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ORIGINAL ARTICLE

Chronomodulated administration of oxaliplatin plus capecitabine (XELOX) as first line chemotherapy in advanced colorectal cancer patients: phase II study

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Abstract
Background The combination of 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (I-OHP) was shown to be both more active against metastatic colorectal carcinoma and better tolerated if the drug delivery rate was chronomodulated according to circadian rhythms rather than constant. The aim of the present study was to define the feasibility and efficacy of XELOX administered through a new chronomodulated schedule in untreated advanced colorectal cancer (CRC) patients.
Methods Chemotherapy-naive patients with advanced CRC were considered eligible for the study accrual. Treatment: oxaliplatin 70 mg/m^2 continuous infusion (c.i.) for 12 h (8:00 a.m. to 8:00 p.m.) days 1, 8 plus chronomodulated oral capecitabine 1,750 mg/m^2/die (h 8:00 a.m. 25% of total dose; h 6:00 p.m. 25% of total dose; h 11:00 p.m. 50% of total dose), days 1–14 every 21 days.
Results Forty-six patients were evaluated for safety and efficacy (male/female, 20/26). Median age was 64 years (range 28–77 years). Median Eastern Cooperative Oncology Group performance status (PS) was 0 (range 0–1). A total of 324 cycles have been administered: median per patient 6 (range 3–10 courses). Median number of metastatic sites was 1. Metastatic sites distribution was as follows: liver (65.2%), lung (34.8%), and nodes (32.6%). Median follow-up was 14 months (range 6.0–40.3 months). In an intent-to-treat efficacy analysis, objective response and stable disease were recorded in 27 (58.6%) and in 16 patients (34.9%), respectively. The median response duration was 8.0 months (95% CI; 5.03–10.96 months). The median time to progression (TTP) was 9.0 months (95% CI; 6.47–11.52 months). The overall survival (OS) was not reached, with a median value > 24 months (95% CI; 23.66–36.30 months). The grade 3 toxicities were diarrhea (8.7%), liver toxicity (13.1%), fatigue (8.7%), neurotoxicity (2.2%), neutropenia (8.7%), and thrombocytopenia (2.2%).
Conclusion This regimen resulted of particular interest for patients with untreated metastatic CRC.

Keywords Capecitabine · Chronomodulation · Oxaliplatin · Untreated metastatic CRC patients

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Introduction

Colorectal cancer (CRC) represents a major health problem in the western world. Approximately 60% of patients with CRC require systemic therapy for metastatic disease, either at diagnosis or at disease recurrence [1, 2]. Until recently, 5-fluorouracil (5-FU)-based therapy was the only drug regularly used for the palliation of patients with metastatic CRC, and it has been reported to have a limited impact on survival [3–6]. The use of prolonged infusion of 5-FU in combination with the biomodulator leucovorin (LV) has improved

safety and efficacy profiles compared with the bolus FU/LV [7, 8]. The introduction of irinotecan led to an effective second-line treatment for those patients who progressed after 5-FU based regimens [9]. The addition of irinotecan to 5-FU plus leucovorin (IFL) also demonstrated to be able to improve the survival of previously untreated patients with advanced disease [10, 11]. Oxaliplatin (1-OHP) is a diaminocyclohexane platinum complex and represents a promising new agent for the treatment of CRC. It demonstrated activity as a single agent [12]. Interesting response rates of oxaliplatin (28–65%) in combination with 5-FU/LV (FU/folinic acid/oxaliplatin) were reported in patients with advanced colon cancer treated in first- and second-line settings, indicating some synergistic effect with fluoropyrimidines [13–15]. In an effort to combine oxaliplatin with a fluoropyrimidine in a more convenient and safety regimen, phase I trials combined oxaliplatin with capecitabine [16]. Capecitabine is an oral fluoropyrimidine that mimics the pharmacokinetics of continuous 5-FU infusion and is preferentially converted to the active 5-FU metabolite within tumor cells by exploiting the higher activity of thymidine phosphorylase (TP) enzyme in tumor tissue compared with normal tissue [17]. The tumor selective activation of capecitabine might be further improved when combined with oxaliplatin that up-regulates TP in tumor cells but not in normal tissues [18]. Twice-daily dosing of oral capecitabine obviates the drawbacks of prolonged infusions of FU. In addition, capecitabine in monochemotherapy showed response rates in metastatic disease similar to infusional fluorouracil regimens at about 25%, with acceptable toxicity and the convenience of an oral administration schedule [19]. Based on phase I trials and the above considerations, several phase I–II trials aimed to evaluate the toxicity profile and the efficacy of the oxaliplatin-capecitabine association in advanced CRC patients [20–23]. A phase I study showed that the combination of capecitabine with oxaliplatin (XELOX) is feasible and established the recommended dose regimen as oxaliplatin 130 mg/m^2 on day 1 followed by oral capecitabine 1,000 mg/m^2 twice daily, from days 1 to 14, in a 3-week cycle [20]. The results of the above mentioned trials suggest that association of oxaliplatin and capecitabine administered twice daily for 14 consecutive days is a therapeutic option with antitumor efficacy and acceptable toxicity.

Chronomodulated 5-FU clinical efficacy is maximum when administered in nocturnal hours with a concentration peak at 4:00 a.m. [24]. Capecitabine mimes continuous infusion (c.i.) of fluorouracil and is terminally converted in 5-FU by TP enzyme which has not shown any specific circadian rhythm [18]. The rational basis of capecitabine administration, especially in nocturnal hours (1/4 dose at 6:00 p.m. and 2/4 dose at 11:00 p.m.), as performed in the present report, is just based on the attempt to mime 5-FU chronomodulated infusion. Oxaliplatin is traditionally administered by a 2-h infusion. In the present trial, we decided to use c.i. of oxaliplatin with the aim to maximize the clinical efficacy, by infusing the drug during the hours of its best anticancer efficacy [25–29]. Its weekly administration is aimed to maximize the demonstrated synergistic effect with the daily schedule of capecitabine. On this basis, our study group recently published a phase II study aimed to evaluate the safety and activity of a new chronomodulated XELOX schedule in heavy pre-treated advanced CRC patients [30]. In this setting of patients this regimen showed a high overall tumor growth control, a remarkable median TTP and OS and a good safety profile. In this paper we report the results of a phase II trial to assess the safety and the response rate of chronomodulated XELOX in untreated metastatic CRC patients. Secondary aims were to evaluate response duration, time to progression (TTP) and median survival of treated patients.

Materials and methods

Eligibility criteria

Eligible patients had pathologically documented CRC not amenable of potentially curative resection or radiotherapy. Measurable disease in at least one site (a lesion that can be accurately measured in size) identified by instrumental examinations was required. All patients were treated with chronomodulated XELOX as first line chemotherapy for metastatic disease. Patients aged between 18 and 80 years with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1 and a life expectance > 3 months were included. Bone marrow function requirements included an absolute neutrophil count $\geq 1{,}500/\text{mm}^3$, a platelet count $\geq 100{,}000/\text{mm}^3$, and hemoglobin $\geq$ 10.0 g/100 ml. Preserved renal function (serum creatinine ≤ 1.5 mg/dl and normal creatinine clearance), hepatic function (total bilirubin ≤ 1.5 mg/dl, AST and ALT ≤ 2.5 times normal without hepatic metastasis and ≤ 4 times normal with hepatic metastasis) and cardiac function were required. Patients could have previously received adjuvant fluoropyrimidine-based chemotherapy with or without concomitant radiation therapy, which had to have been completed at least 6 months before study entry. Moreover, previous palliative radiation therapy was permitted, provided that a

target lesion outside the radiation port was present, and full resolution of toxicities had occurred.

Patients with serious or uncontrolled concurrent medical illness, central nervous system metastases, or a history of other malignancies (with the exception of excised in situ cervical carcinoma or basal skin/squamous cell carcinoma, if appropriately treated) were not eligible for treatment.

Patients were excluded if they have and/or had intolerance to one or more drugs used in the experimental protocol. Moreover, patients with a prior or current peripheral neuropathy, patients who were pregnant or lactating, and patients with not controlled concomitant severe diseases were excluded from this study. An interval time > 6 weeks between tumor staging and the start of the protocol was not allowed. All patients were required to provide a written informed consent before the initiation of treatment, after a complete and opportune explanation. Women in fertile age were informed about risks in case of pregnancy. Patients were excluded if adequate follow-up was not possible (environmental or geographic difficulties, no compliance to undergo necessary clinical-instrumental investigations, etc.).

Treatment plan

Patients received oxaliplatin as an outpatient basis at the dose of 70 mg/m^2 diluted in 100 ml of dextrose 5%, given as a 12-h c.i. (from 8:00 a.m. to 8:00 p.m.) on days 1 and 8 of each cycle via portable pump device. Capecitabine was supplied as film-coated tablets in two dose strengths (150 and 500 mg) and was given orally at a dose of 1,750 mg/m^2/die, according to the following timetable: 1/4 dose at 8:00 a.m.; 1/4 dose at 6:00 p.m. and 1/2 dose at 11:00 p.m. each day for 14 consecutive days (days 1–14). Each treatment cycle was repeated every 21 days. No specific pre-medication for nausea and/or vomiting was provided. Choice of administering drugs for these problems was free. A preventive protonic pump inhibitor (PPI) was advised with gastroprotective aim.

Toxicity and dose modifications

Adverse reactions were evaluated according to the National Cancer Institute Bethesda Common Toxicity Criteria, NCI-CTC [31]. Cumulative toxicity was evaluated and recorded before each treatment cycle. Capecitabine administration was stopped for (G2 hematological toxicity and was restarted in case of toxicity regression to G0-1. Reduction of 25% in capecitabine dosing was applied for G3-4 non-hematological toxicity in the previous cycle. Reduction of 25% in oxaliplatin dosing was applied for G3 non-hematological toxicity and G4 hematological toxicity in the previous cycle. If peripheral neuropathy persisted between two following cycles, the next cycle had to provide a reduction of 50% in oxaliplatin dosing. If pain was associated to the peripheral neuropathy, a reduction of 25% in oxaliplatin dosing was applied. If pain persisted between two following cycles, the next one had to provide a reduction of 40% in oxaliplatin dosing. In case of persistent neuropathy with pain (G3) also after the dose reduction, treatment interruption was provided. The use of hemopoietic growth-factors for white and red cell lines was always allowed in case of toxicity and this was always decided by the investigators in order to safeguard a patient's life. However, priority was always given to the patient's needs.

Study schedule and evaluations

Screening assessments counting medical history, physical examination (including vital signs, height, weight, and ECOG), electrocardiogram (ECG), chest X-ray and tumor measurements, based on the appropriate imaging techniques (i.e., computed tomography scan), were conducted within 14 days before treatment initiation. Laboratory data including complete blood count, blood chemistry and urinalysis were also obtained. During treatment, weekly assessments included vital signs, physical measurements, ECOG, complete blood counts and blood chemistry. For patients continuing treatment beyond 18 weeks, these assessments were carried out at 3-weekly intervals. Urinalysis, chest X-ray, ECG, brain computed tomography scan, and bone scan were performed if clinically indicated. Treatment was continued, for a maximum of nine courses, until disease progression (evaluated with the best instrumental exams applicable in case of metastatic lesions after at least 3 cycles and every 3 cycles), or the development of unacceptable toxicity (according to the National Cancer Institute Bethesda Common Toxicity Criteria, NCI-CTC), or the patient's refusal. All tumor measurements were reviewed and confirmed by an independent panel of radiologists and oncologists. Follow-up was closer, more specific, and recommended from common rules in clinical oncology on the basis of the patient's general status and the extension of the disease. Each relevant happening and medical intervention potentially influencing the protocol results were recorded.

Sample size and statistical considerations

The efficacy analysis was based on the intent-to-treat population. The primary end point was overall confirmed

response rate. A Simon two-stage design was used [32] with early termination of the trial if a predetermined minimum level of activity was not observed after the first stage of accrual. In the first stage, a total of 16 patients were included and at least five responses (both complete and partial responses) were required to continue to the second stage. In the second stage, 30 additional patients were included to a total sample size of 46. Twenty responses were needed to conclude with a 95% confidence that the response rate was > 40%.

Time to progression was calculated from inclusion date to progression documented or death date. Overall survival (OS) was calculated from inclusion date to record of death for any cause. Duration of response means time within partial or complete response was kept. Treated patients would have been followed until disease progression. Safety was analyzed in all patients who received at least one dose of study medication. SPSS software (Version 11.05, SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Patient characteristics

Demographic and other baseline characteristics of patient population are summarized in Table 1. From November 2002 to October 2005 a total of 46 consecutive patients were enrolled into the study.

All patients were assessable for treatment efficacy and safety. The median age of study population was 64 years (range 28–77 years), all patients had an ECOG PS of 0 or 1, and 50% had two or more metastatic sites involving the liver (65.2%), the lung (34.8%), and the nodes (32.6%). Primary tumor site was colon in 67.4% of patients, rectosigmoid junction in 8.7% and rectum in 23.9% of patients. Six patients (13.1%) received adjuvant FU/LV and three (6.5%) preoperative radiotherapy. A total of 324 cycles were administered with a median number of six cycles per patient of 6 (3–10 courses). At the cut-off date (6-month minimum follow-up duration), all data except those relating to the effect of second line treatment were mature.

Safety results

Toxicity was recorded for all the 46 patients enrolled in this study. Thirteen patients (28.2%) withdrew during the experimental phase (nine courses). The majority (nine patients; 19.5%) withdrew because of disease progression. Only one patient (2.2%) withdrew because of adverse events (Table 2).

Table 1 Patient characteristics

Characteristics	Number of patients (%)
Total number	46 (100)
Male/female	20/26 (43.8/56.2)
Age (years)	
Median	64
Range	28–77
Performance status	
Median	0
Range	0–1
Primary tumor site	
Colon	31 (67.4)
Rectum	11 (23.9)
Rectosigmoid	4 (8.7)
Tumor differentiation	
Well differentiated	2 (4.3)
Moderately differentiated	28 (60.9)
Poorly differentiated or undifferentiated	16 (34.8)
Median number of metastatic sites (range)	1 (1–6)
1	23 (50.0)
2	15 (32.6)
3+	8 (17.4)
Sites of metastases	
Liver	30 (65.2)
Lung	16 (34.8)
Nodes	15 (32.6)
Local	4 (8.7)
Other	8 17.4)
Prior adjuvant therapy	
None	40 (86.9)
FU/LV	6 (13.1)
Preoperative radiotherapy	3 (6.5)

Table 2 Reasons for withdrawal during the first nine cycles

Reasons of withdrawal	Number of patients	%
All withdrawals	13	28.2
Progression of MCRC	9	19.5
Adverse events	1	2.2
Death	1	2.2
Refused treatment	2	4.3
Other	0	0

The incidence of G3-4 toxicity is summarized in Table 3. The majority of treatment related adverse events were mild or moderate (G1-2) in intensity. The only grade 3 toxicities were diarrhea (8.7%), hyperbilirubinemia (13.1%), fatigue (8.7%), neutropenia (8.7%), and thrombocytopenia (2.2%). Sensory neuropathy, a frequent side effect of oxaliplatin, was the most common treatment related adverse event, occurring in 97.8% of patients. The majority of neuropathy was mild to moderate, only 2.2% (one patient) experiencing cumulative severe (G3) neurotoxicity. Laryngospasm during the oxaliplatin infusion was never

Table 3 Safety profile (according to NCI/CTC criteria)

Side effects	Number of patients with toxicity (%)				
	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Hematological					
Anemia	12 (26.1%)	2 (4.3%)	0 (0%)	0 (0%)	14 (30.4%)
Leucopenia	17 (36.9%)	6 (13.1%)	1 (2.2%)	0 (0%)	24 (52.2%)
Neutropenia	12 (26.1%)	7 (15.2%)	4 (8.7%)	0 (0%)	23 (50.0%)
Thrombocytopenia	9 (19.5%)	4 (8.7%)	1 (2.2%)	0 (0%)	14 (30.4%)
Non-hematological					
Nausea/vomiting	26 (56.5%)	13 (28.2%)	0 (0%)	0 (0%)	39 (84.7%)
Mucositis	20 (43.5%)	2 (4.3%)	0 (0%)	0 (0%)	22 (47.8%)
Neurotoxicity	26 (56.5%)	18 (39.1%)	1 (2.2%)	0 (0%)	45 (97.8%)
Diarrhea	17 (36.9%)	12 (26.1%)	4 (8.7%)	0 (0%)	33 (71.7%)
Asthenia	15 (32.6%)	18 (39.1%)	4 (8.7%)	0 (0%)	37 (80.4%)
Hand-foot syndrome	6 (13.1%)	1 (2.2%)	0 (0%)	0 (0%)	7 (15.3%)
Hyperbilirubinemia	9 (19.5%)	6 (13.1%)	6 (13.1%)	0 (0%)	21 (45.7%)

observed. No patient experienced G3 hand-foot syndrome. No episode of any grade 4 toxicity occurred. Dose modification due to toxic events was required in 13 patients (27%). The reasons for dose reduction were severe diarrhea (four patients), rising in bilirubin (six patients), persistent grade 2 thrombocytopenia (two patients) and persistent fatigue (one patient) (Table 4). Cycle delays due to toxic events were recorded in 21 patients (45.6%). During the whole treatment period only five hospitalizations were needed because of prolonged refractory diarrhea (three patients) and decrease of clinical conditions (two patients).

Antitumor efficacy

Treatment responses, TTP and OS for all 46 patients enrolled in this study are summarized in Table 5. All patients enrolled in the study were assessable for antitumor efficacy. The overall response rate according to the IRC assessment was 58.6% (95% CI 39.1–63.7%) with 24 partial responses (52.1%) and three complete responses (6.5%). Disease stabilization was obtained in 34.9% of patients (95% CI 24.7–51.6%) and progression in three patients (6.5%). The median response duration was 240 days (8 months) (95% CI: 150.9–329.1 days). The median TTP was 270 days (9 months) (95% CI: 194.2–345.8 days). The median follow-up time for all patients was 14 months. The median OS was not reached [>900 days (>24 months) (95%CI: 710.7–1,089.3 days)]. The Kaplan–Meier curves for median survival and median TTP are depicted in Figs. 1 and 2.

Table 4 Toxicity-related treatment modifications

Treatment modifications	Number of patients	%
Any dose reduction	13	28.2
Any cycle delay	21	45.6
Toxicity-related withdrawals	1	2.2
Time to treatment modification	**Months**	**Range**
Median time to withdrawal	4.5	1.7–6.0

Post-study treatment

A total of 31 patients (67.4%) received second-line treatment. Most of them received irinotecan in combination with FU/LV (25 patients). Thirteen (28.2%) patients received third-line chemotherapy. The most common third-line chemotherapy was cetuximab-based therapy (11 patients). The most common investigational treatment was cetuximab plus irinotecan-based therapy (12 patients). Five patients received bevacizumab-based therapy as second line therapy (Table 6). Five

Table 5 Objectives tumor response rates in advanced untreated CRC patients

Objective responses	Number (%)	Overall response rate (%)	Overall tumor control rate (%)
Complete response	3 (6.5%)	27 (58.6%)	43 (93.5%)
Partial response	24 (52.1%)		
Stable disease	16 (34.9%)		
Disease progression	3 (6.5%)		
Response duration			
Median	8 months		
95% CI	5.03–10.96		
Time to progression			
Median	9 months		
95% CI	6.47–11.52		
Overall survival			
Median	>24 months		
95% CI	23.66–36.30		

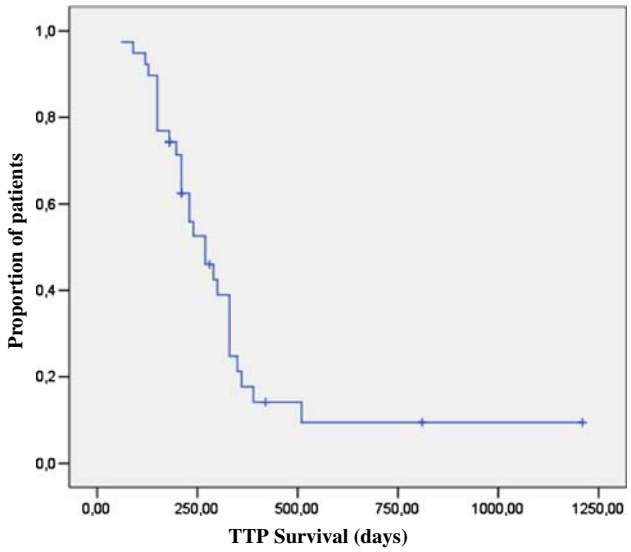

Fig. 1 Kaplan–Meier estimates time to progression

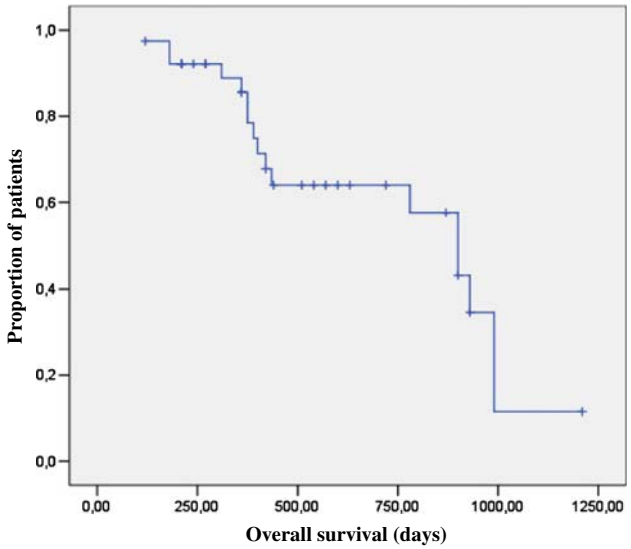

Fig. 2 Kaplan–Meier estimates for overall survival

patients underwent surgery, including four patients who underwent radical hepatic resection (with or without radiofrequency ablation) and one who underwent a radical lung resection.

Discussion

This phase II study assessed the effect of adding c.i. of oxaliplatin to chronomodulated capecitabine in 46 patients with previous untreated metastatic CRC. Objective response documentation was based on extramural review of all available CT scans. The results

Table 6 Chemotherapy after withdrawal from study treatment

Treatment	Second line (n = 31) (67.4%)	Third line (n = 13) (28.2%)
	Number of patients (%)	Number of patients (%)
Irinotecan plus FU/LV	25 (54.3)	0
Oxaliplatin		
As monotherapy	0	0
Plus FU/LV	0	2 (4.3)
Capecitabine		
As monotherapy	0	0
Plus mytomicin	0	0
FU5/LV2	0	0
Cetuximab-based therapy	1 (2.2)	11 (23.9)
Bevacizumab-based therapy	5 (10.9)	0

FU Fluorouracil, *LV* Leucovorin

confirmed that this new modality of oxaliplatin and capecitabine administration achieves 58.6% of response rate with another 34.9% of disease stabilization. The overall response rates obtained in the present study were higher than expected and consistent with those reported in previous studies in untreated patients. The efficacy of capecitabine combined with either irinotecan (XELIRI) or oxaliplatin (XELOX) has been demonstrated in a multitude of phase II trials, with response rates of 55 (XELOX) [33] and 44% (XELIRI) [34]. The survival data are interesting and promising when compared with the data from other phase II studies of first line chemotherapy in CRC patients. In our experience the median TTP of 9 months and the median OS > 24 months obtained are favorably compared with those reported from the other published phase II published studies with capecitabine in combination with oxaliplatin or irinotecan conducted in similar subset of patients, with median TTP ranging from 6.7 [34] to 7.7 months [33] and OS ranging from 19.5 [33] to 24.7 months [35]. Besides efficacy, toxicity is a critical end point useful to assess the utility of a new treatment combination. The present study showed that this new way of combined c.i. of oxaliplatin and chronomodulated capecitabine is generally well tolerated, with favorable safety profiles when comparing with previous studies. As expected, the main toxicities of this new regimen are gastrointestinal disorders. Severe delayed diarrhea was observed in only 8.7% of patients. This incidence does compare favorably with those reported in the other phase II published studies combining oxaliplatin and capecitabine, with G3-4 diarrhea ranging from 16 to 50% [21, 22, 33, 36–40]. Interestingly, G3-4

sensory neuropathy reported in the present experience (2.2%) is very low when compared with those reported with the other XELOX regimens (range 4–17%) [21, 22, 33, 39] and with those described with FU/LV/oxaliplatin regimens (range 12–34%) [14, 41–45]. Moreover, the incidence of G3-4 neutropenia experienced in the present regimen seems to be lower compared with that observed with FU/LV/oxaliplatin regimens (8.7% vs. 42–47%) [14, 46], and similar to that reported during the other XELOX regimens (8.7% vs. 4–7%) [22, 33, 39]. The incidence of G3-4 hand-foot syndrome recorded in the present study does compare favorably with that experienced in other capecitabine-based regimens (0% vs. 2–18%) [21, 23, 39, 47–50].

The favorable toxicity profile of our regimen may have been occurred because of the circadian organization of fluoropyrimidine metabolism, excretion and therapeutic targets. However, it could have been also related to the thrice-daily schedule rather than the usual *bis in die* administration. Moreover, 12 h of c.i of oxaliplatin may have contributed to both the good safety profile and high response rate. As previously reported, the safest time for cisplatin, carboplatin and oxaliplatin infusion is the second half of the daily activity span of each day. In fact, in the present experience, this agent is being infused during a time of day overlapping, at least partially, with its optimal circadian administration time. Therefore, part of the beneficial effect of a 12-h infusion of oxaliplatin may also be related to its daytime circadian timing [25].

In conclusion, the high overall tumor growth control, the remarkable median TTP and OS and the promising safety profile obtained combining chronomodulated capecitabine with continuous oxaliplatin infusion resulted of particular interest for patients with untreated metastatic CRC. These results clearly highlight the need for randomized phase III trials to verify the real clinical impact of this new way to combine oxaliplatin and capecitabine in this subset of patients.

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