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Phase I trial of weekly irinotecan combined with UFT as second-line treatment for advanced colorectal cancer

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Abstract

The aim of this study was to determine the maximum-tolerated dose (MTD) and dose-limiting toxicity (DLT) of weekly Irinotecan (CPT-11) plus UFT, and to assess the antitumour activity of this combination as second-line chemotherapy in patients with advanced colorectal carcinoma, 31 patients with measurable advanced colorectal carcinoma were treated. Cohorts of 3 patients received increasing dose levels of the combination. Levels 1 to 4 included a fixed dose of oral (p.o.) UFT (250 mg/m^2/day) for 21 days of a 28-day cycle combined with increasing intravenous (i.v.) doses of CPT-11 (80, 100, 110 and 120 mg/m^2) on days 1, 8 and 15. Levels 5 and 6 included a higher fixed dose of oral UFT (300 mg/m^2) combined with increasing i.v. doses of CPT-11 (100 and 110 mg/m^2) on days 1, 8 and 15. 147 courses were administered. MTD were reached at level 4 (2 cases of grade 4 diarrhoea and 1 grade 3 asthenia), and level 6 (1 grade 4 diarrhoea, 1 grade 3 diarrhoea and 1 grade 3 febrile neutropenia). Responses in 30 evaluable patients were: 3 partial responses (10%), 15 stable disease (50%) and progressive disease in 12 patients (40%). Median time to progression was 4.5 months (95% Confidence Interval (CI): 3.4–6.6 months) and median survival was 11 months (95% CI: 7.9–14.1 months). The recommended doses for phase II trials are: (a) CPT-11 110 mg/m^2 i.v. on days 1, 8 and 15 every 28 days plus UFT 250 mg/m^2 p.o. on days 1 through to 21 or (b) CPT-11 100 mg/m^2 and UFT 300 mg/m^2.

Keywords: Advanced colorectal carcinoma; Irinotecan; Second-line chemotherapy; UFT

1. Introduction

Colorectal carcinoma is the second leading cause of cancer death in the Western world [1]. Approximately one-half of all patients diagnosed with colorectal carcinoma will die of the disease, with patient prognosis depending on the stage at presentation. Curative surgery is possible for patients who present with early-stage disease. However, the 5-year survival rate is less than 5% in patients who develop distant metastases. For more than 40 years, 5-fluorouracil (5-FU) has remained the mainstay of treatment for patients with advanced colorectal carcinoma [2–4], but therapeutic strategies are changing due to the availability of new active agents (CPT-11, Oxaliplatin and Raltitrexed).

UFT® (Bristol-Myers Squibb) is an oral combination of uracil and tegafur (a prodrug of 5-FU) in a molar ratio of 4:1 developed by Fuji and colleagues [5]. In preclinical studies, this combination increases the intratumoral concentration of 5-FU and this results in enhanced antitumour activity. Plasma 5-FU concentrations with oral administration of UFT are similar to equimolar doses of 5-FU administered as a continuous infusion [6]. The phase I studies of UFT without leucovorin (LV) conducted by Pazdur [7] demonstrated differences in the toxicity profile depending on the schedule followed. Neutropenia was the DLT with the 5-day schedule, while diarrhoea was the DLT with the 28-day schedule. The recommended doses for phase II studies of UFT without LV were 800 mg/m^2/day over 5 days or 360 mg/m^2/day over 28 days every 5 weeks. In clinical practice, the most frequently used dose is 300–400 mg/m^2/day divided in two or three administrations and continued for 21–28 days, followed by a 7-day rest

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period. Phase I studies of UFT with oral LV recommended a dose of UFT of 300 mg/m^2/day plus LV 75–150 mg/day over 28 days followed by a 1-week rest period [8]. These phase I studies served as the basis for the phase II study as first-line treatment of patients with advanced colorectal carcinoma conducted by Pazdur and colleagues that showed a response rate of 42.2% (95% CI: 28–58%) [9]. Subsequently, two phase III first-line trials have been performed by Pazdur and colleagues [10] and Carmichael and colleagues [11], that compared the oral UFT + LV schedule with intravenous 5-FU + LV according to the schedule of the North Central Cancer Treatment Group (NCCTG). These trials showed no differences in the response rate, median time to progression and overall survival between both schedules, but the toxicity profile was better for UFT + LV.

Irinotecan (CPT-11; Campto®; Rhône-Poulenc Rorer) is a new semi-synthetic agent which is a water soluble derivative of camptothecin, that is converted *in vivo* to the active metabolite SN-38 that confers the antitumour activity [12]. CPT-11 is an inhibitor of topoisomerase I, an enzyme that acts in the formation of the DNA double-strand [13]. Phase I studies conducted in Europe recommended a single intravenous (i.v.) dose of CPT-11 of 350 mg/m^2 every 3 weeks, while the proposed dose in the American and Japanese trials is 100–125 mg/m^2 i.v. weekly for 4 weeks out of every 6 weeks. Delayed diarrhoea and neutropenia are the DLT [14,15]. In phase II studies using CPT-11 as second-line treatment of colorectal carcinoma, response rates were 14–23% in patients previously treated with bolus 5-FU, with a median time to progression of 4 months and a median survival of 9.5 months, suggesting an absence of cross-resistance between 5-FU and CPT-11 [16–20]. Two phase III trials have been performed with CPT-11 as second-line treatment following failure of 5-FU + LV. One of them compared CPT-11 with best supportive care and the other with continuous infusion of 5-FU. Both studies demonstrated a benefit for patients treated with CPT-11 in overall survival, time to progression and quality of life [21,22]. Recently, two phase III trials comparing 5-FU + LV + CPT-11 versus 5-FU + LV as first-line treatment of advanced colorectal carcinoma have been published. In both, the combination arm has shown benefit in the response rate, time to progression and median survival [23,24].

To date, only one study of CPT-11 + UFT without LV has been presented. Yamazaki and colleagues [25], in a phase I trial with CPT-11 by continuous infusion over 24 h and UFT in patients with non-small cell lung cancer, found a maximum tolerated dose (MTD) of 160 mg/m^2 of CPT-11 administered on day 8 combined with UFT 400 mg/12 h orally (p.o.) on days 1–7 every 14 days. An additional phase I study was reported by Hill and colleagues [26] tested CPT-11 plus UFT plus LV in patients with colorectal carcinoma; the DLT were febrile neutropenia and diarrhoea. Recommended doses for phase II studies were CPT-11 250 mg/m^2 i.v. over 60 minutes on day 1 combined with UFT 250 mg/m^2/day and LV 90 mg/day, both on days 1–14 every 21 days. Since the tolerance of CPT-11 is significantly better, with respect to neutropenia and alopecia, when administered weekly rather than every 21 days [17,18,20,27–29], and that is also true for UFT, 21–28-day continuous administration being preferred over the shorter periods, we decided to perform a phase I-II trial with weekly CPT-11 in combination with oral UFT given over 21 days of a 28-day course, in patients with advanced colorectal carcinoma previously treated with chemotherapy.

The primary objective of our study was to define the tolerance and safety of CPT-11 combined with UFT by determining the MTD and the DLT. The secondary objective was to assess the activity of this combination as second-line treatment in patients with advanced colorectal cancer.

2. Patients and methods

2.1. Eligibility

Inclusion criteria were: age older than 18 years; advanced colorectal carcinoma not amenable to surgical resection; bi-dimensionally measurable disease in a non-irradiated area; one prior chemotherapy regimen for advanced disease (prior treatment with 5-FU or UFT, but not CPT-11 was allowed); patients were not refractory to the first-line of chemotherapy (just pretreated); life expectancy more than 12 weeks; World Health Organization (WHO) performance status 0-2; adequate renal function, defined as serum creatinine <140 μmol/l; adequate hepatic function, defined as serum bilirubin less than 1.25 times the upper normal limit, transaminases (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) 3 times or less the upper normal limit or 5 times or less above the upper limit in the presence of liver metastases; adequate haematological function, defined as absolute neutrophil count of 2000×10^6 cells/l or higher and platelets of 100×10^9 cells/l or higher. Exclusion criteria were: chronic diarrhoea; bowel obstruction; uncontrolled severe disease; brain metastases; pregnancy or lactation; concomitant treatment with other anti-neoplastic drugs; secondary neoplasias. All the patients gave fully-informed consent prior to recruitment into the study.

2.2. Pretreatment evaluation and follow-up

Evaluation prior to treatment consisted of detailed clinical history and physical examination, full blood count, blood chemistry including electrolytes, renal and

hepatic function tests, electrocardiogram (ECG), chest X-ray and computed tomography (CT) scan of the abdomen. During the treatment period, patient monitoring included weekly assessment of toxicity and blood counts, blood chemistries at each course and physical examination before each course. Response was evaluated every three courses and at the end of treatment.

2.3. Treatment schedule

Vials (5 ml containing 100 mg) of CPT-11 were diluted in 250 ml 0.9% saline serum and infused intravenously over 60 min on days 1, 8 and 15 of each course. Packets containing 100 mg of UFT were given orally in two or three daily doses before meals on days 1–21 of each cycle. Courses were repeated every 28 days. All patients received prophylactic anti-emetic premedication ($5HT_3$-receptor antagonists and dexamethasone) before the CPT-11 infusion. Subcutaneous (s.c.) prophylactic atropine was recommended for subsequent courses in patients with cholinergic syndrome following infusion of CPT-11. Treatment was administered on an outpatient basis.

All the patients were carefully advised, should diarrhoea present, to take 4 mg of oral loperamide immediately and to continue with a dose of 2 mg every 2 h for up to 12 h following the last liquid stool provided that the duration of diarrhoea did not exceed 48 h. If diarrhoea persisted for more than 24 h, an empirical oral antibiotic (ciprofloxacin) was added and if it persisted for more than 48 h, the patient was admitted to hospital.

In case of diarrhoea, mucositis or myelosupression that were grade 1 or worse of the common toxicity criteria scale (NCI-CTC) on the day scheduled for further chemotherapy administration, treatment was delayed until complete recovery. Patients presenting with NCI-CTC grade 3 or worse mucositis had the UFT dose reduced by 20% in the subsequent cycles. Patients presenting with grade 3 or worse haematological toxicity or diarrhoea had the doses of CPT-11 and UFT reduced by 20%. In case of disease progression, unacceptable toxicity or delay in treatment administration of more than 4 weeks, the patient discontinued the trial. In patients who achieved objective response or stable disease, treatment was continued until disease progression or unacceptable toxicities developed.

2.4. Dose escalation

In the first four dose levels, a fixed dose of UFT of 250 mg/m^2/day was administered on days 1–21 with escalation of the dose of CPT-11 from 80 to 120 mg/m^2 on days 1, 8 and 15 every 4 weeks (Table 1). In levels 5 and 6, a fixed dose of UFT of 300 mg/m^2/day on days 1–21 was combined with escalating doses of CPT-11. Initially, 3 patients were assigned to the first dose level and, if no DLT occurred, the next 3 patients were treated at the next dose level. If any one of the first 3 patients at any dose level presented with DLT, 3 further patients were assigned to the same dose level. If 2 of the first 3 patients, or 3 or more patients, presented with DLT, the MTD was considered to have been reached and the next lower dose level was considered as the recommended dose for subsequent studies.

2.5. Toxicity and response evaluation

Toxicity was assessed weekly according to the NCI-CTC scale. The DLT was defined after the first treatment course as any non-haematological toxicity that was grade 3 or worse (except for alopecia, nausea or vomiting) or any haematological toxicity that was grade 4 or grade 3 if it was associated to complications (neutropenic fever or bleeding). Response was assessed by CT scan every three courses and at the end of treatment. Response was defined according to WHO criteria [30].

3. Results

From October 1998 to April 2000, 31 patients with advanced colorectal carcinoma and measurable disease were included in the trial. The patients' characteristics are listed in Table 2. Eleven females and 20 males were treated on six different dose levels (Table 1). The median age of the patients was 61 years (range 39–75 years) and median WHO performance status was 1 (range 0–2). 6

Table 1
Dose levels and DLTs

Dose level	CPT-11 (mg/m^2)	UFT (mg/m^2)	Patients	Cycles	DLT	Toxicity
1	80	250	3	14	0 of 3	
2	100	250	6	35	2 of 6	G3 diarrhoea
3	110	250	3	16	0 of 3	
4	120	250	6	33	3 of 6	G4 diarrhoea (2 patients) and G3 asthenia
5	100	300	7	25	1 of 7	G4 diarrhoea
6	110	300	6	24	3 of 6	G3 and G4 diarrhoea, and febrile neutropenia

DLT, dose-limiting toxicity; G, grade.

Table 2
Patients' characteristics

Sex (M/F)	20/11
Age (years)	
Median (range)	61 (39–75)
Performance status	
0	9 (29%)
1	17 (55%)
2	5 (16%)
Primary tumour	
Colon	14 (45%)
Rectum	17 (55%)
Adjuvant CT	6 (19%)
Adjuvant RT	8 (26%)
1st line CT for advanced disease	
5-FU + LV (NCCTG)	16 (52%)
Raltitrexed	6 (19%)
UFT + LV	6 (19%)
5-FU CI (Spanish Group for Treatment of Digestive Tumours, TTD)	3 (10%)
Metastatic sites	
Liver	20 (65%)
Lung	12 (39%)
Other	18 (58%)
Number of metastatic sites	
1	12 (39%)
2	19 (61%)
CEA (ng/ml)	
Median (range)	48 (0–1776)

NCCTG, North Central Cancer Treatment Group; CEA, carcinoembryonic antigen; 5-FU, 5-fluorouracil; CT, chemotherapy; RT, radiotherapy; LV, leucovorin; M/F, male/female; CI, continuous infusion.

patients (19%) had received 5-FU-based adjuvant chemotherapy and 8 (26%) had received adjuvant radiotherapy. All patients had received one line of chemotherapy for metastatic disease; 16 were given 5-FU + LV (NCCTG scheme), 6 Raltitrexed (3 mg/m^2), 6 UFT + LV (Pazdur scheme) and 3 weekly 5-FU (3.5 g/m^2 in a 48-h continuous infusion). Seventeen patients received third-line chemotherapy treatment (based on oxaliplatin in all cases) following the failure of the study treatment.

All patients received at least one complete course of treatment and were therefore assessable for toxicity. 30 patients were assessable for response. One patient was found on review to have only unidimensionally measurable disease. A total of 147 courses were administered (median of four per patient, range 1–13). The number of cycles administered per dose level is shown in Table 1. No DLTs were observed for dose levels 1 and 3. In dose level 2, 2 patients presented with NCI-CTC grade 3 diarrhoea and 1 of them with grade 2 mucositis. When the dose of CPT-11 was escalated to 120 mg/m^2 (dose level 4) the MTD was reached, with a NCI-CTC grade 4 diarrhoea in 2 of 6 patients and 1 patient experiencing a NCI-CTC grade 3 asthenia. In the second escalation group of patients (dose levels 5 and 6), the MTD was reached at the level 6, in which 3 patients had DLT: 1 with neutropenic fever, another 1 with NCI grade 3 diarrhoea and a third one with NCI grade 4 diarrhoea.

The most frequent side-effect was diarrhoea; 32% of patients presented grade 3–4 diarrhoea throughout the treatment, with 1 patient needing hospitalisation for a period of 4 days; however, all of the patients except for 1, could continue treatment after a 20% dose reduction. Other haematological and non-haematological side-effects were mild and did not exceed NCI-CTC grade 2 (Tables 3 and 4). No significant changes were observed in the serum concentrations of the hepatic enzymes or bilirubin during the treatment. All patients received potent anti-emetic prophylaxis with $5HT_3$-receptor antagonist and dexamethasone. NCI-CTC grade 2 emesis was observed in 25% of the patients during the first course and in 35% of the overall courses. NCI-CTC grade 2 alopecia was observed in 19% of the patients, but no grade 3 was seen. Of note among the other side-effects was the appearance, albeit infrequently, of grade 3 mucositis in 1 patient, grade 3 anaemia in 1 patient and grade 3 asthenia in 2 patients. In the six dose levels, treatment delays and/or dose

Table 3
Grade 3–4 haematologic toxicity

Dose level	1		2		3		4		5		6	
Patients on level	3		6		3		6		7		6	
Number of cycles	14		35		16		33		25		24	
Toxicity grade	3	4	3	4	3	4	3	4	3	4	3	4
First course												
Anaemia	0	0	0	0	0	0	0	0	0	0	1	0
Neutropenia	0	0	0	0	0	0	1	0	0	0	0	1
Platelets	0	0	0	0	0	0	0	0	0	0	0	0
All courses												
Anaemia	0	0	0	0	0	0	0	0	0	0	1	0
Neutropenia	0	0	1	0	0	0	0	0	0	0	0	0
Platelets	0	0	0	0	0	0	0	0	0	0	0	0

Table 4
Grade 3–4 non-haematological toxicity

Dose level	1		2		3		4		5		6	
Patients on level	3		6		3		6		7		6	
Number of cycles	14		35		16		33		25		24	
Toxicity grade	3	4	3	4	3	4	3	4	3	4	3	4
First course												
Nausea/vomiting	0	0	0	0	0	0	0	0	0	0	0	0
Diarrhoea	0	0	2	0	0	0	0	2	0	1	1	1
Mucositis	0	0	0	0	0	0	0	0	0	0	0	0
Asthenia	0	0	0	0	0	0	1	0	1	0	0	0
All courses												
Nausea/vomiting	0	0	0	0	0	0	0	0	0	0	0	0
Diarrhoea	0	0	2	0	1	0	1	1	0	1	2	1
Mucositis	0	0	0	0	0	0	1	0	0	0	0	0
Asthenia	1	0	0	0	0	0	1	0	0	0	0	0

reductions were necessary in only 17 (12%) of the 147 courses administered. No correlation was found between prior adjuvant chemotherapy and/or radiotherapy to the pelvis and the incidence of diarrhoea or the other toxicities observed in this study. No cumulative toxicity was seen, and there were no toxic deaths.

Of the 21 symptomatic patients, 10 (48%) had clinical improvement (pain control, increase in weight and improvement in performance status) with the treatment. Only 5 patients (21%) of 24 with elevated carcinoembryonic antigen (CEA) had a decrease in the level of CEA > 50%. Although the response rate was not the main aim of this study, the antitumour response was assessed. Three of 30 patients evaluable for response achieved a partial response, resulting in an overall response rate of 10% (95% Confidence Interval (CI): 1–19%). 15 patients achieved stable disease (50%; 95% CI: 32.1–67.9%), so the rate of tumour control (complete responses, partial responses and stable disease) was 60% (95%CI: 42.5–77.9%). The median time to progression was 4.5 months (95% CI: 3.4–6.6 months) and the median survival was 11 months (95% CI: 7.9–14.1 months).

4. Discussion

The MTD of the investigational combination of weekly CPT-11 and UFT within a 28-day cycle was found to be: CPT-11 120 mg/m^2 on days 1, 8 and 15 plus UFT 250 mg/m^2 on days 1 to 21 or, alternatively, CPT-11 110 mg/m^2 on days 1, 8 and 15 plus UFT 300 mg/m^2 on days 1 to 21. The DLT, according to the NCI-CTC toxicity scale, were diarrhoea, neutropenia and asthenia. Thus, the recommended doses for future clinical studies are CPT-11 110 mg/m^2 and UFT 250 mg/m^2 or CPT-11 100 mg/m^2 and UFT 300 mg/m^2.

Diarrhoea was also the main side-effect at dose levels below the MTD; however, all cases except one were manageable with prompt oral loperamide. Other non-haematological side-effects were mild except for asthenia, mucositis and NCI-CTC grade 3 constipation that occurred in one case. The incidence of grade 1–2 nausea and vomiting was 16 and 9.6%, respectively, despite the use of prophylactic antiemetic $5HT_3$-antagonists and dexamethasone. This could be related to the overlapping toxicity of both CPT-11 and UFT. However, CPT-11 in monotherapy at a dose of 125 mg/m^2 administered weekly has been shown to induce grade 3–4 vomiting in 16% of patients [18–20]. The lower incidence and severity of emesis in our study could be due to the addition of dexamethasone as a prophylactic anti-emetic. Alopecia is less severe with weekly CPT-11 than when administered every 3 weeks. In our study, none of the patients presented with complete alopecia, although 35% suffered NCI-CTC grade 1–2 alopecia. Similarly, haematological toxicity was infrequent. Of note is the finding that multiple courses of the investigational regimen did not produce neutropenia exceeding NCI-CTC grade 2 except for 1 patient given dose level 6, a dose level that was considered a MTD. In contrast to bolus 5-FU, the DLT of this schedule including UFT in combination with weekly CPT-11 was diarrhoea rather than neutropenia, underlining the different mechanisms of action of fluoropyrimidines when administered as an i.v. bolus or as a prolonged continuous administration.

Different studies with schedules containing 5-FU or UFT (with or without LV) combined with CPT-11 have been investigated, or are currently under clinical evaluation (Table 5). The results of these studies suggest that the combination of CPT-11 with either infusional or bolus 5-FU is tolerable, with diarrhoea or neutropenia, respectively, being the DLT [23–26,31–35].

Although tumour response was not the main objective of this study, the overall response rate of 10% (95% CI: 1–19%) for these pretreated patients with advanced colorectal carcinoma demonstrates an antitumour activity

Table 5
Schedules of CPT-11 with 5-FU/UFT

Author [Ref.]	Trial design	Scheme	LV mg/m^2	UFT mg/m^2	5-FU mg/m^2	CPT-11 mg/m^2	DLT
Saltz [31]	Phase I (1st, 2nd)	Weekly×4/6 week, bolus	20		500	125	Neutropenia
Ducreux [32]	Phase I (2nd)	Biweekly, bolus/infusion	200, day 1–2		400 bolus 600 CI, days 1–2	180	Diarrhoea
Benhammouda [33]	Phase I (2nd)	Every 4 weeks, bolus			375, days 1–5	300	Neutropenia
Hill [26]	Phase I (1st)	Every 3 weeks	90, days 1–14	250, days 1–14		250	Neutropenia and diarrhoea
This study	Phase I (2nd)	Every 4 weeks		300, days 1–21		100, days 1–8–15	Diarrhoea and neutropenia
				250, days 1–21		110, days 1–8–15	Diarrhoea and asthenia
Aranda [34]	Phase I (1st)	Weekly, CI			3000	80	Diarrhoea and neutropenia
Vanhoefer [35]	Phase I (1st)	Weekly×6, CI	500		2600	80	Diarrhoea
Douillard [23]	Phase III (1st)	Biweekly, bolus/infusion	200, days 1–2		400 bolus 600 CI, days 1–2	180	
Saltz [24]	Phase III (1st)	Weekly×4/6 week, bolus	20		500	125	
Yamazaki [25]	Phase I	Biweekly CI		400/12 h days 1–7		160	Diarrhoea and leucopenia

CI, continuous infusion; 1st, first-line; 2nd, second-line; LV, leucovorin; 5-FU, 5-fluorouracil; DLT, dose-limiting toxicity.

for the regimen. This response rate, although low, is in the range that can be expected with CPT-11 as a single agent after failure following 5-FU treatment. Moreover, we observed a high rate of stable disease (50%). Although the number of patients is small, the median survival time of 11 months is noteworthy; however, it could be influenced by the third-line regimen including oxaliplatin that was administered to more than 50% of the patients.

In conclusion, this study demonstrates that a weekly schedule of CPT-11 in combination with UFT is feasible. Diarrhoea, neutropenia and asthenia were the DLT, while other side-effects were mild. The addition of UFT to weekly CPT-11 yields response rates similar to those previously reported for CPT-11 used in monotherapy. Therefore, a large phase II trial of the investigational regimen with UFT 300 mg/m^2 p.o. on days 1–21 and CPT-11 100 mg/m^2 i.v. on days 1, 8 and 15 of a 28-day cycle, as first-line chemotherapy in metastatic colorectal cancer has been initiated.

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