Irinotecan and Chronomodulated Infusion of 5-Fluorouracil and Folinic Acid in the Treatment of Patients with Advanced Colorectal Carcinoma

A Phase I Study

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BACKGROUND. Irinotecan (CPT-11) is an active drug in the treatment of patients with advanced colorectal carcinoma. The infusion of 5-fluorouracil (5-FU) according to circadian rhythms was used previously to decrease toxicity and to increase its therapeutic efficacy. The objective of this study was to establish the maximum tolerated dose (MTD) of CPT-11 together with a chronomodulated infusion of 5-FU and the l-form of folinic acid (FA). Secondary end points were the assessment of activity and quality of life (QoL).

METHODS. Twenty-six patients with advanced colorectal carcinoma who had received previous treatment with 5-FU were entered on this Phase I study. At least three patients were recruited at each dose level. The CPT-11 starting dose was 175 mg/m^2 on Day 1 with an increase of 50 mg/m^2 per dose level. A daily administration of chronomodulated 5-FU (900 mg/m^2; peak delivery rate at 04:00) and FA (175 mg/m^2; peak delivery rate at 04:00) for 5 days every 3 weeks was given with CPT-11. After the first three patients, the 5-FU dose was reduced to 700 mg/m^2 per day due to toxicity. No intrapatient dose escalation was allowed.

RESULTS. One hundred sixty-one courses were delivered. Dose-limiting toxicity was observed during the first course in seven patients (27%). Four patients developed neutropenia, with one patient reporting febrile neutropenia, two patients reporting severe stomatitis, and six patients reporting severe diarrhea. CPT-11 MTD was reached at 350 mg/m^2 when a toxic death was observed with a recommended dose of 325 mg/m^2. Six partial responses were observed (23%). The median duration of response and the progression free and overall survival rates were 199 days, 175 days, and 359 days, respectively. QoL was not affected by the treatment.

CONCLUSIONS. The recommended dose for Phase II trials is 325 mg/m^2 CPT-11 on Day 1, which is similar to the dose given as a single agent, together with a 5-day chronomodulated infusion of 700 mg/m^2 5-FU and 175 mg/m^2 FA. Intensification of this schedule every 2 weeks should be achievable. ***Cancer* 2001;91:712–20.**

KEYWORDS: colorectal carcinoma, chronotherapy, irinotecan, 5-fluorouracil, leucovorin, Phase I study.

The regimens available for the treatment of patients with advanced colorectal carcinoma, currently based on 5-fluorouracil (5-FU), recently were increased by the availability of new drugs, such as irinotecan (CPT-11)[1] and oxaliplatin. These new drugs show activity as single agents and display a mechanism of action completely different from that of 5-FU. CPT-11 is an inhibitor of topoisomerase I, an

enzyme that is responsible for variations in the topologic form of DNA during replication and transcription.[2,3] Inactivation of this enzyme by CPT-11 causes "single-strand breaks" in DNA that prevent its replication and inhibit RNA synthesis and, consequently, cell division. This cytotoxic effect of CPT-11 and of its principal active metabolite, SN-38, is specific for the S-phase of the cell cycle.

In Phase II studies, CPT-11 consistently has demonstrated antitumor activity in both chemotherapy-naïve patients and pretreated patients with advanced colorectal carcinoma, with response rates comparable to those achieved with patients who received modulated 5-FU therapy.[4,5] More important, CPT-11 has exhibited therapeutic activity in patients with disease that progressed under a 5-FU-based regimen, suggesting a lack of cross resistance between the two drugs. In a large series of 455 patients with advanced colorectal carcinoma that was resistant to 5-FU, Van Cutsem et al.[6] showed that CPT-11 produced an overall response rate of 13%, with a median duration of response of 7.6 months and a median survival of 9.5 months. In recent years, quality of life (QoL) has emerged as a relevant endpoint in the assessment of treatment efficacy and tolerability.[7] In two randomized studies in patients with advanced, pretreated colorectal carcinoma, CPT-11 was compared with 5-FU[8] or with best supportive care,[9] and a significant difference was observed in survival for CPT-11-treated patients, without any alterations in patient QoL. The circadian time of administration influences the severity of toxicity and the extent of activity of most anticancer agents in experimental tumors.[10,11] The clinical relevance of drug dosing time was demonstrated for 5-FU and oxaliplatin. Recent results in randomized trials of patients with metastatic colorectal carcinoma have demonstrated that antineoplastic drugs are tolerated better and are more active when given according to a chronomodulated schedule.[12,13] Rhythms in drug tolerance result from circadian changes in drug pharmacokinetics and/or susceptibility of target tissue. 5-FU lethal toxicity is two- to eight-fold less when administered during daylight in resting mice compared with nighttime administration, when mice are active.[14] Less DNA synthesis was found in human bone marrow[15] and in oral and rectal mucosa during night hours compared with day hours. Moreover, circadian changes of dehydropyrimidine dehydrogenase activity are responsible for circadian changes in plasma levels of 5-FU.[16] It was shown subsequently in randomized trials that severe oral mucositis was reduced five-fold when 5-FU was given by chronomodulated infusion rather than by constant infusion[17,18] and that 5-FU dose intensity (DI) is related to efficacy, which may influence overall survival.[17]

In a previous Phase I study of 34 patients, we demonstrated that the maximum tolerated dose (MTD) of 5-FU given as a sinusoidal chronomodulated infusion from 10:00 pm to 10:00 am, with a peak flow at 4:00 am, was 900 mg/m^2 per day for 5 consecutive days and 16 days of rest.[18] In this study, the l-form of folinic acid (FA) was infused concurrently with 5-FU at a fixed dose of 150 mg/m^2 per day (FF$_{5-16}$). Two subsequent Phase II studies with the same starting doses of 5-FU and FA followed. The first study, with the 3-week FF$_{5-16}$ schedule, was conducted at our institute on 48 patients with untreated metastatic disease. A 31% response rate was achieved, with a median response duration of 9 months, a time to progression of 6 months, and a median overall survival of 14 months.[19] The second study was performed by the International Organization for Cancer Cronotherapy in a multicenter setting. The DI of 5-FU was increased, because the 2 drugs were given for 4 days every 2 weeks (FF$_{4-10}$). The response rate in 102 untreated patients was 41%, with an estimated median survival of 15 months.[20]

The therapeutic association of FF$_{5-16}$ and CPT-11 represents a logical step in attempts to increase therapeutic efficacy because of their different mechanisms of action and lack of cross resistance. Therefore, the primary objective of this study was to determine the MTD of CPT-11 when it is given in combination with a chronomodulated infusion of FF$_{5-16}$ in 5-FU-pretreated patients. Secondary objectives were to evaluate the toxicity spectrum of this combination, to evaluate preliminary the activity of the same treatment in this patient population, and to study QoL using the European Organization for Research and Treatment of Cancer (EORTC) QLQC30+3 questionnaire.[21]

MATERIALS AND METHODS

Patient Eligibility

The eligibility criteria were as follows: histologically confirmed diagnosis of locally advanced or metastatic colorectal adenocarcinoma; age between 18 years and 70 years; life expectancy $>$ 3 months; Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$ 1; measurable or evaluable disease; and prior therapy, including patients with at least one previous 5-FU-containing regimen (as adjuvant or palliative) and no more than two 5-FU-containing regimens (with adjuvant and/or palliative intent). The following blood parameters were validated before treatment: white blood cells (WBC) $\geq 3.5 \times 10^9$/L, neutrophils $\geq 2 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, hemoglobin $\geq$ 10

g/dL; bilirubin $\leq 1.25 \times$ upper normal limit (UNL), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ UNL, PT (prothrombin time) $\geq 70\%$ in the absence of liver metastases, or bilirubin $\leq 1.5 \times$ UNL, ALT and AST $\leq 5 \times$ UNL in patients with liver metastases; serum albumin ≥ 3 g/L; and normal renal function, with creatinine clearance of at least 60 mL/minute.

Patients were excluded for one of the following reasons: no prior 5-FU-containing regimen given as either as an adjuvant or palliative treatment; more than two prior lines of 5-FU-containing chemotherapy given as adjuvant and/or palliative treatment; metastatic lesions suitable for surgical resection or elective radiotherapy; previous treatment with CPT-11; inflammatory bowel diseases or chronic diarrhea (requiring therapy); total colectomy or ileostomy; bowel obstruction and/or subobstruction; severe diarrhea (World Health Organization [WHO] Grade 3–4) during prior 5-FU administration; uncontrolled metabolic disorders or active infections; uncontrolled cardiac arrythmias; uncontrolled congestive cardiac failure or severe ischemic heart disease; acute myocardial infarction in the last 6 months; history of significant neurologic or psychiatric disorders; pregnancy or breast feeding; symptomatic cerebral metastases; or ongoing treatment with other anticancer agents or radiotherapy. The study was approved by the ethical committees of the two institutions (the Regina Elena Institute, Rome, and the San Luigi Hospital, University of Turin, Orbassano).

Pretreatment Evaluation

Written informed consent was obtained from each patient. Initial work-up for imaging was then done within 4 weeks prior to the start of treatment as well as initial work-up for blood samples within 1 week prior to the start of treatment. The time between the last administration of 5-FU and registration was at least 4 weeks, provided that patients had recovered from toxic effects. Each patient underwent a surgical placement of a totally implanted, double-lumen, venous access port (Port-A-Cath).

Treatment Plan

5-FU and FA were administered by a chronomodulated infusion using a multichannel, programmable, in-time, ambulatory pump. This pump was equipped with four channels. The chip was programmed using Intellimed software (Aguettant, Lyon, France). The syringes were connected as follows: channels A and B, FA; channels C and D, 5-FU. The infusion was performed from 10:00 pm to 10:00 am with a nocturnal peak at 4:00 am for 5 consecutive days every 3 weeks. The initial doses of 5-FU and FA were chosen according to our previous Phase I study. 5-FU was given at a fixed dose of 900 mg/m^2 per day (Days 1–5), and FA was administered at a fixed dose of 150 mg/m^2 per day (Days 1–5). Because dose-limiting toxicity (DLT) occurred in three of five patients at the first level of the study, the dose of 5-FU was reduced to 700 mg/m^2 per day and then remained fixed for the duration of the study.

A 3-week schedule of CPT-11 was chosen because it is the schedule commonly employed in Europe. CPT-11 was administered as a continuous intravenous infusion for no less than 30 minutes and no longer than 90 minutes. It was dissolved in 250 mL of a 0.9% NaCl solution on Day 1 every 3 weeks. The starting dose of CPT-11 was 175 mg/m^2, and this was escalated by 50 mg/m^2 per step up to 350 mg/m^2.

Dose Escalation Plan

A minimum of three patients, but up to six eligible and evaluable patients, was required per dose level to determine MTD. DLT was defined as follows: any WHO Grade 3 or 4 extrahematologic toxicity, except alopecia, nausea, and emesis; any Grade 3 neutropenia with fever ≥ 38 °C; any Grade 3 thrombocytopenia with bleeding; any Grade 4 neutropenia; or any Grade 4 thrombocytopenia. If no DLT was observed after the first chemotherapy course, then the dose of CPT-11 was escalated in another series of three to six patients. If a DLT was observed in one patient, then three more patients were entered at the same dose level. If no other patients experienced the same DLT, then CPT-11 escalation was continued until the MTD was reached.

The MTD, as in all European studies with CPT-11, was defined as the dose level associated with the same DLT in at least two of three or four of six patients. The recommended dose was defined as the dose level immediately below the MTD. Once the final MTD was reached, three additional patients were entered at the identified recommended dose to define better the toxicity of the combination. No dose escalation was allowed in any individual patient, whatever the dose level. For each patient, treatment was administered every 3 weeks until disease progression, unacceptable toxicity, or patient refusal. Dose reductions and/or administration delays were planned for patients with severe hematologic and/or nonhematologic toxicity during study treatment. Toxicity was evaluated according the National Cancer Institute common toxicity criteria (NCI-CTC); response to treatment was assessed by computed tomography scans every three courses according to WHO criteria.[22]

Premedication

Prophylaxis of emesis with anti-Ht3 was given to all patients. Steroids were not allowed. Premedication with atropine for cholinergic syndrome was recommended from the first course of treatment.

Dose Modifications

Myelosuppression

If the absolute neutrophil count on the day of retreatment was $< 1.5 \times 10^9$/L and/or if platelets were $< 10 \times 10^9$/L, then treatment was delayed for a maximum of 2 weeks.

Diarrhea

For patients with Grade 3–4 diarrhea, CPT-11 was reduced by 50 mg/m^2 for further cycles and by 100 mg/m^2 per day for 5-FU.

Mucositis

In patients with severe mucositis, the 5-FU dose was reduced by 100 mg/m^2 per day. The dose of leucovorin remained unchanged whatever the grade of toxicity. Treatment for patients with acute diarrhea and neutropenia was performed according to Abigerges et al.[23]

QoL

The EORTC QLQ-C30+3 questionnaire was filled by the patient at baseline and at every 9 weeks of therapy. Mean scores were calculated from the entire group of patients and by comparing data from the 6 patients who were treated with 325 mg/m^2 with data from the 17 patients who were treated with at 175 mg/m^2, 225 mg/m^2, and 275 mg/m^2.

RESULTS

Patient Baseline Data

From July 7, 1997 to June 19, 1998, 26 patients were included in the trial. Nineteen patients were included at the Regina Elena Institute in Rome, and 7 patients were included at the San Luigi Hospital, University of Turin, Orbassano. Strict cooperation between the investigators of the two centers with exchange of information, by telephone and facsimile, was implemented to avoid inappropriate levels of inclusion. Patient characteristics are listed in Table 1. Baseline data were good for these patients: eight to five percent of patients had a PS of 0, 81% of patients had colon carcinoma with a previous history of a second tumor in two patients, all patients had received previous treatment with 5-FU, and 31% of patients had received two lines of chemotherapy. The median interval between the first diagnosis of carcinoma and registration in the trial was 15 months (range, 2–55 months), and the interval between the end of previous chemotherapy and the first course of treatment was 3 months (range, 1–12 months).

TABLE 1
Patient Baseline Characteristics

Characteristic	No.	%
No. of patients	26	100
Gender (male:female)	15:11	42:58
Median age in yrs (range)	61 (38–70)	—
WHO performance status		
0	21	85
1	4	15
2	1	4
Mean weight loss during the last 3 months (%)	1 ± 1.67	—
Tumor-related signs and symptoms at baseline	8	31
Primary tumor site		
Colon	21	81
Rectum	6	19
Sites of Metastases		
Liver	22	85
Lung	6	31
Peritoneum	1	4
Lymphonodes	1	4
No. of organs involved		
1	15	58
≥ 2	11	42
Measurable/evaluable	25/1	96/4
Surgery		
Previous surgery		
1	20	77
2	5	19
3	1	4
Permanent colostomy	4	15
Previous radiotherapy	4	15
Chemotherapy		
Previous 5-fluorouracil	26	100
Adjuvant	7	27
Advanced	19	73
No. of previous chemotherapy lines		
1	18	69
2	8	31
Chemotherapy termination due to progression		
First line	15	60
Second line	5	62
Hematologic evaluation before treatment (range)		
Median hemoglobin (g/L)	126 (91–152)	—
Median white blood cells (10^9/L)	63 (41–134)	—
Median platelets (10^9/L)	245 (17–441)	—

WHO: World Health Organization.

Treatment Safety and Determination of MTD

One hundred sixty-one courses were delivered with a median of 7 courses (range, 1–11 courses) per patient; 31 courses were delayed (19%); and only 6 courses involved a dose reduction (3.7%). Dose reduction was required for hematologic toxicity in one course, for nonhematologic toxicity in three courses, and for both reasons in two courses. Treatment was interrupted

TABLE 2
Determination of Maximum Tolerated Dose and Response

CPT-11 (mg/m^2/Day 1)	5-FU (mg/m^2 × 5 Days)	1-FA (mg/m^2 × 5 Days)	Patients	Courses	Dose-limiting toxicity[a]	Response
175	900	150	5	27	2 N_4, 1 M_3	—
175	700	150	3	18	—	1
225	700	150	3	26	—	1
275	700	150	6	37	1 D_4	2
325	700	150	6	43	—	2
350 (MTD)	700	150	3	10	1 N_4, 1 D_3, 1 $N_4D_4M_4$	—
Total	—	—	26	161	7	6 (23%)

CPT-11: irinotecan; 5-FU: 5-fluorouracil; 1-FA: the 1-form of folinic acid; N: netropenia; D: diarrhea; M: mucositis.
[a] The number after each letter corresponds to the National Cancer Institute grading of toxicity. Dose-limiting toxixity was assessed at the first course of treatment.

TABLE 3
The Worst National Cancer Institute Common Toxicity Criteria Toxicity in 26 Patients

Toxicity	Grade 0 (%)	Grade 1 (%)	Grade 2(%)	Grade 3 (%)	Grade 4 (%)
Hemoglobin	19 (73.0)	2 (7.6)	2 (7.6)	3 (11.5)	—
Platelets	22 (84.6)	2 (7.6)	1 (3.8)	—	1 (3.8)
White blood count	13 (50.0)	4 (15.3)	3 (11.5)	6 (23.0)	—
Febrile neutropenia	24 (92.3)	—	—	1 (3.8)	1 (3.8)
Nausea	10 (38.4)	6 (23.0)	7 (26.9)	2 (7.6)	1 (3.8)
Emesis	17 (65.3)	1 (3.8)	4 (15.3)	2 (7.6)	2 (7.6)
Diarrhea	4 (15.3)	9 (34.6)	6 (23.0)	5 (19.2)	2 (7.6)
Stomatitits	16 (61.5)	6 (23)	2 (7.6)	1 (3.8)	1 (3.8)
Alopecia	3 (11.5)	7 (27.0)	—	—	—

because of disease progression in 13 patients, for adverse experience in 2 patients, for patient withdrawal in 7 patients, and for other reasons not related to therapy in 4 patients.

DLT was observed in 7 patients (27%) and consisted of neutropenia in four patients, one of whom had febrile neutropenia; diarrhea in three patients (one patient with Grade 3 and two patients with Grade 4); and stomatitis in two patients (one patient with Grade 3 and one patient with Grade 4). No patients with DLT began the study with an elevated bilirubin concentration. The MTD was reached at a CPT-11 dose of 350 mg/m^2; therefore, the recommended CPT-11 dose was just below this, i.e., 325 mg/m^2. Six patients were treated with 325 mg/m^2 for a total of 43 courses of therapy without observing any DLT (Table 2).

Overall toxicity per patient and per course are shown in Tables 3 and 4, respectively. Neutropenia, evaluated at nadir, was the most frequent Grade 3–4 toxicity in 8 of 26 patients (31%), but febrile neutropenia occurred in only 2 patients (7.6%). There was no cumulative bone marrow depression due to the combination: the mean minimum values of Hb, WBC, neutrophils, and platelets before therapy and at the end of therapy, respectively, were Hb, 11.3 ± 1.57 g/dL versus 11.9 ± 2.12 g/dL; WBC, 3568 10^9/L versus 6200 10^9/L; neutrophils, 2145 ± 1508 10^9/L versus 3852 ± 1595 10^9/L; and platelets, 206,000 ± 92,000 10^9/L versus 208,000 ± 67,000 10^9/L. Diarrhea was the most serious Grade 3–4 toxicity, affecting 26% of patients. The median number of days between the start of treatment and onset of diarrhea was 6 days (range, 3–20 days), and the mean duration of diarrhea was 5 days ± 1.9 days. Although anti-Ht3 was used routinely, nausea was a common problem, and four patients (15.2%) reported Grade 3–4 emesis. Four patients (15%) had mild astenia and one patient had moderate astenia related to treatment. Ten patients (38.4%) had alopecia. One toxic death was recorded: a male patient, with a PS of 2, extensive bone metastases, and a huge lung mass who entered the trial with a CPT-11 dose of 350 mg/m^2. The patient died after the first course of treatment as a result of bone marrow depression with neutropenic fever and thrombocytopenia, uncontrolled diarrhea, and mucositis.

Efficacy

Of 26 patients, 6 patients had a partial responses (23%), 1 patient had a minor response, 10 patients

TABLE 4
Overall National Cancer Institute Common Toxicity Criteria Toxicity in 161 Courses of Treatment

Toxicity	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Hemoglobin	153 (95.0)	2 (1.2)	3 (1.9)	3 (1.9)	—
Platelets	157 (97.5)	2 (1.2)	1 (0.6)	—	1 (0.6)
White blood cells	110 (68.3)	24 (14.9)	18 (11.2)	9 (5.6)	—
Febrile neutropenia	159 (98.8)	—	—	1 (0.6)	1 (0.6)
Nausea	110 (68.3)	29 (18.0)	18 (11.2)	3 (1.9)	1 (0.6)
Emesis	123 (76.4)	22 (13.7)	12 (7.5)	2 (1.2)	2 (1.2)
Diarrhea	84 (52.2)	56 (34.8)	14 (8.7)	5 (3.1)	2 (1.2)
Stomatitis	135 (83.5)	20 (12.4)	4 (2.5)	1 (0.6)	1 (0.6)

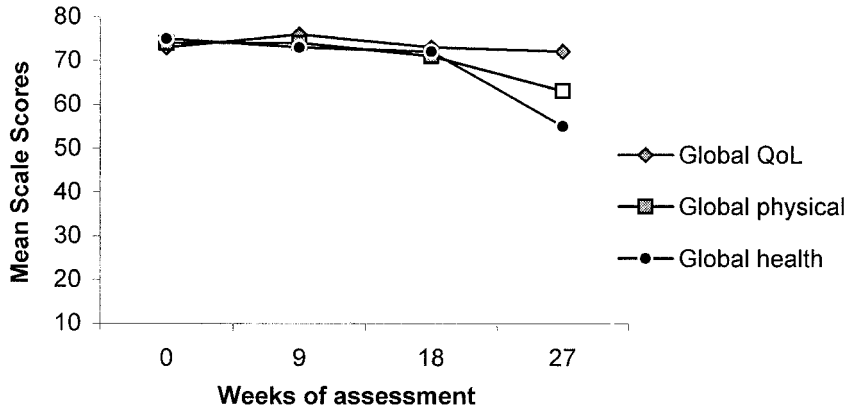

FIGURE 1. Evolution over time of global health, physical, and quality-of-life (QoL) scores.

achieved stabilization of disease, and 4 patients had disease progression. Five patients were not evaluated for tumor response. Tumor growth control was obtained in 17 of 26 patients (65%), with a partial response observed even at the first level. Previous therapy in responsive patients consisted of 5-FU plus FA bolus (Machover schedule) in 3 patients, two for adjuvant therapy and one for advanced disease; FF$_{5\text{-}16}$ in three patients; and 5-FU plus cisplatin in another patient. The median duration of response was 199 days (range 115–289 days). The median progression free survival and the median overall survival were 175 days and 359 days, respectively (Kaplan–Meier curves). QoL mean scores remained stable during the entire course of treatment. There was no worsening of patient QoL in the first 9 weeks of therapy with different CPT-11 doses (Fig. 1).

DISCUSSION

The objective of this study was to establish the MTD of CPT-11 associated with FF$_{5\text{-}16}$. The MTD of CPT-11 in this schedule was 350 mg/m^2 given every 3 weeks. Therefore, the recommended combination dose for Phase II trials is 325 mg/m^2 of CPT-11 on Day 1 followed by a chronomodulated infusion of 700 mg/m^2 5-FU and 150 mg/m^2 FA from Day 1 to Day 5, with each course repeated every 3 weeks. The DLT was found to be diarrhea, which was severe in 26% of patients. The recommended dose of CPT-11 is very similar to the dose given in monochemotherapy, thus indicating that close to a full dose of the drug can be added to FF$_{5\text{-}16}$. In this study, the starting dose of 5-FU was reduced from 900 mg/m^2 to 700 mg/m^2 per day because of the toxicity seen at the higher dose level. However, it should be noted that 700 mg/m^2 per day given by chronomodulated infusion is the 5-FU dose generally employed in the 5-FU, leucovorin, and oxaliplatin (FFL$_{5\text{-}16}$) regimen repeated every 3 weeks, which is an active and well tolerated regimen in patients with advanced colorectal carcinoma.[24,25] Partial responses were obtained in 23% of all patients included in the trial. If minor response and stabilization also are considered, then tumor control was achieved in two of three of the 5-FU-pretreated patients. According to previous experiences with CPT-11 monochemotherapy, the addition of escalating CPT-11 doses to FF$_{5\text{-}16}$ did not cause any impairment of patient QoL.

There are some features of the regimen used in this study that are similar to other reported schedules of CPT-11 plus infusional-modulated 5-FU. For example, the biweekly CPT-11/bolus fluorouracil, continu-

TABLE 5
Comparison of Phase I Trials with Irinotecan and Modulated Infusional 5-Fluorouracil

Author	Patients	Untreated patients (%)	Recommended dose intensity (mg/m^2 week)		Febrile neutropenia (% patients)	Grade 3–4 diarrhea (% patients)	Response rate (%)
			CPT-11	5-FU			
Vanhoefer et al.[26]	26	100	60	1700	0	20	64
Ducreaux et al.[25]	55	0	90	1000	10.9	18	22
Falcone et al.[27]	33	100	83 (Day 3) and 125 (Day 1)	1170	4 and 17	21	39
Current study	26	27	108	1166	7.6	26	23

ous infusion fluorouracil, and high dose leucovorin every 2 weeks (LV5FU2) regimen[26]; the weekly irinotecan, high dose leucovorin, and infusional fluorouracil Association of Medical Oncology of the German Cancer Society (AIO) schedule;[27] and regimen with a 3-week, 48-hour infusion of 5-FU and FA immediately prior to or after CPT-11.[28] In the first study, Ducreux et al.[26] found a CPT-11 recommended dose of 180 mg/m^2 every 2 weeks added to bolus and infusional-modulated 5-FU with a CPT-11 DI of 90 mg/m^2 per week and a 5-FU DI of 1000 mg/m^2 per week. The response rate in 55 pretreated patients was 22%, almost identical to that found in the current study. Febrile neutropenia was seen in 10.9% of patients, and severe diarrhea was seen in 18% of patients. The German study involved chemotherapy-naïve patients and achieved an impressive 64% response rate with no episodes of febrile neutropenia and with 20% of patients suffering from Grade 3–4 diarrhea only at the highest CPT-11 dose level. In this study, NCI-CTC Grade 2 emesis was observed in 52% of patients in the first course and in 64% of patients in all cycles. The DI was 60 mg/m^2 per week for CPT-11 and 1700 mg/m^2 per week for 5-FU, taking into account also the 2 weeks of rest after the 6 weeks of treatment. In the study from Pisa on patients with untreated metastatic colorectal carcinoma, escalating doses of CPT-11 were given immediately prior (Day 1 schedule) or after a 48-hour infusion of 3500 mg/m^2 5-FU and a high dose of 250 mg/m^2 1-FA (Day 3 schedule). Falcone et al.[28] observed that toxicity was reduced with the Day 1 schedule and recommended a CPT-11 dose of 250 mg/m^2 when it was given after 5-FU and 350–400 mg/m^2 when it was given immediately prior to 5-FU. The reduced toxicity was attributed to a reduced SN-38 area under the serum-concentration time curve. DLTs were neutropenia and diarrhea.

In the four studies, including the current one, responses were observed even at the first dose level studied. The duration of response, progression free survival rates, and overall survival rates were very similar. The limiting toxicity, diarrhea and febrile neutropenia, was the same as that for CPT-11 alone, and the severity of toxic events did not appear to be affected by the administration of concurrent 5-FU when it was given at its optimal DI for each schedule (Table 5). It is difficult to assess the impact of CPT-11 DI per se, and it is evident that CPT-11/5-FU synergism most likely plays a major role rather than CPT-11 dose. There is little information on the correlation between CPT-11 dose and antitumoral effect, because it has been studied only at high doses.[29] We have shown previously in $FF_{5\text{-}16}$-pretreated patients who received a higher dose of modulated 5-FU (900 mg/m^2 per day) that the response rate did not exceed 10%,[30] similar to what was seen with the weekly German schedule.[31] The importance of the synergy between CPT-11 and modulated 5-FU was shown in patients with untreated metastatic colorectal carcinoma who were randomized between the biweekly LV5FU2 regimen or the AIO regimen with or without CPT-11.[32] In that study, significant differences in objective response rates and survival were observed in CPT-11-treated patients. Only randomized trials of both treated and untreated patients can define fully which of these schedules is better in terms of efficacy and tolerability.

Another interesting aspect of the work reported here is the frequency of 5-FU administration. The chronomodulated intensification of 5-FU delivery for 4 days every 2 weeks, both alone with $FF_{4\text{-}10}$[20] or in combination with oxaliplatin with $FFL_{4\text{-}10}$,[17,33] resulted in better antitumor activity compared with the 3-week schedule: response rates were increased from 30% to 40% without oxaliplatin and from 50% to 65% with the addition of oxaliplatin. This suggests that the intensification of our CPT-11/$FF_{5\text{-}16}$ schedule by reducing the interval of courses at 2 weeks and the days of 5-FU from 5 days to 4 days may increase efficacy without significantly affecting toxicity. To test this, we have set up a pilot study giving CPT-11 at 180 mg/m^2 on Day 1 followed by $FF_{4\text{-}10}$ with a 5-FU daily dose of 700–800 mg/m^2 from Day 2 to Day 5 every 2 weeks (CPT-11/$FF_{4\text{-}10}$) in 25 patients with advanced colorec-

tal carcinoma. The results show an increase in activity and a better tolerability profile (unpublished data).

A final aspect is whether there is a circadian rhythm in tolerance and in activity for CPT-11 and whether this is relevant clinically. In two independent studies conducted in Japan and France, CPT-11 was tolerated best in healthy mice during the second part of the rest phase.[34,35] In B6D2F mice in which Glascow osteosarcoma was injected subcutaneously, the administration of CPT-11 and oxaliplatin resulted in a significant prolongation of treated animals compared with control animals and with the animals that were treated with the two single drugs only when each drug was given at their best dosing time.[36] This suggests that there may be potential in administering the three active drugs in patients with advanced colorectal carcinoma by chronomodulated infusion. The impact of CPT-11/FF$_{4-10}$ chemotherapy on tumor response and host tolerance with different CPT-11 dosing times needs to be tested and compared with standard schedules.

The current Phase I study has shown that it is possible to deliver CPT-11 together with FF$_{5-16}$ in pretreated patients with advanced colorectal carcinoma without producing overlapping side effects. The recommended dose of CPT-11 was 325 mg/m^2 administered before a chronomodulated infusion of 700 mg/m^2 5-FU and 150 mg/m^2 FA for 5 days every 3 weeks. These doses and their effects in terms of tolerability and efficacy were comparable to other modulated 5-FU/CPT-11 combinations. The intensification of this schedule and the validation of the chronomodulated infusion of CPT-11 will be studied next by our group.

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