EUROPEAN JOURNAL OF CANCER 42 (2006) 3161–3168

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Capecitabine plus oxaliplatin (xelox) versus protracted 5-fluorouracil venous infusion plus oxaliplatin (pvifox) as first-line treatment in advanced colorectal cancer: A GOAM phase II randomised study (FOCA trial)

Andrea Angelo Martoni[a,*], *Carmine Pinto*[a], *Francesca Di Fabio*[a], *Giorgio Lelli*[b], *Fabiola Lorena Rojas Llimpe*[a], *Anna Lisa Gentile*[a], *Vita Mutri*[a], *PierLuigi Ballardini*[c], *Stefania Giaquinta*[a], *Edera Piana*[a]

[a]*Medical Oncology Unit, S.Orsola-Malpighi Hospital, via Albertoni 15, 40138 Bologna, Italy*
[b]*Medical Oncology Unit, S.Anna Hospital, Ferrara, Italy*
[c]*Medical Oncology Unit, Delta Hospital, Lagosanto – Ferrara, Italy*

ARTICLE INFO

Article history:
Received 5 June 2006
Received in revised form
14 August 2006
Accepted 17 August 2006
Available online 13 November 2006

Keywords:
XELOX
Pvi-FU
Advanced colorectal cancer
First-line treatment
Capecitabine
Oxaliplatin

ABSTRACT

This phase II randomised trial compares oxaliplatin plus protracted infusion of 5-fluorouracil (pviFOX) or oxaliplatin plus capecitabine (XELOX) in the first-line treatment of advanced colorectal cancer (ACRC). Methods: From December 2001 to March 2005, 118 patients were randomised to arm A (pviFOX: pvi5-FU by a central venous catheter 250 mg/m2/daily d1-21 + oxaliplatin 130 mg/m2 d1 q3w) (56 pts) or arm B (XELOX: capecitabine 1000 mg/m2 po bid d1-14 + oxaliplatin at the same schedule) (62 pts). Results: Patient characteristics were well-balanced between the two arms. Median number of complete cycles was six. The objective responses were: CR 1 (1.7%) and 3 (4.8%), PR 26 (46.4 %) and 24 (38.7%), SD 13 (23.2%) and 20 (32.3%), P 13(23.2%) and 10 (16.1%), not evaluable 3 (5.4%) and 5 (8.1 %) in arms A and B, respectively; the CR + PR rate was 48.2% (95% confidence limits 34.6%–61.9%) versus 43.5 % (31.0%–56.7%). Median TTP was 7 versus 9 months, respectively. About 50% of the patients with symptoms or low performance status at baseline experienced improvement without major differences between the two arms. G3–4 diarrhoea was observed in 14.0% versus 8.2%, G3 stomatitis in 3.7% versus 0, and G3 neurotoxicity in 18.5% versus 24.6% in arms A and B, respectively. Eight patients in arm A (14.8%) had venous line problems that obliged the temporary suspension (six cases) or stopping (two cases) of the 5-FU infusion. Conclusion: Both pviFOX and XELOX are effective and safe first-line treatments for patients with ACRC. By avoiding intravenous (i.v.) administration by a central catheter, XELOX is favoured in clinical practice.

1. Introduction

For about 30 years, 5-fluorouracil (5-FU) had been the only cytotoxic agent available in the treatment of advanced colorectal cancer (ACRC). Subsequently, its metabolic modulation by folinic acid (LV) or methotrexate[1,2] and its administration by continuous venous infusion (c.i.)[3] have allowed an increase in its antitumour activity as compared

* *Corresponding author:* Tel.: +39 0516362206; fax +39 0516362207.
E-mail address: martoni@aosp.bo.it (A.A. Martoni).
0959-8049/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2006.08.034

with bolus administration, although without survival benefits.

One of the most studied c.i. 5-FU schedules is the protracted venous infusion (pviFU), which induces a higher response rate than the bolus 5-FU,[4] with less haematological toxicity but more hand–foot syndrome. There is no evidence that LV enhances the therapeutic effects of pvi5-FU.[5,6] At the end of 1980s, de Gramont and colleagues[7] proposed a twice-monthly regimen combining LV with bolus and 48-h c.i. 5-FU allowing the doses of 5-FU to be twice as much as those of the 5-FU/LV bolus regimen. This regimen proved to be more effective in terms of objective response and time-to-progression (TTP) and less toxic than the monthly bolus 5-FU/LV regimen. However, even for this regimen, there was no evidence of increased survival.[8]

Capecitabine (CAPE) is an oral 5-FU pro-drug, with high and predictable oral bioavailability, as well as preferential conversion to 5-FU in neoplastic tissues,[9] rationally designed to mimic c.i. 5-FU. In two randomised trials, CAPE was more active than bolus 5-FU/LV in the induction of objective tumour responses, being TTP and survival at least equivalent. At the same time, CAPE demonstrated clinically meaningful benefits in terms of tolerability.[10,11] However, no study has compared CAPE to pviFU that represents the 5-FU most similar administration modality from a pharmacological point of view as it provides for the continuous exposure of the tumour to fluorinated pirimidine.

Oxaliplatin (OXA) is a third-generation platinum derivative whose anti-tumour activity in ACRC has been shown both in 5-FU resistant patients[12] and in first-line therapy.[13] 5-FU and OXA present different action mechanisms and their synergistic antitumour activity has been shown in experimental tumours.[14,15] After the demonstration that FU/LV plus OXA is active in patients previously treated with 5-FU,[16] the combination of the 'de Gramont' regimen with OXA (FOLFOX4) has been able to double the objective remission rate and to prolong the progression-free survival as compared with 5-FU/LV alone in first-line treatment.[17] Similar results were obtained in another phase III trial with the combination of OXA and 5-FU/LV in chrono-modulated infusional administration.[18]

There are fewer experiences on the combination of OXA and pvi5-FU. In a previous phase I–II study, our group observed an objective remission in 22% of 50 patients resistant to bolus 5-FU with a TTP of 4 months and a good tolerability profile. The optimal dose suggested for subsequent studies was 5-FU 250 mg/sm/daily and OXA 130 mg/sm.[19] Similar results were also obtained by another group.[20]

A dose-finding study on the CAPE and OXA combination demonstrated that the dose-limiting side-effect was G3–4 diarrhoea and that the CAPE recommended dose for further studies was 2000 mg/m2/daily in combination with of OXA at 130 mg/m2 on day 1 in a 21-day treatment cycle.[21] Subsequently, a large international phase II trial was performed to evaluate the efficacy and safety of this regimen, named XELOX, as first-line therapy for patients with ACRC.[22] In this study, XELOX showed response rates, TTP, and overall survival similar to those observed with 5-FU/LV/OXA combinations, suggesting CAPE as a possible substitute of FU/LV in the combination with OXA. However, to date, no phase III or phase II randomised trials have compared XELOX to an OXA plus infusional 5-FU with or without an LV modulation regimen in the first-line treatment of ACRC.

The present phase II randomised study compares XELOX to the pviFOX regimen: the two regimens provide the same OXA dose and schedule combined with two different schedules to chronically expose the patient and the tumour to 5-FU obtained either by the oral administration of CAPE or pvi5-FU. The working hypothesis is based on the assumption that if the two regimens are equivalent in terms of activity and tolerability, then the oral fluoropirimidine-containing regimen might represent a more convenient treatment method for patients and healthcare professionals.

2. Patients and methods

2.1. *Patient eligibility*

The inclusion criteria were a histological diagnosis of colorectal carcinoma, measurable tumour lesions, Karnofsky Performance Status (KPS) $\geqslant 70$, age >18 years, life expectancy >3 months, no prior chemotherapy for metastatic disease, adjuvant therapy terminated >6 months before, haemoglobin levels > 10 g/dl, neutrophil count $\geqslant 2000/mm^3$, platelet count $\geqslant 100{,}000/mm^3$, serum creatinine $\leqslant$ 1.2 mg/dl and creatinine clearance according to Cockcroft–Gault formula >55 ml/min, bilirubin and serum transaminase levels $\leqslant$ three times the normal values, staging examinations carried out within 30 days of the beginning of the treatment, and written informed consent. The exclusion criteria were patients with potentially resectable lesions, unresolved intestinal obstruction, previous malignant neoplasia (except for non-melanoma skin carcinomas and adequately treated *in situ* carcinomas of the uterine cervix), dementia or alterations in mental status.

2.2. *Treatment*

The patients were randomised to receive treatment in arms A or B. Arm A: on day 1, dexamethasone 20 mg in 100 cc of saline by the intravenous (i.v.) route in 15 min, granisetron 3 mg in 100 cc of saline i.v. in 15 min, OXA at the dose of 130 mg/m2 in 500 cc of 5% glucose solution i.v. in 2 h and, at the end, 5-FU at the dose of 250 mg/m2/daily in c.i. from the 1st to the 21st day. Before the start of therapy, a central venous catheter (CVC) implant was requested for the administration of 5-FU by elastomeric pump (the Baxter type with a 275 ml reservoir, which allows for a protracted 7-day long infusion). Arm B: on day 1, OXA as above and oral CAPE at the dose of 1000 mg/sm bid from the 1st to the 14th day. Every patient in arm B was given a diary in order to help him/her in the administration of CAPE and in the monitoring of side-effects at home.

In both arms, the treatment was repeated every 21 days and pursued until evidence of disease progression or up to six cycles. Further continuation of the treatment was left to the investigator's discretion.

Dose modifications upon the occurrence of side-effects: diarrhoea or stomatitis: 50% reduction in 5-FU or CAPE dose if G3 or repeated episodes of G2 intensity occurred; definitive suspension of 5-FU or CAPE if G4 intensity occurred. Neurotoxicity: 25% reduction of the dose of OXA if G3 intensity or

definitive suspension of OXA if G4 toxicity occurred; renal function: 50% reduction of the CAPE and OXA doses if the calculated creatinine clearance was reduced to 54–25 mg/min, and the definitive suspension of the two drugs if the calculated creatinine clearance fell by 25 mg/min.

2.3. *Evaluation*

Before beginning the treatment, the patients were submitted to the following controls and tests: recording of symptoms, weight, KPS, physical examination, blood count, blood-chemistry tests of liver and kidney function; serum CEA and CA 19.9, computerised tomography (CT) of the chest, abdomen and pelvis. Subsequently, the recording of the symptoms, side-effects and physical examination was carried out prior to each cycle, blood count and blood-chemistry tests for liver and kidney function before and 10 days after each cycle. Every three cycles, re-evaluation was scheduled with the recording of the symptoms, weight, KPS, physical examination and chest-abdominal-pelvic CT.

Objective response and toxicity were evaluated according to RECIST criteria [23] and CTC criteria,[24] respectively, with the exception of neurotoxicity that was evaluated according to the Lèvi scale.[25] TTP was considered as the time-interval between the start of therapy and the evidence of progression independently of the objective response. A formal evaluation of quality of life was not included in the study protocol. However an evaluation of symptoms such as asthenia, anorexia and pain was done by using a three score code (0 = symptom absent, 1 = symptom of mild/moderate intensity, 2 = symptom of high/severe intensity). Symptomatic improvement was defined as the reduction in the baseline score of the symptom without appearance or worsening of another.

Table 1 – Patient characteristics

	Arm A pviFOX	Arm B XELOX	TOTAL
No. of eligible pts	56	62	118
GENDER			
M *n* (%)	28 (50%)	33 (53.2%)	61 (51.7%)
F *n* (%)	28 (50%)	29 (46.8%)	57 (48.3%)
AGE			
Median	64	67	67
(Range)	(41–79)	(25–79)	(25–79)
KPS			
Median	90	90	90
(Range)	(70–100)	(70–100)	(70–100)
PRIMARY TUMOUR SITE			
Colon *n* (%)	46 (82.1%)	51 (82.3%)	97 (82.2%)
Rectum *n* (%)	10 (17.9%)	11 (17.7%)	21 (17.8%)
PRIMARY TUMOUR SURGICAL RESECTION			
YES *n* (%)	45 (80.4%)	52 (83.9%)	97 (82.2%)
NO *n* (%)	11 (19.6%)	10 (16.1%)	21 (17.8%)
STAGE AT TREATMENT START			
IV *n* (%)	40 (71.4%)	38 (61.3%)	78 (66.1%)
Recurrence *n* (%)	16 (28.6%)	24 (38.7%)	40 (33.9%)
ADJUVANT CHEMOTHERAPY			
YES *n* (%)	13 (23.2%)	18 (29.9%)	31 (26.3%)
NO *n* (%)	43 (76.8%)	44 (71%)	87 (73.3%)
METASTASES LOCALISATION			
Liver ± others	46 (82.1%)	46 (74.2%)	92 (77.9%)
Lung ± others	22 (39.2%)	16 (25.8%)	38 (32.2%)
Lymphnodes ± others	14 (25%)	19 (30.6%)	34 (28.8%)
No. OF METASTATIC SITES			
1 *n* (%)	26 (46.4%)	39 (62.9%)	65 (55.1%)
2 *n* (%)	21 (37.5%)	11 (17.7%)	32 (27.1%)
> 2 *n* (%)	9 (16.1%)	12 (19.4%)	21 (17.8%)
CEA PLASMA LEVELS (ng/ml)			
< 10	23 (41.1%)	25 (40.3%)	48 (40.7%)
10–100	18 (32.1%)	17 (27.4%)	35 (29.7%)
> 100	11 (19.7%)	14 (22.6%)	25 (21.2%)
Not available	4 (7.1%)	6 (9.7%)	10 (8.4%)

KPS: Karnofsky Performance Status.

2.4. Statistical aspects

The primary end-point was the tumour response rate while the secondary end-points were TTP and toxicity. A one-stage randomised phase II trial design was used to determine the number of patients to be included.[26] The study was designed to test the null-hypothesis that the objective remission rate was less than 0.20, a rate that was reckoned to indicate that the regimen provided insufficient benefits; the smallest response probability suggesting that one regimen warranted further studies was 0.35 with a two-sided alpha of 0.05 and a power of 80% (beta = 0.20). On these grounds, the number of patients to be treated per arm was 56. TTP was analysed by the Kaplan–Meier method. Efficacy analyses were based on an intent-to-treat analysis. The *P* values only have a descriptive value in this phase II trial.

The study was approved by the Local Ethical Committee.

3. Results

One hundred and twenty-two patients were enrolled between December 2001 and March 2005. Four patients resulted ineligible and were excluded from the randomisation. The main characteristics of the 118 eligible patients are reported in Table 1.

3.1. Treatment delivery

The description of the delivered treatment is reported in Table 2. A total of 739 therapy cycles were administered: patients in arm A received a higher number of cycles (424 versus 315) and this difference concerned the number of the complete cycles and the cycles in which one of the two drugs was omitted. The median dose intensity, expressed as the percentage of drug administered from the start of the treatment up to its definitive suspension, was 100% for all three cytotoxic drugs. A higher rate of treatment suspension before the completion of six cycles occurred in arm A as compared with arm B (37.7% versus 27.8%) (Table 3): this difference was due to a higher treatment suspension because of disease progression and toxicity. Twenty-seven (48.2%) and 27 (43.5%) patients received full doses of 5-FU and OXA in arm A and CAPE and OXA in arm B throughout the study, respectively. Dose reduction was required for pviFU alone in 27 (42.8%), for CAPE alone in 23 patients (37%), and OXA alone in 10 patients (17.8%) in arm A and in 25 patients (40.3%) in arm B, respectively.

3.2. Safety

Very slight myelotoxicity was observed in both arms (Table 4): no cases of G3/4 neutropenia occurred and G3 thrombocytopenia was reported in one and two cases in arm A and B, respectively. The most frequent non-haematological toxicity was represented by cumulative neurotoxicity with no differences between the two arms being of G3 intensity in 18.5% and 24.6% in arms A and B, respectively. Diarrhoea was also frequently reported, but G3/4 intensity was 13% and 8.2% in arms A and B, respectively, without any statistically significant difference. The only statistically significant difference concerned stomatitis that was observed in 25.9% in arm A

Table 2 – Delivered treatment

	pviFOX	XELOX	TOTAL
TOTAL No. OF DELIVERED CYCLES	315	424	739
Complete cycles (two drugs)	307	363	670
Oxaliplatin only	7	5	12
5-FU only	1	–	1
Capecitabine only	–	56	56
COMPLETE CYCLES (TWO DRUGS)			
Median (range)	6 (1–10)	6 (1–10)	6 (1–10)
DOSE INTENSITY: MEDIAN (RANGE)			
Oxaliplatin	100% (82–100)	100% (15–100)	100% (15–100)
5-FU	100% (13–100)	–	100% (13–100)
Capecitabine	–	100% (14–100)	100% (14–100)

Table 3 – Treatment suspension before six cycles

	pvi FOX N: 53[a]	XELOX N: 60[a]	TOTAL N:113[a]
TOTAL No. OF TREATMENT SUSPENSION REASONS	20 (38%)	16 (27%)	36 (32%)
Progression	12 (23%)	10 (17%)	22 (19%)
Refusal	1 (2%)	1 (2%)	2 (2%)
Death	1 (2%)	2 (3%)	3 (3%)
Toxicity	4 (7.5%)	1 (2%)	5 (4%)
Other	2 (4%)	2 (3%)	4 (3.5%)

a At the moment, five patients (three on arm A and two on arm B, respectively) have yet to complete six cycles.

versus 13.1% in arm B ($P = 0.028$). Nausea, vomiting, hyperbilirubinemia, SGOT and SGPT increase, hand–foot syndrome were all of low incidence and intensity in both arms. The system of protracted venous infusion of 5-FU in arm A, by means of an elastomeric or electronic pump, was generally well-accepted by the patients, with minor limitations to their daily activities and social life, but eight patients (14.8%) had venous line problems that obliged them to suspend temporarily (six cases: one infection, one thrombosis, one dislodged, one bad compliance and two unthreading of the needle from the CVC port) or to stop the 5-FU infusion (two cases: one sepsis, one poor compliance).

The reasons for the toxicity-related treatment suspension were G3 diarrhoea (three cases) and G3 stomatitis (one case) in arm A, and G3 diarrhoea and vomiting (one case) in arm B. Three patients died early on during the treatment: in arm A, one patient presented a rapid general deterioration in conditions after the first cycle; in arm B, one patient died suddenly after the first cycle and so no further information could be collected, while another patient died as a consequence of G4 diarrhoea, dehydration and acute renal failure during the first cycle.

3.3. *Efficacy*

The analysis of objective response is reported in Table 5. Eight patients (three in arm A and five in arm B) were not evaluable as they had only received one cycle[7] or had metastatic lesions documented only by positron emission tomography. Complete remission (CR) occurred in one (1.7%) and three (4.8%) patients and partial remission (PR) in 26 (46.4%) and 24 (38.7%). The CR + PR rate in arm A and B was 48.2% (95% confidence limits 34.6%–61.9%) and 43.5% (95% confidence limits 31.0%–56.7%), respectively. Stable disease (SD) occurred in 13 (23.2%) and 20 (32.3%); by adding up CR + PR + SD the control disease rate was 71.4% and 75.8%, respectively. The median duration of CR + PR was 8 months (4–14) and 9 months (4–25) and the median duration of SD was 8.5 months (4–13) and 6 months (3–13) in arms A and B, respectively. In Table 6 the description of symptom and KPS improvement is reported. About 50% of the patients with disease related symptoms or low KPS at baseline, experienced improvement without major differences between the two arms.

3.4. *Time-to-progression*

The timing of clinical and imaging test re-evaluation was equally distributed between the two arms: 68.6% and 69.0% of patients in arms A and arm B, respectively, had their first re-evaluation before the fourth cycle. The median TTP was 7 months (95% confidence limits 5–9 months) and 9 months (95% confidence limits 8–10 months) (Fig. 1). At the time of this report, 11 and 15 patients in arms A and arm B, respectively, had not shown disease progression.

So far 92 patients have progressed – 45 on arm A and 47 on arm B – while 60 have received a second-line chemotherapy, 25 and 35 in arms A and B, respectively. Second-line chemotherapy chiefly consisted of the FOLFIRI regimen (41 patients),

Table 4 – Side effects

	pviFOX	XELOX	TOTAL
No. of evaluable patients[a]	54	61	115
NEUTROPENIA 0	43 (79.6%)	46 (75.4%)	89 (77.4%)
1	7 (13%)	9 (14.8%)	16 (13.9%)
2	4 (7.4%)	6 (9.8%)	10 (8.7%)
ANAEMIA			
0	29 (53.7%)	35 (57.4%)	64 (55.7%)
1	20 (37%)	24 (39.3%)	44 (38.3%)
2	4 (7.4%)	2(3.3%)	6 (5.2%)
3	1 (1.9%)	–	1 (0.9%)
THROMBOCYTOPENIA			
0	38 (70.4%)	30 (49.2%)	68 (59.1%)
1	14 (25.9%)	24 (39.3%)	38 (33%)
2	1 (1.9%)	5 (8.2%)	6 (5.2%)
3	1 (1.9%)	2 (3.3%)	3 (2.6%)
DIARRHOEA			
0	18 (33.3%)	33 (54.1%)	51 (44.3%)
1	14 (25.9%)	15 (24.6%)	29 (25.2%)
2	15 (27.8%)	8 (13.1%)	23 (20%)
3	6 (11.1%)	4 (6.6%)	10 (8.7%)
4	1 (1.9%)	1 (1.6%)	2 (1.7%)
STOMATITIS[b]			
0	40 (74.1%)	53 (86.9%)	93 (80.9%)
1	6 (11.1%)	8 (13.1%)	14 (12.2%)
2	6 (11.1%)	–	6 (5.2%)
3	2 (3.7%)	–	2 (1.7%)
EPIGASTRALGIA			
0	50 (92.6%)	53 (86.9%)	103 (89.6%)
1	2 (3.7%)	7 (11.5%)	9 (7.8%)
2	2 (3.7%)	–	2 (1.7%)
3	–	1 (1.6%)	1 (0.9%)
HYPERBILIRUBINEMIA			
0	44 (81.5%)	45 (73.8%)	89 (77.4%)
1	7 (13%)	9(14.8%)	16 (13.9%)
2	2 (3.7%)	6 (9.8%)	8 (7%)
3	1 (1.9%)	1 (1.6%)	2 (1.7%)
SGOT, SGPT INCREASE			
0	38 (70.4%)	45 (73.8%)	83 (72.2%)
1	10 (18.5%)	14 (23%)	24 (20.9%)
2	6 (11.1%)	1 (1.6%)	7 (6.1%)
3	–	1 (1.6%)	1 (0.9%)
HAND–FOOT SYNDROME			
0	51 (94.4%)	57 (93.4%)	108 (93.9%)
1	2 (3.7%)	1 (1.6%)	3 (2.6%)
2	–	3 (4.9%)	3 (2.6%)
3	1 (1.9%)	–	1 (0.9%)
NEUROTOXICITY (CHRONIC[c])			
0	12 (22.2%)	13 (21.3%)	25 (21.7%)
1	23 (43.6%)	15 (24.6%)	38 (33%)
2	9 (16.7%)	18 (29.5%)	27 (23.5%)
3	10 (18.5%)	15 (24.6%)	25 (21.7%)
ACUTE NEUROTOXICITY (PHARYNGO-LARYNGOSPASM)			
Yes	13 (24.1%)	15 (24.2%)	28 (24.1%)
No	41 (75.9%)	47 (75.8%)	88 (75.9%)

a Data lacking for three patients (one in arm A and two in arm B).
b Statistically significant difference: $p = 0.028$.
c According to Levi's criteria.

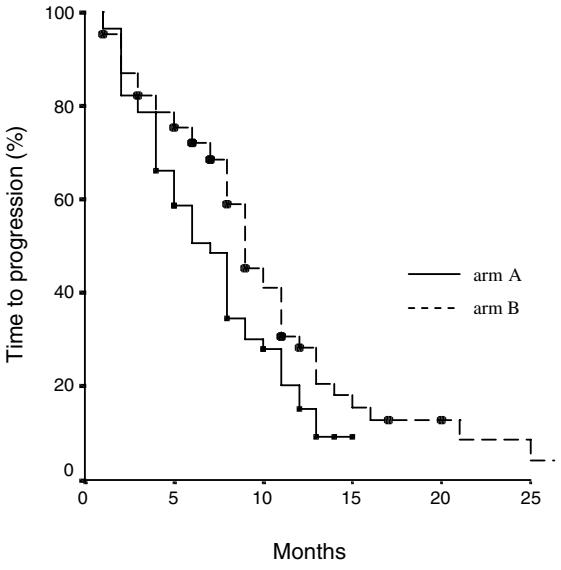
Table 5 – Objective response

	pvi FOX	XELOX	TOTAL
Total no. of pts	56	62	118
CR	1 (1.7%)	3 (4.8%)	4 (3.3%)
PR	26 (46.4%)	24 (38.7%)	50 (42.4%)
CR + PR	27 (48.2%)	27 (43.5%)	54 (45.8%)
(95% confidence limits)	(34.6%–61.9%)	(31.0%–56.7%)	(36.0%–54.4%)
SD	13 (23.2%)	20 (32.3%)	33 (27.9%)
PD	13 (23.2%)	10 (16.1%)	23 (19.5%)
Not evaluable	3 (5.4%)	5 (8.1%)	8 (6.8%)

Table 6 – Symptomatic improvement[a]

	pvi FOX	XELOX	TOTAL
Asthenia	15/27 (56%)	11/26 (42%)	26/53 (49%)
Anorexia	9/15 (60%)	4/10 (40%)	13/25 (52%)
Pain	16/24 (67%)	15/23 (65%)	31/47 (66%)
KPS (<90)	8/16 (50%)	8/17 (47%)	16/33 (48%)

a Number of patients who improved/ number of patients with symptom at baseline.



Patients at risk

Arm A	56	33	18	11	-	-
Arm B	62	47	29	18	17	15

Fig. 1 – Time to progression.

as laid down by the protocol, while the other patients received different regimens, including another six based on irinotecan. Nine patients (7.6%), five in arm A and four in arm B, underwent surgical resection of the liver metastases after first-line chemotherapy (in one lung metastases resection was also performed). Survival analysis was not presented as too few events had occurred by the time of analysis.

4. Discussion

The most popular and widespread schedule for first-line treatment of ACRC in Europe today is the FOLFOX4 regimen.[17] It is now also the reference chemotherapy in the adjuvant treatment of stage III colon cancer.[27]

Pvi5-FU is a 5-FU administration schedule with a higher activity and better tolerability than bolus i.v. 5-FU, but its use has generally been limited to patients pre-treated and/or resistant to other 5-FU based regimens. However, a large multi-centre randomised trial carried out in the United Kingdom has shown that 'de Gramont' and pvi5-FU (at the dose of 300 mg/m2 daily) regimens were similar in terms of survival, quality of life, and response rate in the first-line treatment of ACRC, even if the pvi5-FU regimen was associated with more central line complications and hand–foot syndrome.[28] An economic sub-study running alongside this multi-centre randomised trial demonstrated that, for a comparable clinical outcome, pvi5-FU can be administered at approximately half the cost of the 'de Gramont' regimen.[29] The combination of pvi5-FU with OXA was studied in pre-treated patients with ACRC[19,20] and the results were similar to those obtained with the FOLFOX4 regimen in the same clinical setting.[30,31]

For the first time ever, this study reports results with the combination of pvi5-FU + OXA (pviFOX) in the first-line treatment of ACRC. With a response rate of 48.2% (95% confidence limits 34.6%–61.9%), median TTP of 7 months (95% confidence limits 5–9 months) and G3–4 toxicity limited to diarrhoea in 13% of cases, our study suggests that results can be obtained akin to those reported for FOLFOX4 or the chrono-modulated combination of OXA and 5-day 5-FU infusion.

Many phase II studies have been carried out on the CAPE and OXA combination (XELOX) in pre-treated patients[32] and in the first-line treatment of ACRC.[11,33–38] The antitumour activity of first-line XELOX has been consistently confirmed in all the trials showing an objective response rate range between 37% and 55% and TTP between 5.9 and 8.2 months.[38] All the studies have concluded that the XELOX regimen demonstrates a similar activity and at the same time greater convenience as compared with regimens combining OXA and 5FU/LV i.v. infusion, with most of them supporting prospective comparative trials.

At the present time, no phase III or phase II randomised trials on the comparison of XELOX with an OXA plus infusional 5-FU with or without LV modulation regimen in the first-line treatment of patients with ACRC have been published.

The present study provides such a comparison even if by a small randomised phase II clinical trial. The interpretation of the study results should take account of the characteristics of the trial design. As well known, the purpose of a phase II study is to explore activity, and not to make definitive comparisons between the investigational agent/regimen and the standard therapy, as the study is not adequately designed for direct comparison. As compared with classical phase II studies, randomised phase II designs have the advantage of reducing selection bias, providing a basis for selecting which therapy looks most promising and prioritising agents to carry on to phase III trials. However, the main limitation of this

design continues to be the lack of statistical power to clinically detect significant differences in efficacy and to draw definitive conclusions.

In this study, XELOX produces a response rate of 43.5% (95% confidence limits 31.0%–56.7%), a median TTP of 9 months (95% confidence limits 8–10 months) and symptomatic improvement in about 50% of patients suffering from disease related symptoms such as asthenia, anorexia, pain and low KPS at baseline. The safety profile is very favourable, as the most frequent G3–4 side-effect is represented by diarrhoea in 8.2% of patients. These results confirm and reinforce the findings of previous phase II trials on XELOX by virtue of the randomisation procedure that mitigates the selection bias implied in the phase II trial results. Our trial strongly supports the replacement of pvi5-FU with CAPE on the grounds of the oral administration that avoids CVC implantation, its possible complications such as infection, thrombosis and displacement, and the discomfort for the patient that the prolonged maintenance of the central treatment line can cause, as has recently been discussed.[39] In this regard, a randomised cross-over trial comparing patient preferences for oral CAPE and 5-FU/LV regimens has confirmed that the majority of patients prefer oral to i.v. therapy, due to better convenience, home-based administration and tablet formulation.[40]

In summary, both XELOX and pviFOX are very active and safe regimens in the first-line treatment of patients with ACRC. Their results in terms of response rate, TTP and tolerability profile nearly overlap. Generally speaking, these results are very similar to those reported with other OXA + infusional 5-FU/LV based regimens and, most of all, with the FOLFOX4 regimen. By allowing us to avoid i.v. administration by CVC, XELOX may today be considered one of the choice regimens for the first-line treatment of patients with ACRC.

Conflict of interest statement

None declared.

REFERENCES

1. The Advanced Colorectal Cancer Meta-Analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rata. *J Clin Oncol* 1992; **10**: 896-903.
2. The Advanced Colorectal Cancer Meta-Analysis Project. Meta-analysis of randomized trials testing the biochemical modulation of fluorouracil by methotrexate in metastatic colorectal cancer. *J Clin Oncol* 1994;**12**: 960-969.
3. Lokich JJ, Ahlgren J, Gullo JJ, et al. A prospective randomized comparison of continuous infusion fluorouracil with a convential bolus schedule in metastatic colorectal carcinoma. A Mid-Atlantic Oncology Program study. *J Clin Oncol* 1989;**7**:425–33.
4. Meta-analysis Group In Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998; **16**: 301-308.
5. Budd GT, Fleming TR, Bukowski JD, et al. 5 Fluorouracil and folinic acid in the treatment of metastatic colorectal cancer: A randomized comparison. A Southwest Oncology Group study. *J Clin Oncol* 1987;**5**:272–7.
6. Leichman CG, Fleming TR, Muggia FM, et al. Phase II study of fluorouracil and its modulation in advanced colorectal cancer: A Southwest Oncology Group study. *J Clin Oncol* 1995;**13**:1303–11.
7. de Gramont A, Krulik M, Cady J, et al. High-dose folinic acid and 5-fluorouracil bolus and continuous infusion in advanced colorectal cancer. *Eur J Cancer Oncol* 1988;**24**:1499–503.
8. de Gramont A, Bosset J-F, Milan C, et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: A French Intergroup study. *J Clin Oncol* 1997;**15**:808–15.
9. Miwa M, Ura M, Nishida M, et al. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. *Eur J Cancer* 1998;**34**:1274–81.
10. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: Results of a randomized phase III study. *J Clin Oncol* 2001;**19**:2282–92.
11. Cassidy J, Twelves C, Van Cutsem E, et al. First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. *Ann Oncol* 2002;**13**:566–75.
12. Machover D, Diaz-Rubio E, de Gramont A, et al. Two consecutive phase II studies of oxaliplatin (L-OHP) for treatment of patients with advanced colorectal carcinoma who were resistant to previous treatment with fluoropirymidines. *Ann Oncol* 1996;**7**:95–8.
13. Becouarn Y, Ychou M, Ducreux M, et al. Phase II trial of oxaliplatin as first-line chemotherapy in metastatic colorectal cancer patients. *J Clin Oncol* 1998;**16**:2739–44.
14. Mathé G, Kidani Y, Segiguchi M, et al. Oxalato-platinum or L-OHP, a third-generation platinum complex: An experimental and clinical appraisal and preliminary comparison with cis-platinum and carboplatinum. *Biomed Pharmacother* 1989;**43**:237–50.
15. Tashiro T, Kawada Y, Sakurai Y, et al. Antitumor activity of a new platinum complex, oxalato (trans-1-1,2-diamino-ciclohexane) platinum (II), new experimental data. *Biomed Phamacother* 1989;**43**:251–60.
16. De Gramont A, Vignoud J, Tournigand C, et al. Oxaliplatin with high-dose leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer. *Eur J Cancer* 1997;**33**:214–9.
17. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first line treatment in advanced colorectal cancer. *J Clin Oncol* 2000;**18**:2938–47.
18. Giacchetti S, Perpoint B, Zidani R, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000;**18**:136–47.
19. Martoni A, Mini E, Pinto C, et al. Oxaliplatin and protracted continuous 5-fluorouracil infusion in patients with pretreated advanced colorectal carcinoma. *Ann Oncol* 2001;**12**:519–24.
20. Chau I, Webb A, Cunningham D, et al. Oxaliplatin and protracted venous infusion of 5-fluorouracil in patients with advanced or relapsed 5-fluorouracil pretreated colorectal cancer. *Br J Cancer* 2001;**85**:1258–64.
21. Diaz-Rubio E, Evans TR, Tabernero J, et al. Capecitabine (Xeloda) in combination with oxaliplatin: a phase I, dose-escalation study in patients with advanced or metastatic solid tumors. *Ann Oncol* 2002;**13**:558–65.

22. Cassidy J, Tabernero J, Twelves C, et al. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. *J Clin Oncol* 2004;**22**:2084–91.
23. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;**92**:205–16.
24. Cancer Therapy Evaluation Program: Common Toxicity Criteria, Version 2.0. In: Investigator's Handbook. Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institute of Health, Department of Health and Human Services; 1998.
25. Lévi F, Misset JL, Brienza S, et al. A chronopharmacologic phase II clinical trial with 5-fluorouracil, folinic acid and oxaliplatin using an ambulatory multichannel programmable pump. *Cancer* 1992;**69**:893–900.
26. Simon R, Wittes RE, Ellenberg SS. Randomized phase II clinical trials. *Cancer Treat Rep* 1985;**69**:1375–81.
27. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004;**350**:2343–51.
28. Maughan TS, James RD, Kerr DJ, et al. Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2002;**359**:1555–63.
29. Hale JP, Cohen DR, Maughan TS, Stephens RJ. Costs and consequences of different chemotherapy regimens in metastatic colorectal cancer. *Br J Cancer* 2002;**86**:1684–90.
30. André T, Bensmaine MA, Louvet C, et al. Multicenter phase II study of bimonthly high-dose leucovorin, fluorouracil infusion and oxaliplatin for colorectal cancer resistant to the same leucovorin and fluorouracil regimen. *J Clin Oncol* 1999;**17**:3560–8.
31. Maindrault-Goebel F, Louvet C, André T, et al. Oxaliplatin added to the simplified bimonthlyleucovorin and 5FU regimen as second line therapy for metastatic colorectal cancer. *Eur J Cancer* 1999;**35**:1338–42.
32. Pfeiffer P, Sorbye H, Ehrsson H, et al. Short-time infusion of oxaliplatin in combination with capecitabine (XELOX30) as second-line therapy in patients with advanced colorectal cancer after failure to irinotecan and 5-fluorouracil. *Ann Oncol* 2006;**17**:252–8.
33. Borner MM, Dietrich D, Stupp R, et al. Phase II study of capecitabine and oxaliplatin in first- and second-line treatment of advanced or metastatic colorectal cancer. *J Clin Oncol* 2002;**20**:1759–66.
34. Scheithauer W, Kornek GV, Raderer M, et al. Randomized multicenter phase II trial of two different schedules of capecitabine plus oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2003;**21**:1307–12.
35. Zeuli M, Nardoni C, Pino MS, et al. Phase II study of capecitabine and oxaliplatin as first-line treatment in advanced colorectal cancer. *Ann Oncol* 2003;**14**:1378–82.
36. Shields AF, Zalupski MM, Marshall JL, Meropol NJ. Treatment of advanced colorectal carcinoma with oxaliplatin and capecitabine: a phase II trial. *Cancer* 2004;**100**:531–7.
37. Comella P, Natale D, Farris A, et al. Capecitabine plus oxaliplatin for the first-line treatment of elderly patients with metastatic colorectal carcinoma: final results of the Southern Italy Cooperative Oncology Group Trial 0108. *Cancer* 2005;**104**:282–9.
38. Makatsoris T, Kalofonos HP, Aravantinos G, et al. A phase II study of capecitabine plus oxaliplatin (XELOX): a new first-line option in metastatic colorectal cancer. *Int J Gastrointest Cancer* 2005;**35**:103–9.
39. Saif MW. Capecitabine versus continuous-infusion 5-Fluorouracil for colorectal cancer: a retrospective efficacy and safety comparison. *Clin Colorectal Cancer* 2005;**5**:89–100.
40. Twelves C, Gollins S, Grieve R, Samuel L. A randomised cross-over trial comparing patient preference for oral capecitabine and 5-fluorouracil/leucovorin regimens in patients with advanced colorectal cancer. *Ann Oncol* 2006;**17**:239–45.