Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial

J Y Douillard, D Cunningham, A D Roth, M Navarro, R D James, P Karasek, P Jandik, T Iveson, J Carmichael, M Alakl, G Gruia, L Awad, P Rougier

Summary

Background Irinotecan is active against colorectal cancer in patients whose disease is refractory to fluorouracil. We investigated the efficacy of these two agents combined for first-line treatment of metastatic colorectal cancer.

Methods 387 patients previously untreated with chemotherapy (other than adjuvant) for advanced colorectal cancer were randomly assigned open-label irinotecan plus fluorouracil and calcium folinate (irinotecan group, n=199) or fluorouracil and calcium folinate alone (no-irinotecan group, n=188). Infusion schedules were once weekly or every 2 weeks, and were chosen by each centre. We assessed response rates and time to progression, and also response duration, survival, and quality of life. Analyses were done on the intention-to-treat population and on evaluable patients.

Findings The response rate was significantly higher in patients in the irinotecan group than in those in the no-irinotecan group (49 *vs* 31%, p<0·001 for evaluable patients, 35 *vs* 22%, p<0·005 by intention to treat). Time to progression was significantly longer in the irinotecan group than in the no-irinotecan group (median 6·7 *vs* 4·4 months, p<0·001), and overall survival was higher (median 17·4 *vs* 14·1 months, p=0·031). Some grade 3 and 4 toxic effects were significantly more frequent in the irinotecan group than in the no-irinotecan group, but effects were predictible, reversible, non-cumulative, and manageable.

Interpretation Irinotecan combined with fluorouracil and calcium folinate was well-tolerated and increased response rate, time to progression, and survival, with a later deterioration in quality of life. This combination should be considered as a reference first-line treatment for metastatic colorectal cancer.

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Centre René Gauducheau, 44805 Saint Herblain, France (J Y Douillard MD)**; Royal Marsden Hospital, London, UK** (D Cunningham MD)**; Hospital Cantonal, Geneva, Switzerland** (A D Roth MD)**; Hospitale Duran y Reynals, Barcelona, Spain** (M Navarro MD)**; Maidstone Hospital, Barming, UK** (R D James MD)**; Masaryk Memorial Cancer Institute, Brno, Czech Republic** (P Karasek MD)**; University Hospital, H Kralove, Czech Republic** (P Jandik MD)**; Royal South Hants Hospital, Southampton, UK** (T Iveson MD)**; City Hospital, Nottingham, UK** (Prof J Carmichael MD)**; Rhône Poulenc, Rorer, France** (M Alakl MD, G Gruia MD, L Awad MSc)**; and Hospital A Paré, Boulogne, France** (Prof P Rougier MD)

Correspondence to: Dr J Y Douillard

Introduction

Standard therapy for metastatic colorectal cancer is fluorouracil, commonly modulated by calcium folinate, which typically yields a median survival time of 10–14 months.[1,2] Fluorouracil can be used as first-line or second-line therapy and a different regimen of fluorouracil can be administered as second-line treatment if first-line treatment fails. Survival time in these patients is typically short. Quality of life in patients receiving this treatment is generally poor.[3–10]

Irinotecan inactivates topoisomerase I and thereby inhibits cell division.[11–13] The drug has no cross-resistance with fluorouracil and functions via a novel molecular mechanism.[14] Phase III studies of patients whose disease had not responded to first-line fluorouracil, or patients whose disease had progressed after first-line fluorouracil treatment, showed increased survival times in patients given irinotecan compared with those receiving best supportive care[15] or high-dose fluorouracil and calcium folinate alone by continuous infusion.[16] Data suggest that the development of well-tolerated regimens that combine irinotecan and high-dose fluorouracil and calcium folinate may be beneficial in the first-line treatment of colorectal cancer.

Phase I dose-escalation studies were done to test combined irinotecan with fluorouracil and calcium folinate weekly or every 2 weeks.[17,18] These regimens were selected for first-line treatment of advanced colorectal cancer, based on promising antitumour efficacy and an acceptable safety profile. The choice of regimen was left to investigators, according to local clinical practice, since the two regimens are widely used in Europe. The irinotecan combination and fluorouracil and calcium folinate alone were expected to differ by similar magnitudes in each regimen. Analysis of pooled data for efficacy showed that irinotecan gave a significant survival advantage.

We did a phase III multicentre randomised trial that was designed to assess whether the addition of irinotecan to fluorouracil and calcium folinate would benefit patients previously untreated with chemotherapy (other than adjuvant) for metastatic colorectal cancer.

Methods

Patients

From May, 1997, to February, 1998, we enrolled patients who met the following eligibility criteria: histologically proven adenocarcinoma of the colon or rectum; age 18–75 years; WHO performance status of 2 or less and life expectancy of more than 3 months; haemoglobin 100 g/L or more; absolute neutrophil count $2{\cdot}0\times10^9$/L; platelets 150×10^9/L or more; creatinine 1·25 or less times the upper limit of normal; total bilirubin 1·25 or less times the upper limit of normal; aspartate aminotransferase and alanine aminotransferase 3·0 or less times the upper limit of normal (if liver metastases present, 1·5 or less times for bilirubin and 5·0 or less times for aspartate and alanine

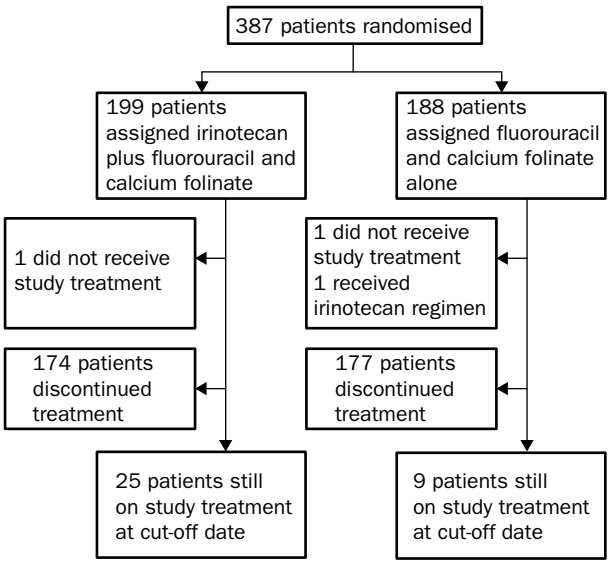

Figure 1: **Trial profile**

aminotransferases); and no previous (other than adjuvant) chemotherapy, finished more than 6 months before randomisation. We obtained written informed consent from each patient before enrolment. Approval was obtained from the ethics committee of each participating centre.

Patients with the following criteria were not eligible: central-nervous-system metastasis, unresolved bowel obstruction or diarrhoea, and known contraindications to fluorouracil (angina pectoris, myocardial infarction in the past 6 months).

Study design

We did the trial in 13 European countries, Israel, and South Africa. We randomly assigned patients irinotecan combined with fluorouracil and calcium folinate (irinotecan group) or fluorouracil and calcium folinate only (no-irinotecan group, figure 1). Randomisation was done centrally in the study sponsor's office by a computer-generated random scheme, and was stratified by centre. Before the start of the study, each investigator chose one of two proposed regimens for fluorouracil and calcium folinate, according to local clinical practice or preference (De Gramont [every 2 weeks] or Arbeitsgemeinschaft Internische Onkologie, cooperative German group for oncology [once weekly]). These regimens were used for combined treatment and fluorouracil and calcium folinate alone.

For the irinotecan group, the regimens were: once weekly, irinotecan 80 mg/m^2 with fluorouracil 2300 mg/m^2 by 24 h infusion, plus calcium folinate 500 mg/m^2 (n=54); or, every 2 weeks, irinotecan 180 mg/m^2 on day 1 with fluorouracil 400 mg/m^2 bolus and 600 mg/m^2 by 22 h infusion, plus calcium folinate 200 mg/m^2 on days 1 and 2 (n=145). For the no-irinotecan group, the regimens were: once-weekly, fluorouracil 2600 mg/m^2 by 24 h infusion plus calcium folinate 500 mg/m^2 (n=43); or every 2 weeks, fluorouracil and calcium folinate at the same doses and administration as in the irinotecan-group 2-weekly regimen (n=143).

Treatment was given until disease progressed, the patient developed unacceptable toxic effects, or consent was withdrawn. Irinotecan was administered according to the guidelines used for irinotecan monotherapy, including recommendations for the use of concurrent antiemetics, atropine, and loperamide. We lowered doses for irinotecan and fluorouracil by 20% if severe toxic effects occurred. At the end of the treatment period, patients were followed up for progression every 3 months. Further cancer treatment was also recorded. During the follow-up period, we traced any continuing adverse effects related to the study treatment until resolution.

Our primary endpoint was response rate. The secondary endpoints for efficacy were time to progression, duration of response, time to treatment failure, and overall survival. Time to progression was the time from randomisation to progression. The duration of response was the time from first infusion to progression in responding patients. The duration of response and stabilisation was the time from first infusion to progression in responding and stable patients. The time to treatment failure was the time from randomisation to treatment discontinuation or progression of disease, whichever came first. Survival lasted from the date of randomisation to the date of death.

Characteristic	Irinotecan group (n=198)	No-irinotecan group (n=187)
Demography		
Male/female	132 (66·7%)/66 (33·3%)	99 (52·9%)/88 (47·1%)
Median (range) age (years)	62·0 (27·0–75·0)	59·0 (24·0–75·0)
WHO performance status		
0	102 (51·5%)	96 (51·3%)
1	83 (41·9%)	77 (41·2%)
2	13 (6·6%)	14 (7·5%)
Weight loss >5%	49 (24·7%)	44 (23·5%)
Number of organs involved		
1–2	169 (85·3)	170 (90·9%)
⩾3	29 (14·6%)	17 (9·1%)
Sites of disease		
Liver	152 (76·8%)	149 (79·7%)
Liver alone	89 (44·9%)	93 (49·7%)
Liver plus other sites	63 (31·8%)	56 (29·9%)
Lung	52 (26·3%)	43 (23·0%)
Lymph nodes	28 (14·1%)	24 (12·8%)
Peritoneum/retroperitoneum	20 (10·1%)	22 (11·8%)
Other sites	47 (23·7%)	38 (20·3%)
Time-related variables		
Median (range) time from first metastasis to randomistaion (months)	1·4 (0–67·2)	1·6 (0–91·6)
Median (range) time from first diagnosis to first metastasis (months)*	18·9 (3·4–87·2)	21·1 (3·4–102·7)
0–3	110 (55·6%)	121 (64·7%)
3–12	22 (11·1%)	14 (7·5%)
>12	66 (33·3%)	52 (27·8%)
Before treatment		
Synchronous metastases†	110 (55·6%)	121 (64·7%)
Previous adjuvant chemotherapy	51 (25·8%)	44 (23·5%)
At least one tumour-related symptom at baseline	95 (48·0%)	96 (51·3%)
At least one abnormal laboratory value at baseline	177 (89·4%)	157 (84·0%)
CEA >10 ng/mL	144 (72·7%)	128 (68·4%)
Alkaline phosphatase >ULN	89 (44·9%)	75 (40·1%)
Lactase dehydrongenase >ULN	68 (34·3%)	70 (37·4%)

CEA=carcinoembryonic antigen; ULN=upper limit of local laboratory reference range.
*In patients without synchronous metastases. †⩽3 months between first diagnosis and first metastasis.

Table 1: **Patients' characteristics at baseline**

Responses were assessed after each treatment cycle, according to WHO criteria. For the weekly regimen, each treatment cycle was 7 weeks and for the 2-weekly regimen, 6 weeks. Tumours were assessed by an external response-review committee, which was masked to treatment group.

We also assessed quality of life. We used the validated QLQ-C30 questionnaire of the European Organization for Research and Treatment of Cancer. The questionnaire includes five scales for functioning, one scale for global health status, and nine symptom scales.[19] Patients completed questionnaires before each cycle (every 6–7 weeks).

Statistical analysis

We needed to include 338 evaluable patients to show a significant difference in response rate between treatment groups, assuming response rates of 35% in the no-irinotecan group and 50% in the irinotecan group, by use of two-tailed χ^2 tests (α=0·05, power 0·80).

Based on the assumption that time to progression would be 6 months in the no-irinotecan group and 9 months in the irinotecan group, we calculated that 286 patients were needed to show a significant difference for this variable. For analysis by two-

	Evaluable population (n=338)		Intention-to-treat population (n=385)	
	Irinotecan group (n=169)	No-irinotecan group (n=169)	Irinotecan group (n=198)	No-irinotecan group (n=187)
Complete reponse	6 (3·6%)	0	6 (3·0%)	0
Partial response	63 (37·3%)	39 (23·1%)	63 (31·8%)	41 (21·9%)
Overall response*	69 (40·8%)	39 (23·1%)	69 (34·8%)	41 (21·9%)
Stable disease	64 (37·9%)	84 (49·7%)	70 (35·4%)	86 (46·0%)
Progressive disease	36 (21·3%)	46 (27·2%)	38 (19·2%)	49 (26·2%)
Not evaluable	0	0	21 (10·6%)	11 (5·9%)

*p<0·001 in evaluable population and p=0·005 in intention-to-treat population.

Table 2: **Response rates**

tailed log-rank test (α=0·05, power of 0·80), with the assumption that accrual and minimum follow-up would last for 6 months and 9 months, respectively, we had to include 143 patients in each treatment group.[20] To accommodate an anticipated 5% loss of patients to follow-up, we planned to include at least 151 patients in each group (total 302).

We analysed the intention-to-treat population and calculated response rates for the intention-to-treat and evaluable populations. χ^2 tests were used to compare categorical variables between treatment groups. For continuous variables, we used Student's *t* tests. We estimated survival curves by the Kaplan-Meier method, and compared the two groups by the log-rank test. We tested for interaction between treatment and regimen by log-rank tests and, additionally, we did a log-rank test stratified by regimen. We constructed a country variable by separating the countries into three classifications, according to the number of patients included. The first group included countries that had recruited more than 30 patients (UK, Spain, France, Czech Republic, Germany, and Austria), the second countries that had recruited 10–30 patients (Belgium, Israel, South Africa, Switzerland, and Italy), and the third countries that had recruited fewer than ten patients (Greece, Portugal, and the Netherlands). We did log-rank tests stratified by this variable.

Multivariate analyses were done on the intention-to-treat population. A logistic-regression model was used to identify the prognostic factors for response. We tested the nine following variables: sex, WHO performance status (<2 and ≥2), weight loss (≤5% and >5%), number of organs involved (<3 and ≥3), primary tumour site (colon or rectum), organ involvement (liver only or other sites), time from first diagnosis to first metastasis (0–3, >3–12, >12 months), previous surgery, and previous adjuvant therapy. For time to progression, Cox's proportional hazards modelling was used, with the following variables: sex, age (<58 and ≥58 years), WHO performance status (<2 and ≥2), weight loss (≤5% and >5%), number of organs involved (<3 and ≥3), primary tumour site (colon or rectum), liver involvement, lymph-node involvement, time from first diagnosis to first metastasis (0–3, >3–12, >12 months), previous surgery, previous adjuvant therapy, time from first diagnosis and first infusion (<9 and ≥9 months). We based the selection of models of prognostic factors on a forward stepwise procedure, with the treatment being forced in the model. To enter and remove terms in the model we used p=0·08 and p=0·10, respectively.

The QLQ-C30 questionnaaire was analysed with the global health status/QoL scale (QL) as the primary endpoint and the other 14 scales as secondary endpoints.

Repeated-measure mixed analysis of variance was used to compare the two treatment groups, treatment and time×treatment being considered as the fixed effects, with time window as a repeated factor and patients as a random factor. To assess the potential bias induced by missing data, we did the same analysis after use of two data-imputation methods, based on the identified reason for data being missing. In each of the methods, dead patients' missing data were imputed as zero scores. Missing data concomitant to grade 3 or 4 adverse events were imputed as the mean of the worst scores from patients with grade 3 or 4 adverse events. In the first imputation method, missing data after progressive disease were imputed as the mean worst scores from progressive patients, and in the second method the last value of the progressive patients was carried forward.

The time to definitive deterioration from baseline by 5%, 10%, 20%, and 30% was analysed by the Kaplan-Meier method. We used log-rank tests to compare the two groups.

Results

Patients and treatment

387 patients were randomly assigned treatment. 385 patients received at least one infusion. Two patients received no study treatment because consent was withdrawn. Of the 385 patients treated in the study, only 97 (25%) received treatment by the weekly regimen (54 in the irinotecan group and 43 in the no-irinotecan group). The other 288 patients received treatment every 2 weeks (145 in the irinotecan group and 143 in the no-irinotecan group).

Baseline demographic and pretreatment characteristics were similar in the two groups (table 1). A higher proportion of women were assigned fluorouracil and calcium folinate alone than the irinotecan regimen, and the rectum was the primary tumour site in a higher proportion of patients in the irinotecan group than in the no-irinotecan group.

Tumour characteristics and history in the two groups were comparable, except for previous surgery, since 89% of patients had had surgery in the irinotecan group and 95% in the no-irinotecan group. The frequency and profile of tumour-related symptoms and laboratory abnormalities were typical of advanced colorectal cancer and similar in the two groups.

The median duration of treatment was longer in the irinotecan than in the no-irinotecan group, irrespective of regimen (24·0 *vs* 21·0 weeks for the weekly regimen, 24·6 *vs* 18·0 for the 2-weekly regimen).

In the irinotecan group, the relative dose intensity was 0·82 for irinotecan and 0·81 for fluorouracil in the weekly regimen, and 0·93 and 0·92, respectively, in the 2-weekly regimen. In the no-irinotecan group, the relative dose intensity was 0·90 in the weekly regimen and 0·96 in the 2-weekly regimen.

39·4% of patients in the irinotecan group and 58·3% in the no-irinotecan group received further chemotherapy; 31·0% of the no-irinotecan group subseqently received irinotecan. Similar proportions of patients received further treatment with oxaliplatin in the two groups (15·7 *vs* 12·8%).

Efficacy

In the evaluable population, the response rate was 49% in the irinotecan group, compared with 31% in the no-irinotecan group (p<0·001). The confirmed responses (after 6–7 weeks) resulted in response rates of 41% (95%

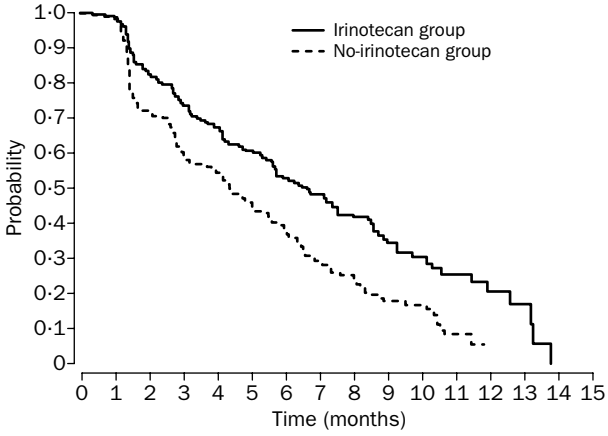

Figure 2: **Time to progression**

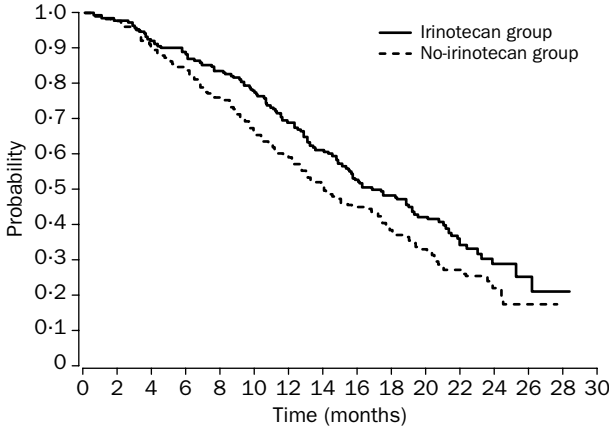

Figure 3: **Survival**

CI 33·3–48·6) and 23% (17·0–30·2), respectively. In the intention-to-treat population, response rate was also significantly higher in the irinotecan group than in the no-irinotecan group (34·8 [28·2–41·9] *vs* 21·9% [16·2–28·5], p=0·005; table 2). The median time to onset of response was 8·9 (range 4·7–25·4) weeks in the irinotecan group and 11·4 (5·3–29·6) weeks in the no-irinotecan group.

The median duration of response was 9·3 (2·8–13·1) months in the irinotecan group and 8·8 (3·7–11·8) months in the no-irinotecan group (p=0·08). Duration of response and stabilisation was longer in the irinotecan group (8·6 [1·6–13·6] *vs* 6·2 [1·1–11·8] months, p<0·001). Time to progression was longer in the irinotecan than in the no-irinotecan group (median 6·7 [0+–13·8+] *vs* 4·4 [0+–11·8+] months, p<0·001; figure 2). The interaction between treatment and regimen was not significant. The log-rank test stratified by regimen and that stratified by country were significant (each p<0·001). Median follow-up was 23·3 (20·0–29·7) months.

Survival in the irinotecan group was significantly longer than in the no-irinotecan group (median 17·4 [0·4–28·4+] *vs* 14·1 [0·5–27·6+] months, p=0·031; figure 3). The probability of survival in the irinotecan group was 82·1% at 9 months and 69·1% at 12 months, and in the no-irinotecan group was 71·6% and 59·1%, respectively. The interaction between treatment and regimen was not significant. This finding supported the hypothesis that the difference in the two regimens would be similar in the two treatment groups and allowed the pooling of data. The log-rank test stratified by regimen was significant (p=0·03), as was that stratified by country (p=0·04).

There was insufficient power to compare the efficacy between groups in the weekly regimen because of the small number of patients who received this regimen. Intention-to-treat analyses showed that for the weekly regimen, the response rates in the irinotecan and no-irinotecan groups did not differ significantly (39·6 [95% CI 26·5–54·0] *vs* 25·0% [13·2–40·3]). Median time to progression was 7·2 (range 0+–13·8) months and 6·5 (0+–12·3+) months. The gradual decrease of the survival curves around 50% did not enable provision of an accurate estimation of the medians.[21] The probability of survival in the irinotecan group was 84·9% at 9 months and 75·5% at 12 months, and in the no-irinotecan group was 77·3% and 62·7%, respectively. In the intention-to-treat analysis of the 2-weekly regimen, the response rate was, for the irinotecan group and the no-irinotecan group, 33·1% (95% CI 25·5–41·4) and 21·0% (14·6–28·6, p=0·021); median time to progression was 6·5 (range 0+–13·2) months and 3·7 (0+–13·1+) months (p=0·001); and median survival was 17·4 (0·4–28·3+) months and 13·0 (0·5–27·6+) months. The log-rank test was significant (p=0·0098). The probability of survival in the irinotecan group was 81·0% at 9 months and 66·7% at 12 months, and in the no-irinotecan group was 69·8% and 54·8%, respectively.

Covariate	Parameter estimate	Wald χ^2	p	Hazard ratio (95% CI)
Treatment group				
No irinotecan				1·00
Irinotecan	0·780	9·558	0·002	2·18 (1·33–3·58)
Weight loss				
>5%				1·00
≤5%	0·804	6·829	0·009	2·23 (1·22–4·08)
Time between first diagnosis and first metastasis (months)				
>12				1·00
3–12	1·001	4·689	0·030	2·72 (1·10–6·73)
0–3	1·063	11·831	0·001	2·90 (1·58–5·31)

Table 3: **Logistic regression of predictive factors for response rate**

Covariate	Parameter estimate	Wald χ^2	p	Hazard ratio (95% CI)
Treatment group				
Irinotecan	. .	. .	. .	1·00
No irinotecan	0·522	15·731	<0·001	1·69 (1·30–2·18)
Number of organs involved				
<3	. .	. .	. .	1·00
≥3	0·443	5·776	0·016	1·56 (1·09–2·23)
Age (years)				
≥58	. .	. .	. .	1·00
<58	0·248	3·643	0·056	1·28 (0·99–1·65)

Table 4: **Cox's model for time to progression**

In the stepwise multivariate logistic regression (table 3), weight loss of 5% or less at baseline and time between first diagnosis and first metastasis were predictive of response. The effect of treatment was significant (p<0·001); the hazard ratio for response was 2·6 times higher in the irinotecan group than in the no-irinotecan group, given the same degree of weight loss at baseline and the same time between first diagnosis and first metastasis.

In Cox's multivariate analysis of time to progression (table 4), age and number of organs involved were significantly predictive. In patients younger than 58 years, the risk of progression increased by about 28%, all other variables being fixed. If three or more organs were involved, the risk of progression was increased by about 56%. The treatment effect was significant (p<0·001). The risk of progression for a patient in the no-irinotecan group

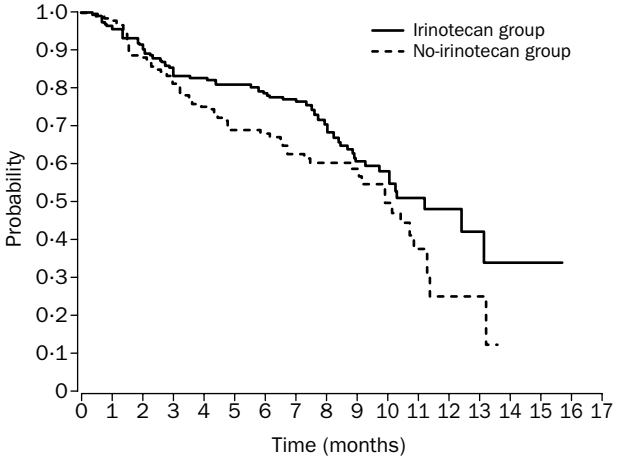

Figure 4: **Time to definitive deterioration in performance status**

Non-haematological toxic effects	Irinotecan group (n=145)		No-irinotecan group (n=143)		p*
	Total	Grade 3 or 4	Total	Grade 3 or 4	
Diarrhoea	48 (88·9%)	24 (44·4%)	28 (65·1%)	11 (25·6%)	0·055
Nausea	39 (72·2%)	4 (7·4%)	25 (58·1%)	2 (4·7%)	0·57
Vomiting	30 (55·6%)	6 (11·1%)	19 (44·2%)	2 (4·7%)	0·25
Asthenia	23 (42·6%)	4 (7·4%)	6 (14·0%)	· ·	0·068
Alopecia	20 (37·0%)	· ·	7 (16·3%)	· ·	. .
Anorexia	16 (29·6%)	4 (7·4%)	6 (14·0%)	1 (2·3%)	0·26
Mucositis	14 (25·9%)	· ·	15 (34·9%)	1 (2·3%)	0·26
Abdominal pain	12 (22·2%)	3 (5·6%)	1 (2·3%)	1 (2·3%)	0·47
Cholinergic syndrome	11 (20·4%)	1 (1·9%)	. .	· ·	0·37
Hand and foot syndrome	9 (16·7%)	· ·	17 (39·5%)	2 (4·7%)	0·11
Fever in absence of infection without concomitant grade 3–4 neutropenia	6 (11·3%)	· ·	4 (9·3%)	· ·	. .
Cutaneous signs	4 (7·4%)	· ·	4 (9·3%)	· ·	. .
Pain	4 (7·4%)	1 (1·9%)·	6 (14·0%)	1 (2·3%)·	0·87
Weight loss	4 (7·4%)	1 (1·9%)	· ·	· ·	0·37
Infection without concomitant grade 3–4 neutropenia	2 (3·7%)	· ·	2 (4·7%)	· ·	. .
Haematological toxic effects					
Anaemia	51 (94·4%)	3 (5·6%)	41 (97·6%)	. .	0·12
Neutropenia	37 (71·2%)	15 (28·8%)	9 (21·4%)	1 (2·4%)	0·001
Leukopenia	40 (74·1%)	11 (20·4%)	16 (38·1%)	1 (2·4%)	0·009
Fever in absence of infection with concomitant grade 3–4 neutropenia	5 (9·3%)	5 (9·3%)	1 (2·3%)	1 (2·4%)	0·16
Infection with concomitant grade 3–4 neutropenia	1 (1·9%)	1 (1·9%)	· ·	· ·	0·37

*Based on comparison of frequency of grade 3 or 4 toxic effects.

Table 5: **Patients with any adverse event and with grade 3–4 adverse events related to study treatment (weekly regimen)**

was increased by about 69% compared with that for a patient in the irinotecan group when all other variables were equal.

The median time to treatment failure was 5·3 (0·4–15·7+) months in the irinotecan group and 3·8 (0·4–11·5+) months in the no-irinotecan group (p=0·0014).

The time to definitive deterioration in performance status was significantly longer in the irinotecan group than in the no-irinotecan group (median 11·2 [0·1+–15·7+]) *vs* 9·9 [0+–13·6+] months, p=0·046; figure 4).

Safety

In the irinotecan group, diarrhoea and neutropenia were the most common toxic effects in each regimen, and were significantly more frequent and severe than in the no-irinotecan group.

For toxic effects that occurred at a frequency of 3% or higher, diarrhoea was the most frequent grade 3 or 4 non-haematological toxic effect in each of the treatment groups, irrespective of regimen. Grade 3 and 4 toxic effects occurring at a frequency of 3% or more are shown in tables 5 and 6. With the 2-weekly regimen, diarrhoea was more frequent in the irinotecan group than in the no-irinotecan group, and the difference was close to siginificance in the weekly regimen. This adverse effect occurred more frequently with the weekly than with the corresponding 2-weekly regimen in the two treatment groups. Among patients receiving the weekly regimen, diarrhoea led to hospital admission for 17 (31·5%) in the irinotecan group and five (11·6%) in the no-irinotecan group. For the 2-weekly regimen, 16 (11·0%) patients in the irinotecan group and two (1·4%) in the no-irinotecan group were admitted for diarrhoea. Diarrhoea was the main reason for dose reduction or discontinuation of treatment in the weekly regimen, and neutropenia was the main reason for dose delay in the 2-weekly regimen.

Grade 3 or 4 neutropenia and leukopenia were significantly more frequent in the irinotecan group than in the no-irinotecan group, irrespective of regimen. In the irinotecan group, admission was required for fever in the absence of infection with concomitant grade 3 or 4 neutropenia for five (9·3%) patients on the weekly regimen and one (0·7%) on the 2-weekly regimen; for the no-irinotecan group, admission was required for one (2·3%) patient on the weekly regimen and none on the 2-weekly regimen.

Asthenia was the second most frequent non-haematological toxic effect in the irinotecan group, and grade 3 or 4 asthenia was significantly more frequent in this group than in the no-irinotecan group for the 2-weekly regimen. Grade 3 or 4 infection without grade 3 or 4 neutropenia was significantly more frequent in the irinotecan group than in the no-irinotecan group. In the irinotecan group, about 25% of patients developed cholinergic syndromes that were rarely severe.

Doses were reduced because of toxic effects more frequently for the weekly regimen than for the 2-weekly regimen, and more in the irinotecan than in the no-irinotecan group. Doses were reduced in 29·6% of patients on the weekly regimen and 18·6% on the 2-weekly regimen in the irinotecan and no-irinotecan groups, respectively, and in 20·9% and 4·9% on the 2-weekly regimen.

Most dose reductions occurred during the first two cycles in the weekly regimen. One patient treated with the irinotecan combination on the 2-weekly regimen did not receive appropriate therapy for the management of diarrhoea and died early in the first cycle, probably because of septic shock concomitant with grade 4 neutropenia.

Despite the high frequency of side-effects, in the irinotecan group, the relative dose intensity was preserved compared with the no-irinotecan group.

Quality of life

1161 questionnaires were obtained from the 385 patients in the intention-to-treat population. The rate of return was similar in the two treatment groups—62% in the irinotecan group and 59% in the no-irinotecan group. The two groups did not differ significantly at baseline, except for cognitive function (mean 89·9 [SE 1·1] *vs* 86·1

Non-haematological toxic effects	Irinotecan group (n=54)		No-irinotecan group (n=43)		p*
	Total	Grade 3 or 4	Total	Grade 3 or 4	
Diarrhoea	99 (68·3%)	19 (13·1%)	55 (38·5%)	8 (5·6%)	0·028
Nausea	85 (58·6%)	3 (2·1%)	71 (49·7%)	2 (1·4%)	0·66
Alopecia	82 (56·6%)	· ·	24 (16·8%)	· ·	. .
Asthenia	65 (44·8%)	9 (6·2%)	50 (35·0%)	1 (0·7%)	0·011
Vomiting	60 (41·4%)	4 (2·8%)	40 (28·0%)	1 (0·7%)	0·18
Mucositis	56 (38·6%)	6 (4·1%)	41 (28·7%)	3 (2·1%)	0·32
Cholinergic syndrome	41 (28·3%)	2 (1·4%)	1 (0·7%)	· ·	0·16
Anorexia	25 (17·2%)	3 (2·1%)	9 (6·3%)	1 (0·7%)	0·32
Cutaneous signs	16 (11·0%)	1 (0·7%)	24 (16·8%)	· ·	0·32
Abdominal pain	14 (9·7%)	1 (0·7%)	7 (4·9%)	· ·	0·32
Hand and foot syndrome	13 (9·0%)	1 (0·7%)	18 (12·6%)	1 (0·7%)	0·99
Pain	12 (8·3%)	· ·	7 (4·9%)	1 (0·7%)	0·31
Fever in absence of infection without concomitant grade 3–4 neutropenia	9 (6·2%)	· ·	6 (4·2%)	1 (0·7%)	. .
Infection without concomitant grade 3–4 neutropenia	7 (4·8%)	4 (2·8%)·	5 (3·5%)	· ·	0·045
Weight loss	6 (4·1%)	2 (1·4%)	2 (1·4%)	· ·	0·16
Haematological toxic effects					
Anaemia	140 (97·2%)	3 (2·1%)	130 (90·9%)	3 (2·1%)	0·99
Neutropenia	118 (82·5%)	66 (46·2%)	68 (47·9%)	19 (13·4%)	0·001
Leukopenia	117 (81·3%)	25 (17·4%)	60 (42·0%)	5 (3·5%)	0·001
Fever in absence of infection with concomitant grade 3–4 neutropenia	5 (3·4%)	5 (3·4%)	1 (0·7%)	1 (0·7%)	0·10
Infection with concomitant grade 3–4 neutropenia	3 (2·1%)	3 (2·1%)	· ·	· ·	0·08

*Based on comparison of frequency of grade 3 or 4 toxic effects.

Table 6: **Patients with any adverse event and with grade 3–4 adverse events related to study treatment (2-weekly regimen)**

[1·5], p=0·05). QL did not differ significantly between groups. When missing data for death, progressive disease, or grade 3–4 adverse events were taken into account with the two imputation methods, results were biased in favour of the no-irinotecan group. The analysis of variance on QL showed significantly better quality of life in the irinotecan group after the first imputation method was used (p=0·03). The same trend was seen with the second imputation method.

Definitive deterioration in quality of life occurred consistently later in the irinotecan group, for a deterioration from baseline by 5% (p=0·03), 10% (p=0·06), 20% (p=0·04), and 30% (p=0·06).

Discussion

Combination of irinotecan with fluorouracil and calcium folinate significantly increased response rates, time to progression, and survival. The survival advantage was reached, despite a higher proportion of patients receiving further chemotherapy in the no-irinotecan group (58·3 *vs* 39·4%).

This study population was large (385 patients treated), and the patients were representative of candidates for first-line chemotherapy in clinical practice, except that an unexpectedly high proportion of them had synchronous metastases at baseline and, consequently, a relatively low proportion of them had had previous adjuvant chemotherapy.

The higher frequency of adverse events in the irinotecan group than in the no-irinotecan did not affect the median duration of treatment. The rate of grade 3 or 4 diarrhoea was similar to that previously seen with irinotecan administered as a single agent.[15,16] Overall, toxic effects seen with the irinotecan combination treatment were reversible, non-cumulative, and manageable.

No other combination therapy has shown such high antitumour efficacy over high-dose continuous infusion of fluorouracil and calcium folinate to date. In two phase-III studies,[22,23] for oxaliplatin in combination with infusional fluorouracil and calcium folinate, the response rate and progression-free survival were better than with fluorouracil and calcium folinate alone. Those studies did not, however, show survival benefits. Moreover, there was a trend towards shorter survival in the oxaliplatin group in one study.[23] Another phase III study that compared irinotecan combined with bolus fluorouracil and fluorouracil alone[24] consistently provided significantly higher response rates (33 *vs* 18%, p<0·001) and median time to treatment failure (5·0 *vs* 3·8 months, p<0·05) in the irinotecan group.

Moreover, irinotecan combined with fluorouracil and calcium folinate is the only treatment to show a survival advantage in metastatic colorectal cancer over high-dose continuous infusion fluorouracil and calcium folinate alone.

The results we achieved with the irinotecan combination treatment show that the addition of irinotecan to weekly or 2-weekly regimens of fluorouracil and calcium folinate by infusion brings clear clinical benefit and should be considered as a first-line reference treatment in metastatic colorectal cancer as well as for advanced disease.

Contributors

P Rougier and G Gruia designed the trial. P Rougier coordinated the study. J Y Douillard, D Cunningham, A D Roth, M Navarro, R D James, P Karasek, P Jandik, T Iveson, and J Carmichael contributed significantly to accrual. L Awad was responsible for the statistical analysis. M Alakl and G Gruia managed the study, data documentation, and the writing of the study report.

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