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A National Cancer Institute of Canada Clinical Trials Group Study – IND.135: Phase I/II study of irinotecan (camptosar), oxaliplatin and raltitrexed (tomudex) (COT) in patients with advanced colorectal cancer

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ARTICLE INFO

Article history:
Received 18 July 2005
Accepted 2 August 2005
Available online 5 December 2005

Keywords:
Phase I/II study
Combination chemotherapy
Metastatic colorectal cancer

ABSTRACT

Thirty-one patients with metastatic colorectal cancer were enrolled in this phase I/II trial of a triple combination of camptosar (C), oxaliplatin (O) and tomudex (T), all given on day one of a convenient three-week schedule. Patients received 257 cycles (1–18) in five cohorts. Toxicity was manageable and haematological toxicity was mild to moderate. Diarrhoea was the main dose-limiting toxicity; nausea and vomiting were common. Fatigue was frequent, moderate in severity and a reason for discontinuation in some patients. The recommended phase II doses were (C) 220 mg/m^2, (O) 100 mg/m^2, (T) 2.75 mg/m^2. A 50% response rate in 30 evaluable patients was confirmed by an independent radiology review board; progression-free survival and overall median survival were 7.3 months and 16.6 months, respectively. Of the 16 patients treated at the recommended dose, 9 (56.3%) experienced partial response. Further evaluation in a randomized study compared to sequential doublets is warranted. Triple combinations could be relevant in curative settings for high-risk patients.

1. Introduction

Colorectal cancer (CRC) is the second leading cause of cancer death in men and women [1]. Although curable by surgery when diagnosed early, almost 45% of patients will eventually develop metastatic disease. The majority of patients with unresectable metastases are incurable and treatment remains palliative.

Treatment with 5-flurouracil (5FU) has been the mainstay of both adjuvant and palliative therapies. For patients with stage III colon cancer, 5FU based adjuvant chemotherapy improves survival [2,3]. In metastatic disease, 5FU has been associated with about 20% response rates and limited benefit in survival.

New agents with activity in CRC have become available in recent years. These include other thymidylate synthase (TS)

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doi:10.1016/j.ejca.2005.08.037

inhibitors, raltitrexed and oral capecitabine [4]; agents such as irinotecan, a topoisomerase I inhibitor; and oxaliplatin a third generation platinum. These drugs have provided effective second and third-line therapies and opportunities for potent combinations. Combinations of irinotecan or oxaliplatin with 5FU/Leucovorin (LV) have shown significant improvements in response rates, progression-free and overall survival in first-line for metastatic CRC. [5–8]. Also, randomized clinical trials of raltitrexed demonstrated equivalent response rates with less toxicity when compared to 5FU/LV, although less conclusive results were found for survival duration [9].

The exploration of triple drug combinations could represent an appropriate next step for clinical evaluation in an attempt to improve overall outcome.

Raltitrexed, irinotecan and oxaliplatin have proven activity in CRC. All three drugs can be administered in a convenient three-week schedule. They have incompletely overlapping toxicities and preclinical studies suggest synergy or at least additive effects when the combination of any two of the three drugs were tested [10–12]. Although there is no clear evidence of schedule dependency, one study suggested that optimal efficacy is obtained when irinotecan is administered prior to raltitrexed [13]. Phase I/II studies using individual doublet combinations demonstrated that when raltitrexed was combined with either oxaliplatin or irinotecan the recommended single agent doses of each drug could be used, i.e., raltitrexed 3 mg/m^2 with oxaliplatin 130 mg/m^2, or irinotecan 350 mg/m^2, respectively. These combinations were associated with promising response rates and manageable toxicities [14,15]. The combination of irinotecan with oxaliplatin was associated with neutropenia and diarrhoea as dose-limiting toxicities and the recommended phase II doses were 85 mg/m^2 oxaliplatin and 200 mg/m^2 of irinotecan [16,17].

We report here on a non-randomized, non-blinded dose-seeking phase I/II study conducted in two Canadian academic cancer centres. The objectives were to determine the recommended dose(s) of irinotecan followed by raltitrexed then oxaliplatin administered on day 1 every 3 weeks and to evaluate the tolerance and efficacy of this combination in first line treatment of patients with metastatic CRC.

2. Patients and methods

2.1. *Eligibility*

Patients were eligible if they had histologically proven advanced or metastatic carcinoma of the colon or rectum with measurable lesions; age $\geqslant$18; ECOG performance status $\leqslant$2; no prior chemotherapy for metastatic disease; and adequate haematological and biochemical functions. Prior adjuvant therapy with fluoropyrimidines with or without radiotherapy was permitted but patients with prior adjuvant irinotecan or oxaliplatin were excluded. Prior radiation was acceptable if completed >4 weeks prior to enrollment and affected $\leqslant$20% of marrow reserve. Patients with previous malignancies, unless considered cured, were excluded. Patients receiving concurrent treatment with other experimental drugs or anti-cancer agents were not eligible. Effective contraception was required if applicable. Patients with documented brain metastases or neuropathy $\geqslant$grade 2 (CTC version 2.0) and serious medical conditions were also excluded. The protocol was reviewed and approved by each Institutional Ethical Review Board. All patients signed an informed consent.

3. Treatment schedule

3.1. *Rationale for selection of the starting dose*

Raltitrexed can be given in full-recommended doses with either oxaliplatin or irinotecan. Oxaliplatin and Irinotecan in combination can be given at approximately 60% of each single agent recommended dose. Therefore, the starting doses of the combination of irinotecan, oxaliplatin and raltitrexed were selected to ensure both patient's safety and antitumour activity.

3.2. *Starting dose and schedule*

The starting dose of the combination consisted of irinotecan 200 mg/m^2 intravenous (IV) followed by raltitrexed 2.75 mg/m^2 then oxaliplatin 90 mg/m^2 given on day 1 and repeated every 3 weeks. Premedication for nausea and vomiting was recommended and prophylactic atropine could be given for diarrhoea or abdominal cramping within 24 h of irinotecan at the discretion of the investigator. At first sign of loose stool, loperamide was given every two hours until symptoms had resolved for 12 h.

3.3. *Study design*

In the phase I component, cohorts of three patients were accrued at each dose level with dose escalation between cohorts. In view of the complexity of evaluating a three drug regimen, the magnitude of escalation of each drug was dependent on the analysis of toxicity occurred during the previous cohort of patients and on a decision of which drug to escalate and to what extent. If one of three patients exhibited a dose-limiting toxicity (DLT), then three more patients were to be entered in that cohort. If less than two out of six patients experienced a DLT, accrual was initiated at the next dose level. If two or more patients out of six exhibited a DLT, then the dose level was declared the maximum tolerated dose (MTD). The next lower dose after MTD was to be the recommended phase II dose (RP2D). The study was then to be expanded to accrue a total of 16 response evaluable patients at the RP2D. If necessary, an oxaliplatin-high and irinotecan-high RP2D would be defined if adequate therapeutic doses of all three drugs could not be given.

Dose reductions/delays were made for haematologic toxicities (based on nadir and duration of recovery of nadir); infection or bleeding; treatment day counts; creatinine clearance; and non-haematologic toxicities ($\geqslant$grade 3 major organ toxicity). Oxaliplatin doses were adjusted in the presence of neurotoxicity, and oxaliplatin was discontinued if grade 3 neurotoxicity occurred; patients could continue on irinotecan and raltitrexed alone at the investigators discretion. Once the dose has been reduced for a patient, no dose re-escalation was permitted.

4. Definition of dose-limiting toxicity

Haematologic toxicity with an absolute granulocyte count $<0.5 \times 10^9$/l for $\geqslant$7 days; febrile neutropenia; thrombocytopenia $<50 \times 10^9$/l or grade 3 thrombocytopenic bleeding; grade 3 or 4 non-haematologic toxicity (excluding unpremedicated nausea or vomiting and transient transaminase elevations); and creatinine clearance <40 ml/min or $\geqslant$grade 2 neurotoxicity of at least 5 days duration were considered DLTs if occurring during the first cycle of chemotherapy.

5. Response criteria

All patients who had received at least one cycle of therapy and had their disease re-evaluated were considered evaluable for response. Patients with objective progression prior to the end of cycle 1 were also considered evaluable. Response and progression were evaluated according to the response evaluation criteria in solid tumours (RECIST) [18]. Responses were defined as follows:

Complete response. Disappearance of all clinical and radiological evidence of tumour, determined by two observations not less than 4 weeks apart with no tumour-related symptoms.

Partial response. Decrease (30% or greater) in the overall sum of measurable lesions determined by two observations not less than 4 weeks apart. No simultaneous increase in the size of any lesion or the appearance of any new lesions may occur. Non-measurable lesions must have remained stable or regressed.

Response duration. The time from when response criteria were first met until disease progression was objectively documented.

Stable disease. Steady state of disease with sufficient shrinkage to neither qualify for partial response, or sufficient increase to qualify for progressive disease.

Stable disease duration. The time of start of therapy until disease progression.

Progressive disease. An unequivocal increase of at least 20% in the sum of measurable lesions as compared to baseline, or the nadir sum of lesions. Appearance of any new lesions also constituted progressive disease. An independent radiology review was conducted for all reported complete or partial responses.

6. Statistical considerations

Descriptive statistical methodology was used to design and analyse the dose-escalation component of this study. For the phase II component, conducted as an expansion of the RP2D level, a response rate of at least 25% was considered of interest. Seven patients were to be accrued. If 2 or more responses were observed in the first 7 patients, an additional 9 evaluable patients would be accrued. If less than 4 responses were observed in the final set of 16 evaluable patients, then we would conclude the regimen as disappointing at this dose and schedule. The observation of 4 or more responses will allow the conclusion that the treatment was promising unless other considerations indicate otherwise. In case irinotecan-high and oxaliplatin-high regimens were tested and both were active, the choice of regimen for further studies would be based on toxicity and tolerability.

We have used hypothesis testing based on confidence intervals. The procedure described above tests the null hypothesis (H_0) that the true response rate is $\leqslant$25% in the phase II component versus the alternative hypothesis (H_a) that the true response rate is >25%. If the observed confidence interval included the 25% response value, the activity of the regimen would be considered unsatisfactory.

7. Results

Between June 2000 and February 2002, thirty-one patients were entered in the trial. The median age was 60 years (range 44–77). There were 21 males and 10 females. Thirty patients had ECOG performance status 0 and 1. Twenty-four patients had colon cancer and seven had rectal cancer. Ten patients had prior 5FU based adjuvant therapy and four had radiation therapy. Twenty patients had 1–2 metastatic sites of disease, 11 patients had $\geqslant$3 sites. The most common metastatic sites were liver, lung and lymph nodes. Details of patient characteristics are shown in Table 1.

Details of therapy in the five cohorts are shown in Table 2. A total of 257 cycles were administered with a range of 1–18 cycles. The actual dose intensity of each drug per cohort was satisfactory, varying between 78% and 100% of the dose planned. All patients have completed therapy and are off study. Fifteen patients discontinued protocol therapy due to progressive disease, two patients with symptomatic disease progression, four patients were taken off study due to toxicity (two patients with gastrointestinal toxicity, one patient with prolonged myelosuppression, one patient with abnormal creatinine clearance). Two patients were censored and removed

Table 1 – Patients characteristics

	No. of patients n = 31 (%)
Age (years), median (range)	60 (44–77)
Male:female	21 (68):10 (32)
ECOG performance status	
0	12 (39)
1	18 (58)
2	1 (3)
Prior therapy	
Adjuvant chemotherapy	10 (32)
Radiotherapy	4 (13)
None	17 (55)
Malignancy type	
Colon	24 (77)
Rectum	7 (23)
Sites of disease	
Liver	25 (81)
Lung	9 (29)
Nodes	12 (39)
No. of metastatic sites	
1	12 (39)
2	8 (26)
3+	11 (35)

Table 2 – Protocol therapy and accrual

Dose level	C (mg/m^2)	O (mg/m^2)	T (mg/m^2)	No. patients	No. cycles
1	200	90	2.75	3	27
2	210	95	2.75	4	19
3	235	105	2.75	4	27
4	210	100	2.75	4	45
5	220	100	2.75	16	139
Total				31	257
Median (range)					8 (1–18)

from the study as they became eligible for surgery for liver metastases and retroperitoneal masses, respectively. Five patients refused further therapy after prolonged treatment (a range of 7–16 cycles was completed). One patient was taken off study due to intercurrent illness and one patient died on study due to progressive disease and bowel obstruction.

8. Toxicity

Thirty patients were evaluable for haematological toxicity (one patient did not repeat blood work according to protocol). Grade 4 granulocytopenia occurred in 50% of patients in cohort 4 and 13% in cohort 5. Febrile neutropenia occurred in 1 patient only. Thrombocytopenia was less common with grade 3 documented in 25% of patients in cohort 3 and 13% in cohort 5 (overall incidence in 10%) (Table 3). Although haematological toxicity was significant in incidence and severity, it was not considered dose-limiting, as per protocol. Delays in dose administration and some dose reductions were required because of neutropenia in cohorts 2–6. The magnitude of dose-adjustments seemed related mostly to the dose level of irinotecan.

9. Non-haematologic toxicity

As shown in Table 4, non-haematological toxicity was common and was dose-limiting. Gastro-intestinal toxicities (diarrhoea, nausea, vomiting and anorexia) were most commonly seen. Early onset diarrhoea was mainly grades 1 and 2 and was documented in 13 patients (42%). Late onset diarrhoea was dose limiting and occurred in 29 patients (93%). It was grades 1–2 in 25 patients (78%) and grade 3 in five patients (16%). Nausea and vomiting occurred in most patients and were grades 1–2 in 25 patients (80%) and 19 patients (61%), respectively, and grade 3 in 6 and 8 patients (19% and 26%), respectively. Grades 1–2 anorexia were documented in 21 patients (68%) and grade 3 anorexia occurred in five patients (16%). Stomatitis was infrequent with grades 1 and 2 in 13 patients (42%). Fatigue was a common side-effect and was quite bothersome to some patients, contributing in some instances to patients declining further protocol treatment.

One patient on dose level 3 died on study following the first dose of treatment. The patient had extensive intra-abdominal disease with persistent nausea and vomiting requiring admission to hospital. Following admission he aspirated and required ventilation support in the intensive care unit. Disease assessment demonstrated progression of intra-abdominal disease with bowel obstruction and the patient deteriorated further leading to his demise. It was concluded that the main causes of death were complications from disease progression and bowel obstruction. This was not considered as a DLT, though the therapy very likely contributed to his clinical problem.

As expected with oxaliplatin, sensory neurotoxicity was common (Table 5). Neuromotor symptoms occurred in 10 patients (33%). Neurosensory symptoms occurred in 25 patients (81%) of patients and were grades 1–2 in severity. Typically these symptoms were worse on cold exposure and increased in severity and duration in subsequent cycles. At cycles 8–16 oxaliplatin was reduced or omitted in four patients. Interestingly, two patients who had oxaliplatin discontinued due to neurotoxicity were subsequently retreated with the drug with no significant neurotoxicity and with some clinical benefit.

10. Dose-limiting toxicity and maximum tolerated dose

There were no DLT's in the first two and at the fourth dose levels (Table 6). At the third dose level (irinotecan 235 mg/m^2, oxaliplatin 105 mg/m^2 and raltitrexed 2.75 mg/m^2), two patients experienced dose limiting gastro-intestinal toxicity (grade 3 diarrhoea; grade 2 vomiting and grade 3 dehydration).

In the fifth cohort, the dose of irinotecan was escalated to 220 mg/m^2; patients were instructed to increase their fluid intake during the first few days of the cycle and monitored closely for diarrhoea. There were only two DLTs in the six patients at this dose level: of the first three patients registered, one experienced a DLT with grade 3 diarrhoea, nausea

Table 3 – Haematologic toxicity grades 3–4 (worst grade per patient according to NCI CTC grading criteria Version 2)

Dose level	Granulocytopenia				Leukopenia				Thrombocytopenia			
	Grade 3		Grade 4		Grade 3		Grade 4		Grade 3		Grade 4	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
1 (*n* = 3)	–	–	–	–	–	–	–	–	–	–	–	–
2 (*n* = 4)	1	25	–	–	–	–	–	–	–	–	–	–
3 (*n* = 4)	1	25	–	–	2	50	1	25	1	25	–	–
4 (*n* = 4)	2	50	2	50	2	50	–	–	–	–	–	–
5 (*n* = 15)	1	7	2	13	2	13	1	7	2	13	–	–
Total evaluable (*n* = 30)	5	17	4	13	6	20	2	7	3	10	–	–

Table 4 – Non-haematologic toxicity (worst grade per patient according to NCI CTC Version 2)

Toxicity	DL 1 (n = 3)		DL 2 (n = 4)		DL 3 (n = 4)		DL 4 (n = 4)		DL 5 (n = 16)		Total (n = 31)	
	n	%	n	%	n	%	n	%	n	%	n	%
Early onset diarrhoea												
Grades 1–2	1	33	–	–	2	50	2	50	7	44	12	39
Grades 3–4	–	–	–	–	1	25	–	–	–	–	1	3
Late onset diarrhoea												
Grades 1–2	3	100	2	50	2	50	4	100	13	81	24	77
Grades 3–4	–	–	–	–	2	50	–	–	3	19	5	16
Nausea												
Grades 1–2	3	100	3	75	2	50	4	100	13	81	25	80
Grades 3–4	–	–	1	25	2	50	–	–	3	19	6	19
Vomiting												
Grades 1–2	3	100	4	100	3	75	1	25	8	50	19	61
Grades 3–4	–	–	–	–	1	25	2	50	5	31	8	26
Anorexia												
Grades 1–2	3	100	2	50	2	50	3	75	11	69	21	68
Grades 3–4	–	–	1	25	2	50	–	–	2	13	5	16
Fatigue												
Grades 1–2	3	100	3	75	1	25	3	75	10	63	20	65
Grades 3–4	–	–	–	–	2	50	1	25	–	–	3	10
Stomatitis												
Grades 1–2	2	67	2	50	3	75	3	75	3	19	13	42
Infection w/o neutropenia												
Grades 1–2	–	–	1	25	–	–	–	–	3	19	4	13
Infection with neutropenia												
Grades 1–2	–	–	–	–	–	–	–	–	–	–	–	–
Grades 3–4	–	–	–	–	–	–	–	–	1	6	1	3
Grade 5	–	–	–	–	1	25	–	–	–	–	1	3
AST elevation												
Grades 1–2	2	66	3	75	3	75	3	75	12	75	23	74
Grades 3–4	1	33	–	–	1	25	1	25	1	6	4	13

Table 5 – Neurologic toxicity (worst grade per patient according to NCI CTC Version 2)

Toxicity	DL 1 (n = 3)		DL 2 (n = 4)		DL 3 (n = 4)		DL 4 (n = 4)		DL 5 (n = 16)		Total (n = 31)	
	n	%	n	%	n	%	n	%	n	%	n	%
Neuro-motor symptoms												
Grades 1–2	2	67	2	50	–	–	–	–	3	19	7	23
Grades 3–4	–	–	–	–	2	50	–	–	1	6	3	10
Neuro-sensory symptoms												
Grades 1–2	3	100	2	50	3	75	4	100	13	81	25	81
Grades 3–4	–	–	–	–	–	–	–	–	–	–	–	–
Inner ear/hearing												
Grades 1–2	2	67	–	–	–	–	–	–	–	–	2	6
Grades 3–4	–	–	–	–	–	–	–	–	–	–	–	–

and vomiting, resulting in the accrual of an additional three patients. The second DLT in this cohort was due to grade 3 vomiting unresponsive to stemetil. This patient also experienced grade 3 diarrhoea after hospitalization.

There were two additional toxic events in this cohort, that were not considered to be DLTs, both patients developed grade 3 nausea and vomiting but neither of them had received optimal anti-emetic prophylaxis. One of the patients also developed grade 2 diarrhoea unrelated to treatment. In conformity with the protocol, these two events were not considered DLTs.

Three additional patients were accrued to a total of nine patients at this dose level. It was recommended that subsequent patients receive a 5-HT3 antagonist plus steroid as pre-medication for nausea and vomiting. At this re-expanded dose level, one patient who did not receive the recommended

Table 6 – Dose-limiting toxicity

Dose level	DLTs
1	–
2	–
3	1. Grade 3 dehydration, diarrhoea, grade 2 vomiting 2. Grade 3 diarrhoea
4	–
5	1. Grade 3 nausea/vomiting diarrhoea, 2. Grade 3 diarrhoea, nausea and dehydration[a]

a Patient did not receive recommended antiemetics or treatment for diarrhoea.

prophylaxis or management of diarrhoea had a DLT with grade 3 diarrhoea, nausea and dehydration.

Otherwise, therapy was overall well-tolerated and this dose was recommended for further phase II studies. The 5th dose level was expanded to a total of 16 evaluable patients as part of the planned phase II component of the trial, and, subsequently, the study was closed.

11. Efficacy

Thirty patients were evaluable for response. One patient died after the first cycle and was not evaluable. An independent radiology review was conducted on all patients in whom a response was claimed. Objective responses were documented at each dose level with partial remissions documented in 15 patients for an overall response rate of 48% (95% CI: 31–68%). Nine patients (29%) had stable disease as best response (Table 7). The median time to progression was 7.3 months (95% CI: 6.51–9.20) and the overall median survival was 16.6 months (95% CI: 13.5–21.3). Out of the 16 patients treated at the recommended phase II dose level (220 CPT-11, 2.75 tomudex, 100 oxaliplatin), there were nine partial responses for a response rate of 56.3% (95% CI: 29.9–80.2).

12. Discussion

In this study, 31 patients with previously untreated metastatic colorectal cancer received 257 cycles of triple combination of irinotecan, oxaliplatin and raltitrexed. Raltitrexed was selected as the third drug based on published evidence of its efficacy and its potentially synergetic effect in chemotherapy doublets with irinotecan or oxaliplatin in advanced colorectal cancer. Furthermore, some favorable aspects of its toxicity profile reported in the literature at the time of study start warranted the use of raltitrexed. Overall, the schedule of once every three weeks was easy to administer and toxicity was manageable with minimal haematologic toxicity. Non-haematological toxicity was more frequent and mostly gastrointestinal, consisting of nausea, vomiting, anorexia, early and dose-limiting late onset diarrhoea. Fatigue was frequently documented and although only grades 1–2 in 64% of cases, this symptom was quite troublesome for some patients. The neurotoxicity was mostly neurosensory. Typically it was exacerbated by cold exposure. The overall incidence was 80% (grades 1–2) with few cases of laryngopharyngeal dysesthesia and neuromotor signs. Neurological symptoms were manifested early in therapy when they occurred for a brief period, initially with a gradual increase in duration and severity with each additional cycle, necessitating discontinuation of the drug in four patients despite ongoing clinical benefit.

A common reason for discontinuing treatment (5 of 31 patients), recorded as patient refusal, was low-grade fatigue and prolonged duration of treatment beyond 10 cycles. This phenomenon is increasingly seen with the availability of new effective combinations in metastatic colorectal cancer. Strategies for maintaining benefit with less intensive therapy such as single agent or biologic targeted therapy after achieving maximum benefit might be necessary as long-term therapy. These will need to be assessed in future studies.

Responses were documented at all dose levels and indicated activity of the combination from the first cohort treated. The overall objective response rate in 30 evaluable patients was 50% and the response rate in the 16 patients treated at the recommended phase II dose was 56.3%. The median time to progression and overall survival were 7.3 and 16.6 months, respectively. Although the results met the protocol defined criteria to be of interest, they were not clearly superior to results recently reported with other doublet combination regimens for metastatic colorectal cancer, such as the sequential combinations of FOLFIRI/FOLFOX [19] where the overall median survival with either sequences was 21 months. Either of these sequential doublets would be the appropriate control arm in a future randomized study designed to assess the value and efficacy of a triple combination.

Several triple combination regimens are under evaluation with early data demonstrating promising results with response rates ranging from 40% to 70% [20–22]. One triple

Table 7 – Best response

Best response (intent to treat)	Cohort (DL)					Total
	1	2	3	4	5	
	n = 3 (%)	*n* = 4 (%)	*n* = 4 (%)	*n* = 4 (%)	*n* = 16 (%)	*n* = 31(%)
Complete response	–	–	–	–	–	–
Partial response	3 (100)	1 (25)	1 (25)	1 (25)	9 (56)	15 (48)
Stable disease	–	1 (25)	1 (25)	3 (75)	4 (25)	9 (29)
Disease progression	–	2 (50)	1 (25)	–	3 (19)	6 (19)
Not evaluable[a]	–	–	1 (25)	–	–	1 (3)

a Death before response evaluation.

combination of particular interest was reported recently by Falcone [23] where irinotecan and oxaliplatin were combined with 5FU/LV infusion in a phase II study of 49 patients. The overall response rate was 72%, including 12% CRs and a median survival of 27 months was reported. These promising results are under evaluation in a follow up phase III study. The superior results reported with irinotecan, oxaliplatin and infusional 5FU compared to our study could be explained by the use of the infusional 5FU schedule shown to be superior to bolus therapy. A phase I/II study combining irinotecan, oxaliplatin and capecitabine is ongoing in our centre, to assess the value of substituting an infusional FU schedule with Capecitabine given orally.

In conclusion, the use of triple combinations in metastatic CRC looks promising. This approach needs further evaluation in comparison to sequential combination therapies. In addition, testing triple regimens in the adjuvant and neo-adjuvant settings may be particularly relevant as an increase in response rates and survival could lead to higher cure rates in both high risk patients following surgery as well as in patients whose liver metastases can be rendered resectable and potentially curable.

Conflict of interest statement

None declared.

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