A randomised phase II multicentre trial of irinotecan (CPT-11) using four different schedules in patients with metastatic colorectal cancer

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The purpose of this phase II trial was to compare the efficacy, safety and pharmacokinetics of four irinotecan schedules for the treatment of metastatic colorectal cancer. In total, 174 5-fluorouracil pretreated patients were randomised to: arm A (n = 41), 350 mg m⁻² irinotecan as a 90-min i.v. infusion q3 weeks; arm B (n = 38), 125 mg m⁻² irinotecan as a 90-min i.v. infusion weekly × 4 weeks q6 weeks; arm C (n = 46), 250 mg m⁻² irinotecan as a 90-min i.v. infusion q2 weeks; or arm D (n = 49), 10 mg m⁻² day⁻¹ irinotecan as a 14-day continuous infusion q3 weeks. No significant differences in efficacy across the four arms were observed, although a shorter time to treatment failure was noted for arm D (1.7 months; P = 0.02). Overall response rates were in the range 5–11%. Secondary end points included median survival (6.4–9.4 months), and time to progression (2.7–3.8 months) and treatment failure (1.7–3.2 months). Similarly, there were no significant differences in the incidence of grade 3–4 toxicities, although the toxicity profile between arms A, B, and C and D did differ. Generally, significantly less haematologic toxicity, alopecia and cholinergic syndrome were observed in arm D; however, there was a trend for increased gastrointestinal toxicity. Irinotecan is an effective and safe second-line treatment for colorectal cancer. The schedules examined yielded equivalent results, indicating that there is no advantage of the prolonged vs short infusion schedules.

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Irinotecan (CPT-11, Campto®) is a semisynthetic water-soluble derivative of the plant alkaloid camptothecin. Irinotecan is used for the first- and second-line treatment of advanced colorectal cancer following 5-fluorouracil (5-FU)-based therapy (Cunningham et al, 1998; Stewart et al, 1998). The cytotoxic effect of irinotecan and SN-38 is cell cycle specific and therefore prolonged infusions could increase the antitumour activity (Hsiang et al, 1989b; Burris et al, 1992).

Preclinical data and some clinical data support the use of prolonged exposure schedules of camptothecins (Furuta and Yokokura, 1990; Houghton et al, 1995; O’Reilly and Rowinsky, 1996). Phase I studies have employed different administration schedules and dosages of irinotecan, including a prolonged infusion schedule. Diarrhoea and/or neutropenia were the major dose-limiting toxicities in these studies (Masuda et al, 1996; O’Reilly and Rowinsky, 1996; Herben et al, 1999). Three schedules with short infusions were used in phase II studies, a 90-min infusion once every 3 weeks, a 90-min weekly infusion and a fortnightly 90-min infusion (Shimada et al, 1993; Rothenberg et al, 1996; Pilut et al, 1997; Rouzier et al, 1997; Cunningham et al, 1998;
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MATERIALS AND METHODS

Inclusion/exclusion criteria

Patients were included in the study if they had histologically proven adenocarcinoma of the colon or rectum and metastatic disease at study entry (within 6 months of the last thymidylate synthase inhibitor administration). Only patients with measurable metastatic disease were included, and if only one metastatic lesion was present a histologic examination was mandatory. Other inclusion criteria included: age 18–75 years, World Health Organization (WHO) performance status (PS) ≤2, and estimated life expectancy of >3 months (Anonymous, 1979). Patients had to have sufficient haematologic function, defined as neutrophil count \( \geq 1.0 \times 10^9/\text{l} \), haemoglobin \( \geq 6.5 \text{ g/dl} \) and platelet count \( \geq 50 \times 10^9/\text{l} \); adequate hepatic and renal function, defined as total bilirubin \( \leq 1.5 \times \text{the upper normal limit (UNL)} \), transaminases \( \leq 3 \times \text{UNL or } \leq 5 \text{ times when related to liver metastases and serum creatinine } \leq 1.5 \times \text{UNL} \).

All patients should have received adjuvant and/or palliative chemotherapy based on thymidylate synthase inhibitors (5-FU or raltitrexed) within 6 months of study entry. Patients could not have undergone chemotherapy or surgery within at least 4 weeks before entry into the study, or 6 weeks in the case of mitomycin C, nitrosourea or extended field radiation therapy. The overall number of prior chemotherapy regimens could not exceed 2, if one of them was given with adjuvant intent, or 1 if only a palliative regimen was given. Patients had to be suitable and willing to undergo insertion of a portable device and indwelling catheter (Port-a-Cath).

Exclusion criteria included a history of treatment with any topoisomerase inhibitor, chronic enteropathy (Crohn’s disease, ulcerative colitis), bowel obstruction or sub-obstruction, prior or current history of chronic diarrhea, symptomatic brain metastasis, current infection, other serious illness or medical conditions or a history of other cancer, except adequately treated in situ cervical carcinoma or nonmelanoma skin cancer. The study protocol was approved by an independent Ethics Committee, in agreement with local legal prescriptions. All patients gave written informed consent.

Trial design

This was a prospective, nonblinded, multicentre, phase II study, which planned to comprise at least 148 eligible and evaluable patients. A total of 17 centres in Europe participated in this study: two in Denmark, one in Ireland, four in The Netherlands, five in Norway, two in Sweden and three in Russia. Patients were treated with four different schedules of irinotecan. Randomisation was performed centrally by Aventis Pharma R&D, Antony Cedex, France. The primary end point of this study was response rate; the Simon design was used to rank these results. A total of 37 evaluable patients per arm had to be included. With this sample size and the hypothesis that the lowest expected baseline response rate would be 10%, there was a 90% probability of selecting the best treatment group on categorical variables.

Treatment plan

Patients randomised to arm A received 350 mg m\(^{-2}\) irinotecan as a 90-min i.v. infusion every 3 weeks, patients in arm B received 125 mg m\(^{-2}\) irinotecan as a 90-min i.v. infusion weekly for 4 weeks every 6 weeks and patients in arm C received 250 mg m\(^{-2}\) irinotecan as a 90-min infusion every 2 weeks. Patients in arm D were treated with irinotecan given as a 14-day infusion at a dose level of 10 mg m\(^{-2}\) day\(^{-1}\), which was repeated every 3 weeks. One treatment course was defined as one 90-min infusion in arms A, B or C (every 3 weeks, weekly or every 2 weeks, respectively) and a continuous infusion over 14 days administered every 3 weeks in arm D. A cycle was defined as a treatment period of 6 weeks; a complete cycle for patients in arms A and D consisted of two courses of irinotecan, yielding total dose intensities of 700 and 280 mg m\(^{-2}\) per 6 weeks, respectively, a cycle in arm B consisted of four courses yielding a dose intensity of 500 mg m\(^{-2}\) per 6 weeks and a cycle for patients in arm C consisted of three courses of irinotecan, yielding a dose intensity of 750 mg m\(^{-2}\) per 6 weeks.

Toxicity and response evaluation

Pretreatment evaluation included a complete medical history and complete physical examination. Before each course, blood chemistry and haematology profiles were checked. Haematology was checked weekly. Tumour measurements were performed every other cycle (6 weeks) and responses were scored according to WHO criteria (Anonymous, 1979). An external response review committee (ERRC) was established during the study to perform assessments of tumour response. All toxicities were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) (Anonymous, 2004). Adverse events that were not reported according to NCI-CTC were graded as mild, moderate, severe, or life threatening.

Pharmacokinetics

A pharmacokinetic evaluation was performed using a population approach; 88 patients from arms A, B and C were evaluated during the first course of treatment. The sampling strategy consisted of three different sampling schedules (with three sampling times in each): schedule 1: 30 min before the end of the infusion, 5 min and 3–4 h post-infusion; schedule 2: 30 min before the end of the infusion, 10 min and 5–7 h post-infusion; schedule 3: 5 min before the end of the infusion, 30 min and 20–24 h post-infusion. In a few cases, an additional sample was taken in schedules 1 and 2 after 24 h. All patients at one site were sampled according to the same schedule. The aim of the sampling strategy was to define the full kinetic profile over the whole population, by drawing a small number of samples at different times from a large number of patients. This approach is previously referred to as the full-screen approach (Sheiner and Benet, 1985).

Blood samples (5 ml) were collected in heparinised tubes and immediately immersed in ice-water. Plasma was obtained by centrifugation of the samples (5 min; 3000 r.p.m., 4°C) and stored at −20°C or lower until analysis. Plasma levels of total (lactone plus carboxylate) irinotecan and metabolite SN-38 were determined by a reversed-phase high-performance liquid chromatography method using a fluorescence detection (Vergniol et al,
AUC of SN-38 per cycle \((AUC_c)\) was estimated by multiplying the estimated. The metabolic ratio of irinotecan was defined as the \((AUC)\) and total body clearance \((CL, \text{ irinotecan only})\) was also estimated under the plasma concentration – time curve from 0 to infinity.

Student’s \(t\)-test was used to compare the treatment groups on continuous variables, if a normal distribution could be assumed, to compare treatment groups on categorical variables. For the significance level of difference. The Fisher exact test was used to compare the groups. Differences in pharmacokinetic parameters between the four treatment arms were evaluated using one-way analysis of variance (ANOVA) combined with least significant difference (LSD) method \((P \text{ was set at } 0.05)\) and the Student’s \(t\)-test was used to calculate the \(P\)-value of significant differences. The Pearson correlation coefficient \((r)\) was calculated between dose and pharmacokinetic parameters. Statistical analyses were performed with SPSS (version 10.0.7 for Windows, SPSS Inc.). All tests for significance were two-tailed.

**RESULTS**

**Patient enrollment and evaluability**

A total of 174 patients entered the study. Of these patients, 168 (97%) actually received medication and comprised the intent to treat population (treated patients analysed in the arm to which they were assigned by randomisation). In all, 41 patients were included in arm A, 37 patients in arm B, 46 patients in arm C and 44 patients in arm D. A total of 149 (86%) patients were not in the per protocol population (treated, eligible and evaluable for response). Table 1 describes the reasons why patients were in the per protocol population. A total of 88 (51%) patients were evaluable for pharmacokinetics. At the cutoff date, all but seven patients had discontinued the treatment. In all treatment arms, the majority of patients discontinued treatment because of progressive disease: 81% in arm A, 57% in arm B, 61% in arm C and 55% in arm D. More patients discontinued treatment due to toxicity (from the study drug) in arm D (21%) compared with arm A (0%), arm B (14%) and arm C (11%) \((P = 0.03)\); the main reasons were diarrhoea in arm B (8%) and C (7%), diarrhoea (14%) and vomiting (14%) in arm D.

**Patient characteristics**

Patient characteristics at baseline were well balanced across the four treatment arms and are summarised in Table 2. The majority of patients had colon carcinoma. Diagnosis of the primary disease was made more than a year before the patients were randomised.

**Treatment delivery**

A total of 247 courses were administered to 41 patients in arm A, 98 courses to 37 patients in arm B, 368 courses to 46 patients in arm C and 133 courses to 44 patients in arm D. All patients received at least one course. The median numbers of weeks on study were 18.6, 12.0, 15.2 and 7.0 in arms A, B, C and D, respectively. Details of treatment delivery and dose intensity are shown in Table 3. In arm A, the main reasons for treatment delay were vomiting and infection (two patients, two cycles); in arm B...
neutropenia (10 patients, 13 cycles); and in arms C and D diarrhoea (five patients, five cycles and six patients, eight cycles, respectively). Few cycles had dose reductions. The main reasons for dose reductions were diarrhoea in arm A (four patients, four cycles), arm C (five patients, five cycles) and arm D (seven patients, 10 cycles) and neutropenia in arm B (seven patients, seven cycles). More protocol-planned doses were administered in arms A, B and C compared with arm D, where the relative dose intensity (RDI) was the lowest.

**Efficacy**

Table 4 summarises the overall response rates of the full analysis population by treatment arm. There were no significant differences in response rate across the four treatment arms \((P = 0.7)\). Table 5 summarises the secondary efficacy parameters. Again, no significant differences in duration of response and disease stabilisation, time to treatment failure, time to progression or survival were observed. However, a notably shorter time to treatment failure was observed for arm D (1.7 months; \(P = 0.02\)).

**Safety**

The number of patients with at least one grade 3–4 adverse event possibly or probably related to irinotecan administration was 12 (29%) in arm A, 11 (30%) in arm B, 14 (30%) in arm C and 22 (50%) in arm D \((P = 0.1)\). Table 6 provides a summary of

### Table 3 Irinotecan treatment and extent of exposure

|          | Arm A | Arm B | Arm C | Arm D |
|----------|-------|-------|-------|-------|
| Number of patients | 41    | 37    | 46    | 44    |
| Total courses/cycles | 247/124 | 392/98 | 368/123 | 133/67 |
| % cycles reduced | 11 % | 12.0 % | 15.2 % | 7.0 % |
| % cycles delayed | 11 % | 13 % | 8 % | 14 % |
| **RDI** | 0.98 (0.69–1.02) | 0.97 (0.60–1.11) | 0.99 (0.61–1.05) | 0.90 (0.21–1.04) |

*Median. **Median (min–max).*

### Table 4 Response results in the intent-to-treat population

|          | Arm A | Arm B | Arm C | Arm D |
|----------|-------|-------|-------|-------|
| Complete response | 0 % | 0 % | 0 % | 1 % |
| Partial response | 3 % | 7 % | 2 % | 5 % |
| Stable disease | 18 % | 44 % | 23 % | 62 % |
| Progressive disease | 19 % | 46 % | 7 % | 19 % |
| Not evaluable | 1 % | 2 % | 5 % | 14 % |

**Overall response (CR+PR)**

|          | Arm A | Arm B | Arm C | Arm D |
|----------|-------|-------|-------|-------|
| % Patients/%Cycles | 3 % | 7 % | 2 % | 5 % |
| 95% confidence interval | 1.5–19.9 | 0.7–18.2 | 3.6–23.6 | 0.6–15.5 |

### Table 5 Secondary efficacy parameters in the intent-to-treat population

|          | Arm A | Arm B | Arm C | Arm D |
|----------|-------|-------|-------|-------|
| Duration of response and stabilisation | 5.9 (0.8–12.7) | 3.9 (1.0–13.0) | 5.3 (1.3–8.9) | 3.4 (1.3–6.9) |
| Time to progression | 2.7 (1.0–12.8) | 3.5 (0.0–13.2) | 3.8 (0.0–8.9) | 2.8 (0.0–7.0) |
| Time to treatment failure | 2.7 (1.0–12.8) | 2.3 (0.6–8.3) | 3.2 (0.4–7.1) | 1.7 (0.5–7.1) |
| Survival | 9.4 (1.0–15.3) | 7.1 (0.6–13.5) | 8.6 (0.7–16.7) | 6.4 (1.1–15.1) |

*Data are represented as median (min–max).*

### Table 6 Haematologic toxicity

|          | Arm A | Arm B | Arm C | Arm D |
|----------|-------|-------|-------|-------|
| Leukocytopenia | | | | |
| All grades | 73/70 | 68/53 | 70/56 | 30/24 |
| Grade 3–4 | 20/15 | 14/6 | 15/6 | 5/3 |
| Neutropenia | | | | |
| All grades | 73/65 | 61/50 | 65/57 | 23/15 |
| Grade 3–4 | 34/21 | 25/12 | 28/20 | 9/5 |
| Febrile neutropenic infection | 75 | 5/2 | 71 | — |
| Anaemia | | | | |
| All grades | 98/92 | 92/87 | 91/90 | 9/83 |
| Grade 3–4 | 2/1 | 3/1 | 4/4 | 0/0 |
| Thrombocytopenia | | | | |
| All grades | 24/14 | 11/6 | 15/6 | 9/8 |
| Grade 3–4 | 0/0 | 0/0 | 0/0 | 5/3 |

*Percentages of patients developing toxicity in all courses/percentage of cycles in which toxicity developed; worst grade during study. Number of patients is 41 in arm A, 37 in arm B, 46 in arm C and 44 in arm D; number of cycles is 127 in arm A, 98 in arm B, 130 in arm C and 76 in arm D. \*Arm D is significantly different from arms A, B and C \((P < 0.004)\). \*Arm D is significantly different from arms A and C \((P < 0.004)\). \*Arm A is significantly different from arms B, C and D \((P < 0.001)\).*
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Clinical

Cholinergic syndrome 68a —4 1 a —6 1 a 27 a —

Infection 7 2 11 5 11 — 11 7

Fever in absence of infection 12 2 19 - 15 4 16 —

Fatigue 51 7 38 3 61 4 52 7

Other

Anorexia 12 — 14 — 17 — 34 5

Gastrointestinal pain 17 2 16 3 17 2 23 2

Vomiting 54 10 57 3 50 9 59 16

Nausea 73 15 73 5 65 9 80 23

Toxicity type % of patients /C0

Arm Dose (mg m$^2$) N Cl (l h$^{-1}$) $C_{\text{max}}$ (umol l$^{-1}$) AUC (umol h l$^{-1}$) $C_{\text{max}}$ (umol l$^{-1}$) AUC (umol h l$^{-1}$) AUC$_C$ (umol h l$^{-1}$) Metabolic ratio

| Arm | Dose (mg m$^2$) | N | Cl (l h$^{-1}$) | $C_{\text{max}}$ (umol l$^{-1}$) | AUC (umol h l$^{-1}$) | $C_{\text{max}}$ (umol l$^{-1}$) | AUC (umol h l$^{-1}$) | AUC$_C$ (umol h l$^{-1}$) | Metabolic ratio |
|-----|----------------|---|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| A   | 350            | 30| 22.3 ± 7.3     | 7.91 ± 1.10$^c$ | 47.8 ± 19.0$^c$ | 0.151 ± 0.069$^d$ | 2.08 ± 0.96$^d$ | 4.16 ± 1.93$^e$ | 0.044± 0.008$^e$ |
| B   | 125            | 28| 26.8 ± 9.6     | 2.62 ± 0.39$^a$ | 14.6 ± 6.9$^a$  | 0.065 ± 0.021$^a$ | 0.76 ± 0.29$^a$  | 3.03 ± 1.17$^b$  | 0.054± 0.014$^b$ |
| C   | 250            | 30| 24.0 ± 8.4     | 5.52 ± 0.90$^a$ | 32.7 ± 13.5$^c$ | 0.117 ± 0.057$^d$ | 1.48 ± 0.71$^c$  | 4.44 ± 2.12$^c$  | 0.046± 0.010$^e$ |
|     | 140$^b$        |   | 30.4± 8.2      | ND             | 12.8 ± 3.9      | ND             | 1.4 ± 0.3       | 4.2 ± 0.9        | 0.12 ± 0.02$^e$  |

Table 7 Nonhaematologic toxicity

Table 8 Pharmacokinetic parameters of irinotecan and SN-38

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DISCUSSION

Irinotecan monotherapy is recognised as the treatment of choice in second-line therapy (after failure of 5-FU) in metastatic colorectal cancer (Cunningham et al, 1998; Douillard et al,
2000). Several administration schedules have been developed in the past; this study was set out to find the optimal schedule. This is the first report of a randomised phase II study of irinotecan given at four different schedules to patients with metastatic colorectal cancer.

After analysing the primary and secondary end points, no significant superiority of one of the four treatment schedules could be observed; this may be because the sample size was too small. There is a trend for an increased response rate in arm C; however, this does not translate to better survival. In addition, the response rate in arm D is possibly biased because of the relatively high number of nonevaluable patients, the relatively shorter duration of treatment and the lower RDI. Median survival in this study was the highest for arm D (24.8 months), whereas the median survival reported by Cunningham et al (1998) (9.2 months) and Rogier et al (1997) (10.8 months) using the same schedule.

The main toxicities were of gastrointestinal origin for all four treatment arms and haematologic toxicity was generally mild. We found no significant differences in the intensity of toxicity; however, there was a distinct difference in toxicity profiles. There was a trend for increased gastrointestinal toxicity in arm D (prolonged infusion) compared with the other treatment arms (short infusions). Furthermore, there was significantly less alopecia in arm D compared with arms A and C, and cholinergic syndrome was significantly greater in arms A, B, and C compared with arm D. The alopecia and cholinergic syndromes are probably more closely related to peak concentrations of irinotecan and SN-38, than to total dose intensity. This is in accordance with the results of a phase I study with prolonged schedules of irinotecan, where no cholinergic syndrome was observed. It has been found that the observed cholinergic syndrome after the administration of irinotecan is caused by a rapid reversible inhibition of acetylcholinesterase by irinotecan (Rivory et al, 1996). Furthermore, support for schedule-dependent toxicity was recently given by Fuchs et al (2003). In this study, a similar schedule as given in treatment arm A was compared with 125 mg m\(^{-2}\) irinotecan weekly for 4 weeks, followed by 2 weeks rest. A significantly lower incidence of severe diarrhoea was reported, while efficacy was comparable for both treatment arms. In addition, Hwang et al reported significantly less diarrhoea when 125 mg m\(^{-2}\) irinotecan was administered once a week for 2 weeks, followed by a week rest vs ‘schedule B’. However, in this study, no significantly higher haematologic toxicity and neutropenia were observed (Hwang et al, 2003). Regarding haematologic toxicities, leukocytopenia and neutropenia were generally significantly milder in arm D compared with the other treatment arms in our study. Thrombocytopenia was significantly higher in arm A compared with the other treatment arms. These differences in toxicity profile are probably related to the schedule of administration rather than the dose per cycle (highest in arm C) or the exposure to SN-38 per cycle (lowest in arm B). Schedule dependency of topo-isomerase I inhibitors, with regard to cytotoxicity, was also shown in vitro and in vivo in tumour-bearing mice and in clinical studies with different camptothecins (Burris et al, 1992; Dodds and Rivory, 1999; Gerrits et al, 1999). The results of an early phase II study with irinotecan support the use of prolonged exposure schedules in patients with lymphomas (Ohno et al, 1990). Schedule dependency of irinotecan in patients with solid tumours is less obvious (Takeuchi et al, 1991; Sakata et al, 1994). Tumour response and safety of irinotecan may not only be schedule dependent but also tumour-type dependent. Increased carboxylesterase activity has been found in some tumour types and might influence conversion of irinotecan to SN-38 (Wakui and Taguchi, 1992; Guichard et al, 1999). Systemic exposure to SN-38 was found to be higher in mice bearing human neuroblastoma xenografts as compared with nontumour-bearing mice (Guichard et al, 1999).

We compared our pharmacokinetic parameters with the pharmacokinetics of patients treated with a prolonged infusion of irinotecan as described by Herben et al (1999), which is similar to the schedule used in arm D. We found a significant difference in exposure to SN-38 as estimated by the AUC\(_C\). The exposure to SN-38 was increased in arms A and C compared with arm B. The estimated exposure per cycle to SN-38 of patients treated by 14-day prolonged infusion of 10 mg m\(^{-2}\) day\(^{-1}\) irinotecan was comparable with arms A and C (Table 8) (Herben et al, 1999). This difference in exposure did not lead to differences in activity between arm B and arms A and C, nor could it explain for the differences found in toxicity profile. The AUC and \(C_{\text{max}}\) were strongly correlated with the dose of irinotecan. The metabolic ratios of SN-38 after the short infusions in arms A, B and C found in this study were 0.04, 0.05 and 0.04, respectively. A similar metabolic ratio was also found in a previous study where a metabolic ratio of 0.05 was noted after a standard 90-min infusion of 350 mg m\(^{-2}\) irinotecan (Rogier et al, 1997). This is lower than the metabolic ratio of 0.12, as found for the prolonged infusion of irinotecan (Table 8) (Herben et al, 1999). The difference in metabolic ratio between bolus and prolonged infusions agrees with other previously published data (Chabot et al, 1995; Gupta et al, 1997; Zamboni et al, 1998). We also found a significant difference between the metabolic ratio of SN-38 between arms A and B, and B and C. A low, but very significant inverse correlation between dose and metabolic ratio of SN-38 was observed for arms A, B, and C. A possible explanation for this change in metabolic ratio is saturation of the carboxylesterase reaction. The carboxylesterase reaction converting irinotecan into SN-38 in humans is very inefficient and deacylation dependent (Rivory et al, 1996; Hix et al, 1997; Takimoto et al, 2000). The saturation of this enzymatic reaction may be of relevance for prolonged infusion schedules of irinotecan. The metabolic ratio of SN-38 is not solely dependent on the formation of SN-38 by carboxylesterases, but also on the effect of dose on the metabolism of irinotecan via other pathways, such as the formation of APC, the saturation of its conversion to SN-38 glucuronide or enterohepatic recycling. SN-38, the active metabolite of irinotecan, is about a 100–1000 times more potent topo-isomerase I inhibitor than its parent compound in vitro models (Slatter et al, 1997). The observed extensive metabolism of irinotecan to its active form, SN-38, may thus explain in part the low recommended dose for the continuous infusion schedule (Herben et al, 1999). The extent of metabolism of irinotecan to SN-38 seems to be dependent upon the administration schedule and administered dose of irinotecan. This effect has no clinical relevance with the administration schedules used in arms A, B and C (short infusions). However, it provides a rationale for prolonged administration schedules with low-dose irinotecan, despite the slightly less favourable toxicity profile of prolonged intravenously administered irinotecan, as found in this study.

Recently, an oral formulation of irinotecan has been developed and has entered phase I clinical trials (Schoemaker et al, 2002). Since chronic infusions are cumbersome and expensive, an oral formulation provides an excellent method to administer irinotecan over a prolonged period at low doses. However, future studies should examine whether the balance between efficacy and safety is most optimal in chronic (oral) treatment schedules.

In summary, the four irinotecan schedules used in this study can generally be considered equivalent, in terms of efficacy and toxicity. However, more patients may have been required for us to observe any significant differences. The schedule used in arm D resulted in more gastrointestinal toxicity but the least haematologic toxicity. Prolonged intravenous administration of irinotecan (arm D) showed no clinical benefit over the short infusion schedules and is therefore not a feasible treatment option because of the disadvantages associated with this mode of administration. Irinotecan can be administered safely as a second-line treatment to patients with colorectal cancer according to local clinical practice, using either weekly, every 2-week or every 3-week short infusion schedules.

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