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ORIGINAL ARTICLE

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High-dose, single-agent irinotecan as first-line therapy in the treatment of metastatic colorectal cancer

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Abstract *Purpose:* The efficacy and safety of single-agent, high-dose irinotecan (CPT-11, Campto) 500 mg/m^2 every 3 weeks were investigated as first-line treatment for advanced colorectal cancer (CRC). *Patients and methods:* Patients were enrolled into the study to receive a first cycle of therapy with irinotecan at a dose of 350 mg/m^2 every 3 weeks, which could be escalated to 500 mg/m^2 for the second and subsequent cycles depending on toxicity. Efficacy, safety and pharmacokinetics were determined in the intent to treat (ITT) population and the high-dose population (i.e. patients who had received at least three cycles of irinotecan, the second and third at 500 mg/m^2). *Results:* Of 49 patients enrolled into the study (ITT population), 31 (63%) received at least three cycles of treatment with cycles 2 and 3 at an irinotecan dose of 500 mg/m^2 (the high-dose population). The response rates (RR) for the ITT and high-dose populations were 24.5% and 35.5%, respectively. The main grade 3/4 toxicities per cycle in the ITT and high-dose populations were neutropenia 22% and 17%, febrile neutropenia 5% and 3%, and diarrhoea 12% and 7%, respectively. The pharmacokinetics of irinotecan and its metabolite SN-38 were investigated in 31 patients in cycle 1 and 22 patients in cycle 2. Irinotecan clearance and SN-38 exposure were not sufficiently correlated with toxicity in cycle 1 to identify patients for dose increase in subsequent cycles. The exposure to irinotecan and SN-38 increased in proportion to dose from 350 to 500 mg/m^2. *Conclusion:* These results suggest that high-dose irinotecan can be safely administered as first-line monotherapy to approximately two-thirds of patients who present with advanced CRC following a selective first cycle.

Keywords Irinotecan · CPT-11 · Campto · First-line · CRC · Metastatic CRC · High-dose

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Introduction

Colorectal cancer (CRC) is second in the league of cancer deaths worldwide, and the commonest cancer in France with 33,000 new cases and 17,000 deaths annually [1]. Primary treatment for CRC is surgical resection, but 50% of patients will develop metastatic disease. Systemic therapy based on 5-fluorouracil (5-FU) has been the mainstay of palliative treatment for patients with advanced CRC for more than 40 years. During this time, biomodulation with folinic acid (FA, leucovorin) [2] and methotrexate [3], and administration as a continuous infusion rather than as an intravenous (i.v.) bolus [4, 5, 6], have both been associated with increases in response rate (RR). More recently, the topoisomerase 1 inhibitor irinotecan (CPT-11, Campto) has been found, amongst other agents, to show at least similar efficacy to 5-FU [7, 8, 9] in first-line therapy, as well as

efficacy in patients who have relapsed following 5-FU-based therapy [8, 9, 10, 11, 12, 13, 14, 15], with RRs ranging from 8.8% to 25% being achieved.

Furthermore, a clear survival advantage has been demonstrated for irinotecan, 300–350 mg/m^2 every 3 weeks, over best supportive care (BSC) [12] and infusional 5-FU alone [13], coupled with an improvement in quality of life compared to BSC. However, a review of the initial phase I studies conducted in Japan, France and the US has suggested that irinotecan might exhibit a schedule- or dose-dependent antitumour activity [16]. Three different French phase I trials using three different schedules were included in this analysis [17, 18, 19]. One of the French phase I studies in which single-dose irinotecan every 3 weeks was used [18] resulted in a recommended a dose of 350 mg/m^2 on safety grounds, although it was suggested that with careful monitoring of gastrointestinal toxicity a higher dose of 500 mg/m^2 might be achievable in ''good-risk'' patients. As a continuation of this study, the feasibility of treating patients with advanced CRC, with high-dose irinotecan at either 600 mg/m^2, the MTD in the phase I study [18], or 500 mg/m^2, the level below, was investigated [20]. At the 600 mg/m^2 dose level 50% of patients had at least one dose reduction and one toxic death was reported. As a result accrual at this dose level was stopped and was continued at the 500 mg/m^2 dose level, with careful monitoring. Six partial responses (PRs) were recorded among 17 patients who had not been heavily pretreated. All six patients had received prior chemotherapy and four had exhibited disease progression on prior 5-FU-based chemotherapy. The 35% RR in this study is high compared with the studies referred to above, and the safety at this dose level was considered acceptable.

Although irinotecan in combination with 5-FU/FA is the currently recommended first-line therapy for patients with metastatic CRC in both Europe and the US [21, 22], different doses and schedules of single-agent irinotecan continue to be investigated as first-line (present study; [23]) and second-line [24, 25, 26, 27] therapy, with a view to optimizing the therapeutic outcome for these patients. The aim of the present study was to assess the efficacy and patient tolerance of single-agent high-dose irinotecan (500 mg/m^2) administered once every 3 weeks as first-line treatment of metastatic CRC following a first cycle of therapy in which irinotecan was administered at the standard recommended dose of 350 mg/m^2. The results are discussed in relation to the currently available efficacy and safety data for irinotecan, either alone or in combination with other agents, in the treatment of patients with metastatic CRC.

Patients and methods

Patient selection

Patients with histologically proven adenocarcinoma of the colon or rectum were eligible for inclusion if they had not received prior chemotherapy other than neoadjuvant or adjuvant treatment and fulfilled the following criteria: metastatic measurable disease outside a previously irradiated field, age between 18 and 70 years, good performance status ≤ 1, without chronic diarrhoea requiring treatment, adequate haematological function (absolute neutrophil count $\geq 2.0\times10^9$/l, platelets $\geq 100\times10^9$/l), renal (serum creatinine level ≤ 135 μmol/l) and hepatic function (total bilirubin not more than the upper normal limit (UNL) and alkaline phosphatase not more than 2.5 times the UNL except for patients with bone metastasis). Patients were excluded if they had at least one of the following: no measurable disease, prior palliative chemotherapy for metastatic disease or prior treatment with topoisomerase I inhibitor, unresolved bowel obstruction or semiobstruction, prior enteropathy or extensive intestinal resection, uncontrolled severe infection, clinical evidence of major organ failure or other serious illness or medical condition, or a history of a previous malignancy other than CRC, unless it was curatively treated non-melanoma skin cancer or in situ carcinoma of the cervix. All participating patients had to provide written informed consent. The study was approved by the French ethical committee, and was conducted in accordance with good clinical practice guidelines.

Treatment administration

Irinotecan was administered by i.v. infusion over 30 min once every 3 weeks. During the first cycle irinotecan was administered at a dose of 350 mg/m^2. For the second cycle the irinotecan dose was administered according to the toxicities recorded during the first cycle, and formed the basis of the selection of the high-dose population used in subsequent analyses.

In the absence of NCI toxicity of grade 2 or more, irinotecan was administered at a dose of 500 mg/m^2. In patients in whom grade 3/4 neutropenia was reported or no haematological recovery was recorded by day 21 of the first cycle, irinotecan was administered at a dose of 500 mg/m^2 plus G-CSF (granulocyte-colony stimulating factor) at a dose of 263 μg/day on days 2–10 of the cycle in order to maintain the high-dose treatment. In patients in whom grade 3/4 toxicities were seen in the first cycle (except for neutropenia or nausea and vomiting) irinotecan was administered at a dose of 300 mg/m^2 for two cycles or discontinued at the investigator's discretion. Dose escalation was not allowed and further treatment (irinotecan or other) was given at the investigator's discretion. For subsequent cycles the dose of irinotecan was determined by the toxicities observed during the previous cycle (Table 1) with G-CSF support where appropriate.

If an infusion was to be delayed by more than 1 week, the dose was reduced to the level below. If in spite of this dose reduction the same toxicity persisted, the treatment was stopped. If no recovery was observed after a delay of 4 weeks, the patient was withdrawn from the study. Prophylactic antiemetic treatment was administered routinely at the discretion of the investigator, and when cholinergic syndrome occurred it was treated with atropine (0.25 mg administered subcutaneously), which was used prophylactically, where appropriate, in subsequent cycles. Patients were treated curatively for delayed diarrhoea with loperamide (one capsule every 2 h for a maximum of 24 h). If diarrhoea persisted for more than 24 h, despite the recommended treatment, fluoroquinolone-based therapy was given as prophylactic treatment.

Treatment was continued for up to nine cycles or until disease progression, unacceptable toxicity was recorded or the patient refused further treatment. Following completion of treatment, patients were followed up every 3 months until death or the cut-off date.

Patient assessment

Prior to inclusion patients were subjected to a pretrial evaluation that included a physical examination (height, weight, WHO performance status), clinical history and clinical evaluation of the tumour, haematological assessment, biochemical assessment and

Table 1. Dose modifications

Toxicity in previous cycle	Action in subsequent cycles	
	Patient not receiving G-CSF	Patient already receiving G-CSF
Absence of NCI toxicity more than grade 2	Previous cycle irinotecan dose	Previous cycle irinotecan dose
Grade 4 neutropenia or no haematological recovery by day 21	Irinotecan dose of the previous cycle with G-CSF	Irinotecan dose reduction to dose level below (420 or 350 mg/m^2) If patient already treated at 350 mg/m^2, treatment discontinued
Grade 3/4 toxicities (except neutropenia, nausea/vomiting)	Irinotecan dose reduction to dose level below (420 or 350 mg/m^2) If patient already treated at 350 mg/m^2, treatment discontinued	Irinotecan dose reduction to dose level below (420 or 350 mg/m^2) If patient already treated at 350 mg/m^2, treatment discontinued

tumour assessment by chest radiography if necessary and/or CT scan.

During the trial patients received a physical examination before each cycle and at the end of treatment. All adverse events experienced during the study were recorded and graded according to NCI common criteria (NCI Guidelines version 1), or if not applicable as 1 mild, 2 moderate, 3 severe, 4 life threatening. Patients were subjected to a weekly haematological assessment comprising RBC, haemoglobin, WBC, ANC, platelet count and prothrombin time. Biochemical assessments were made before each cycle and at the end of treatment and comprised sodium, potassium, calcium, serum creatinine, protein levels, total and conjugated bilirubin, alkaline phosphatase, liver enzymes, LDH and CEA.

Efficacy assessment

The primary efficacy endpoint was the RR. Tumour assessments (CT scan) were made every three cycles and at the end of treatment, and responses were evaluated according to standard WHO criteria. All responses and stabilizations were reviewed by an external response review committee (ERRC). All uni- and bidimensionally measurable lesions were assessed after cycles 3, 6 and 9. Additional assessments to confirm response were made 28 days after the initial response had been observed. All evaluable and nonevaluable lesions (ascites, and pleural and pericardial effusions) were reported and assessed together. Secondary efficacy endpoints included duration of response, time to progression (TTP, defined as the time from first infusion to first documentation of progression or death due to progression) and survival. All patients enrolled in the study and who had received at least one dose of irinotecan (ITT population) were assessed for efficacy. To be evaluable for response, patients had to have had at least three protocol-defined cycles of treatment (i.e. 9 weeks on study), with at least one follow-up tumour assessment and measurable disease. However, if disease progression was observed earlier than 9 weeks from entry into the study (early progression), the patient was still evaluated for response.

Pharmacokinetic methods

For pharmacokinetic assessment, heparinized blood samples (5 ml) were collected for the first two cycles of treatment following a limited sampling strategy based on the multiple linear regression approach proposed by Chabot [28]: predose and 0.5, 1.0 and 6.0 h after the beginning of the i.v. bolus infusion. Blood was immediately centrifuged at 2000 rpm for 5 min and the plasma was frozen at –20°C until analysis.

Plasma samples were analysed for irinotecan and SN-38 concentration using a HPLC method which is described in Aventis files. Briefly the method involved measurement of total (lactone plus carboxylate) forms by a validated reversed-phase HPLC method with solid-phase extraction and fluorescence detection. The use of a pH-3 buffer allowed carboxylate forms to turn into lactone forms. The assay was linear from 10.0 to 10,000 ng/ml for irinotecan and from 2.5 to 2500 ng/ml for SN-38. The coefficients of determination (r^2) for standard curves of irinotecan and SN-38, respectively, ranged from 0.9944 to 0.9987 and from 0.9957 to 0.9999 over the analysis period. Accuracy, defined as the percent difference between the nominal and the mean measured concentrations of quality controls ranged from −3.7% to 4.0% for irinotecan and from –3.9% to 1.2% for SN-38. The precision of the assay, established by coefficients of variation of the quality controls, ranged from 2.7% to 7.7% for irinotecan and from 3.6% to 7.9% for SN-38 in plasma over the analysis period. The method demonstrated adequate precision and accuracy for the measurement of both analytes, irinotecan and SN-38.

Pharmacokinetic analysis

The plasma concentration-time profiles of irinotecan and SN-38 were analysed using non-linear mixed-effect modelling as implemented in the NONMEM program (University of California at San Francisco, San Francisco, Calif.). Pharmacokinetic parameters were determined using the Bayesian approach with the concentration-time data from each patient and the population model previously defined. Three- and two-compartment structural models were used for irinotecan and SN-38, respectively. Pharmacokinetic parameters, including maximum plasma concentration (Cmax), time to reach the maximum plasma concentration (tmax), and area under the plasma concentration-time curve from 0 to infinity (AUC) were determined. For irinotecan, total body clearance (CL) was estimated and for SN-38 the AUC_N normalized to the 1-mg irinotecan dose was calculated.

Statistical analysis of pharmacokinetic data

The log-transformed values of the pharmacokinetic parameters (CL of irinotecan and dose-normalized AUC of SN-38) at each dose level were compared. The mixed procedure of SAS software (version 6.12; SAS Institute, Cary, N.C.) was used, taking the treatment cycle as the fixed effect and the subject as the random effect.

Statistical analysis

The required number of patients for this phase II study was determined according to a two-stage Simon design. The design parameters assessed the treatment to be insufficiently active if the objective RR was less than 15% and sufficiently active if the objective RR was at least 30%. A maximum of 48 evaluable patients needed to be included in the study, assuming an α error rate of 0.05 and a β error rate of 0.20. The efficacy analysis was performed on all patients. The 95% confidence limits were provided for RRs using the exact method. Time-related parameters were analysed using the Kaplan-Meier method.

The safety analysis was performed on the data from all patients who had received at least one dose of irinotecan. The safety

analysis for high-dose irinotecan was performed on the data from all patients who had received full high-dose irinotecan for at least cycles 2 and 3 (500 mg/m^2).

Results

Patient characteristics

This was an open-label, multicentre phase II study. The baseline characteristics of the patients are presented in Table 2. A total of 49 patients with metastatic CRC were enrolled in the study and treated (the ITT population), and eventually 31 patients received at least two cycles of high-dose irinotecan, cycles 2 and 3 (the high-dose population; Fig. 1). In order to allow the maximum dose intensity, if after the first injection (first cycle) grade 3/4 neutropenia and/or other haematological toxicities were observed, which had not recovered by day 21, the patient went on to receive high-dose irinotecan plus G-CSF support on days 2–10 of the next cycle. For further cycles, G-CSF administration was permitted in the event of grade 3/4 neutropenia. G-CSF support was also permitted to maintain the initial standard dose of irinotecan if necessary. Efficacy and safety analyses were performed on the data from all patients (Fig. 1). The results are discussed in terms of the ITT and high-dose populations, but it should be noted that no statistical comparisons could be made, because the high-dose population was a subgroup of the ITT population.

There were no obvious differences in the baseline characteristics of the patients to indicate whether or not they could receive high-dose irinotecan or if they would present with toxicity during the first cycle. Overall, 94% and 97% of patients had undergone prior surgery and 22% and 23% prior radiotherapy in the ITT and high-dose patient groups, respectively (Table 2). The high number of patients who had received prior radiotherapy was a reflection of the number of patients with rectal cancer.

Overall, nine patients failed to receive high-dose irinotecan (Fig. 1), seven due to grade 3/4 nonhaematological toxicity, one due to persistent grade 2 asthenia and weight loss, and one due to an early death related to disease progression.

In the ITT population (Fig. 1), all patients were evaluable for safety. However, five patients were none-valuable for response by the ERRC. These included four patients who stopped treatment early because of a nonhaematological grade 3/4 toxicity after the first cycle at an irinotecan dose of 350 mg/m^2, and one patient who was assessed by the ERRC as having a nonmeasurable lesion and therefore as being ineligible.

Table 2. Summary of patient characteristics at study entry

	ITT population ($n=49$)	High-dose population ($n=31$)
Gender		
Male	30 (61.2%)	20 (64.5%)
Female	19 (38.8%)	11 (35.5%)
Age (years)		
Median	56	63
Range	35–71	35–71
WHO performance status		
0	34 (69%)	23 (74%)
1	15 (31%)	8 (26%)
Primary tumour site		
Colon	36 (73.5%)	22 (71%)
Rectum	13 (26.5%)	9 (29%)
Prior treatment		
Surgery	46 (94%)	30 (97%)
Radiotherapy	11 (22%)	7 (23%)
Chemotherapy (adjuvant and/or neo-adjuvant)	18 (37%)	12 (39%)
No. of metastatic organs involved		
1	26 (53%)	15 (48%)
2	17 (35%)	12 (39%)
3 or more	6 (12%)	4 (13%)
Sites of disease		
Liver	40 (82%)	25 (81%)
Lung	22 (45%)	16 (52%)
Abdominal lymph nodes	10 (20%)	6 (19%)
Thoracic lymph nodes	3 (6%)	2 (6%)
Pelvic lymph nodes	1 (2%)	1 (3%)
Locoregional relapse	1 (2%)	1 (3%)
Peritoneum	0	0
Bone	0	0
Other	2 (4%)	1 (3%)

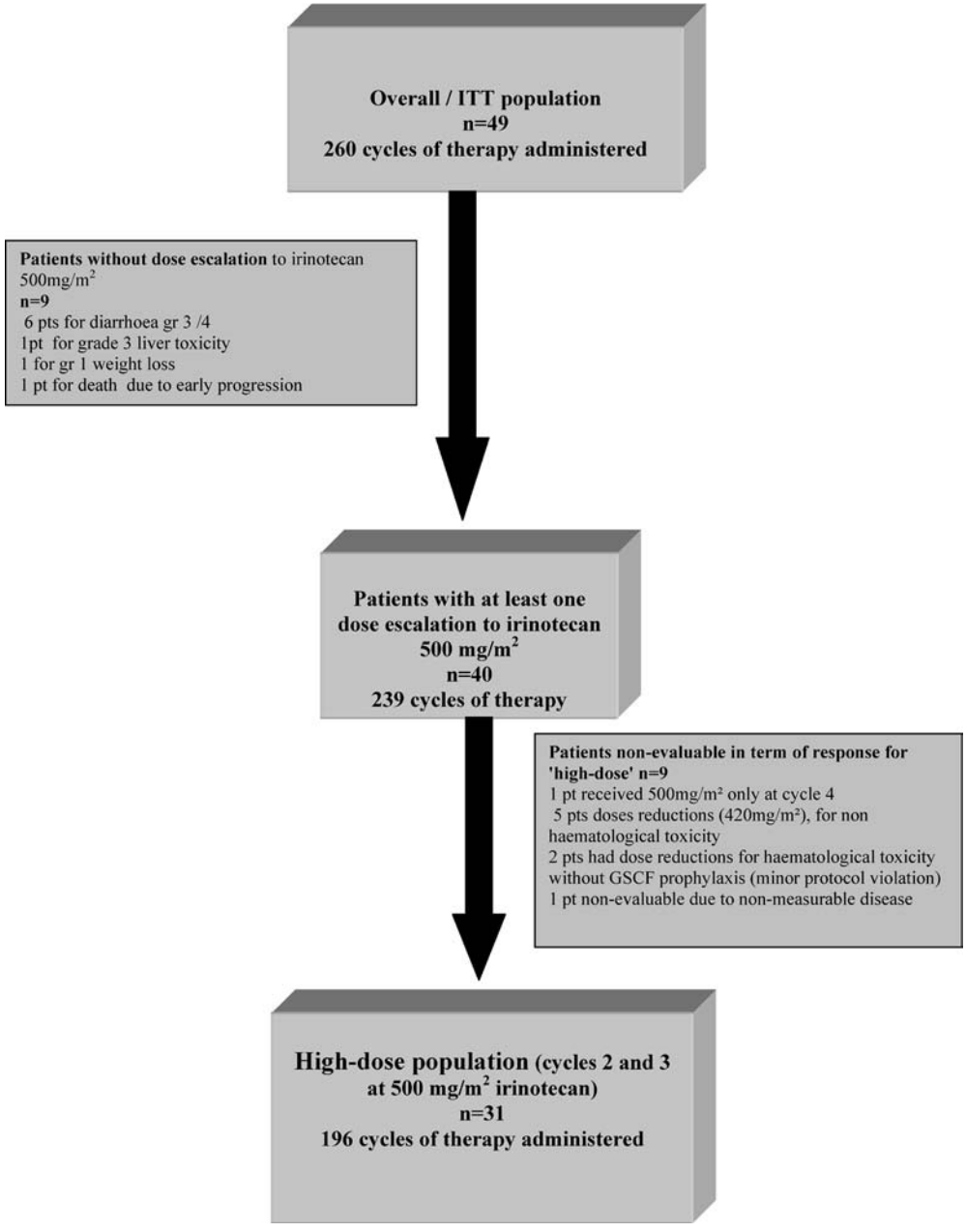

Fig. 1. Summary of patient populations and treatment cycles

Efficacy

As stated above, the primary efficacy endpoint of this study was the RR. The median follow-up time for the ITT population was 30.4 months (95% CI 25.2–36.7). Overall, there were 12 ERRC-confirmed responses in the ITT population of which 11 were observed in the high-dose population yielding RRs of 24.5% (95% CI 13.4–38.9) and 35.5% (95% CI 19.2–54.6), respectively (Table 3). Five patients had stable disease (SD) because PRs were not confirmed. Three of these patients were in the high-dose population. Among the 13 patients with SD, 8 were considered to have had minor responses (5 in the high-dose population). Overall, 51% and 64.5% tumour growth control (PR plus SD) was reported for the ITT and high-dose populations, respectively. Of 13 patients who went on to receive surgical resections, 8 received surgical resection of their metastatic lesions following their response to first-line irinotecan treatment, and the remaining 5 received surgical resections following response to second-line therapy.

The median time to response was identical for both populations at 2.0 months. The median duration of responses was 8.4 months (95% CI 6.3–14.4) in the ITT population and 7.8 months (95% CI 6.3–10.1) in the high-dose population. The median duration of disease stabilization was 6.4 months for both populations. The median TTP was 4.4 months (95% CI 2.1–6.7) in the ITT population and 5.7 months (95% CI 2.6–6.7) in the high-dose population. Median overall survival was

Table 3. Efficacy data for the treated populations. All the responses were confirmed by a CT scan 4 weeks after the first noting of response and reviewed by the ERRC

Efficacy parameter	ITT population ($n=49$)	High-dose population ($n=31$)
Partial response [n (%)]	12 (24.5)	11 (35.5)
Stable disease [n (%)]	13 (26.5)	9 (29.0)
Progressive disease [n (%)]	19 (38.8)	11 (35.5)
Not evaluable [n (%)]	5 (10.2)	–
Duration of response (months)		
Median	8.4	7.8
95% CI	6.3–14.4	6.3–10.1
Time to progression (months)		
Median	4.4	5.7
95% CI	2.1–6.7	2.6–7

19.5 months (95% CI 15.7–20.2) for the ITT population. Overall, 29% of patients were alive at 2 years. Of 41 patients who received second-line chemotherapy, 18 received the "de Gramont" schedule, 17 oxaliplatin-based therapy, and 6 various other schedules.

Drug exposure

A total of 260 cycles of therapy were administered to 49 patients. The median number of cycles per patient administered was six (range one to nine). The actual dose intensities of irinotecan for the ITT and high-dose populations were 143.9 and 152.4 mg/m^2 per week, respectively. After the third cycle, the relative dose intensity obtained in the high-dose treatment was 0.98, indicating the feasibility of maintaining the high dose. Excluding cycle 1 administered at a dose of 350 mg/m^2 irinotecan, 99% of cycles were given at a higher dose of irinotecan, 90% (148/164) at 500 mg/m^2 and 9% (15/164) at 420 mg/m^2 irinotecan. Only five patients and six cycles were associated with dose reductions in the high-dose population, after cycle 4. Of the five patients in the high-dose population, two had a dose reduction for grade 4 neutropenia without fever (despite one of them receiving G-CSF), two for grade 3 nonhaematological toxicities (diarrhoea in one and vomiting in the other), and one due to prescription error.

Treatment delays were more common than dose reductions. For the high-dose population, 18 out of 164 cycles (11%) were delayed by 3 days or more, and 7 cycles were delayed more than 7 days, in a total of 16 patients. For 13 (81%) of these patients in the high-dose group the delayed cycles were unrelated to treatment and were either at the request of the patient or due to a delayed appointment for tumour evaluation prior to the next cycle. Other reasons for cycle delays were haematological toxicity (one patient) and nonhaematological toxicity (two patients). Only one cycle was both delayed and reduced in the high-dose population.

Safety

All 49 patients treated in this study were evaluable for safety. All NCI grade 3/4 haematological and nonhaematological toxicities are summarized in relation to the ITT and high-dose patient populations in Table 4.

Table 4. Haematological grade 3/4 toxicity and grade 3/4 adverse events possibly related to study treatment (worst grade by patient and worst grade by cycle). Values are number (%) of patients/cycles

Grade 3/4 toxicity/adverse event	ITT population		High-dose population	
	Patients ($n=49$)	Cycles ($n=259/260$[a])	Patients ($n=31$)	Cycles ($n=194/195$[a])
Neutropenia	29 (59%)	58 (22%)	15 (48%)	33 (17%)
Febrile neutropenia	10 (20%)	14 (5%)	4 (13%)	5 (3%)
With concomitant infection	–	–	–	–
Anaemia	7 (14%)	15 (6%)	3 (10%)	6 (3%)
Thrombopenia	1 (2%)	2 (1%)	–	–
Gastrointestinal toxicity				
Diarrhoea	20 (41%)	31 (12%)	7 (23%)	13 (7%)
Nausea	11 (22%)	13 (5%)	4 (13%)	5 (3%)
Vomiting	9 (18%)	9 (3%)	4 (13%)	4 (2%)
Other toxicity				
Cholinergic syndrome	2 (4%)	3 (1%)	2 (6%)	3 (2%)
Anorexia	10 (20%)	12 (5%)	3 (10%)	5 (3%)
Asthenia	16 (33%)	22 (8%)	6 (19%)	8 (4%)
Mucositis	–	–	–	–
Infection without neutropenia	2 (4%)	2 (1%)	–	–
Alopecia grade 2	22 (45%)	104 (40%)	13 (42%)	69 (35%)

[a]One patient did not have any blood count during one cycle and so was not evaluable for one cycle

The main haematological toxicity was neutropenia, which occurred in 88% of patients and 57% of cycles (data not shown) with 59% of patients (ITT population) experiencing grade 3/4 neutropenia in 22% of cycles (Table 4). This included febrile neutropenia without any concomitant infection, which was reported in 20% of patients and 5% of cycles. The incidence of all grade 3/4 haematological toxicities was lower in the high-dose population (Table 4) with 48% of patients experiencing grade 3/4 neutropenia in 17% of cycles. Febrile neutropenia in the absence of concomitant infection occurred in only 13% of patients and 3% of cycles (Table 4).

G-CSF was administered on days 2 to 10 in 15 patients (59 of 211 cycles) in the ITT population and in 10 patients (39 of 164 cycles) in the high-dose population. Five patients received G-CSF although they were not in the high-dose population. These included one patient who did not receive high-dose 500 mg/m^2 irinotecan in cycle 2 and 3, but did receive this dose in cycles 4, 5 and 6, one patient who had persisting grade 2 asthenia and received only 420 mg/m^2 in subsequent cycles, two patients who received reduced-dose irinotecan and G-CSF in cycle 3 due to febrile neutropenia during the cycle, and one patient who experienced grade 3 diarrhoea during cycle 2 at high-dose and received a reduced dose of 420 mg/m^2 of irinotecan in cycle 3 and continued treatment at this level with G-CSF from cycle 4 onwards.

The main nonhaematological toxicities in the ITT population were gastrointestinal, namely diarrhoea, which occurred in 90% of patients and 71% of cycles, with 41% of patients in 12% of cycles experiencing grade 3/4 toxicity (Table 4). In the high-dose population three patients experienced severe diarrhoea leading to hospitalization and each event was associated with febrile neutropenia. Apart from these gastrointestinal toxicities, the main nonhaematological events were alopecia, that was expected, in 84% of patients and asthenia in 80% of patients and 51% of cycles.

Several patients had graded liver transaminase levels at study entry and during the study one of these patients experienced grade 3 alanine and aspartate transaminase increases leading to hospitalization, which were not related to liver metastases. This patient withdrew from the study after the first cycle.

Discontinuations

There was one early death on day 11 of cycle 1 due to hepatic failure. The background to this was that the patient experienced grade 4 general status deterioration with grade 4 vomiting and grade 3 diarrhoea and was hospitalized on day 11. Rapid progression of the liver metastasis was considered to be the probable cause of death. A further ten patients (20.4%) withdrew from the study due to toxicity, five patients following treatment in cycle 1 with 350 mg/m^2 irinotecan, one patient during treatment in cycle 4 at 420 mg/m^2 with grade 4 febrile neutropenia, one patient during treatment in cycle 6 at 350 mg/m^2 with grade 3 diarrhoea and grade 4 febrile neutropenia and three patients in the high-dose population (one patient in cycle 3 with grade 3 asthenia, one patient in cycle 5 with grade 4 diarrhoea and grade 4 febrile neutropenia, and one patient in cycle 8 with grade 3 asthenia and grade 3 neurological signs).

Pharmacokinetic data

Pharmacokinetics were assessed in 31 patients in cycle 1 and 22 patients in cycle 2. The values obtained for the pharmacokinetic parameters were in accordance with those obtained in previous phase I and phase II studies [29, 30]. The total body clearance values for irinotecan and the dose-normalized AUC values for SN-38 were dose-independent (Table 5). No statistically significant difference between the first cycle (dose 350 mg/m^2) and

Table 5. Main pharmacokinetic parameters. Data are expressed as means ± SD (CV%) except for tmax which is median (fifth to ninth percentile)

	Cycle 1 ($n=31$)			Cycle 2 ($n=22$)
	Patients receiving cycle 2 ($n=22$)	Patients not receiving cycle 2 ($n=9$)	Total patients ($n=31$)	
Dose (mg/m^2)	350			500/420[a]
Infusion duration (h)	0.50–0.87			0.42–0.84
Irinotecan				
Cmax (mg/l)	6.58 ± 0.94 (14)	6.40 ± 1.31 (20)	6.53 ± 1.04 (16)	9.67 ± 1.34 (14)
AUC (mg·h/l)	25.9 ± 11.3 (43)	25.0 ± 12 (48)	25.7 ± 11.3 (44)	39.2 ± 16.8 (43)
CL (l/h/m^2)	13.3 ± 4.2 (32)	13.8 ± 4.8 (34)	13.4 ± 4.3 (32)	12.6 ± 4.2 (33)
SN-38				
tmax (h)[b]	–	–	0.6 (0.5–0.8)	0.6 (0.5–0.8)
Cmax (μg/l)	75.7 ± 31.3 (41)	72.0 ± 24.8 (34)	74.6 ± 29.2 (39)	98.6 ± 44.2 (45)
AUC (μg·h/l)	830 ± 400 (48)	800 ± 340 (43)	823 ± 377 (46)	1162 ± 554 (48)
AUC_N (μg·h/l)[b]	2.2 ± 0.9 (45)	2.2 ± 0.9 (40)	2.2 ± 1.0 (43)	2.2 ± 1.1 (48)

[a]Only one patient treated at 420 mg/m^2
[b]Normalized to 1 mg CPT-11 dose

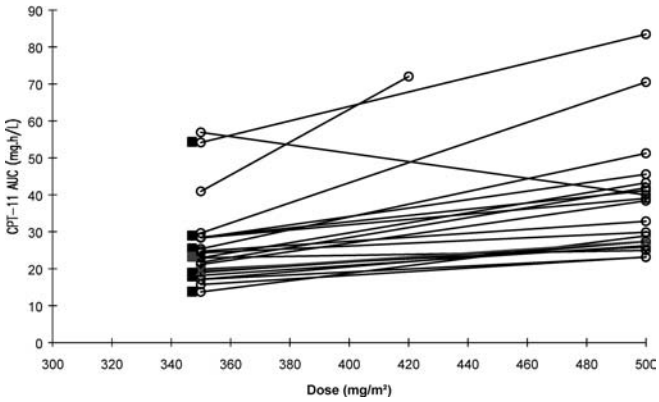

Fig. 2. Irinotecan AUC versus dose (*solid squares* patients treated only during cycle 1, *open circles* patients treated during cycle 1 and cycle 2)

the second cycle (dose 500 mg/m^2) was found for these parameters, as the *P* values were 0.26 for the CL of irinotecan (90% CI 85–103%) and 0.72 for the dose-normalized AUC of SN-38 (90% CI 88–109%). These data confirm the linearity of irinotecan pharmacokinetics over the 350 to 500 mg/m^2 dose range (Fig. 2).

During the first treatment cycle, exposures to irinotecan and SN-38 were similar between patients who were subsequently treated at 500 mg/m^2 and those who were not (Table 5). Irinotecan clearance and metabolite SN-38 exposure were not sufficiently correlated with toxicity in cycle 1 to identify patients for dose increase in subsequent cycles.

Discussion

This phase II multicentre study clearly demonstrated that it was possible to increase the dose of irinotecan above the recommended dose of 350 mg/m^2 in monotherapy every 3 weeks in 63% of selected patients (31/49) receiving this treatment as first-line therapy. This increase in dose seemed to be associated with an increase in activity, as indicated in the phase II study of Merrouche et al. [20]. The efficacy data presented in Table 3 suggest that the activity of irinotecan was dose-dependent, with the highest RR (35.5%) being observed in the high-dose population that received at least two cycles of irinotecan at a dose of 500 mg/m^2 and the lowest (24.5%) in the ITT population that included nine patients who had not received any high-dose irinotecan.

These findings are also supported by the observations made in previous phase I studies [16, 17, 18, 19, 20]. The RR for the ITT population (24.5%) was the highest RR recorded by an ERRC for a single agent (e.g. oxaliplatin, topotecan, raltitrexed, capecitabine) tested in a phase II study for the treatment of metastatic CRC. The RR of the high-dose population in the present study (35.5%, reviewed by an ERRC) is also higher than those obtained for the recommended dose of irinotecan in studies of the first-line treatment of CRC [7, 8, 9, 10, 16, 22] and is of a similar order of magnitude to those obtained for irinotecan in combination with 5-FU/FA in the pivotal European and US phase III studies [21, 22]. In fact, in a previous multicentre phase II study, the single-agent first-line response for irinotecan administered at a dose of 350 mg/m^2 every 3 weeks was 18.8% [10], and in the pivotal US phase III study, in which irinotecan was delivered at 125 mg/m^2 as an i.v. bolus weekly for 4 weeks in every 6 weeks, it was 18% [22]. Furthermore, the overall survival in the present study (19.5 months) was higher than the survival reported overall in phase II studies. The overall survival in chemonaive patients in the phase II study of Rougier et al. [10] was only 12 months. Consistent with these observations, the pharmacokinetic data showed linearity between the administered dose and the pharmacokinetic values over the 350–500 mg/m^2 dose range.

In the present study, the dose of irinotecan administered during the first cycle was 350 mg/m^2. This dose of irinotecan was escalated to 500 mg/m^2 in patients without nonhaematological grade 3/4 toxicities during cycle 1, especially diarrhoea. Patients with toxicity received subsequent cycles at 350 mg/m^2 or dropped out of the study. In those patients who had not achieved haematological recovery by day 21 of the cycle, irinotecan was administered at the higher dose with G-CSF support. This individual dose adaptation allowed the selection of a subpopulation of patients with the potential to benefit from high-dose irinotecan and the avoidance of severe toxicity in those patients who were never going to tolerate well even the recommended 350-mg/m^2 irinotecan dose level. Overall, 63% of patients were able to receive high-dose therapy for at least cycles 2 and 3, and only 18% of patients did not receive any high-dose therapy (Fig. 1). Following a similar line of thought, i.e. optimization of the dose of irinotecan, Van Cutsem et al. have reported the preliminary data from a phase II trial of irinotecan dose adaptation based on safety and prognostic factors [25]. In patient groups B and C in the study by Van Cutsem et al., the first irinotecan dose in cycle 1 was 250 mg/m^2 every 3 weeks, which was then increased to 350 mg/m^2 and 500 mg/m^2. This dose adaptation was based on safety for group B and prognostic factors for group C. In group B, 32% of patients were able to receive 500 mg/m^2 irinotecan, and 27% of them received nine cycles.

In conclusion, the efficacy, safety and pharmacokinetic data generated in the present study show that high-dose irinotecan (500 mg/m^2) can be administered to approximately two-thirds of patients who present with advanced CRC following a selective first cycle at the standard 350-mg/m^2 dose. Compared to currently available efficacy and safety data for irinotecan in the treatment of patients with metastatic CRC, increased efficacy was obtained in our subpopulation selected for high-dose treatment, in the absence of any significant increase in toxicity, in a certain subset of patients. Thus,

although this study was not randomized as noted above (the high-dose population was a subgroup of the ITT population), its findings indicate that irinotecan dose adaptation may enhance clinical benefit without impairing quality of life. Of the 49 patients, 41 went on to receive second-line chemotherapy and 13 went on to receive surgical resections, 8 following response to first-line irinotecan monotherapy and 5 after responding to second-line chemotherapy.

These results suggest that high-dose irinotecan, following a first cycle at the standard recommended dose, may be useful as first-line therapy in patients with contraindications to 5-FU/FA (e.g. angina pectoris, dihydropyrimidine dehydrogenase insufficiency) or as second-line therapy after progressive disease, where irinotecan has already shown a survival benefit at a dose of 350 mg/m^2.

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