Irinotecan and capecitabine as second-line treatment after failure for first-line infusional 24-h 5-fluorouracil/folinic acid in advanced colorectal cancer: a phase II study

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The efficacy of combination therapy with irinotecan and capecitabine has been demonstrated for the first-line treatment of metastatic colorectal cancer (MCRC). The aim of this trial was to evaluate the efficacy and safety of this combination in MCRC as second-line treatment after failure of 24-h infusional 5-fluorouracil (5-FU_{24h}) and folinic acid (FA). Patients pre-treated with 5-FU_{24h}/FA were recruited at two institutions to receive 6 × weekly irinotecan 70 mg/m^2 and capecitabine (1000 mg/m^2 b.i.d. days 1–14 and 22–35). Courses were repeated on day 50. In elderly patients (>65 years) a 20% dose reduction of both drugs was scheduled. Twenty-eight patients [M/F 20/8; median age 65 years (range 44–79); median ECOG score 1] were enrolled. The most frequent sites of metastases were liver, *n* = 20, lymph nodes and lungs, *n* = 10, respectively. Half of the patients had two or more metastatic sites. A total of 71 treatment courses (median 2, range 1–8) were administered. Main toxicities [worst per patient (%); CTC grade 1/2/3/4] were: anaemias 18/14/–/–; leukocytopenia 11/21/–/–; thrombocytopenia 11/–/–/–; diarrhea 18/36/21/–; nausea/vomiting 43/29/4/–; mucositis 4/11/–/–; alopecia 7/25/–/–; hand–foot syndrome 7/21/–/–; fatigue 14/14/–/–; renal insufficiency (caused by diarrhea and exsiccosis) –/–/–/7. Dose intensity in the first course was [median/mean (%)]: irinotecan 92/83; capecitabine 88/82. Twenty-three patients are evaluable for response analysis (five did not complete the first course): three patients showed partial remissions (13%) and 11 patients had stable disease (48%). Median time to progression was 3.0 months for the total population (range 1.4–17.3) and 6.5 months for responders (partial response plus no change). Seventy-four percent of the patients received a third-line therapy. Overall survival was 15.7 months calculated from the start of study treatment. Second-line therapy with irinotecan and capecitabine yielded a tumor control in 61% of patients with MCRC. Efficacy and toxicity data are comparable to 5-FU/irinotecan combinations, although the likelihood of severe diarrhea appears to be higher with capecitabine/irinotecan. *Anti-Cancer Drugs* 16:39–45

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Introduction

Until recently 5-fluorouracil (5-FU) has been the mainstay and the sole treatment option for patients with metastatic colorectal cancer (CTC). The therapeutic armamentarium has been significantly improved by the implementation of oxaliplatin and irinotecan in routine practice [1–3]. First-line combination chemotherapy with infusional 5-fluorouracil (5-FU)/folinic acid (FA) and irinotecan (e.g. FOLFIRI) or oxaliplatin (e.g. FOLFOX) is widely accepted as the standard of care due to an improvement in time to tumor progression (TTP) and response rate in comparison with infusional 5-FU/FA treatment alone [4–6]. Nevertheless, sequential application of the active drugs may be justified in a subset of patients [7].

One of the most important questions currently addressed in randomized studies is whether oral 5-FU pro-drugs such as capecitabine can replace infusional 5-FU/FA in combination schedules. Combination regimen of capecitabine and irinotecan have been evaluated in several trials [8–10]. Both drugs have been shown to possess significant synergistic activity in xenograft models [9,11], and, accordingly, the clinical results obtained by this combination in first-line treatment of CRC are promising with response rates in the range of 40–45% and a TTP of about 8 months [8–10].

Since irinotecan has shown prolongation of survival in comparison with best supportive care and infusional 5-FU regimen in patients pre-treated with 5-FU bolus regimen,

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it is frequently used as second-line therapy [12,13]. Two irinotecan dosing schedules have been employed for second-line chemotherapy: 100–125 mg/m^2 applied weekly × 4, q6 weeks or 300–350 mg/m^2 q3 weeks. No differences in efficacy (TTP_{weekly} 4.0 versus $TTP_{3\text{-weekly}}$ 3.0 months; survival 9.9 months, respectively) or quality of life measures have been observed between both regimen in a phase III study [14]. However, the q3-week schedule was associated with a significantly lower incidence of severe diarrhea (36 versus 19%), but a slightly higher rate of neutropenia (29 versus 34%). The results of a trial reported by Tsavaris *et al.* favor the more frequent application of irinotecan (twice during a 3-week period instead of 3-weekly) [15].

It is widespread clinical practice to use 5-FU in combination with irinotecan in the second-line setting [2,16–18] because the co-administration of 5-FU might improve irinotecan single-agent activity, thus sparing irinotecan dosage and improving the toxicity profile [19]. Nevertheless, in contrast to the second-line treatment with oxaliplatin which needs co-administration of 5-FU [20], regimens using irinotecan and 5-FU beyond progression after 5-FU (± oxaliplatin) have so far not shown advantages over irinotecan monotherapy.

In a previous trial we have investigated weekly irinotecan (80 mg/m^2) in combination with infusional 24-h 5-FU (2000 mg/m^2) and FA (200 mg/m^2) as second-line treatment after progression on the German AIO (Arbeitsgemeinschaft für Internistische Onkologie) regimen [18]. In the present second-line study we sought to replace infusional 5-FU treatment by the standard combination schedule of capecitabine together with weekly irinotecan. Second-line trials with irinotecan and capecitabine have not been reported up until now. In an attempt to have comparable phase II populations we included the same patient group (pre-treated with AIO regimen) as in our previous study [18].

Patients and methods

Patients

Patients with histologically proven advanced colorectal adenocarcinoma after progression on infusional 5-FU and FA (24-h 5-FU 2600 mg/m^2 preceded by 2-h FA 500 mg/m^2, AIO regimen) 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 ≤ 2, adequate bone marrow function (WBC count $> 4000/\mu l$, platelet count $> 100\,000/\mu l$), renal function (serum creatinine < 1.4 mg/dl or creatinine clearance > 60 ml/min calculated according to Cockcroft and Gault), 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 Institutional Review Board, and treatment was performed according to the Declaration of Helsinki at two centers.

Treatment schedule, toxicity and dose modification

Treatment was routinely given in the outpatient setting. Capecitabine was administered at a dose of 1000 mg/m^2 twice daily (approximately every 12 h) on days 1–14 and 22–36. Daily doses were rounded up to the nearest calculated dose and adjustments were made if indicated. Irinotecan was applied at a dose of 70 mg/m^2 in 250 ml of saline solution 0.9% by i.v. infusion over 90 min weekly for 6 weeks. Each course of chemotherapy consisted of 6 weeks of treatment followed by a 1-week rest period (50 days in total). A 20% dose reduction in elderly patients (> 65 years) was scheduled by the protocol.

Adverse events were evaluated weekly and classified according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. The study protocol required delay of therapy in case of diarrhea, mucositis/stomatitis, leukocytopenia, thrombocytopenia and skin toxicity on the scheduled day. Treatment was postponed until full recovery of diarrhea and mucositis (grade 0), and amelioration of myelosuppression, skin toxicity and other adverse events to grade 1 or below. We made use of a 25% reduction of irinotecan and capecitabine in case of diarrhea grade ≥ 1, mucositis/stomatitis grade > 1 and leukocytopenia grade ≥ 2. In case of the re-occurrence of toxicities grade ≥ 2, doses were reduced by 50%. The treatment was continued until progression or unacceptable toxicities developed. Adverse events (especially diarrhea) were treated in accordance with the recommendations given by Rothenberg *et al.* [21].

Evaluation of response and survival

Evaluation procedures, including physical examination, serum biochemistry and tumor markers were evaluated every 7 weeks; complete blood cell count was checked weekly. Indicator lesions were assessed every 7 weeks. Response was classified according to standard WHO criteria.

Statistical analysis was performed within the full analysis set (intent-to-treat). Overall and progression-free survival were calculated from the first day of treatment until death or progression according to Kaplan and Meier. The 95% confidence intervals (CI) for survival and TTP were calculated using the method of Brookmeier. For parameter estimation of binomial distributions, the two-sided method of Clopper and Pearson was in place at a 95% level (statistical calculations were performed with the DKFZ Statistics Package ADAM, version 2.20).

Results

Patient characteristics

Twenty-eight patients met the inclusion criteria and were enrolled into this study from February 2002 to November 2003. Patient characteristics are shown in Table 1. Median age was 65 years. Median ECOG performance status was 1 (range 0–2).

Eight patients had undergone curative surgery and four of these had received adjuvant chemotherapy, while 20 patients had primary metastatic disease. Nineteen of these patients have had palliative resection of the primary tumor. Seven patients received (neo-) adjuvant chemo-radiation for rectal cancer. All patients had been pre-treated with infusional 5-FU and FA as requested by protocol.

Liver ($n = 20$), lung ($n = 10$) or lymph node ($n = 10$) metastases were the most common tumor sites; 50% of the patients showed two or more sites of metastases.

Safety and dose intensity

A median of 2 cycles (range 1–8) and a total of 71 cycles were administered. Twelve patients received 3 or more cycles of chemotherapy. Five patients (18%) did not complete the first cycle of chemotherapy (toxicity $n = 4$, radiotherapy required due to painful bone metastasis $n = 1$).

Table 1 Patient characteristics

	n	%
Patients enrolled	28	
male	20	71
female	8	29
Age (years) [median (range)]	65 (44–79)	
ECOG performance status		
0	9	32
1	17	61
2	2	7
Primary tumor site		
colon	14	50
rectum	14	50
Metastatic disease at the time of diagnosis	20	71
Localized primary tumor	8	29
Prior (neo)adjuvant therapy		
chemotherapy with bolus 5-FU/FA	8	29
radio-chemotherapy (50.4 Gy and 5-FU)	7	25
Metastatic sites		
1	14	50
2	8	29
≥ 3	6	21
Tumor involvement		
liver	20	71
lungs	10	36
local recurrence	2	7
peritoneum	2	7
lymph nodes	10	36
bone	2	7
Median activity of lactic dehydrogenase (range)	228 U/l (137–770)	
Median activity of alkaline phosphatase (range)	159 U/l (72–1096)	
Median CEA value (range)	19 μg/l (1–1200)	
Median CA 19-9 value (range)	32 kU/l (2–557)	

Normal ranges: lactic dehydrogenase: <248 U/l; alkaline phosphatase: 36–126 U/l; CEA: <3.0 μg/l: CA 19-9: <37 kU/l.

The actually administered doses of capecitabine and irinotecan during the first cycle of treatment relative to the planned doses are shown in Figure 1. Considering the intent-to-treat population, a median 88% of the scheduled capecitabine (mean 82%) and 92% of the irinotecan-dose (mean 83%) were administered during the first cycle. Ignoring five patients not completing the first cycle, the values calculated for the per-protocol group of patients ($n = 23$) were as follows [median/mean (%)]: capecitabine 96/90; irinotecan 100/92. Therapy was postponed due to toxicity in eight out of 23 patients (35%) during cycle 1 for a median of 14 days (range 7–28 days). During the second treatment cycle median dose intensity was 92% of capecitabine (mean 86%) and 100% of irinotecan (mean 83%).

All 28 patients are evaluable for toxicity. The toxicity observed is listed in Table 2. No grade 3 hematological toxicity was reported. Gastrointestinal toxicity was pronounced, with diarrhea grade 3 in six and vomiting/nausea grade 3 in one patient. Two patients suffering from diarrhea grade 3 were hospitalized due to exsiccosis and consequent renal failure, which was reversible in either case. Both events occurred during the first treatment cycle. Two more patients did not complete the first treatment cycle for toxicity reasons.

Efficacy

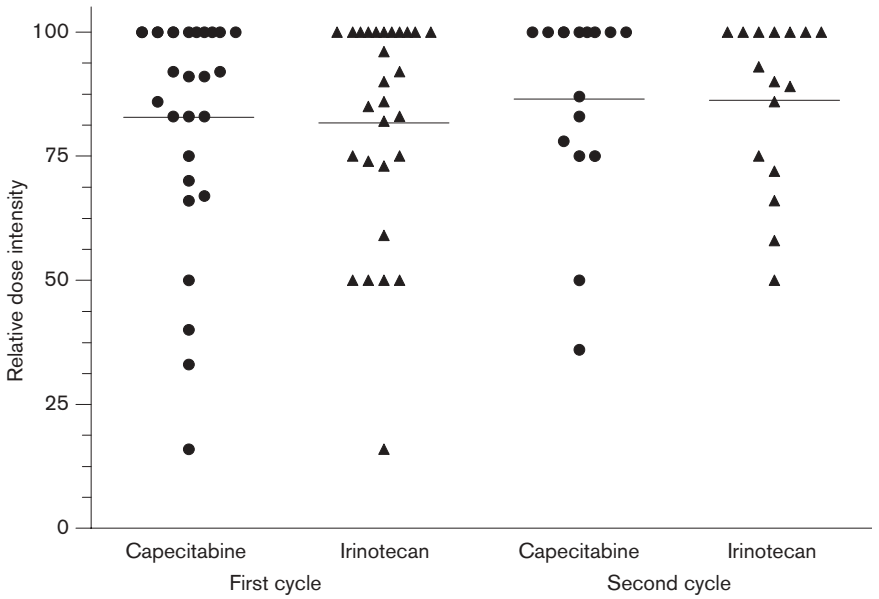
Twenty-three patients were evaluable for response and all patients for survival. The results are listed in Table 3. Three patients achieved a partial remission (13%: 95% CI 3–34%). Eleven patients (48%) had stable disease, whereas nine patients (39%) showed disease progression.

At the time of analysis (May 2004) 17 patients had died (61%). In the intent-to-treat analysis the median TTP was calculated 3.0 months (95% CI 2.5–6.5) ranging from 1.4 to 17.3 months. The median TTP for responders (partial response plus no change) was 6.5 months. The median overall survival for the whole study population calculated from the start of second-line treatment was 15.7 months (95% CI 9.3–18.7 months), ranging from 3.0 to 26.0 months. Adjusted 1-year survival was 57%. The median survival calculated from the start of first-line treatment with infusional 5-FU/FA was 25.2 months (95% CI 17.6–48.4 months). The Kaplan–Meier estimates for overall survival and TTP are shown in Figures 2–4.

Consecutive therapies after second-line failure

At the time of analysis, 26 patients had progressed under second-line therapy. One patient was lost to follow-up and one patient still had stable disease. Of the remaining 26 patients, 19 (74%) were amenable to third-line therapy using oxaliplatin-based regimen in 16 patients.

Fig. 1



Scattergram of the relative dose intensities of capecitabine (dots) and irinotecan (triangles) administered during the first and second cycle of chemotherapy (intent-to-treat population; $n=28$).

Table 2 Worst toxicity per patient ($n=28$) during the study period, classified according to NCI-CTC criteria (version 2.0)

Toxicity	Grade (%)			
	1	2	3	4
Hematological				
anemia	18	14	0	0
leukocytopenia	11	21	0	0
thrombocytopenia	11	0	0	0
Gastrointestinal				
nausea/vomiting	43	29	4	0
diarrhea	18	36	21	0
mucositis/stomatitis	4	11	0	0
Skin				
alopecia	7	25	0	0
hand–foot syndrome	7	21	0	0
Fatigue	14	14	0	0
Renal insufficiency	0	0	0	7

Table 3 Response of 23 patients with advanced CRC receiving second-line treatment (per-protocol analysis)

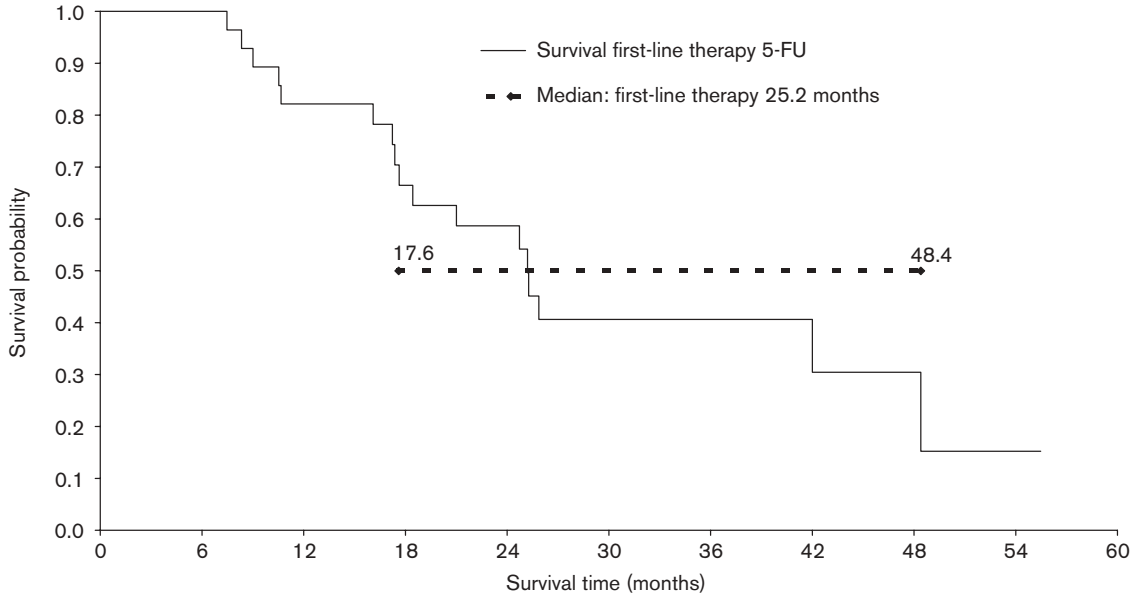
Response	*n*	%	95% CI (two-sided Clopper–Pearson)
Complete response	0	0	
Partial response	3	13	3–34
No change	11	48	27–69
Progressive disease	9	39	20–62

Discussion

This study aimed at determining the activity and safety of irinotecan and capecitabine combination after failure of infusional 5-FU and FA in patients with metastatic CRC. Irinotecan is the evidence-based standard treatment in this situation, but laboratory data and a number of clinical trials provide evidence, that co-administration of 5-FU or capecitabine might augment the single-agent activity of irinotecan, although lower doses of irinotecan are used [9,11,16–18]. In our former study on a comparable patient group (pre-treated with infusional 5-FU/FA), we found infusional 5-FU/FA and irinotecan to be an active and safe second-line treatment [18]. The tumor growth control rate (partial response plus no change) of 57%, the median TTP of 3.3 months and the overall survival of 8.4 months compared adequately with other irinotecan-based second-line schedules, while toxicity, especially diarrhea, appeared to be lower. In the current trial we found very similar efficacy data with a tumor growth control rate of 61% and a median TTP of 3.0 months. Median survival was 15.7 months, which can be explained be effective third- or even fourth-line treatment in 74% of the patients. Twelve patients received at least 3 cycles of treatment and we observed progression-free intervals up to 17 months, suggesting that this combination therapy is a promising treatment option even in the second-line setting.

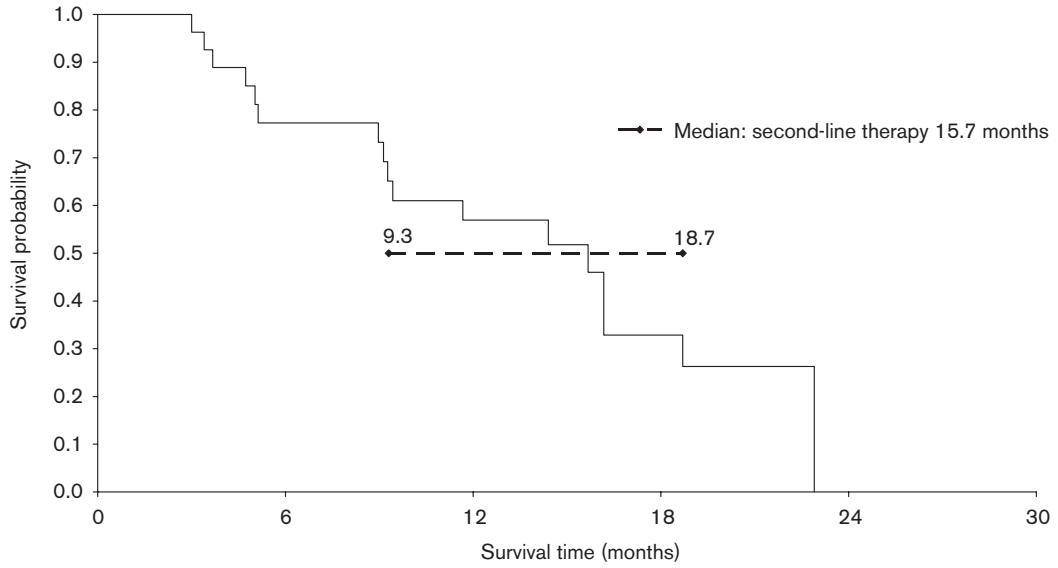
Nevertheless, four patients did not complete the first cycle due to toxicity, two of whom had to be hospitalized with renal failure due to diarrhea. This observation is in accordance with what was experienced in first-line therapy with irinotecan/capecitabine regimen. In a randomized phase II study reported by Grothey *et al.*, the CapIri regimen (capecitabine 1000 mg/m^2 b.i.d. days

Fig. 2



Overall survival calculated according to Kaplan–Meier for patients with advanced CRC ($n=28$). The curve refers to survival after start of first-line therapy with infusional 5-FU_{24h}. Median survival was 25.2 months.

Fig. 3

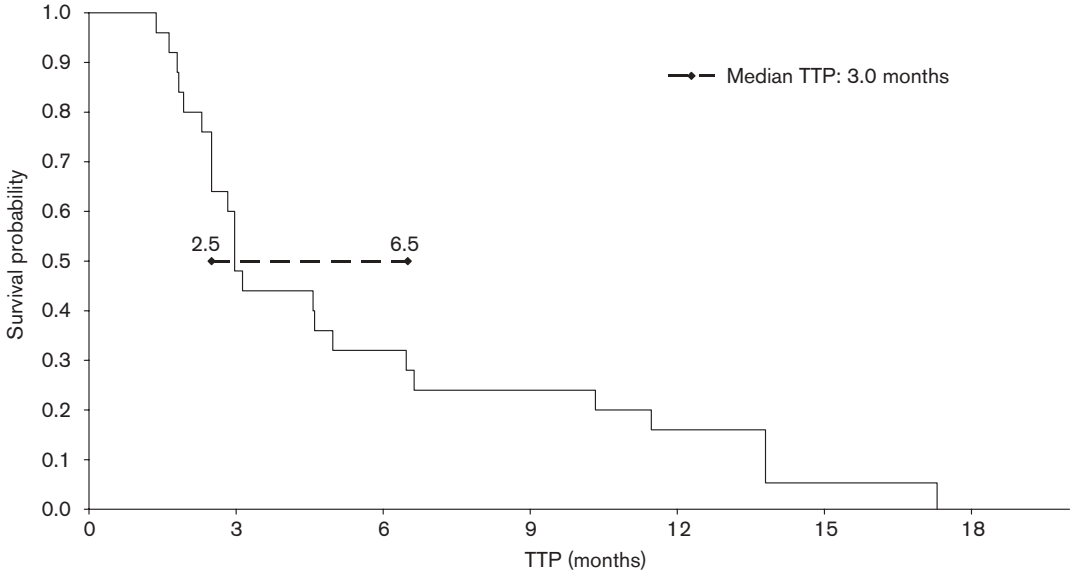


Overall survival calculated according Kaplan–Meier for patients with advanced CRC ($n=28$). The plot refers to survival after start of second-line therapy. Median survival was 15.7 months.

1–14, irinotecan 100 mg/m^2 days 1 and 8, repeated day 22) proved to be too toxic with a 10% 60-day all-cause mortality (four of the first 40 patients) [10]. Consequently, the irinotecan dose was reduced to 80 mg/m^2 (days 1 and 8 in a 21-day cycle).

In a randomized phase II study by Bajetta *et al.*, two XelIri regimen were studied using capecitabine 1250 mg/m^2 b.i.d. (days 2–15) in combination with irinotecan applied either 300 mg/m^2 day 1 (Arm A) or 150 mg/m^2 days 1 and 8 (Arm B) every3 weeks [8]. During the course of this

Fig. 4



TTP calculated according Kaplan–Meier for patients with advanced CRC ($n=25$). Median TTP was 3.0 months.

study, enrolment was continued using lower doses of irinotecan (Arm A: 240 mg/m^2; Arm B 120 mg/m^2) and capecitabine (1000 mg/m^2 b.i.d. in both arms) due to toxicity. After lowering the doses, an acceptable safety profile was observed, particularly when irinotecan was administered on day 1 only. Currently, the EORTC is comparing the XelIri regimen (capecitabine 1000 mg/m^2 b.i.d. days 1–14, irinotecan 250 mg/m^2 day 1, repeated day 22) ± celecoxib in a randomized phase III study with an infusional 5-FU-based regimen (FOLFIRI) ± celecoxib. This study is currently on hold because of increased all-cause mortality in the XelIri ± celecoxib arm.

Reviewing the data of several first-line studies using different capecitabine/irinotecan regimen, the efficacy data compare adequately with infusional 5-FU/irinotecan regimen. Our data show that this combination is an effective alternative therapy for the second-line treatment as well. Nevertheless, regardless of the irinotecan schedule applied, the combination of capecitabine/irinotecan appears to bear a significantly increased risk, especially of severe diarrhea, in comparison to infusional 5-FU/irinotecan regimen. To date it is unknown whether this risk might be lowered by administering irinotecan less frequently (e.g. day 1, repeated day 22). As long as our knowledge of risk factors for the emergence of such toxicity with the capecitabine/irinotecan combination regimen should be regarded preliminary, thorough weekly monitoring of adverse events especially during cycle 1 should be guaranteed, and early and rigorous dose reduction is mandatory.

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