A Multicenter, Phase II Trial of Weekly Irinotecan (CPT-11) in Patients with Previously Treated Colorectal Carcinoma

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BACKGROUND. This multicenter, Phase II trial was performed to evaluate the antitumor activity and toxicity of irinotecan (CPT-11) in patients with metastatic colorectal carcinoma that had recurred or progressed after 5-fluorouracil (5-FU)-based chemotherapy.

METHODS. CPT-11 was given as a 90-minute intravenous infusion in repeated 6-week (42-day) courses comprising weekly treatment for 4 consecutive weeks followed by a 2-week rest. Tumor measurements were obtained after every second course of therapy. Toxicity was assessed weekly using the National Cancer Institute Common Toxicity Criteria.

RESULTS. A total of 166 patients were entered into the trial. The first 64 patients received a starting dose of 125 mg/m^2. An additional 102 patients were enrolled at a starting dose of 100 mg/m^2 to determine whether a reduction in the starting dose would result in lower toxicity without sacrificing efficacy. Objective responses to CPT-11 were observed in 18 patients (1 complete response and 17 partial responses) (response rate [RR] = 10.8%; 95% confidence interval [CI], 6.1-15.6%). An additional 67 patients (40.4%) had stable disease as their best response. At the 125 mg/m^2 starting dose, the RR was 14.1% (9 of 64 patients; 95% CI, 5.5-22.6%). Among patients given a starting dose of 100 mg/m^2, the RR was 8.8% (9 of 102 patients; 95% CI, 3.3-14.3%). The overall median survival was 9.9 months (range, 0.3-36.8 months). The most frequently observed Grade 3/4 toxicities were gastrointestinal events (i.e., diarrhea [27.1%], nausea [15.1%], emesis [9.6%], abdominal cramping [22.2%], and neutropenia [19.9%]). There were no significant differences in the frequencies of Grade 3/4 toxicities between the 125 mg/m^2 and 100 mg/m^2 starting dose levels except for Grade 3/4 emesis (21.9% vs. 2%; $P < 0.001$). Patients age $\geq$ 65 years were twice as likely (38.6% vs. 18.8%; $P < 0.008$) to develop Grade 3/4 diarrhea compared with younger patients when all courses of therapy were evaluated. However, older age did not significantly predict for a higher incidence of first-course diarrhea (25.0% vs. 14.7%; $P = 0.106$).

CONCLUSIONS. CPT-11 can induce tumor regression in patients with metastatic colorectal carcinoma that has progressed during or shortly after 5-FU-based chemotherapy. Gastrointestinal events and neutropenia were the most common serious toxicities. Given the trend toward a higher response rate without substantially greater toxicity, 125 mg/m^2 has been selected as the preferred starting dose for further studies. Careful attention to appropriate CPT-11 dose modification and early intervention with loperamide may be especially important in elderly patients.
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KEYWORDS: CPT-11, irinotecan, topoisomerase I, colorectal carcinoma, clinical trial.

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Colorectal carcinoma is the fourth most common cancer and the second leading cause of cancer-related mortality in the U. S.[1] Approximately 1 in 16 people will develop colorectal carcinoma (lifetime risk: 6.15%), and 1 in 38 people will die of this disease (lifetime risk: 2.65%).[2] Of all patients diagnosed, nearly 50% present with or develop metastatic disease.[1]

The most commonly used first-line systemic treatment for metastatic colorectal carcinoma has been chemotherapy with 5-fluorouracil (5-FU), most often given in conjunction with leucovorin.[3,4] Until recently, patients have had no standard second-line treatment options after disease progression on a 5-FU-containing regimen.

Irinotecan (CPT-11) (7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin) (Camptosar™; Pharmacia & Upjohn, Kalamazoo, MI) is a new chemotherapeutic agent that is converted rapidly in vivo to an active metabolite, SN-38, that appears to account for the antineoplastic activity of the drug.[5-8] The primary target of SN-38 is topoisomerase I.[9] The function of topoisomerase I is to introduce transient, single stranded breaks in DNA that maintain its proper three-dimensional conformation by removing supercoils generated during replication and transcription.[9] SN-38 binds to and stabilizes the topoisomerase I-DNA complex and prevents the religation of DNA after it has been cleaved by topoisomerase I. Subsequent collision between this stable complex and an advancing replication fork results in lethal double stranded DNA breaks and cellular death through apoptosis.

Clinical trials with CPT-11 have identified significant antitumor activity against a wide variety of solid tumors.[10,11] Objective responses in patients with metastatic colorectal carcinoma that had progressed despite 5-FU-based chemotherapy have been reported in both Phase I and Phase II clinical trials.[12-17] The current trial was designed to expand on these results by evaluating the efficacy and safety of CPT-11 in a multicenter setting. The specific goals of the study were to estimate the antitumor activity of CPT-11 in patients with previously treated colorectal carcinoma and to assess the frequency and severity of toxicities of weekly CPT-11 when administered with clear guidelines for the prevention and treatment of gastrointestinal side effects. The trial also was designed to evaluate the pharmacokinetics of CPT-11 and SN-38 in a larger population of patients using a limited sampling schedule. Those results have been reported elsewhere.[18]

PATIENTS AND METHODS

Eligibility Criteria

To be eligible for the study, patients were required to have metastatic colorectal carcinoma that had progressed or recurred within 6 months of 1 prior course of therapy with a 5-FU-based regimen (used in either the adjuvant setting or to treat metastatic disease). Additional enrollment criteria included disease measurable in 2 dimensions (> 1 cm $\times$ 1 cm on radiologic examination or > 2 cm $\times$ 2 cm on physical examination); a Southwest Oncology Group performance status (PS) of 0, 1, or 2; and adequate pretreatment bone marrow, renal, and hepatic function (granulocyte count $> 1500/mm^3$, hemoglobin > 9 g/dL, platelet count $> 100{,}000/mm^3$, serum creatinine < 2 mg/dL, serum bilirubin < 2.0 mg/dL [regardless of whether the liver was involved by tumor], and aspartate aminotransferase < 3 times the upper limit of normal, or < 5 times the upper limit of normal if the liver was involved with tumor). Patients with prior pelvic radiotherapy, central nervous system metastases, or serious concomitant medical conditions (e.g., infection, heart disease, or prior malignancy), those who were pregnant or lactating, or those taking warfarin were excluded from treatment. Both males and females of reproductive potential were requested to use effective contraception. All patients were informed of the investigational nature of this study and written informed consent was provided in accordance with institutional and federal guidelines.

Treatment Protocol and Dose Modifications

CPT-11 in 500 mL of 5% dextrose injection was administered as a 90-minute intravenous infusion in repeated 6-week courses comprising weekly treatment for 4 consecutive weeks followed by a 2-week rest. Therapy was to be continued until disease progression, unacceptable toxicity, or withdrawal of patient consent.

The original CPT-11 starting dose was 125 mg/m^2; 64 patients began treatment at this dose level. A subsequent 102 patients were enrolled to evaluate the efficacy and toxicity of CPT-11 at a 100 mg/m^2 starting dose. After the first CPT-11 treatment, doses were adjusted upward or downward based on individual patient tolerance. The range of allowable doses was 150, 125, 100, 75, and 60 mg/m^2. There were two settings in which dose modifications were made during this study. During a course of treatment, doses were adjusted based on the worst toxicity that had occurred since the previous week of treatment and/or toxicity that was present at the time of scheduled

TABLE 1
Dose Modification during a Course of Treatment

Toxicity grade	Hematologic tox	Nonhema tox
0	None	None
1	None	None
2	↓1 dose level	↓1 dose level
3	Omit dose[a]	Omit dose[a,b]
4	Omit dose[b]	Omit dose[b]
Neutropenic fever	Omit dose[b]	

tox: toxicity; Nonhema: nonhematologic.

[a] Dose should be omitted if there is National Cancer Institute Common Toxicity Criteria Grade 3 hematologic toxicity or Grade 3 diarrhea on the day of scheduled treatment. On resolution of toxicity to ≤ Grade 2, treatment may be restarted at a one-dose level reduction from the previous weeks' dose and maintained at that level for the remainder of that course.

[b] Dose should be omitted in the event of Grade 4 hematologic toxicity, Grade 3/4 nonhematologic toxicity (with the exception of Grade 3 diarrhea), or neutropenic fever. On resolution of toxicity to ≤ Grade 2, treatment may be restarted at a 2-dose level reduction from the previous weeks' dose and maintained at that level for the remainder of that course.

TABLE 2
Dose Modification for the Next Course of Treatment (Based on Worst Toxicity Observed during the Preceding Course)

Toxicity grade	Hematologic tox	Nonhema tox
0	↑1 dose level	↑1 dose level
1	None	None
2	None	↓1 dose level[a]
3	↓1 dose level	↓2 dose levels[b,c]
4	↓2 dose levels[c]	↓2 dose levels[c]
Neutropenic fever	↓2 dose levels[c]	

tox: toxicity; Nonhema: nonhematologic.

All dose adjustments are made in relation to the dose level used at the initiation of the preceding course of treatment.

[a] Patients who experience National Cancer Institute Common Toxicity Criteria Grade 2 diarrhea as their only Grade 2 nonhematologic toxicity should receive the same dose of chemotherapy as was given at the initiation of the preceding course of treatment.

[b] Patients who experience Grade 3 diarrhea as their only Grade 3 nonhematologic toxicity should be dose reduced by one dose level (not two).

[c] A dose of 60 mg/m^2 is the lowest dose level allowed. Patients who experience toxicity and require dose modification to levels <60 mg/m^2 will be removed from treatment due to toxicity.

Week 2, 3, or 4 treatments (Table 1). At the initiation of a new course of treatment, doses were modified based on the worst toxicity that had occurred during the entire previous course of therapy (Table 2). Dose escalations were allowed only at the start of a new course of treatment in patients who had experienced no toxicity during the preceding course. Treatment courses were to be repeated at 42-day intervals. However, if treatment was withheld on Week 4, the next course of therapy could begin 1 week earlier (i.e., on Day 36) if all toxicities were of Grade 0 or 1 by that time.

Supportive Care

Treatment with antidiarrheal agents was specified and was to begin at the earliest sign of diarrhea. The choice of antidiarrheal therapy depended on whether the diarrhea occurred during CPT-11 infusion (early diarrhea) or between CPT-11 treatments (delayed diarrhea). Atropine, 0.5-1.0 mg, could be given intravenously, subcutaneously, or intramuscularly to alleviate the cholinergic syndrome of lacrimation, diaphoresis, flushing, abdominal cramping, or early diarrhea that can manifest during or shortly after CPT-11 infusion.[15,16,19] Delayed diarrhea was to be treated with loperamide, 4 mg orally, at the first change in bowel habits, followed by 2 mg orally every 2 hours during the day, and 4 mg orally every 4 hours at night until the patient was free of diarrhea for at least 12 hours.[20] Dexamethasone, 10 mg intravenously 30 minutes prior to CPT-11, was recommended as antiemetic prophylaxis. Other antiemetic agents were permitted except for prochlorperazine, which was not allowed on the day of infusion due to its possible association with akathisia,[15] but was permitted on other days within the treatment cycle.

Patient Evaluation

Tumor reassessment was to be performed after every other course of treatment (i.e., at 12-week intervals). Standard criteria were used to determine objective complete or partial response, stable disease, or progressive disease; all objective responses were required to be sustained for at least 4 weeks (as documented by confirmatory scans). All complete or partial responses were reviewed for confirmation of response by an independent review panel of radiologists and medical oncologists. Although not used to evaluate tumor response, carcinoembryonic antigen (CEA) levels were to be obtained at the start of each new course of therapy in those patients whose values were elevated at baseline. Complete blood counts, review of systems, and toxicity evaluations were performed weekly. In addition, physical examination and assessment of PS was repeated prior to each course of treatment. PS was evaluated using the Southwest Oncology Group scale. Toxicities were graded according the National Cancer Institute Common Toxicity Criteria. Neutropenic fever was defined as the simultaneous occurrence of Grade 4 neutropenia (absolute neutrophil count < 500 mm^3) and $\geq$ Grade 2 fever (temperature ≥ 38.1 °C)

Statistical Methods

The primary efficacy parameter was a tumor response to treatment, defined as the total percentage of patients who experienced either a complete response or

a partial response to CPT-11 therapy. Secondary efficacy parameters were: duration of response (the period from the first documentation of response to the first documentation of disease progression), time to response (the interval from the first dose of CPT-11 to the first documentation of response), time to tumor progression (the period from the date of initial treatment to the date of first objective documentation of disease progression), and survival (the interval from the initial date of CPT-11 treatment to the date of death). All efficacy analyses were performed using the intent-to-treat population of patients who received at least one dose of CPT-11. Duration of response, time to response, time to disease progression, and survival time were analyzed using Kaplan-Meier methods. Dose intensity (mg/m^2/week) was calculated by dividing the total dose administered during a course of therapy by 6 (the number of weeks in the course). Exploratory subgroup analysis was performed to evaluate the influence of age, gender, baseline PS, number of measured metastatic sites, response to prior 5-FU-based regimen, classification of prior 5-FU therapy (i.e., given as adjuvant therapy or for metastatic disease), CPT-11 starting dose, and baseline bilirubin on efficacy and toxicity. Cox proportional hazards model techniques were employed to measure the effects of baseline variables on time-to-event data. For analysis of these variables as predictors of toxicity, comparisons were performed using Fisher's exact test for parameters with binary outcomes and an extension of Fisher's exact test for parameters with more than two outcomes. To account for multiple exploratory comparisons, the significance level was set at 0.01.

RESULTS

Patient Characteristics

Between April and September of 1994, 167 patients consented to participate in the study. However, one patient died at home of unknown causes prior to receiving CPT-11. Therefore, a total of 166 patients received at least 1 infusion of CPT-11 and were analyzed for CPT-11 efficacy and safety. The first 64 patients enrolled received a starting dose of 125 mg/m^2 and an additional 102 patients were enrolled at a starting dose of 100 mg/m^2 to determine whether a reduction in starting dose would result in lower toxicity without sacrificing efficacy. Baseline patient characteristics are summarized in Table 3. The majority of patients (57.8%) had Dukes Stage D disease at original diagnosis. Fifty percent of the patients were symptomatic at the time of entry onto this study, as reflected by a PS of 1 or 2. Greater than 50% of the patients (56.6%) had $\geq$ 3 measurable metastatic lesions. The most common site of metastases was the liver (74.7%). In 64.5% of patients, disease progression had occurred during or within 3 months after 5-FU-containing first-line treatment for metastatic disease, whereas 27.1% of patients had developed a disease recurrence while receiving or within 6 months of the completion of adjuvant 5-FU-based therapy. Of the 116 patients who previously had received treatment for metastatic disease, only 3 (2.6%) had responded to the prior regimen. Analysis of baseline demographic and disease-related characteristics between starting dose groups

TABLE 3
Baseline Characteristics

Characteristic	125 mg/m^2 (N = 64)	100 mg/m^2 (N = 102)	All (N = 166)
Age median (yrs) (range)	60.5 (42–84)	63.5 (25–84)	62 (25–84)
Gender			
Male	32 (50.0)	50 (49.0)	82 (49.4)
Female	32 (50.0)	52 (51.0)	84 (50.6)
Dukes Stage at original diagnosis (no., %)			
B	4 (6.3)	13 (12.7)	17 (10.2)
C	19 (40.0)	31 (30.4)	50 (30.1)
D	40 (62.5)	56 (54.9)	96 (57.8)
Baseline SWOG performance status (no., %)			
0	38 (59.4)	45 (44.1)	83 (50.0)
1	21 (32.8)	52 (51.0)	73 (44.0)
2	5 (7.8)	5 (4.9)	10 (6.0)
No. of measured metastatic lesions (no., %)			
1	10 (15.6)	21 (20.6)	31 (18.7)
2	15 (23.4)	26 (25.5)	41 (24.7)
≥3	39 (60.9)	55 (53.9)	94 (56.6)
Sites of measured disease (no., %)			
Liver	51 (79.7)	73 (71.6)	124 (74.7)
Lung	19 (29.7)	34 (33.3)	53 (31.9)
Lymph nodes	14 (21.9)	19 (18.6)	33 (19.9)
Soft tissue	12 (18.8)	14 (13.7)	26 (15.7)
Other	8 (12.5)	18 (17.6)	26 (15.7)
Prior therapy (no., %)			
5-FU plus leucovorin	46 (71.9)	72 (70.6)	118 (71.1)
5-FU plus levamisole	12 (18.8)	15 (14.7)	27 (16.3)
5-FU plus others	6 (9.3)	15 (14.7)	21 (12.6)
Reason for prior therapy (no., %)			
Adjuvant Rx	17 (26.6)	30 (29.4)	47 (28.3)
Metastatic Rx	47 (73.4)	69 (67.6)	116 (69.9)
Unclassified	0	3 (2.9)	3 (1.8)
Response to prior 5-FU-based therapy (no., %)[a]			
Complete or partial[b]	2 (4.3)	1 (1.4)	3 (2.6)
Stable or progressive disease	45 (95.7)	66 (95.7)	111 (95.7)
Unknown	0 (0.0)	2 (2.9)	2 (1.7)

SWOG: Southwest Oncology Group; 5-FU: 5-fluorouracil; Rx: therapy.

[a] Includes only 116 patients (47 patients at 125 mg/m^2 and 69 patients at 100 mg/m^2) who received prior 5-fluorouracil for metastatic disease.

[b] Responses to 5-fluorouracil were based on investigator judgment and were not subjected to independent confirmation.

revealed no statistically significant differences. However, there was a trend toward a higher proportion of patients with disease-related symptoms (PS = 1 or 2) among those who started therapy at 100 mg/m^2 than in the group who began treatment at 125 mg/m^2 (55.9% vs. 40.6%,; $P = 0.079$).

Treatment Delivery

A total of 2148 CPT-11 doses were administered in 592 courses of therapy between April 1994 and March 1996. The projected dose intensity was 83.3 mg/m^2/week for the 125 mg/m^2 starting dose and 66.7 mg/m^2/week for the 100 mg/m^2 starting dose. The actual median dose intensity for the entire duration of treatment was 61.0 mg/m^2/week (73% of projected) for those patients beginning treatment with the 125 mg/m^2 dose and 53.9 mg/m^2/week (81% of projected) for patients treated with the 100 mg/m^2 starting dose. Within each of the two starting dose groups there was no significant difference in median dose intensity by age, gender, baseline PS, or other baseline characteristics.

The most common reasons for dose reduction were delayed diarrhea, neutropenia, and leukopenia. Patients whose treatment was initiated with the 125 mg/m^2 dose had a somewhat greater proportion of courses modified for late diarrhea than did patients whose treatment was initiated with the 100 mg/m^2 dose (14.9% [34 of 228] vs. 8.1% [27 of 334]) but had fewer courses reduced for neutropenia (2.2% vs. 4.8%) and leukopenia (1.3% vs. 4.5%). Only 116 (5.1%) of the planned 2264 doses were omitted.

Efficacy

Based on the independent review committee assessment, 18 of the 166 patients had an objective responses to CPT-11 (including 1 complete response and 17 partial responses) for an overall response rate of 10.8% (95% confidence interval [95% CI], 6.1-15.6%) (Table 4). Nine of the 64 patients who received CPT-11 at a starting dose of 125 mg/m^2 responded (1 complete response and 8 partial responses) for a response rate of 14.1% (95% CI, 5.5-22.6%). Among the 102 patients who began CPT-11 therapy at a starting dose of 100 mg/m^2, 9 patients had partial responses, resulting in a response rate of 8.8% (95% CI, 3.3-14.3%). This difference in response rate by starting dose was not statistically significant ($P = 0.314$). The majority (10 of 18) of patients who responded to CPT-11 therapy did so by their initial reassessment, and identical median times (2.8 months [range, 1.3-11.0 months]) to response were observed for patients at each starting dose (Table 4). The median duration of response was 6.4 months (range, 2.8-12.8 months) and did not differ appreciably between responders at either CPT-11 starting dose level (5.6 months at 125 mg/m^2 vs. 6.4 months at 100 mg/m^2).

TABLE 4
Efficacy Parameters

Endpoint	125 mg/m^2 (N = 64)	100 mg/m^2 (N = 102)	All (N = 166)
Overall response (%)	14.1%	8.8%	10.8%
(95% CI)	5.5–22.6%	3.3–14.3%	6.1–15.6%
Complete response (no., %)	1 (1.6%)	0 (0.0%)	1 (0.6%)
Partial response (no., %)	8 (12.5%)	9 (8.8%)	17 (10.2%)
Stable disease (no., %)	28 (43.8%)	39 (38.2%)	67 (40.4%)
Progressive disease or no F/U scan (no., %)	27 (42.2%)	54 (52.9%)	81 (48.8%)
Median time to response (mos) (range)	2.8 (2.5–9.4)	2.8 (1.3–11.0)	2.8 (1.3–11.0)
Median duration of response (mos) (range)	5.6 (2.8–12.8)	6.4 (3.0–10.8)	6.4 (2.8–12.8)
Median TTP (mos) (range)	5.1 (0.4–16.6)	3.3 (0.1–12.4)	3.9 (0.1–16.6)
Median survival (mos) (range)	10.6 (0.3–36.8)	9.3 (0.6–32.8)	9.9 (0.3–36.8)

95% CI: 95% confidence interval; F/U: follow-up; TTP: time to progression (of disease).

Of the 15 CPT-11 responders who had received prior 5-FU-based treatment for metastatic disease, none had experienced an objective response to the previous therapy, and 80% (12 of 15) had documented evidence of disease progression during or within 3 months of completing prior 5-FU. Among those patients who had received prior 5-FU as therapy for metastatic disease, the overall response rate to CPT-11 was 12.9% (15 of 116). The CPT-11 response rate among patients who had received previous 5-FU as adjuvant therapy was 6.4% (3 of 47). When analyzing baseline patient characteristics, none proved to be significant predictors of response.

As has been observed previously with CPT-11 therapy in colorectal carcinoma patients,[15,16,21] a substantial proportion of patients achieved stable disease as their best response. Overall, 67 of 166 patients (40.4%; 95% CI, 32.9-47.8%) were categorized as having stable disease, including 28 of 64 (43.8%; 95% CI, 31.6-55.9%) of the patients in the 125 mg/m^2 starting dose group and 39 of 102 (38.2%; 95% CI, 28.8-47.7%) of the patients in the group that had therapy initiated at 100 mg/m^2. Of these 67 patients with stable disease, 16 (23.9%) had minor responses ($>$ 25% but $<$ 50% decrease in tumor area).

Evaluation of serial serum CEA levels recently has been acknowledged by an American Society of Clinical Oncology expert panel to be an appropriate means for following the course of disease in patients with colorectal carcinoma.[22] Although not formally employed

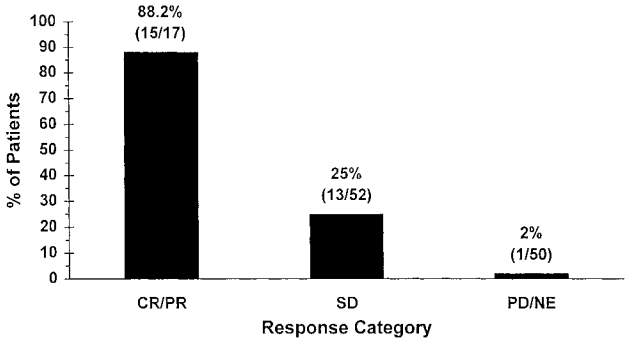

FIGURE 1. Percentage of patients with > 50% reduction in carcinoembryonic antigen (CEA) from baseline (of 119 patients with CEA > 5 ng/mL at baseline). CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: no effect.

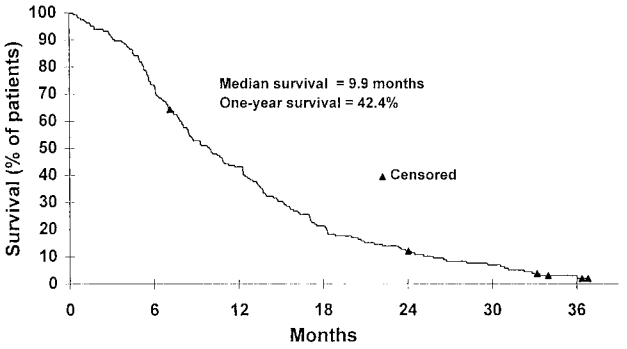

FIGURE 2. Overall survival (N = 166).

as a measure of objective response in this study, serial determinations of CEA were obtained from 140 of the 166 patients (84.3%) with 119 having abnormal baseline CEA levels (> 5 ng/mL). Of the 18 responding patients, 17 were shown to have abnormal baseline CEA determinations and 15 of these 17 patients (88.2%) had decreases of > 50% in CEA for at least 2 consecutive courses of therapy (Fig. 1). Of the 67 patients characterized as having stable disease, 52 had an abnormal CEA at baseline and 13 of these patients (25.0%) had a decrease in CEA of > 50%. Of the 81 patients characterized as having progressive disease, 50 had an abnormal CEA at baseline, and only 1 of these 50 patients (2.0%) had a decrease in CEA of > 50%. These data suggest that there is an association between a decrease in CEA of > 50% and the achievement of tumor response or stabilization during treatment with CPT-11.[23-27]

The median time to tumor progression for all 166 patients was 3.9 months (range, 0.1-16.6 months). (Table 4) No baseline variable clearly was predictive of the duration of time to tumor progression. The median survival in all patients was 9.9 months (range, 0.3-36.8 months) with 4 of the 166 patients still alive as of May 1997. Assessment of patient characteristics predicting for improved survival showed that asymptomatic patients (PS of 0) had a longer median survival than those patients with disease-related symptoms at baseline (PS of 1 or 2); this difference (13.0 months vs. 7.7 months) was statistically significant ($P = 0.0002$). Starting dose and other baseline variables did not influence survival. The Kaplan-Meier estimate of 1-year survival was 42.4%. The survival curve for patients participating in this study is depicted in Figure 2.

TABLE 5
Worst Grade of Nonhematologic Toxicities during Any Course of Treatment (% of Patients Affected)

Toxicity[a]	125 mg/m^2 (N = 64)	100 mg/m^2 (N = 102)	All (N = 166)
Late diarrhea			
Any	93.7	87.2	89.7
Grade 3	25.0	17.6	20.5
Grade 4	7.8	5.9	6.6
Emesis			
Any	70.3	53.9	60.2
Grade 3	18.8	2.0	8.4
Grade 4	3.1	0.0	1.2
Asthenia			
Any	84.4	82.4	83.1
Grade 3	15.6	16.7	16.3
Alopecia			
Any	56.2	55.8	56.0
Grade 2	28.1	22.6	24.7

[a] Toxicity graded according to National Cancer Institute Common Toxicity Criteria.

Safety

The most common clinically significant toxicities associated with CPT-11 administration were gastrointestinal events (diarrhea, nausea and emesis) (Table 5) and myelosuppression (primarily neutropenia) (Table 6). Among the gastrointestinal events, the most prominent toxicity was delayed diarrhea. Approximately 89.8% of patients experienced some grade of late diarrhea at least once during their treatment. Grade 3 delayed diarrhea occurred in 20.5% (34 of 166) of the patients and in 7.9% (47 of 592) of the courses; Grade 4 delayed diarrhea was observed in 6.6% (11 of 166) of the patients and in 1.9% (11 of 592) of the courses. The frequency of Grade 3/4 delayed diarrhea was somewhat higher in patients who began CPT-11 therapy at the 125 mg/m^2 dose level compared with those starting treatment at the 100 mg/m^2 dose level (32.8% vs. 23.5% of the patients), but this result did not reach statistical significance ($P = 0.212$). The median time to

TABLE 6
Worst Grade of Hematologic Toxicities during Any Course of Treatment (% of Patients Affected)

Toxicity[a]	125 mg/m^2 (N = 102)	100 mg/m^2 (N = 64)	All (N = 166)
Neutropenia			
Any	42.2	44.1	43.4
Grade 3	10.9	11.8	11.4
Grade 4	7.8	8.8	8.4
Anemia			
Any	34.4	48.0	42.8
Grade 3	4.7	4.9	4.8
Grade 4	0.0	0.0	0.0
Thrombocytopenia			
Any	4.7	3.4	4.2
Grade 3	1.6	0.0	0.6
Grade 4	0.0	0.0	0.0

[a] Toxicity graded according to National Cancer Institute Common Toxicity Criteria.

onset of delayed diarrhea was 8 days, and the median duration of an episode of delayed diarrhea was 2 days. Grade 3/4 delayed diarrhea was more common in patients age $\geq$ 65 years (27 of 70; 38.6%) than in younger patients (18 of 96; 18.8%) ($P = 0.008$) when all cycles of therapy were analyzed. However, older age did not significantly predict for a higher incidence of first-course diarrhea (24.3% vs. 14.6%; $P = 0.157$) and there was substantial variability in the severity of diarrhea as related to age. A majority of patients (141 of 166, 84.9%) received antidiarrheal therapy at some point during treatment. However, late diarrhea was a reason for discontinuation of therapy in only 3 patients (1.8%).

From past experience, it is known that a transient early cholinergic syndrome of diaphoresis, lacrimation, abdominal cramping, vasodilation, hypotension, bradycardia, rhinitis, increased salivation, and occasional diarrhea can occur during or shortly after CPT-11 administration and generally resolve rapidly.[28] In an analysis of such events that began on the day of dosing and ended by the following day, the overall incidence at any grade of event was 22.9% with 4.2% of toxicities scoring as Grade 3/4. The incidence of Grade 3 diarrhea was 1.2%; there were no cases of Grade 4 early diarrhea. Only 11.4% of patients received atropine as treatment for early diarrhea. One patient (0.6%) discontinued treatment due to diarrhea that may have had a cholinergic component.

Emesis also was noted as a consequence of CPT-11 administration. This appeared to be dose-related: 21.9% of patients starting treatment at 125 mg/m^2 had Grade 3/4 vomiting whereas this was observed in only 2.0% of patients beginning treatment with CPT-11 at a dose of 100 mg/m^2 ($P < 0.001$). Other baseline characteristics were not significantly predictive of the occurrence of Grade 3/4 vomiting. There were no discontinuations of therapy due to nausea or emesis. Some degree of asthenia was observed in 83.1% of patients, but was severe in only 16.3%. The extent to which this was related to treatment versus underlying disease was unclear. Alopecia was observed in 56% of patients, but Grade 2 (complete) alopecia affected only 24.7% of patients.

The majority of patients did not develop significant myelosuppression; Grade 4 neutropenia was noted in only 7.8% of patients and 1.7% of courses when CPT-11 was given at a starting dose of 125 mg/m^2, and was observed in 8.8% of patients and 2.8% of courses when the starting dose was 100 mg/m^2. As a consequence, neutropenic fever (Grade 4 neutropenia with Grade 2 fever) occurred in just 1.2% of patients (2 of 166). Both episodes occurred in patients starting treatment at a dose of 100 mg/m^2. Both patients were hospitalized and recovered after antibiotic therapy. Only 4.2% of patients (7 of /166) received granulocyte-colony stimulating factor at any time during treatment. Discontinuation of therapy due to neutropenia occurred in 3 patients (1.8%) with Grade 4 neutropenia.

Hospitalization in association with at least 1 drug-related adverse event occurred in 24.1% of patients (40 of 166). The primary adverse events at the time of these hospitalizations were diarrhea (24 of 166; 14.5%) and nausea and/or emesis (13 of 166; 7.8%). Grade 3/4 neutropenia/leukopenia was described in association with hospitalization in 5.4% of patients (9 of 166). Seven patients died during or within 30 days of the last CPT-11 administration; none of the deaths were considered to be drug-related by the physicians who treated these patients.

DISCUSSION

This Phase II trial was designed to characterize the antitumor activity and toxicity of CPT-11 in patients with metastatic colorectal carcinoma who had developed recurrent or progressive disease within 6 months of a prior 5-FU-based regimen. Altogether, 167 patients were enrolled and 166 were treated. Initially, 64 patients were treated with CPT-11 at a starting dose of 125 mg/m^2. However, given the rates of toxicity and hospitalization observed with this starting dose, the trial was amended to treat additional patients at a starting dose of 100 mg/m^2; 102 patients initiated treatment with CPT-11 at this dose. Although potentially confounded because of changing practices as a result of increasing physician experience with the drug, this sequential evaluation of two different dose levels has allowed exploratory assessment of the im-

pact of starting dose on efficacy and safety parameters.

Eighteen patients responded to treatment with CPT-11, for an overall independently confirmed, intent-to-treat response rate of 10.8%. The response rate for the 125 mg/m^2 starting dose group was 14.1% (9 of 64; 95% CI, 5.5-22.6%), and the response rate of the 100 mg/m^2 starting dose group was 7.8% (8 of 102; 95% CI, 3.3-14.3%). The overall dose intensity was higher for patients starting at the 125 mg/m^2 dose (61.0 mg/m^2/week) compared with those starting at the 100 mg/m^2 dose (53.9 mg/m^2/week). Although suggestive that a higher starting dose or greater initial dose intensity are associated with a higher response rate, statistical comparison did not confirm a definite difference in response rates between the two starting dose groups ($P = 0.314$). The higher proportion of patients with a PS of 0 among those patients beginning CPT-11 at a dose of 125 mg/m^2 compared with those receiving the 100 mg/m^2 starting dose (59.4% vs. 44.1%; $P = 0.079$) may help to explain this difference given information suggesting that PS can be a predictor of CPT-11 response,[16,29] as has been observed with other chemotherapeutic agents. Although there was a trend toward higher response rates to CPT-11 in patients previously treated with 5-FU for metastatic disease compared with those who received 5-FU in the adjuvant setting (12.9% vs. 6.4%), this difference was not statistically significant ($P = 0.277$).

Of the 15 patients responding to CPT-11 who had received prior 5-FU for metastatic disease, none had shown an objective response to prior 5-FU. These data suggest little cross-resistance between the two drugs. In vitro data comparing drug resistance between CPT-11's active metabolite, SN-38, and 5-FU also do not appear to suggest an association in resistance pattern between the two drugs.[30]

In general, the tumor response rates noted in this study are similar to those observed in two prior U. S. Phase II trials of CPT-11 for previously treated metastatic colorectal carcinoma.[15,31] In those trials, patients were treated with the same weekly schedule of CPT-11 administration. At a starting dose of 125 mg/m^2, response rates of 20.8% (10 of 48) (95% CI, 9.3-32.3%)[15] and 13.3% (12 of 90) (95% CI, 6.3-20.4%)[31] were noted. Japanese investigators giving CPT-11 at starting doses of either 100 mg/m^2 weekly (without a rest period) or 150 mg/m^2 every 2 weeks noted an overall response rate of 21.7% (10 of 46) (95% CI, 9.8-33.7%)[12] in previously treated patients. French investigators who gave 350 mg/m^2 of CPT-11 every 3 weeks noted a 15.6% intent-to-treat response rate (23 of 147) (95% CI, 10.1-22.5%) in a population of patients with metastatic colorectal carcinoma who had received prior 5-FU.[16] Collectively, these data suggest that various schedules of intermittent CPT-11 administration yield comparable response rates.

Although they were not used as a formal measure of response, CEA levels were followed serially in patients participating in this study. In those patients with elevated CEA levels at baseline, there appeared to be a correlation between tumor response or stabilization and substantial (i.e., $>$ 50%) decrease in CEA. Although this finding is provocative, larger trials will be needed to define this association in a prospective fashion and determine whether CEA may be a useful surrogate endpoint in this patient population.

Consistent with the previous experience using the weekly administration schedule of CPT-11,[15,31] delayed diarrhea, nausea, emesis, and neutropenia were the most notable toxicities of CPT-11. Although Grade 3/4 nausea and emesis occurred significantly more frequently among patients started at the higher CPT-11 dose level, there were no significant differences between the 125 mg/m^2 and 100 mg/m^2 starting dose groups in the frequency of Grade 3/4 diarrhea or neutropenia. There also were no significant associations between these Grade 3/4 events and gender, baseline PS, or other baseline variables, except that the frequency of Grade 3/4 late diarrhea was significantly higher in patients age $\geq$ 65 years compared with younger patients (38.6% vs. 18.7%; $P = 0.008$) when all cycles of treatment were examined. Although this correlation between age and diarrhea may suggest the need to consider a lower starting dose in patients of a certain age, extreme variability in the severity of diarrhea by age and the lack of a significant effect of age on first-course diarrhea tend to preclude a definite recommendation in this regard. An additional U. S. Phase II trial has been performed to evaluate patient age as a risk factor for CPT-11-associated diarrhea. Preliminary data indicate that the frequency of late diarrhea is declining in all patients, but particularly in those age $>$ 65 years, and that there is not a significantly greater frequency of diarrhea among older patients compared with younger ones.

It is interesting to note that the 32.8% frequency of delayed Grade 3/4 diarrhea at the 125 mg/m^2 starting dose in this study is similar to rates of Grade 3/4 toxicity in prior U. S. Phase II trials of CPT-11 in patients with previously treated colorectal carcinoma (35.9% vs. 33.3%). However, the occurrence of Grade 4 delayed diarrhea in patients whose therapy was initially administered at a dose of 125 mg/m^2 was less in this study (7.8% vs. 23.1% and 21.1%, respectively, in the prior studies). These data tend to corroborate earlier experience[15,33] indicating that loperamide does not eradicate diarrhea completely, but may reduce

diarrhea intensity. This information also reinforces the need for antidiarrheal treatment to be initiated at the first sign of loose or more frequent stools. In addition, these data also suggest that the increasing familiarity of healthcare professionals with CPT-11 administration and the routine, thorough education of patients in supportive care measures may assist in reducing the intensity of diarrhea.

Emesis was observed during therapy in the majority (60.2%) of patients receiving CPT-11. Given this emetic potential, and the possibility of dehydration that can occur with simultaneous emesis and diarrhea, it is important that adequate antiemetic therapy be instituted routinely in patients receiving this drug. Currently, we are recommending use of intravenous dexamethasone and a serotonin antagonist (e.g., ondansetron or granisetron) prior to administration of CPT-11. Oral antiemetic support should be provided, as needed, for any delayed emesis.

The results of this study confirm that CPT-11 can induce tumor regressions in patients who have developed disease progression during or shortly after first-line 5-FU-based treatment and that attendant toxicities are manageable. Based on the substantial clinical experience at the 125 mg/m^2 dose level, the generally comparable toxicities between the 125 mg/m^2 and 100 mg/m^2 starting dose levels, and the ability to adjust drug dose on a weekly basis based on patient tolerance, 125 mg/m^2 appears to be the preferred starting dose for weekly CPT-11 administration at this time. Definitive comparison of the efficacy and tolerability of the 125 mg/m^2 and 100 mg/m^2 starting dose levels would require a prospective, randomized clinical trial. It is more likely that a follow-up trial will be comprised of a comparison between the weekly, every-other-week, and every-3-weeks schedules rather than between 2 starting doses for the weekly schedule.

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