Phase II study of irinotecan (CPT-11) administered every 2 weeks as treatment for patients with colorectal cancer resistant to previous treatment with 5-fluorouracil-based therapies: comparison of two different dose schedules (250 and 200 mg/m^2) according to toxicity prognostic factors

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Our objective was to assess the antitumoral activity and toxicity of irinotecan (CPT-11) 60-min i.v. infusion every 2 weeks as second-line monotherapy of advanced colorectal cancer. Two doses were studied (250 and 200 mg/m^2) according to the risk of developing toxicity. Two groups of patients were studied: high-risk group (HR, 200 mg/m^2, $n=45$; Karnofsky score 60–80% and/or the record of prior pelvic irradiation) and low-risk-group (LR, 250 mg/m^2, $n=51$; Karnofsky score >80% and without prior pelvic irradiation). The mean number of cycles per patient was 7: 6.6 (HR group) and 8.3 (LR group). Median RDI was 0.96. The overall response rate was 8.9% [95% confidence interval (CI) 2.5–21.2%; HR group] and 15.7% (95% CI 7.0–28.5%; LR group), respectively. The LR group showed two complete responses and a higher percentage of stable disease (56.9 versus 33.3% in HR group). The median survival was 7.1 months (95% CI 5.2–8.9 months, HR group) and 11.7 months (95% CI 8.4–15.1 months, LR group). The median time to disease progression was 3.2 months (95% CI 1.0–5.4 months, HR group) and 5.3 months (95% CI 3.8–6.7 months, LR group). Both CPT-11 treatments were well tolerated. Grade 3/4 toxicity incidence was low, e.g. granulocytopenia (7% of patients in HR group and 9% in LR group) and delayed diarrhea (18% of patients in HR group and 14% in LR group). We conclude that the treatment of patients with the adjusted dose of CPT-11 according to prognostic factors for toxicity resulted in the improved toxicity profile, but showed poorer efficacy outcome. Therefore, the dose reduction in patients with low performance and treated with radiotherapy needs further investigation to provide some new insights on the benefit:risk ratio of such treatment. *Anti-Cancer Drugs* 15:835–841 © 2004 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2004, **15**:835–841

Keywords: biweekly, colorectal cancer, CPT-11, prognostic factors

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Received 7 March 2004 **Revised form accepted** 2 June 2004

Introduction

Inhibitors of topoisomerase I have proven to be one of the most promising new classes of antineoplastic agents introduced into the clinical setting during recent years [1]. Irinotecan (CPT-11), a semisynthetic camptothecin derivative with a novel mechanism of action, has provided a new and effective treatment option for colorectal cancer (CRC) in first- and second-line chemotherapy. The administration schedule of CPT-11 approved in the US for second-line CRC chemotherapy is 125 mg/m^2 given as a 90-min i.v. infusion once weekly for 4 of 6 weeks [2]. In Europe, the most widely used dosing regimen is 350 mg/m^2 given as a 60-min i.v. infusion once every 3 weeks [3]. In Japan, 100 mg/m^2 every week or 150 mg/m^2 every other week are the schedules more commonly used [4]. Several phase II studies on second-line CPT-11 monotherapy showed objective tumor response rates of 16–27% with disease stabilization occurring in another 40–60% of patients [5–8]. Two further phase III trials established CPT-11 monotherapy as a new standard of care in the second-line treatment of 5-fluorouracil (5-FU)-pretreated colorectal cancer [9,10].

CPT-11 chemotherapy is administered on a palliative basis; therefore, finding CPT-11 schedules that might reduce the severe toxicity usually associated with this

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chemotherapeutic agent, without affecting efficacy outcomes, constitutes a relevant endpoint. The toxicity and antitumor activity profiles of the two most commonly used CPT-11 schedules (weekly or once-every-3-weeks) are quite similar. Delayed-onset diarrhea, myelosuppression (neutropenia), nausea and vomiting are the most common toxicities for both schedules [11]. The similar safety and efficacy profiles found with these two CPT-11 schedules have been related to relatively equal contributions of absolute dose and frequency of dose administration [3,12,13]. A previous study assessing the every-3-weeks schedule tailored the CPT-11 dose according to baseline performance status: patients with a baseline Karnofsky score >80 received 350 mg/m^2, while patients with a baseline Karnofsky score of 70–80 received 250 mg/m^2 [14]. The result was an important response rate (19%) associated with tolerable toxicity in patients with poor baseline PS.

Few studies have been published on a new CPT-11 schedule based on a biweekly administration. Previously, CPT-11 250 mg/m^2 administered every 2 weeks has been reported to be a tolerable and active alternative to weekly or every-3-week single-agent CPT-11 therapy [15]. The present phase II study assessed the antitumoral activity and toxicity of CPT-11 administered every 2 weeks as second-line monotherapy in patients with advanced colorectal cancer. Two doses were studied (250 and 200 mg/m^2) according to the risk of developing toxicity based on baseline Karnofsky scores and prior pelvic radiotherapy.

Methods

Patients

The patients were enrolled at 14 Spanish oncology centers between March 1999 and November 2000. Their Ethics Committees approved the study protocol and all patients provided their written informed consent. The inclusion criteria were as follows: (i) histological diagnosis of advanced CRC with proven resistance to 5-FU therapy (progression during 5-FU palliative treatment or within 6 months after the last adjuvant 5-FU administration), (ii) one or more bidimensionally measurable target lesions (multiple lung/hepatic metastases: diameter >2 cm; unique hepatic metastasis: diameter >3 cm; hepatic affectation $<50\%$), (iii) age ≥ 18 years, (iv) life expectancy ≥ 3 months and (v) Karnofsky performance score $\geq 60\%$. The laboratory data requirements before inclusion in the study were the following: polymorphonuclear neutrophil (PMN) count $\geq 1500/\text{mm}^3$, platelet count $>100\,000/\text{mm}^3$, Hb ≥ 10 g/dl, serum creatinine level ≤ 135 μmol/l and bilirubin level $<1.25\times$ upper normal limit (N); if liver metastases were present, the bilirubin level could be $<1.5\times$ N.

Those patients with the following criteria were not eligible: (i) previous treatment with CPT-11, (ii) high risk of poor outcome due to concomitant non-malignant disease (inflammatory enteropathy, major organic failure, uncontrolled severe infection), (iii) no measurable diseases (ascites, peritoneal carcinomatosis, pleural bleeding, lymphangitic lung, and diffuse hepatic impairment), (iv) metastases in the central nervous system, (v) previous cancer history (except for resolved cervical carcinoma or basal cutaneous carcinoma), (vi) bowel obstruction and (vii) lactating, pregnant women or patients with reproductive potential not implementing adequate contraceptive measures.

Chemotherapy regimen

The patients were classified into the treatment groups according to the evaluation of prognostic factors for toxicity following two criteria: Karnofsky score and existence of prior pelvic irradiation record. Thus, the high-risk group (HR) was formed with patients with Karnofsky score 60–80% and/or a record of prior pelvic irradiation, and the low-risk group (LR) with those with Karnofsky score $>80\%$ and without prior pelvic irradiation. The HR patients were treated with CPT-11 (CAMPTO; Prasfarma, Sant Just Desvern, Barcelona, Spain; Rhone-Poulenc Rorer, Anthony, France) 200 mg/m^2 given as a 60-min i.v. infusion every 2 weeks. The LR patients were treated with CPT-11 250 mg/m^2 using the same schedule. The guidelines for CPT-11 dose modification due to toxicity are shown in Table 1. The patients were to receive at least five biweekly infusions before the first assessment of tumor response, except in the case of progressive disease or severe toxicity. The

Table 1 Dose modification guidelines for toxicity

	At the time of i.v. infusion	At any time
Hematological toxicity		
absolute neutrophil count	$<1.5\times10^9$/l	$\leq 0.5\times10^9$/l or $\leq 1.0\times10^9$/l plus fever/infection
platelet count	$<100\times10^9$/l	$\leq 20\times10^9$/l
Non-hematological toxicity		
treatment-related diarrhea	>grade 1	grade 3/4
mucositis	>grade 1	grade 3/4
actions	postpone i.v. infusion for 1 week	postpone i.v. infusion for 1 week until ANC $\geq 1.5\times10^9$/l, platelet count $\geq 100\times10^9$/l, diarrhea $\leq$ grade 1 and mucositis $\leq$ grade 1
next doses	complete dose	20% reduction

After 2 weeks of delayed infusion, the treatment had to be discontinued.

patients who responded or showed stable disease could continue receiving treatment for a maximum of further five cycles. Then, the patients could continue the CPT-11 treatment on a compassionate basis, as judged by the investigator.

No concomitant antineoplastic therapies were allowed, save for localized radiation therapy for analgesia of bone lesions. However, the irradiated target tumors were not considered for evaluation. Prophylaxis with antiemetic agents was allowed. No prophylactic treatment was permitted for early diarrhea, but if severe cholinergic symptoms were observed during or after CPT-11 infusion, atropine (0.25–0.50 mg s.c.) was recommended as definitive treatment and prophylaxis for subsequent cycles. Specific guidelines for the treatment of delayed diarrhea were provided; these recommended 2 mg of loperamide every 2 h for 12 h after the last episode of diarrhea and for a maximum of 48 h consecutively. If diarrhea persisted for more than 24 h, an oral prophylactic broad-spectrum quinolone antibiotic was prescribed. If diarrhea persisted for more than 48 h, the patients were admitted to hospital for parenteral rehydration. All patients with febrile neutropenia were hospitalized and treated with antibiotherapy and specific support.

Assessment of response and toxicity

A clinical history and physical examination (including assessment of body surface, performance status, and tumor measurement by imaging techniques), complete blood cell count, measurement of tumor markers, and a plasma biochemical profile were conducted prior to treatment and during the study. Response to treatment was classified according to WHO criteria [16]. All patients who were withdrawn from the study before completing the treatment (five cycles) due to disease progression were classified as treatment failures. Other secondary efficacy endpoints were the time to disease progression, overall survival, duration of response and time of disease stabilization [i.e. time elapsed from inclusion to progression in those patients showing antitumoral activity (with response or stable disease)]. All toxicities experienced during the study were recorded and graded according to the National Cancer Institute's (NCI) common toxicity criteria [17]. Thus, all clinical and laboratory toxicities were graded following CALGB Toxicity Grading criteria (from 0 to 4).

Statistical analysis

A sample size of 80 enrolled patients, 40 in each group, was estimated using the Fleming's method [18] and assuming a minimum acceptable response rate of 15%. Statistical analyses were performed using the SPSS software (SPSS, Chicago, IL). Efficacy and toxicity analyses were performed on an 'intention-to-treat' basis. Kaplan–Meier estimations were used for the analysis of survival curves and compared using a two-tailed log-rank test. Adverse events were calculated by punctual estimation with a 95% confidence interval (CI).

Results

Characteristics of patients

Ninety-six patients were enrolled into the study: 45 in the HR group and 51 in the LR group. Their baseline characteristics are shown in Table 2. Five patients in the HR group showed an initial Karnofsky score of 60. All patients received at least one previous chemotherapy line: this consisted in 5-FU plus leucovorin (64.8%), 5-FU (10.4%), 5-FU plus levamisole (4%) or other, mainly tegafur-based, combinations (20.8%). None of patients received any chemotherapy during the 6 months right before the study. A total of 115 previous chemotherapy lines were reported; three corresponded to second-line therapies. First-line chemotherapy was 63.5% palliative and 36.5% adjuvant. Second-line chemotherapy was 87.5% palliative and 12.5% adjuvant (i.e. patients who received second-line chemotherapy and later underwent surgery). Fifteen patients of the HR group received prior radiotherapy; this was adjuvant in 11 patients (73.3%) and palliative in four patients (26.7%). Ninety-four patients (97.9%) had previously undergone surgery: 53 (56.4%) curative intent and 41 (43.6%) palliative. Ninety-two patients (96.8%) showed metastases and only three patients (3.1%) showed locally advanced disease. The mean number of disease sites was 3 (range 1–9). The liver was the organ most affected by metastases (44.8%). Fifty-three patients (55%) showed symptoms at inclusion; these were mild except for

Table 2 Patient and disease characteristics [*n* (%)] at baseline (*n*=96)

Characteristic	HR (*n*=45)	LR (*n*=51)	All (*n*=96)
Gender			
men	26 (57.8)	35 (68.8)	61 (63.5)
women	19 (42.2)	16 (31.4)	35 (36.5)
Age (years)			
median	64	65	65
range	31–77	31–79	31–79
Primary site			
colon	25 (55.6)	42 (82.4)	67 (69.8)
rectum	20 (44.4)	9 (17.6)	29 (30.2)
Metastatic sites			
liver	16 (35.6)	27 (52.9)	43 (44.8)
lung	5 (11.1)	4 (7.8)	9 (9.4)
liver and lung	4 (8.9)	5 (9.8)	9 (9.4)
other	7 (15.6)	5 (9.8)	12 (12.5)
liver + other	6 (13.3)	4 (7.8)	10 (10.4)
lung + other	2 (4.4)	2 (3.9)	4 (4.2)
liver and lung + other	4 (8.9)	3 (5.9)	7 (7.3)
locally advanced	1 (2.2)	1 (2)	2 (2.1)
Previous treatment			
surgery	43 (95.6)	51 (100)	94 (97.9)
radiotherapy	15 (33.3)	–	15 (15.6)
chemotherapy	45 (100)	51 (100)	96 (100)

'Other' represent 12 patients with peritoneal, bone, ganglionic or pleural metastasis. Any of those patients had more than one metastatic site of those types.

asthenia and pain for which some severe cases (grade 3 or higher) were found.

Treatment

A total of 717 CPT-11 cycles were administered: 295 in the HR group and 422 in the LR group. The mean number of cycles per patient was 7: 6.6 in the HR group and 8.3 in the LR group. Forty-seven patients (49.0%) withdrew from the study due to disease progression: 24 in the HR group and 23 in the LR group.

Thirty-one patients (32%) showed delays in the administration of infusion: 15 in the HR group and 16 in the LR group. Fifty-five cycles (7.7%) were delayed: 27 in the HR group and 28 in the LR group. Most delays were unrelated to CPT-11 (48%); 27% were due to hematological toxicity and 21.8% to non-hematological toxicity. No significant differences were found between groups. The dose was reduced in eight patients (8.3%): two in the HR group and six in the LR group. In all these patients, only one cycle was affected and 78% of dose reductions were due to non-hematological toxicity. The median relative dose intensity was 0.96 with no significant differences found between the groups.

Response to CPT-11 treatments

Table 3 shows the overall objective response to CPT-11 treatment. Seven patients were not evaluable for response: two due to consent withdrawal, two due to toxicity (grade 4 diarrhea and neutropenia), two due to protocol deviation and one due to deterioration of general status. Two complete responses were found in the LR group. The overall response rate was 8.9% (95% CI 2.5–21.2%) in the HR group and 15.7% (95% CI 7.0–28.5%) in the LR group. The median duration of response was 7.6 months (95% CI 4.9–10.4 months) in the HR group and 8.8 months (95% CI 7.2–10.3 months) in the LR group. Besides a high response rate, the LR group also showed a higher percentage of stable disease (56.9 versus 33.3% in the HR group).

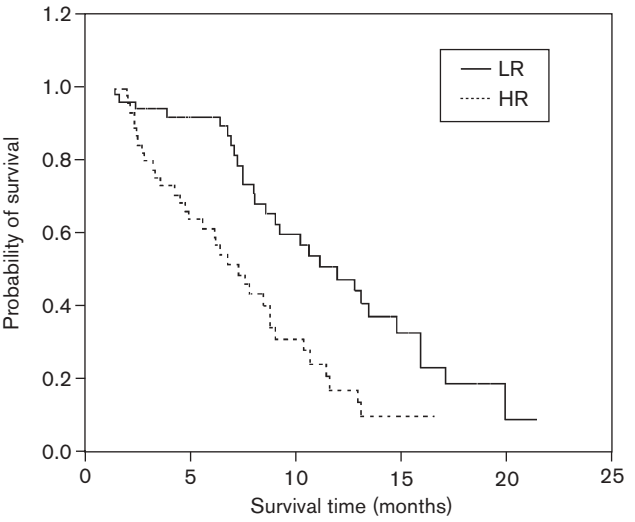
The median survival was 7.1 months (95% CI 5.2–8.9 months) in the HR group and 11.7 months (95% CI 8.4–15.1 months) in the LR group ($p = 0.0009$, Fig. 1). Progression of the disease was documented in 82 patients (85%): 41 in each group of treatment. The median time to disease progression was 3.2 months (95% CI 1.0–5.4 months) in the HR group and 5.3 months (95% CI 3.8–6.7 months) in the LR group ($p = 0.0132$, Fig. 2).

The median time of disease stabilization in those patients who showed antitumoral activity was 7.1 months (95% CI 2.8–8.8 months) in the HR group and 7.6 months (95% CI 4.9–10.4 months) in the LR group.

Table 3 **Overall objective response rate [*n* (%)] to treatment**

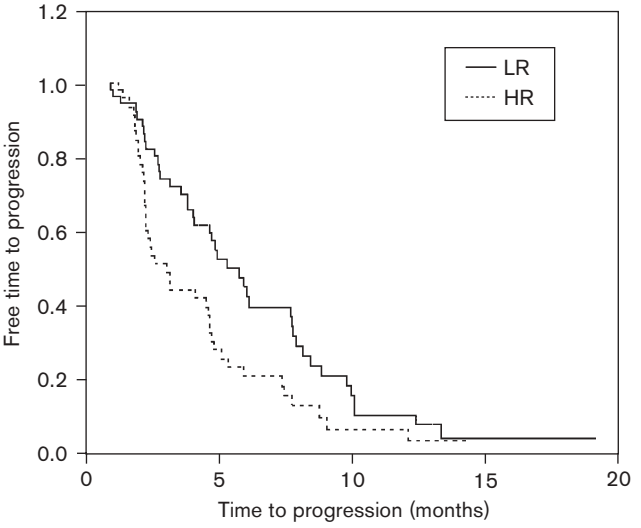
	HR ($n=45$)	LR ($n=51$)	All ($n=96$)
Complete response	–	2 (3.9)	2 (2.1)
Partial response	4 (8.9)	6 (11.8)	10 (10.4)
Stable disease	15 (33.3)	29 (56.9)	44 (45.8)
Progressive disease	20 (44.4)	13 (25.5)	33 (34.4)
Not assessable	6 (13.3)	1 (2.0)	7 (7.3)

Fig. 1



Survival curves for HR ($n=45$; dotted line) and LR ($n=51$; solid line) groups. $p=$ 0.0009 (log-rank).

Fig. 2



Time to disease progression for HR ($n=45$; dotted line) and LR ($n=51$; solid line) groups. $p=0.0132$ (log-rank).

Table 4 Grade 3/4 treatment-related toxicity per patient and infusion [*n* (%)]

Toxicity	HR		LR	
	Patients ($n=45$)	Cycles ($n=295$)	Patients ($n=51$)	Cycles ($n=422$)
Hematological				
anemia	3 (7)	3 (1)	–	–
granulocytopenia	3 (7)	4 (1)	4 (9)	4 (1)
neutropenia	1 (2)	1 (0.3)	2 (4)	2 (0.5)
Non-hematological				
asthenia	14 (31)	18 (6)	4 (8)	8 (2)
delayed diarrhea	8 (18)	9 (3)	7 (14)	9 (2)
stomatitis	–	–	1 (2)	1 (0.2)
nausea	2 (4)	2 (1)	4 (8)	4 (1)
vomiting	3 (7)	3 (1)	1 (2)	1 (0.2)

Graded following CALGB Toxicity Grading Criteria (0–4).

Toxicity

Eight patients (8.3%) showed a mild and transient cholinergic syndrome after infusion of CPT-11: two (4.4%) in the HR group and five (5.9%) in the LR group. The main treatment-related toxicities are summarized in Table 4. Overall, both CPT-11 treatments were well tolerated. Grade 3/4 hematological toxicity was uncommon, granulocytopenia being the most often found (7% of patients affected in the HR group and 9% in the LR group). Grade 3/4 non-hematological toxicities included asthenia, delayed diarrhea, nausea and vomiting in both groups, HR and LR. Additionally, a case of stomatitis was reported in the LR group. No toxic deaths were found.

Discussion

The present study shows that CPT-11 administered every 2 weeks is a feasible and active treatment for CRC patients after failure of a 5-FU-based chemotherapy. A main conclusion of previous phase I pharmacokinetic trial was the recommendation of a dose of 250 mg/m^2 for phase II evaluation of CPT-11 without granulocyte colony stimulating factor (G-CSF) and 300 mg/m^2 for phase II trials with CPT-11 and G-CSF [15]. Thus, in the present study, a starting dose of 250 mg/m^2 of CPT-11 was administered to CRC patients with low risk of developing toxicity (i.e. with relatively high baseline performance score and without prior pelvic radiotherapy). A 20% lower dose (250 mg/m^2) of CPT-11 was administered to patients with a high risk of developing toxicity (i.e. Karnofsky score 60–80% and prior pelvic radiography). Both baseline performance status and prior pelvic irradiation have been found to be prognostic factors for tumor response and toxicity in metastatic colorectal cancer patients given CPT-11 chemotherapy after 5-FU failure [19,20].

Patients treated with 250 mg/m^2 showed an objective response rate of 15.7% (with two complete responses). Moreover, 56.9% of the patients showed stabilization of their previously progressive and 5-FU refractory disease. Therefore, 72.6% of the patients were benefited from the therapy with CPT-11 250 mg/m^2 every 2 weeks. These antitumoral activity results are similar to those found using other CPT-11 schedules (i.e. tumor response rates of 16–27% with disease stabilization occurring in a further 40–60% of patients) [21]. The median survival (11.7 months), time to disease progression (5.3 months) and duration of response (8.8 months) were also closer to the range found with other CPT-11 regimens (i.e. median overall survival of 8.3–10.0 months and median duration of response of 6.0–9.1 months) [21].

Another group of patients with high risk for developing toxicity was treated in the present study using a lower starting dose: 200 mg/m^2. In this group the antitumoral activity obtained was quite lower than that found in the low risk group: an objective response rate of 8.9% and stable disease occurring in 33.3% of the patients. This group also showed shorter median survival (7.1 months) and time to disease progression (3.2 months).

Nevertheless, the toxicity results in both the high-risk and the low-risk groups proved the every-2-week schedule as a well-tolerated chemotherapy regimen. Reductions or delays in the administration of infusions did not affect the planned CPT-11 dose: both groups of treatment showed a median relative dose intensity closer to 1. The incidence of cholinergic syndrome was almost minimal and only affected about 5% of the patients treated in either group. Generally, CPT-11 is generally considered to be a moderately hematological toxic drug, with grade 3/4 neutropenia in approximately 25% of patients and granulocytopenia in 32% [22].

The principal dose-limiting toxicity observed for all dosing regimens of CPT-11 is delayed diarrhea, with or without neutropenia [1]. This was also the case in this study where asthenia and diarrhea (non-hematological

toxicities) and granulocytopenia and neutropenia (hematological toxicities) were the most common toxicities in both groups. It is worth noting that grade 3/4 delayed diarrhea associated with CPT-11 was an infrequent toxicity with this dosing schedule (14–18% of patients affected) and according to phase I results [15]. Early loperamide treatment undoubtedly contributed to these findings, but this practice is also usual in other trials that reported higher rates using other CPT-11 schedules: 31% with 125 mg/m^2 given on a weekly schedule [23] or 22% with 300–350 mg/m^2 every 3 weeks [9,10]. Other severe non-hematological toxicities (nausea, vomiting) were also infrequent except for asthenia, which showed a higher incidence in the high-risk group (31% of patients) than in the low-risk group (8%). Regarding hematological toxicities, in the prior phase I study on every-2-week CPT-11, febrile neutropenia represented the dose-limiting toxicity just at higher doses (300 mg/m^2), but it did not appear at doses of 250 or 200 mg/m^2 [15]. In the present study, granulocytopenia was the most frequent hematological toxicity, but its incidence (7–9%) was also lower than that previously found with weekly or every-3-week single-agent CPT-11 therapies [1,24]. No relevant differences were found in the rates of hematological toxicity between the HR and LR groups of patients, except for a low presence of anemia in the HR group (2% of patients). Therefore, the reduction of the starting dose by 50 mg/m^2 in patients with high risk at baseline of developing toxicity seemed to have the additional effect of preventing a high rate of hematological adverse events. Nevertheless, this question needs to be clarified in further trials using a design including patients with a similar baseline condition but treated with different CPT-11 doses.

In conclusion, the present results show CPT-11 250 mg/m^2 administered every 2 weeks to be an active and well-tolerated regimen of second-line chemotherapy for patients with colorectal cancer refractory to 5-FU-based therapies. The results of a phase I trial [15] identified this dose as the starting dose for phase II, and other phase II trials [25] are now studying this new schedule and dose to provide an alternative regimen for intermittent administration of single-agent CPT-11. The present study also shows that the reduction of the CPT-11 dose to 200 mg/m^2 using this every-2-week schedule in patients with a higher risk for developing toxicity maintained a low incidence of severe hematological events, but decreased the response rate. Further specific studies would be required to decide which dose provides a better benefit:risk ratio.

Acknowledgments

Other investigators who participated in this study on behalf of the ACROSS Cooperative Group were: O. Gallego, Hospital Comarcal de la Selva, Blanes, Spain; P. Vicente, Hospital General de Granollers, Granollers, Spain; M. Boleda, Hospital San Camil, Sant Pere de Ribes, Spain, and M. Llobera, Hospital Verge de la Cinta, Tortosa, Spain. The authors wish to thank G. Urrutia, M. Roqué, R. Romero, J. Farrés, V. Alfaro, A. Tanovic, J. Ocaña and M. Balcells for their support.

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