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Original Paper

CPT-11 (Irinotecan) Addition to Bimonthly, High-dose Leucovorin and Bolus and Continuous-infusion 5-Fluorouracil (FOLFIRI) for Pretreated Metastatic Colorectal Cancer

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CPT-11 (irinotecan) has shown activity in patients with advanced colorectal cancer resistant to leucovorin (LV) and 5-fluorouracil (5-FU). In this study, the simplified bimonthly LV–5-FU regimen was combined with CPT-11 (FOLFIRI) as third-line therapy for patients with advanced colorectal cancer. Continuous infusion of 5-FU was administered with disposable pumps as outpatient therapy. FOLFIRI consisted of CPT-11 180 mg/m^2 as a 90-min infusion day 1; LV 400 mg/m^2 as a 2-h infusion during CPT-11, immediately followed by 5-FU bolus 400 mg/m^2 and 46-h continuous infusion of 2.4–3 g/m^2 every 2 weeks. Among the 33 patients treated, 2 had partial responses for an overall response rate of 6%; 20 patients were stabilised (61%) and 11 had disease progression (33%). From the start of FOLFIRI, median progression-free survival was 18 weeks and median survival was 43 weeks. For the 242 cycles analysed, NCI-CTC toxicities grade 3–4 per patient were nausea 15%, diarrhoea 12% and neutropenia 15%. Overall, 10 patients (30%) experienced grade 3–4 toxicity. 7 patients (21%) had grade 2 alopecia. FOLFIRI generated activity and acceptable toxicity, in heavily pretreated patients, with limited diarrhoea, mostly asymptomatic neutropenia and manageable nausea and relatively uncommon alopecia. This regimen is suitable for studies in chemotherapy-naïve patients. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: irinotecan (CPT-11), 5-fluorouracil, leucovorin, metastatic colorectal cancer
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INTRODUCTION

TREMENDOUS PROGRESS has been made in the medical treatment of advanced colorectal cancer over the past 2–3 years due to the availability of several new drugs, especially oxaliplatin and CPT-11 (irinotecan). CPT-11 has activity against advanced metastatic colorectal cancer both in chemotherapy-naive and pretreated patients whose disease progressed on 5-fluorouracil (5-FU) [1, 2]. Two large, randomised, multicentre studies, on patients with 5-FU bolus-resistant metastatic colorectal cancer, established the superiority of CPT-11 over best supportive care [3] or 5-FU continuous-infusion regimens [4].

Combining CPT-11 and 5-FU is a logical approach to attempt to improve the results obtained with CPT-11 or 5-FU-based treatments alone. Since the publication of studies [5] showing that leucovorin (LV) enhances the efficacy of 5-FU against advanced colorectal carcinoma, progress has been made in developing LV–5-FU regimens to improve the therapeutic ratio. High-dose LV plus bolus and continuous-infusion 5-FU twice monthly (LV5FU2) [6] improved the response rate and progression-free survival (PFS) and generated less toxicity compared with the 5-day Mayo Clinic regimen. A new, simplified, bimonthly regimen, which combines

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LV and 5-FU bolus and 46-h high-dose infusion [7, 8], has low toxicity, is at least as active as the other LV–5-FU regimens and less burdensome for the patients, as it is administered less frequently on an outpatient basis with the use of disposable pumps. Preclinical experiments on cell cultures and human tumour xenografts have indicated potential synergy when CPT-11 is combined with 5-FU and LV. *In vitro*, synergy has appeared to be optimal when CPT-11 exposure preceded 5-FU [9]. Preliminary analysis of pharmacokinetic data has suggested a minor interaction between CPT-11 and 5-FU that resulted in statistically significantly lower 5-FU catabolism [10, 11]. Various administration schedules of CPT-11–5-FU combinations have been investigated in phase I studies in Japan, the U.S.A. and Europe. Preliminary results have indicated that concurrent administration of different doses of CPT-11, 5-FU and LV is feasible in terms of safety. The maximum tolerated dose of CPT-11, when given every 2 weeks in combination with the LV5FU2 fixed regimen [6], in patients with colorectal cancer resistant or refractory to 5-FU, was 180 mg/m^2 [12].

In light of these promising data and considering the *in vitro* and *in vivo* studies suggesting potential synergistic activity of the CPT-11, LV and 5-FU combination, a phase II study was undertaken. The primary objective of this study was to determine the toxicity profile and the feasibility of this regimen (FOLFIRI: FOLinic acid, 5-FU, IRInotecan) and the second was to assess its efficacy in patients with metastatic progressive disease (PD) after administration of at least two lines of chemotherapy including bimonthly LV–5-FU and oxaliplatin (FOLFOX regimens) [13, 14].

PATIENTS AND METHODS

Inclusion criteria

Patients were required to be 18–80 years old, and have histologically confirmed adenocarcinoma of the colon or rectum. The patients had to have PD as defined by the World Health Organization (WHO) ($\geq$25% increase of assessable disease or the appearance of new neoplastic lesion(s) whilst under second-line chemotherapy for metastatic disease with FOLFOX regimens) [13–15]. An interval of at least 2 weeks must have elapsed since prior treatment and the time lapse between the last 5-FU infusion and progression assessment was $<$3 weeks for all patients. Other eligibility criteria were: no central nervous system metastases, WHO performance status 0–2, initial evaluation $\leq$2 weeks before inclusion by computed tomography (CT) scan prior to initiation of therapy and feasibility of regular follow-up. Required laboratory parameters included: neutrophil count $>$1500/mm^3, platelet count $>$100 000/mm^3, serum creatinine $<$300 μmol/l, serum alkaline phosphatase $<$3 times the upper normal limit, partial thromboplastin time $>$50%, and bilirubin $\leq$1.5 the upper limit of the normal range. Written informed consent was obtained from all patients.

Treatment administration

CPT-11 (180 mg/m^2) was given intravenously in 500 ml of 5% dextrose solution over 90 min on day 1, LV (DL racemic mixture 400 mg/m^2) was infused on day 1 over 2 h during CPT-11 infusion but without mixing, immediately followed by 5-FU bolus (400 mg/m^2) and 46-h infusion (2.4–3 g/m^2) every 2 weeks (Figure 1). This regimen required only 2.5–3 h in hospital because continuous infusion of 5-FU was administered with disposable pumps as outpatient therapy. For the first two cycles, each patient received 2.4 g/m^2/46 h of 5-FU; the dose was increased to 3 g/m^2/46 h for subsequent cycles when the maximum toxicity was National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grade 0 or 1. This regimen was to be administered until progression as long as the neutrophil count was $>$1500/mm^3, the platelet count was $>$100 000/mm^3 and if toxicity was tolerable (NCI-CTC grade 0 to 2). In the case of toxicity $>$grade 2, the 5-FU continuous infusion dose was to be reduced from 3 to 2.4 g/m^2 and from 2.4 to 2 g/m^2. When neutropenia, thrombocytopenia or diarrhoea exceeded grade 1, the CPT-11 dose was to be lowered from 180 to 150 mg/m^2. If neutropenia, thrombocytopenia or diarrhoea $>$grade 1 persisted at this latter dose, therapy was discontinued.

Supportive care

Specific anti-emetic prophylaxis was left to the investigator's discretion. For patients who experienced an early cholinergic syndrome (lacrimation, diaphoresis, abdominal cramps and/or diarrhoea) occurring during or shortly after CPT-11 administration, atropine sulphate (0.25 mg) could be given subcutaneously. To manage delayed diarrhoea, it was recommended that loperamide (2 mg every 2 h) be given immediately after the first liquid stools and discontinued 12 h after the last loose stool [16]; if the diarrhoea was not controlled after 3 days, other supportive measures, including hospitalisation, were to be considered.

Study parameters

Before each cycle, patients underwent a clinical examination, and blood cells were counted. Carcinoembryogenic antigen (CEA), bilirubin, serum alkaline phosphatases, serum creatinine, lactate dehydrogenase, chest X-ray and CT scans were repeated every 12 weeks (that is every six cycles) or earlier in the case of clinical deterioration. Only patients with bidimensionally measurable lesions on a CT scan were considered assessable for tumour responses. Complete response (CR) was defined as the complete disappearance of all assessable disease for at least 4 weeks; partial response (PR) was defined as a decrease of at least 50% of the sum of the products of the diameters of measurable lesions for at least 4 weeks. Stable disease (SD) was defined as a decrease of less than 50% or an increase of less than 25% of the disease. PD was defined as an increase of at least 25% or the appearance of new neoplastic lesion(s) [17] or a significant clinical deterioration that could not be attributed to CPT-11 or medical conditions other than colorectal cancer. For rectal cancers, assessable metastases had to be outside the irradiated pelvis. Therapy was discontinued when disease progressed or intolerable toxicity occurred. The disappearance or attenuation of tumour-related symptoms (performance status, pain and/or fever) was assessed for those patients who had such

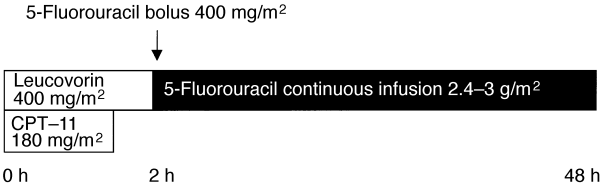

Figure 1. FOLFIRI regimen was repeated every 2 weeks. CPT-11 was administered as a 90-min infusion (day 1) during leucovorin infusion without prior mixing.

symptoms at baseline. Weight gain was defined as a ≥2 kg increase of baseline weight.

Statistical considerations

Survival was calculated from the start of FOLFIRI until death. Time to progression was calculated from the first day of FOLFIRI to the date of progression for all patients entering the study. Survival curves were obtained using the Kaplan–Meier method [18]. All end-points were updated on 12 October 1998.

RESULTS

Patient characteristics

From December 1996 to November 1997, 33 patients met all eligibility criteria and were included in the study. Their characteristics are given in Table 1. All had experienced disease progression whilst on a FOLFOX regimen. The median age was 60.8 years (range, 31–78 years). Overall, 30% of the patients had symptoms attributed to advanced disease.

Table 1. Patient characteristics *(*n = 33*)*

Characteristic	*n*	%
Median age (range)	60.8 (31–78) yrs	
Gender		
Male	15	45
Female	18	55
Primary tumour		
Colon	23	70
Rectum	10	30
Site of metastases		
Liver	28	85
Lung	14	42
Other	14	42
Involved sites		
1	15	45
2 (liver and other)	15	45
>2	3	9
WHO performance status		
0	17	52
1	14	42
2	2	6
Tumour-related symptoms		
None	23	70
Yes	10	30
Alkaline phosphatase		
Within normal range	12	36
Elevated	21	64
Elevated CEA		
Increased >10 ng/ml	30	91
Increased >100 ng/ml	15	45
Previous chemotherapy		
First-line		
Bimonthly LV–5-FU*	28	85
5-FU bolus and LV	5	15
Second-line		
Bimonthly LV–5-FU*	33	100
With oxaliplatin (FOLFOX)†		

CEA, carcinoembyromic antigen; LV, leucovorin; 5-FU, 5-fluorouracil. *Bimonthly LV–5-FU: 2-day bimonthly regimen: LV5FU2 or FOLFUHD or simplified LV–5-FU [8]. †FOLFOX, 2-day bimonthly regimen of LV, 5-FU and oxaliplatin [13–15].

Treatment

The median number of treatment cycles administered was six (range, 2-30). 16 patients (49%) received more than six cycles. 28 patients (85%) were withdrawn from the study because of PD. 2 patients (6%) refused to continue (personal convenience with toxicity <2) and 3 others (9%) stopped treatment because of its toxicity (1 for grade 4 diarrhoea and 2 for severe asthenia).

Toxicity

The incidence of the main toxic effects according to the NCI-CTC grade scale [19] are listed in Table 2. Two hundred and forty-two cycles could be evaluated. Neutropenia reached grade 3–4 in 5 patients (15%), including 2 patients (6%) who had one episode of febrile neutropenia. Neutropenia did not recur after 5-FU and CPT-11 dose reductions in those patients who had experienced grade 3–4 neutropenia. Grade 3–4 delayed diarrhoea developed in 4 patients (12%) and only 1 patient (without febrile neutropenia) required hospitalisation and discontinued the FOLFIRI regimen for this reason. The other grade 3–4 toxicities observed were nausea/vomiting in 5 patients (15%). Mild side-effects also included conjunctivitis and fatigue. Alopecia was grade 1 in 8 patients (24%) and grade 2 in 7 patients (21%). Overall, 10 patients (30%) experienced grade 3–4 toxicity. 13 (39%) received the maximal 5-FU dose scheduled, that is 3 g/m^2/46 h. No toxic death occurred. CPT-11 administration was associated with an early cholinergic syndrome that developed in 15 patients (45%) during or immediately after infusion. These adverse events were usually mild to moderate in severity and short in duration, and could be prevented or their duration shortened by atropine sulphate which was given when this syndrome accompanied the first administration of CPT-11.

Objective tumour responses and survival

The objective response rate for all patients was 6% ($n = 2$; 95% confidence interval, 0–13). The two PRs lasted 22 and 28 weeks. Sixty-one per cent of the patients ($n = 20$) had SD and 33% ($n = 11$) had PD disease. Median PFS was 18 weeks and median survival was 43 weeks from the start of FOLFIRI (Figure 2). Median duration of SD was 23 weeks.

Palliative and biological effects

Pain disappeared in 2 of the 6 patients (33%) who had experienced pain at baseline. 8 patients (24%) gained ≥2 kg. Performance status improved for 8 of the 16 (50%) patients

Table 2. *Percentage toxicities per patient (maximum NCI-CTC grade) evaluated for* 242 *cycles given to* 33 *patients*

	NCI-CTC grade (%)				
Side-effect	0	1	2	3	4
Nausea/vomiting	30	40	15	15	0
Mucositis	49	36	15	0	0
Delayed diarrhoea	43	30	15	9	3
Hand–foot syndrome	64	27	9	0	0
Anaemia	76	18	6	0	0
Neutropenia	49	24	12	9	6
Thrombocytopenia	67	30	3	0	0
Alopecia	55	24	21	–	–
Maximum grade of toxicity	0	24	46	21	9

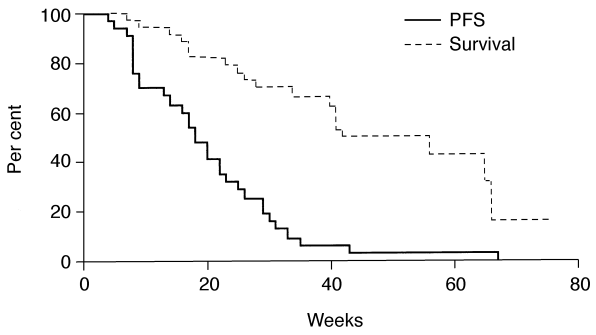

Figure 2. Survival and progression-free survival (PFS) observed under FOLFIRI for pretreated advanced colorectal cancer.

whose baseline performance status had been ≥ 1. Among the 30 patients with elevated CEA levels at the start of therapy, values normalised or decreased >50% for 4 (13%).

DISCUSSION

This phase II study assessed the toxicity of the combination of the simplified LV–5-FU regimen with CPT-11 (FOLFIRI) as third-line therapy for patients with disease progression while on FOLFOX. Various combinations of CPT-11 and 5-FU with or without LV have been tested in phase I–II studies in the U.S.A. [20–22], Europe [10–12, 23] and Japan [24, 25]. In accordance with the findings of the present study, those studies showed clinical activity against colorectal cancer, including patients who had been heavily pretreated. Neutropenia and diarrhoea were the main toxicities observed but were, in this and several other studies, less frequent and severe than in the studies with CPT-11 alone given at 350 mg/m^2 every 3 weeks, 250 mg/m^2 every 2 weeks or 125 mg/m^2 weekly [1, 2, 26]. The predominant toxicities per patient in those three studies were grade 3–4 neutropenia (47, 38 and 22%, respectively) and grade 3–4 diarrhoea (38, 18 and 36%, respectively). The lower rates of grade 3–4 delayed diarrhoea (12%) and neutropenia (15%) in the present study, with only 1 patient discontinuing treatment, can be explained by the lower CPT-11 dose. Fatigue was a frequent symptom and led to treatment withdrawal for 2 patients.

The response rate of 6% (95% confidence interval, 0–13) and 61% SD in this study suggests that third-line therapy is feasible and can be helpful in patients with metastatic colorectal cancer especially if the median SD duration of 23 weeks is considered. 11 patients (33%) had documented PD before or just after six cycles (time of their first tumour assessment), which suggests that efficacy should be evaluated earlier to avoid ineffective and costly cycles. CPT-11 alone as second-line therapy, at a higher-dose intensity compared with FOLFIRI, achieved a response and SD rates between 54.5% and 71% [1, 2, 4]. The addition of CPT-11 to LV–5-FU as third-line therapy achieved results comparable with second-line CPT-11 alone, which suggests either some *in vivo* synergism between the drugs or that the activity of CPT-11 alone is similar in patients whose cancers are resistant to 5-FU and those resistant to 5-FU and oxaliplatin. This report also confirms that the acceptable toxicity of the simplified regimen allows other antitumour drugs to be combined to enhance its activity [14].

In conclusion, as third-line therapy in patients with metastatic colorectal cancer, FOLFIRI has an acceptable toxicity profile and some antitumour activity. This regimen is now being evaluated in first- or second-line chemotherapy in a randomised, first-line study.

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