Pergamon

European Journal of Cancer Vol. 32A, Suppl. 3, pp. S18–S23, 1996

Printed in Great Britain
0959-8049/96 $15.00 + 0.00

PII: S0959-8049(96)00293-6

Characterisation and Clinical Management of CPT-11 (Irinotecan)-induced Adverse Events: The European Perspective

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CPT-11 (Campto®, irinotecan) is a promising new agent in the treatment of advanced colorectal cancer. Its safety has been assessed in light of the results from recent European phase II studies. In a pivotal French study in which CPT-11 350 mg/m^2 was administered once every 3 weeks, neutropenia and delayed diarrhoea were the major adverse events: transient neutropenia occurred in 80% of patients, and severe neutropenia and febrile neutropenia in 47 and 15%, respectively. Delayed diarrhoea occurred in 87% of patients, with 39% having severe (grade 3 or 4) diarrhoea and 16% requiring hospitalisation. None of these adverse events was cumulative. Results of a pilot study to elucidate the mechanism of CPT-11-induced delayed diarrhoea suggest that this toxicity has a secretory mechanism with an exudative component. Early appropriate management of delayed diarrhoea may improve the safety profile of CPT-11. Indeed, the safety profile of CPT-11 was clearly improved in a later (currently ongoing) pan-European study: incidences of severe (grade 3 or 4) delayed diarrhoea and febrile neutropenia (± infection) were reduced from 39% to 23% (grade 4: 8% to 2.5%) and from 12% to 6%, respectively. Such an improvement could be attributed to a better understanding of the mechanisms of diarrhoea, improved patient selection criteria, better education of patients and physicians about management of delayed diarrhoea and the use of broad spectrum antibiotics when diarrhoea persisted despite loperamide therapy. Copyright © 1996 Elsevier Science Ltd

Key words: chemotherapy, cancer, colorectal, CPT-11, toxicity, diarrhoea

Eur J Cancer, Vol. 32A, Suppl. 3, pp. S18–S23, 1996

INTRODUCTION

CHEMOTHERAPEUTIC OPTIONS in the treatment of colorectal cancer chemotherapy are disappointingly low. Despite an objective response rate in advanced metastatic disease, which is generally around only 20% or less, 5-fluorouracil (5-FU)-based regimens remain the most effective therapies for colorectal cancer [1]. Furthermore, 5-FU is associated with systemic toxicity (particularly gastrointestinal and haematological events for bolus intravenous 5-FU, and neurological events for continuous infusion) which may be dose-limiting. Since its introduction in 1957 into clinical practice, the optimal dosage and administration schedule for 5-FU is still being investigated, and recent prospective comparisons of bolus 5-FU monotherapy versus other single-agent or combination 5-FU-based regimens have provided valuable objective data on this issue [2, 3]. In particular, the use of continuous infusions of 5-FU rather than intravenous bolus doses has been shown to improve the tolerability profile of 5-FU (Table 1). Furthermore, as a result of improved patient selection criteria, the toxic death rate associated with 5-FU-based therapy has fallen from 5% in 1989 [3] to 1% today [2]. However, the suggestion that biochemical modulation or schedule alteration of 5-FU would, by improving response rates, extend survival compared with 5-FU bolus monotherapy [1, 4, 5] has been shown only in some of the prospective comparative studies, and is not supported by the results of a recent randomised study comparing seven 5-FU-based regimens, in which median survival times for infusional and/or combination schedules of 5-FU ranged from 11 to 15 months, compared with 14 months for standard 5-FU bolus monotherapy [2]. This may partly be explained by the fact that, after failing on a first-line treatment, patients were given another potentially active treatment. Thus, there is an urgent need for more effective and

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Table 1. Comparison of the safety profiles of various regimens of 5-fluorouracil (5-FU) compared prospectively in 589 eligible patients with advanced colorectal cancer (adapted from Leichman et al. [2]).

Schedule	1 ($n = 88$)	2 ($n = 85$)	3 ($n = 85$)	4 ($n = 85$)	5 ($n = 81$)	6 ($n = 83$)	7 ($n = 82$)
Incidence of severe neutropenia (grade 3–4)	47%	47%	8%	1%	1%	4%	11%
Incidence of severe diarrhoea (grade 3–4)	10%	12%	27%	6%	11%	11%	10%
Number of toxic deaths	0	2 (sepsis)	0	1 (cardiac infarction)	0	1 (cardiac arrest)	3 (sepsis); 1 (cardiac ischaemia)

CI, continuous infusion; i.v., intravenous; PALA, phosphonacetyl-L-aspartate.
Dosage schedules: 1: 5-FU 500 mg/m^2 i.v. bolus, days 1–5 every 5 weeks; 2: 5-FU 425 mg/m^2 and folinic acid 20 mg/m^2 i.v. bolus, days 1–5 every 4 weeks for two cycles, then every 5 weeks; 3: 5-FU 600 mg/m^2 i.v. bolus plus folinic acid 500 mg/m^2 3 h infusion weekly for 6 weeks then 2-week break; 4: 5-FU 300 mg/m^2/day CI, days 1–28, then 1-week break; 5: 5-FU 200 mg/m^2/day CI, days 1–28, then 1-week break, plus folinic acid 20 mg/m^2 i.v. bolus, days 1, 8, 15 and 22 of each 5-week cycle; 6: 5-FU 2600 mg/m^2 24 h infusion weekly (no breaks); 7: 5-FU 2600 mg/m^2 24 h infusion weekly plus PALA 250 mg/m^2 over 15 min, 24 h before each 5-FU infusion.

better tolerated chemotherapy, particularly for patients not responsive to 5-FU.

CPT-11 (irinotecan) is a promising new agent that is currently under investigation for the treatment of advanced colorectal cancer. It is a semisynthetic derivative of the plant alkaloid camptothecin which produces antitumour activity through inhibition of the eukaryotic DNA enzyme topoisomerase I. In European phase I and phase II studies, intravenous CPT-11 has demonstrated activity in the treatment of chemotherapy-naive and 5-FU-pretreated patients with advanced colorectal cancer, producing response rates (15 to 32%) comparable to those seen with 5-FU-based chemotherapy [6]. As there is no cross-resistance with 5-FU, CPT-11 could be of paramount importance for patients who relapse after 5-FU-based chemotherapy. In these studies, which used a once-every-3-weeks schedule, the dose-limiting toxicities of CPT-11 were neutropenia and delayed diarrhoea (defined as diarrhoea occurring >24 hours after drug infusion), both of which were shown to be schedule-dependent, but not cumulative [7–9]. Other frequent adverse events included an early cholinergic-like syndrome, asthenia, alopecia, nausea and vomiting.

The early cholinergic syndrome associated with CPT-11 therapy is observed during and immediately following drug administration; lower doses of CPT-11 (100–260 mg/m^2) are primarily associated with gastrointestinal cramps, diarrhoea and diffuse sweating, while patients receiving higher doses (300–750 mg/m^2) may, in addition, experience salivation, visual accommodation disturbances and lacrimation [7]. Abdominal cramps and diarrhoea associated with this cholinergic syndrome are generally controllable with atropine therapy. Delayed diarrhoea, which is not part of the early cholinergic syndrome, is defined as the passing of in excess of two stools daily, the first incidence of which is at least 24 h after drug administration. Indeed, the median time to onset of the first episode of delayed diarrhoea has been shown to be 6 days following CPT-11 administration [7].

In the present article, we review the safety profile of CPT-11 on the basis of data from two consecutive studies in colorectal cancer: a recent pivotal French study [10] and a currently ongoing pan-European phase II study. The main emphasis of this article is CPT-11-induced delayed diarrhoea, which can be particularly troublesome and which, when associated with neutropenia, may increase the risk of infectious complications and related death. The pathophysiology of delayed diarrhoea, the need for an adequate grading system with which it can be assessed, and the clinical management of this symptom in patients with advanced colorectal cancer, are also discussed.

A pivotal phase II study of 3-weekly CPT-11 in advanced colorectal cancer

Methods. This French multicentre open study investigated the efficacy and tolerability of CPT-11, administered at a dosage of 350 mg/m^2 once every 3 weeks as a 30-min intravenous (i.v.) infusion, in 213 patients with histologically proven metastatic or unresectable colorectal cancer [10]. This particular dosage schedule was chosen since it was associated with the highest dose intensity and best safety profile of the schedules investigated in European phase I studies [6]. In addition, this schedule is well suited for use in the outpatient setting. Patients included in the study ranged in age from 18 to 75 years, having a life expectancy of $\geqslant 3$ months and a WHO performance status of $\leqslant 2$. Of these patients, 48 were chemotherapy-naive; the remainder had previously received one or more 5-FU-based regimens.

A total of 1195 treatment cycles were administered during the study, with a median of six cycles per patient. It is important to note that 84% of treatment cycles were given without dosage reduction or treatment delay and the relative dose intensity (dose intensity given/dose intensity planned) was 0.96. Episodes of delayed diarrhoea were to be treated with oral loperamide 2 mg every 2 h for a maximum of 48 h. It was recommended that loperamide therapy be initiated directly after the first liquid stool occurred and continued for 12 h after the last episode of diarrhoea.

Safety profile of CPT-11. Neutropenia and delayed diarrhoea occurred in 80% and 87% of patients, respectively. Eighty-five per cent of patients experienced an acute cholinergic syndrome comprising facial flushing, nausea/vomiting,

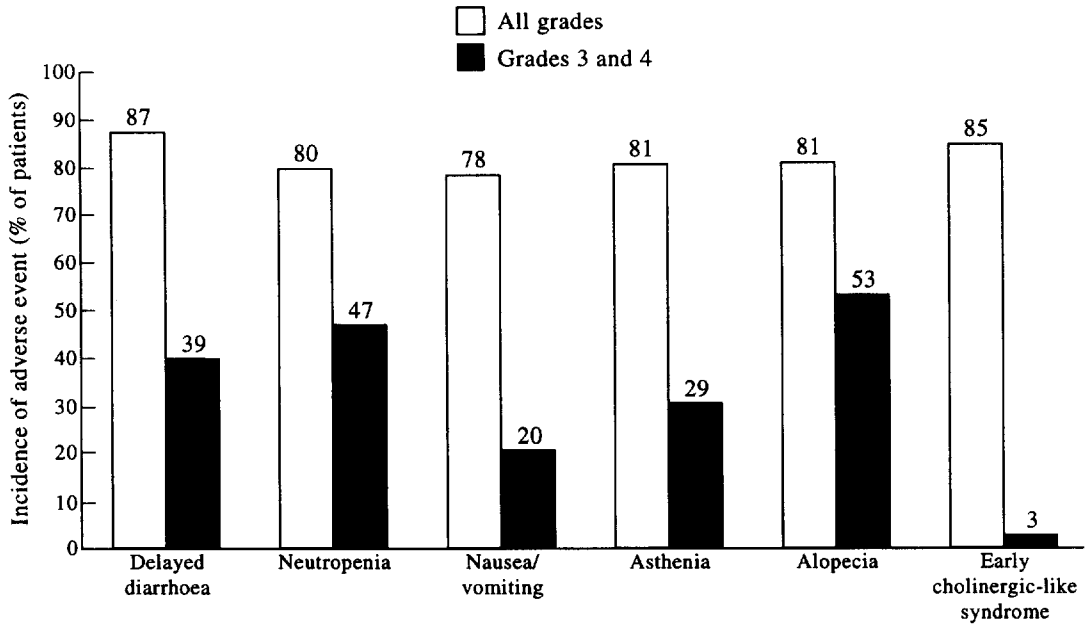

Figure 1. Incidence of adverse events in a multicentre study of CPT-11 350 mg/m^2 once every 3 weeks in 213 patients with metastatic or unresectable colorectal cancer.

abdominal cramps and diarrhoea, which occurred during or soon after drug administration. Other frequent adverse events were alopecia and asthenia, both of which occurred in 81% of patients (Figure 1). Therefore, adverse events associated with CPT-11 in this study were similar, both in nature and frequency, to those reported in phase I studies of CPT-11 conducted in Europe, Japan and the U.S.A. [6].

In the present study, the incidence of severe (grade 3–4) neutropenia was 47% (21% of cycles), febrile neutropenia occurred in 15% of patients and 'life-threatening' septicaemia in 3%. CPT-11-induced neutropenia did not show cumulative characteristics—it was short-lived, with a median time to nadir of 8 days, and total recovery occurred by day 21 in 97% of cycles.

Delayed diarrhoea occurred in 87% of patients (57% of cycles). The incidence of grade 3–4 delayed diarrhoea was 39% (12% of cycles) with 8% at grade 4, and 16% of patients (6.5% of cycles) requiring hospitalisation. Although the occurrence of delayed diarrhoea was unpredictable, most of the problems occurred during the first two or three cycles. As with neutropenia, the incidence and severity of delayed diarrhoea was not cumulative and actually seemed to decrease during repeated treatment cycles. This particular manifestation of CPT-11-induced toxicity was more frequent and severe in elderly patients (> 65 years of age), those with a WHO performance status of >1 or those who had undergone prior abdominopelvic radiotherapy. Patients with concomitant severe diarrhoea and neutropenia were at an increased risk of developing severe infectious complications: of the 4 deaths which were considered probably related to treatment, 3 were wholly or partially associated with delayed diarrhoea.

An ongoing phase II study of CPT-11

Methods. The safety profile of CPT-11 has been further investigated in a pan-European phase II study. This ongoing study was initiated in February 1995 to assess the antitumour activity of CPT-11 in patients with metastatic colorectal cancer who were truly refractory to 5-FU therapy (defined as experiencing progression during or within 4 weeks of 5-FU-based chemotherapy). Particular attention was paid to the selection of patients, who were required to have a good performance status (without bulky tumour or bowel obstruction) and to be less than 70 years of age. CPT-11 350 mg/m^2 was administered once every 3 weeks, the same schedule as in the earlier French study described above except that the duration of infusion was 90 min rather than 30 min. The conclusions from the French study were used in order to improve the management of diarrhoea. Patients and physicians were well informed about CPT-11-induced delayed diarrhoea and its management; in particular, special care was taken regarding the need for prompt measures after any episode of diarrhoea.

As recommended in the French study, delayed diarrhoea was treated with oral loperamide 2 mg every 2 h for a maximum of 48 h. The treatment was initiated after the first soft or liquid stool and continued for 12 h after the last episode of diarrhoea. However, in contrast to the French study, guidelines for the management of diarrhoea were clearly established before the study started, and patients were to receive oral broad spectrum antibiotics for the next 7 days if diarrhoea persisted for more than 24 h despite loperamide therapy. If diarrhoea was not under control after 48 h, patients had to be hospitalised.

Safety profile of CPT-11: a comparison with data from the French study. The safety profile of CPT-11 observed in the ongoing study was considered alongside that of a comparable patient group in the earlier French study. As these are two different phase II studies, however, no statistical analysis was performed. Thus, the data from 73 patients from the French study who were truly refractory to 5-FU were included in this analysis and compared with the data from the 79 patients available for analysis in the ongoing study. The two groups of patients were comparable in terms of their median age, performance status and primary tumour location. The median number of CPT-11 cycles received per patient was higher in the French study than in the ongoing study (five versus three cycles). However, the number is likely to change upon completion and final analysis of the latter study. In the ongoing study, the majority of cycles (approximately 94%) were given without dosage reduction or treatment delay and the relative dose intensity was 0.99.

In general, the incidence of adverse events in the ongoing study appeared to be lower than in the completed study (Table 2). A similar incidence of the early cholinergic-like syndrome (hyperacute abdominal cramps, early diarrhoea, diffuse sweating), controlled by atropine, occurred in both studies during CPT-11 infusion.

Although the incidence of delayed diarrhoea was similar in both studies (87% versus 86%), severe (grade 3 or 4) delayed diarrhoea has been observed in only 23% of patients in the ongoing study compared with 39% in the French study. The proportional decrease in the incidence of grade 4 diarrhoea was even greater (from 8 to 2.5%). Furthermore, delayed diarrhoea was less persistent in the ongoing study, lasting for >7 days in 10% of episodes compared with 29% of delayed diarrhoea episodes in the French study.

The frequency of severe neutropenic episodes associated with fever and/or infection seems to be lower in the ongoing study compared with the French one (6% versus 12%).

Based on the data currently available, these results suggest an improvement in the safety profile of CPT-11 in the ongoing phase II study compared with that seen in the earlier French study, as indicated by: (i) a lower incidence of febrile neutropenia and infection; (ii) a lower incidence of severe delayed diarrhoea; (iii) a shorter duration of delayed diarrhoea. These results should be considered only as indicative since in the ongoing study the follow-up period is shorter and fewer cycles of chemotherapy have been administered, compared with the earlier study. Of note, severe adverse events have been shown to occur mainly during the first cycle, and it is, therefore, unlikely that the frequency of these events will increase after a longer follow-up period. It should also be kept in mind that definite comparison can only be obtained from randomised trials.

Table 2. Safety profiles of CPT-11 in two studies of patients with advanced colorectal cancer

Adverse event	Completed study ($n = 73$)	Ongoing study ($n = 79$)
Delayed diarrhoea		
All grades	86%	87%
Grades 3 and 4	31.5%	23%
Grade 4	8%	2.5%
Neutropenia*		
All grades	76%	68%
Grades 3 and 4	41%	33%
Grade 4	23%	18%
Febrile ± infection	12%	6%
Early cholinergic-like syndrome	82%	65%
Nausea/vomiting	85%	78%
Asthenia	78%	51%
Alopecia	84%	86%

*Incidence of neutropenia was assessed in 70 patients in the completed study and in 78 patients in the ongoing study.

Pathophysiological basis for the management of CPT-11-induced delayed diarrhoea: a pilot study

Chemotherapy-related diarrhoea is a common occurrence in cancer patients, particularly in those who are treated with 5-FU and/or cisplatin, and its clinical management remains a problem [11]. If severe, it may reduce the patient's compliance and even develop into a potentially life-threatening disorder. At present, the most commonly used symptomatic treatments include loperamide and diphenoxylate piperidine derivatives [11].

The exact mechanism of CPT-11-induced delayed diarrhoea is unknown. Therefore, a phase I study was initiated to explore the pathophysiology of delayed diarrhoea in CPT-11 treated patients and to assess the efficacy of Tiorfan® (a new enkephalinase inhibitor) and/or loperamide therapy in controlling this disorder.

Methods. A pilot study was conducted in 28 patients with advanced colorectal cancer who had previously been treated with 5-FU. CPT-11 was administered as a 30-min intravenous infusion at a dose of 350 mg/m^2 once every 3 weeks. Two successive cohorts of 14 patients each had different therapeutic protocols for delayed diarrhoea. Patients showing signs of delayed diarrhoea were to be treated initially with Tiorfan® alone (group 1) or Tiorfan® plus loperamide (group 2).

In group 1, 11 patients were treated with Tiorfan® 100 mg three times daily. The treatment was initiated immediately after the second loose stool and was considered successful if diarrhoea stopped within 48 h. In group 2, 12 patients were treated with Tiorfan® 100 mg three times daily plus loperamide 2 mg three times daily, initiated after the first loose stool.

If diarrhoea persisted for more than 48 h, high-dose loperamide (2 mg every 2 h) was administered to both treatment groups for up to 12 h after the last liquid stool.

Results. During the study period, the number of CPT-11 cycles associated with delayed diarrhoea, defined as the passing of >2 stools daily, the first episode occurring ⩾ 24 h after drug administration, was 36 (55%) in group 1 and 33 (41%) in group 2. The majority of episodes of delayed diarrhoea occurred during the first two treatment cycles (in 70% of patients during the first cycle and in 16% during the second cycle). The duration of delayed diarrhoea was shoter in group 2 than in group 1 patients (median 2 versus 4 days). Severe diarrhoea was also less common in group 2 patients (2.5 versus 7.7% of cycles). Concomitant abdominal pain occurred in 21% of all cycles with similar frequency in the two groups. There were no bloody stools

Table 3. Established grading system for the evaluation of diarrhoea

Grade	WHO	CTC/NCI
1	Transient (< 2 days)	2–3 stools/day
2	Tolerable (⩾ 2 days)	4–6 stools/day, night stools, moderate cramps
3	Intolerable, requiring therapy	7–9 stools/day, incontinence, severe cramps
4	Haemorrhage, dehydration	⩾ 10 stools/day, haemorrhage, intravenous rehydration required

WHO, World Health Organization; CTC/NCI, Clinical Trials Centres of the U.S. National Cancer Institute.

in either group. Night stools and weight loss (⩾ 2 kg) were more common in group 1 (34 and 21% of cycles, respectively) than in group 2 (19 and 9%, respectively). In contrast, rehydration was required less frequently in group 1 than in group 2 (3 versus 12% of cycles). Compared with baseline, patients' quality of life was impaired in 28% and 12% of cycles in groups 1 and 2, respectively.

It is important to remember that the association of severe delayed diarrhoea with neutropenia could lead to life-threatening septicaemia. In the present study, the incidence of neutropenia was high (66% and 79% of cycles in groups 1 and 2, respectively). The frequency of severe neutropenia was 45% in group 1 and 35% in group 2. These results are in agreement with previous data [6].

Investigation of the putative mechanisms of CPT-11-induced delayed diarrhoea was accomplished through a series of specific tests performed at baseline, to be repeated when there were episodes of diarrhoea. Of all the pathophysiological tests performed in the study, only α_1-antitrypsin clearance was abnormal, being elevated in all 4 of the patients in whom it was measured. This increase in α_1-antitrypsin clearance suggests the presence of a secretory component to CPT-11-induced delayed diarrhoea. The remainder of the tests (gastrointestinal transit rate, stool examination (faecal fat, osmolarity, culture), D-xylose absorption test, serum biochemistry (triglycerides, cholesterol, lipase, amylase and carboxylesterase), and gastrointestinal hormone assays (VIP, glucagon, gastrin and somatostatin)) were normal or unchanged versus baseline. These data indicate that there is also an exudative component to the delayed diarrhoea associated with CPT-11.

This suggestion was confirmed by the successful treatment of the first episode of delayed diarrhoea with Tiorfan® plus loperamide. In group 1, cessation of diarrhoea within 48 h of treatment occurred in 36% of patients who received Tiorfan® alone. The response rate reached 100% when high-dose loperamide was added. In group 2, cessation of diarrhoea within 48 h of treatment with Tiorfan® plus loperamide was achieved in 11 of 12 (92%) patients. The patient who did not respond to this treatment remained non-responsive to the high-dose loperamide therapy.

Therefore, it is probable that CPT-11-induced delayed diarrhoea has a secretory mechanism with an exudative component. When Tiorfan® alone fails to control delayed diarrhoea in CPT-11 recipients, the addition of loperamide is generally effective in controlling this toxicity. Early treatment (initiated immediately after the first loose stool) with a combination of Tiorfan® and loperamide appears to be effective in controlling delayed diarrhoea.

CONCLUSION

Delayed diarrhoea and neutropenia are the main toxicities associated with CPT-11 therapy in patients with metastatic colorectal cancer. The results of these studies indicate that, although there is concern over the high incidence of severe diarrhoea and severe neutropenia, particularly when they occur simultaneously, these toxicities are clearly manageable. Nevertheless, the pathophysiology of CPT-11-induced diarrhoea and its management require further elucidation and are being currently investigated. There are two established grading systems for the evaluation of diarrhoea, those of the World Health Organization (WHO) and the Clinical Trials Centers of the U.S. National Cancer Institute (CTC/NCI) (Table 1).

Although widely used, both systems have limitations. The WHO system grades diarrhoea by duration of effect but does not include objective measures such as the frequency of stools; conversely, the CTC/NCI system incorporates more objective measures of symptom severity, but does not assess the duration of these effects. A more specific grading system for diarrhoea would be helpful in facilitating early identification of delayed diarrhoea and for defining effective treatment regimens. Such a grading system is currently being elaborated by a task force of experts.

In conclusion, the education of patients and physicians about the diagnosis and management of CPT-11-induced adverse events could improve the safety profile of this promising new anticancer agent. Further clinical studies are required to confirm these data and further improve the safety profile, to fully evaluate the pathophysiology of CPT-11-induced delayed diarrhoea and to optimise regimens for controlling this effect in patients with advanced colorectal cancer.

1. 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.
2. Leichman CG, Fleming TR, Muggia FM, *et al.* Phase II study of fluorouracil and its modulation in advanced colorectal cancer: a Southwest Oncology Group study. *J Clin Oncol* 1995, **13,** 1303–1311.
3. Petrelli N, Douglass HO Jr, Herrera L, *et al.* The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: a prospective randomized phase III trial. *J Clin Oncol* 1989, 7, 1419–1426.
4. Advanced Colorectal Cancer Meta-Analysis Project. Meta analysis of randomised trials testing the biochemical modulation of fluorouracil by methotrexate in metastatic colorectal cancer. *J Clin Oncol* 1994, **12,** 960–969.
5. Kemeny N, Younes A, Seiter K, *et al.* Interferon alpha-2a and 5-fluorouracil for advanced colorectal carcinoma. *Cancer* 1990, **66,** 2470–2475.
6. Armand JP, Ducreux M, Mahjoubi H, *et al.* CPT-11 (irinotecan) in the treatment of colorectal cancer. *Eur J Cancer* 1995, **31A,** 1283–1287.
7. Abigerges D, Chabot GG, Armand J, *et al.* Phase I and pharmacologic studies of the camptothecin analogue irinotecan administered every 3 weeks in cancer patients. *J Clin Oncol* 1995, **13,** 210–221.
8. Catimel G, Chabot GG, Guastalla JP, *et al.* Phase I and pharmacokinetic study of irinotecan (CPT 11) administered daily

for three consecutive days every three weeks in patients with advanced solid tumours. *Ann Oncol* 1995, **6**, 133–140.

9. De Forni M, Bugat R, Chabot GG, *et al.* Phase I and pharmacokinetic study of the camptothecin derivative irinotecan, administered on a weekly schedule in cancer patients. *Cancer Res* 1994, **54**, 4347–4354.
10. Rougier P, Culine S, Bugat R, *et al.* A phase II study of CPT-11 (irinotecan) in the treatment of advanced colorectal cancer in chemotherapy-naive patients and patients pretreated with 5-FU-based chemotherapy. *J Clin Oncol* 1996, in press.
11. Cascinu S. Drug therapy in diarrheal diseases in oncology hematology patients. *Crit Rev Oncol/Hematol* 1995, **18**, 37–50.