5-Fluorouracil as a protracted continuous infusion plus irinotecan (CPT-11) in patients with advanced colorectal cancer treated with fluoropyrimidine-based regimens as first line

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We carried out a single-center series with the combination of irinotecan (CPT-11) plus protracted 5-fluorouracil (5-FU) infusion as second-line chemotherapy for patients previously treated with a single-agent fluoropyrimidine as monotherapy or in combination with oxaliplatin. Twenty-five patients diagnosed with advanced colorectal cancer (CRC) received CPT-11 300 mg/m^2 every 3 weeks plus 5-FU 250 mg/m^2/day as a protracted infusion. Results were as follows. Twenty-four of 25 patients were evaluable for response. Two patients achieved a complete response and five a partial response, resulting in an overall response rate of 28%. Disease stabilization was obtained in 10 patients (40%), resulting in a tumor growth control rate of 68% (17 patients) and disease progression in seven (28%). Median progression-free interval was 6 months and median overall survival was 12 months. Neutropenia and diarrhea appeared as the most frequent adverse events, being grade 3/4 in 12 and 16% of patients, respectively. Mucositis, emesis, and hand and foot syndrome were mild. We conclude that protracted 5-FU infusion plus CPT-11 is an active and safe regimen for patients with advanced CRC. A phase III trial comparing this schedule with conventional CPT-11 monotherapy is warranted. *Anti-Cancer Drugs* **14:543–547 © 2003 Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2003, **14**:543–547

Keywords: 5-fluorouracil, colorectal cancer, irinotecan

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Received 18 February 2003 **Revised form accepted** 13 May 2003

Introduction

Two phase III studies comparing irinotecan (CPT-11) to best supportive care treatment [1] and to the administration of 5-fluorouracil (5-FU) as a continuous infusion [2] demonstrated that the topoisomerase inhibitor achieved a survival benefit with at least similar quality of life. Therefore CPT-11 monotherapy was considered as standard after 5-FU failure treatment of metastatic colorectal cancer (CRC). Streit *et al.* showed that the administration of 5-FU as a continuous infusion can elicit responses in patients who progressed with bolus administration of the same drug [3]. In 1997, our center, in collaboration with the Hospital 12 de Octubre, performed a phase I study of the combination of CPT-11 administered every 3 weeks together with prolonged continuous venous infusion of 5-FU. The dose-limiting toxicities were neutropenia and diarrhea, and the recommended doses for phase II studies were 300 mg/m^2 of CPT-11 and 250 mg/m^2/day of 5-FU [4].

We report here the results obtained with this therapeutic regimen used as second-line therapy in patients who had previously received a single-agent fluoropyrimidine as monotherapy or combined with oxaliplatin.

Patients and methods

Patients

All patients provided their informed consent. The inclusion criteria were as follows: (i) histologically confirmed metastatic CRC, (ii) measurable disease on computed tomography scan or magnetic resonance imaging, (iii) ECOG performance status 0–2, and (iv) absolute neutrophil count (ANC) $>1500/mm^3$, platelet count $>100\,000/mm^3$, and serum creatinine and bilirubin levels within the normal ranges. Patients with ischemic heart disease and central nervous system involvement were excluded.

Chemotherapeutic regimen

Patients were treated with a regimen of CPT-11 300 mg/m^2 as a 30-min infusion followed by prolonged continuous infusion of 250 mg/m^2/day of 5-FU through a Rosenblatt Dual Slimport implantable vascular access device (Laboratories BARD and Baxter-Ambulatory Medication Systems of Infusion).

0959-4973 © 2003 Lippincott Williams & Wilkins DOI: 10.1097/01.cad.0000086653.37889.7f

Emetic prophylaxis was carried out in all patients with dexamethasone and ondansetrone. Patients who experienced cholinergic syndrome with the CPT-11 infusion were given s.c. atropine as prophylaxis in the following cycles. Patients were instructed to take loperamide 2 mg orally every 2 h as soon as delayed diarrhea appeared.

Assessment of response and toxicity

Response to treatment was evaluated after every 3 cycles of chemotherapy, according to WHO criteria. Progression-free survival (PFS) was measured from the onset of chemotherapy until the demonstration of disease progression. The overall survival (OS) of patients was calculated from the onset of chemotherapy to death or loss to follow-up. The PFS and OS curves were calculated with the Kaplan–Meier method.

All adverse events were graded for severity according to the NCI-CTC recommendations before each treatment cycle.

Results

Patient characteristics

Between October 1998 and February 2001, 25 patients were included. The characteristics of patients are shown in Table 1. It should be emphasized that 13 patients (52%) were over 70 years old at the onset of treatment. Five patients were involved after disease progression during or immediately following adjuvant chemotherapy. Eight of the 25 patients (32%) had previously responded to first-line chemotherapy.

Table 1 Patient and disease characteristics at baseline ($n=25$)

Characteristic	*N*	%
Age [(years); mean (range)]	67 (47–83)	
Gender (M/F)	11/14	44/56
Performance status (Karnofsky)		
90–100	17	68
80	3	12
60–70	5	20
No. of metastatic sites		
1	11	44
2	10	40
>2	4	16
Stage at diagnosis		
II	4	16
III	8	32
IV	13	52
Prior adjuvant treatment (yes/no)	9/16	36/64
First-line chemotherapy		
5-FU bolus + LV	8	32
UFT + LV	10	40
5-FU c.i.	2	8
oxaliplatin + 5-FU c.i.	4	16
oxaliplatin + capecitabine	1	4
Previous radiotherapy (yes/no)	3/22	12/88

Table 2 Toxicity according to NCI-CTC classification (per patient)

Toxicity	Grade 1/2 [*N*(%)]	Grade 3/4 [*N* %)]
Hematological		
anemia	11(44)	2(8)
neutropenia	5(20)	3(12)
Non-hematological		
alopecia	12(48)	0(0)
diarrhea	14(56)	4(16)
emesis	12(48)	1(4)
hand–foot syndrome	6(24)	0(0)
mucositis	11(44)	0(0)
sensory peripheral neuropathy	0(0)	1(4)

Treatment administration

A total of 142 cycles of chemotherapy were administered, with a median of 6 cycles per patient. The dose of one or both drugs had to be reduced in 56% of patients due to toxicity. Nevertheless, median absolute dose intensities administered were 96 mg/m^2/week for CPT-11 (96% of the planned dose) and 1487 mg/m^2/week for 5-FU (85% of the planned dose), respectively.

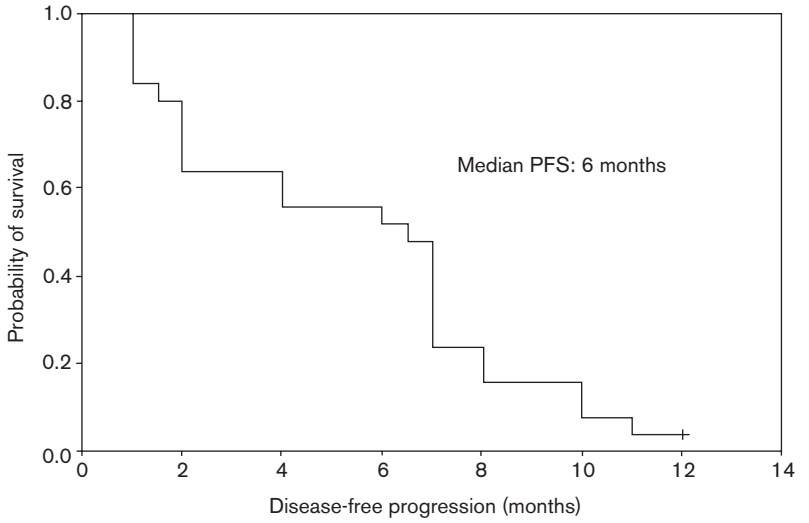
Toxicity

All patients were evaluable for toxicity (Table 2). Grade 3/4 neutropenia was recorded in only three patients, with one case of febrile neutropenia. Grade 3 anemia was recorded in two patients and there was no grade 3/4 platelet toxicity. The main non-hematological toxicity was diarrhea, which occurred in 72% of patients, being of grade 3/4 in only 16% of patients. Severe emesis was exceptional and no grade 3/4 mucositis was observed. Grade 2 hand and foot syndrome was presented in four patients. One patient had grade 3 sensory peripheral neuropathy after 4 cycles of chemotherapy in the absence of previous exposure to oxaliplatin and without hand and foot syndrome simultaneously. Nine patients had cholinergic syndrome with the administration of CPT-11, although it was mild in all cases and resolved rapidly with s.c. atropine. Only one toxic death secondary to grade 4 diarrhea was reported, with acute grade 4 kidney failure after the fourth treatment cycle due to dehydration.

Efficacy

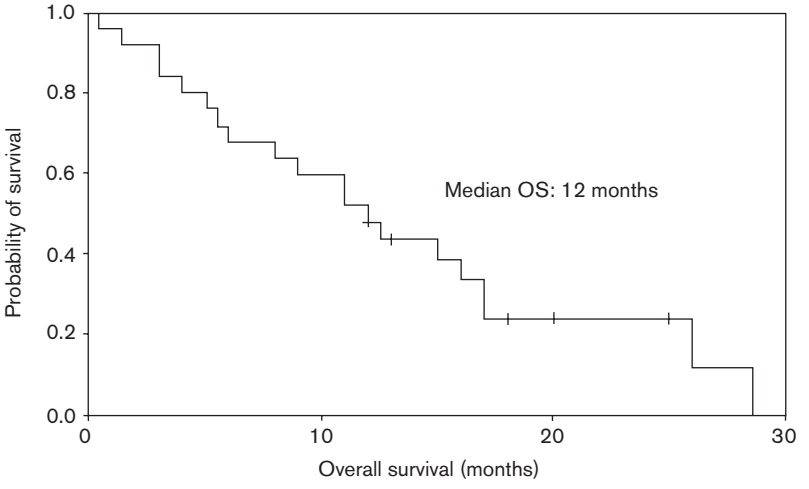
Twenty-four of 25 patients were evaluable for response. Response rate was analyzed by intention-to-treat. One patient was not evaluable due to early death because of digestive hemorrhage in the absence of thrombocytopenia. Two patients achieved a complete response (CR) and five a partial response (PR), resulting in an overall response rate (ORR) of 28% (CI 95% 12.0–49.3%). Disease stabilization (DS) was observed in 10 patients (40%), resulting in a tumor growth control rate of 68% (17 patients) and disease progression (DP) in 7 (28%). Best overall responses achieved in the five patients who received an oxaliplatin combination as first-line chemotherapy were 1 CR, 1 PR, 2 DS and 1 DP. Four of the five patients who received the treatment after early failure of adjuvant treatment were evaluable for response, obtaining 1 CR, 2 DS and 1 DP. Figures 1 and 2 show the actual curves of PFS and OS. With a median follow-up of

Fig. 1



PFS by the Kaplan–Meier method.

Fig. 2



OS by the Kaplan–Meier method.

18 months, median PFS was 6 months and median OS was 12 months (range 0.5–28.5 months). The 1-year survival rate was 32%.

Discussion

In 1998, after the publication of the studies of Cunningham [1] and Rougier [2] which showed that irinotecan monotherapy achieved a better survival rate than continuous infusion of 5-FU and best supportive care, irinotecan treatment was established as standard second-line treatment of advanced CRC after 5-FU failure. The continuous infusion of 5-FU is an active treatment in patients with previous exposure to bolus 5-FU [3] with a favorable toxicity profile, which makes it an ideal candidate for combination with CPT-11 administered every 3 weeks. In a phase I study performed in our center in collaboration with Hospital 12 de Octubre the recommended doses for CPT-11 and protracted 5-FU were 300 mg/m^2 every 3 weeks and 250 mg/m^2/day, respectively. With this second-line treatment regimen, we obtained an objective response rate of 28%, with a

median overall survival of 12 months and 32% of patients are still alive at 1 year of follow-up. This objective response rate was higher than those obtained in studies of irinotecan as a single agent, which range from 11 to 23% [5–12]. However, these differences must be interpreted with caution, since our study is based on a single-center series of a small number of patients who presented no criteria of true resistance to 5-FU, in contrast to the baseline population of some of the studies of CPT-11 monotherapy that have been published [6,8,10,11]. Other studies of irinotecan in combination in second- and third-line treatment have been published recently. André *et al.* [13], with the FOLFIRI scheme [biweekly administration of CPT-11 180 mg/m^2 associated with a regimen of leucovorin (LV) followed by bolus and a 46-h c.i. of 5-FU] achieved an objective response rate of 6%, although it was administered as third-line treatment after progression with 5-FU + LV and then with a combination of oxaliplatin + LV/5-FU bolus/5-FU c.i. A later study of sequential chemotherapy compared the overall TTP after two lines of chemotherapy—either FOLFIRI followed by FOLFOX or FOLFOX followed by FOLFIRI. When FOLFIRI was given after first-line treatment with the FOLFOX regimen the objective response rate was low (4%) [14]. Higher rates of objective response in second-line have been obtained with combinations of irinotecan and other drugs like mitomycin C [15] or oxaliplatin [16,17]. The last combination has obtained a response rate of 23–42% with a moderate toxicity in patients refractory to 5-FU, although some patients received prophylactic granulocyte colony stimulating factor. Currently, new combinations of irinotecan are being developed in which 5-FU is replaced by new-generation oral fluoropyrimidines, although these have yet to be compared to continuous infusion 5-FU. Alonso *et al.*, in a phase I trial, recommended a combination of UFT 250 mg/m^2/day × 21 days in addition to irinotecan 110 mg/m^2 on days 1, 8 and 15, in 4-week cycles [18]. With this regimen they found a 10% response rate to second-line treatment of patients with advanced CRC. It has also been shown to be feasible to combine irinotecan 70 mg/m^2/week × 6 weeks with capecitabine 1000 mg/m^2/12 h on days 1–14 and 22–35, in cycles every 50 days [19]. Schemes of the administration of capecitabine 1250 mg/m^2/12 h × 14 days combined with irinotecan, 300 mg/m^2 on day 1 or 150 mg/m^2 on days 1 and 8 every 3 weeks have demonstrated a notable rate of response in preliminary analyses (71%) [20]. Recently, encouraging results have been obtained by Kerr *et al.* in a phase I/II trial combining CPT-11 250 mg/m^2 plus capecitabine 1000 mg/m^2 every 12 h for 14 days, in a every-3-weeks scheme [21].

The median OS reported with this schedule (12 months, range 0.5–28.5) was slightly higher than that found in the two large phase III studies of irinotecan as monotherapy (10.8 and 9.2 months). Similarly, the median time to progression (6 months) was at least comparable with that of CPT-11 alone (6 versus 4.2 months). However, it should be emphasized that 44% of our patients received a third-line chemotherapy based on combinations with oxaliplatin, which could have contributed to an increase in overall survival.

The toxicity of this combination is mild-to-moderate and basically extramedullary. In this study, diarrhea is the main manifestation, appearing as grade 3 or 4 in 16% of patients. This low toxicity rate contrasts with that recently observed with the combination of irinotecan and bolus 5-FU/LV [22] and is consistent with the European schedule of continuous infusion of 5-FU associated to irinotecan.

In conclusion, the administration of irinotecan + 5-FU as a protracted continuous infusion is an active and safe second-line treatment of advanced CRC. At present, it would be important to know its activity in the subgroup of patients treated previously with oxaliplatin plus continuous infusion 5-FU combinations, and to determine through a randomized phase III study if this schedule could give a survival advantage compared with single-agent irinotecan as second-line treatment of patients with advanced CRC.

Acknowledgments

We would like to thank Beatriz Gil-Alberdi (Aventis Pharma SA) for assistance in the preparation of the manuscript.

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