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Randomised phase II study of standard versus chronomodulated CPT-11 plus chronomodulated 5-fluorouracil and folinic acid in advanced colorectal cancer patients

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ABSTRACT

In this study, a randomised phase II trial explored the effects of 6-h chronomodulated CPT-11 infusion in advanced colorectal cancer patients. Sixty-eight pre-treated patients were randomly assigned to CPT-11 administered at 180 mg/m^2 on day 1, by 1-h infusion (Arm A) or 6-h sinusoidal infusion with peak timing at 5:00 a.m. (Arm B). All patients also received chronomodulated folinic acid/5-fluorouracil (FA/5-FU). Patients in Arm B obtained a 25.7% response rate for 7.0 months duration, a progression-free survival for 8.0 months and a median survival of 28 months. The same data in Arm A were 18.2%, 4.5, 6.0 and 18 months, respectively. No differences in drugs dose-intensity or increased toxicity with prolonged chronomodulated infusion were detected. Major grade 3–4 toxicity was diarrhoea: 10 patients in Arm A and 13 in Arm B. In conclusion, this study has shown that chronomodulated infusion of CPT-11 and FA/5-FU is safe, active and can be integrated with oxaliplatin (EORTC 05011) for the treatment of advanced colorectal cancer.

1. Introduction

Colorectal cancer is one of the principal causes of death in western countries. Modern treatment of advanced disease is based on combination chemotherapy with the most active drugs available including 5-fluorouracil (5-FU), modulated by folinic acid (FA), irinotecan (CPT-11) and oxaliplatin (L-OHP). CPT-11 is a topoisomerase I (Topo I) inhibitor, whose main toxicities are leucopoenia and diarrhoea and has shown synergistic effects with 5-FU.[1] CPT-11 does not appear to cross-react with 5-FU either and is converted by carboxylesterases in vivo to the active metabolite SN-38. SN-38 is released mostly by the liver and has a terminal half-life of 13–18 h.[2] The first combination chemotherapy demonstrating an improvement in overall survival in first line treatment of advanced colorectal cancer included CPT-11 plus FA–5-FU infusion.[3] In this study, and in other phase III trials recently reported, CPT-11 was given as a 1-h infusion together with 48- or 24-h 5-FU infusion modulated by FA with a median overall survival of 17.4 and 20.1 months.[4]

Chronotherapy is based on exploiting circadian rhythms to make antineoplastic drugs more effective.[5,6] Circadian rhythms are ubiquitously found in a wide-ranging species from flies, rodents and human beings. They are endogenous to cells and persist even in constant environmental conditions. Circadian rhythms are coordinated by the presence of

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a central clock that is located in the hypothalamus suprachiasmatic nucleus. It was recently shown that cellular rhythms are associated with the production of particular proteins by genes that have been identified and sequenced as *Per1*, *Per2*, *clock*, *Bmal*, *Cry1*, *Cry2*.[7,8] These genes regulate expression of other genes involved in metabolism, cellular kinetics and other cellular functions.[9,10] An appreciation of the clinical relevance of chronomodulation in cancer patients comes mainly from phase I, II and III trials conducted in the last 15 years on advanced colorectal cancer. These studies have shown benefit of chronomodulation for single agents 5-FU[11,12] and L-OHP[13] and for the combination of the two drugs with FA.[14,15] CPT-11, in two independent studies, was better tolerated in healthy mice during the second part of the rest phase that corresponds to 5:00 a.m.[16,17] early morning in humans. In humans, Giacchetti et al.[18] have shown that when chronomodulated infusion of CPT-11 is compared to standard 1-h infusion, it is associated with a lower CPT-11 maximal plasmatic concentration (Cmax) (2.91 versus 5.53 μg/ml) and better SN-38/CPT-11 area under the curve (AUC) ratio (2.53% versus 1.89%, coefficient variation (CV) 33.8 versus 31.4).

We have previously shown in a phase I study combining CPT-11 at 325 mg/m^2 on day 1 together with a 5-day chronomodulated infusion of 700 mg/m^2 5-FU and 175 mg/m^2 FA every three weeks was feasible, with a response rate of 23% in pre-treated patients with an overall median survival of one year.[19] In order to investigate a possible role for chronomodulation in CPT-11 administration and to intensify 5-FU schedule, we have designed this current randomised phase II trial in advanced colorectal cancer patients. This study compares standard 1-h infusion with a 6-h sinusoidal chronomodulated CPT-11 infusion with peak time at 5:00 a.m. followed by a 4-day chronomodulated 5-fluorouracil and folonic acid 4-days on and 10-days off (FF_{4-10}). Preliminary results have already been presented elsewhere.[20]

2. Patients and methods

2.1. Patient evaluation

The eligibility criteria for inclusion in the study were: presence of colon or rectum adenocarcinoma; unresectable metastases; aged between 18 and 80 years; life expectancy >3 months; WHO performance status (PS) of 0–2; measurable $\geqslant$2 cm or evaluable disease and prior therapy, including patients with more than one previous 5-FU containing regimen and previous monotherapy with CPT-11 was allowed. Adequate bone marrow (haemoglobin $\geqslant$10 g/dl, WBC $\geqslant 3.0 \times 10^9$/l, neutrophils $\geqslant 2.0 \times 10^9$/l, platelets $\geqslant 90 \times 10^9$/l), liver (total bilirubine $\leqslant 2 \times$ N and GOT/GPT $\leqslant 3.0 \times$ N) and renal function (creatinine $\leqslant 1.5 \times$ N) were confirmed within 14 days of enrolment. Each patient underwent a surgical placement of a totally implanted, double-lumen, and venous access port. Disease assessment included CT of chest, liver and whole abdomen completed within 30 days of first course[21]. No evaluation of response by ultrasound was allowed. Blood analysis was repeated every 2 weeks while tumour assessment every 12 weeks with response being confirmed after another 8–12 weeks. Patients with serious concurrent medical illness, CNS metastases or a previous history of other malignancies (with the exception of excised cervical or basal skin/squamous cell carcinoma) were excluded. All patients gave informed consent according to institutional guidelines before study registration.

2.2. Treatment protocol

Chemotherapy consisted of courses once every 2 weeks of CPT-11 180 mg/m^2 day 1, given as a 1-h infusion in 250 ml of 5% dextrose (Arm A: standard infusion) or CPT-11 180 mg/m^2 day 1, given as a 6-h sinusoidal infusion from 2:00 to 8:00 a.m. with peak flow at 5:00 a.m. in 250 ml of 5% dextrose (Arm B: chronomodulated). Both Arms received chronomodulated infusion of 5-FU and FA from 10:00 p.m. to 10:00 a.m. with peak flow at 4:00 a.m. for 4 consecutive days from day 2 to day 5 (Fig. 1). A multichannel, programmable ambulatory pump was used in an outpatient basis for delivering chronomodulated infusions. In both treatment Arms, therapy was continued until progression, unacceptable toxicity or patient refusal. Concomitant antiemetic medications included anti-Ht3 during all the 5 days of treatment however, steroids were not allowed. Premedication with atropine for cholinergic syndrome was recommended from the first course of treatment.

2.3. Toxicity and dosage modifications

Toxicity was evaluated using the National Cancer Institute – Common Toxicity Criteria.[22] If the absolute neutrophil count on the day of treatment was $<1.5 \times 10^9$/l and/or if platelets were $<10 \times 10^9$/l, the treatment was delayed for a maximum of 2 weeks. CPT-11 was reduced by 50 mg/m^2 for diarrhoea grade 3–4 while 5-FU was reduced for grade 3–4 diarrhoea or mucositis by 100 mg/m^2 per day for further courses. The dose of FA remained unchanged.

2.4. Study objectives and assessment of response

Primary end point was response rate. Secondary end points were analysis of dose-intensity, toxicity, duration of response, progression free survival (PFS) and survival. All tumour measurements were done and confirmed by internal radiologists together with principal investigators (CG and BV). All responses were confirmed after 4 weeks.

2.5. Sample size and statistical considerations

This prospective study was designed as a randomised phase II trial. For each Arm a single-stage design as described by Hern[23] was used. A sample size of 33 patients was considered sufficient to give a 90% probability of rejecting a baseline response rate of 10% with an exact 5% one-sided significance test when the true response rate is 30%. The drug regimen should have been rejected if less than 7 responses were observed. Randomisation was balanced for PS, measurable disease and previous chemotherapy for advanced disease. No formal comparison was planned.

All patients enrolled were considered intention-to-treat population. This population was evaluated for efficacy and

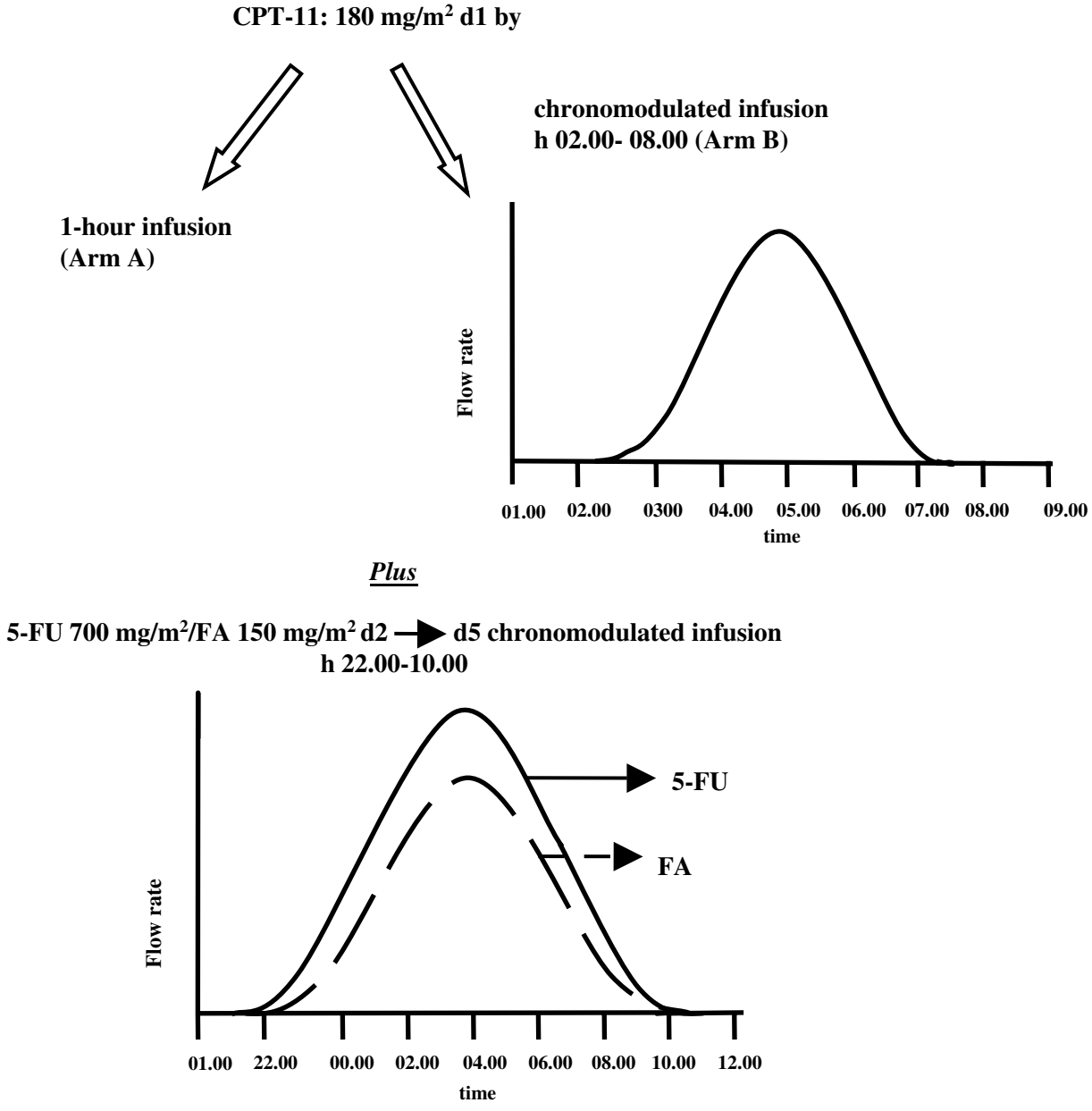

Fig. 1 – Study design.

safety analysis. The standard summary statistics were used for both continuous and discrete variables. The objective response rate was reported with its 95% confidence interval. Chi-square test was used for comparison of proportions. Time to event analysis was performed according to the Kaplan–Meier method.[24]

3. Results

3.1. *Patient baseline data*

From October 1998 to August 2002, 68 patients were included in this randomised trial: 33 in Arm A and 35 in Arm B. Patient characteristics are listed in Table 1. Patients were well distributed for major pre-treatment variables with no statistical differences for PS 0–1, primary colon tumour, synchronous versus metachronous metastatic disease and liver involvement. Three patients in Arm A (9%) and 4 in Arm B (11%) had non-measurable disease. In Arm A, after residual microscopic peritoneal seeding, treatment was delivered subject to liver resection and oophorectomy for metastatic disease in 2 patients. In Arm B, treatment was administered after liver resection in 2 cases (further to lung resection and residual microscopic peritoneal disease). In Table 2, the treatments before and after the current regimen are shown. Most of the patients in Arm A 25/33 (76%) and in Arm B 26/35 (74%) have previously received at least one line of chemotherapy for advanced disease. Median survival from diagnosis of metastatic disease to current therapy was the same in both Arms of 9 months. More than 80% of treated patients received subse-

Table 1 – Patient characteristics

Characteristic	Arm A (%)	Arm B (%)
No. of patients	33	35
Gender (male/female)	19 (58)/14 (42)	22 (63)/13 (37)
Median age years (range)	62 (35–77)	61 (28–77)
WHO performance status		
0	22 (67)	22 (63)
1	9 (27)	12 (34)
2	2 (6)	1 (3)
Primary tumour site		
Colon	28 (85)	28 (80)
Rectum	5 (15)	7 (20)
Metastases		
Syncronous	22 (67)	25 (71)
Metacronous	11 (33)	10 (29)
Sites of metastases		
Liver	20 (61)	23 (66)
Lung	6 (18)	9 (26)
Lynphonodes	5 (15)	5 (14)
Peritoneum	4 (12)	3 (9)
Number of organs involved		
1	20 (61)	19 (54)
⩾2	10 (30)	13 (37)
NM	3 (9)	4 (11)
Radiotherapy		
Adjuvant	1 (3)	3 (9)
Palliative	1 (3)	–
Adjuvant chemotherapy	9 (27)	7 (20)
Number of previous chemotherapy lines		
1	18 (55)	20 (57)
2	2 (6)	3 (9)
⩾3	5 (15)	3 (9)
CEA (ng/ml)	9.95 (1–4501)	20.5 (1–3735)
Ca 19.9 (U/l)	58 (1–2730)	57 (1–8730)

Table 2 – Chemotherapy before and after current study

	Arm A No. 33 (%)	Arm B No. 35 (%)
Previous treatment		
1	18 (55)	20 (57)
2	2 (6)	3 (9)
⩾3	5 (15)	3 (9)
Previous chemotherapy	25 (76)	26 (74)
5-FU	5 (16)	12 (34)
5-FU + Tomudex	1 (3)	0 (0)
5-FU + L-OHP	8 (24)	9 (26)
L-OHP + Tomudex	1 (3)	0 (0)
5-FU + MMC	10 (30)	3 (8)
CPT-11	0 (0)	2 (6)
Median survival from diagnosis of metastatic disease to current treatment, months (range)	9 (7–11)	9 (2–16)
No. of patients receiving further chemotherapy after current treatment	27 (82)	31 (88)
1	16 (49)	23 (66)
⩾2	11 (33)	7 (20)
Thymedilate synthetase inhibithors + L-OHP based treatments	19 (56)	22 (63)
CPT-11 + FFL ≈	9 (27)	6 (17)
FFL ≈	4 (12)	4 (11)
FOLFOX	3 (9)	9 (26)
L-OHP + Capecitabine	1 (2)	0 (0)
L-OHP + Tomudex	2 (6)	1 (3)
L-OHP + CPT-11	0 (0)	2 (6)
Median time spent on further treatment until last progression, months (range)	9 (6–9)	11 (5–18)

5-FU: 5-fluorouracil; L-OHP: oxaliplatin; MMC: mytomicin-c; FFL ≈: chronomodulated 5-fluorouracil, folinic acid and oxaliplatin.

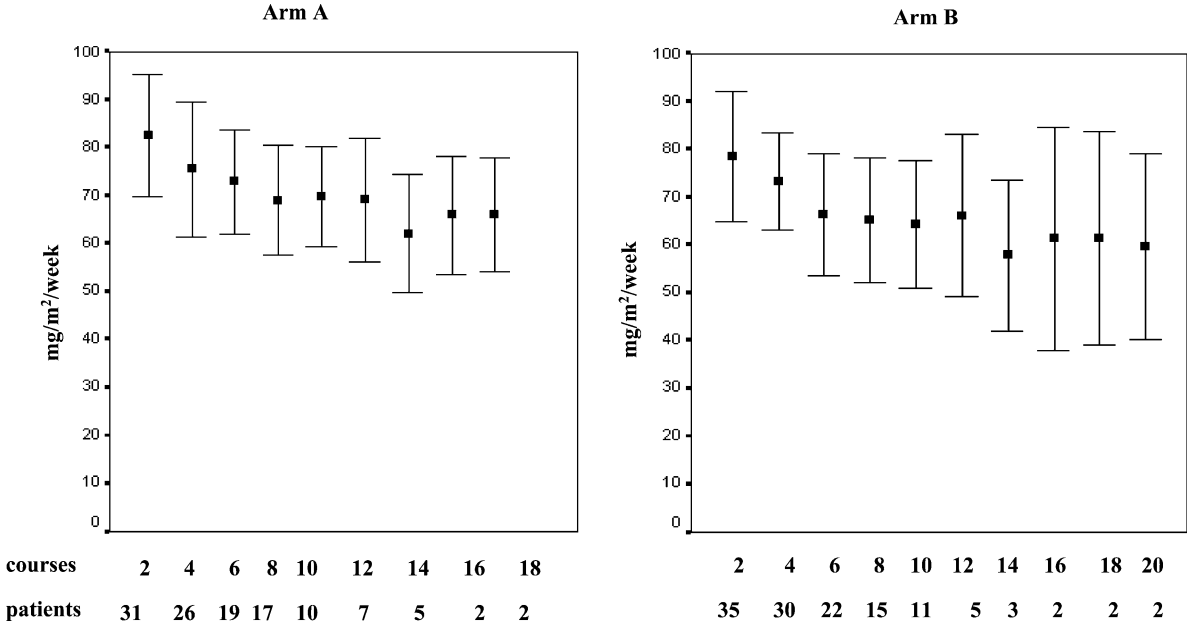

Fig. 2 – CPT-11 dose-intensity for courses and patients.

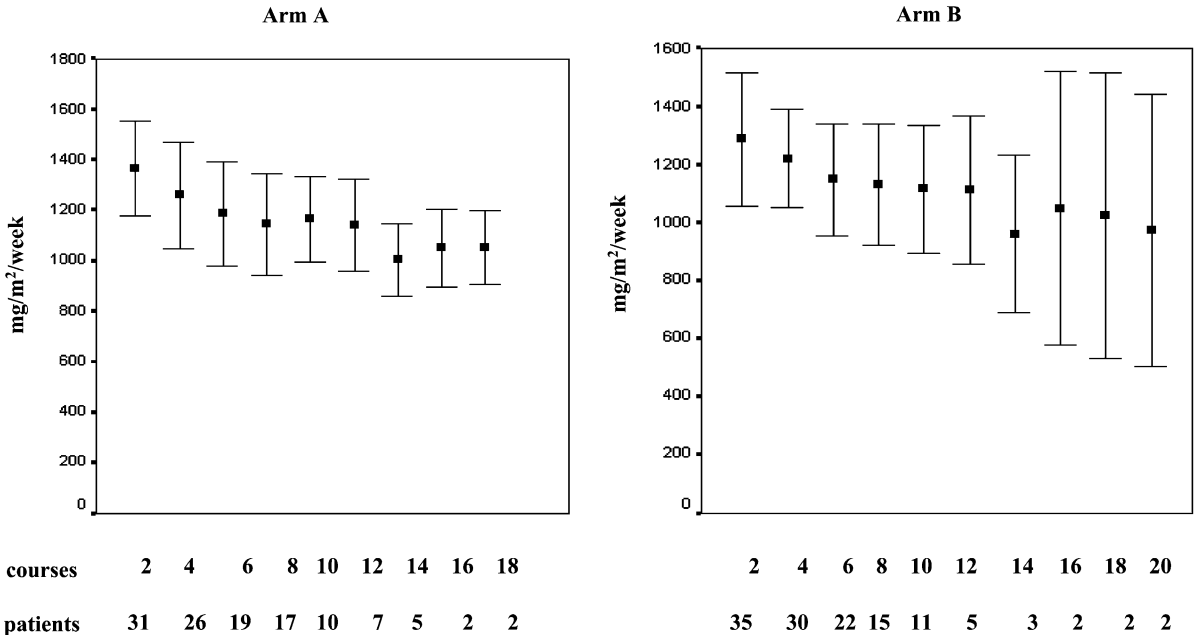

Fig. 3 – 5-Fluourouracil dose-intensity for courses and patients.

quent chemotherapy: 16 patients in Arm A (49%) had another line of chemotherapy and 23 in Arm B (66%); 11 (33%) in Arm A and 7 (2%) in Arm B had two or more treatment lines.

3.2. *Treatment compliance and dose-intensity (DI)*

The median number of delivered courses in both Arms was 7 (1–21) with a range of 1–18 in Arm A and 2–21 in Arm B. The median received dose intensity for CPT-11 and 5-FU did not differ in the two Arms (Figs. 2 and 3). Received CPT-11 DI at fourth course was 82% of theoretical for Arm A and 81% for Arm B and 81% and 70% at eighth course. Received 5-FU DI at fourth course was 89% of theoretical DI for Arm A and 84% for Arm B and 89% and 80% at eighth course indicating that there were no decreases in drug dose-intensities during treatment Table 3.

3.3. *Toxicity*

Toxicity was recorded in all patients: in 246 courses in patients receiving standard CPT-11 and in 266 courses in those receiving chronomodulated CPT-11 (Table 4). Haematological toxicity was virtually absent in both Arms, with no grade 3–4 anaemia or piastrinopenia. Grade 3 neutropenia affected only 1 patient in Arm A and 2 in Arm B. Non-haematological toxicities were the most relevant in both Arms (Fig. 4). The most serious side-effect was grade 3–4 diarrhoea which affected 10 patients (31.3%) in 13 courses (5%) in Arm A

Table 3 – Activity and efficacy

	Arm A ($n = 33$)		Arm B ($n = 35$)	
	No.	%	No.	%
Complete remission	–	–	1	2.9
Partial remission	6	18.2	8	23.5
Stable disease	10	30.3	9	25.7
Progression	11	33.3	9	25.7
Not evaluable	3	9.1	4	11.4
Not measurable	3	9.1	4	11.4
Overall response rate	6	18.2	9	25.7
95% Confidence interval (%)		5.0–31.3		11.6–41.3
Median duration of response, months		4.5		7.0
95% Confidence interval		3.0–12		4.0–12
Median progression free survival, months		6.0		8.0
95% Confidence interval		4.0–7.0		4.0–12
Median overall survival, months		18		28
95% Confidence interval		10–26		13–42

Table 4 – Toxicity per patient and per course

	G0		G1		G2		G3		G4	
	A (%)	B (%)	A (%)	B (%)	A (%)	B (%)	A (%)	B (%)	A (%)	B (%)
Anaemia										
Patients	23 (70)	29 (83)	5 (15)	5 (14)	5 (15)	1 (3)	–	–	–	–
Courses	225 (91)	256 (96)	14 (6)	9 (3)	7 (3)	1 (1)	–	–	–	–
Leucopenia										
Patients	13 (40)	21 (60)	13 (40)	11 (31)	6 (17)	1 (3)	1 (3)	2 (6)	–	–
Courses	196 (80)	231 (87)	36 (14)	29 (10)	12 (5)	5 (2)	1 (1)	2 (1)	–	–
Neutropenia										
Patients	16 (48)	16 (46)	10 (30)	11 (31)	5 (15)	7 (20)	2 (3)	1 (3)	–	–
Courses	205 (83)	219 (82)	28 (11)	30 (11)	11 (5)	16 (6)	2 (1)	1 (1)	–	–
Trombocitopenia										
Patients	32 (97)	35 (100)	1 (3)	–	–	–	–	–	–	–
Courses	245 (99)	266 (100)	1 (1)	–	–	–	–	–	–	–
Nausea										
Patients	6 (18)	5 (14)	7 (21)	10 (29)	13 (40)	15 (43)	7 (21)	5 (14)	–	–
Courses	146 (59)	163 (61)	54 (23)	52 (19)	38 (15)	44 (16)	8 (3)	7 (4)	–	–
Vomiting										
Patients	8 (24)	10 (29)	8 (24)	8 (23)	6 (19)	12 (34)	9 (27)	5 (14)	2 (6)	–
Courses	178 (72)	192 (73)	39 (16)	41 (15)	15 (6)	27 (10)	11 (5)	6 (2)	3 (1)	–
Diarrhoea										
Patients	4 (12)	2 (6)	9 (28)	7 (20)	10 (30)	13 (37)	8 (24)	12 (34)	2 (6)	1 (3)
Courses	139 (56)	150 (56)	64 (26)	64 (24)	31 (13)	37 (14)	10 (4)	14 (5)	2 (1)	1 (1)
Mucositis										
Patients	20 (61)	10 (29)	5 (15)	4 (11)	4 (12)	14 (40)	3 (9)	7 (20)	1 (3)	–
Courses	213 (87)	201 (76)	16 (6)	31 (12)	11 (4)	28 (10)	4 (2)	6 (2)	1 (1)	–
Cutis										
Patients	28 (85)	26 (73)	2 (6)	3 (9)	2 (6)	3 (9)	1 (3)	3 (9)	–	–
Courses	236 (94)	244 (91)	7 (3)	7 (3)	2 (2)	12 (5)	1 (1)	3 (1)	–	
Asthenia										
Patients	5 (15)	11 (31)	10 (30)	9 (26)	16 (48)	10 (29)	2 (6)	5 (14)	–	–
Courses	162 (66)	203 (76)	49 (19)	41 (15)	31 (13)	17 (7)	4 (2)	5 (2)	–	–

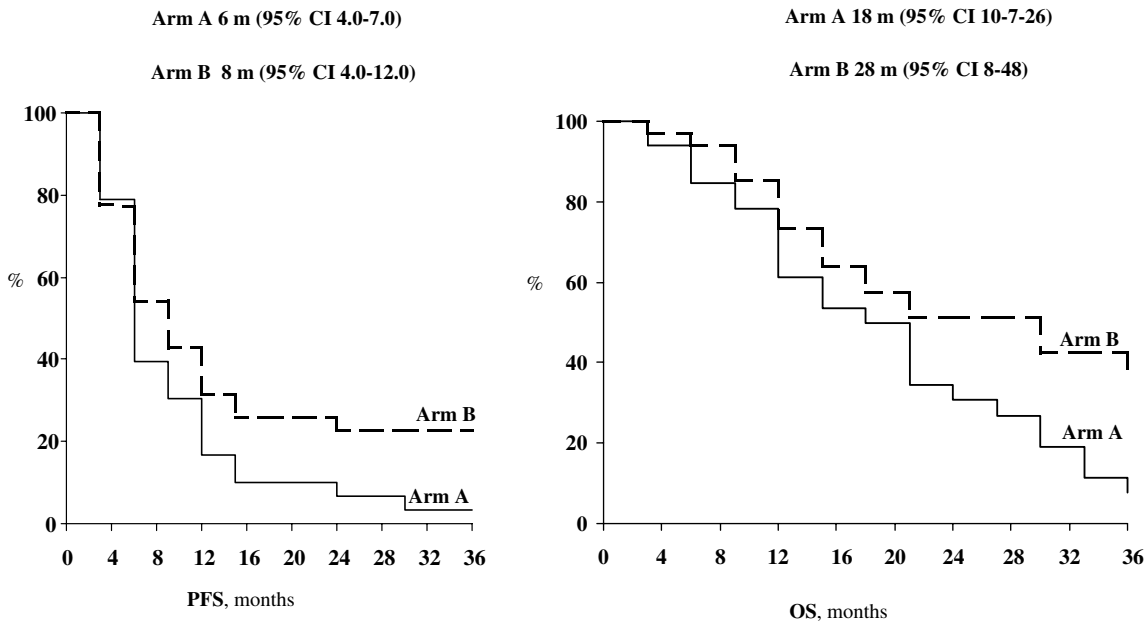

Fig. 4 – Progression-free survival (PFS) and overall survival (OS) curves.

and 13 patients (37%) in 15 courses (6%) in Arm B. Nausea and vomiting were most frequent with standard CPT-11 infusion: grade 3 nausea affected 7 patients in Arm A (21.9%) and 5 in Arm B (14.3%) and grade 3–4 vomiting 11 patients in Arm A (34.4%) and 5 in Arm B (14.3%). Conversely, grade 3–4 oral mucositis was less present with 4 patients (12.5%) in Arm A compared to Arm B with 7 patients (20%). No patient was hospitalised for toxicity and no toxic death was reported. No statistical difference in grade 3–4 toxicity per Arm was detected.

3.4. *Antitumour activity*

Antitumour activity and efficacy are summarised in Table 4. All patients were included in the analysis. Objective response, which was the main study end-point, was evaluated on an intention to treatment basis. Three patients in Arm A and 4 in Arm B were not evaluable for early progression and patient refusal. No complete response was observed in Arm A and only one in Arm B (2.9%). Six out of 33 patients obtained a partial response in Arm A and 8 (22.8%) in Arm B with an overall response rate of 18.2% in Arm A (95% confidence interval 5.0–31.3%) and 25.7% in Arm B, (95% confidence interval 11.2–40.2). Response rate in Arm A did not satisfy statistical requirements. The median response duration was 4.5 months in Arm A (range 3.0–2.0) and 7.0 months in Arm B (4.0–12.0). Stable disease was observed in 10 patients (30.3%) in Arm A and 9 patients (25.7%) in Arm B, while progression affected 11 patients in Arm A (33.3%) and 9 patients (25.7%) in Arm B.

No patient underwent resection of liver metastases after treatment, but one patient was submitted to surgery for a mass in the abdominal wall and another for cerebral metastases in Arm A; 3 patients received surgery in Arm B, one for lung metastases resection, one pelvic lesion and one patient was subjected to peritonectomy followed after 3 years by hepatic resection.

Median PFS was 6.0 months (95% confidence interval 4.0–7.0) in Arm A and 8.0 months (95% confidence interval 4.0–12.0) in Arm B, while median overall survival was 18 months (95% confidence interval 10–26) in Arm A and 28 (95% confidence interval 13–42) in Arm B. After a median follow-up of 22 months (range 3–50) 9/68 patients were still alive, 1 in Arm A and 8 in Arm B; 48 patients died, and we have lost to follow-up 11 patients, 5 in Arm A and 6 in Arm B.

4. Discussion

This randomised phase II trial in advanced colorectal cancer patients showed a response rate of 18.6% in the standard 1-h infusion of CPT-11 combined with a 4-day chronomodulated $FF_{4–10}$. Response rate was 25.7% with the 6-h chronomodulated CPT-11 plus the same $FF_{4–10}$. CPT-11 and 5-FU dose-intensities and grade 3–4 toxicities were similar in the two Arms. Nausea and vomiting was more frequent in Arm A and oral mucositis in Arm B while diarrhoea was the most frequent side effect in both Arms. A benefit in efficacy was observed in the CPT-11 chronomodulated Arm with a longer duration of response (7.0 versus 4.5 months), a prolonged PFS (8.0 versus 6.0 months) and survival (28 versus 18 months).

The focus of this trial was based on the prolonged timing-dependent infusion of CPT-11. The animal data showed a better haematological and gastrointestinal tolerance for this drug when administered in the last part of rest phase, which corresponds to late phase of night in humans. A prolonged infusion regimen is appropriate for cell-cycle specific activity of CPT-11, as this will provide longer CPT-11 exposure to cells in the S-phase. Higher stability of the DNA–topoisomerase I complex from the presence of CPT-11 and better conversion of CPT-11 to SN-38 are other possible positive effects of a prolonged infusion. Moreover, lower peak plasma concentration of irinotecan may prevent saturation of carboxylesterases resulting in more efficient conversion of CPT-11 to SN-38. In this trial, a prolonged infusion of CPT-11 was not associated with reduced dose-intensity or with increased toxicity as observed with other more prolonged flat infusions.

There are several lines of data with prolonged constant infusion of CPT-11 as single agent including: a recommended dose for phase II trial of 30 mg/m^2/day for 5 days every three weeks,[25] 10 mg/m^2/day for 4 days in two every 3 weeks[26] or 20 mg/m^2/day for 7 days every three weeks,[27] with a dose-intensity of 50, 13 and 47 mg/m^2/week, respectively. In all cases, diarrhoea was found to be the dose-limiting toxicity. In our study, a 6-h chronomodulated infusion of CPT-11, with a theoretical 90 mg/m^2/week dose-intensity allowed delivering 80% of projected DI after 8 courses of therapy.

The chronomodulation modality is one of the best possible options to combine CPT-11 with 5-FU and FA. It is noteworthy that this combination is absolutely safe with regard to haematological toxicity, has an excellent tolerability profile with no neutropenia, febrile neutropenia, hospital admissions or toxic death. The night administration of infusional 5-FU seems to contribute to prevent these life-threatening conditions if combined with severe diarrhoea.

The trial was not designed to find any differences in major efficacy end-point such as PFS and survival. It is of course difficult to try to explain the difference in survival between the two Arms and the first and probably most important reason is the limited number of patients included in the trial. Moreover, data was collected from a single institution and without an external panel for response review. The benefit in survival from chronomodulation must be further explored as an important phase III trial comparing a chronomodulated infusion of 5-FU–FA–L-OHP versus FOLFOX2 regimen in advanced colorectal cancer patients failed to demonstrate any survival advantage (EORTC 05963).[28] Other explanations for the discrepancy between activity and efficacy should be proposed as it was possible to find differences in efficacy end-points in a randomised phase II trial by Scheitauer et al.,[29] where they compared two different schedules of capecitabine and L-OHP and found a statistical difference in PFS with no difference in response rate. No significant differences in patient data regarding tumour characteristics, previous or further treatment were detected in our study. It seems that the initial benefit in response rate, its duration and related PFS observed in the chronomodulated Arm could be even prolonged when patients are crossed on further regimens. Other possible explanations of the difference in survival can be proposed

by imaging that patient survival is due to at least two components: the activity of chemotherapy on the tumour and the activity of chemotherapy on the patient. In this regard, Buyse et al.[30] demonstrated that response is a good surrogate for survival in advanced colorectal cancer but it can be responsible for not more than one third of overall survival. We can hypothesise that optimal timing of drug delivery can affect biological patient structures more than it is currently believed. Shepton et al.[31] clearly demonstrated that alterations in cortisol rhythm in advanced breast cancer patients could anticipate a striking difference in survival at 7 years. In the study by Mormont et al.,[32] they found that alterations in circadian rhythm, basically rest–activity rhythm, was an independent prognostic factor for survival in advanced colorectal cancer patients. In addition, Ohdo et al.[33] demonstrated that profound disturbances of "clock function" can result from delivery of drugs such as interferon, which disrupted intrinsic biological rhythm regulation. They subsequently discovered that this action of interferon was mediated by alterations in the expression of clock genes such as CLOCK and BMAL1.[34]

In this respect, we could hypothesise that survival of cancer patients is composed of two components: the capacity of drugs to achieve tumour shrinkage and the possibility that chemotherapy drugs can act on normal biological *patient equilibrium* such as 24-h rhythm coordination. Optimal drug delivery time would then have to reflect circadian clock control structures to avoid disturbances/damages to the internal clock and patient biological equilibrium. If this hypothesis is true, then timing the delivery of chemotherapy could become an important parameter. The next step would be to demonstrate this hypothesis by performing phase III trials, even though this type of end-point would be difficult to evaluate. Another possibility is to design new type of studies, with timing of peak administration as first end-point. Already the EORTC Chronotherapy Group is running such trials, with EORTC 05011 trial comparing 6 different peak timing of CPT-11 followed by chronomodulated FFL to investigate optimal CPT-11 delivery timing in advanced colorectal cancer patients.

Conflict of interest statement

None.

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