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ORIGINAL ARTICLE

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Two different schedules of irinotecan (CPT-11) in patients with advanced colorectal carcinoma relapsing after a 5-fluorouracil and leucovorin combination. A randomized study

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Abstract *Purpose*: To evaluate the efficacy and safety of irinotecan as second-line treatment in patients with advanced colorectal cancer (ACC) failing or relapsing after 5-fluorouracil (5-FU) plus leucovorin (LV) standard chemotherapy. *Patients and methods*: Irinotecan was randomly administered in two different schedules (once every 3 weeks, and every 10 days) in patients failing prior 5-FU plus LV. Patients were randomized to two treatment groups: group A received irinotecan 350 mg/m^2 every 21 days and group B received irinotecan 175 mg/m^2 days 1 and 10 every 21 days. *Results*: Group A comprised 60 patients: 34 male/26 female, median age 64 years (range 48–70 years), and median Karnofsky performance status (PS) 90. Their metastatic sites included liver ($n=47$), lymph nodes ($n=27$), lung ($n=14$), abdomen ($n=14$), pelvis ($n=8$), "other" ($n=2$), and local recurrence ($n=12$). Group B comprised 60 patients: 36 male/24 female, median age 62 years (46–70 years), and median PS 90. Their metastatic sites included liver ($n=49$), lymph nodes ($n=29$), lung ($n=17$), abdomen ($n=16$), pelvis ($n=11$), "other" ($n=2$), and local recurrence ($n=13$). Group A showed the following responses: complete response (CR) 2, partial response (PR) 12, stable disease (SD) 21, progressive disease (PD) 26, overall response rate (ORR) 23%, tumor growth control 58%. Group B showed the following responses: CR 1, PR 14, SD 22, PD 23; ORR 25%; tumor growth control 62%. Toxicities included acute cholinergic syndrome (group A 53%, group B 19%; $P<0.0001$), late-onset diarrhea grade 1/2 (group A 21%, group B 46%) and grade 3/4 (group A 41%, group B 66%; $P<0.0001$), nausea and vomiting grade 1/2 (group A 34%, group B 59%) and grade 3/4 (group A 30%, group B 12%; $P<0.0001$), neutropenia grade 3/4 (group A 27%, group B 28%; $P<0.03$), with febrile neutropenia seen in only four patients in group A, anemia grade more than 2 (group A 28%, group B 12%; $P<0.05$), asthenia grade more than 3 (group A 24%, group B 18%; $P<0.001$), and alopecia grade more than 3 (group A 40%, group B 34%; $P<0.2$). *Conclusions*: The present study indicates that, in patients with ACC who have relapsed after 5-FU plus LV, the administration of irinotecan fractionated into two doses every 21 days yields a similar efficacy to, but a much lower incidence of toxicity than, the same total dose of irinotecan administered once every 21 days.

Keywords Irinotecan (CPT-11) · Colorectal cancer · Chemotherapy

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Introduction

Irinotecan (CPT-11) is a topoisomerase I inhibitor, originally developed in Japan. Preclinical data suggested

that colon tumors might be sensitive to inhibition of topoisomerase I [1, 2]. In various phase II studies, response rates ranging from 15% to 25% have been observed in patients refractory to 5-fluorouracil (5-FU) [3]. The toxicities of irinotecan are primarily neutropenia and diarrhea, the severity of which may be related to the extent of glucuronidation of the drug and its primary metabolite, SN-38 [4]. Schedule-dependent cytotoxicity of irinotecan is known in the clinic with different methods of administration, and different recommended dosages or schedules [5]. Three schedules have been investigated: a 30 to 90-min infusion once every 3 weeks, a weekly 90-min infusion, and a fortnightly 90-min infusion (however, the last of these is infrequently used). The different schedules have demonstrated comparable activity in the treatment of advanced colorectal cancer [6, 7, 8, 9].

In an attempt to achieve acceptable toxicity and fewer toxicity-related admissions to hospital without compromising response in patients with advanced colon carcinoma failing or relapsing after 5-FU plus leucovorin (LV) standard chemotherapy, we evaluated two schedules of irinotecan administration: a single dose every 21 days and the same total dose fractionated into two doses on day 1 and on day 10 every 21 days. We did not elect to test the fortnightly (every 2-week) schedule of irinotecan administration, as this results in a relatively compromised dose intensity of the drug, and has been used in fewer studies.

Patients and methods

Eligibility criteria

All patients had a histologic diagnosis of adenocarcinoma of the colon or rectum. Patients had to have measurable disease, a Karnofsky performance status (PS) of ≥70, age <70 years, a life expectancy >3 months, absence of brain metastases or active ischemic cardiac disease and normal hematologic, renal or hepatic function tests unless the abnormalities were the result of direct tumor invasion (up to three times the normal limits). Patients with any other severe or active diseases were excluded from the study. All had previously received 5-FU and LV and had relapsed during or after this treatment, which ended at least 6 weeks prior to study entry. All patients presented clinical and laboratory signs of progressive disease. Informed consent was obtained from all patients according to our institutional policy.

Patient randomization

Randomization was actually carried out by stratifying patients according to disease extent, PS, and relapse/progression from prior chemotherapy. Patients were allocated to the two treatment groups (A and B) by a simple randomization method (closed envelopes). Baseline characteristics were well balanced between the study groups (Table 1), and all patients were eligible.

Patient groups and chemotherapy

After inclusion in the study, patients started chemotherapy with 8 mg dexamethasone i.v. push, followed by 100 ml with 8 mg ondansetron i.v. over 15–20 min. Patients in group A continued with 250 ml 0.9% normal saline combined with irinotecan 350 mg/m^2 i.v. infusion over 90 min on day 1 every 21 days, and patients in group B received 175 mg/m^2 i.v. infusion over 90 min on days 1 and 10 every 3 weeks.

Treatment was carried out in an outpatient setting, and was continued until tumor progression or unacceptable toxicity. In the event of myelosuppression, diarrhea, and mucositis of grade more than 2 (WHO classification) [10] treatment was delayed until recovery. In order to avoid prospective treatment days falling over the weekend, treatment was initiated in patients in the every-10-days schedule on Monday, Tuesday, and Wednesday.

Table 1 Patient characteristics

	Group A	Group B
Patients (*n*)	60	60
Male/female (*n*)	34/26	36/24
Age (years)		
Median	64	62
Range	48–70	46–70
Karnofsky performance status (%)		
100	17	22
90	19	17
80	24	21
Primary site (*n*)		
Colon	19	21
Sigmoid	27	23
Rectum	14	16
Metastatic site (*n*)		
Liver	47	49
Lymph nodes	27	29
Abdomen	14	16
Pelvis	8	11
Lung	14	17
Bone	1	1
Brain	0	0
Adrenals	1	0
Skin	0	1
Local recurrence (*n*)	12	13
Previous chemotherapy (*n*)	60	60

Dose modifications and response evaluation

The doses of irinotecan were kept stable if no toxicity was encountered. For each grade of toxicity involving myelosuppression, diarrhea, acute cholinergic syndrome and mucositis the dose of irinotecan was decreased by 10% (grade 1 10%, grade 2 20%, grade 3 30%). Patients with cholinergic toxicity of grade more than 3 continued therapy with 250 mg/m^2 if they had started as group A. In the case of severe toxicity, treatment was discontinued. Selected patients who showed a complete response (CR) or partial response (PR), i.e. in remission, after the completion of chemotherapy with a single metastasis, especially in the pelvis, received consolidation radiotherapy at that site.

Before each treatment cycle, all patients had a complete blood count (CBC), SMA-12 (biochemical profile), ECG, chest roentgenography, and abdominal CT scan. Between the treatment cycles CBC was performed weekly. Patients were evaluated for response between treatment cycles every three cycles for the 21-day schedule (group A) and every six cycles for the 10-day schedule (group B).

A CR was defined as a complete disappearance of all clinically evident disease for at least 1 month. PR was defined as a decrease of more than 50% in the sum of the products of the largest perpendicular diameters of the measurable lesions for at least 1 month. A 25%–50% decrease, without satisfying the criteria for a PR was defined as stable disease (SD). Progressive disease (PD) was defined as an increase in the above measurements or the appearance of new lesions.

Table 2 Responses to chemotherapy in each group (number of patients)

Response	Group A	Group B	*P* value
Complete	1	1	1.0
Partial	12	14	0.8
Stable disease	21	22	1.0
Progressive disease	26	23	0.7

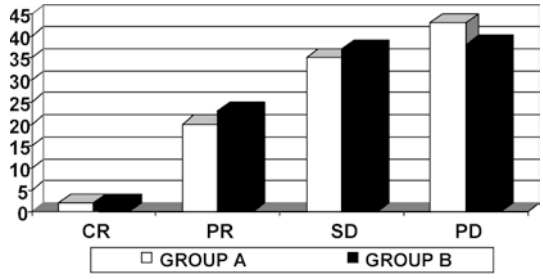

Fig. 1 Response (%) to chemotherapy by group (A versus B)

Toxicity

Toxicity was estimated according to WHO criteria [10]. Acute cholinergic syndrome was evaluated as severe (grade 3), moderate (grade 2), mild (grade 1), or absent (grade 0); severe was defined as intensive symptoms controlled with therapy, moderate as symptoms controlled with therapy, and mild when therapy was not always necessary.

Statistical analysis

The Pearson chi-squared test (Exact algorithm) was used to explore treatment response and toxicity. The Kaplan-Meier method was used to compute the survival times of the two groups, and the log-rank test (or Mantel-Cox) was used to explore the differences in the survival functions [11, 12]. With a sample size of 55 patients per treatment arm, the type I error rate was 5% with a power of 80%.

Results

Patients

Between June 1998 and December 2000, 120 patients were randomized in the present study and all were evaluable for response and toxicity. Their characteristics were balanced with no significant differences between the treatment groups (Table 1). All patients had previously received chemotherapy with LV and 5-FU and had progressed during or after the completion of treatment.

Response

One patient in each group (2%) achieved CR, 12 (20%) in group A and 14 (23%) in group B had a PR, 21 (35%) in group A and 22 (36%) in group B had SD, whereas 26 (43%) in group A and 23 (38%) in group B developed PD (Table 2, Fig. 1). Overall response rates (ORR) were 22% in group A and 25% in group B, and tumor growth control rates (CR + PR + SD) were 57% in group A and 61% in group B. No significant differences in ORRs were detected between groups at $\alpha = 5\%$ (chi-squared = 0.23 with three degrees of freedom, $P = 0.97$). Patients in group A had a median duration of response of 4.5 months (95% CI 3.6–5.4) and patients in group B 5.5 months (95% CI 4.6–6.4). No significant differences were detected between groups in terms of response duration (log-rank test = 0.46 with one degree of freedom, $P = 0.49$).

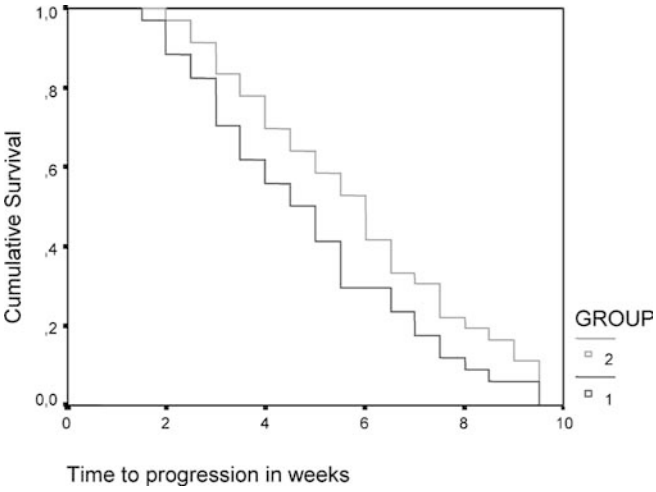

Fig. 2 Time to progression. Group A patients had a median duration of response of 4.5 months (95% CI 3.4–5.6 months) and group B patients 6.0 months (95% CI 5.0–7.0 months). No significant differences were detected between groups in terms of time to progression (log-rank test 2.48 with one degree of freedom, $P = 0.11$)

Time to progression and survival

Median time to progression in group A was 4.5 months (95% CI 3.4–5.6) and in group B was 6.0 months (95% CI 5.0–7.0). The difference between the groups in terms of time to progression was not significant (log-rank test = 2.48 with one degree of freedom, $P = 0.11$; Fig. 2).

Median survival in group A was 7 months (95% CI 6.0–8.0) and in group B was 9 months (95% CI 8.0–10.0). Survival in group B was marginally significantly longer than that in group A at $\alpha = 5\%$ (log-rank test = 3.67 with one degree of freedom, $P = 0.055$; Fig. 3).

Follow-up

None of the patients in group A or in group B (total 120 patients) was alive at the time of the analysis in June 2002 (36 months after initiation of the study). Two patients from group B achieving PR underwent liver metastasectomy and continued chemotherapy with other

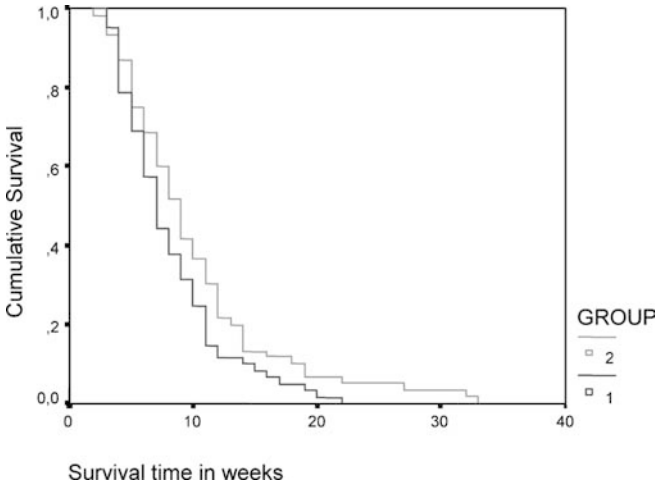

Fig. 3 Survival (all patients, no censoring). Median survival in group A was 7 months (95% CI 6.0–8.0 months), and in group B was 9 months (8.0–10.0 months). Survival in group B was marginally significant higher than in group A at $\alpha = 5\%$ (log-rank test 3.67 with one degree of freedom, $P = 0.055$)

cytostatic drugs. Five patients stopped chemotherapy with irinotecan (four in group A, one in group B). Five patients underwent surgery alone without continuing chemotherapy until they died (one in group A, four in group B). The remaining 108 patients continued chemotherapy until progression with one of the following drugs: oxaliplatin, raltitrexed, capecitabine (55 in group A, 53 in group B).

Toxicity

Toxicities included: acute cholinergic syndrome (group A 53%, group B 19%; $P < 0.0001$); late-onset diarrhea grade 1/2 (group A 21%, group B 46%) and grade 3/4 (group A 41%, group B 66%; $P < 0.0001$); nausea and vomiting grade 1/2 (group A 34%, group B 59%) and grade 3/4 (group A 30%, group B 12%; $P < 0.0001$); neutropenia grade 3/4 (group A 27%, group B 28%; $P < 0.03$), with febrile neutropenia seen in only four patients in group A; anemia grade more than 2 (group A 28%, group B 12%; $P < 0.05$); asthenia grade more than 3 (group A 24%, group B 18%; $P < 0.001$); and alopecia grade more than 3 (group A 40%, group B 34%; $P < 0.2$). These results are presented in Table 3.

Dose intensity

The mean dose intensity for all patients was 15.27 mg/m^2 per day (95% CI 15.08–15.46 mg/m^2 per day), with a median value of 15.5 mg/m^2 per day. The mean value for group A patients was 14.67 mg/m^2 per day (range 14.42–14.92 mg/m^2 per day) with a median of 15.0 mg/m^2 per day, and the mean value for group B patients was 15.87 mg/m^2 per day (range 15.68–16.06 mg/m^2 per day) with a median of 16.0 mg/m^2 per day. Significant differences in dose intensity were detected between groups based both on the parametric Student's *t*-test (value 7.55 with one degree of freedom, $P < 0.001$) and the non-parametric Mann-Whitney test (value 6.36, $P < 0.001$). Group B patients had a significantly higher dose intensity at $\alpha = 5\%$. It should be noted that there was no difference between the groups in terms of survival at the level of $\alpha = 10\%$ ($P = 0.66$) if adjustment for dose intensity was carried out.

Table 3 Incidence of toxicity in each group

Parameter	Grade	Percent of cycles		*P* value
		Group A	Group B	
Acute cholinergic syndrome		53	19	0.0001
Late-onset diarrhea	1/2	21	46	0.0001
	3/4	41	66	0.0001
Nausea and vomiting	1/2	34	59	0.0001
	3/4	30	12	0.0001
Neutropenia[a]	1/2	5	11	0.08
	3/4	27	28	0.05
Anemia	>2	28	12	0.05
Asthenia	>3	24	18	0.001
Alopecia	>3	40	34	0.2

[a]Febrile neutropenia occurred in four patients in group A and in none of the patients in group B

Table 4 Other parameters evaluated in relation to the number of patients

Parameter	Group A	Group B	*P* value
Loperamide (no. of tablets)	3662	2408	0.020
Glycosylated G-CSF (no. of 34-MIU doses)	215	95	0.0001
Performance status			
Improvement	18	22	0.438
Stable	10	11	0.810
Worsening	32	27	0.465
Pain			
Improvement	8	10	0.595
Stable	40	37	0.888
Worsening	12	13	0.82
Erythropoietin			
No. of patients	24	14	0.187
No. of 10,000-U ampoules	576	294	0.0007
Blood transfusion units	17	6	0.06
Hospital			
Admissions	8	2	0.1
Days	46	9	0.0001
Weight gain >5%	2	7	

Other treatment parameters

Patients in group A received a greater number of loperamide tablets ($P < 0.02$), and more doses of G-CSF ($P < 0.0001$) and erythropoietin ($P < 0.0001$) than those in group B (Table 4). There were more hospital admissions in group A ($P = 0.1$), and for more days

($P < 0.0001$), and patients in this group needed more blood units for transfusions ($P = 0.06$). More patients in group A had worsening in their PS, but this did not reach statistical significance. Pain improvement was similar between the groups, and more patients in group B had a weight gain of $> 5\%$ ($P = 0.1$).

Discussion

Various regimens have been tested in irinotecan monotherapy of which the two most recommended are 350 mg/m^2 i.v. every 3 weeks [5] and 125 mg/m^2 i.v. weekly for 4 weeks every 6 weeks [13]. The principal dose-limiting toxicities in these schedules are neutropenia and delayed diarrhea [14, 15, 16]. Diarrhea appears to occur more frequently with the weekly schedule. In addition, some authors have observed interpatient variations in terms of toxicity and pharmacokinetics [16, 17]. These schedules have demonstrated comparable activity in the treatment of advanced colorectal cancer [13].

In 5-FU-resistant patients, an objective response rate of 13% has been shown [9]. This clinically important activity was the basis for the phase III studies that have positioned irinotecan as the standard treatment in 5-FU-refractory advanced colorectal cancer [18, 19]. Two large randomized clinical studies have established irinotecan as the standard second-line treatment against either 5-FU/LV and continuous 5-FU regimens or best supportive care alone, respectively [18, 19], in patients with advanced colorectal cancer failing prior 5-FU/LV regimens. This was associated with a longer median time to progression and a longer median survival when compared to infusional or conventional 5-FU-based chemotherapy or best supportive care. More than 40% of patients had disease stabilization in second-line treatment.

In the present trial, we found that the administration of a fractionated dose of irinotecan on day 1 and day 10 every 3 weeks shows equal activity and less toxicity compared with 350 mg/m^2 every 21 days. An important point is the longer survival, which was marginally longer in group B, almost reaching statistical significance; it is difficult to explain this difference. Survival was not influenced by dose intensity, but the better PS during therapy among patients in group B (less hematologic toxicity, less severe diarrhea, and less asthenia) may have played a role. The cost (or units consumed) seemed to be higher in group A (more loperamide, glycosylated G-CSF, erythropoietin doses, incidence of febrile neutropenia, and more days in hospital as a result of treatment-related morbidity).

The value of the present study is that it provides additional information for an alternative method of administration between the initial with the total dose administered every 21 days and every week. The biweekly schedule of irinotecan administration has attracted considerable interest as an alternative to the 3-weekly schedule because of an acceptable toxicity profile and the convenience of combining it with oxaliplatin and 5-FU/LV (de Gramont's schedule). However, its dose intensity is relatively compromised when compared to the 3-weekly schedule and the every-10-days schedule, and it has not been widely accepted as a single-agent therapy for refractory colorectal cancer.

The same fractionated schedule of irinotecan was tested in a phase II study by Ulrich-Pur et al. [17] in 38 second-line colorectal cancer patients who had failed oxaliplatin plus 5-FU/FA. The overall response rate was 21%, median progression-free survival was 4.8 months, and median survival had not yet been reached at the time of publication. The authors also concluded that the fractionated regimen has substantial activity with a favorable toxicity profile. The results of the present study as well as those of the study by Ulrich-Pur et al. [17] provide a rationale for further clinical trials with fractionated doses of irinotecan in the second-line setting. In addition, irinotecan is used in several other malignancies apart from colorectal cancer, and these data may be useful in forming the basis for combinations of irinotecan with other cytotoxic drugs.

As an overall conclusion, this study demonstrated that the fractionated schedule of irinotecan administration in comparison to the standard every-21-day schedule yields an equal response rate and more acceptable toxicity. Both schedules were associated with different requirements in supportive measures, such as administration of loperamide, glycosylated G-CSF, erythropoietin, and blood transfusions, and these were lower with the fractionated schedule of irinotecan administration.

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