Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer

David Cunningham, Seppo Pyrhönen, Roger D James, Cornelis J A Punt, Tamas F Hickish, Reino Heikkila, Tom B Johannesen, Hans Starkhammar, Clare A Topham, Lucile Awad, Christian Jacques, Patrice Herait

Summary

Background In phase II studies, irinotecan is active in metastatic colorectal cancer, but the overall benefit has not been assessed in a randomised clinical trial.

Methods Patients with proven metastatic colorectal cancer, which had progressed within 6 months of treatment with fluorouracil, were randomly assigned either 300–350 mg/m^2 irinotecan every 3 weeks with supportive care or supportive care alone, in a 2:1 ratio.

Findings 189 patients were allocated irinotecan and supportive care and 90 supportive care alone. The mean age of the participants was 58·8 years; 181 (65%) were men and 98 (35%) were women. WHO performance status was 0 in 79 (42%) patients, 1 in 77 (41%) patients, and 2 in 32 (17%) patients. Tumour-related symptoms were present in 134 (71%) patients and weight loss of more than 5% was seen in 15 (8%) patients. With a median follow-up of 13 months, the overall survival was significantly better in the irinotecan group (p=0·0001), with 36·2% 1-year survival in the irinotecan group versus 13·8% in the supportive-care group. The survival benefit, adjusted for prognostic factors in a multivariate analysis, remained significant (p=0·001). Survival without performance-status deterioration (p=0·0001), without weight loss of more than 5% (p=0·018), and pain-free survival (p=0·003) were significantly better in the patients given irinotecan. In a quality-of-life analysis, all significant differences, except on diarrhoea score, were in favour of the irinotecan group.

Interpretation Our study shows that despite the side-effects of treatment, patients who have metastatic colorectal cancer, and for whom fluorouracil has failed, have a longer survival, fewer tumour-related symptoms, and a better quality of life when treated with irinotecan than with supportive care alone.

Lancet 1998; **352:** 1413–18
See Commentary page ???

Royal Marsden Hospital, Sutton, Surrey, and Royal Marsden Hospital Chelsea, London, UK (D Cunningham MD)**; Helsinki University Hospital, Helsinki, Finland** (S Pyrhönen MD)**; Christie Hospital, Manchester, UK** (R D James MD)**; University Hospital, Nijmegen, Netherlands** (C J A Punt MD)**; Royal Bournemouth and Poole Hospitals, Dorset, UK** (T F Hickish MD)**; Rogaland Hospital, Stavanger, Norway** (R Heikkila MD)**; and Tromso University Hospital, Tromso, Norway** (T B Johannesen MD)**; Linkoping University Hospital, Linkoping, Sweden** (H Starkhammar MD)**; St Luke's Hospital, Guildford, UK** (C A Topham MD)**; and Rhône-Poulenc Rorer/Research and Development, Antony, France** (L Awad, C Jaques PhD, P Herait MD)

Correspondence to: Dr D Cunningham, Department of Medicine, Royal Marsden Hospital, Sutton, Surrey SM2 5PT, UK

Introduction

Colorectal cancer is one of the most common adult malignant tumours, affecting one person in twenty in the USA and in most developed countries. Although 40–50% patients may be cured with surgery, many will develop metastatic disease.[1] For these patients, treatment with fluorouracil, usually modulated by folinic acid, is the only option and the median survival is 10–12 months.[2] When the tumour progresses after first-line treatment with fluorouracil, there is no standard treatment. Survival is short[3,4] and associated with weight loss, onset or worsening of tumour-related symptoms,[5] and poor quality of life.[6] Because cytotoxic agents have low response rates and can be associated with severe side-effects, many patients receive supportive care. In first-line chemotherapy, fluorouracil with folinic-acid is better than supportive care (or delayed chemotherapy) for survival and quality of life,[5,7] but the value of second-line chemotherapy in metastatic colorectal cancer has not yet been proven.

Irinotecan is a topoisomerase I inhibitor that blocks the DNA replication step of the enzyme, leading to multiple single-strand DNA breaks, which eventually blocks cell division.[8] In phase II studies, irinotecan has objective antitumour activity in patients with metastatic colorectal cancer, even in those with documented fluorouracil-resistant tumours, with response rates of 11–23%.[9–12] An additional 40% of patients experienced tumour stabilisation for a median of 5 months.[12] Common side-effects included delayed diarrhoea, neutropenia, early cholinergic syndrome, nausea and vomiting, alopecia, and asthenia. The dose-limiting toxic effects were severe diarrhoea and neutropenia.[12]

The trial we report was started in 1995 to compare irinotecan with supportive care alone for survival, quality of life, and other clinical variables. The participants were patients with metastatic colorectal cancer in whom fluorouracil chemotherapy had failed.

Methods

Endpoints

Overall survival was the primary endpoint. The secondary objectives were the impact of treatment on performance status, bodyweight, tumour-related symptoms, and quality of life.

Patients' selection

To be eligible for randomisation, patients had to meet the following criteria: histologically proven metastatic colorectal cancer; progressive metastatic disease documented on the basis of either a 25% increase in the size of target lesions or an increase in carcinoembryonic antigen by 1·25 times an initial reference value and a baseline value of more than 10 μg/L, which allowed inclusion of patients with non-measurable disease (peritoneal carcinomatosis and pelvic recurrences); progression documented by two measurements not separated by more than 6 months and tumour progression while on fluorouracil or within 6 months of the last fluorouracil infusion;

Safety guidelines for treatment with irinotecan

Side effect	Treatment
Cholinergic syndrome	Atropine sulphate (0·25 mg subcutaneously). If severe, prophylactic treatment at further cycles.
Nausea/vomiting	Systemic prophylactic antiemetics.
First loose stool	Early high-dose loperamide (4 mg at the first loose stool, then 2 mg every 2 h for 12 h after the last loose stool for a maximum of 48 h)
Diarrhoea for >24 h	Oral prophylactic broad-spectrum antibiotherapy—eg, fluoroquinolone (to prevent the risk of severe infection)
Diarrhoea for >48 h	Admission to hospital for parenteral support and replacement of antidiarrhoeal treatment—eg, octreotide
Grade 4 neutropenia or grade 3 or 4 diarrhoea	Dose reduction at further cycles: 300 mg/m^2 then 250 mg/m^2 (or 250 mg/m^2, then 200 mg/m^2 if start dose 300 mg/m^2)

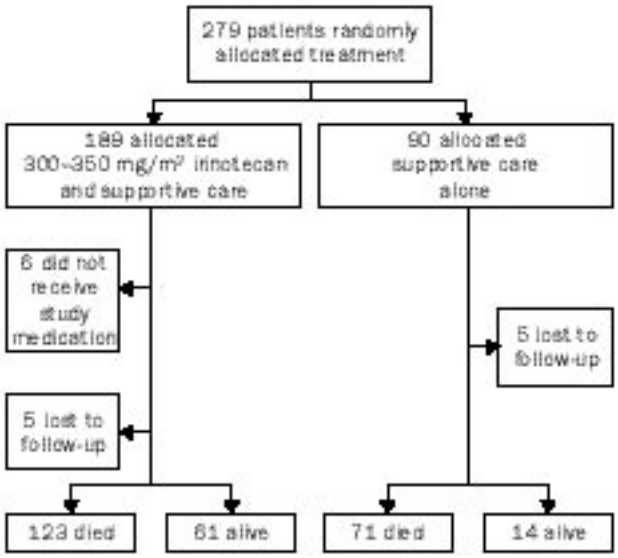

Figure 1: **Trial profile**

having had one adjuvant and/or no more than two palliative fluorouracil-based regimens; age 18–75 years; WHO performance status 0–2; neutrophils 2×10^9/L or more; platelets 100×10^9/L or more; total bilirubin 1·25×the institutional upper normal limit (IUNL), or less; liver transaminases 3×IUNL (in case of liver metastases: bilirubin ⩽1·5×IUNL and transaminases ⩽5×IUNL), or more; serum creatinine 135 μmol/L or less; wash-out of 4 weeks for radiotherapy or chemotherapy; and written informed consent.

Patients with the following criteria were not eligible: previous treatment with topoisomerase I inhibitors, bulky disease (involving more than 50% of the liver volume or 25% of the lung volume, or abdominal mass ⩾10 cm), metastases in the central nervous system, or unresolved bowel obstruction or diarrhoea.

Randomisation and study treatments

Registration forms were sent to Rhône-Poulenc Rorer Research and Development (Antony, France) where eligibility criteria were electronically checked. If all criteria were fulfilled, the randomisation was done electronically in the ratio of irinotecan to supportive care 2:1, with stratification by centre.

In the irinotecan group, patients were given best supportive care and irinotecan 350 mg/m^2, diluted in 250 mL normal saline or dextrose, over a 90 min intravenous infusion every 3 weeks (or 300 mg/m^2 if aged ⩾70 years or WHO performance status 2, according to previously recognised risk factors for developing toxicity). Guidelines were provided for the management of side-effects (panel). Treatment was to be started no longer than 8 days after randomisation. In the supportive-care alone group, patients were given best supportive care and were seen every 3 weeks. Supportive care was defined as the best care available as judged by the attending physician, according to institutional standards for each centre. Supportive care included antibiotics, analgesics, transfusions, corticosteroids, or any other symptomatic therapy (except iriontecan or other topoisomerase I inhibitor), and/or assistance of a psychotherapist. Localised radiation therapy to alleviate symptoms such as pain was allowed provided that the total dose delivered was in the palliative range according to institutional standards.

Analysis of best supportive care

Supportive care and concomitant medications were reported at each visit (every 3 weeks in both groups). They were classified with the WHO dictionary; further subclassification was done with the WHO code for anatomical therapeutic class (ATC). With these classifications, analgesics were divided into opioids or non-opioids and analysed in 3-week blocks.

Follow-up

Patients visited the investigator for assessment and treatment every 3 weeks. All adverse events were reported according to the National Cancer Institute's common toxicity criteria.[13] After discontinuation of treatment in the irinotecan group, patients were regularly assessed as in the supportive care group (tumour status, symptoms, or side-effects, every 3 weeks) until death or for at least a year. Beyond 1 year, only date of death was traced.

Quality of life

Quality of life was assessed with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire (including five function scales, one global health-status scale, and nine symptom scales),[14] which was filled in at baseline, at 3 weeks, 6 weeks, and then every 6 weeks. After discontinuation of treatment in the irinotecan group, patients continued to fill in QLQ-C30 questionnaires every 6 weeks as in the supportive-care group.

Statistical analysis

Survival curves were estimated with the Kaplan-Meier method on the randomised population and compared by a two-tailed logrank test.[6] With p=0·05 and power of 0·80, 264 patients were required (176 in the irinotecan group and 88 in the supportive-care group) to show a significant difference in 1-year survival from 20% (supportive care) to 35% (irinotecan).

The randomisation was stratified by centre. A retrospective stratification was planned to take into account the baseline prognostic factors (sex, age, performance status, weight loss, presence of liver metastases, site of primary tumour, number of metastatic sites, response to and duration of fluorouracil treatment as well as its intent [adjuvant or palliative], haemoglobin, white blood cells, platelets, lactate dehydrogenase, transaminases, alkaline phosphatase, bilirubin, protein, and carcinoembryonic antigen).

The analysis was by intention to treat and patients were analysed according to the arm to which they were assigned. The association of prognostic factors with survival was estimated with Cox's proportional hazards model for censored survival data. Model selection for identifying the variables having an effect on survival was based on a forward stepwise procedure. p values to enter and to remove were 0·05 and 0·06, respectively. After the prognostic model had been determined, the effect of treatment after adjusting for other prognostic factors was estimated by including it in the model. Survival without weight loss of more than 5% survival without performance-status deterioration, and pain-free survival were estimated by the

	Irinotecan (n=189)	Supportive care (n=90)
Sex (men/women)	129/60	52/38
Median age (range, years)	59 (22–75)	62 (34–75)
WHO performance status*		
0	89 (47%)	28 (31%)
1	73 (39%)	41 (46%)
2	26 (14%)	21 (23%)
Weight loss >5%	13 (7%)	10 (11%)
With symptoms	130 (69%)	69 (77%)
Primary tumour site		
Colon right	40 (21%)	18 (20%)
Colon left	61 (32%)	27 (30%)
Rectum	76 (40%)	38 (42%)
Number of organs involved		
1	82 (43%)	42 (47%)
2	75 (40%)	31 (34%)
⩾3	32 (17%)	17 (19%)
Sites of metastases		
Liver	151 (80%)	69 (77%)
Lung	69 (37%)	27 (30%)
Peritoneum	13 (7%)	9 (10%)
CEA		
Median CEA concentration (range; μg/L)	108 (0–43 000)	151 (0–35 300)
Documentation of tumour progression by CEA increase only	27 (14%)	9 (10%)
Mean increase (CEA_{rand}/CEA_{ref}) for those assessed by CEA only	2·24	2·83
Documented tumour progression while on previous fluorouracil	133 (70%)	57 (63%)
Previous treatment		
Surgery	188 (99%)	88 (98%)
Radiotherapy	49 (26%)	24 (27%)
Chemotherapy		
Adjuvant only	18 (10%)	15 (17%)
One regimen for metastatic disease with or without adjuvant	125 (66%)	52 (58%)
⩾2 regimens for metastatic disease with or without adjuvant	44 (23%)	23 (26%)
Best response to previous fluorouracil for metastatic disease		
Complete/partial regression	40 (24%)	24 (32%)
Stabilisation	57 (34%)	24 (32%)
Progression	64 (38%)	24 (32%)
Abnormal biological value		
Haemoglobin <110 g/L†	23 (12%)	20 (22%)
White blood cells >8×10^9/L	89 (47%)	40 (44%)
LDH/IUNL	106 (56%)	40 (44%)
Alkaline phosphatases >IUNL	102 (54%)	49 (54%)
CEA>10 μg/L	139 (74%)	57 (63%)
Median haemoglobin concentration (range; g/L)	128 (63–163)	125 (86–167)

*p=0·02, †p=0·03. LDH=lactate dehydrogenase, CEA=carcinoembryonic antigen, CEA_{rand}=CEA at randomisation; CEA_{ref}=CEA used as reference value for estimating progression, IUNL=institutional upper normal limit.

Table 1: **Baseline characteristics**

Kaplan-Meier method and compared with a two-tailed logrank test. Quality-of-life variables were compared with multivariate and univariate analyses of variance on values at baseline, during study, on patients' worst score over the trial period, and changes from baseline. Kaplan-Meier estimates and logrank tests were done on time to definitive quality-of-life deterioration, with eight different thresholds for deterioration.

Results

Patients' data

189 patients were randomly allocated irinotecan and supportive care and 90 patients were allocated supportive care alone (figure 1). The patients' characteristics are shown in table 1. These characteristics were similar for both groups except for performance status (more patients having poor performance status in

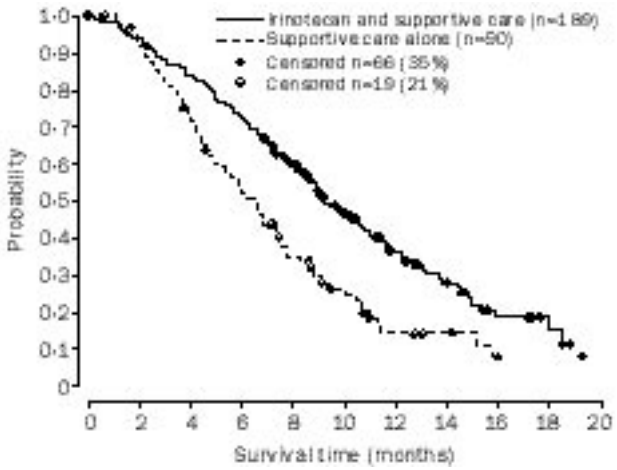

Figure 2: **Probability of survival of the 279 patients**

the supportive-care group) and anaemia. Only 27 (14%) of patients in the irinotecan group and nine (10%) in the supportive-care group were assessed by carcinoembryonic antigen only, with mean antigen ratios versus reference values of 2·24 and 2·83, respectively.

Six patients in the irinotecan group did not receive irinotecan. Irinotecan was given for a median of 4·1 (0·7–12·6) months and 172 (91%) patients received their first infusion within 8 days of randomisation. 40 (21%) patients in the irinotecan group received subsequent anticancer chemotherapies (31 a fluorouracil regimen,

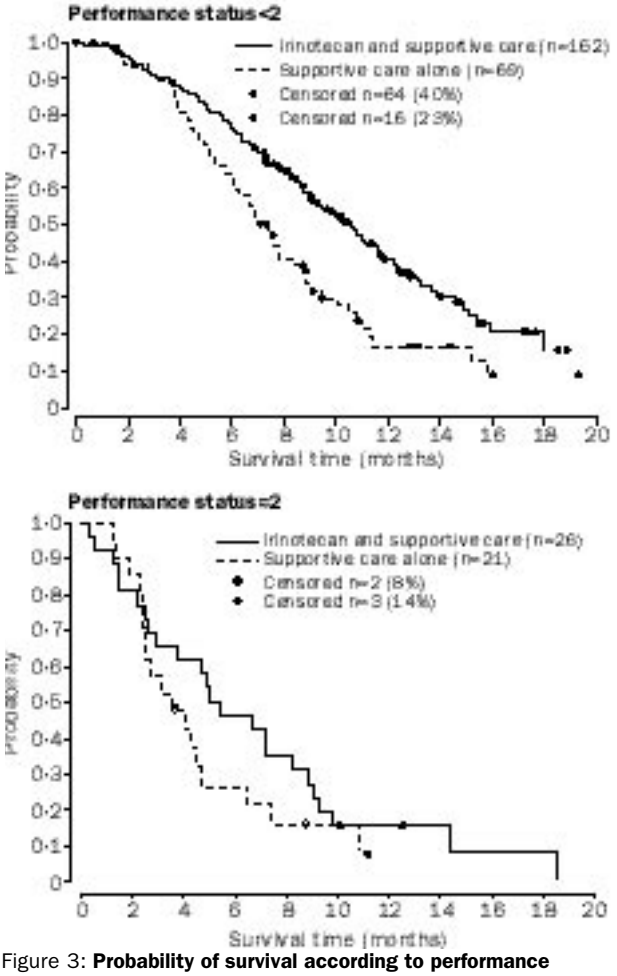

Figure 3: **Probability of survival according to performance status**

	Risk ratio	p
Treatment group		
Irinotecan and supportive care		
Supportive care alone	1·71	0·001
Weight loss during previous 3 months (%)		
≤5		
>5	3·42	<0·001
WHO performance status		
0–1		
2	2·00	<0·001
Haemoglobin (g/L)		
≥110		
<110	2·06	<0·001
Liver metastases		
No		
Yes	1·64	0·021
Alkaline phosphatases (×UINL)		
<1·67		
≥1·67	1·66	0·007
Number of organs involved		
1		
≥2	1·54	0·008

Table 2: **Multivariate Cox's analysis**

nine a drug other than irinotecan). In the supportive-care group 28 (31%) of patients received chemotherapy (21 a fluorouracil regimen, nine other drugs, and one irinotecan). 17 (19%) patients in the supportive-care group received chemotherapy within 1 month of randomisation compared with two (1%) in the irinotecan group. Concomitant medications at baseline were similar in both groups and consisted mainly of analgesics.

Overall survival

Kaplan-Meier estimates of survival are presented in figure 2. There were 123 (65%) events in the irinotecan group, median duration of which was 9·2 (range 0–18·9) months. The survival probability for this group at 6 months was 72·2%, at 9 months 52·6%, and at 12 months 36·2%. In the supportive-care group there were 71 (79%) events, the median duration of which was 6·5 (range 0·7–19·3) months. In this group the survival probability at 6 months was 54·1%, at 9 months 29·1%, and at 12 months 13·8%. Median follow-up was 12·9 months. Patients in the irinotecan group lived significantly longer than those in the supportive-care group (p=0·0001). This benefit appeared after 2 months and became more apparent throughout the study period. 1-year survival was 36·2% and 13·8% in the irinotecan and supportive-care groups, respectively. Median survival was 9·2 and 6·5 months, respectively.

A univariate Cox's model showed that patients with performance status 0 or 1 shared the same prognosis, which was notably better than that for patients with performance status 2. Figure 3 shows that the benefit of treatment occurred in all performance-status groups. With a performance status of less than two there were 98 (60%) events in the irinotecan group, median duration of which was 10·5 (range 0–18·9) months. The survival probability for this group at 6 months was 76·3%, at 9 months 57·2%, and at 12 months 40·1%. In the supportive-care-alone group there were 53 (77%) events, median duration 7·4 (0·7–19·3) months. In this group the survival probability at 6 months was 62·5%, at 9 months 33·2%, and at 12 months 16·2%. With a performance status of two there were 24 (92%) events in the irinotecan group, median duration of which was 5·1

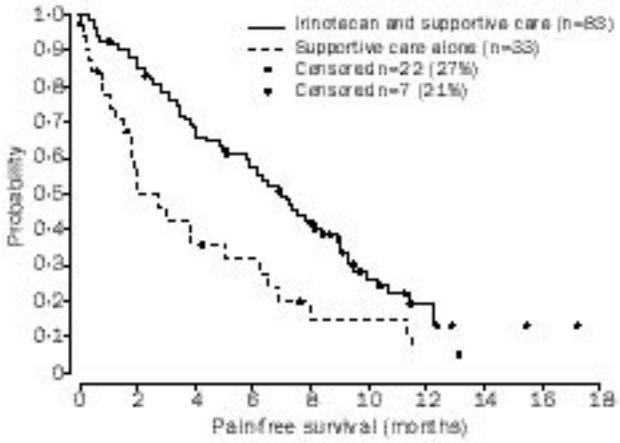

Figure 4: **Probability of pain-free survival in 116 patients without pain at baseline**

(range 0·3–18·5) months. The survival probability for this group at 6 months was 46·2%, at 9 months 26·9%, and at 12 months 15·4%. In the supportive-care group there were 18 (86%) events, the median duration of which was 3·5 (range 1·1–11·0) months. In this group the survival probability at 6 months was 26·5%, at 9 months 15·9%, and at 12 months 7·9%. Multivariate Cox's regression confirmed the importance of other known prognostic factors (table 2).[15–18] When the treatment group was included in the model, the survival benefit for the irinotecan group remained significant (p=0·001).

Secondary endpoints

Survival without weight loss of more than 5% (p=0·018) and survival without performance-status deterioration (p=0·0001) were significantly longer in the irinotecan group. More patients with a performance-status of worse than 0 at baseline improved their performance status: 35% versus 11% (p=0·002). Pain-free survival in patients without pain at baseline (figure 4) was significantly longer in the irinotecan group than in the supportive-care group (p=0·003), despite a higher proportion of patients on opioids in the supportive-care group. There were 61 (73%) events in the irinotecan group, median duration of which was 6·9 (range 0·3–17·2) months. The survival probability for this group at 6 months was

	Irinotecan (n=158) mean (SE)	Supportive care alone (n=73) mean (SE)	p
Functioning scale			
Physical	61·66 (2·51)	41·23 (3·96)	<0·001
Role	54·11 (3·21)	36·30 (4·28)	0·002
Cognitive	77·64 (1·81)	68·04 (3·31)	0·006
Emotional	69·06 (1·68)	64·99 (2·67)	0·19
Social	59·39 (2·36)	47·03 (4·13)	0·006
Global quality of life	47·57 (1·97)	38·47 (2·80)	0·009
Symptoms			
Fatigue	50·60 (2·07)	61·34 (3·45)	0·006
Nausea/vomiting	26·69 (1·95)	28·31 (3·04)	0·647
Pain	39·98 (2·39)	53·42 (3·27)	0·001
Dyspnoea	30·17 (2·13)	39·27 (4·03)	0·03
Sleep disturbance	38·40 (2·45)	46·12 (3·94)	0·087
Appetite loss	36·08 (2·49)	54·79 (4·57)	<0·001
Constipation	26·58 (2·33)	39·73 (3·77)	0·004
Diarrhoea	31·86 (2·33)	18·26 (2·76)	<0·001
Financial impact	21·10 (2·31)	25·11 (4·10)	0·361

Table 3: **Worst score during study for each EORTC QLQ-C30 scale**

Adverse event	Irinotecan	Supportive care alone
Anaemia	13 (7%)	6 (7%)
Leukopenia/neutropenia	42 (22%)	0
Thrombocytopenia	2 (1%)	0
Fever or infection with grade 3 or neutropenia	6 (3%)	0
Nausea	26 (14%)	3 (3%)
Vomiting	26 (14%)	7 (8%)
Diarrhoea	42 (22%)	5 (6%)
Constipation	19 (10%)	7 (8%)
Cholinergic syndrome	23 (12%)	0
Asthenia	28 (15%)	17 (19%)
Mucositis	4 (2%)	1 (1%)
Anorexia	9 (5%)	6 (7%)
Cutaneous signs	4 (2%)	0
Neurological symptoms	23 (12%)	12 (13%)
Cardiovascular symptoms	15 (8%)	3 (3%)
Pain (abdominal excluded)	36 (19%)	24 (22%)
Abdominal pain	26 (14%)	14 (16%)
Infection (without grade 3 or 4 neutropenia)	17 (9%)	3 (3%)
Any grade 3 or 4	150 (79%)	60 (67%)

Table 4: **Patients with National Cancer Institute common toxicity criteria grade 3 or 4**

56·8%, at 9 months 36·6%, and at 12 months 18·8%. In the supportive-care group there were 26 (79%) events, median duration 2·0 (0–13·0) months. In this group the survival probability at 6 months was 31·5%, at 9 months 14·7%, and at 12 months 4·9%. Within 23 weeks of randomisation, the rate of patients with opioid consumption by 3-week blocks ranged from 25% to 34% in the irinotecan group and from 40% to 56% in the supportive-care group.

In the quality-of-life analysis, compliance of patients was about 80% in both groups at the beginning of study and decreased during the study to about 50%. Compliance decreased more rapidly in the supportive-care group, probably due to earlier deterioration in the patients. On difference from baseline multivariate analysis of variance was significant (p=0·0001).

The univariate analyses of variance were significantly in favour of the irinotecan group for the cognitive functioning score (p<0·001), the global quality-of-life score (p<0·001), the pain score (p=0·008), dyspnoea (p=0·04), appetite loss (p<0·002), and financial-impact scores (p<0·001). The diarrhoea score was significantly better in the supportive-care group (p=0·02). Analyses on worst patient score during the study are shown in table 3: all results were significantly in favour of irinotecan except for emotional, nausea, sleep disturbance, and financial scores. Diarrhoea score was significantly lower in the supportive-care group. Time to definitive quality-of-life deterioration was significantly longer in the irinotecan group, whichever the chosen threshold for deterioration (all p values <0·002).

Safety

Table 4 shows the incidence of grade 3 or 4 adverse events (drug related or not) by patient. Patients on supportive-care alone experienced a high incidence of severe adverse events, especially pain and asthenia, although significantly more patients in the irinotecan group experienced severe events, especially neutropenia, nausea, vomiting, and diarrhoea. Two (1·1%) of 183 patients treated with irinotecan died of drug-related causes although, in one, the association with adverse events (diarrhoea and/or febrile neutropenia) has not been clearly established. Admission for adverse events occurred in 136 (72%) of patients in the irinotecan group and 57 (63%) of patients in the supportive-care-alone group for a cumulative median of 15 (range 1–168) days and 11 (2–87) days, respectively.

Discussion

This study showed that treatment with irinotecan and supportive care alone, compared with supportive care, prolonged the life of patients with metastatic colorectal cancer. This benefit was clinically meaningful because the probability of surviving 1 year was 2·6 times greater in patients given irinotecan compared with that of patients given supportive care alone. Other efficacy endpoints, such as survival without weight loss, survival without performance status deterioration, pain-free survival, and quality-of-life, were all significantly in favour of irinotecan.

The survival advantage for the irinotecan group remained highly significant after adjustment of performance status, a well-recognised prognostic factor.[15–17] More generally, the multivariate regression showed that the difference in survival between the two groups remained significant even after adjusting for the effect of well-known prognostic factors. The survival data were also consistent with those observed in the phase II studies of irinotecan.[11,12]

The study also showed an advantage for irinotecan for quality of life. The results were consistent with other clinical variables (performance status deterioration, weight loss, and pain control). The analysis of the EORTC QLQ-C30 symptoms scale was consistent with the safety data. This suggests that the EORTC QLQ-C30 questionnaire is sensitive, contrary to a previous report.[18]

The safety profile of irinotecan was acceptable. The incidence of treatment-related grade 3 or 4 diarrhoea with irinotecan (21%) was lower than that reported in previous studies (39%).[9,10] This result, observed in a multicentre trial, is probably accounted for by the more rigorous implementation of guidelines for the management of diarrhoea than in earlier studies. Grade 3–4 neutropenia was reported in 22% and grade 3–4 vomiting in 14% of patients. Asthenia, pain, and neurological symptoms were more frequent in the supportive-care group.

Some say that patients with advanced cancer who are treated with supportive care alone will have a short but peaceful end to their life, protected from the side-effects of chemotherapy. Our study showed that as many as 67% of patients receiving supportive care experienced severe symptoms and as a result, 63% were admitted for a median of 11 days. Furthermore, irinotecan improved the symptoms of patients and delayed the onset of tumour-related symptoms such as performance-status deterioration, weight loss, and pain. These data were supported by the quality-of-life analysis which suggested that the side-effects of irinotecan were favourably balanced by reduced tumour-related events.

We have shown a survival advantage and a clinical benefit from second-line chemotherapy in patients with metastatic colorectal cancer no longer responding to fluorouracil. Many patients had poor prognostic factors, which implies that the results will be applicable in the daily practice. The value of irinotecan was confirmed in terms of survival, quality of life, and other clinical variables. Irinotecan can therefore be recommended as

the standard second-line therapy in colorectal cancer and as a new reference for forthcoming clinical trials.

Contributors

D Cunningham and P Hérait designed the trial. DC coordinated the study. S Pyrrhonen, R D James, C J A Punt, T F Hickish, R Heikkila, T B Johannesen, H Starkhammer, and C A Topham contributed significantly to accrual. L Awad was responsible for the statistical analysis. C Jacques managed the study, data documentation, and the writing of the study report. PH and DC prepared the first draft of the manuscript to which everyone then contributed.

Acknowledgments

We thank the following for their participation: P G Harper,T Iveson, M Soukop, S M Crawford, S J Falk, M T Seymour, S J Karp, M O'Brien, F Daniel, M L Slevin, J L Mansi, T Maughan, J Cassidy, R Glynn-Jones, C C Wilson, (UK); B Glimelius, C Svenson, B Gustavson, T Linne, M Malmberg, B W Jeppsson (Sweden); J Mardiak, S Spanik (Slovakia); J Zso, J Szanto (Hungary); P Kellokumpu-Lehtinen on behalf of the research group of Tampere (Finland); R Smaland (Norway); L Heslop, W R Bezwoda, G Falkson, G Landers (South Africa); D J Richel, R Van Rijswijk, J W R Nortier, (Netherlands); M Ghosn, J Kattan (Lebanon); A Shani (Israel); J Crown (Ireland). We also thank E Ong, M Mesbah, Ch Blanc, C Cote, B Fages, D Sibaud (France) for their support.

D Cunningham has served on national and international advisory boards for Rhône -Poulenc Rorer for which he received consultancy fees. Rhône-Poulenc Rorer Research and Development (Antony, France) provided free irinotecan and funding on a per-patient basis for this study.

References

1 Cohen AM, Minsky BD, Schilsky RL. Cancer of the colon. In: De Vita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology, 5th edn. Philadelphia: Lippincott-Raven, 1997: 1145–97.

2 The Advanced Colorectal Cancer Meta-Analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992; **10:** 896–903.

3 Fages B, Cote C, Gruia G, et al. Tumor response and stabilization rates are worthwhile surrogate endpoints in metastatic colorectal cancer. analysis of data in 455 5FU-resistant patients treated with CPT-11. *Proc ASCO* 1997; **16:** 288a (abstr).

4 Glimelius B, Hoffman RN, Graf W, et al. Quality of life during chemotherapy in patients with symptomatic advanced colorectal cancer. *Cancer* 1994; **73:** 556–62.

5 The Nordic Gastrointestinal Tumor Adjuvant Project. Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. *J Clin Oncol* 1992; **10:** 904–11.

6 Marsoni S, Hoth D, Simon R, et al. Clinical drug development. An analysis of phase II trials, 1970–1985. *Cancer Treat Rep* 1987; **71:** 7180.

7 Scheithauer W, Rosen H, Kornek GV, et al. Randomized comparison of combination chemotherapy plus supportive care or supportive care alone in patients with metastatic colorectal cancer. *BMJ* 1993; **306:** 752–55.

8 Creemers GJ, Lund B, Verweij J. Topoisomerase I inhibitors: topotecan and irinotecan. *Cancer Treat Rev* 1994; **20:** 73–96.

9 Pitot HC, Wender DB, O'Connell MJ, et al. Phase II trial of irinotecan in patients with metastatic colorectal carcinoma. *J Clin Oncol* 1997; **15:** 2910–19.

10 Rougier P, Bugat R, Douillard JY, et al. Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naïve patients and patients pretreated with fluorouracil-based chemotherapy. *J Clin Oncol* 1997; **15:** 251–60.

11 Rothenberg ML, Eckardt JR, Kuhn JG, et al. Phase II trial of irinotecan in patients with progressive or rapidly recurrent colorectal cancer. *J Clin Oncol* 1996; **14:** 1128–35.

12 Van Cutsem E, Rougier P, Droz JP, et al. Clinical benefit of irinotecan (CPT-11) in metastatic colorectal cancer (CRC) resistant to 5-FU. *Proc ASCO* 1997; **16:** 268a (abstr).

13 Guidelines for the Reporting of Adverse Drug Reactions. Besthesda: Division of Cancer Treatment. National Cancer Institute, 1988.

14 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85:** 365–76.

15 Rougier P, Milan C, Lazorthes F, et al. Prospective study of prognostic factors in patients with unresected hepatic metastases from colorectal cancer. *Br J Surg* 1995; **82:** 1397–400.

16 Kemeny N, Niedzwiecki D, Shurgot B, et al. Prognostic variables in patients with hepatic metastases from colorectal cancer. *Cancer* 1989; **63:** 742–47.

17 Earlam S, Glover C, Fordy C, et al. Relation between tumor size, quality of life and survival in patients with colorectal liver metastases. *J Clin Oncol* 1996; **14:** 171–75.

18 Ross P, Webb A, Cunningham D, et al. Chemotherapy for colorectal cancer: relationship between toxicity and quality of life. *Ann Oncol* 1996; **7:** 34 (abstr).