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ORIGINAL ARTICLE

Use of the folinic acid/5-fluorouracil/irinotecan (FOLFIRI 1) regimen in elderly patients as a first-line treatment for metastatic colorectal cancer: a Phase II study

Eric François · Jean-François Berdah · Emmanuel Chamorey · Gérard Lesbats · Eric Teissier · Jean-François Codoul · Jean-Luc Badetti · Christophe Hébert · Véronique Mari

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Abstract
Background The aim of this study was to evaluate the effects of a combination of folinic acid, 5-fluorouracil (5FU) and irinotecan (FOLFIRI 1) administered every 2 weeks in a population of elderly subjects with advanced colorectal cancer.
Patients and methods Patients with metastatic colorectal cancer included in this study were aged at least 70 years, with a performance status of 0/1, without geriatric syndrome and without previous palliative chemotherapy. They received irinotecan [180 mg/m^2 intravenous (iv) infusion over 90 min] followed by folinic acid (400 mg/m^2 iv over 2 h), then 5FU (400 mg/m^2 iv bolus) and 5FU (2,400 mg/m^2 continuous iv infusion for 46 h) every 2 weeks.
Results Forty eligible patients were included. The median age was 77.3 years (range 70–84.7). The objective response rate was 40% and the stabilisation rate was 45%. Median progression-free survival was 8 months, overall survival was 17.2 months and cancer-related specific survival was 20.2 months. In total, 300 cycles of chemotherapy were administered with a median number of eight cycles per patient (range 1–18). Tolerance was good; grade 3/4 toxicities included diarrhoea (15%), asthenia (15%), nausea/vomiting (7.5%) and neutropenia (7.5%). One toxic death was observed due to grade 4 diarrhoea.
Conclusion The FOLFIRI 1 regimen is a valid therapeutic option for elderly patients in good clinical condition.

Keywords Colorectal cancer · Elderly · Irinotecan · 5-Fluorouracil · Phase II

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E. François (✉) · E. Chamorey · C. Hébert · V. Mari
Centre Antoine-Lacassagne, 33 Ave de Valombrose, 06189 Nice Cedex 2, France
e-mail: eric.francois@cal.nice.fnclcc.fr; eric.francois@nice.fnclcc.fr

J.-F. Berdah
Clinique de l'Espérance, Hyères, France

G. Lesbats
Clinique Saint-Laurent, Saint Laurent du Var, France

E. Teissier
Clinique Plein Ciel, Mougins, France

J.-F. Codoul
Centre Hospitalier, Draguignan, France

J.-L. Badetti
Hôpital des Broussailles, Cannes, France

Introduction

Cancer is the primary cause of mortality and morbidity in the elderly. Demographic data show that one in four Europeans will be above 65 years of age in 2020 [1], and elderly people have a ten times higher risk of developing cancer than those under 65 years [2]. In particular, this is true for colorectal cancer, which is common in Western countries, with a median age for diagnosis in Europe and the United States at around 70 years [2, 3]. Furthermore, approximately 50% of patients with colorectal cancer will develop metastases and the majority of these patients will not survive for more than 18 months. Chemotherapy in general and polychemotherapies in particular, both in adjuvant and metastatic settings, have led to significant improvements in the prognosis for patients. The use of irinotecan and/or oxaliplatin in combination with 5FU and folinic acid is linked with an improvement in median survival and/or progression-free survival [4–6]. However, these combined treatments cause more toxicity, in

particular digestive effects [5, 6], and neurological effects for oxaliplatin [6]. The increase in side effects is nevertheless still moderate, and does not significantly increase the toxic death rate [4–6]. However, many clinical trials have excluded elderly subjects because of the potentially greater toxicity of chemotherapy [4], despite the fact that this has not been confirmed by epidemiological studies or clinical trials [7, 8], or have included a low proportion of elderly patients [5, 9]. Few prospective studies relating to the use of irinotecan in elderly subjects have been published, and none has used the FOLFIRI 1 regimen [10], which could improve tolerance of this drug combination [11].

We report the results of a Phase II, prospective, multicentre study to analyse the effects of the FOLFIRI 1 regimen in subjects aged at least 70 years with metastatic colorectal cancer.

Population and methods

Eligibility criteria

Patients aged at least 70 years with an inoperable metastatic adenocarcinoma of the colon or rectum were included in this prospective multicentre study. The patients were eligible if they had not received treatment for their metastatic disease. Adjuvant chemotherapy based on 5FU was authorised if the metastasis occurred at least 6 months after the end of any adjuvant treatment. The disease was measured according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [12]; the patients had to have a performance status of 0 or 1 and a life expectancy of at least 3 months, with adequate haematological (haemoglobin >100 g/l; neutrophil count $\geq 1.5 \times 10^9$/l; platelet count $\geq 100 \times 10^9$/l), renal (creatinine ≤ 130 µmol/l) and hepatic functions [aspartate aminotransferase, alanine aminotransferase and alkaline phosphatise levels $<3 \times$ the upper limit of the normal range (ULN) or $<5 \times$ ULN in the case of hepatic metastases; total bilirubin $\leq 1.25 \times$ ULN]. Patients with a previous cancer, apart from a basocellular cutaneous cancer or a carcinoma in situ of the uterine cervix, those with an inflammatory disease of the small intestine or colon, those with a geriatric syndrome, a serious unstable disease or those whose comprehension did not allow them to follow therapy instructions in the event of diarrhoea were not able to take part in this study. All patients gave their signed informed consent. The study complied with French regulations and followed the recommendations of the Declaration of Helsinki and Good Clinical Practice.

Treatment

Irinotecan (Campto®, Pfizer) was administered at a dose of 180 mg/m^2 by infusion over 90 min on day 1. Folinic acid was given on day 1 at a dose of 400 mg/m^2 by infusion over 2 h followed by 400 mg/m^2 of 5FU by iv bolus, and finally 5FU was administered by infusion over 46 h at a dose of 2,400 mg/m^2. In the absence of any contraindications, chemotherapy was repeated every 14 days. Chemotherapy was given on an outpatient basis by means of an implanted central venous catheter. The treatment was continued for 12 cycles without progression of the disease, unacceptable toxicity, significant change to the quality of life or withdrawal of patient consent. In some cases, chemotherapy could be continued beyond 12 cycles. The patients received antiemetic treatment, prescribed according to the practices of each chemotherapy centre, with a medium to high antiemetic effect. Atropine premedication was allowed from the first cycle. Patients were informed of the procedure to follow in the event of delayed diarrhoea induced by irinotecan: loperamide to be taken at a dose of 2 mg every 2 h, high fluid intake, and the need to contact the oncologist in the event of the problem persisting beyond 24 h or in the event of fever or haemorrhagic diarrhoea. Treatment was postponed for 7 days in the event of grade 3 toxicity, and then, on recovery, the irinotecan dose was reduced by 25% and the 5FU bolus was withheld. In the event of hand–foot syndrome or grade 3 stomatitis, only the 5FU was reduced by 25%. In the event of grade 4 toxicity, or if chemotherapy was postponed for at least 2 weeks due to toxicity, the patients were taken out of the study. The preventative use of granulocyte growth factor was not authorised.

Evaluation

Pre-therapeutic evaluation included a full clinical examination with a detailed medical history. Patients were evaluated on the Cumulative Illness Rating Scale [13]. The following investigations were carried out: a full blood test, hepatic and renal evaluations, and measurement of electrolyte concentrations and plasma albumin levels. A thoracic and abdominal scan and an electrocardiogram were carried out in the 28 days before the start of treatment; determination of carcinoembryonic antigen level was optional. During treatment, a full blood test and hepatic, renal and blood biochemistry tests were carried out every 14 days except in the presence of grade 3 toxicity when they were carried out every 7 days. A tumour evaluation was carried out every 2 months (four cycles).

The tumoral responses were evaluated by the investigators on the basis of the RECIST criteria [12]. The toxicities were evaluated for each cycle on the basis of the National Cancer Institute's Common Toxicity Criteria scale (NCI-CTC, version 2.0, 1998).

The quality of life was measured on admission to the study, then at least every four cycles using the Spitzer Uniscale analogical visual scale [14].

Overall survival and progression-free survival were measured from the date of inclusion in the study to the progression documented or the death of the patient. The specific overall survival was measured as in previous studies and took into account only deaths linked to the cancer.

Statistical considerations

This Phase II study was carried out on the basis of Fleming's one-stage method to detect a response rate of at least 35% [15]. Based on a level of significance of 95% (α error 0.05) and a statistical power of 85% (β error 0.15), a minimum of 38 evaluable patients had to be included in this study; allowing for a 10% non-evaluable response rate, a total of 42 patients had to be included. The descriptive and analytical statistical analyses were conducted on Windows R1.7.1 software. All the tests were carried out as a bilateral hypothesis with a significance threshold of 5% and the survival probability without progression and overall survival were estimated using the Kaplan–Meier method. A logrank test was performed to identify the interaction between comorbidities and survival. The highest level of toxicities for each patient for all the chemotherapy cycles was used to analyse toxicity according to the NCI-CTC criteria.

Results

Patient characteristics

Between September 2002 and July 2005, 43 patients from six centres were included in the study. Three patients were excluded from the analysis as a result of non-compliance with inclusion criteria (one patient was under 70 years old (69), and one patient had a history of bladder cancer) or because of the absence of available data (one patient moved away and thus withdrew from the study). Forty patients were evaluable for tolerance and efficacy. Details of the characteristics of the population are given in Table 1. The median age was 77.3 years (range 70–84.7); 11 patients were at least 80 years old. The performance status was 0/1 for all but three patients (information was not available for these three patients). The median body mass index was 23.9 (range 18.3–31.6). Seventeen (42.5%) of the patients had metastases in a minimum of two sites. Thirty-four patients (85%) had at least one comorbidity; 23 (57.5%) had three or more comorbidities. Arterial hypertension was found in 19 (47.5%) of the patients, rheumatological disorders in 17 (42.5%), diabetes in seven (17.5%), cardiac rhythm disorders in eight (20%) and coronary insufficiency in eight (20%). All patients with heart disease had a stabilized disease and recent cardiac evaluation before inclusion in the study. None of the patients had geriatric syndrome. In 22 patients (55%), the disease was diagnosed at the metastatic stage. Secondary localisations were essentially hepatic and pulmonary for 31 (77.5%) and 10 (25%) of the patients, respectively. Adjuvant chemotherapy was given to eight patients (20%) and adjuvant radiation to two patients (5%).

Table 1 Patient characteristics ($n = 40$)

Characteristics	Patients (n)	%
Age		
Median	77.3	
Extremes	70–84.7	
<80	29	72.5
≥80	11	27.5
Sex		
Male	30	75.0
Female	10	25.0
Performance status		
0	21	52.5
1	16	40.0
Unknown	3	7.5
Metastatic sites		
Liver	31	77.5
Lungs	10	25.0
Lymph nodes	7	17.5
Peritoneum	7	17.5
Other	5	12.5
Number of metastatic sites		
1	23	57.5
2	16	40.0
≥3	1	2.5
Previous treatment		
Surgery	32	80.0
Adjuvant radiotherapy	2	5.0
Adjuvant chemotherapy	8	20.0
Comorbidity factors		
0	3	7.5
1	2	5.0
2	9	22.5
≥3	23	57.5
Unknown	3	7.5

Compliance with the treatment

Three hundred cycles of chemotherapy were administered (median eight; range one to 18). Nineteen of the 300 cycles (6.3%) were postponed, mainly as a result of toxicity (16 of the 19 cycles), and 21 cycles had a reduction in dose (7%), again mostly because of toxicity (20 of the 21 cycles). A total of 10 cycles (3%) were postponed, with a reduction in dose for six patients.

The absolute and relative median intensity doses were 179 mg/m^2 per 2 weeks and 99% for irinotecan, 386 mg/m^2 per 2 weeks and 96% for folinic acid, 400 mg/m^2 per 2 weeks and 100% for 5FU bolus, and 2,397 mg/m^2 per 2 weeks and 99% for 5FU infusion, respectively.

Tolerance

Details of haematological and non-haematological toxicities are given in Table 2. Neutropenia and diarrhoea are the principal toxicities observed in our study. Grade 3/4 neutropenia affected three patients (7.5%); we observed no febrile neutropenia. Diarrhoea affected 26 (65%) of the 40 patients; five (12.5%) had grade 3 toxicity and one patient presented with grade 4 toxicity which resulted in her death. Following hospital treatment to control the diarrhoea, the patient's general health deteriorated, with complications of decubitus, culminating in death. Other significant gastrointestinal disorders were vomiting, abdominal pain and stomatitis. Grade 3 asthenia was observed in six (15%) of the patients and ischaemic coronary disorders were observed in three patients (7.5%), one of whom had pain characteristic of angina pectoris which led to stopping the 5FU.

Efficacy

With intention to treat, two full responses (5%) and 14 partial responses (35%) were observed [i.e. an objective response rate of 40% (95% CI, 25–55%)], and 18 patients (45%; 95% CI, 30–60%) were stabilised. The median progression-free survival was 8.0 months (95% CI, 6–unreached). The overall median survival was 17.2 months (95% CI, 11.6–22.2 months). The survival rate at 1 year was 64% and the death rate at 60 days was 5%. In patients under 80 years of age, overall median survival was 20.2 months (95% CI, 11.6–unreached) and for those over 80 years of age it was 11.7 months (95% CI, 3.2–unreached). In terms of specific survival, median survival was 20.2 months (95% CI, 11.7–25.4 months); 21.2 months (95% CI, 13.1–unreached) for those under 80 years of age and 11.7 months (95% CI, 3.2–unreached) for those over 80 years of age. We demonstrated no statistically significant correlation between the comorbidity factors and overall survival, specific survival or progression-free survival.

It should be noted that 19 (47.5%) of the patients received at least one second-line course of palliative chemotherapy. One-third of these patients received oxaliplatin-based chemotherapy.

Analysis of the quality of life based on the Spitzer visual scale ranges from an average score of 75.1/100 at the start of treatment to 71.3/100 on the 4th cycle, 80.9/100 on the 8th cycle and 87.2/100 on the 12th cycle ($P = 0.0015$).

Discussion

The combination of irinotecan with 5FU and folinic acid is considered to be one of the standard treatments for patients with metastatic colorectal cancer. Prospective randomised studies have shown that this combination could improve overall survival or progression-free survival compared to protocols without irinotecan [4, 5, 9]. However, elderly subjects have often been excluded or under-represented in these studies for fear of excessive toxicity, even though they represent the majority of patients for this pathology. There is therefore little practical information regarding the benefits and risks of polychemotherapy. We conducted a prospective Phase II study using the FOLFIRI 1 regimen [10] for patients with metastatic colorectal cancer aged at

Table 2 Toxicity by patient based on National Cancer Institute's Common Toxicity Criteria scale (NCI-CTC) 2.0 criteria ($n = 40$)

Toxicity	Grade				
	0	1	2	3	4
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Neutropenia	17 (42.5)	11 (27.5)	9 (22.5)	2 (5.0)	1 (2.5)
Anaemia	5 (12.5)	23 (57.5)	12 (30.0)		
Thrombopenia	26 (65.0)	14 (35.0)			
Asthenia	14 (35.0)	8 (20.0)	12 (30.0)	6 (15.0)	
Nausea/vomiting	21 (52.5)	9 (22.5)	7 (17.5)	3 (7.5)	
Diarrhoea	14 (35.0)	13 (32.5)	7 (17.5)	5 (12.5)	1 (2.5)
Abdominal pains	31 (77.5)	5 (12.5)	3 (7.5)	1 (2.5)	
Stomatitis	35 (87.5)	2 (5.0)	1 (2.5)	2 (5.0)	
Skin	35 (87.5)	4 (10.0)	1 (2.5)		
Heart	35 (87.5)	1 (2.5)	3 (7.5)	1 (2.5)	
Alopecia	30 (75.0)	7 (17.5)	2 (5.0)	1 (2.5)	

least 70 years. It emerges that the results are identical to those observed in younger subjects. We found an objective response rate of 40%, which is similar to previously reported results [4, 5]. This same FOLFIRI 1 regimen, however, was used to obtain higher response rates [16]. Progression-free survival (8.0 months) and overall survival (17.2 months) were similar to previously reported results with polychemotherapy [4, 5], although it is difficult to compare a Phase II study in a selected population and phase III studies. Our results were obtained in a selected population of elderly patients in good clinical condition. For other groups of elderly patients specific studies need to be performed. Median survival reported in the litterature is largely influenced by the percentage of patients who received irinotecan and oxaliplatin [17]. In our study, 54% of patients were able to receive second-line chemotherapy; 33% of these patients received oxaliplatin and the others received 5FU-based chemotherapy. Analysis of the specific survival (20.2 months), which was notably longer than overall survival (17.2 months), demonstrated the impact of comorbidities which play a considerable role in elderly patients. We did not, however, find a statistically significant correlation between these comorbidities and the different types of survival, possibly because their type and intensity also affect the non-cancer prognosis. Our study was not designed to statistically compare population subgroups, but patients over 80 years of age had a median survival of 11.7 months compared with 20.2 months in those under 80 years of age. Aparicio and colleagues [18] also observed in their retrospective study that patients aged over 80 years had a shorter median survival than subjects aged between 75 and 79 years (9.9 versus 12.1 months). Comorbidities may play an important role in these patients, but the size of this subgroup prevented us from performing statistical tests. It would therefore appear that the results are worse in patients over 80 years, including in selected patients. The use of several lines of treatment and/or the use of targeted therapies could improve these results. For the moment, however, their impact in the sub-population of elderly subjects is unknown.

Quality of life was measured using the Spitzer Uniscale analogical visual scale. We noted a significant improvement in the quality-of-life score, which ranged from 75.1 at the start of treatment to 87.2 on the 12th cycle. Souglakos et al. [19] also noted maintenance or even a trend towards improvement of the quality of life with a similar chemotherapy regimen. This improvement in quality of life is important in a palliative setting, particularly for elderly subjects.

Tolerance of this regimen was good and, as for younger subjects, the greatest clinical toxicity was diarrhoea [4, 5, 9]. The chemotherapy regimen did not seem to significantly influence the risk of occurrence of severe diarrhoea [19, 20]; only the results of Comella et al [21] showed a lower rate of diarrhoea (6%) but the number of patients in their study was low [18]. There was one toxic death—a patient with severe diarrhoea requiring hospitalisation died as a result of complications linked to decubitus. In elderly patients, severe toxicity can often be caused by underlying pathologies and it is therefore important to select patients on the basis of rigorous criteria. The use of a multifunctional geriatric evaluation should improve selection and probably enable chemotherapy to be better adapted [22]. Other clinical toxicities were infrequent, apart from asthenia which was severe in 15% of our patients. This fatigue is evaluated in various ways in different studies; it is one of the clinical symptoms most frequently found in elderly subjects with all types of malignancies and particularly cancer of the colon [8, 19, 20]. For a younger population, it seems to be lower with the FOLFIRI 1 regimen compared with the LV5FU2–irinotecan combination [11]. One patient also presented with severe cardiac toxicity (angina pectoris) leading to 5FU being stopped and two other patients presented minor disorders. Such cardiovascular disorders are not rare [20] and lead to a systematic cardiac evaluation being carried out before starting a polychemotherapy

Table 3 Percentage of patients with grade 3/4 toxicities with different 5FU/irinotecan regimens

	Comella [21]	Sastre [20]	Souglakos [19]	Present study
Regimen	IRIFAFU	5FU (TTD) CPT11	LV5FU2 CPT11	FOLFIRI 1
Subjects (*n*)	17	85	30	40
Neutropenia	31.0	21.0	20.0	7.5
Febrile neutropenia	0	1.0	6.0	0
Anaemia	6.0	4.0	0	0
Thrombopenia	6.0	1.0	3.0	0
Diarrhoea	6.0	18.0	24.0	15.0
Nausea/vomiting	6.0	6.0	13.0	7.5
Stomatitis	ND	2.0	0	5.0
Asthenia	ND	13.0	10.0	15.0
Toxic deaths	0	2.3	3.3	2.5

ND not done

Therapy regimens:

FOLFIRI 1 irinotecan 180 mg/m^2 (90-min infusion) on day 1, folinic acid 400 mg/m^2 (2-h infusion), 5FU 400 mg/m^2 (iv bolus) followed by 5FU 2,400 mg/m^2 (46-h infusion) every 2 weeks

IRIFAFU irinotecan 200 mg/m^2 iv (1-h infusion) on day 1, folinic acid 250 mg/m^2 iv (1-h infusion) plus 5FU 850 mg/m^2 iv bolus on day 2 every 2 weeks

5FU (TTD) CPT11 irinotecan180 mg/m^2 (30-min infusion) plus 5FU 3,000 mg/m^2 in a 48-h continuous infusion every 2 weeks

LV5FU2 CPT11 irinotecan 180 mg/m^2 (90-min infusion) on day 1, folinic acid 200 mg/m^2 (2-h infusion), 5-FU 400 mg/m^2 (iv bolus) followed by 600 mg/m^2 (22-h infusion) given on days 1 and 2 every 2 weeks

regimen in subjects with a history of cardiovascular disease, even if the pathology seems to be controlled. Haematological toxicities were not significant as only three patients (7.5%) presented with grade 3/4 neutropenia and none presented febrile neutropenia. Selection of the therapeutic regimen probably explains this good tolerance as the FOLFIRI 1 regimen results in fewer cases of neutropenia than the LV5FU2–irinotecan regimen [11] in initial tests in younger subjects. In elderly subjects, a comparison of grade 3/4 neutropenia rates shows that the rate varies greatly from one study to another, ranging from 7.5% to 31% [19–21] (Table 3). The use of 5FU by continuous infusion thus reduces the risk of neutropenia and, therefore, of infection. It allows haematopoietic growth factors to be used only in the management of chemotherapy-induced neutropenia and thus reduces the cost of treatment. Analysis of other series confirms the low risk of platelet or erythrocyte disorders [19–21].

In conclusion, the results of our study confirm the feasibility in advanced colorectal cancer of irinotecan-based polychemotherapy in patients aged at least 70 years in good general condition. Results in patients selected in terms of efficacy of and tolerance to FOLFIRI 1 are similar to those previously published. The systematic use of geriatric evaluation in this population will enable patient care to be further improved.

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