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Bimonthly Chemotherapy with Oxaliplatin, Irinotecan, Infusional 5-Fluorouracil/Folinic Acid in Patients with Metastatic Colorectal Cancer Pretreated with Irinotecan- or Oxaliplatin-Based Chemotherapy

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Summary

This study was conducted to assess the tolerability and efficacy of a ternary bimonthly irinotecan (CPT-11) - oxaliplatin (OHP) - infusional 5-fluorouracil (5-FU)/folinic acid (FA) combination in advanced colorectal cancer patients who had received prior CPT-11 and/or OHP-based chemotherapy regimen. Colorectal cancer patients were given bimonthly CPT-11 as a 90-min infusion, followed by OHP (85 mg/m^2), FA (200 mg/m^2) 2-h infusions and 5-FU (48-h infusion). CPT-11 and 5-FU doses were escalated as reported below. 26 patients were recruited. Fourteen patients had received a prior CPT-11-, 6 patients a prior OHP-based chemotherapy regimen and 6 patients both regimens. Three dose levels were investigated: CPT-11 100, 120 and 140 mg/m^2 and 5-FU 1500, 1800 and 2100 mg/m^2 in 6, 12 and 8 patients, respectively. All patients were evaluable for toxicity, 24 for antitumor activity. At all dose levels toxicity was acceptable. Grade 4 toxicity occurred in two patients only (neutropenia in one case and stomatitis in another one, 3.8%). Grade 3 toxicities included nausea and vomiting (34.6%), asthenia (26.9%), neurosensory toxicity (15.4%), neutropenia (3.8%) and diarrhea (3.8%). Hematological toxicity was infrequent and generally mild. At the third dose level, a higher, although not significantly different incidence of hematological and neurosensory toxicity (both occurring in 62.5% of cases, all grades) was observed compared to the other two, while nausea and vomiting were significantly less frequent (37.5% vs 100%). Overall, we observed 2 complete responses, 9 partial responses (OR 45.8%), 8 stable disease (33.3%), and 5 disease progression (20.8%). Median overall survival was 18 months and median time-to-progression 5.5 months. This combination showed moderate toxicity and promising antitumor activity in CPT-11 and/or OHP pretreated colorectal cancer patients. The second dose level using CPT-11 at 120 mg/m^2 and 5-FU at 1800 mg/m^2 is recommended for further phase II studies in this patient population.

Key words: **Colorectal cancer, combination chemotherapy, 5-fluorouracil, irinotecan, oxaliplatin.**

INTRODUCTION

5-Fluorouracil (5-FU)-based combination chemotherapy is still the reference treatment for advanced colorectal cancer. In this stage of disease the administration of 5-FU combined with folinic acid (FA), which potentiates the antitumor activity of fluoropyrimidines by increasing the 5,10-CH_2FH_4 pool and consequently enhancing the formation of the thymidylate synthase (TS)–inhibitor - coenzyme ternary complex, induces an

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objective response (OR) in about 20% of patients and prolongs median survival to about 11 months [1]. Preclinical *in vitro* and *in vivo* evidence has shown a schedule-dependent antitumor activity for 5-FU [2-5]. Long term 5-FU infusional administration is characterized by greater antitumor activity and a more favorable toxicity profile over bolus administration [6].

In the clinic, other drugs such as oxaliplatin (OHP) and irinotecan (CPT-11) have shown considerable activity in metastatic colorectal cancer and have been successfully integrated into 5-FU/FA regimens as the standard cytotoxic drug backbone of first-line systemic therapeutic approach to this disease [7]. These drugs exert their antitumor activity by different mechanisms compared to 5-FU. OHP is a diaminocyclohexane derivative of cisplatin that blocks DNA replication and transcription by the formation of cross-linking adducts [8]. CPT-11 inhibits topoisomerase I, thus impeding DNA uncoiling which leads to double-stranded DNA breaks [9]. Lack of laboratory and clinical cross-resistance to CPT-11 and OHP has been demonstrated in 5-FU-resistant tumors [5,10,11]. Combinations of these two drugs with 5-FU have also been explored in preclinical studies in which drug synergism or additivity have been shown [12-14]. Randomized trials with these combinations (FOLFIRI or FOLFOX) have demonstrated increased clinical activity over the 5-FU/FA combination in previously untreated patients[15-18]. Interestingly, patients who progressed after first-line treatment with FOLFIRI or FOLFOX experienced a survival benefit when the opposite drug regimen was used as second-line treatment [19]. Second-line response rates were not completely satisfactory (FOLFIRI 4% and FOLFOX 15%, respectively), however [19]. The combination of CPT-11 and OHP (IROX regimen) has also been investigated with some success both as second [20,21] and first-line treatment [22].

These findings along with the demonstration of synergism or additivity of the ternary combination of CPT-11, OHP and 5-FU in preclinical studies[23], have attracted considerable attention to the ternary combination of these drugs in the clinic. This ternary combination has shown marked clinical activity in phase I-II trials performed in both previously treated [24-29] and untreated [30-34] metastatic colorectal cancer patients at doses comparable to those used in binary combinations. These results are consistent with the superiority of the ternary combination of these drugs over their binary combinations. However, the use in the ternary combination of doses similar to those used in the binary combinations has frequently led to relevant toxicities including grade 4 neutropenia, grade 3-4 diarrhea, 3-4 stomatitis and grade 2-3 neurotoxicity. More rarely, fatal toxic episodes have been observed [34]. Despite these studies, there are still few data available on the use of this ternary combination as second-line treatment for patients pretreated with OHP- or CPT-11-based chemotherapy [25,26,28,29].

On the basis of the above considerations, we designed a study to assess the tolerability of a ternary bimonthly CPT-11 - OHP-infusional 5-FU/FA combination at lower and potentially more tolerable drug doses in colorectal cancer patients who had received prior CPT-11 and/or OHP-based chemotherapy. A secondary objective of our study was to define the antitumor activity of this combination.

PATIENTS AND METHODS

Patient eligibility

The inclusion criterion was documentation of histological diagnosis of colorectal carcinoma with metastatic lesions. All patients were required to have a Karnofsky performance status (PS) ≥80, age >18 years, life expectancy >12 weeks; one or more previous lines of chemotherapy for metastatic disease with combined 5-FU and CPT-11 or OHP, normal bone marrow (defined by WBC count ≥4 x 10^9/L; absolute neutrophil count (ANC) ≥1.5 x 10^9/L; platelet (PLT) count ≥100 x 10^9/L; hemoglobin ≥10 g/dL), renal (serum creatinine ≤1.5 x upper normal limit [UNL]), hepatic (total bilirubin level ≤1.25 x UNL; and AST, ALT, and alkaline phosphatase <2.5 x UNL, or <5 x UNL if hepatic metastases were present) function. Patients who participated gave their written informed consent.

Exclusion criteria included chemotherapy or radiotherapy within 4 weeks before study entry, previous malignant neoplasia or concomitant tumor (except for non-melanoma skin carcinoma and *in situ* carcinoma of the uterine cervix), previous neurotoxicity (≥grade 2) experienced during first-line treatment with OHP, pregnancy and breast-feeding, cardiac disease, alterations in mental state, any reason that could have hindered a proper follow-up.

Treatment plan

The treatment, repeated every 2 weeks, was carried out according to the following schedule: dexamethasone 20 mg (or equivalent dose of another corticosteroid) in 100 ml of saline solution by i.v. route over 15 minutes and HT3 receptor antagonists (granisetron 3 mg or ondansetron 8 mg) in 100 ml of saline solution i.v. over 15 minutes, CPT-11 (at variable dose level, see below) in 250 ml of saline solution as a 90 min infusion, OHP 85 mg/m^2 in 500 ml of 5% glucose solution as a 2-h infusion, FA 200 mg/m^2 as a 2-h infusion and 5-FU (at variable dose level, see below) as protracted infusion (48 hours). Atropine 0.25 mg s.c. was given before CPT-11 to avoid cholinergic syndrome and loperamide (4 mg at the first episode, 2 mg at the followings) was suggested to the patient in case of need for delayed diarrhea. Granulocyte colony stimulating factors were admitted in case of febrile neutropenia.

Three dose levels for CPT-11 and 5-FU were investigated: CPT-11 100 mg/m^2 and 5-FU 1500

mg/m^2; CPT-11 120 mg/m^2 and 5-FU 1800 mg/m^2; CPT-11 140 mg/m^2 and 5-FU 2100 mg/m^2.

Every patient was required to have an implanted central venous access port.

Controls and tests prior to cycles

Symptoms, weight and PS, physical examination, blood-chemistry tests for liver and kidney function, serum CEA and CA19-9 were conducted on day 1 of every cycle; blood count was conducted every week; a re-evaluation of the patient (site of metastases and response) was planned with computerized tomography every four cycles.

Evaluation of toxicity

All toxicities, except peripheral sensory neuropathy, were scored according to WHO criteria [35] and neurosensory toxicity by specific criteria proposed for OHP [36].

Recycling rules and dose reduction

Courses were repeated every 2 weeks in the presence of ANC ≥1.5 x 10^9/L, PLT ≥100 x 10^9/L, and recovery of any extra-hematological toxicity. Otherwise, treatment was postponed for 1 or 2 weeks until recovery. In the presence of WHO grade 4 hematological toxicity, the subsequent cycles were administered, after recovery from side-effects, with a 25% dose reduction of all cytotoxic drugs. In the presence of grade ≥3 non-hematological toxicity (neurotoxicity excluded), the subsequent cycles were administered, after recovery from side-effects, with a 25% dose reduction of CPT-11 and 5-FU. If recovery required more than 2 weeks the patient went off study. In case of grade 3 neurotoxicity according to the Levi scale, OHP was reduced by 25%; if there was no recovery at the time of recycling after this dose reduction, treatment was discontinued.

Assessment of efficacy

Objective responses (ORs) were recorded according to standard WHO response criteria [35] after a minimum of four cycles of treatment. Median time to progression (TTP) and overall survival (OS) were calculated according to the Kaplan-Meier method [37]. Statistical significance was defined as p≤0.05.

RESULTS

Patient population

The characteristics of the 26 patients entered into this study from July, 2001 to April, 2005 are shown in *Table 1*. All patients had a PS of 100. About 50% of patients had at least two organs involved and 8 patients had already received two previous lines of chemotherapy. All patients had received chemotherapy with 5-FU; 53.8% (n=14) as FOLFIRI, 23.1% (n=6) as FOLFOX and 23.1% (n=6) as both FOLFIRI and FOLFOX. All patients were evaluable for toxicity and 24 for response.

TABLE 1 - *Patients' characteristics.*

	No. of pts. (%)
Total number of patients	26 (100)
Sex	
Male	15 (57.7)
Female	11 (42.3)
Age (years)	
Median	63
Range	43-76
Performance status (Karnofsky)	
Median	100
Range	(100-100)
Site of the primary tumor	
Colon	15 (57.7)
Rectum	8 (30.8)
Sigma	3 (11.5)
Stage at first diagnosis (TNM)	
I	2 (7.7)
II	4 (15.4)
III	3 (11.5)
IV	16 (61.6)
Unknown	1 (3.8)
Number of metastatic sites at the beginning of treatment	
1 site	14 (53.8)
2 sites	6 (23.1)
3 sites	5 (19.2)
5 sites	1 (3.8)
Number of patients by metastatic sites	
Liver	17 (65.4)
Lung	9 (34.6)
Lymphonodes	8 (30.8)
Pelvis	4 (15.4)
Peritoneal carcinosis	3 (11.5)
Retroperitoneal lesions	2 (7.7)
Pericardium	1 (3.8)
Adrenal gland	1 (3.8)
Bone	1 (3.8)
Spleen	1 (3.8)
Previous chemotherapy	
Adjuvant	9 (34.6)
For metastatic disease	
1 line	18 (69.2)
2 lines	8 (30.8)

Treatment administration

A total of 188 cycles of treatment with a median number of 6 cycles (range 2-14) were administered

TABLE 2 - *Number of patients and cycles for different doses.*

Group	Dose	Number of patients	Median number of cycles (range)	Total number of cycles
1	CPT-11 100 mg/m^2 day 1 L-OHP 85 mg/m^2 day 1 5-FU 1500 mg/m^2 48-h CI	6	7 (5-11)	46
2	CPT-11 120 mg/m^2 day 1 L-OHP 85 mg/m^2 day 1 5-FU 1800 mg/m^2 48-h CI	12	6 (4-14)	92
3	CPT11 140 mg/m^2 day 1 OHP 85 mg/m^2 day 1 5-FU 2100 mg/m^2 48-h CI	8	7 (2-10)	50
All groups	CPT-11 100-140 mg/m^2 day 1 L-OHP 85 mg/m^2 day 1 5-FU 1500-2100 mg/m^2 48-h CI	26	6 (2-14)	188

CI, continuous infusion

through the 3 dose levels of CPT-11 and 5-FU combined with 85 mg/m^2 OHP. The distribution of patients by different dose levels, median and total number of administered cycles, median relative dose-intensities (RDI) are reported in *Table 2*. Twenty-four patients received at least 4 cycles and two fewer than 4 cycles, due to early progression (1 patient) and toxicity (1 patient).

Nine patients (34.6%) required dose reduction: 2 patients (33.3%) at the first dose level, 5 (41.7%) at the second and 2 (25%) at the third. This corresponded to 49 cycles (26.1%) administered at reduced drug doses.

The mean cumulative dose was 814 mg/m^2 (280-1680) for CPT-11, 603 mg/m^2 (170-1190) per OHP and 12200 mg/m^2 (4200-25200) per 5-FU. The RDIs (given DI/planned DI) calculated individually for all cycles given to each patient were 97.6% per OHP, 94.5% per CPT-11 and 5-FU.

Toxicity

Details on the treatment-related worst toxicity are reported in *Table 3*. The prevalent side effects were nausea and vomiting (80.8% of patients, 34.6% grade 3), asthenia (61.5% of patients, 26.9% grade 3) and neurosensory toxicity (38.5% of patients, 15.4% grade 3). However, this last adverse effect was transient and completely reversible by the end of the treatment. Asthenia (grade 3) and neurosensory toxicity (grades 2-3) occurred both in 33.3% and 50% of patients previously treated with OHP while in 21.4% and 14.3% of patients previously treated with CPT-11, respectively. However, these differences were not statistically significant. Diarrhea occurred in 38.5% of patients and in 3.8% as grade 3 (one patient). Stomatitis was reported in 23.1% of cases and in one patient as grade 4 (3.8%). In this case a delay of 2 weeks in recycling and drug dose reduction were required.

Neutropenia occurred in 38.5% of patients and in most of cases was mild with the exception of a grade 4 occurring in one patient (3.8%) who experienced also a grade 2 thrombocytopenia requiring drug dose reduction in the following cycles. Thrombocytopenia and anemia were less frequent (26.9%, and 11.5, respectively) and mild (no grade 3 level). Anorexia and alopecia were negligible (both occurring in 3.8% as grade 1).

At the first dose level of treatment, nausea and vomiting was noted in all patients but only in one case (16.7%) as grade 3; diarrhea was reported in 50% of patients (grade 3, 16.7%); asthenia occurred in 50% of cases (always as grade 3) and stomatitis in 50% of patients (grade 4, 16.7%).

Also at the second dose level nausea and vomiting was the prevalent side effect (100%) reaching grade 3 in 7 patients (58.3%). Asthenia occurred in 66.7% but only in one case (8.3%) as grade 3. Neutropenia occurred in a limited number of patients (25.0%) and was mild-moderate except in one patient (grade 4, 8.3%). Diarrhea was reported in 41.5% of cases (grade 1-2).

At the third dose level of treatment, both hematological toxicity (neutropenia and thrombocytopenia) and neurotoxicity (asthenia and neurosensory toxicity) occurred in 62.5% of cases. In particular, grade 3 neurosensory toxicity occurred in 50% of patients and in one patient the treatment was stopped; grade 3 asthenia occurred in 37.5% of patients.

Overall, the incidence of nausea and vomiting was higher at the first ($p=0.031$) and second treatment levels ($p=0.004$) (both 100%) compared to that observed at the third level (37.5%); the incidence of thrombocytopenia was higher at the third level (62.5%) compared to the other two (16.7% and 8.3% respectively)

TABLE 3 - *Grade (WHO) and incidence of toxicity related to the dose.*

Grade	Group I (n=6)			Group II (n=12)			Group III (n=8)			All Groups (n=26)		
	1-2 (%)	3 -4 (%)	Total (%)	1-2 (%)	3-4 (%)	Total (%)	1-2 (%)	3-4 (%)	Total (%)	1-2 (%)	3-4 (%)	Total (%)
Neutropenia	2 (33.3)	-	2 (33.3)	2 (16.7)	1 (8.3)	3 (25.0)	4 (50.0)	1 (12.5)	5 (62.5)	8 (30.8)	2 (7.7)	10 (38.5)
Anemia	1 (16.7)	-	1 (16.7)	1 (8.3)	-	1 (8.3)	1 (12.5)	-	1 (12.5)	3 (11.5)	-	3 (11.5)
Thrombocytopenia	1 (16.7)	-	1 (16.7)	1 (8.3)	-	1 (8.3)	5 (62.5)	-	5 (62.5)	7 (26.9)	-	7 (26.9)[a]
Nausea-vomiting	5 (83.3)	1 (16.7)	6 (100)	5 (41.7)	7 (58.3)	12 (100)	2 (25.0)	1 (12.5)	3 (37.5)	12 (46.1)	9 (34.6)	21 (80.8)[b/c]
Stomatitis	2 (33.3)	1 (16.7)	3 (50.0)	3 (25.0)	-	3 (25.0)	-	-	-	5 (19.2)	1 (3.8)	6 (23.1)[d]
Diarrhea	2 (33.3)	1 (16.7)	3 (50.0)	5 (41.5)	-	5 (41.5)	2 (25.0)	-	2 (25.0)	9 (34.6)	1 (3.8)	10 (38.5)
Neurotoxicity	2 (33.3)	-	2 (33.3)	3 (25.0)	-	3 (25.0)	1 (12.5)	4 (50.0)	5 (62.5)	6 (23.1)	4 (15.4)	10 (38.5)
Asthenia	-	3 (50.0)	3 (50.0)	7 (58.3)	1 (8.3)	8 (66.7)	2 (25.0)	3 (37.5)	5 (62.5)	9 (34.6)	7 (26.9)	16 (61.5)
Anorexia	1 (16.7)	-	1 (16.7)	-	-	-	-	-	-	1 (3.8)	-	1 (3.8)
Alopecia	-	-	-	1 (8.3)	-	1 (8.3)	-	-	-	1 (3.8)	-	1 (3.8)

[a] p=0.018 second vs third level
[b] p=0.031 first vs third level
[c] p= 0.004 second vs third level
[d] p=0.055 first vs third level

(p=0.137 first vs third level; p=0.018 second vs third level). A trend for a higher incidence of stomatitis at the first level of treatment (50.0% of patients) versus the third level (no case) was also observed (p=0.055).

No other statistically significant differences were observed. However, the incidence of neutropenia was higher at the third level of treatment compared to the other two levels as well as the incidence of neurosensory toxicity.

No treatment-related deaths were observed.

Efficacy and survival

Twenty-four patients were evaluable for response after a minimum of four cycles of treatment (*Table 4*). The overall response rate was 45.8% (95% confidence interval 27.8% to 65.1%). In particular, 2 complete remissions (CRs) were noted; their duration ranged from 5.5 to 12.3 months. Nine partial remissions (PRs) were also reported with a median duration of 5.5 months (range 4-13 months). Also the median duration of CR + PR was 5.5 months (range 4-13 months). Stable disease (SD) was noted in 8 patients (33.3%) with a median duration of 7 months (range 3.7-10.0). Five patients (20.8%) had disease progression (PD).

Concerning the relationships between dose levels and response we observed: 3 PRs (50%) at the first dose level; 1 CR and 3 PRs (36.4%) at the second level; one CR and 3 PRs (57.1%) at the third level. No statistically significant difference was observed among the three groups of patients.

CRs were achieved in 2 CPT-11 pretreated patients, PRs in 3 CPT-11, in 2 OHP and in 4 CPT-11 and OHP pretreated patients, respectively (*Table 4*). No statistically significant difference was observed.

The percentage of ORs observed in patients treated with one previous line of therapy was comparable to that observed in patients treated with two previous lines (43.7% and 50%, respectively, p=1.0).

Out of the 13 evaluable patients with one site of disease, one experienced CR and 7 PRs, (61.5%); out of the 11 evaluable patients with two or more sites of disease, one experienced CR and 2 PRs (27.3%).

After chemotherapy, 3 patients (12.5%) who experienced PRs and one patient (4.2%) who was stable underwent radical hepatic resection 4, 4.5, 10 and 3.7 months after the start of treatment, respectively.

The median time-to-progression was 5.5 months (range 1.6 - 15.8 months, n=20) and the median OS was 18 months (range 4-48 months, n=20). To avoid the risk of bias in time to progression (TTP) and OS results, reported data do not include the 4 patients who underwent radical metastasectomy after chemotherapy.

DISCUSSION

The availability of novel drugs has helped to significantly increase survival in patients with advanced colorectal cancer. In particular FOLFOX and FOLFIRI

TABLE 4 - *Objective response analysis reported by dose level, number of previous lines of chemotherapy and type of previous chemotherapy*

Dose	***n***	**CR**	**PR**	**S**	**P**
100/1500	6	0	3	3	0
120/1800	11	1	3	4	3
140/2100	7	1	3	1	2
All patients	**24**	**2 (8.3%)**	**9 (37.5%)**	**8 (33.3%)**	**5 (20.8%)**
Previous lines of chemotherapy					
1	16	2	5	6	3
2	8	0	4	2	2
All patients	**24**	**2 (8.3%)**	**9 (37.5%)**	**8 (33.3%)**	**5 (20.8%)**
Previous drug exposure					
CPT-11	13	2	3	5	3
L-OHP	5	–	2	2	1
CPT-11 + OHP	6	–	4	1	1
All patients	**24**	**2 (8.3)**	**9 (37.5)**	**8 (33.3)**	**5 (20.8)**

have provided important clinical activity in untreated metastatic colorectal cancer patient [15-18,22]. Results obtained by sequentially using non-cross-resistant regimens such as FOLFOX followed by FOLFIRI and vice versa have not been completely satisfactory [19].

The primary objective of our study was to determine the tolerability of the combination of 5-FU/FA, OHP and CPT-11 administered every 2 weeks in CPT-11 and/or OHP pretreated colorectal cancer patients. We chose a bimonthly schedule on the basis of previous studies (see below) with the same chemotherapeutic agents in which this interval provided good activity and, generally, a complete recovery of toxicities.

Twenty-six patients were treated; all patients were evaluated for safety, 24 for efficacy. We planned three different dose levels for CPT-11 and 5-FU and a fixed dose for OHP. 5-FU was administered as a 48h continuous infusion in function of the safest toxicity profile of this type of administration.

Through the three different dose levels, the most frequent adverse events observed were consistent with those expected with the use of these drugs. In particular, for patients previously treated with OHP, acute or late-onset cumulative sensory neuropathy was frequently observed. However, both hematological and non-hematological toxicity was acceptable, with the occurrence of only one grade 4 neutropenia and stomatitis.

More frequent hematological toxicity and neurological toxicity were observed at the third dose level. All patients enrolled in this study had a good PS and about a half of them only one site of metastasis. Thus, one can speculate that a triple regimen might cause increased toxicity in pretreated patients with more unfavorable clinical characteristics.

Although tumor response was not the primary endpoint of this study, out of 24 evaluable patients, 11 objective responses were observed (45.8%) and tumor growth control (CRs plus PRs plus SDs) occurred in 19 patients (79.2%). No substantial differences in response rates were observed among the three dose levels employed. The median duration of CR + PR was 5.5 months, the median time to progression 5.5 months and the median OS was 18 months.

The dose level using CPT-11 at 120 mg/m^2 and 5-FU at 1800 mg/m^2 appears to be appropriate for phase II studies in these patients.

The combination of 5-FU, folinic acid, OHP and CPT-11 has been studied in colorectal cancer patients either untreated for metastatic diseases [30-34] or pretreated with 5-FU [24-29]. In a minority of the pretreated patients, 5-FU was administered as part of combination regimens with either CPT-11 and OHP [25,26,29]. Only the study of Stathopoulos *et al* [28] reports results obtained with the triple combination in patients all previously treated with FOLFIRI. The main characteristics of these studies in terms of treatment schedules and the therapeutic results are shown in *Tables 5* and *6*. In most of these studies 5-FU was used as a protracted [25,30,32,33] or short (90 min) [34] infusion regimen, or as a hybrid regimen (bolus + infusion) [24,27,31]. In three studies 5-FU was administered as a bolus injection [26,28,29]. The majority of these studies constitute phase I-II trials since dose-finding for 5-FU [26], FA [27], CPT-11 [26,27,30,33] and OHP [26,27,33] has been employed. These varying study characteristics do not permit an exact compari-

TABLE 5 - *Clinical trials with CPT-11, OHP and 5-FU/FA in pretreated patients with colorectal cancer (efficacy results).*

Drugs	Drug dose (mg/m²) and schedule	Frequency (q wks)	N. pts (n)	OR (%)	Median TTP (mo.)	Median OS (mo.)	Adjuvant only (n)	Previous chemotherapy for advanced disease	Author and ref. no.
Second-line treatment									
CPT-11 **OHP** **5-FU** **FA**	180 (d1) 85 (d15) 400 bolus →600 c.i. (22h) (d1,2) (q 2 wks) 200	4	32	6	8.2	9.8	2	n=30 (5-FU, n=30)	Becouarn et al., 2001[24]
CPT-11 **OHP** **5-FU** **FA**	250 (d1); 300 (d1) 120 (d1) 2500 mg/d i.a. (d1-4); 2600 c.i. (24h) (d1,15) 500 (only with 5-FU c.i.)	2	53 (28; 25)	54.7	10	18	6	n=30 (CPT-11, n=4; OHP, n=11; 5-FU, n=13; RTX, n=2)	Calvo et al., 2002[25]
CPT-11 **OHP** **5-FU** **FA**	150-200 (d1) 85-110 (d1) 650-800 bolus (d2) 250	1	43*	27.5	7.3	15.6	8	n=35 (CPT-11, n=3; OHP, n=5; 5-FU, n=27)	Comella et al, 2002[26]
CPT-11 **OHP** **5-FU** **FA**	90-220 (d1) 60-85 (d1) 400 bolus→600 c.i. (22h) (d1,2); 400 bolus→2400 c.i. (46h) (d1,2) 200-400	2	34**	32.3	7	1.1-24.5***	NR	n=32 (NR, no CPT-11 and/or OHP)	Ychou et al., 2003[27]
CPT-11 **OHP** **5-FU** **FA**	135 (d1) 135 (d1) 500 bolus (d1) 200	3	57	38.9	8	10	0	n=57 (CPT-11, n=57)	Stathopoulos et al, 2006[28]
CPT-11 **OHP** **5-FU** **FA**	175 (d1) 110 (d1) 800 bolus (d2) 250 (d2)	2	41	45	7.5	14.4	12	n=29 (CPT-11, n=8) (OHP, n=8) (5-FU, n=13)	Comella et al., 2006[29]

* 39 colorectal cancer patients; ** 11 colorectal cancer patients (OR 45.4%); *** range

TABLE 6 - *Clinical trials with CPT-11, OHP and 5-FU/FA in pretreated patients with colorectal cancer (grade 3-4 toxicity results).*

Author and ref. no.	Neutropenia	Thrombocytopenia	Diarrhea	Stomatitis	Neurotoxicity	Asthenia
Second-line treatment						
Becouarn et al., 2001[24]	53	3	19	NR	3	9
Calvo et al., 2002[25]	52.8	5.7	45.3	13.2	0	NR
Comella et al, 2002[26]	67.4	8.7	40	2.2	4.3	NR
Ychou et al., 2003[27]	78	2.4	27	4.9	37	41.5
Stathopoulos et al, 2006[28]	3.7	0	11.1	NR	0	0
Comella et al., 2006[29]	68	0	34	10	15	NR

son of their results. In previous second line clinical trials a high incidence of grade 3-4 neutropenia was observed (varying from 52.8% to 78.0% of patients with the exception of the study of Stathopoulos *et al.* [28] reporting grade 3 neutropenia only in 3.7% of patients) as well as of grade 3-4 diarrhea (varying from 11.1 to 45.3% of patients) [24-29]. In these case series febrile neutropenia (2.0%-13.0%, when reported), grade 3-4 thrombocytopenia (0-5.7%) and stomatitis (2.2-13.2%, when reported) were also observed [24-29].

In the study by Calvo *et al.*[25] a toxic death rate of 5.7% of 53 patients was reported. In this case series higher doses of CPT-11, 5-FU and FA were used.

Also in first-line studies hematological and non-hematological toxicities were not negligible. Grade 3-4 neutropenia was observed in percentages variable from 20 to 86% of patients (febrile neutropenia from 6% to 23.0% of cases), grade 3-4 diarrhea in 16-32% of cases. Grade 3-4 thrombocytopenia and stomatitis were somewhat rarer, varying from 0 to 9% and 0 to 10% of cases, respectively [30-34]. In the study of McWilliams *et al.,* [34] a fatal event (grade 5) due to diarrhea and dehydration was reported.

Neurosensory toxicity and asthenia varied widely. They were usually infrequent in untreated patients (0-10% neurotoxicity and 7-10% asthenia, when reported) [30-34] as well as in pretreated patients (from 0 to 15.0% and from 0 to 9.0% when reported, respectively) with the exception of the study by Ychou *et al.* [27] which reported 37% neurosensory toxicity and 41% asthenia in 34 pretreated patients. This occurred despite relatively low OHP doses (60-85 mg/m^2 q 2 weeks OHP) used in this study.

The frequencies of substantial to severe hematological and gastrointestinal toxicities (diarrhea, stomatitis) observed in our study compare favorably to those observed in the above studies. Incidence of neurotoxicity and asthenia in our study appears higher than that observed in previous studies with the exception of Ychou *et al.* [27]. This may be due to the higher percentage of OHP-pretreated patients (46.1%) in our study compared to other studies in which there were none or few OHP-pretreated patients.

Encouraging efficacy data have been reported in phase I-II studies in pretreated patients. Overall responses range from 27.5% to 54.7% [25-29] with the exception of the study by Becouarn *et al.* [24] in which a fairly long interval between treatment cycles was used (4 weeks) (6% overall response). As previously stated, pretreatment in these case series consisted mostly of single-agent 5-FU treatment. In a minority of patients in the study by Calvo *et al.* [25], Comella *et al.* [26,29], 5-FU was combined with CPT-11 or OHP. No specific response rates in these subpopulations have been reported with the exception of Comella *et al.* [29] in which 50% and 37.5% of pretreated patients with CPT-11 and OHP, respectively, responded to the triple combination. In addition a 38.9% objective response rate was obtained by Stathopoulos *et al.* [28] in 57 patients previously treated with FOLFIRI.

With the exception of the study by McWilliams *et al.* [34], even higher response rates have been reported when the ternary combination was used as first-line treatment (58.1%-78.0%), accompanied by long-term survival (25.4 – 28.4 months) [30-33]. These data have been recently confirmed by a phase III trial by Falcone *et al.* [38] but not by Souglakos *et al.* [39].

Our results (45.8% overall response rate and median overall survival of 18 months) are particularly relevant since they were obtained in a patient population pretreated with 5-FU combined with OHP (23.1%) or CPT-11 (53.8%), or with both these combinations sequentially (23.1%).

Another interesting result of our study is the possibility for patients with unresectable hepatic metastases to undergo radical hepatic resection after treatment with this combination chemotherapy (16.7%). This finding is in agreement with results of Masi *et al.* [40] who report surgical resection of hepatic metastases after the administration of CPT-11, OHP and 5-FU in 26% of a series of mostly untreated patients.

In conclusion, the efficacy of the ternary combination as second-line chemotherapy of metastatic colorectal cancer patients pretreated with OHP- or CPT-11-based regimens is appreciable and its toxicity profile is acceptable at drug doses used in the present study. This combination, at the intermediate doses of CPT-11 and 5-FU used, represents an effective and

safe salvage treatment even for this heavily pretreated patient population. These results warrant confirmation in controlled comparative clinical studies.

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