

# Phase I/II study of first-line irinotecan combined with 5-fluorouracil and folinic acid Mayo Clinic schedule in patients with advanced colorectal cancer

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## Abstract

**Background:** This multicentre phase I/II study was designed to determine the maximum tolerated dose of irinotecan when combined with 5-fluorouracil and folinic acid according to the Mayo Clinic schedule and to evaluate the activity of this combination as first-line therapy in patients with advanced colorectal cancer.

**Methods:** Sixty-three patients received irinotecan (250 or 300 mg/m<sup>2</sup>, 30- to 90-minute intravenous infusion on day 1), immediately followed by folinic acid (20 mg/m<sup>2</sup>/day) and 5-fluorouracil (425 mg/m<sup>2</sup>, 15-minute bolus infusion) days 1 to 5, every four weeks.

**Results:** Diarrhoea was dose limiting at 300 mg/m<sup>2</sup> irinotecan in combination with 5-fluorouracil and folinic acid, and this was determined to be the maximum tolerated dose. Grade 3–4 neutropenia was the most frequently reported toxicity. The recommended dose of irinotecan for the phase II part of the study was 250 mg/m<sup>2</sup>. The response rate for the evaluable patient population was 36% (13/36), and 44% (16 patients) had stable disease (including 19% of minor response). For the intention-to-treat population, the response rate was 29% (14/49) and 35% (17 patients) stable disease (including 14% of minor response). The median time to progression was 7.0 months and the median survival was 12.0 months. Grade 3–4 non-haematological drug-related toxicities included delayed diarrhoea, stomatitis, fatigue, and nausea/vomiting. There were three deaths due to septic shock that were possibly or probably treatment-related.

**Conclusions:** This regimen of irinotecan in combination with the Mayo Clinic schedule of bolus 5-fluorouracil/folinic acid every four weeks showed activity as first-line therapy in patients with advanced colorectal cancer. In keeping with other published results of studies using bolus 5-fluorouracil combined with irinotecan, the use of this regimen is limited by a relatively high rate of grade 3–4 neutropenia, and the combination of irinotecan and infusional 5-fluorouracil / folinic acid should remain the regimen of first choice.

## Background

Until recently, 5-fluorouracil (5-FU) in combination with folinic acid (FA) has been the mainstay of treatment for advanced colorectal cancer (CRC) [1,2]. Of the numerous schedules and doses of 5-FU investigated, the Mayo Clinic bolus schedule, in which both 5-FU and FA are injected daily for five days every four weeks [3-5], emerged as one of the most widely used schedules worldwide for the first-line treatment of advanced CRC.

Irinotecan (CPT-11, Campto<sup>®</sup>) is an S-phase specific derivative of camptothecin, which interferes with DNA replication and cell division inhibiting topoisomerase I [6]. Irinotecan demonstrated antitumour activity against metastatic CRC when used alone either as first-line treatment [7-9] or as second-line treatment after the failure of 5-FU [9-12], with overall response rates ranging from 13% to 32%. In randomised phase III trials, irinotecan administered second-line prolonged survival significantly when compared with either best supportive care [13] or infusional 5-FU/FA [14]. The most frequently reported adverse events associated with irinotecan are neutropenia, delayed diarrhoea, acute cholinergic syndrome, alopecia, fatigue, nausea and vomiting [12].

Early studies in which irinotecan was combined or alternated with 5-FU/FA regimens showed promising first-line efficacy in advanced CRC [15-19]. Two studies had assessed the feasibility of irinotecan (administered every three weeks in the European study or weekly for four weeks followed by two weeks' rest in the US study) alternating with the Mayo Clinic schedule [16,17]. Seventy patients [16] and 33 patients [17] were treated and the overall response rate was around 30%, with a median time to progression of seven months in both studies. The safety profile was satisfactory without overlapping toxicities. These data, coupled with the emerging data from the US and European phase III trials [20,21], suggested that a study of irinotecan in combination with the Mayo Clinic schedule every four weeks was warranted.

The present phase I/II study was designed to determine the maximum tolerated dose (MTD), the recommended dose and the safety profile of irinotecan when combined with the 5-FU/FA Mayo Clinic schedule every four weeks in the treatment of advanced CRC. The antitumour activity of this combination was also evaluated.

## Methods

### Patient eligibility

Patients with histologically proven, measurable, advanced adenocarcinoma of the colon or rectum, with no potentially resectable metastases, were eligible for inclusion in the study. Other inclusion criteria were: age between 18 and 75 years; a World Health Organization (WHO) per-

formance status (PS) 0-2; a life expectancy >3 months; adequate haematological function (haemoglobin  $\geq 10$  g/dL, neutrophils  $\geq 2 \times 10^9/L$  and platelets  $\geq 150 \times 10^9/L$ ); satisfactory renal and hepatic functions (total bilirubin  $\leq 1.25 \times$  upper normal limit [UNL], creatinine  $\leq 1.25 \times$  UNL, aspartate aminotransferase [ASAT] and alanine aminotransferase [ALAT]  $\leq 3 \times$  UNL; or in the case of liver metastases: total bilirubin  $\leq 1.5 \times$  UNL, ASAT and ALAT  $\leq 5 \times$  UNL); no prior chemotherapy or only (neo) adjuvant chemotherapy completed more than six months prior to study entry, and no radiotherapy within the four weeks prior to study entry. Exclusion criteria included: evidence of brain metastases, current infection, unresolved bowel obstruction or sub-acute obstruction, uncontrolled Crohn's disease or ulcerative colitis, and a current history of chronic diarrhoea. This study was approved by the local Ethics Committees of each centre, and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. Pretreatment evaluations included a complete medical history and physical examination, complete blood cell count and blood chemistry, electrocardiogram (ECG), complete tumour imaging (X-ray, computed tomography, ultrasound) performed within three weeks before first infusion, and an assessment of tumour markers. The first treatment administration was made within eight days of registration for the study.

### Treatment

Irinotecan (Campto<sup>®</sup>) was supplied by Aventis Pharma (Antony, France) as a sterile solution of 20 mg/ml in 5 ml vials. 5-FU and FA were used in commercially available formulations. Irinotecan (starting at a dose of 250 mg/m<sup>2</sup>) was administered as a 30- to 90-minute intravenous [IV] infusion on day 1, immediately followed by FA 20 mg/m<sup>2</sup>/day IV bolus followed by 5-FU at a fixed dose of 425 mg/m<sup>2</sup>/day IV bolus, on days 1-5. All patients received a 15-minute bolus infusion of 5-FU/FA. The treatment was administered every four weeks up until disease progression, unacceptable toxicity or withdrawal of patient consent.

Concomitant medication included subcutaneous atropine 0.25 mg as curative treatment for severe cholinergic symptoms, including early diarrhoea. For the treatment of delayed diarrhoea, high-dose loperamide (2 mg every two hours for at least 12 hours) was given as soon as the first liquid stool occurred and continued for up to 12 hours after the last liquid stool, without exceeding a total treatment duration of 48 hours. If the diarrhoea persisted for more than 48 hours despite loperamide treatment, or in the case of severe diarrhoea or diarrhoea associated with vomiting, fever or severe neutropenia, patients received a seven-day course of prophylactic broad spectrum oral antibiotics (fluoroquinolone or cotrimoxazole) and were

hospitalised for rehydration. Patients with febrile neutropenia had to be hospitalised to receive IV antibiotic therapy.

### Study design

#### Phase I study

The starting dose of irinotecan was 250 mg/m<sup>2</sup> (dose level I) and the subsequent planned dose levels were 300 mg/m<sup>2</sup> (dose level II) and 350 mg/m<sup>2</sup> (dose level III). At least three consecutive patients were to be entered at each dose level with a one-week interval between the entry of the first patient and the next two patients. If one out of three patients at one dose level experienced a dose-limiting toxicity (DLT) in the first cycle, at least three more patients were entered at the same dose level. If three out of six patients experienced the same DLT, this dose level was considered to be the MTD of irinotecan in this combination. In the absence of DLT, the next dose level was explored. Once the MTD, as defined above, was reached, the dose immediately below the MTD was explored for determination of the recommended dose. At least six patients were to be included at the MTD and at the recommended dose. Intra-patient dose escalation was not allowed. DLT during the first cycle was defined as the occurrence of any grade 3 or 4 non-haematological toxicity (except alopecia), platelets <25 × 10<sup>9</sup>/L, symptomatic thrombocytopenia (haemorrhage), febrile neutropenia (fever ≥38.0°C with concomitant grade 3–4 neutropenia in the absence of documented infection), grade 3–4 infection, grade 4 neutropenia ≥7 days, grade 3–4 neutropenia associated with severe infection. Second and further cycles of treatment were administered when the neutrophil count was ≥1.5 × 10<sup>9</sup>/L, platelets ≥100 × 10<sup>9</sup>/L and non-haematological toxicity (except alopecia) ≤grade 2, otherwise treatment had to be delayed but not for more than two weeks. If the delay was greater than two weeks, the patient was withdrawn from the study.

#### Phase II study

According to the optimal two-stage Simon design [22] used to define the total number of patients required to detect the activity of the treatment, up to 43 evaluable patients had to be included in the study. Dose reductions of 20% for irinotecan and 5-FU were planned in case of grade 3–4 haematological and/or non-haematological toxicities. There was no dose reduction schedule for FA. As for the phase I part of the study, if the treatment delay was greater than two weeks, the patient was withdrawn from the study.

Relative dose intensities (RDI, the ratio between the actual dose delivered and the planned dose) for the different components of the treatment were regimen were calculated for both the phase I and phase II parts of the study.

### Toxicity and response evaluation

Toxicity, graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 1, was assessed by clinical examination every cycle, weekly for haematology and every two cycles for biochemistry. Tumour responses were assessed every eight weeks (or two cycles of treatment) using the same method of assessment used at baseline, and according to WHO criteria. Responses were defined as follows: complete response (CR), partial response (PR), minor response (MR), stable disease (SD), and progressive disease (PD). The overall response rate was defined as the percentage of patients with a CR or PR. The duration of response, in responding patients, was calculated from the date of first infusion to the date of documented progression. The time to disease progression (TTP) was calculated from the time of the first infusion to the date of documented progression or death due to malignant disease. Deaths for other reasons than malignant disease were censored.

### Statistical analysis

Analyses were performed using SAS® Software version 8.0 within Windows. The primary end-point of the phase I part of the study was to analyse the DLT observed during the first cycle and to determine the MTD of irinotecan in combination with the 5-FU/FA Mayo Clinic schedule. The secondary objectives were to determine the recommended dose of irinotecan for the phase II part of the study and the safety profile of the combination regimen. In the phase II part of the study, the response rate was reported within 95% confidence intervals (CI). Efficacy analyses were performed for both the intent-to-treat (ITT) and evaluable (eligible patients with measurable lesion, who had received a minimum of two cycles of treatment, i.e. eight weeks on study) populations.

The Kaplan-Meier method was used to analyse TTP and overall survival. Safety analyses were performed on all patients receiving at least one administration of irinotecan.

## Results

### Patient characteristics

Between June 19, 1999 and March 26, 2001, 63 patients from three countries (Austria, South Africa, and United Kingdom) were entered: 14 patients in the phase I part of the study and 49 patients in the subsequent phase II part of the study (Table 1). Four patients were not eligible in the phase II part of the study due to the absence of adequate biochemical/haematological function (one of these patients also had no measurable lesion and one had received adjuvant chemotherapy less than six months prior to study entry). Demographic and baseline disease characteristics are listed in Table 1. Seven men and 7 women with a median age of 59 years entered the phase I

**Table 1: Patient characteristics**

Characteristics*	Phase I (n = 14)	Phase II (n = 49)
<b>Eligible</b>	14 (100%)	45 (92%)
<b>Evaluable</b>	11 (79%)	36 (73%)
<b>Median age (range) years</b>	59.0 (30.0–69.0)	63.0 (37.0–71.0)
<b>Sex</b>		
Male	7 (50%)	33 (67%)
Female	7 (50%)	16 (33%)
<b>WHO performance status</b>		
0	4 (29%)	14 (29%)
1	10 (71%)	31 (63%)
2	0	4 (8%)
<b>Primary tumour site</b>		
Colon	9 (64%)	17 (35%)
Rectum	4 (29%)	22 (45%)
Colon rectosigmoid	1 (7%)	10 (20%)
<b>Organ involved</b>		
Median number	2 (1–4)	2 (1–4)
Liver	10 (71%)	42 (86%)
Lung	6 (43%)	17 (35%)
Lymph node	1 (7%)	10 (20%)
Other soft tissue	0	11 (22%)
Abdominal cavity	2 (14%)	3 (6%)
Peritoneum	1 (7%)	0
Bone	1 (7%)	0
Skin	0	1 (2%)
Other	2 (14%)	5 (10%)
<b>Prior therapy</b>		
Surgery	12 (86%)	42 (86%)
Radiotherapy	3 (21%)	14 (29%)
Adjuvant chemotherapy	4 (29%)	12 (24%)
Surgery + radiotherapy	3 (21%)	12 (24%)
Surgery + chemotherapy	4 (29%)	12 (24%)
Radiotherapy + chemotherapy	2 (14%)	7 (14%)
Surgery + radiotherapy + chemotherapy	2 (14%)	7 (14%)

\*N (%) unless otherwise stated. WHO = World Health Organization.

part of the study. Thirty-three men and 16 women with a median age of 63 years entered the phase II part of the study. In both parts of the study, the majority of patients had a WHO PS of 1 and two organs involved (median 2, range 1–4), with the liver being the most common site of metastatic disease. Most patients underwent prior surgery (86% in both parts of the study). Prior radiotherapy was given to 21% of phase I patients and to 29% of phase II patients. Prior adjuvant chemotherapy had been administered to 29% and 24% of phase I and phase II patients, respectively.

#### **Maximum tolerated dose, recommended dose, phase I part of the study**

Six patients received irinotecan at dose level I (250 mg/m<sup>2</sup>). Eight patients received irinotecan at dose level II (300 mg/m<sup>2</sup>). DLTs in the first cycle of treatment are shown in Table 2. The MTD was determined to be irinote-

can 300 mg/m<sup>2</sup> combined with 5-FU 425 mg/m<sup>2</sup> and FA 20 mg/m<sup>2</sup>. At this dose level, a total of four patients (out of eight) experienced a grade 3 or 4 non-haematological toxicity, comprising diarrhoea (three patients), fatigue or pain (one patient each). The haematological DLT was grade 3–4 neutropenia with severe infection (one patient). The recommended dose level for irinotecan was defined as 250 mg/m<sup>2</sup> combined with 5-FU 425 mg/m<sup>2</sup> and FA 20 mg/m<sup>2</sup>. Of the six patients treated at this dose level, four experienced a non-haematological grade 3–4 toxicity, comprising stomatitis, nausea, fatigue, diarrhoea or pulmonary toxicity. One patient also experienced febrile neutropenia.

#### **Treatment compliance**

##### **Phase I**

In total, 60 cycles of irinotecan combined with 5-FU/FA were administered to 14 patients (median number of

**Table 2: Dose-limiting toxicity during first cycle of irinotecan combined with 5-FU/FA Mayo Clinic schedule according to dose levels in phase I study (n = 14)**

Dose level	I	II	Overall
Irinotecan (mg/m <sup>2</sup> )	250	300	250/300
5-FU (mg/m <sup>2</sup> )	425	425	425
FA (mg/m <sup>2</sup> )	20	20	20
	No. of cycles:		
Total number	18	42	60
Median [range]	3 [1-6]	6 [2-8]	4 [1-8]
No. of patients	6	8	14
	Dose limiting toxicity (grade)*:		
Any grade 3-4 non-haematological toxicity:	4	4	8
Pain (3)	-	1	1
Stomatitis (3)	1	-	1
Nausea (3)	2	-	2
Fatigue (3)	2	1	3
Pulmonary (4)	1	-	1
Diarrhoea (3-4)	2	3	5
Febrile neutropenia**	1	0	1
Grade 3-4 infection	0	0	0
Grade 3-4 neutropenia with severe infection	0	1	1
No. patients with at least one DLT	4 (67%)	4 (50%)	8 (57%)

\*Patient may have more than one dose-limiting toxicity (DLT). \*\*Fever ≥38.0°C with concomitant grade 3-4 neutropenia in the absence of documented infection.

cycles four, range, 1-8). Six cycles (10%) were delayed (22% at dose level I and 5% at dose level II), and in two cycles (3%), the dose was reduced due to non-haematological toxicity (one cycle) and prescription error (one cycle).

**Phase II**

In total, 218 cycles were administered to 49 patients (median four cycles, range, 1-12). The median RDI was 90% (range, 52-110%) for irinotecan, 88% (range, 19-108%) for 5-FU and 98% (range, 20-135%) for FA. A total of 22 cycles (10%) had to be delayed due to haematological (seven cycles) and non-haematological toxicity (six cycles), non-study-related adverse events (two cycles) and other reasons (seven cycles: patient convenience, five cycles; surgery, two cycles). The dose of both irinotecan and 5-FU was reduced in 34 cycles (16%), due to haematological toxicity (15 cycles), non-haematological adverse events (17 cycles), haematological and non-haematological toxicity (one cycle) and weight loss (one cycle).

**Haematological toxicity**

**Phase I**

Neutropenia was the main adverse event. At dose level I, grade 3-4 neutropenia occurred in 83% (5/6) of patients (Table 3). The median time to neutrophil nadir was 13 days. The median durations of grade 3 and grade 4 neutro-

penia were one day and two days, respectively. At dose level II, grade 3-4 neutropenia occurred in 63% (5/8) of patients (Table 3). The median time to neutrophil nadir was 20.5 days. At dose level I, grade 3-4 thrombocytopenia occurred in 17% (1/6) of patients. At dose level II, no grade 3-4 thrombocytopenia was observed. Febrile neutropenia was seen in one patient at dose level I, whilst one patient had severe anaemia at dose level II (Table 3).

**Phase II**

Neutropenia was also the main adverse event for this phase of the study, with grade 3-4 toxicity reported for 77% (38/49) of patients. Three patients experienced febrile neutropenia. The median time to neutrophil nadir was 15 days. The median duration of grade 3 and grade 4 neutropenia was one day. Grade 3-4 thrombocytopenia and anaemia were infrequent and occurred in one and two patients, respectively.

**Non-haematological toxicities**

**Phase I**

The most frequent grade 3-4 non-haematological adverse events possibly or probably related to the treatment were delayed diarrhoea, fatigue, pain, stomatitis, alopecia, nausea, anorexia, vomiting, fever and infection. Grade 3-4 adverse events possibly or probably related to treatment included delayed diarrhoea (57% of patients), fatigue

**Table 3: Haematological toxicity of irinotecan combined with 5-FU 425 mg/m<sup>2</sup> and FA 20 mg/m<sup>2</sup> Mayo Clinic schedule (worst grade by patient)**

Dose level	Irinotecan (mg/m <sup>2</sup> )	No. of patients	Neutropenia grade				Thrombocytopenia grade				Anaemia grade				Febrile neutropenia	
			I	2	3	4	I	2	3	4	I	2	3	4		
Phase I	I	250	6	0	1	1	4	2	0	1	0	2	3	0	0	1
	II	300	8	1	0	3	2	1	0	0	0	0	2	0	1	0
	Overall		14	1 (7%)	1 (7%)	4 (29%)	6 (43%)	3 (21%)	0	1 (7%)	0	2 (14%)	5 (36%)	0	1 (7%)	1 (7%)
Phase II	250	49	3 (6%)	6 (12%)	7 (14%)	31 (63%)	8 (16%)	1 (2%)	0	1 (2%)	11 (22%)	9 (18%)	2 (4%)	0	3 (6%)	

**Table 4: Most common grade 3–4 non-haematological toxicity possibly or probably related to irinotecan combined with 5-FU/FA Mayo Clinic schedule according to dose levels (worst grade by patient)**

Dose level	Phase I			Phase II
	I	II	Overall	
Irinotecan (mg/m <sup>2</sup> )	250	300	250/300	250
5-FU (mg/m <sup>2</sup> )	425	425	425	425
FA (mg/m <sup>2</sup> )	20	20	20	20
Number of patients	6	8	14	49
Delayed diarrhoea	4	4	8 (57%)	16 (33%)
Fatigue	2	3	5 (36%)	11 (22%)
Pain	3	1	4 (29%)	9 (18%)
Stomatitis	4	1	5 (36%)	13 (26%)
Alopecia	1	0	1 (7%)	2 (4%)
Nausea	2	0	2 (14%)	8 (16%)
Anorexia	1	1	2 (14%)	0
Vomiting	1	0	1 (7%)	7 (14%)
Fever	0	1	1 (7%)	0
Infection	0	0	0	8 (16%)

(36% of patients), stomatitis (36% of patients), and pain (29% of patients) (Table 4). Hepatic tolerance was very good (no grade 3/4 increase for transaminases).

*Phase II*

The safety profile of the recommended dose combination was close to that observed for the phase I patients. Grade 3–4 adverse events related to study drugs included diarrhoea in 33% of patients, stomatitis in 26% of patients, fatigue in 22% of patients, infection in 16% of patients, nausea in 16% of patients, vomiting in 14% of patients, and pain in 18% of patients (Table 4). Hepatic tolerance was good: one patient had a grade 3 increase in alkaline phosphatase and one had a grade 3 increase in bilirubin. However, three (out of 49) patients died of neutropenic septic shock during the first cycle due to probable or possible treatment-related toxicity (these deaths occurred

within the first fifteen days of treatment). One of these patients had a WHO PS of 1 and two had a WHO PS of 2.

**Efficacy results**

*Phase I*

In the phase I part of the study, three eligible patients were not evaluable for efficacy because two full cycles of treatment were not completed (n = 1) and/or the method of tumour assessment following treatment differed from that used at baseline (n = 3). PRs were seen in 18% (2/11) of evaluable patients (0/4 at dose level I and 2/7 at dose level II). In addition, 45% of evaluable patients had at least stabilisation of their disease (four MR and one SD).

*Phase II*

In the phase II part of the study, nine of the eligible patients were not evaluable for efficacy because two full

**Table 5: Efficacy of irinotecan 250 mg/m<sup>2</sup> combined with 5-FU 425 mg/m<sup>2</sup> and FA 20 mg/m<sup>2</sup> Mayo Clinic schedule in patients in phase II study**

	Evaluable population (n = 36)		ITT population (n = 49)	
	No.	%	No.	%
Complete response	3	8	3	6
Partial response	10	28	11	22
Minor response	7	19	7	14
Stable disease	9	25	10	20
Progressive disease	7	19	8	16
Not evaluable*	-	-	10	20
Overall response rate (95% CI), %	36 (21–54)		29 (16–42)	
Median duration of response (95% CI), months	10.4 (5.9–11.1)		10.4 (4.5–11.1)	
Median duration of stabilisation (95% CI), months	5.8 (4.0–8.3)		6.4 (4.0–8.3)	
Median time to progression (95% CI), months	7.0 (4.5–10.1)		5.9 (4.0–8.1)	
Median time of survival (range), months	-		12.0 (8.0–15.2)	

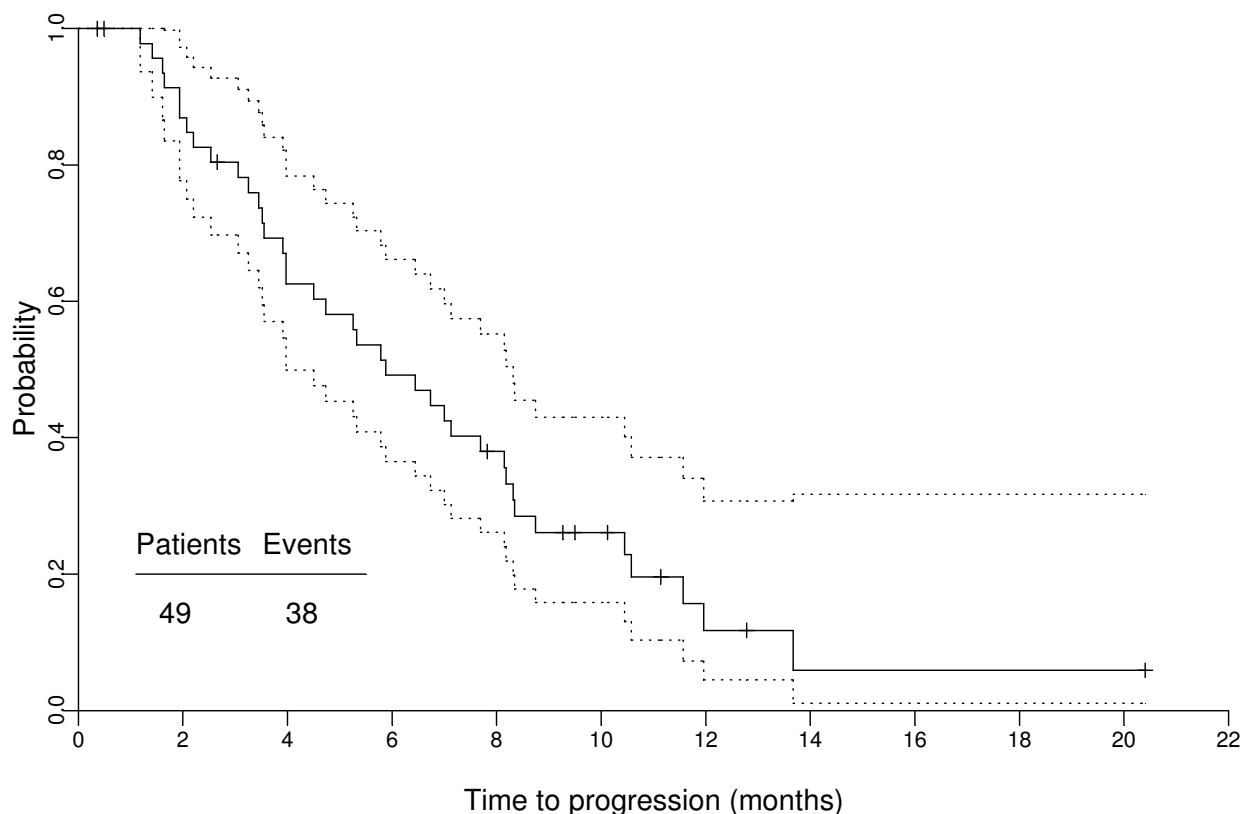
\*Nine patients did not receive two full cycles and had method of measurement different from baseline and one patient had method of measurement different from baseline.

cycles of treatment were not completed (n = 8) and/or the method of tumour assessment following treatment differed from that used at baseline (n = 9). Among evaluable patients there were three CR and 10 PR, giving an overall response rate of 36% (13/36) (29% in the ITT population) (Table 5). Seven patients had a MR and nine patients had SD, leading to 44% SD. The median duration of stabilisation was 5.8 months (95% CI, 4.0–8.3 months). The median duration of response was 10.4 months (95% CI, 5.9–11.1 months). The median TTP was 7.0 months (95% CI, 4.5–10.1 months) in the evaluable population and 5.9 months (95% CI, 4.0–8.1 months) in the ITT population (Figure 1). The median survival time was 12.0 months (95% CI, 8.0–15.2 months) (Figure 2).

## Discussion

The main objective of this multicentre, open phase I/II study was to evaluate the efficacy of the combination of irinotecan administered as a 30- to 90-minute IV infusion combined with the commonly used 5-FU/FA Mayo Clinic schedule (bolus infusion daily for five days, every four weeks) in patients with advanced CRC after determination of the recommended dose in the phase I part of study. Delayed diarrhoea was dose limiting at an irinotecan dose level of 300 mg/m<sup>2</sup> (dose level II) combined with 5-FU 425 mg/m<sup>2</sup> and FA 20 mg/m<sup>2</sup>. The recommended dose for the phase II part of the study was, therefore, irinotecan 250 mg/m<sup>2</sup> combined with 5-FU 425 mg/m<sup>2</sup> (as a 15-minute IV bolus) and FA 20 mg/m<sup>2</sup>. At this dose level, 18 cycles of irinotecan were administered to six patients in the phase I part of the study and 218 cycles to 49 patients in the phase II part of the study. In the phase II study, the median RDI was superior or equal to 87% for each drug.

The combination of irinotecan and 5-FU/FA demonstrated clinical activity, as evidenced by an overall response rate of 29% among the ITT population and of 36% among the evaluable population. This is similar to the response rate reported recently in a phase II study of an alternating regimen of irinotecan and the Mayo Clinic schedule (30%) [23]. However, the response rate is lower than that reported among the ITT populations of a phase II study investigating the Nordic bi-weekly schedule of irinotecan/bolus FU/FA (39%) [24]. While our study was being conducted, results were published from the two pivotal phase III randomised trials confirming the benefits of irinotecan combined with either the bi-weekly de Gramont or the weekly German A.I.O. (Arbeitsgemeinschaft Internische Onkologie) infusional regimens (European trial) [21] or the weekly bolus Saltz regimen (North American trial) [20] compared with 5-FU/FA alone. The response rates in the ITT populations of the irinotecan-containing arms of both trials (35% and 50%) were higher than that seen in our current study. The median TTP was similar in our study, the phase II study using the alternating irinotecan/Mayo Clinic schedule and the phase III trials (approximately 7.0 months). However, the median survival time in the ITT populations were higher in both the phase II alternating irinotecan/Mayo Clinic study (17 months) [23] and the phase III trials (14.8 and 17.4 months) [20,21] than in our study (12.0 months). One possible explanation for the shorter median survival time observed in our study could be the relatively lower dose of irinotecan used (250 mg/m<sup>2</sup> every four weeks), compared with the doses used in the European trial (80 mg/m<sup>2</sup>/week or 180 mg/m<sup>2</sup>/2 weeks) [21] and the American trial (125 mg/m<sup>2</sup>/week) [20]. However, the recently reported trial of alternating irinotecan/Mayo Clinic sched-



**Figure 1**

Kaplan-Meier plot of time to progression in ITT population. Three patients were censored (1 at 0.4 months, 2 at 0.5 months) due to deaths from neutropenic sepsis related to study treatment. The patient censored at 2.7 months died of bowel obstruction not related to study treatment.

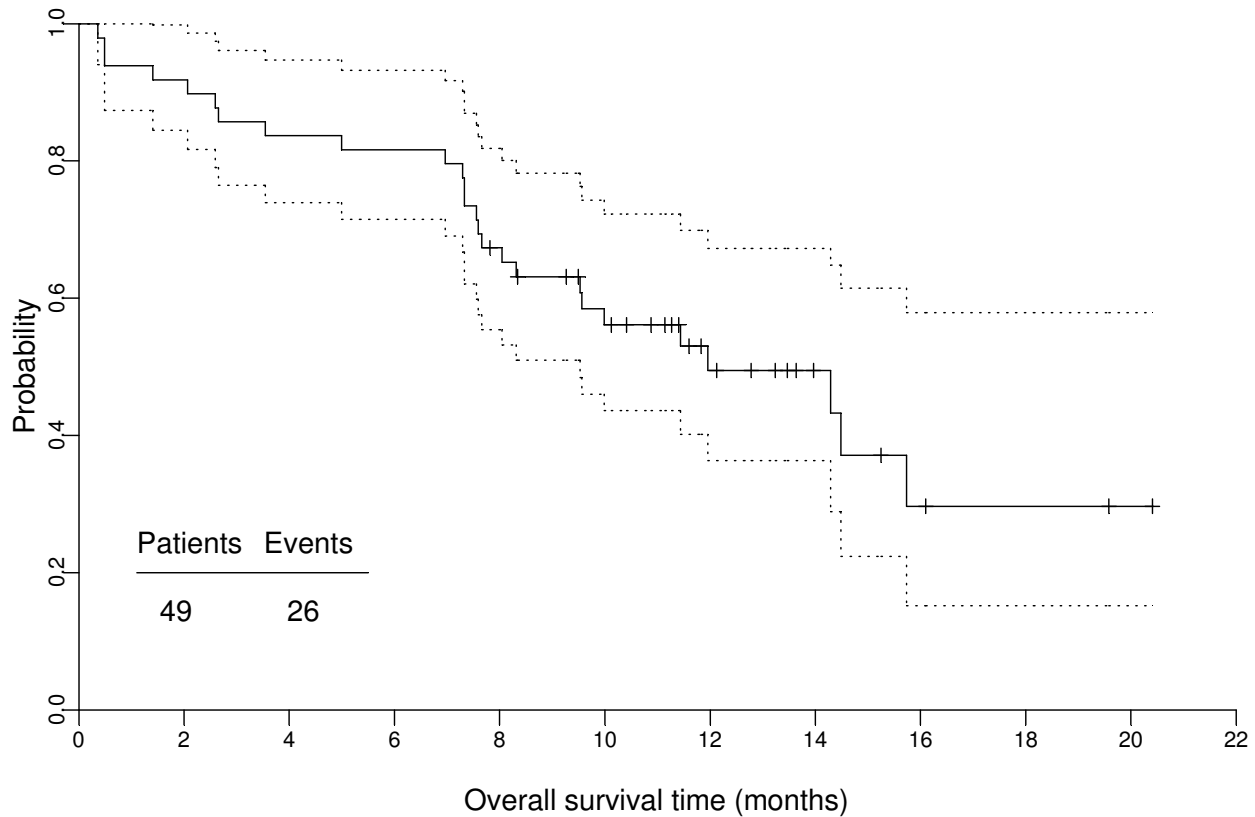
ule used an irinotecan dose of 350 mg/m<sup>2</sup> every six weeks [23]. It is possible therefore that the schedule of administration may be an influencing factor in outcome.

In the present study, neutropenia was the main toxicity. The incidence of grade 3–4 neutropenia in the phase II part of the study (77% of patients) was comparable to that reported by Buroker et al. with the 5-FU/FA Mayo Clinic schedule alone [4]. However, it was higher than that reported with an alternating schedule of irinotecan/Mayo Clinic schedule [23] and that reported by Saltz et al. in their phase III study comparing irinotecan/bolus 5-FU/FA (54%) with 5-FU/FA Mayo Clinic schedule alone (66%) [20]. Although the incidence of grade 3–4 delayed diarrhoea in the present study (33% of patients in the phase II study) was comparable to that obtained with irinotecan as a single agent [20,25,26], it was higher than that reported with the alternating irinotecan/Mayo Clinic schedule

(22%) [23] and the Saltz irinotecan/bolus 5-FU/FA (23%) regimen [20]. The incidences of grade 3–4 infection (16% of patients) and grade 3–4 stomatitis (26% of patients) were also significant in the phase II part of our study.

Three treatment-related deaths occurred within the 60 days after the first infusion and were due to complications following haematological toxicity. Since the initiation of this trial, data have been published regarding the association between some regimens of bolus 5-FU/FA, in combination with irinotecan or oxaliplatin, and early deaths of patients [27–29]. Recommendations of an independent panel for the use of irinotecan plus bolus 5-FU/FA include the weekly assessment of patients, particularly up until week 3 or 4 of treatment, and the prompt management of diarrhoea and/or neutropenia and/or fever [28].





**Figure 2**  
Kaplan-Meier plot of overall survival in ITT population

### Conclusions

Although infusional regimens of 5-FU/FA in combination with irinotecan seem to have better safety profiles than the use of bolus 5-FU/FA, they are not always a practical therapeutic option, and bolus-based regimens still have a role to play in the treatment of metastatic CRC. The results of the present phase I/II study show that the combination of irinotecan (250 mg/m<sup>2</sup>) and the Mayo Clinic schedule of bolus 5-FU/FA administered once every four weeks demonstrated activity in the first-line treatment of metastatic CRC. However, this regimen was associated with a relatively high level of neutropenia. Three treatment-related deaths amongst 49 patients were reported. Therefore, this regimen requires a close follow-up of the patients. Infusional 5-FU/FA in combination with irinotecan should be the regimen of choice instead of bolus 5-FU/FA.

### Competing interests

None declared.

### Authors' contributions

TK was the chairman of the study. He had the initial idea for the study and participated in the writing of the protocol and review of the draft manuscript.

TK, PR, BR, SF, FD, CJ, ND, JT and JC were investigators on the study and participated in the review and commentary of documents relative to the study.

Final editing of the manuscript was performed by TK, PR, BR and BB.

All authors read and approved the final manuscript.

### 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 rate.** *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. Poon MA, O'Connell MJ, Moertel CG, Wieand HS, Cullinan SA, Everson LK, Krook JE, Mailliard JA, Laurie JA, Tschetter LK: **Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma.** *J Clin Oncol* 1989, **7**:1407-1418.
  4. Buroker TR, O'Connell MJ, Wieand HS, Krook JE, Gerstner JB, Mailliard JA, Schaefer PL, Levitt R, Kardinal CG, Gesme DH Jr: **Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer.** *J Clin Oncol* 1994, **12**:14-20.
  5. Leichman CG, Fleming TR, Muggia FM, Tangen CM, Ardalán B, Doroshow JH, Meyers FJ, Holcombe RF, Weiss GR, Mangalik A: **Phase II study of fluorouracil and its modulation in advanced colorectal cancer: a Southwest Oncology Group Study.** *J Clin Oncol* 1995, **13**:1303-1311.
  6. Creemers GJ, Lund B, Verweij J: **Topoisomerase I inhibitors: topotecan and irinotecan.** *Cancer Treat Rev* 1994, **20**:73-96.
  7. Conti JA, Kemeny NE, Saltz LB, Huang Y, Tong WP, Chou TC, Sun M, Pulliam S, Gonzalez C: **Irinotecan is an active agent in untreated patients with metastatic colorectal cancer.** *J Clin Oncol* 1996, **14**:709-715.
  8. Pitot HC, Wender DB, O'Connell MJ, Schroeder G, Goldberg RM, Rubin J, Mailliard JA, Knost JA, Ghosh C, Kirschling RJ, Levitt R, Windschitl HE: **Phase II trial of irinotecan in patients with metastatic colorectal carcinoma.** *J Clin Oncol* 1997, **15**:2910-2919.
  9. Rougier P, Bugat R, Douillard JY, Culine S, Suc E, Brunet P, Becouarn Y, Ychou M, Marty M, Extra JM, Bonneterre J, Adenis A, Seitz JF, Ganem G, Namer M, Conroy T, Negrier S, Merrouche Y, Burki F, Mousseau M, Herait P, Mahjoubi M: **Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naïve patients and pretreated patients with fluorouracil-based chemotherapy.** *J Clin Oncol* 1997, **15**:251-260.
  10. Rothenberg ML, Eckardt JR, Kuhn JG, Burris HA, Nelson J, Hilsenbeck SG, Rodriguez GI, Thurman AM, Smith LS, Eckhardt SG, Weiss GR, Elfring GL, Rinaldi DA, Schaaf LJ, Von Hoff DD: **Phase II trial of irinotecan in patients with progressive or rapidly recurrent colorectal cancer.** *J Clin Oncol* 1996, **14**:1128-1135.
  11. Van Cutsem E, Cunningham D, Ten Bokkel Huinink WW, Punt CJ, Alexopoulos CG, Dirix L, Symann M, Blijham GH, Cholet P, Fillet G, Van Groeningen C, Vannetzel JM, Levi F, Panagos G, Unger C, Wils J, Cote C, Blanc C, Herait P, Bleiberg H: **Clinical activity and benefit of irinotecan (CPT-11) in patients with colorectal cancer truly resistant to 5-fluorouracil (5-FU).** *Eur J Cancer* 1999, **35**:54-59.
  12. Vanhoefler U, Harstrick A, Achterrath W, Cao S, Seeber S, Rustum YM: **Irinotecan in the treatment of colorectal cancer: clinical overview.** *J Clin Oncol* 2001, **19**:1501-1518.
  13. Cunningham D, Pyrhönen S, James RD, Punt CJ, Hickish TF, Heikkilä R, Johannesen TB, Starkhammar H, Topham CA, Awad L, Jacques C, Herait P: **Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer.** *Lancet* 1998, **352**:1413-1418.
  14. Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, Navarro M, Morant R, Bleiberg H, Wils J, Awad L, Herait P, Jacques C: **Randomised trial of irinotecan versus fluorouracil by continuous infusion after failure in patients with metastatic colorectal cancer.** *Lancet* 1998, **352**:1407-1412.
  15. Saltz LB, Kanowitz J, Kemeny NE, Schaaf L, Spriggs D, Staton BA, Berkery R, Steger C, Eng M, Dietz A, Locker P, Kelsen DP: **Phase I clinical and pharmacokinetic study of irinotecan, fluorouracil, and leucovorin in patients with advanced solid tumors.** *J Clin Oncol* 1996, **14**:2959-2967.
  16. Rothenberg ML, Pazdur R, Rowinsky EK, Cohn AL, Alberts DS, Petit RG, Miller LL, Elfring GL, Murphy TC, Mayer RJ: **A phase II multicenter trial of alternating cycles of irinotecan and 5FU/LV in patients with previously untreated metastatic colorectal cancer [abstract].** *Proc Am Soc Clin Oncol* 1997, **16**:266a.
  17. Van Cutsem E, Pozzo C, Starkhammar H, Dirix L, Terzoli E, Cognetti F, Humblet Y, Garufi C, Filez L, Gruia G, Cote C, Barone C: **A phase II study of irinotecan alternated with five days bolus of 5-fluorouracil and leucovorin in first line chemotherapy of metastatic colorectal cancer.** *Ann Oncol* 1998, **9**:1199-1204.
  18. Vanhoefler U, Harstrick A, Köhne CH, Achterrath W, Rustum YM, Seeber S, Wilke H: **Phase I study of a weekly schedule of irinotecan, high dose leucovorin, and infusional fluorouracil as first-line chemotherapy in patients with advanced colorectal cancer.** *J Clin Oncol* 1999, **17**:907-913.
  19. Ducreux M, Ychou M, Seitz JF, Bonnay M, Bexon A, Armand JP, Mahjoubi M, Mery-Mignard D, Rougier P: **Irinotecan combined with bolus fluorouracil, continuous infusion fluorouracil, and high-dose leucovorin every two weeks (LV5FU2 regimen): a dose finding and pharmacokinetic study in patients with pretreated metastatic colorectal cancer.** *J Clin Oncol* 1999, **17**:2901-2908.
  20. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirootta N, Elfring GL, Miller LL: **Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2000, **343**:905-914.
  21. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L, Rougier P: **Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial.** *Lancet* 2000, **355**:1041-1047.
  22. Simon R: **Optimal two-stage designs for phase II clinical trials.** *Controlled Clinical Trials* 1998, **10**:1-10.
  23. Bouzid K, Hkalfallah S, Tujakowski J, Piko B, Purkalne G, Plate S, Padrik P, Serafy M, Pshveloutsky EM, Boussard B, Irinotecan Study Group: **A randomized phase II trial of irinotecan in combination with infusional or two different bolus 5-fluorouracil and folinic acid regimens as first-line therapy for advanced colorectal cancer.** *Ann Oncol* 2003, **14**:1106-1114.
  24. Glimelius B, Ristamaki R, Kjaer M, Pfeiffer P, Skovsgaard T, Tveit KM, Linne T, Frodin JE, Boussard B, Oulid-Aissa D, Pyrhonen S: **Irinotecan combined with bolus 5-fluorouracil and folinic acid Nordic schedule as first-line therapy in advanced colorectal cancer.** *Ann Oncol* 2002, **13**:1868-1873.
  25. Rowinsky EK, Grochow LB, Ettinger DS, Sartorius SE, Lubejko BG, Chen TL, Rock MK, Donehower RC: **Phase I and pharmacological study of the novel topoisomerase I inhibitor 7-ethyl-10-[4-(1-piperidino)-1 piperidino] carbonyloxy camptothecin (CPT-11) administered as a ninety-minute infusion every 3 weeks.** *Cancer Res* 1994, **54**:427-436.
  26. Abigeres D, Chabot GG, Armand JP, Hérait P, Gouyette A, Gandia D: **Phase I and pharmacologic studies of the camptothecin analog irinotecan administered every 3 weeks in cancer patients.** *J Clin Oncol* 1995, **13**:210-221.
  27. Morton RF, Goldberg RM, Sargent DJ, Fuchs CS, O'Connell MJ: **Oxaliplatin or CPT-11 combined with 5-FU/Leucovorin in advanced colorectal cancer: an NCCTG/CALGB study [abstract].** *Proc Am Soc Clin Oncol* 2001, **20**:125a.
  28. Rothenberg ML, Meropol NJ, Poplin EA, Van Cutsem E, Wadler S: **Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel.** *J Clin Oncol* 2001, **19**:3801-3807.
  29. Sargent DJ, Niedzwiecki D, O'Connell MJ, Schilsky RL: **Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer.** *N Engl J Med* 2001, **345**:144-145.

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