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ORIGINAL ARTICLE

Multicentre phase II study using increasing doses of irinotecan combined with a simplified LV5FU2 regimen in metastatic colorectal cancer

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Abstract
Purpose Irinotecan at 180 mg/m² combined with an infusional 5-fluorouracil/leucovorin (5-FU/LV) regimen (FOLFIRI) is a standard first line therapy for metastatic colorectal cancer (mCRC). This phase II study aimed to assess whether increasing the irinotecan dose in the first line FOLFIRI regimen would benefit mCRC patients.
Patients and methods Patients received FOLFIRI every 2 weeks for up to six cycles, comprising a 5-FU/LV regimen combined with irinotecan at 180 mg/m² (cycle 1), increasing to 220 mg/m² (cycle 2) and 260 mg/m² (cycle 3 and subsequent cycles) dependent on toxicity. Efficacy and safety were determined in the intention to treat (ITT) population and in patients able to receive irinotecan at 260 mg/m² for at least four cycles [high-dose (HD) population].
Results Fifty-four eligible patients were included. Among them, 44 (81.5%) formed the HD population. The ITT objective response rate was 48% (90%CI: 36–60) with 25/26 of the responses in the HD population. The disease control rate was 76% (90%CI: 65–85) and median overall survival was 20.4 months (90%CI: 6.4–27.1). The main grade 3/4 toxicities (ITT/HD populations) were neutropenia (61%/59%), and diarrhoea (18%/11%), respectively.
Conclusions This study confirms the feasibility of increasing the standard dose of the irinotecan component of FOLFIRI to 260 mg/m², for more than 80% of patients but does not support a clear advantage of this strategy on unselected mCRC patients.

Keywords Colorectal cancer · Dose optimisation · Irinotecan · FOLFIRI · First line

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Introduction

Colorectal cancer is the second leading cause of cancer-related death in Europe [3]. Patients with metastatic colorectal cancer (mCRC) have an extremely poor prognosis, with 5-year survival rates typically around 10% [8].

Among the numerous 5-FU-based schedules, infusional 5-FU regimens (and particularly LV5FU2) have proven their superiority in terms of efficacy and safety [1, 4]. Newer agents such as irinotecan (campto®) have shown significant anti-tumour activity more particularly in combination with 5-FU/LV as first- or second-line treatment, regardless of the specific 5-FU regimen

used [5, 9, 11, 12]. Irinotecan at 180 mg/m² combined with LV5FU2 or simplified LV5FU2 regimen is one of the standard therapies for the first-line treatment of mCRC [5]. Similar efficacy with better tolerance was obtained by Tournigand [14] when using the simplified LV5FU2 regimen instead of LV5FU2 as the 5-FU component of FOLFIRI. A first-line objective response rate (ORR) of 56% (95% CI: 47–65%), and a median progression-free survival (PFS) of 8.5 months (95% CI: 7–9.5) were achieved with an overall median survival after crossover to FOLFOX6 of 21.5 months (range 16.9–25.2). This efficacy was also associated with a lower toxicity profile, with severe neutropenia and less frequent digestive toxicity. In addition, we had previously demonstrated that high-dose (HD) irinotecan could be safely administered to mCRC patients as first line monotherapy (500 mg/m² every 3 weeks from the second cycle on), with an ORR of 35.5% (95%CI 19.2–54.6) and a median time to progression (TTP) of 5.7 months (95%CI 2.6–6.7) in the HD population [16]. Finally, a phase I study combining an increasing dose of irinotecan to a fixed LV5FU2 regimen, reached the MTD at 300 mg/m² of irinotecan [6]. Therefore, on the basis of these considerations, we have attempted to assess whether increasing the dose of irinotecan (from 180 to 260 mg/m²) in the FOLFIRI regimen would benefit first line mCRC patients in terms of efficacy and safety. This is the aim of this phase II multicentre trial.

Patients and methods

Inclusion criteria

The eligibility criteria for inclusion in the study were: advanced and bidimensionally measurable, histologically proven adenocarcinoma of the colon or rectum; age 18–75 years, World Health Organisation (WHO) performance status ≤2 and a life expectancy of more than 3 months; patients needed adequate haematological, hepatic and renal functions defined by: haemoglobin ≥10 g/dl, absolute neutrophil count $\geq 2 \times 10^9\,l^{-1}$, platelets count $\geq 100 \times 10^9\,l^{-1}$, total bilirubin ≤1.5 × the upper limit of normal (ULN), alkaline phosphatase ≤5 ULN (with or without liver metastasis), and serum creatinine level ≤35 μmol/l. Patients should have had no previous other than adjuvant chemotherapy which must have finished more than 6 months prior to inclusion. Patients were excluded: if they had received previous chemotherapy including irinotecan, had undergone extensive intestinal resection, had experienced prior entheropathy or prior or current (≥grade 2) or uncontrolled severe diarrhoea, had an uncontrolled serious infection, clinical evidence of major organ failure, history of unresolved previous malignancy; were pregnant or were patients of reproductive age not using any form of contraception. The study was approved by the French ethics committee and all participating patients were informed of the study and had to provide signed written informed consent before enrolment.

Chemotherapy

Chemotherapy was administered every 2 weeks intravenously using implantable ports and a programmable pump and was continued for up to six cycles or until disease progression, unacceptable toxic effects or patient refusal. During the first cycle, FOLFIRI consisted of *l*-LV 200 mg/m² or *dl*-LV 400 mg/m² as a 2-h infusion and irinotecan 180 mg/m² as a 90-min infusion concomitantly via a Y-connector. This was immediately followed by a bolus injection of 5-FU 400 mg/m² and a 46-h infusion of 5-FU 2,400 mg/m². In the absence of NCI-CTC grade 3–4 toxicities other than alopecia and haematological toxicity, the dose of irinotecan in the FOLFIRI regimen, was increased to 220 mg/m² at cycle 2, and then to 260 mg/m² at cycle 3 and for all subsequent cycles. The dose of irinotecan was reduced to the previous level for patients who experienced grade 3–4 neutropenia or for those who did not recover from haematological toxicity by day 15 of the cycle, after receiving 263 μg/day of granulocyte-colony stimulating factor (G-CSF) on days 2–10. For subsequent cycles, in case of serious (>grade 2) non-haematological toxicity or delayed diarrhoea occurring despite recommended preventive treatment by sucralfate (Ulcar®) and nifuroxazide (Ercefuryl®)[7], or in case of infusion delays of more than 1 week, the dose of irinotecan was reduced to the previous level; if, in spite of the dose reduction, the toxicity persisted, the treatment was stopped. Prophylactic antiemetic treatment was administered routinely at the discretion of the investigator and atropine (0.25 mg administered subcutaneously) was used, when needed, for the management of irinotecan-related cholinergic syndrome.

At the same time, a pharmacokinetic study was planned in patients of this trial, to investigate inter- and intra-individual variability of irinotecan and SN38 plasma levels. The results of this study and the pharmacokinetic–pharmacodynamic relationships were the subject of an earlier paper [10].

Patient assessment

The primary endpoint of this trial was the ORR. Secondary endpoints included: toxicity, response

duration, TTP and overall survival (OS). Basal evaluations included a physical examination (height, weight, WHO performance status), clinical history and clinical evaluation of the tumour, ECG, chest radiograph, haematological assessment, biochemical assessment and tumour assessment by computed tomography scan. During the trial, patients underwent a physical examination and a biochemical assessment before each cycle and at the end of treatment; haematological assessment was performed every week but in the case of diarrhoea, it had to be performed again immediately. Toxicity and all adverse events experienced during the study were recorded and graded according to NCI common criteria version 2.0. Tumour assessments were made every six cycles and responses were evaluated according to standard WHO criteria. All responses were reviewed by an external review committee. An ORR was defined as a reduction of at least 50% in the area of all measurable lesions. Tumour progression was defined as an increase of at least 25% in the overall area of the tumour or the appearance of new lesions. Stable disease required a less than 50% decrease or an increase less than 25% in metastatic lesions. To be evaluable for response, patients had to receive at least six cycles of chemotherapy or had to be discontinued for progression, whatever the number of cycles. Response duration was calculated from the date of inclusion until progression among partial responders and from the date of complete response to progression among complete responders. Tumour growth control was defined as objective responses and stable disease. TTP was measured from the start of the study to the first evidence of progression, whatever the response to treatment. PFS and OS were calculated from the date of inclusion to progression (relapse, second cancer or cancer death) and death from any cause, respectively.

Statistical considerations

The Simon two-stage minimax design was used to determine the number of patients to be included [13]. The selected design parameters p0 (response rate in null hypothesis) and p1 (response rate in alternative hypothesis) were 35 and 52.5%, respectively. When considering a 10% error probability for both α and β, the first stage of the study required 26 patients and enrolment was continued if at least nine objective responses were observed. A total of 54 patients were required for the second stage. If at least 24 patients responded after the second accrual stage, the treatment was considered promising. Toxicity per patient and per cycle was assessed for all treated patients who received at least one cycle of chemotherapy. Survival curves (TTP, relapse-free survival (RFS), OS) and duration of response were estimated using the Kaplan–Meier method. The analysis was performed in intention to treat (ITT) and response rates and toxicity were also evaluated in patients who had received at least six cycles of chemotherapy, including four HD irinotecan cycles (HD population).

Results

Patient characteristics

From February 2001 to July 2002, 26 patients were included (first stage). The ten objective responses obtained allowed to enrol 29 additional patients, until June 2003 as previously planned. Overall, 55 patients were included in this multicentre phase II study, although one patient who had never been treated, was immediately lost to follow up. No data were available for this subject.

All of the 54 eligible patients included received at least one cycle of treatment and were assessable for toxicity (ITT population). Table 1 describes the baseline characteristics of patients. Three patients were not evaluable for response because they discontinued treatment: one due to toxic death (five cycles) and two due to severe toxicity (three cycles). The median duration of treatment was 24.5 weeks (range 7–52).

Ninety-one percent of the patients had undergone prior curative (49%) or palliative (51%) surgery. Twenty percent of the patients had received prior radiotherapy (most of them for rectal cancer). Among the 54 patients included, 44 (81.5%) received at least four HD irinotecan cycles (a total of 492 cycles). Of the ten patients who failed to receive HD irinotecan, five patients discontinued their treatment prematurely (before the 6th cycle): one patient died early, in the 5th cycle (day six) from pulmonary oedema concomitant with various toxic events (major digestive toxicity and grade 4 neutropenia in spite of G-CSF administration during the second cycle); two patients withdrew from the study at cycle 3 (grade 3 neutropenia) and cycle 5 (grade 4 neutropenia), respectively; one patient withdrew at cycle 4 due to grade 2 asthenia and geographical distance and progressed quickly, Fast progression (cycle 5) was observed in a second patient in whom treatment was interrupted. Another five patients could not maintain their treatment at 260 mg/m^2 during at least four cycles: in one patient, the dose of irinotecan neither increased to 220 nor 260 mg/m^2 due to failure to adhere to the protocol; in four patients, 260 mg/m^2 was maintained during less than four cycles due to

Table 1 Patient characteristics

Characteristics	ITT population ($n = 54$)	%	High-dose population ($n = 44$)	%
Sex				
Male	29	53.7	24	54.5
Female	25	46.3	20	45.5
Age (years)				
<60	26	48.1	22	50.0
≥60	28	51.9	22	50.0
Median age (range)	60.0 (27.0–74.0)		59.5 (27.0–73.0)	
Primary tumour				
Colon	49	72.2	31	70.5
Rectum	15	27.8	13	29.5
Number of involved sites				
1	27	50.0	23	52.3
2	15	27.8	12	27.3
>2	12	22.2	9	20.4
Organ involvement				
Liver	46	85.2	39	88.6
Lung	24	44.4	17	38.6
Other	26	48.0	10	23.8
Prior adjuvant chemotherapy	9	16.7	6	13.6
ACE				
<10 ng/ml	15	27.8	10	22.8
10–100 ng/ml	19	35.2	17	38.6
≥100 ng/ml	20	37.0	17	38.6
Median	61.00		65.40	
PAL				
$< N$	16	29.6	10	22.7
$\geq N$	38	70.4	34	77.3
Median	280.00		289.00	

severe toxicity (mainly gastrointestinal). Overall, 51 patients were assessed for response.

Drug exposure

A total of 555 chemotherapy cycles were administered to 54 patients during the study with a median number of cycles per patient of twelve (range 3–26).

We observed irinotecan dose intensities of 111.4 and 114 mg/m² per week for the ITT and HD populations, respectively. For irinotecan, the median relative dose intensity calculated as the median of the ratio of the observed and expected dose intensity was 0.90 (range 0.66–1.01) and 1.24 (range 0.80–1.42) with or without dose adaptation, respectively. Overall, 49 patients (90.7%) received an increased dose of 260 mg/m² at least once and 44 patients (81.5%) received at least four HD irinotecan cycles. G-CSF was used for 171 cycles (34.1%) in 31 patients (57.4%). Fifteen patients and 17 cycles were associated with more than 10% of dose reductions; among them, 12 patients (in 14 cycles) underwent a dose reduction related to irinotecan (nine patients due to severe toxicity). Treatment delays were more common than dose reductions. Sixty-three out of 501 cycles (12.6%) were delayed by 3 days or more (median 8, range 4–35 days) in 40 patients (74%). Five patients underwent both dose reductions and cycle delays; for four of them, treatment modifications were related to severe clinical toxicity. Only one of these belonged to the HD population. A total of 29 patients (54% of the ITT population) received further second line FOLFOX chemotherapy.

Efficacy

The primary endpoint of this study was the response rate. The median follow-up time was 22.7 months (95% CI: 6.1–35.0). Table 2 shows the response rates in ITT population: There were 26 objective responses in this population, of which 25 were observed in the HD population (ORR of 48.1% (90% CI: 36.3–60.1) and 56.8% (90% CI: 43.3–69.6), respectively). Only one complete response was observed; the rate of stable and progressive diseases was 29.6 and 13.6% in the HD population, respectively. Tumour growth control was 86.4% (90% CI 74.8–93.9) in this last group of patients. Among the 26 objective responses, 13 showed a size reduction of more than 75% (median = −90.5% (95%CI: −99.9 to −77.4). The median duration of responses was 13 months (95% CI 3.7–41.9); the median TTP was 9 months (95% CI: 2.6–41.9), the median PFS was 8.7 months (95% CI: 2.5–41.9). The median OS

Table 2 Efficacy for response

CR *n* (%)	1 (1.9)
PR *n* (%)	25 (46.3)
SD *n* (%)	15 (27.8)
PD *n* (%)	10 (18.5)
Non-evaluable *n* (%)	3 (5.6)
ORR *n* (%)[a]	26 (48.1)
[90% CI]	[36.3–60.1]
Disease control *n* (%)[b]	41 (76.0)
[90% CI]	[64.5–85.1]

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

[a] *ORR* objective response rate: complete + partial responses

[b] Disease control: complete + partial responses + stable disease

was 20.4 months (95% CI: 3.5–41.9). Overall, 41.6% (95% CI: 26.2–56.3) of the patients were alive at 2 years.

Safety

All the 54 patients treated in the study were evaluable for safety. All NCI toxicities are summarised in Table 3. Neutropenia was the main grade 3–4 haematological toxicity occurring in 61% of patients. Anaemia was seen frequently (90.8% of patients and 66.8% of cycles) but only grades 1 and 2 episodes were observed. Grades 3–4 febrile neutropenia occurred in two patients (7.7%) during two cycles (0.8%). The incidence of all grade 3–4 haematological toxicities was similar in the HD population (grade 3–4 neutropenia in 59% of the patients, including the two previous patients with febrile neutropenia). Seventeen patients (31.4%) experienced at least one grade 3–4 gastrointestinal toxicity, during 26 cycles (4.8%). Diarrhoea, occurring in ten patients (18.5%) and 14 cycles (2.6%), was the most frequent grade 3–4 non-haematological toxic effect. One hundred and ninety-four cycles (35%) required treatment for diarrhoea; among them, 131 required only one drug. On the whole, non-haematological toxicity was mild to moderate. Asthenia and alopecia, expected side effects of irinotecan treatment, were very frequent, but of low grade in most cases (only 4 and 9% of patients with grade 3, respectively and no grade 4). More generally, grade 3–4 toxicity per cycle was very low. Five patients discontinued their treatment prematurely (before the 6th cycle): these patients have been already described at the end of patient characteristics section.

We did not observe the most severe toxicities in the HD population.

Discussion

This phase II multicentre study confirmed that it is feasible to increase the dose of irinotecan from 180 to 260 mg/m² and to maintain it during at least four cycles in more than 80% of the patients receiving a FOLFIRI regimen (irinotecan combined with simplified LV5FU2 regimen).

This increase in dose seemed to be associated with a high disease control rate (Tumour growth control) (76%) in the ITT population and an increase of activity (response rate of 57%) for the patients with the HD of irinotecan with an acceptable toxicity profile.

This trial has been justified by the results of various previous studies investigating the use of individual dose-optimisation of irinotecan based on toxicity: the

Table 3 Toxicity per patient for ITT population ($n = 54$) and HD population ($n = 44$)

	Per patient *n* (%)					
	ITT population			HD population		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Haematological (534 cycles)						
Neutropenia	16 (29.7)	25 (46.3)	8 (14.8)	14 (32.0)	20 (45.4)	6 (13.6)
Thrombopenia	17 (31.5)	1 (1.9)	–	15 (34.0)	1 (2.3)	–
Anaemia	49 (90.8)	–	–	39 (88.6)	–	–
Non-haematological (544 cycles)						
Anorexia	23 (42.6)	2 (3.7)	1 (1.9)	18 (41.0)	–	–
Nausea	39 (72.2)	–	1 (1.9)	32 (72.7)	–	–
Vomiting	27 (50.0)	5 (9.3)	1 (1.9)	23 (52.3)	3 (6.8)	–
Diarrhoea	32 (59.3)	9 (16.7)	1 (1.9)	29 (65.9)	4 (9.1)	1 (2.3)
Fever	16 (29.6)	1 (1.9)	–	12 (27.2)	–	–
Asthenia	43 (79.6)	2 (3.7)	–	37 (84.1)	–	–
Mucositis	26 (48.1)	2 (3.7)	–	24(54.5)	–	–
Infection	13 (24.1)	1 (1.9)	–	8 (18)	1 (2.3)	–
Alopecia	38 (70.4)	5 (9.3)	–	31(70.4)	5 (11.3)	–

dose-dependent activity of irinotecan as single agent has been demonstrated in first line patients by Ychou et al. [16] and Van Cutsem et al. [15] in pre-treated patients. Dose-escalation of irinotecan in combination with LV5FU2 regimen was thought to be feasible in a phase I study [6]. Therefore, it seemed justified to investigate the anti-tumour efficacy of an increased irinotecan dose in patients receiving FOLFIRI regimen, which is considered as one of the standard combined therapies, safer than IFL [12].

Unfortunately, our results have proven disappointing even if the intensified schedule was applicable to more than 81.5% of the patients compared with 61% of the patients in a previous study using single-agent HD irinotecan [16]. Encouraging results have been observed in 80% of the population receiving HD irinotecan. This population is a subgroup of patients and consequently, HD FOLFIRI cannot be proposed as a standard treatment until properly tested in phase III, where it should be compared with the standard FOLFIRI regimen. In addition, our results were obtained from a non-randomised phase II study and comparing this type of data with outcomes from other studies is always difficult because they may involve populations with very different baseline characteristics. In fact, the only trials where these results could be possibly compared with are the randomised studies reported by Douillard et al. [5] and Tournigand et al. [14]. Douillard and colleagues used LV5FU2 combined with standard doses of irinotecan and showed an ORR of 35% and a TTP of 6.7 months in ITT population. Tournigand and colleagues (GERCOR study) were the first to use the new simplified LV5FU2 regimen combined with either irinotecan (FOLFIRI) or oxaliplatin (100 mg/m²) (FOLFOX 6), in first line patients. They reported an ORR of 56%, a disease control rate of 79% and a median PFS of 8.5 months for the FOLFIRI arm. This is the only study showing such a high ORR but 22% of the patients had received an increased dose of 5-FU (3,000 mg/m² for at least one cycle). Furthermore, the selected population in the Tournigand study had a better prognosis than ours: 59% of their population only had one site invaded compared to 50% in ours, and 44% of their patients had normal PALs as opposed to 30% for us. These differences could perhaps explain the slight discrepancy in the response rates between our study and theirs.

As expected, neutropenia represented the dose limiting toxicity with approximately 60% of patients experiencing grade 3–4 reactions. This toxicity is probably related to the increased dose of irinotecan and is similar to that experienced by patients receiving HD of irinotecan (500 mg/m²) in monotherapy [16]. The observed grade 3–4 neutropenia rate (61%) was higher than that reported in previous studies [5, 14] using standard dose of irinotecan (46 and 24%, respectively). The digestive toxicity profile was relatively mild in the present study and in agreement with that observed in other studies using the simplified LV5FU based-FOLFIRI [14]. This mildness was probably due to a good management of delayed diarrhoea [7]. As a whole, safety is rather good and best in the HD population in spite of intensified doses of irinotecan. Patients who experienced severe toxicity from the first cycle were not able to receive a HD therapy. In the remaining patients (those experiencing a low toxicity), the toxicity profile did not become worse as the doses administered were intensified further. In addition, patients who had reacted well to the chemotherapy from the first cycle, had to wait for the third cycle before receiving the higher dose. The treatment could have been more effective for them if 260 mg/m² of irinotecan had been administered sooner (at least from the second cycle). Pharmacogenetic features such as UGTA1 profile have been thought to play a significant role in the variable toxicity reported [2]; some genotypes could explain the severe and early toxicity in some patients, probably related to impaired glucuronidation of irinotecan and we need prospective trials based on these variable polymorphisms.

The intensified schedule used in this phase II trial actually allowed a reduction in the size of metastases by more than 75% in approximately 50% of the patients. However, in this trial, patients were not selected to have liver metastases that could be rendered resectable in case of good response after chemotherapy; that explains the absence of significant secondary resection in this study. Such data provided a strong rationale for comparing standard FOLFIRI with HD FOLFIRI as well as two other intensified schedules (FOLFOX and FOLFIRINOX) in the METHEP trial. The objective of this ongoing study is to evaluate the relative efficacy of these regimens in rendering resectable, initially unresectable CRC liver metastases. The hope is that by increasing the resection rate for such patients, the long-term OS rate will be improved. This schedule could be therefore justified in the future as an effective neoadjuvant treatment in advanced unresectable disease.

In conclusion, this study confirms that it is feasible to increase the dose of irinotecan from 180 to 260 mg/m² in the FOLFIRI regimen for more than 80% of the patients with mCRC, but does not support a clear advantage of this strategy on unselected population.

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