</td>
</tr>
</tbody>
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* ECOG, Eastern Cooperative Oncology Group.

### Table 3 Dose-limiting toxicities (DLTs)

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>Courses/patients (new)</th>
<th>Hematological</th>
<th>Nonhematological</th>
<th>New patients</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ANC &lt;500/μl &gt;5 days</td>
<td>PLT &lt;50,000/μl</td>
<td>Grades 3-4 nausea, vomiting, anorexia</td>
<td>Grade 4 diarrhea</td>
<td>First courses, with DLTs*</td>
</tr>
<tr>
<td>100</td>
<td>14</td>
<td>3 (3)</td>
<td></td>
<td></td>
<td>0/3</td>
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<tr>
<td>150</td>
<td>9</td>
<td>4 (3)</td>
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<td>0/3</td>
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<tr>
<td>200</td>
<td>18</td>
<td>1 (5)</td>
<td>1</td>
<td>1</td>
<td>0/3</td>
</tr>
<tr>
<td>240</td>
<td>72</td>
<td>3 (11)</td>
<td>4</td>
<td>1</td>
<td>1b</td>
</tr>
<tr>
<td>290</td>
<td>22</td>
<td>10 (9)</td>
<td>3</td>
<td>1</td>
<td>1b</td>
</tr>
<tr>
<td>345</td>
<td>8</td>
<td>2 (3)</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

* Refers to numbers of patients and courses associated with DLTs. More than one DLT may have been experienced by the same patient during a single course.

b Before routine institution of antiemetic premedication regimen.
patients experienced profound warmth, diaphoresis, and flushing during treatment which was followed immediately by severe abdominal cramps, vomiting, and diarrhea. Flushing, warmth, diaphoresis, and abdominal cramps resolved immediately after the administration of diphenhydramine, 50 mg/m² i.v., in these patients and in other patients who experienced similar symptoms after receiving CPT-11 at doses ≥240 mg/m². In addition, both patients who developed acute, severe gastrointestinal toxicities during their first course of CPT-11 at 240 mg/m² given without premedications experienced only mild to moderate gastrointestinal effects during subsequent courses in which prophylactic premedications preceded CPT-11. Despite the premedication regimen, 5 of 10 patients treated at the 290-mg/m² dose level developed severe grades 3 and 4 (dose-limiting) nausea, vomiting, and/or anorexia during 3 and 3 of 22 courses, respectively. At 345 mg/m², grades 3 and 4 nausea, vomiting, and/or anorexia was noted in 1 and 0 of 8 courses, respectively. Grades 3 and 4 (dose-limiting) diarrhea and/or abdominal cramps were observed in 2 and 3 of 22 courses, respectively, at 290 mg/m² and in 1 and 2 of 8 courses at 345 mg/m².

**Hematological Toxicity.** Neutropenia and thrombocytopenia were the principal hematological effects of CPT-11 in this study (Table 5). Nadir ANCs were generally noted on days 8–12 and recovery usually occurred by day 22, while nadir platelet counts were generally observed on day 15. However, dose-limiting neutropenia (ANC <500/µl for >5 days) and thrombocytopenia were rare. Dose-limiting neutropenia was experienced by only one heavily pretreated patient at CPT-11 doses below 240 mg/m². This patient developed grade 4 neutropenia during her first and second courses of CPT-11 at 240 and 200 mg/m² and grade 3 neutropenia during her third course at 150 mg/m². In addition, two other patients, including one heavily and one minimally pretreated patient, experienced dose-limiting neutropenia at the recommended phase II dose, 240 mg/m²; both patients previously required dose reductions due to severe neutropenia at the 290- and 345-mg/m² dose levels. Neutropenia associated with fever requiring hospitalization for empiric antibiotics was experienced by only 1 patient during 1 of 144 courses; the patient’s WBC andANC nadirs were 2200/µl and 1232, respectively. Similarly, dose-limiting thrombocytopenia was noted during only one course involving a minimally pretreated patient who had a nadir platelet count of 45,000/µl at the 240-mg/m² dose level. This patient also developed severe neutropenia concurrently, as well as during previous courses at higher doses.

CPT-11 induced negligible effects on RBC. Seventeen patients developed ≥4% decreases in their hematocrit values during 39 of 144 courses (27%). However, anemia was rarely clinically significant; RBC transfusions were required by 5 patients during 6 courses (4%).

**Miscellaneous Toxicity.** As previously discussed (see “Gastrointestinal Toxicities”), warmth, flushing, and diarrhea were frequently noted during treatment and were often associated with severe nausea and vomiting. At CPT-11 doses <240 mg/m², 0 of 9 new patients developed these manifestations; however, 9 of 23 new patients experienced these symptoms at CPT-11 doses ≥240 mg/m². In addition, alopecia was usually noted in patients receiving CPT-11 doses ≥240 mg/m². Although the partial loss of scalp hair generally occurred, hair loss was cumulative and complete alopecia was usually noted after patients received ≥4 courses at CPT-11 doses ≥240 mg/m². Four patients treated at 200 mg/m² (2), 290 mg/m² (1), and 345 mg/m² (1) also complained of mild mucositis. Two patients complained of mild pain at the infusion site, including one patient in which drug extravasation was documented. One patient with pulmonary metastases developed dyspnea on exertion and a decreased DLCO after 11 courses of CPT-11 at 240 mg/m². These manifestations improved during a treatment delay and did not reoccur during 10 sub-

### Table 4 Gastrointestinal toxicity

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>Courses</th>
<th>Patients</th>
<th>Highest grade/course</th>
<th>Diarrhea/ cramping</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>14</td>
<td>3</td>
<td>1</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>150</td>
<td>9</td>
<td>4</td>
<td>1</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>200</td>
<td>18</td>
<td>5</td>
<td>1</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>240</td>
<td>72</td>
<td>13</td>
<td>1</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>290</td>
<td>22</td>
<td>10</td>
<td>1</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>345</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>0 1 2 3 4</td>
</tr>
</tbody>
</table>

* Includes one patient who developed grade 3 and grade 4 toxicities without premedications.

* Includes two patients who developed grade 3 toxicity during 2 courses without premedications.

### Table 5 Hematological toxicity

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>Courses</th>
<th>Mean ANC nadir (range)</th>
<th>Neutrophils</th>
<th>Mean platelet nadir (range)</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>14</td>
<td>1880 (800–6048)</td>
<td>3</td>
<td>3 4 4</td>
<td>308 (164–675)</td>
</tr>
<tr>
<td>Minimally pretreated</td>
<td>13</td>
<td>1559 (800–4697)</td>
<td>2 3 4 4</td>
<td>298 (194–675)</td>
<td>441</td>
</tr>
<tr>
<td>Heavily pretreated</td>
<td>1</td>
<td>6048</td>
<td>1</td>
<td>298 (194–675)</td>
<td>441</td>
</tr>
<tr>
<td>150</td>
<td>9</td>
<td>3769 (700–6048)</td>
<td>8</td>
<td>1 1 1</td>
<td>288 (107–477)</td>
</tr>
<tr>
<td>Minimally pretreated</td>
<td>6</td>
<td>3948 (2184–6048)</td>
<td>6</td>
<td>1 1 1</td>
<td>304 (107–477)</td>
</tr>
<tr>
<td>Heavily pretreated</td>
<td>3</td>
<td>3390 (700–5120)</td>
<td>2 1 1</td>
<td>255 (176–303)</td>
<td>3</td>
</tr>
<tr>
<td>200</td>
<td>18</td>
<td>3000 (192–5481)</td>
<td>15 1 1 1</td>
<td>3058 (154–403)</td>
<td>18</td>
</tr>
<tr>
<td>Minimally pretreated</td>
<td>17</td>
<td>3175 (1995–5481)</td>
<td>15 1 1 1</td>
<td>314 (179–403)</td>
<td>18</td>
</tr>
<tr>
<td>Heavily pretreated</td>
<td>1</td>
<td>192</td>
<td>1 1</td>
<td>314 (179–403)</td>
<td>18</td>
</tr>
<tr>
<td>240</td>
<td>72</td>
<td>2058 (93–7040)</td>
<td>32 14 14 8 4</td>
<td>218 (45–483)</td>
<td>62 3 6 1</td>
</tr>
<tr>
<td>Minimally pretreated</td>
<td>30</td>
<td>1464 (166–3927)</td>
<td>8 3 8 8 3</td>
<td>139 (45–300)</td>
<td>20 3 6 1</td>
</tr>
<tr>
<td>Heavily pretreated</td>
<td>42</td>
<td>2467 (93–7040)</td>
<td>24 11 6 1</td>
<td>273 (125–483)</td>
<td>42</td>
</tr>
<tr>
<td>290</td>
<td>22</td>
<td>2106 (177–5112)</td>
<td>10 3 3 3 4</td>
<td>218 (51–333)</td>
<td>19 1 2</td>
</tr>
<tr>
<td>Minimally pretreated</td>
<td>12</td>
<td>2701 (177–5112)</td>
<td>8 1 3</td>
<td>175 (51–274)</td>
<td>10 2</td>
</tr>
<tr>
<td>Heavily pretreated</td>
<td>10</td>
<td>1380 (208–1914)</td>
<td>1 2 3 2 1</td>
<td>260 (85–491)</td>
<td>9 1</td>
</tr>
<tr>
<td>345</td>
<td>8</td>
<td>3492 (420–6468)</td>
<td>6</td>
<td>2 2 2 2</td>
<td>240 (61–344)</td>
</tr>
</tbody>
</table>
sequent courses. Other toxicities included dose-related malaise and taste perversions. Hemorrhagic cystitis was not observed.

All patients evaluated for study eligibility had negative CPT-11 prick tests and hypersensitivity phenomena were not observed.

Responses

Major objective responses were noted in three patients. One PR (18 months) occurred in a 52-year-old male with colorectal cancer metastatic to liver and lungs who was treated with 21 courses of CPT-11 at 240 mg/m². His disease progressed through prior treatment with 5-fluorouracil, leucovorin, and cisplatin. Computerized tomographic scanning revealed reductions in his liver metastases by at least 95% and disappearance of his lung metastases; carcinoembryonic antigen values decreased from a pretreatment level of 121 units to 5 units.

A 50% reduction in tumor dimension (240 mg/m²) occurred in a 52-year-old male with colorectal cancer metastatic to liver and lungs who was treated with 21 courses of CPT-11 at 200 mg/m²; however, a second confirmatory scan was not obtained. MRs (4, 11, and 11 months) were also documented in three other patients with colorectal carcinoma who had received prior treatment with 5-fluorouracil and leucovorin. A 50% reduction in tumor dimensions (4 months) also occurred in a 48-year-old male with metastatic renal cell carcinoma to lung who received five courses of CPT-11 at 290 mg/m²; however, a second confirmatory scan was not obtained. MRs (4, 11, and 11 months) were also documented in three other patients with colorectal carcinoma, including one patient who had a reduction in his carcinoembryonic antigen from a pretreatment level of 277 units to 116 units and received 11 total courses of CPT-11 at doses ranging from 240 to 345 mg/m² and a second individual who was treated with 5 total courses of CPT-11 at 200 mg/m². The third MR was characterized by reductions in hepatic and pulmonary metastases in a patient who was treated with 12 total courses of CPT-11 at 240 mg/m². In addition, a PR (5 months) was noted in a 40-year-old female with cervical cancer that was metastatic to lymph nodes and received five courses of CPT-11 at 290 mg/m². Her disease was previously demonstrated to be refractory to ifosfamide, mitoxantrone, and cisplatin.

Pharmacology

Pharmacokinetics. Thirty-one of the 32 patients had plasma sampling performed during the first dose of CPT-11. Pharmacokinetic parameters pertaining to the plasma disposition of total CPT-11 and SN-38 were derived for 31 and 25 patients, respectively, while pharmacological parameters relating specifically to the plasma disposition of the lactone and hydroxy acid forms of CPT-11 and SN-38 were derived for 22 and 29 patients, respectively. Four representative plasma disappearance curves reflecting the behavior of both total CPT-11 and SN-38 and their respective lactones are displayed in Fig. 2. The plasma clearance data of total CPT-11 were fit adequately by a biexponential model of drug elimination with harmonic mean \( \alpha \) and \( \beta \) half-lives of 4.9 min and 3.9 h (range, 0.75–12.2 h), respectively. Noncompartmental pharmacokinetic parameters for CPT-11 and SN-38 are listed in Tables 6 and 7, respectively. Scatterplots of AUCs for both total CPT-11 and CPT-11 lactone as a function of dose are displayed in Fig. 3, A and B. For total CPT-11, there was significant interindividual variability in AUC values at all dose levels but the relationship appears linear \( (r = 0.63, P = 0.0002) \). The mean clearance rate was lower at 345 mg/m² but this was not statistically significant. In addition, \( t_{1/2} \) elim values and \( V_{ss} \) values for CPT-11 did not change with dose, indicating linear pharmacokinetic behavior for the produrg over the dose range studied. Mean values ± SE for pertinent parameters for total CPT-11 were: clearance rate, 352 ± 34 ml/min/m²; harmonic mean \( t_{1/2} \) elim, 5.2 h; \( V_{ss} \), 88 ± 27 liters/m²; and \( VD_{ss} \), 148 ± 20 liters/m². The mean percentage of the administered dose excreted in the urine over 48 h was 37.4 ± 4.3% (range, 15.4–94%).

The hydrolysis of the CPT-11 lactone to the hydroxy acid was much less complete compared with the hydrolysis reported for the other water-soluble CPT analogue, topotecan (21, 37). Maximum plasma concentration \( (C_{max}) \) values for the lactone were observed at the end of infusion. Typically, 33–66% of CPT-11 remained unhydrolyzed from the end of infusion to 24 h postinfusion, and the AUC for the lactone comprised 44 ± 4% (range, 21–83%) of the total AUC for CPT-11. Large interindividual differences in \( C_{max} \) values were observed for both total CPT-11 and CPT-11 lactone at each dose level; however, the relationship between \( C_{max} \) for total CPT-11 and dose was linear \( (r = 0.52, P = 0.0026) \).

There was also significant overlap in the magnitude of individual \( C_{max} \) and AUC values for both total SN-38 and SN-38 lactone at all
Table 6 Pharmacokinetic parameters: CPT-11

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>No. of patients</th>
<th>Cmax (μmol/liter)</th>
<th>AUC (μmol/liter-min)</th>
<th>Clearance (ml/min/m²)</th>
<th>Harmonic mean T½ elim (h)</th>
<th>CPT-11 (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lactone</td>
<td>Total</td>
<td>Lactone</td>
<td>Total</td>
<td>Lactone</td>
<td>Total</td>
</tr>
<tr>
<td>100</td>
<td>3</td>
<td>1.8 ± 0.2</td>
<td>416 ± 32</td>
<td>359 ± 26</td>
<td>3.9</td>
<td>104 ± 13</td>
</tr>
<tr>
<td>150</td>
<td>3</td>
<td>2.1 ± 0.1</td>
<td>673 ± 103</td>
<td>347 ± 58</td>
<td>5.8</td>
<td>132 ± 20</td>
</tr>
<tr>
<td>200</td>
<td>3</td>
<td>2.3 ± 0.5</td>
<td>935 ± 526</td>
<td>462 ± 260</td>
<td>3.9</td>
<td>151 ± 58</td>
</tr>
<tr>
<td>240</td>
<td>11</td>
<td>2.1 ± 0.3</td>
<td>605 ± 140</td>
<td>932 ± 167</td>
<td>6.4</td>
<td>123 ± 16</td>
</tr>
<tr>
<td>290</td>
<td>8</td>
<td>3.0 ± 0.4</td>
<td>689 ± 115</td>
<td>752 ± 117</td>
<td>4.3</td>
<td>209 ± 62</td>
</tr>
<tr>
<td>345</td>
<td>3</td>
<td>4.5 ± 1.2</td>
<td>683 ± 310</td>
<td>1116 ± 445</td>
<td>3.9</td>
<td>141 ± 79</td>
</tr>
</tbody>
</table>

Mean ± SE

44 ± 4  891 ± 20  352 ± 34  5.0  5.2  148 ± 20  9.1 ± 1.0  37 ± 4

Mean parameters ± SE at each dose level.

Table 7 Pharmacokinetic parameters: SN-38

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>No. of patients</th>
<th>Cmax (μmol/liter)</th>
<th>Tmax (h)</th>
<th>AUC (μmol/liter-min)</th>
<th>SN-38 (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lactone</td>
<td>Total</td>
<td></td>
<td>Lactone</td>
<td>Total</td>
</tr>
<tr>
<td>100</td>
<td>3</td>
<td>52 ± 5</td>
<td>75 ± 14</td>
<td>9.4 ± 0.4</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>150</td>
<td>3</td>
<td>21 ± 5</td>
<td>47 ± 19</td>
<td>10 ± 4</td>
<td>35 ± 16</td>
</tr>
<tr>
<td>200</td>
<td>3</td>
<td>32 ± 6</td>
<td>56 ± 19</td>
<td>18 ± 3</td>
<td>37 ± 4</td>
</tr>
<tr>
<td>240</td>
<td>11</td>
<td>47 ± 6</td>
<td>80 ± 9</td>
<td>21 ± 4</td>
<td>40 ± 7</td>
</tr>
<tr>
<td>290</td>
<td>8</td>
<td>54 ± 10</td>
<td>119 ± 34</td>
<td>27 ± 10</td>
<td>59 ± 17</td>
</tr>
<tr>
<td>345</td>
<td>3</td>
<td>89 ± 51</td>
<td>191 ± 94</td>
<td>56 ± 26</td>
<td>97 ± 40</td>
</tr>
</tbody>
</table>

Mean ± SE

2.2 ± 0.1  51 ± 3  5.9  10.0 ± 1.0

Mean parameters ± SE at each dose level.

dose levels as displayed in Fig. 3, C and D. Plasma concentrations of SN-38 were maximal at 2.2 ± 0.1 h (range, 1.5–3.75 h) postinfusion. Similar to CPT-11, plasma concentrations of the SN-38 lactone were approximately 33–66% of total SN-38 concentrations from Tmax to 24 h postinfusion, and the AUC for the lactone comprised 51 ± 4% (range, 7–75%) of the total AUC for SN-38. Mean Cmax values for both total SN-38 and the SN-38 lactone at each dose level were 25–47-fold lower than comparable values for CPT-11. Similarly, mean AUC values were 12–34-fold lower for both total SN-38 and the SN-38 lactone compared with respective values for CPT-11. Although
the relationship between CPT-11 dose and AUC for the SN-38 lactone appeared linear (Fig. 3C), the slopes of these relationships were lower for the SN-38 lactone compared with that for total CPT-11; mean AUC values for total CPT-11 increased 5-fold compared with 3-fold for total SN-38 within the narrow dosing range of 100-345 mg/m². MRTs for both SN-38 and CPT-11 were relatively long; 10.0 ± 1.0 h and 9.1 ± 1.0 h, respectively.

**Pharmacodynamics.** Relationships between gastrointestinal and hematological toxicities and pharmacokinetic parameters for both CPT-11 and SN-38 were assessed. Neither the symptom complex consisting of diarrhea and abdominal cramps nor the symptom complex of nausea, vomiting, and anorexia could be related to Cmax or AUC values for total or lactone forms of either CPT-11 or SN-38. With respect to myelosuppression, the relationship between the mean percentage change in ANCs and AUC for total SN-38 was fit to a sigmoidal Emax model which roughly described the relationship. Fig. 4A is a scatterplot depicting this relationship using data from first courses. With this model, the AUC predicted to yield a 50% decrease in ANC (AUC50) was 51 μmol/min/liter (95% confidence interval, 20-82 μmol/min/liter) and k was 0.7 (95% confidence interval, 0.12-1.28). Examination of the scatterplots revealed no relationship between hematological effects and either Cmax or AUC values for total CPT-11 and CPT-11 lactone. A better relationship between hematological effects and AUC could not be developed by using a linear sum of the AUC for each species weighted by their relative potencies.

**DISCUSSION**

CPT-11 may be one of the most important antineoplastic agents developed over the last several years, with significant antineoplastic activity documented in a broad range of refractory tumor types including advanced small and non-small cell lung, colorectal, cervical, and ovarian carcinomas, as well as refractory lymphomas and leukemias (reviewed in Refs. 1 and 24–30). Thus far, there has been no clear evidence for a dose-response relationship. In addition, an optimal dosing range, optimal pharmacological end points to guide dosing, and optimal administration schedules have not yet been defined. Activity has been noted using a broad range of doses and administration schedules (26–30). However, the principal toxicities of CPT-11 have been reported to be related to the schedule of administration, with diarrhea predominating on intermittent and continuous dosing schedules (38, 39) and neutropenia predominating on a single dosing schedule (24). In contrast, no single toxicity limited the escalation of CPT-11 doses in the phase I study described in this report in which the agent was administered as a 90 min infusion every 3 weeks. Instead, a constellation of severe hematological and nonhematological toxicities, including prolonged neutropenia, abdominal cramps, diarrhea, nausea, vomiting, and/or anorexia, were observed consistently above CPT-11 doses of 240 mg/m², and subsequently established 240 mg/m² as the MTD and recommended phase II dose for CPT-11 on a single 90-min infusion every-3-week dosing schedule. Although this dose is similar to maximum tolerated and recommended phase II doses (240 and 200 mg/m², respectively) established in a previous phase I study of CPT-11 in Japan (31), investigators at the Institute Gustave Roussy have escalated CPT-11 doses above 500 mg/m² with a 30-min infusion every-3-week schedule (40).

The lack of consistent dose-limiting hematological toxicity for CPT-11 in this dose range has also been recently corroborated in the phase I study at the Institute Gustave Roussy (40). In an attempt to ameliorate diarrhea, patients were treated aggressively with high doses of loperamide, 2 mg every 2 h (6 times daily), after their first episode of diarrhea. Although this supportive regimen was not used in patients treated in the study described in this report, other toxicities in addition to diarrhea, including nausea, vomiting, and anorexia, abdominal cramps, and neutropenia, precluded the repetitive administration of CPT-11 doses above 240 mg/m² despite aggressive attempts to prevent and minimize these gastrointestinal effects.

Although efforts to prevent and ameliorate acute toxicities such as nausea, vomiting, cramps, and flushing with serotonin antagonists, anticholinergic agents, and antihistamines and to reduce subacute and chronic diarrhea with antidiarrheal agents have been successful in permitting the escalation of CPT-11 doses on a single dosing schedule, clinical and pharmacological data suggest that the pursuit of maximal dose intensity at the risk of substantial toxicity may not be necessary. First, antitumor activity has been noted consistently in Japan and the United States in phase I and II trials with schedules and doses that result in an absolute dose intensity similar to that achieved at the MTD in this phase I trial (80 mg/m²/week) (24, 39). These schedules and doses include: (a) CPT-11 150 mg/m² every 2 weeks (dose intensity, 75 mg/m²/week) (27, 29, 30); and (b) CPT-11 100 to 125 mg/m²/week or weekly for 6 of 8 weeks (dose intensity, 85 to 100 mg/m²/week) which is currently being utilized in phase II evaluations in the United States (24–26, 29, 30, 40). Second, although mean AUCs for the various CPT-11 and SN-38 chemical species increase with dose, the relationship is weakest for the SN-38 lactone (r = 0.46 and 0.45 for total SN-38 and SN-38 lactone, respectively, compared with 0.63 for total CPT-11) as shown in Fig. 2. This indicates that the kinetics of conversion of CPT-11 to SN-38 may be nonlinear in this dose range, possibly due to saturable plasma carboxylesterase-converting enzymes (41). In addition, interindividual variability in pharmacological parameters has been substantial (Fig. 2), suggesting pharmacogenetic variations in drug conversion. Therefore, aggressive efforts to escalate doses of CPT-11 further may not result in proportional increases in exposure to the most active metabolite, the SN-38 lactone. Third, higher doses of CPT-11 may result in disproportionate increases in Cmax values and AUCs for other drug species, such as the CPT-11 lactone and the hydroxy acids of both CPT-11 and SN-38, which may be responsible for toxicity. Fourthly, Cmax values for SN-38 at the MTD approach concentrations that are cytotoxic in vitro (11, 23, 37, 42). The relatively long T1/2elim values and MRTs for SN-38 also indicate that cytotoxic concentrations may be sustained. Previous
studies have not measured both lactone and hydroxy acid species of CPT-11 and SN-38. The results described in this report indicate that larger than expected fractions of both CPT-11 and SN-38 are present as the lactone form for prolonged periods. This may be due to either decreased elimination of the hydroxy acid forms relative to other CPT analogues or decreased susceptibility for the lactone rings of CPT-11 and SN-38 to undergo pH-dependent hydrolysis compared with other CPT analogues (21, 37). Finally, the large interindividual variability in the pharmacological behavior of CPT-11, possibly due to differences in the activity of plasma carboxylesterase that convert CPT-11 to SN-38 (41), may be accentuated at higher doses and may increase the likelihood for profound toxicity in susceptible individuals.

The acute gastrointestinal effects of CPT-11, such as severe nausea, vomiting, diarrhea, and abdominal cramps, which were occasionally associated with flushing, warmth, and diaphoresis; the prompt resolution of these symptoms immediately after treatment with diphenhydramine; and the successful use of the premedications ondansetron and diphenhydramine to permit further dose escalations and treatment of patients who previously experienced severe acute toxicities in the absence of premedications, is intriguing. Gandia et al. have also noted similar toxicities during and immediately following 30 min infusions of CPT-11 at doses ranging from 100 to 500 mg/m² every 3 weeks (40). These investigators also reported that a substantial proportion of patients developed acute abdominal cramps followed immediately by diarrhea in the periinfusion period. These symptoms were usually associated with diaphoresis, salivation, lacrimation, and visual disturbances. The temporal nature of these acute effects relative to drug administration suggests that the mechanism is not related to a direct cytotoxic effect on gastrointestinal mucosa. It seems more likely that these toxicities are mediated by vasoactive substances such as histamine, serotonin, and cholinergic agonists or substances resembling these chemical mediators. Since similar toxicities were not observed in studies of CPT or other CPT analogues, Gandia et al. (40) proposed that CPT-11, itself, may have inherent cholinergic properties. These investigators also proposed that the structure of CPT-11, which possesses a [4-(1-piperidino-1-piperidino)] carbonyloxy group at the R’ position (carbon 10), resembles dimethylphenoxy piparizinum, a highly selective and potent stimulator of nicotinic receptors in autonomic ganglion (43). In addition, Gandia et al. demonstrated that the inhibition of cholinesterases by CPT-11 was not a likely mechanism for these effects since cholinesterase activity in serum and RBC was not abnormal in patients developing severe, acute toxicities, and there were no significant differences in enzyme activity between baseline and posttreatment states. Although relationships between diarrhea and pharmacological parameters could not be discerned in the study described in this report, other investigators have demonstrated positive correlations between diarrhea and AUCs for total SN-38 (44) and total CPT-11 (28). Nonetheless, it is clear that the mechanism for the acute toxic effects of CPT-11, as well as the optimal means of prophylaxis and treatment, require additional prospective evaluations during subsequent clinical investigations.

Although weekly administration schedules have received the most attention to date, grade 4 diarrhea has been reported in up to 21% of patients treated with CPT-11 on weekly schedules in phase II trials (25–27). In addition, the development of combination chemotherapy regimens with CPT-11 and 5-fluorouracil, which is a next logical step in the further development of CPT-11 for colorectal cancer, may be associated with substantial additive gastrointestinal toxicity, especially if a weekly CPT-11 schedule is selected for development (45). Therefore, CPT-11 should also be evaluated on alternative schedules, and every attempt should be made to determine schedules with optimal risk-benefit indices from which combination regimens could be developed.

This study demonstrated that CPT-11 is well tolerated at the MTD, 240 mg/m², when administered with premedications as a 90-min infusion every 3 weeks. At this dose, repetitive treatment without delays was feasible in all patients. Diarrhea was a dose-limiting (grade 4) event in only 3 of 72 courses at the MTD and all 3 courses involved a single patient whose dose had been previously reduced to 240 mg/m² due to severe diarrhea at higher doses. In fact, dose-limiting diarrhea occurred in 0 of 65 courses in new patients at the MTD. In addition, 4 patients received more than 10 courses at the MTD. From a pharmacological perspective, the single dosing schedule has several other advantages. Although intermittent dosing schedules have been demonstrated to be superior to single dosing schedules for the topoisomerase I inhibitors CPT and topotecan in some preclinical tumor models (reviewed in Ref. 1), biologically relevant concentrations of the active metabolite of CPT-11, SN-38, can be maintained for relatively long durations after a single dose, possibly alleviating the need for intermittent or continuous administration schedules. In addition, the occurrence of objective responses in previously treated patients with colorectal, cervical, and renal cancers in this study indicates that the single dosing schedule should be evaluated in the phase II setting and that these tumor types should be among those evaluated in subsequent disease-directed studies of CPT-11.

ACKNOWLEDGMENTS

The authors wish to thank Mary Duer for assistance with data collection; Lisa Hurowitz and Shirley George for technical assistance with pharmacological assays; and the referring medical staff and medical and nursing staffs of The Johns Hopkins Oncology Center for the care of the patients in this study.

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