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Triplet schedule of weekly 5-Fluorouracil and alternating irinotecan or oxaliplatin in advanced colorectal cancer: A dose-finding and phase II study

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Abstract. A weekly administration of alternating irinotecan or oxaliplatin associated to 5-Fluorouracil in advanced colorectal cancer was planned in order to evaluate a new schedule maintaining dose intensities of each drug as in double combinations and tolerability of the triplet association. The following weekly schedule was administered: irinotecan, days 1 and 15; oxaliplatin, days 8 and 22; 5-fluorouracil (5-FU) over 12-h (from 10:00 p.m. to 10:00 a.m.) timed flat infusion, days 1-2, 8-9, 15-16 and 22-23, every 4 weeks. Dose-finding and phase II study were planned. Thirteen patients were enrolled in the dose-finding study and 23 in the phase II study. The recommended doses of our study are: irinotecan 160 mg/m^2; oxaliplatin 80 mg/m^2; 5-FU 900 mg/m^2. The dose-limiting toxicity was diarrhea (35% of patients) but no cases of febrile neutropenia were observed. In 30 patients assessable for response two complete (6.7%) and 18 partial (60%) responses were observed, for an overall response rate of 66.7% (α0.05, CI±17). The triplet association using this weekly alternating schedule is an active and well-tolerated outpatient regimen. Surgical removal of residual disease was considered in 5 patients and a radical resection was performed in 5 patients (14%).

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Introduction

Several phase I-II-III studies in metastatic colorectal cancer (CRC) patients have been reported using different schedule of triplet combinations of irinotecan (CTP-11), oxaliplatin (l-OHP) and 5-fluorouracil (5-FU), showing higher response rate than double associations of 5-FU with CPT-11 or l-OHP. Nevertheless the triplet combinations show G3-4 diarrhea and/or febrile neutropenia as main toxic effects at the recommended dose (RD) justifying a variable reduction of dose-intensity (DI).

We previously showed that 12-h (10 p.m.-10 a.m.) timed-flat-infusion (TFI) of 5-FU in combination with docetaxel in advanced breast cancer (1) and with CPT-11 in advanced CRC (2) is associated to an increased tolerability and high 5-FU/DI. The 12-h (10 p.m.-10 a.m.) TFI/FU infusion traces the 12-h circadian-timed infusion of 5-FU (10 p.m.-10 a.m. with maximum delivery at 4 a.m.) and was chosen to exploit the increased activity in the mononuclear cells of dehydropyrimidine dihydrogenase (DPD), the enzyme involved in 5-FU intracellular catabolism, and the reduced proliferation of normal target tissue, such as the bone marrow and the oral/rectal mucosa, during the night hours (3-5).

LV modulation of infusional 5-FU, alone or in combination with new drugs such as CPT-11, increases gastrointestinal toxicity without increasing clinical benefit (6-8).

Thus, a weekly administration schedule of alternating CPT-11 or l-OHP associated to TFI/5-FU, without leucovorin (LV), was planned in order to maintain the DI of each drug on the same level of the two drugs combinations and evaluate tolerability. L-OHP was administered over 2-h as an intravenous infusion, from 3 p.m to 5 p.m., as the chronomodulated infusion of l-OHP, peaking at 4 p.m., is less toxic than the constant-rate infusion (9). Here, we present an analysis of the safety and activity of this triplet schedule in metastatic CRC, as first-line chemotherapy.

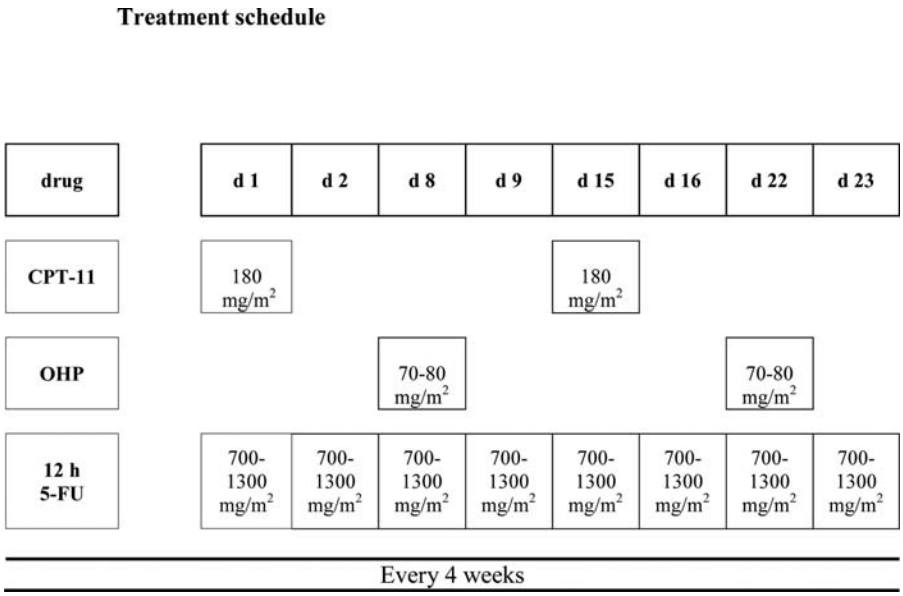

Figure 1. Treatment schedule.

Materials and methods

Patient selection. All the patients fulfilled the following criteria: histologically confirmed diagnosis of CRC with clinical evidence of metastatic disease; age between 18 and 75 years; WHO performance status ≤2; WBC count ≥4x10^3/mm^3, neutrophils ≥2x10^3/mm^3, platelets ≥100x10^3/mm^3, hemoglobin ≥10 g/dL, serum creatinine ≤1.2 mg/dL, serum bilirubin ≤1.5 mg/dL, AST and ALT ≤2.5 times normal value; life expectancy more than 3 months. Exclusion criteria included: prior chemotherapy for metastatic disease, peripheral neuropathy, uncontrolled infection, diabetes, cardiac diseases.

The study was conducted in accordance with the Helsinki declaration and the guidelines on good clinical practice. In addition, the study protocol was approved by the appropriate ethics review boards and each patient provided written consent prior to study entry.

Treatment. The following weekly schedule was administered on an outpatient basis: CPT-11, days 1 and 15; l-OHP over 2-h as an intravenous infusion (from 3:00 p.m. to 5:00 p.m.), days 8 and 22; 5-FU over 12-h (from 10:00 p.m. to 10:00 a.m.) timed flat infusion, days 1-2, 8-9, 15-16 and 22-23, every 4 weeks. In the dose-finding study eight escalation dose levels were planned: CPT-11 180 mg/m^2 and l-OHP 70 mg/m^2 associated to 5-FU 700, 800 and 900 mg/m^2/day in the first 3 dose-levels, respectively; then, l-OHP was increased at 80 mg/m^2 and 5-FU dose-levels were increased from 900 to 1300 mg/m^2/day according to a 100 mg/m^2/d increase for each dose-level in the other 5 steps. Placement of an implanted venous access device was required. 5-FU was administered by means of a portable pump (CADD Plus, SEVIT), programmed to administer 5-FU at a given constant rate and to automatically start the infusion at 10:00 p.m. for a period of 12 h. No prophylactic treatment with granulocyte colony-stimulating factor was used. To prevent nausea and vomiting, 5-HT3 antagonist i.v. were administered before chemotherapy and atropine 0.25 mg was given prophylactically in order to avoid cholinergic syndrome (Fig. 1).

Dose-finding study design. The dose-escalation strategy combined the intra- and inter-patient approach (10). The accelerated design included only one patient per cohort until one patient experienced dose-limiting toxicity (DLT) or at least two patient experienced grade (G) 2 toxicity (except nausea or vomiting) during any course of treatment. After the initial accelerated phase, the study resorted to standard cohorts of 3 patients. If one or 2 patients experienced a DLT, a second cohort was treated at the same dose-level. If no more than two out of 6 patients experienced a DLT, the next cohort of patients was treated at the subsequent dose-level. The maximum tolerated dose (MTD) was defined as the dose at which at least 50% of the newly treated patients developed DLT.

Patients were evaluated for toxicity every week according to National Cancer Institute Common Toxicity Criteria version 2.0 (NCI-CTC). DLT included: G3 or G4 non-hematological toxicity (except nausea or vomiting), G4 neutropenia, febrile neutropenia or any other hematological G4 toxicity or any toxicity determining a treatment delay longer than 2 weeks.

Phase II study design. The phase II patients were treated at the recommended doses. The primary end points of the phase II study were the best overall response rate and the safety.

The design parameters p0 (null hypothesis) and p1 (alternative hypothesis) selected were 0.4 and 0.6, respectively.

According to the Simon minimax two-stage design, a final sample size of 28 patients with 14 responding patients should have required to refuse the null hypothesis (α0.10, ß0.20). The first stage of the study required 16 patients and if at least 6 objective responses were observed, the second stage required a total of 28 patients.

Tumor imaging was repeated every 3 treatment cycles (12 weeks). Tumor response was assessed and defined according

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linical features of patients enrolled.

	Total no. (%)
No. of patients	36
Sex	
Male	22
Female	14
Age, years	
Median	62
Range	39-74
>65 years	14 (39)
WHO performance status	
0	30 (83)
1-2	6 (17)
Primary tumor	
Colon	26 (72)
Rectum	10 (28)
No. of involved sites	
1	26 (72)
≥2	10 (28)
Sites of metastases	
Liver	22 (61)
Lung	8 (22)
Lynph nodes	7 (19)
Local	4 (11)
Other	6 (17)
Liver metastases	
Single	3 (8)
Multiple	19 (53)
Previous adjuvant chemotherapy	9 (25)
FA/5-FU bolus	6 (17)
5-FU bolus + i.c.	2 (6)
Irinotecan/5FU	1 (3)
Previous radiotherapy	2 (6)
RT alone	-
RT+CT (5-FU i.c.)	2 (6)

WHO, World Health Organization.

to Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Patients were considered assessable for therapeutic response if they had measurable lesions and if they received more than 3 cycles.

Secondary end points were time to progression and survival. The time to disease progression and survival were assessed using the methods of Kaplan and Meier.

Results

Patients. Thirteen patients meeting eligibility criteria were enrolled in the dose-finding study and 23 in the phase II study. A summary of patients' baseline clinical features is shown in Table I. The median age was 62 years (range 39-74); WHO performance status was 0 in 30 patients (83%); 22 (61%) had liver metastases (53% multiple) and 9 (25%) had received previous adjuvant chemotherapy with 5-FU.

The median number of cycles administered in the dose-finding and in the phase II study was 6 (range 0.5-9).

DLT and MTD. Table II describes the observed DLTs in treated patients and cycles administered according to dose levels.

Eight escalation dose-levels were planned, but MTD was reached at the fifth dose level (5-FU DI 2000 mg/m^2/week; CPT-11 DI 90 mg/m^2/week; l-OHP 40 mg/m^2/week). The first enrolled patient received the treatment according to the intra-patient dose escalation from the first to the eighth dose-level without showing G2 toxicity. The preliminary analysis of the toxicity at fifth dose-level in 5 patients (the sixth patient refused the dose-escalation), all previously treated even at lower dose levels, did not detect any DLT. In two cohorts of new patients enrolled at this dose-level DLTs were observed in 3/6 new patients: one patient experienced G3 diarrhea; one patient experienced G1 fever, requiring a 2-week delay in chemotherapy and another one G3 hypotension.

The fourth dose-level (5-FU DI 1800 mg/m^2/week; CPT-11 DI 90 mg/m^2/week; l-OHP 40 mg/m^2/week) represented the RD: 7 patients were treated at this dose-level (3 pre-treated at lower dose-levels and 4 newly treated) for a total 12 cycles. G3 diarrhea was observed in one patient, previously treated at lower dose levels.

At the RD the G1-2 diarrhea was observed in 42% of patients and 25% of cycles; G1-2 stomatitis in 28% of patients and 25% of cycles; G1-2 nausea in 85% of patients and 58% of cycles; G1-2 neurotoxicity in 28% of patients and 33% of cycles.

Phase II toxicity and dose intensity. The most common toxic effects were diarrhea and stomatitis. Among 23 patients of phase II study, eight (35%) had G3 diarrhea, eight (35%) had G1-2 stomatitis (Table III), one (4%) had G4 neutropenia, three (13%) had G3 neutropenia, six (26%) had G2 neutropenia and one (4%) G3 peripheral neurotoxicity (Table IV). Although the use of G-CSF was not planned, it was used in 10/126 (8%) of cycles and 4/23 (17%) of patients: in 1 patient in secondary prevention after experience of G4 neutropenia, in 3 patients because persistent G2 leucopenia on the day of recycle did not permit maintaining the planned weekly schedule. One patient experienced G3 liver toxicity that required one week delay until normalization of transaminases.

One patient (4%) experienced G4 neutropenia and no cases of febrile neutropenia were observed (Table IV). No toxic death occurred and no case of thrombosis correlated to venous access device has been registered.

In the first 18 patients enrolled in the phase II study we observed 37.5% G3 diarrhea at a median received dose-intensity (rDI) of CPT-11 70 mg/m^2/week (78%). Thus, we amended the protocol at 160 mg/m^2 irinotecan dose for the subsequent enrollment.

In the dose-finding study, 5-FU/rDI for each patient was: the median 5-FU/rDI 1667 mg/m^2/w (range 1143-2000)

Table II. Dose-limiting toxicities according to the dose-escalation scheme.

Dose levels	CPT11 (mg/m^2 d1,15)-l-OHP (mg/m^2 d8, 22)-5-FU (mg/m^2/d d1-2, 8-9, 15-16, 22-23)	No. of patients[a] (new patients)	No. of cycles	No. of patients with DLT[b]/total patients (%)	No. of new patients with DLT/new patients (%)	No. of cycles with DLT/total cycles (%)	DLTs
I	180-70-700	2 (2)	2	-	-	-	-
II	180-70-800	3 (1)	3	-	-	-	-
III	180-70-900	3 (0)	3	-	-	-	-
IV	180-80-900	7 (4)	12	1/7 (14)	-	1 (8)	G3 Diarrhea
V	180-80-1000	11 (6)	30	3/11 (27)	3/6 (50)	3 (10)	G3 Diarrhea G1 Fever with delay >2 weeks G3 Hypotension

[a]Intra- and inter-patient dose escalation; [b]dose-limiting toxicity.

Table III. Non-haematological toxicity of phase II study.

	NCI-CTC grade (%) per cycles				NCI-CTC grade (%) per patients			
Adverse events	1	2	3	4	1	2	3	4
Nausea	30 (24)	12 (9.5)	-	-	10 (43)	6 (26)	-	-
Vomiting	13 (10)	11 (9)	-	-	7 (30)	6 (26)	-	-
Diarrhea	18 (14)	18 (14)	11 (9)	-	3 (13)	8 (35)	8 (35)	-
Stomatitis	16 (13)	1 (1)	-	-	6 (26)	2 (9)	-	-
Asthenia	33 (26)	16 (13)	1 (1)	-	9 (39)	9 (39)	1 (4)	-
Neurotoxicity	54 (43)	6 (5)	1 (1)	-	14 (61)	2 (9)	1 (4)	-

NCI-CTC, National Cancer Institute Common Toxicity Criteria.

and the average 1606 mg/m^2/w (α0.05, CI±149). In the phase II study 5-FU/rDI for each patient were: the median 5-FU/rDI 1476 mg/m^2/w (range 900-1800) and the average rDI 1407 mg/m^2/w (α0.05, CI±94).

The received dose-intensity of 5-FU for patients was 82% of planned DI, 87.5% of l-OHP and 82% of CPT-11.

Antitumor activity. For the evaluation of activity, data from the 13 patients enrolled in the dose-finding study were considered together with data of the 23 patients enrolled in the phase II study and treated at the recommended dose, since the average dose intensity received by the two groups were quite similar.

Of the 33 patients included in the intent-to-treat population, 30 patients were protocol-qualified. Reasons for failure to satisfy protocol criteria included: not measurable disease in 2 patients enrolled in phase I study and one patient was lost to follow-up (3 patients had not received at least 3 cycles of treatment).

In the intent-to-treat analysis we observed 2/33 complete responses and 21/33 partial responses with an overall response rate of 69.6% α0.05, CI±16). In 30 patients considered assessable for response (as treated), two complete (6.7%) and 18 partial (60%) responses were observed, for an overall response rate of 66.7% (α0.05, CI±17). We observed 3 stable disease (10%) for a disease control rate of 76.7%. Response data are summarized in Table V. Surgical removal of residual disease was considered in 5 patients and a radical resection (R0) was performed in 5 patients (all liver resections).

At 19 months of median follow-up, 23 deaths were observed (64%). The median time to progression was 12 months (range 3+ - 61+). The median overall survival was 20 months (range 3+ - 61+).

Discussion

Our data propose the weekly 5-FU/TFI, without LV, in association with alternating CPT-11/l-OHP characterized by rDIs for each single drug equivalent to that proposed in schedules of double associations (5-FU/CPT-11; 5-FU/l-OHP).

The recommended doses of our study are: CPT-11 at the dose of 160 mg/m^2, days 1 and 15; l-OHP over 2-h infusion from 03:00 p.m to 05:00 p.m. at the dose of 80 mg/m^2, days 8

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Haematological toxicity of phase II study.

	NCI-CTC grade (%) per cycles				NCI-CTC grade (%) per patients			
Adverse events	1	2	3	4	1	2	3	4
Anemia	13 (10)	3 (2)	-	-	5 (22)	3 (13)	-	-
Leucopenia	19 (15)	17 (13)	-	-	3 (13)	8 (35)	-	1 (4)
Neutropenia	10 (8)	21 (17)	7 (5.5)	1 (1)	3 (13)	6 (26)	3 (13)	1 (4)
Thrombocytopenia	10 (8)	4 (3)	-	-	3 (13)	3 (13)	-	-

NCI-CTC, National Cancer Institute Common Toxicity Criteria.

Table V. Objective tumor response.

	Assessable patients (%)	Intention to treat analysis (%)
No. of patients	30	33
CR	2 (6.7)	2 (6)
PR	18 (60)	21 (63.6)
SD	3 (10)	3 (9)
PD	7 (23.3)	7 (21.2)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

and 22; 5-FU over 12-h (from 10:00 p.m. to 10:00 a.m.) timed flat infusion at a dose of 900 mg/m^2, days 1-2, 8-9, 15-16 and 22-23, every 4 weeks. The 12-h infusion of 5-FU is more easily administered in comparison with a chrono-modulated infusion and demonstrates an high antitumor activity and a tolerable toxic profile.

The relative dose-intensity of our schedule ranged between 82 and 87.5% of planned dose (CPT-11/DI 70; OHP/DI 35; 5-FU/DI 1476 mg/m^2/week) and was characterized by G3 diarrhea in 35% of patients, G4 neutropenia in one patient (4% of patients) and no febrile neutropenia.

The phase I-II studies of triplet associations in advanced CRC, using different infusion of 5-FU and different DIs of the three drugs, showed mainly severe diarrhea (range 2-72.2%) and/or febrile neutropenia (range 1-25%) at recommended doses (11-32).

Most of these studies included LV. In our previous doublet study we proposed a schedule excluding leucovorin (1,2). Cals *et al* recommend a tolerable, weekly alternating schedule characterized by higher 5-FU/DI (2.4 g/m^2/w, 24-h infusion) without LV, equivalent l-OHP (DI 32 mg/m^2/w) but lower (<50%) CPT-11/DI (40 mg/m^2/w) than the present study (17). The phase I-II study by Seium *et al* propose a regimen with very high efficacy (the response rate was 78%) but two febrile neutropenia episodes (one fatal) and diarrhea (23% of patients; 3% of grade 4) were recorded (23).

The most active phase II studies were the following: Ychou *et al* (16) reported a triplet combination according to the De Gramont infusion of 5-FU with G3-4 diarrhea in 29.4% and febrile neutropenia in 3% of patients, respectively and the response rate (RR) was 70.6% (31); Calvo *et al* reported G3-4 diarrhea in 34.5% of patients and the overall RR was 69.2% (13). The most tolerable phase II study, as first-line advanced chemotherapy, was proposed by Ferrari *et al*, but the antitumor activity of triplet combination with bolus 5-FU was lower (RR 50%) (26).

The relative dose-intensity of schedule recommended by Falcone *et al* ranged between 82 and 87% of planned dose (CPT-11/DI 82.5; OHP/DI 42.5; 5-FU/DI 1600 mg/m^2/week) and was characterized by G3-4 diarrhea, G4 neutropenia and febrile neutropenia in 20, 17 and 5% of patients, respectively. The response rate confirmed by external panel was 60% and in particular 15% of patients underwent to radical surgery in the FOLFOXIRI arm (34).

This triplet regimen is an active (RR 66.7%) and usually well-tolerated outpatient regimen. Surgical removal of residual disease was considered in 5 patients and a radical resection (R0) was performed in 5 patients (14%).

Present data show that the triplet combination in ACC may be administered according to a weekly alternating administration without leucovorin. This schedule is equally effective as the schedules showing higher activity and shows better tolerability concerning neutropenia.

It also shows almost equivalent activity as doublet combinations adding Bevacizumab or Cetuximab. Ongoing studies are exploring the possibility of adding antitargets to the triplet schedules in advanced colorectal cancer.

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