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Clinical report

Adding weekly irinotecan to high-dose 5-fluorouracil and folinic acid (HD-5-FU/FA) after failure for first-line HD-5-FU/FA in advanced colorectal cancer—a phase II study

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Irinotecan (CPT-11) has been shown to prolong survival and improve quality of life in comparison to best supportive care in colorectal cancer patients with pretreatment of bolus 5-fluorouracil (5-FU). After first-line 24-h high-dose (HD) 5-FU/folinic acid (FA) an objective response rate of 11% with 3-weekly CPT-11 350 mg/m^2 was reported. In the present study we investigated weekly CPT-11 in combination with 24-h HD-5-FU/FA as second-line treatment after prior exposure to 24-h HD-5-FU. Synergy between 5-FU and CPT-11 is the rationale to combine both substances for second-line therapy in order to overcome resistance to 5-FU. Thirty-five patients were recruited in a single institution to receive 6 × weekly CPT-11 80 mg/m^2, FA 200 mg/m^2 and 24-h HD-5-FU 2000 mg/m^2. Treatment was repeated on day 57. Patient characteristics: M/F=20/15, median WHO performance status 1, range (0–2). Thirty-four patients were evaluable for response: partial response 17% and no change 40%. Median time to progression and overall survival were 3.3 and 8.4 months, respectively. All patients were evaluable for toxicity analysis (National Cancer Institute Common Toxicity Criteria grade 3): leukocytopenia 3%, diarrhea 12% and vomiting/nausea 6%. Of the assigned doses, a median 100% of 5-FU and 92% of CPT-11 were administered during the first cycle of chemotherapy. We conclude that weekly CPT-11 and HD-5-FU/FA is an active and safe combination chemotherapy resulting in response rates in the upper range of other CPT-11-based second-line regimen. The toxicity profile in our series compared to 3-weekly CPT-11 seems favorable. [© 2002 Lippincott Williams & Wilkins.]

Key words: Colorectal cancer, folinic acid, high-dose 5-fluorouracil, irinotecan, salvage chemotherapy.

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Introduction

Since the 1960s 5-fluorouracil (5-FU) has been the mainstay of therapy for patients with metastatic colorectal cancer (CRC). Many patients are eligible for second-line treatment after failure of 5-FU-based first-line chemotherapy. Irinotecan (CPT-11) has been shown to prolong survival and improve quality of life in CRC after pretreatment with 5-FU relative to best supportive care.[1] When compared with infusional 5-FU as second-line treatment after bolus application of 5-FU, CPT-11 yielded higher response rates and improved survival.[2] Thus, CPT-11 currently has best evidence in this setting and is generally recommended.

Two CPT-11 dosing regimens are commonly used for second-line chemotherapy: a CPT-11 starting dose of 100–125 mg/m^2 given weekly 4, q6 weeks[3] or a starting dose of 350 mg/m^2 q3 weeks (300 mg/m^2 in patients aged 70 years, performance status 2 or prior pelvic irradiation).[1,2] No significant differences in therapeutic efficacy [time to progression $(TTP)_{CPT\text{-}11\ weekly}$ 4.1 months versus $TTP_{CPT\text{-}11\ 3\text{-}weekly}$ 3.0 months; survival $_{CPT\text{-}11\ weekly}$ 8.9 versus $survival_{CPT\text{-}11\ 3\text{-}weekly}$ 9.7 months] or quality of life measures between both schedules were observed in a phase III study.[4] However, the q3-week schedule was associated with a significantly lower incidence of National Cancer Institute Common Toxicity Criteria (NCI CTC) grade 3–4 late diarrhea (37% weekly, 20% 3-weekly; $p=0.002$) but a slightly higher, not significant rate of neutropenia (28% weekly, 34% 3-weekly; $p=0.37$).

Meanwhile, first-line CPT-11 in combination with weekly bolus[5] or biweekly infusional 5-FU and folinic acid (FA)[6] have been shown to improve survival relative to the 5-FU/FA regimens, providing evidence for the pre-clinically known synergy of both compounds.[7] Thus, combining CPT-11 with 5-FU/FA for second-line treatment may contribute to augment CPT-11 single-agent antitumor activity. So far, only a few prospective phase II trials have been published, mostly in abstract form, for second-line combination of CPT-11 with 5-FU/FA after failure for 5-FU.[8–11] Most of these studies have included patients with 5-FU failure without exactly stipulating the 5-FU schedule to be used as front-line therapy. This might lead to incomparable data.

One phase II study of second-line CPT-11 therapy with a uniformly pretreated first-line population assessed the efficacy of 3-weekly CPT-11 350 mg/m^2 after progression on the German 24-h infusional 5-FU schedule [Arbeitsgemeinschaft für Internistische Onkologie (AIO) schedule: 24-h high-dose (HD) 5-FU 2600 mg/m^2 preceded by 2-h FA 500 mg/m^2].[12] In this study, after first-line HD-5-FU/FA, an objective response rate of 11% with 3-weekly CPT-11 350 mg/m^2 was reported. Main toxicity (NCI CTC grade 3–4) in this study was neutropenia 16%, diarrhea 23% and nausea 12%.

In the present study, we investigated weekly CPT-11 in combination with HD-5-FU and FA as second-line treatment after documented progression on the aforementioned AIO schedule.

Patients and methods

Patients

Patients with histologically proven advanced colorectal adenocarcinoma after progression on infusional HD-5-FU and FA (24-h HD-5-FU 2600 mg/m^2 preceded by 2-h FA 500 mg/m^2, AIO schedule) were eligible. Adjuvant chemo- or radiochemotherapy was allowed. Bidimensionally measurable disease was mandatory to assess response to treatment according to WHO criteria. ECOG performance status $\leqslant 2$, adequate bone marrow function (white blood cell count $>4000/\mu$l, platelet count $>100\,000/\mu$l), renal function (serum creatinine <1.4 mg/dl), and adequate cardiac, normal pulmonary and liver function (bilirubin <2 mg/dl) were mandatory. All patients gave written informed consent. Appropriate contraception was required in fertile patients. The protocol was reviewed and approved by the local Institutional Review Board. Treatment was performed according to the Declaration of Helsinki on a monocentric basis.

Treatment, toxicity and dose modification

Treatment was given once weekly for a total of 6 weeks followed by a 2-week rest period. Thus, one course equaled 8 weeks. CPT-11 was administered weekly at a dose of 80 mg/m^2 as a 60–90 min infusion. 5-FU was given weekly at a dose of 2000 mg/m^2 as a 24-h continuous infusion, preceded by 200 mg/m^2 FA as a 2-h infusion. A permanent venous access (port system) had been implanted in all patients in order to enable continuous 5-FU infusion.

Adverse events were evaluated weekly and classified according to the NCI CTC. The study protocol required delay of therapy in case of diarrhea, mucositis, leukocytopenia or thrombocytopenia NCI CTC grade >1 on the scheduled day. It made use of a 25% reduction of CPT-11 and 5-FU in case of the mucositis, leukocytopenia or thrombocytopenia grade 2 or 3. In the case of diarrhea grade 2 or 3, only CPT-11 was to be reduced. Finally, in the case of grade 3 (second occurrence) or 4, doses were reduced by 50%. The treatment was continued until progression or unacceptable toxicities developed.

Evaluation of response

Evaluation procedures, including physical examination, serum biochemistry and tumor markers, were evaluated every 8 weeks; complete blood cell count was checked weekly. Indicator lesions were assessed every 8 weeks by a computed tomography scan, chest radiography or ultrasonography. According to WHO criteria, complete response (CR) was defined as the disappearance of all clinical evidence of disease and partial response (PR) as reduction of $\geqslant 50\%$ in the sum of products of the perpendicular diameters of all initial measurable masses for at least 4 weeks, documented by two subsequent examinations. Progressive disease (PD) was defined as a $\geqslant 25\%$ increase in the products of measurable diameters or the development of a new lesion. No change (NC) was any measurement not fulfilling these criteria for response or progression.

Statistical analysis was performed within the full analysis set (intent-to-treat). Survival and TTP were calculated from the first day of treatment until death or progression.

Results

Patient characteristics

Thirty-five patients met the inclusion criteria and were enrolled into this study from October 1999 to

Table 1. Patient characteristics

	Patients	
	n	%
Patients enrolled	35	100
male	20	57
female	15	43
Median age (years)	61	
range	26–78	
Primary tumor site		
cecum/colon transversum	7	20
colon descendens/rectum	28	80
Primary tumor resection		
curative	16	46
palliative	18	51
not done	1	3
Adjuvant therapy		
chemotherapy with bolus 5-FU/FA	8	23
radiochemotherapy (50.4 Gy and bolus 5-FU/FA)	8	23
ECOG performance status		
0	13	37
1	20	57
2	2	6
Metastatic sites		
1	20	57
2	11	31
$\geqslant 3$	4	11
Tumor involvement		
lung	4	11
liver	32	91
local recurrence	6	17
peritoneal carcinomatosis	8	23
others (bone, pancreas)	5	14

June 2001. Patient characteristics are shown in Table 1. Fifty-four percent of the patients were older than 60 and 14% older than 70 years. The median ECOG performance status was 1 (range 0–2).

A total of 16 patients had undergone curative surgery and adjuvant (radio)chemotherapy with 5-FU/FA-based bolus-regimens. The time to relapse in this group of patients was 18 months (range 2–50 months). Eighteen patients were subject to palliative resection of the primary, while one patient refused surgical treatment. All patients had been pretreated with HD-5-FU and FA as requested by protocol.

Liver metastases ($n=32$), peritoneal carcinomatosis ($n=8$) as well as local recurrence ($n=6$) were the most common tumor sites. Forty-three percent of the patients had two or more metastatic sites.

Safety and dose intensity

A median of two cycles (range 1–6) and a total of 92 cycles was administered. Eighty-six percent of the patients received two and 37% received three or more cycles of chemotherapy. Three patients (9%) did not complete the first cycle of chemotherapy (non-study-related reasons $n=1$, consent withdrawn $n=1$ and early progression $n=1$).

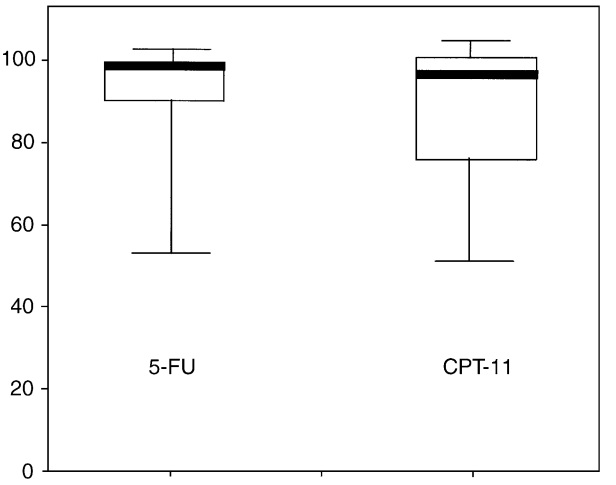

Figure 1. Box-whiskers diagram of 5-FU and CPT-11 doses administered during the first cycle of chemotherapy. A median 100% of the planned 5-FU dose and 92% of the planned CPT-11 dose was administered (means 94 and 88%, respectively)

The actually administered doses of 5-FU and CPT-11 during the first cycle of treatment relative to the planned doses are shown in Figure 1. A median 100% of the scheduled 5-FU (mean 94%) and 92% of the CPT-11 dose (mean 88%) were administered during the first cycle. Three patients did not complete the first cycle, which resulted in the lower whiskers in the 5-FU and CPT-11 boxes. Ignoring these, 25 patients received 100% of the planned 5-FU dose and 19 patients 100% of the scheduled CPT-11 dose. Therapy was delayed for toxicity in eight patients (23%) during the first cycle for a median of 7 days (mean 10 days). During the study period, 10 patients were in need of dose reduction (mean dose reduction 32%) and in 17 patients therapy was delayed for a median of 9 days.

All 35 patients were evaluable for toxicity. In general, the treatment was well tolerated. The toxicities observed are listed in Table 2. Hematological toxicity was mild and leukocytopenia grade 3 was only seen in one patient. More pronounced was gastrointestinal toxicity, with diarrhea grade 3 in four, vomiting grade 3 in two and nausea grade 2 in 10 patients. In one case, catheter obstruction was observed.

Table 2. Toxicity (%) of patients (n=35) during the study period, classified according to NCI CTC criteria

Toxicity	NCI-CTC grade (%)			
	1	2	3	4
Hematological				
leukocytopenia	11	9	3	0
anemia	71	17	0	0
thrombocytopenia	3	0	0	0
Gastrointestinal				
nausea	57	29	0	0
vomitus	31	17	6	0
diarrhea	42	20	12	0
Stomatitis	11	3	0	0
Cholinergic syndrome	17	3	0	0
Alopecia	6	11	0	0

Efficacy

Thirty-four patients were evaluable for response and all 35 patients for survival. The results are listed in Table 3. One patient had undergone initial staging more than 4 weeks before the start of chemotherapy and was not amenable to response analysis. Six patients achieved a PR (17%). Fourteen patients (40%) had stable disease, whereas 14 patients (40%) showed PD.

At the time of analysis (February 2002) 26 patients had died (74%). The median overall survival for the whole study population calculated from the start of second-line treatment was 8.4 months (95% CI: 6.5–15.7), ranging from 3.4 to 24 months. Adjusted 1-year survival was 43%. In the intent-to-treat analysis the median TTP was calculated as 3.3 months (95% CI: 2.3–5.6), ranging from 0.7 to 12.8 months. The Kaplan–Meier estimates for overall survival and TTP are shown in Figures 2 and 3, respectively.

Table 3. Response and survival of 35 patients with advanced CRC receiving second-line treatment (intent-to-treat analysis)

Response	No. of patients	%
CR	0	0
PR	6	17
NC	14	40
PD	14	40
Not evaluable	1	3

Survival
Median overall survival: 8.4 months (95% CI: 6.5–15.7) [range 3.4–24.0]
1-year-survival (adjusted): 43%
Median TTP: 3.3 months (95% CI: 2.3–5.6) [range 0.7–12.8]

Consecutive therapies after second-line failure

At the time of analysis, 31 patients had progressed under second-line therapy. Of these, 24 (77%) were amenable to third-line therapy (oxaliplatin n=19, raltitrexed n=2, capecitabine n=2 and monoclonal antibody BIBH-1 n=1).

Discussion

In accordance with the study rationale, i.e. preclinical evidence and clinical proof of synergy between CPT-11 and 5-FU in first-line chemotherapy, we found that this second-line schedule is an active and safe regimen for the outpatient treatment. The tumor growth control rate (PR + NC) of 57%, the median TTP of 3.3 months and the overall survival of 8.4 months compares adequately with other CPT-11-based second-line schedules. In a similar trial on second-line treatment of CRC, Schöffski *et al.*[12] reported a tumor growth control rate of 76% (PR 11%, NC 65%), TTP of 4 months and overall survival of 9 months in patients who had received the same first-line regimen as the patients in our study. In this trial, patients had been treated with CPT-11 350 mg/m^2 as salvage regimen. Among the NCI CTC grade 3–4 toxicities in this study were neutropenia in 39% and delayed diarrhea in 20% of the patients, respectively.

Compared to the data obtained by Schöffski, we observed relatively low toxicity in our study with NCI CTC grade 3 leukocytopenia amounting to 3%, diarrhea 12% and nausea/vomiting 6%. The toxicity is in the lower range of that reported by Douillard *et al.*[6] in the European pivotal first-line trial in the patient group receiving weekly CPT-11 (80 mg/m^2), 24-h HD-5-FU (2300 mg/m^2) preceded by 2-h FA 500 mg/m^2. In this patient group (n=54)—despite being treated first-line with a presumably better performance status—NCI CTC grade 3–4 toxicity was reported for leukocytopenia 20.4%, diarrhea 44.4% and nausea 7.4%. The difference to our study might be due to the lower doses of 5-FU (2000 mg/m^2) and FA (200 mg/m^2) used in our study. In the EORTC phase III study 40986, comparing first-line AIO schedule alone with CPT-11 (80 mg/m^2), FA 500 mg/m^2 and 24-h HD-5-FU (2300 mg/m^2), the 5-FU-dose had to be reduced from 2300 to 2000 mg/m^2 because of initially high toxicity in an interim analysis.[13] Another explanation for the lower toxicity in our study could rely on the early and rigorous dose reduction according to our protocol (see 'Dose modification'). Nevertheless, a median 100% of the

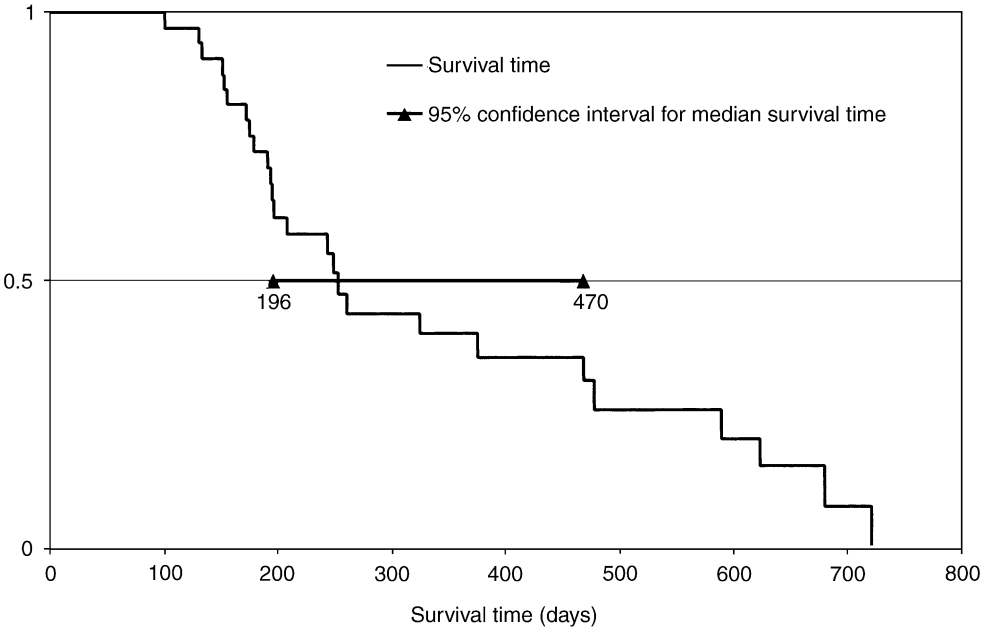

Figure 2. Kaplan–Meier estimates for overall survival of 35 patients with advanced CRC receiving second-line treatment. Median survival was 8.4 months (95% CI: 6.5–15.7).

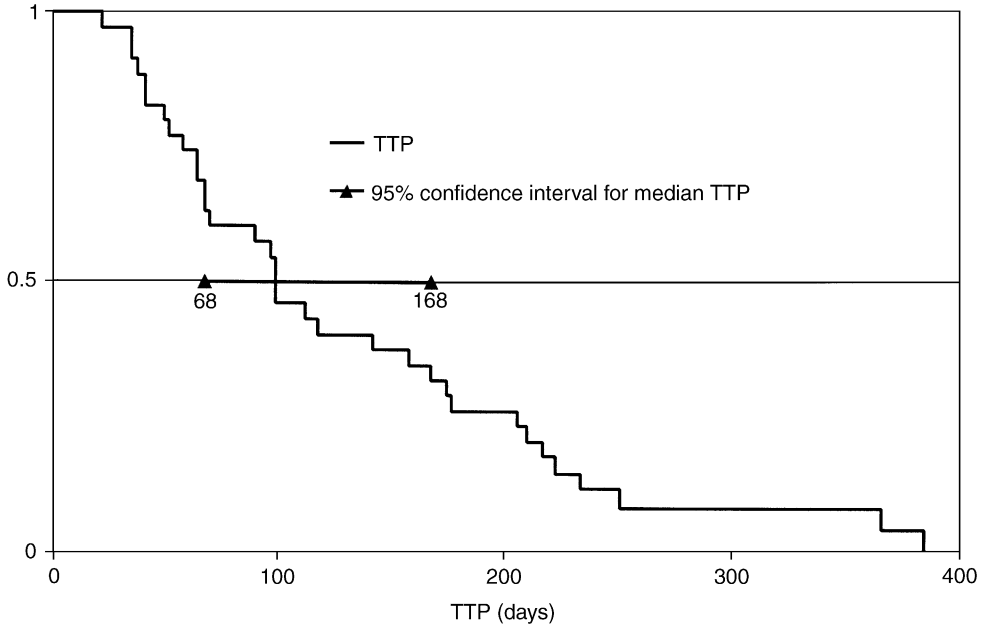

Figure 3. Kaplan–Meier estimates for TTP of 35 patients with advanced CRC receiving second-line treatment. The median time to progression was 3.3 months (95% CI: 2.3–5.6).

scheduled 5-FU and 92% of the CPT-11 dose could be administered during the first cycle. Ignoring three patients who did not complete the first treatment cycle, 25 patients received 100% of the scheduled 5-FU and 19 patients 100% of the planned CPT-11 dose. During the whole study period, 10 patients were in need of dose reduction (mean dose reduction 32%) and in 17 patients a delay of therapy for a median of 9 days was required.

Summarizing the data from several clinical trials, CPT-11 combined with HD 5-FU/FA is a safe and well-tolerated therapy for patients with advanced CRC in

first- as well as in second-line regimen. The results of our second-line trial suggest that especially the rate of leukocytopenia can be reduced compared with 3-weekly CPT-11, as indicated by our data without loss of efficacy.

At the time of final analysis, 31 patients had been documented with progressive disease under second-line therapy. Of these, 24 (77%) were amenable even to third-line therapy and most of them were treated with oxaliplatin. Apparently, our chosen CPT-11 schedule with adequate dose reduction in time according to toxicity maintains the general performance status of the patients, enabling them to have further treatment in the case of tumor progression.

In conclusion, our results suggest that this combination may be considered as an effective and safe salvage regimen in FA-modulated infusional 5-FU-pretreated patients with progressive CRC. The question whether CPT-11 should be used as monotherapy or in combination with 5-FU as second-line treatment is currently under investigation in a randomized phase III study of second-line treatment (CPT-11 versus CPT-11 plus 5-FU/FA) of the AIO in Germany. This study might elucidate if the potential disadvantages of combination therapy (weekly therapy requiring more complex infusional devices) can be outweighed by the higher efficacy or lower toxicity of second-line combination therapy.

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