Weekly Irinotecan Plus Protracted Venous Fluorouracil Infusion (WI-FI) in Advanced Colorectal Cancer: A Phase II Study

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Abstract. *Background: Irinotecan (IRI) is a topoisomerase I inhibitor active as first- or second-line chemotherapy in advanced colorectal cancer (ACRC). Its combination with fluorouracil (FU) increases the response rate and prolongs survival. In order to identify a new effective and less toxic schedule of administration, we planned this phase II study with weekly IRI and protracted venous infusion of FU (WI-FI regimen). The primary endpoint was the objective response rate. Secondary aims were to detect toxicity, progression-free survival (PFS) and overall survival (OS) of patients (pts). Materials and Methods: On May 2000, a monoinstitutional study commenced with the following schedule of administration: IRI 80 mg/m² on days 1, 8, 15, 22, 29 plus a 28-day protracted venous infusion of FU 200 mg/m²/day. The treatment was repeated every 35 days. Cycles were administered until a maximum of 6 courses, disease progression or unacceptable toxicity. Results: By March 2005, 52 patients (30 males and 22 females) had entered the study. Their median age was 61.5 years and the median ECOG PS was 1. In total, 223 courses were administered (median 5 cycles/patient). Toxicity was low: neutropenia G3 and asthenia G3 were the most observed toxicities (5 pts each). No other grade 3-4 toxic side-effects were seen. Weekly IRI was interrupted in 11 pts, mostly related to problems with the central venous catheter. Following RECIST criteria, we observed 5 complete responses, 15 partial responses, 17 pts had stable disease, while in 15 disease progressed. The overall response rate was 38.5% and the disease control rate was 71.2%. Thirteen pts underwent surgical resection of their relapsing disease. The median PFS was 8.2 months and the median OS was 16.3 months. Conclusion: The WI-FI regimen is an active treatment with a good safety profile in patients with CRC. The low incidence of grade 3-4 toxicities justifies further evaluation of this combination.*

Worldwide, colorectal cancer is the fourth most commonly diagnosed malignant disease, with one million new cases and 500,000 deaths each year. The incidence varies according to geographic location. In Europe, incidence is close to 50 cases/100,000. Approximately 70% of these cancers arise in the colon, whereas 30% occur in the rectum. A half of all patients develop locally recurrent and/or metastatic disease (1, 2).

For four decades, fluorouracil (FU), modulated and administered in different ways, has been the only drug available both for adjuvant and palliative treatment. In the latter setting, FU modulated with folinic acid (FA) achieves a tumor response in approximately 20% of patients and prolongs median survival from about 6 to 11 months (1-3).

In the last ten years, new drugs, both cytotoxic and molecular targeted, were introduced with success in the palliative setting. The availability of many active compounds and the possibility to combine them variously has moved prognosis from 11 to over 20 months. Better results are evident when patients are treated with these drugs, although currently the best way to combine and sequence them is not yet clear and is the subject of considerable and continuous interest and investigation (3-6).

Fluorouracil is still the fundamental component of the most efficacious regimens. FU has a short half-life in humans (20±4.6 minutes). Bolus infusion of FU, modulated with FA, is more toxic and seems less effective than protracted venous infusion (7-14). A meta-analysis comparing FU infusion with bolus administration showed an improved response rate (22% *vs.* 14%; *p*=0.0002) and a slight improvement in survival (*p*=0.04) with a decreased incidence of hematological toxicity but a higher frequency

of hand-foot syndrome (13-14). Lokich *et al.* introduced the concept of protracted nonstop FU venous infusion in 1989 at the dose of 300 mg/m^2/day with an overall response rate of 38% (15). Maughan *et al.* compared the Lokich schedule with the de Gramont scheme in a large randomized trial. The overall response rate was 25% for Lokich and 23% for de Gramont, with a median survival of 302 and 294 days, respectively; these differences were not statistically significant (12).

Irinotecan (IRI) is an S-phase-specific derivative of camptothecin which interferes with DNA replication and cell division by inhibiting topoisomerase-I (16). Irinotecan administered alone, at the dose of 350 mg/m^2 every 3 weeks, has demonstrated antitumor activity against metastatic colorectal cancer when used as second-line treatment after the failure of FU, with an overall response rate of 13%. In randomized trials, second-line IRI has been able to significantly extend survival when compared with best supportive care or infusional FU (17-18). Adverse events most frequently recorded at this dose were neutropenia, acute cholinergic syndrome, fatigue, nausea and vomiting, delayed diarrhea and alopecia (17). The mechanism of action and single agent efficacy of IRI, combined with the apparent absence of any cross resistance with FU provided the rationale for combining IRI with FU and FA as the firstline therapy for metastatic colorectal cancer (18).

Irinotecan has thus been tested in combination with most important infusional FU/FA schedule at different dosages and different intervals of administration. Vanhoefer *et al.* tested IRI in a weekly setting in combination with the AIO German FU/FA schedule in a phase I study. They reached the maximum tolerated dose (MTD) of weekly IRI at 100 mg/m^2 and recommended further studies with a lower dose (80 mg/m^2) (19). Ducreux combined IRI with the FU/FA de Gramont schedule and defined the recommended bimonthly dose of IRI at 180 mg/m^2 (20). In a large phase III study by Douillard *et al.* this combination was statistically superior to the de Gramont regimen alone in terms of response rate (34.8% *vs.* 21.9%), time to progression (TTP) (6.7 *vs.* 4.4 months) and survival (17.4 *vs.* 14.1 months) (21). From that time, that IRI combination with FU/FA significantly increases response rates, TTP and survival in patients with metastatic colorectal cancer has become more evident (22-24).

Following these studies of IRI in combination with different FU/FA regimens, we conducted a phase II study designed to evaluate the activity and safety of weekly IRI with protracted venous infusion of FU (WI-FI schedule) as first-line chemotherapy in patients with advanced colorectal cancer (ACRC). The primary endpoint was response rate. Secondary aims were to detect toxicities, progression-free survival (PFS) and overall survival (OS) of all the treated patients.

Patients and Methods

On May 2000, a mono-institutional study with weekly IRI and FU infusion (WI-FI) commenced. The schedule of administration was: IRI 80 mg/m^2 on days 1, 8, 15, 22, 29 plus a 28-day protracted venous infusion of FU 200 mg/m^2/day. The treatment was repeated every 35 days. Cycles were administered until a maximum of 6 courses, progression of the disease, unacceptable toxicity or patient refusal. Granisetron at 3 mg in 100 ml of 0.9% saline solution was administered before the infusion of IRI. Irinotecan was administered in 250 ml of 0.9% saline solution by an intravenous infusion pump over 30 minutes, followed by FU given by a mechanical pump in a 7-day protracted infusion.

Only patients with a histologically confirmed diagnosis of adenocarcinoma of the colon or rectum with at least one measurable lesion and no potentially resectable metastasis were recruited into the study. Other inclusion criteria were: age between 18 and 75 years, previously untreated or pretreated with only first-line chemotherapy not including IRI or protracted infusion of FU. Only patients treated with prior adjuvant radiotherapy were enrolled. No concomitant radiotherapy for advanced disease was allowed. Patients needed to have a good performance status (ECOG PS equal to or less than 2) and a life expectancy of more than three months and no current uncontrolled medical illness. Adequate organ function was required: white blood cell (WBC) count ≥4×10^9/l, neutrophils ≥2×10^9/l, platelets ≥100,000×10^9/l, hemoglobin ≥10×g/dL, serum creatinine ≤1.2 mg/dl, serum transaminase levels ≤2 times the upper normal limit, total bilirubin ≤1.5 times the upper normal limit. Patients with a history of myocardial infarction or angor, other malignancies, intracerebral metastases and psychological conditions precluding informed consent were excluded from the treatment.

The study was approved by the local Ethical Committee and was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided a written informed consent before starting chemotherapy.

Every patient had a central venous catheter inserted at least one week before the beginning of chemotherapy. Pretreatment evaluation consisted of a complete medical history and physical examination, complete blood cell count, serum biochemistry including electrolytes, renal and liver functions and CEA. Chest x-ray and computed tomography (CT) scan of the abdomen and pelvis were performed at baseline. A CT scan of chest was carried out only in the presence or in suspicious of pulmonary metastatic disease. All sites of disease were documented by CT scan before starting chemotherapy.

Complete blood cell count, serum biochemistry, electrolytes, creatinine and liver function were monitored weekly in order to detect toxicities. Physical examination was performed every two weeks. Patients were evaluated every two cycles with CT scan of target lesions. When a progression of the tumor was detected, the treatment was stopped and the patient was evaluated for receiving either another different chemotherapy or best supportive care.

After the completion of therapy, in cases of complete response (CR), partial response (PR) and stable disease (SD), during the follow-up period complete blood cell count, serum biochemistry including electrolytes, renal and liver functions, CEA, chest X-ray and CT scan of the abdomen and pelvis were performed every two months until disease progression.

Toxicities were recorded according to the NCI-CTC grade scale (25). In cases of toxicities not permitting the regular administration

Table I. *Patient characteristics*.

Characteristic	No. (N=52)	%
Gender		
Male	30	57.7
Female	22	42.3
Age (years)		
Median	61.5	
Range	18-75	
Performance status (ECOG)		
0	22	42.3
1	17	32.7
2	13	25.0
Primary tumor		
Colon	39	75.0
Rectum	13	25.0
Site of metastatic disease		
Liver	37	71.5
Lung	12	23.1
Peritoneum	11	21.5
Lymph nodes	6	11.5
Local relapse	5	9.6
Ovary	1	1.9
Number of metastatic sites		
1	26	50.0
2	14	26.9
>2	12	23.1
Prior therapies		
Surgery	30	57.7
Adjuvant chemotherapy	19	36.5
Adjuvant radiotherapy	11	21.2

Table II. *Main toxicities*.

Toxicity	Grade 2		Grade 3	
	No.	%	No.	%
Fatigue	37	71.2	5	9.6
Nausea & vomiting	27	51.9		
Diarrhoea	24	46.2		
Neutropenia	23	44.2	5	9.6
Hand-foot syndrome	6	11.6		
Acute cholinergic syndrome	3	5.8		

Table III. *Toxicities that caused a delay in chemotherapy (50 episodes)*.

Toxicity	No. episodes	%
Neutropenia	21	42
Nausea & vomiting	8	16
Diarrhoea	6	12
Hand-foot syndrome	6	12
Dysfunction of central venous catheter	4	8
Fatigue	3	6
Other	2	4

of the courses of chemotherapy, the treatment was delayed for one week. A 20% dose reduction was allowed only in cases of mild but persistent toxicity.

Tumor response was assessed according to RECIST criteria as CR, PR, SD or progressive disease (PD) (26). The overall response rate was defined as the percentage of patients with CR or PR. The disease control rate was defined as the percentage of patients with CR, or PR, or SD. Progression-free survival was the time from the beginning of treatment to the documented progression of the disease and OS as the time from the beginning of treatment to the patient's death.

To define the sample size, the Minimax two-stage Simon design for phase two clinical trials was utilised. For an alpha error of 0.05 and a beta error of 0.10, the total number of patients to be recruited was 45 (27). Survival was estimated by the Kaplan-Meier method and the confidence interval for overall response rate and disease control rate were calculated using methods for exact binomial conferences intervals (CIs). The software employed was SYSTAT® version 10 (SPSS Inc., Chicago, IL, USA) for Windows™.

Results

From June 2000 until December 2004, we enrolled 52 consecutive patients (22 females and 30 males) with ACRC according to eligibility criteria. The median age of the patients was 61.5 years (mean 58.2 and range 18-75 years)

and median performance status according ECOG was 1. Thirty-nine patients (75%) had a primary colon carcinoma and 13 had a rectal cancer. The site of metastatic disease was mostly the liver (37 patients, 71.5%). Patients' characteristics and disease sites are summarized in Table I.

A total of 223 courses of chemotherapy were administered (median 5 courses, mean 4.29, range 1-6). All patients were evaluable for response and toxicity and the response rate was determined according to the intention to treat (ITT) aim.

Grade 3 neutropenia and fatigue were the most important toxicities recorded, both involving 5 patients. All grade 2 and 3 toxicities are summarized in Table II. On 50 occasions; chemotherapy courses had to be delayed for a week mainly for neutropenia. Table III represents the more important causes of treatment delay. Eleven patients had a definitive interruption of chemotherapy: 4 because of problems related to the management of the central venous catheter, 2 on the patient's decision, 2 for early PD and in 1 case each for bowel obstruction, acute cholinergic syndrome and for unacceptable fatigue.

Assessments of response were carried out every two courses of therapy. We recorded 5 CR (9.6%) and 15 PR (28.8%) with an overall response rate of 38.5% (95% C.I. 25% to 52%). Moreover, we had 17 patients with SD (32.7%) and 15 patients with PD (28.8%) for a disease control rate of 71.2% (95% C.I. 58% to 84%).

Thirteen patients (25%), previously judged inoperable, underwent surgical resection for their recurrent disease. Nine

Table IV. *Response rate in an intention-to-treat analysis.*

Response characteristics	No.	%
Complete response	5	9.6
Partial response	15	28.8
Stable disease	17	32.7
Progressive disease	15	28.8
Overall response rate	20	38.5 (95% CI 25-52%)
Disease control rate	37	71.2 (95% CI 58-84%)

CI: Confidence interval.

Figure 1. *Kaplan-Meier curves for overall survival and progression-free survival.*

patients were operated for metastases of the liver, 3 of lung and 1 for combined lung and liver metastases. In only 10 cases was resection considered macroscopically radical. The response rate following intention-to-treat are summarized in Table IV.

With a median follow-up period of 21 months, we detected a median PFS of 8.2 months (95% C.I. 6.1 to 10.1 months) and an OS of 16.3 months (range 4-58 months, 95% C.I. 14.8 to 17.9 months). Figure 1 shows the PFS and OS curves. Progression-free survival and OS for responders were 15.0 and 27.9 months respectively. Examining only the subgroup of patients who underwent surgical resection of their metastatic disease, the OS was 31.8 months. At the time of writing, two patients are alive without signs of recurrence at more than 6 years from the beginning of the treatment.

Discussion

The present study indicates that the WI-FI schedule is an active and well-tolerated combination for the treatment of patients with metastatic colorectal cancer. The response rate, the primary endpoint of this study, was 38.5%. Data from the literature report a response rate between 35% and 56% when results are expressed following the intention to treat (21, 28-31). The differences are probably the result of different patient selection. In our series, we included a good number of patients having an ECOG performance status of 2 that better represents the general population at the time of first relapse of colorectal tumor. The 5 patients who had a complete response all had disease limited to the liver. Thus resection was judged not feasible before therapy started; 13 patients underwent surgical resection for their metastatic disease after 4 to 6 courses of chemotherapy. Despite Vauthey *et al*. demonstrating a significant relationship between IRI therapy and morbidity and mortality after liver resection, our patients had no life-threatening post-surgical complications (32). The percentage (25%) of patients treated with the WI-FI regimen and subsequently operated
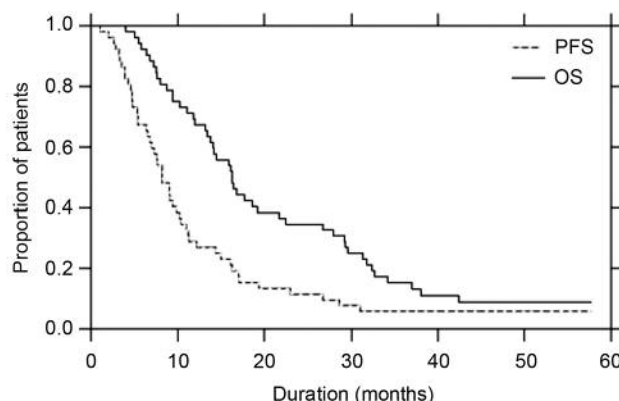
on is slightly higher than what would be expected. It will be interesting to match our schedule with one of the new biological target drugs which have been demonstrated to enhance the efficacy of traditional chemotherapies, in particular in increasing rates of operability (33-35).

The toxicity profile of the WI-FI regimen was mild. No grade 4 toxicities were recorded. Grade 3 neutropenia was the most important hematological side-effect, involving 9.6% of patients; it was also the most frequent reason for one-week delays of chemotherapy (21 episodes). Unexpectedly, the most important nonhematological side-effect was grade 3 fatigue (9.6% of patients). The finding that no patient developed grade 3 diarrhea, nausea, vomiting or acute cholinergic syndrome is highly significant. Despite this low toxicity profile, confirmed by the evidence that the median number of courses administered was 5, 11 patients interrupted the treatment early. Four of them had problems related to the management of the central venous catheter: in three cases the patient developed a deep venous brachial or jugular thrombosis and in one the venous catheter ruptured. In this latter case, the subsequent procedures to recover the broken part induced the patient to decide to stop the treatment. In our opinion, the problems with the venous catheters are a field in which the substitution of the protracted infusion of FU with oral fluoropyrimidine could result in better cost effectiveness (36). However, the recent data from the BICC-C study, a randomized trial comparing the standard FOLFIRI regimen to IRI and bolus FU/FA (IFL regimen) and to an association of IRI plus capecitabine, reports the control arm to be superior in terms of response rate, PFS and OS with a better toxicity profile. This study can reaffirm the importance of the infusional FU-based therapies even in the era of oral fluoropyrimidines (37).

An 8.2-month median PFS is exactly what we expected from the literature, although the median survival was slightly inferior (21, 28-31).

Finally, this study demonstrates that the WI-FI combination is well tolerated and could be proposed as an effective first- as well as second-line treatment for ACRC. In our opinion, it represents a valid alternative to the common IRI and FU/FA combination regimens and we think that future study could focus on the association of the WI-FI regimen with biological target drugs.

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