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Original Paper

Clinical Activity and Benefit of Irinotecan (CPT-11) in Patients with Colorectal Cancer Truly Resistant to 5-Fluorouracil (5-FU)

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The aim of this prospective study was to assess the efficacy, clinical benefit and safety of CPT-11 (irinotecan) in patients with stringently-defined 5-fluorouracil-resistant metastatic colorectal cancer (CRC). 107 patients with documented progression of metastatic CRC during 5-FU were treated with CPT-11 350 mg/m^2 once every 3 weeks in a multicentre phase II study. Tumour response and toxicity were assessed using WHO criteria. Changes in performance status (PS), weight and pain were also measured. The WHO response rate was 13/95 (13.7%, 95% CI 7.5% to 22.3%) eligible patients with a median duration of response of 8.5 months (37 weeks, range: 18–53+). There was also a high rate of disease stabilisation (44.2%) with a median duration of 4.8 months. The probability of being free of progression at 4 months was 50%. Median survival from first administration of CPT-11 was 10.4 months or 45 weeks (range: 3–66+ weeks). There was weight stabilisation or gain in 81% (73/90) of patients, a favourable outcome in PS in 91% (82/90) (improvement of WHO PS 2 or stabilisation of PS 0-1), and pain relief in 54% (26/48). There were no toxic deaths. Neutropenia was short-lasting and non-cumulative. Diarrhoea grade $\geq$3 occurred in 7% of cycles and 28/107 (26%) of patients. CPT-11 350 mg/m^2 once every 3 weeks has an encouraging degree of activity in progressive metastatic CRC truly resistant to 5-FU with a relatively high rate of tumour growth control translated into clinical benefit. The toxicity profile of CPT-11 is becoming better understood and has been considerably improved. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

METASTATIC COLORECTAL cancer (CRC) has often been treated with systemic chemotherapy to palliate symptoms rather than to improve survival [1]. However, two studies have shown that patients who receive palliative chemotherapy at the time of diagnosis of metastatic CRC do better than those who receive it only at the onset of symptoms [2], or than those who do not receive chemotherapy [3], obtaining significant improvement in both survival and quality of life.

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Although numerous cytotoxic agents have been tested in metastatic CRC, regimens based on 5-fluorouracil (5-FU) have proved to be the most effective, and a combination of 5-FU and leucovorin (LV) is considered to be the standard first-line chemotherapy [4]. There is, however, no standard treatment for patients in whom 5-FU-based chemotherapy has failed; no other cytotoxic agent has proved to be effective. A review by National Cancer Institute investigators found an overall response rate for all new agents in this setting of 2.4% [5]. Therefore, most attempts at second-line chemotherapy comprise further 5-FU-modulated treatments. Overall, approximately 10% of patients at most will respond to second-line 5-FU-based chemotherapy, whatever the schedule of 5-FU and/or the modulator agents might be [6, 7].

The water-soluble camptothecine derivative irinotecan [8] (CPT-11), a DNA topoisomerase I inhibitor has a unique mechanism of action. In previous phase II studies, CPT-11 has demonstrated activity in the treatment of both chemotherapy-naïve and previously treated patients with CRC, showing response rates of 15% to 32% [9–11]. In one large French multicentre study, the response rate of metastatic CRC to CPT-11 350 mg/m^2 once every three weeks was 18% in 178 eligible patients (48 previously untreated and 130 previously treated with 5-FU) [12]. Ten responses were observed in 62 eligible patients (16.1%) whose disease had progressed whilst receiving prior 5-FU-based chemotherapy, this subgroup meeting the most stringent criteria for 5-FU-resistant disease. In an American study, 48 patients with advanced CRC who were previously treated with a 5-FU-based regimen were treated with CPT-11 125 to 150 mg/m^2 weekly for 4 weeks every 6 weeks. A response rate of 23% was reported in 43 evaluable patients [11]. 37 of the patients (77%) had progressed during prior 5-FU-based chemotherapy; the response rate in this subgroup was not reported.

The present multicentre study was the first study conducted to assess prospectively the efficacy, clinical benefit and safety of CPT-11 (Campto®; Rhône-Poulenc Rorer, Paris, France) in patients with stringently-defined 5-FU-resistant disease since, in the previous studies, 5-FU resistance was not shown in all patients. In the light of previous experience, the present protocol also placed particular importance on vigilance and prompt aggressive treatment for delayed-onset diarrhoea.

PATIENTS AND METHODS

Twenty-five centres participated in this open-label, phase II multicentre study. Ethics committee approval was obtained and all patients gave written informed consent to participate. Only patients with metastatic CRC who had developed documented tumour progression during 5-FU administration were admitted to the study.

Other inclusion criteria were: histologically proven cancer of the colon or rectum; one prior chemotherapy regimen (two if one was adjuvant); a washout period of at least 4 weeks since the last treatment (6 weeks for mitomycin C, nitrosourea or extensive radiotherapy). Progression on 5-FU-based therapy was defined as follows: two successive imaging investigations within 6 months showing more than 25% growth in target lesions or appearance of new lesions. An adequate dosage and regimen of the prior 5-FU-based regimen was required (5-FU more than 500 mg/m^2/week bolus or 600 mg/m^2/week infusional). Other criteria were: measurable disease outside a previously irradiated field; age 18 to 70 years; WHO performance status (PS) of ≤ 2; life expectancy of at least 12 weeks; normal haematological profile and adequate renal and hepatic function.

Ineligibility criteria were: bulky disease (> 25% of lung or > 50% of liver involved, or palpable abdominal mass); previous treatment with CPT-11 or any topoisomerase I inhibitor; past inflammatory enteropathy or extensive bowel resection; known brain metastases; history of other cancer; severe uncontrolled infection; major organ failure; bowel obstruction; childbearing potential.

Patients were treated with CPT-11 350 mg/m^2 (maximum 700 mg) by intravenous (i.v.) infusion for 90 minutes once every 3 weeks, with provision for dose reduction (to 300 mg/m^2 and further to 250 mg/m^2) or delay if severe toxicity (diarrhoea grade ≥ 3; neutropenia grade ≥ 3) occurred. Treatment was to be continued for up to 9 cycles in the event of either disease stabilisation or complete or partial response but was to be terminated in the event of disease progression, major toxicity or patient refusal. Efficacy was evaluated after every 3 cycles. All progressions on 5-FU and all response assessments were reviewed by an independent external response review committee. Responses were determined according to WHO criteria. Changes in performance status, weight and pain were also measured. Safety was monitored at each cycle (except haematology: weekly) and graded according to WHO criteria where applicable. Diarrhoea was assessed by means of a special questionnaire in addition to WHO grading.

Preventive anti-emetic treatment was given routinely. If cholinergic syndrome occurred it was to be treated with atropine 0.25 mg subcutaneously (s.c.), and this could be used prophylactically for subsequent cycles.

Both patients and physicians were alerted to the importance of recognising and reacting immediately to the onset of delayed diarrhoea. If delayed diarrhoea occurred, it was to be treated promptly with high-dose loperamide (2 mg every 2 h for at least 12 h after the last loose stool). If it persisted for more than 24 h despite loperamide treatment, an oral broad-spectrum quinolone antibiotic was to be prescribed for 7 days. If the diarrhoea persisted for > 48 h loperamide was stopped and the patient had to be hospitalised for parenteral rehydration.

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was to be filled in by patients at baseline and before each cycle. The patients graded pain as absent, mild, moderate and severe.

The sample size was determined on the basis of a single-stage Fleming design [13]. Using the assumption that CPT-11 would not be of further interest in 5-FU-resistant CRC if the response rate was less than 6%, but that a response rate of 16% would be of definite interest in this population, a minimum sample size of 79 evaluable patients was needed. The data are presented using descriptive statistics and Kaplan–Meier estimations were employed for the analysis of censored data.

RESULTS

Patient characteristics

107 patients received treatment in this study. Baseline characteristics of the treated population are shown in Table 1. The median time between last chemotherapy and entry to the present study was 1.6 months (range: 0.3–13.7) and the median time since documentation of progression on 5-FU

was 1.5 months (0.2 to 13.8). The median delay between the two computer tomography (CT) scans proving tumour progression on 5-FU was 3.2 months (maximum 6 months). 14 patients (13%) relapsed whilst receiving adjuvant therapy. 60 patients (56%) were symptomatic at study entry, as reflected by a PS of 1 or 2. 12 patients were ineligible: 5 had no available baseline tumour assessment or were considered not to have measurable disease by the external response review committee; in 4 patients, disease progression was not confirmed by the external response review committee; 2 had bowel obstruction at baseline; 1 had more than one prior palliative chemotherapy regimen; 1 had liver involvement of more than 50%; 1 had a PS greater than 2. 2 of the 12 patients each had two reasons for ineligibility. Therefore, 95 (89%) patients are eligible.

Baseline lactic dehydrogenase (LDH) and white blood cells were increased in 52 and 40% of patients, respectively.

Drug exposure

A total of 588 cycles of CPT-11 were administered; 483 (82%) at the planned dose of 350 mg/m^2. The median number of cycles given was 6 (range: 1–12). 36 patients (34%) received more than 6 cycles. Infusions were delayed by 7 days or more in 11 cycles (2%) and the dose was reduced once or more in 27 patients (25%) and in 100 cycles (17%). The median relative dose intensity (defined as the actual dose administered divided by the planned dose) was 0.97 (range: 0.62–1.08).

Among the 107 treated patients, the most frequent reason for discontinuation of treatment was disease progression (76 patients including 1 patient who died during the study due to this cause). 4 patients withdrew due to toxicity (described below). Another 5 patients refused further treatment, and 19 discontinued because they had completed the nine cycles called for in the study protocol. One patient was lost to follow up. Median follow up was 57 weeks (range: 35–72).

Efficacy of CPT-11

The principal efficacy results, based on the assessment of the independent external response review committee, are summarised in Table 2. 5 of the 95 eligible patients were not evaluable: 2 because of inappropriate or missing evaluations; 1 each because of withdrawn consent, loss to follow-up, and withdrawal due to toxicity before first assessment.

The overall objective response rate in the 95 eligible patients was 13.7% (95% CI 7.5% to 22.3%). Median duration of response was 8.5 months or 37 weeks (range: 18–53 + weeks). Six of the 13 partial responses (PR) occurred at cycle 3. Of the remaining 7, 1 occurred at cycle 4 and 6 at cycle 6. In addition to the 13 patients with a partial response, a further 42 (44.2%) had stabilisation of their disease, which had been progressive at baseline (Table 2). Included in the stable disease category are 5 patients with 'minor' responses, defined as a regression of between 25 and 49% of the overall tumour mass. In two cases, the observed tumour shrinkage exceeded 40% at cycle 6. Median duration of stable disease as best response was 4.8 months or 21 weeks (range: 15–64 +). Responses on CPT-11 were seen in 18% (3/17) patients having a previous response to 5-FU, as well as in 21% (7/33) patients with progressive disease as best evaluation on 5-FU. PRs occurred in 5 of the 40 patients with liver as only site of disease, 2 of the 7 patients with lung metastases as the only site of disease, 2 of the 13 patients with liver and lung as the only site of disease and 4 of the 35 patients with multiple sites including the liver.

The median time to progression was 17 weeks (range: 1–64 +). The probability of being free from progressive disease was, therefore, 50% at 4 months (6 cycles); 27% at 6 months.

Median survival from first administration of CPT-11 was 10.4 months or 45 weeks (range: 3–66 + weeks).

Evolution of body weight was considered in terms of the number of patients with ≥ 3 cycles of therapy who experienced weight loss $\geq 5\%$, stabilisation or gain $\geq 5\%$. Out of 90 evaluable patients, 73 (81%) had a stabilisation or gain in weight. For WHO PS, a successful outcome was defined as improvement from a baseline PS 2 for at least two consecutive cycles (64% had an improvement of PS 2 to 0–1 after 3 cycles and 77% after 6 cycles), or stabilization of baseline PS 0-1 (69% of patients with PS 0 at baseline had PS 0 after 3 cycles and 68% after 6 cycles; of patients with PS 1 at baseline, 62 and 72% remained at PS 1 after 3 and 6 cycles, respectively, and 11 and 24% improved to PS 0 after 3 and 6 cycles, respectively). On this criterion, 82 of the 90 evaluable patients (91%) had a successful outcome in terms of evolution of WHO PS.

Of 48 patients who had pain at entry to the study, 26 (54%) had complete relief from pain. Of 59 patients who had no pain at entry to the study, 50 (85%) remained free of pain.

These clinical benefits were particularly evident among the patients who were free from disease progression at the end of

Table 1. *Characteristics of patients at baseline*

	Treated patients ($n = 107$)
Sex (M/F)	63/44
Median age (range) in years	58 (28–72)
Median WHO performance status (range)	1 (0–2)
Primary tumour	
Colon	73 (68%)
Rectum	28 (26%)
Rectosigmoid	6 (6%)
Intent of prior 5-FU regimen	
Adjuvant only	14 (13%)
Palliative only	76 (71%)
Adjuvant + palliative	17 (16%)
Best response to last palliative 5-FU regimen ($n = 85$ pts with evaluable response))	
Complete or partial response	17 (20%)
Stable disease	35 (41%)
Progressive disease	33 (39%)
Eligible patients	95 (89%)

Table 2. *Response rate to CPT-11 in 95 eligible patients (documented progressive disease on 5-FU) as determined by the independent response review committee*

Response	Number of patients (%)
Complete response	0 –
Partial response	13 (13.7)
Stable disease	42 (44.2)
Progressive disease	35 (36.8)
Not evaluable	5 (5.3)

cycle 6. Seventy-three per cent of these patients were free of pain, with PS 0 or 1 and without weight loss.

Safety and tolerability of CPT-11

One patient died due to progressive disease during the study; there were no deaths attributed to toxicity of CPT-11. 4 patients discontinued treatment with CPT-11 due to adverse events (1 due to haematological toxicity at cycle 1; 2 due to diarrhoea at cycles 1 and 7, respectively; 1 due to deterioration in performance status at cycle 1). 27 patients (25%) were hospitalised (15 due to diarrhoea) due to adverse events possibly or probably related to CPT-11; there were 37 episodes of hospitalisation (6% of cycles) comprising: 18 for diarrhoea with or without vomiting, 4 for diarrhoea associated with febrile neutropenia/infection, 7 for febrile neutropenia/infection, 6 for vomiting, 1 for drug-related fever and chills, and 1 for anaemia requiring blood transfusion. Thus diarrhoea was a causal event in 22/37 episodes of hospitalisation (59%).

The principal haematological toxicity was neutropenia. 16% (17/107) of the patients had a grade 3 neutropenia and 25% (27/107) a grade 4. 10% of the cycles resulted in grade 3 and 7% in grade 4 neutropenia. The median nadir in neutrophil count was 1.9×10^9 (range 0 to 9). The median number of days to nadir was 8 (range: 0–30). Of 93 cycles resulting in grade 3 or 4 neutropenia, only one lasted longer than 7 days. Neutropenia did not appear to be cumulative.

Fever and/or infection concomitant with grade 3 or 4 neutropenia occurred in 9 patients (8%) and 9 cycles (2%). Antibiotics were given in all cases.

Anaemia occurred in 61 of 106 evaluable patients (58%); grade 3 or 4 in 12 patients (11%). Mild to moderate thrombocytopenia occurred in 6% (6/107) of patients and 2% of cycles.

Non-haematological adverse events possibly or probably related to treatment with CPT-11 that occurred in $\geq 3\%$ of patients are summarised in Table 3. Although the most frequent were alopecia, asthenia, nausea/vomiting, diarrhoea and cholinergic syndrome, the most frequently serious in clinical terms was delayed-onset diarrhoea.

WHO Grade 3 or 4 delayed-onset diarrhoea occurred in 26% (28/107) of patients and 7% of cycles. However, the median duration of any grade of diarrhoea was 3 days and of grade 3 or 4 diarrhoea 5 days. The characteristics of delayed-onset diarrhoea are detailed in Table 4. The incidence may be overestimated, as the protocol stipulated that antidiarrhoeal treatment with loperamide should be started as soon as the first liquid stool was observed. 18 cycles (5% of the 350 with diarrhoea) resulted in only one liquid stool. Of the 94 patients with at least one episode of diarrhoea, 79 (84%) had

Table 3. Non-haematological adverse events possibly or probably related to treatment with CPT-11 and affecting more than 3% of patients

Type of adverse event	Number (%) of patients with event ($n=107$)			Number (%) of cycles with event ($n=588$)		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Alopecia	97 (91)	63 (59)	–	–	–	–
Nausea/vomiting	94 (88)	17 (16)	3 (3)	325 (55)	54 (9)	3 (1)
Diarrhoea	94 (88)	25 (23)	3 (3)	350 (60)	38 (7)	3 (<1)
Cholinergic syndrome*	88 (82)	10 (9)	–	275 (47)	13 (2)	–
Asthenia*	71 (66)	9 (8)	–	232 (40)	14 (2)	–
Mucositis (oral)	25 (23)	2 (2)	–	36 (6)	2 (<1)	–
Anorexia*	25 (23)	3 (3)	–	60 (10)	5 (1)	–
Neurologic function	12 (11)	–	–	35 (6)	–	–
Constipation	8 (7)	–	–	16 (3)	–	–
Fever in absence of infection without grade 3/4 neutropenia	8 (7)	–	–	11 (2)	–	–
Infection without grade 3/4 neutropenia	4 (4)	–	–	6 (1)	–	–

*For literal terms, 1, mild; 2, moderate; 3, severe; 4, life-threatening.

Table 4. Characteristics of delayed-onset diarrhoea in 580 evaluable cycles

	Diarrhoea	
Characteristic	All grades	Grade 3/4
Cycles with diarrhoea (%)	350 (60)	G3: 38 (7) G4: 3 (<1)
Median time in days to first onset (range)	6 (1–25)	6 (1–11)
Median duration in days (range)	3 (1–22)	5 (1–17)
Median no. of stools per day (range)	3 (1–21)	6 (2–21)
No. (%) of cycles resulting in:		
Nocturnal stools	140 (24)	30 (5)
Abdominal pain	183 (32)	32 (6)
Blood	6 (1)	1 (<1)
No. (%) cycles resulting in patient treatment	280 (48)	40 (7)
No. (%) cycles resulting in patient hospitalisation	21 (4)	16 (3)
No. (%) cycles resulting in patient rehydration	47 (8)	21 (4)

Table 5. *Number and percentage of cycles resulting in fever and/or infection according to neutropenia and diarrhoea*

	WHO grade of neutropenia	
	0, 1 or 2	3 or 4
WHO grade of diarrhoea		
0, 1 or 2	12/437 (3%)	11/86 (13%)
3 or 4	2/34 (6%)	2/7 (29%)

their first episode at cycle 1. Diarrhoea led to discontinuation of treatment in two cases (2%). The incidence of fever and/or infection was increased in the presence of grade 3 or 4 diarrhoea, as shown in Table 5. Furthermore, there was an even higher incidence of fever and/or infection if there was concomitant grade 3 or 4 diarrhoea and grade 3 or 4 neutropenia.

The cholinergic syndrome consists of abdominal cramps, sweating, salivation, diarrhoea, malaise and hypotension. 88 patients (82%) and 275 cycles (47%) had at least one cholinergic symptom but severe events were uncommon. Atropine sulphate was required in 104 cycles (18% of all cycles; 38% of those with cholinergic syndrome). In no case was discontinuation of CPT-11 required, although the dose was reduced in two cycles and the infusion interrupted in five. The syndrome appeared at the first cycle in 77/88 (88%) of affected patients. In patients affected by severe cholinergic syndrome, atropine was used prophylactically in 113 subsequent cycles, of which 46 (41%) were free of any cholinergic symptoms.

Nausea and vomiting occurred in 94 patients (88%) and 325 cycles (55%) and was severe (grade 3 or 4) in 20 patients (19%) and 57 cycles (10%). Curative anti-emetic therapy was required in 216/325 affected cycles (66%). In no case was cessation of CPT-11 treatment required.

Quality of life

Although not easily interpretable in a non-randomised study, the median Global Health Status improved with successive cycles, probably due to selection of patients with treatment benefit. When only patients still on study at cycle 6 were considered, the median Global Health Status remained stable across the 6 cycles (baseline 66.7; subsequently ranging from 66.7–83.3). When considering the global health status of patients with at least 6 cycles, it was higher than that of patients with 3 cycles at the most. Their status improved whilst that of patients leaving the study early decreased. This trend in time may be indicative of a treatment benefit. The median global health status of patients who had a PR was 75.9 compared with 63.1 in non-responders and 58.3 in patients with progression as a best response.

DISCUSSION

This prospective study in patients with well-documented 5-FU-resistant metastatic CRC shows that CPT-11 at a dose of 350 mg/m^2 once every 3 weeks is an effective treatment. The overall response rate was 13.7% and the probability of being free of progression at 4 months (6 cycles) was 50%. The median survival from the start of second-line treatment was 10.4 months, which is of clinical importance in patients with metastatic CRC that has failed 5-FU therapy, especially as they had poor prognostic factors: strictly defined progression on 5-FU within a short period of time (median 3.2 months); short interval (median 1.5 months) from progression to start of treatment with CPT-11 (both excluding slow-growing tumours); 45% of patients had pain at entry to the study, whereas most first-line patients with CRC are asymptomatic.

The response rate of 13.7% in the present study is consistent with that reported in the subgroup of patients with 5-FU resistant disease in the earlier French multicentre study and American studies [11, 12]. The response rate to second-line CPT-11 in the present study compares favourably with 5-FU in first-line therapy (18%). Responses were seen on CPT-11, whatever the response to prior 5-FU was. A response rate of 21% (7/33) was observed among the patient subgroup which had disease progression as the best response to prior 5-FU therapy and of 18% (3/17) among the patient subgroup having PR/CR as best response. These data confirm the lack of clinical cross-resistance between 5-FU and CPT-11.

The majority of second-line regimens are currently 5-FU-based, using different schedules of administration and/or modulator agents. Published results concern small studies with a heterogeneous selection of regimens and methods of assessment, the great majority having no independent review of responses. Certainly none is directly comparable with the present study and neither can any of the various 5-FU-based regimens described in the literature be regarded as having been validated or representing a standard. The response rates in full publications range from 0–25% [7, 14–20]. It is noteworthy that most of the objective responses observed with 5-FU-based second-line regimens occurred either in patients who had previously responded to 5-FU or in patients who had previously received suboptimal doses of 5-FU. Indeed it appears that previous treatment with 5-FU/LV regimens predicts a poor response to a second 5-FU-based regimen [7].

Other new chemotherapeutic agents have also been tried after 5-FU failure in CRC, but mostly in very small studies and usually with little success. Response rates are rarely (and then not reproducibly) above 10% with any of the new agents tested [20]. Oxaliplatin has also a relatively low activity as single agent in second line treatment [21, 22], but one small phase II trial reported an unusual high response rate in second line treatment with the combination of oxaliplatin—5-FU/LV [23].

In addition to the encouraging response rate in the present study, there was a high rate of disease stabilisation (44.2%) which was of long duration (median 4.8 months) and a median time to disease progression of 3.9 months or 17 weeks. This median time to progression is clinically meaningful in terms of tumour-growth control in patients with documented rapid prior progression at study entry, since it is accompanied by improvement or stabilisation of weight and PS in a majority of patients. It would indeed have been expected that all such patients with rapid progression on 5-FU would have progressed on an ineffective treatment, with deterioration in PS, weight loss and onset or worsening of tumour-related symptoms. The global health status, as evaluated by the EORTC-QLQ-C30 questionnaire, was in this study higher in patients who received 6 cycles compared with patients who received 3 cycles at the most.

Other studies have shown that stabilisation of progressive CRC is associated with both prolonged survival and subjective improvement. An analysis of the relationship between tumour response and survival in chemotherapy of advanced

colorectal cancer [24] has shown that any degree of objective tumour response of 4 months duration is associated with a definite survival advantage. The survival advantage conferred by SD was almost as great as that associated with PR. In a prospective study of quality of life using interviews or questionnaires during chemotherapy for advanced CRC [25] benefit in terms of quality of life was associated with anti-tumour effect, which did not necessarily have to be sufficiently large to qualify as an objective response on WHO criteria.

The present study also provides important safety data which indicate that the safety profile of CPT-11 is becoming better understood and more amenable to medical management. There were no deaths attributed to CPT-11 in the present study. Eighty-two per cent of cycles were given at the initial planned dose level and the median relative dose intensity was 0.97.

Twenty-five per cent of patients in the present study required hospitalisation for drug-related adverse events, compared with 21% patients who received the Mayo Clinic regimen of 5-FU/LV in a recent study [26]. In the present study diarrhoea was a causal event in 15/27 (56%) of patients requiring hospitalisation for adverse events.

The most frequent and severe non-haematological toxicity was delayed-onset diarrhoea. Compared with previous published experience in a comparable setting [12] the overall incidence of this toxicity was similar, but the incidence of grade 3 or 4 delayed diarrhoea in the present study was less (26% of patients compared with 39% in the previous study and 7% of cycles compared with 12%) as was the rate of cessation of treatment due to this toxicity (2% compared with 10%) and the median duration of diarrhoea was shorter (3 days; range 1–22, as compared with 5 days; range: 1–34).

In conclusion, approximately 50% of patients with metastatic CRC that has progressed on a single previous 5-FU-based palliative chemotherapy are likely to benefit in terms of tumour growth control from treatment with CPT-11 350 mg/m^2 administered once every 3 weeks. This tumour growth control is reflected in clinical benefit, in terms of improvement or stabilisation of weight and PS, and pain relief. In addition, the safety profile of CPT-11 is becoming better understood and more amenable to medical management. CPT-11 represents a significant step forward in this traditionally chemoresistant disease and its assessment in first-line chemotherapy is, therefore, warranted.

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