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ORIGINAL ARTICLE

The combination of capecitabine and irinotecan in treating 5-Fluorouracil- and Oxaliplatin-pretreated metastatic colorectal cancer

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Abstract
Purpose Since the combination of capecitabine and irinotecan has successfully been used as a first-line treatment in metastatic colorectal cancer (MCRC), we expected promising results when given as a second-line treatment to metastatic colorectal patients who had been pretreated with 5-Fluorouracil and Oxaliplatin.
Methods Thirty-three MCRC patients participated in this study and received an oral dose of 1,000 mg/m^2 capecitabine twice daily on days 1–14 and a dose of 100 mg/m^2 irinotecan infused over 90 min on days 1 and 8, every 3 weeks.
Results The overall response rate in intent-to-treat was 33.3% (95% CI, 21.5–58.3%), including one complete response (3.0%) and ten partial responses (30.3%); 12 patients (36.4%) had disease stabilization and only 9 (27.3%) progressed. The median time to progression was 6.7 months (95% CI, 4.8–8.6 months). After a median follow-up time of 12 months, nine patients (27.3%) were still alive with metastatic disease. The median response duration for all patients was 6.7 months (95% CI, 3.9–9.5 months) and the median overall survival was 13.4 months (95% CI, 11.0–15.8 months) with a 1-year survival rate of 55.4%. Myelosuppression was commonly observed; NCI-CTC (v 2.0) grade 3/4 neutropenia, however, occurred in eight (24%) patients and grade 3 anemia was seen in one patient (3%). The most common (grade 3/4) non-hematological toxicity was diarrhea (15%) and the other severe grade 3/4 toxicities included nausea/vomiting in one patient (3%), stomatitis in one patient (3%), hand-foot syndrome in one patient (3%).
Conclusions The combination of capecitabine and irinotecan is an effective and well-tolerated regimen for second-line treatment of metastatic colorectal cancer. However, further phase III trials are required to clarify its use in the treatment of metastatic colorectal cancer patients who have been pretreated with 5-fluorouracil and oxaliplatin.

Keywords Capecitabine · Irinotecan · Metastatic colorectal cancer · Second-line chemotherapy

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Introduction

Colon cancer is one of the most common malignant diseases in the world and is the second cause of cancer-related deaths in the western world [1]. During the course of the disease, 40–50% of patients develop metastatic disease and approximately 50–80% of patients with metastatic colorectal cancer (MCRC) receive second-line therapy. Because of the recent advances in the field of systemic chemotherapy for MCRC, like irinotecan, oxaliplatin, capecitabine, and targeted agents, there is an expansion of second-line regimens for patients with MCRC which were available as first-line therapies [2]. In addition, two randomized phase III trials evaluated the benefit of irinotecan in patients failing treatment with 5-Fluorouracil (5-FU) bolus regimens and both trials provided evidence of the survival benefit of irinotecan as a second-line treatment in MCRC [3, 4].

In recent years, two new agents, irinotecan and oxaliplatin, have been introduced as chemotherapeutic agents that can enhance the therapeutic efficacy of 5-FU [5]. Irinotecan is an inhibitor of the DNA enzyme topoisomerase I and

oxaliplatin is a platinum-based chemotherapeutic agent. Capecitabine (Xeloda®; Roche, Nutley, NJ, USA) is an oral fluoropyrimidine designed for preferential conversion into the active compound 5-FU by thymidine phosphorylase (TP) in malignant tumors [6]. In metastatic colorectal cancer, it was shown to have improved tolerability and response rate compared with bolus 5-FU, with comparable time to progression and survival [7, 8]. Capecitabine has gained widespread acceptance as an alternative to intravenous (i.v.) 5-FU [9]. Recently, preclinical evidence indicates that irinotecan up-regulates TP expression [10], providing a synergistic antitumor activity with the irinotecan and capecitabine combination. Capecitabine and irinotecan combination in first-line treatment of CRC provides promising response rates of 35 to 61% and time to progression of 17–25 months [11].

Based on the promising antitumor activity and favorable toxicity of the combination of irinotecan and capecitabine as a first-line treatment, we conducted this study to confirm the efficacy and toxicity of this regimen in MCRC patients who had been pretreated with oxaliplatin-based chemotherapy.

Patients and methods

Patient eligibility

For this study, we enrolled patients with histologically proven metastatic adenocarcinoma of colorectal cancer that had progressed during or after an oxaliplatin-based chemotherapy regimen.

Patients had to be ≥18 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and a life expectancy >3 months. Laboratory criteria included an absolute neutrophil count (ANC) ≥1,500 cells/mm^3, platelets ≥100,000 cells/mm^3, hemoglobin ≥10 g/dl, serum creatinine ≤1.5 mg/dl, bilirubin ≤1.5 mg/dl and transaminases ≤2.5 times the upper limit of normal. Patients with non-measurable disease were excluded. A local research ethics committee approved the trial protocol and the clinical trial was carried out in accordance to the Good Clinical Practice guidelines. All patients had to give their written informed consent in order to participate in the study.

Treatment

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily on days 1–14 and irinotecan at a dose of 100 mg/m^2 infused over 90 min on days 1 and 8, every 3 weeks. A prophylactic antiemetic medication consisting of 5-hydroxytryptamine-3 antagonists was administered.

If acute cholinergic symptoms during or within 24 h of irinotecan administration occurred and were considered to be severe, 0.25 mg atropine was administered subcutaneously. For delayed diarrhea occurring more than 24 h after administration, 4 mg loperamide was administered orally and then 2 mg orally every 2 h for at least 12 h after the last liquid stool. No prophylactic use of granulocyte colony-stimulating factor was allowed. The patients were evaluated for toxicity after each course and the adjustment for optimal dosage was based on minimizing hematologic and non-hematologic toxicities. Adverse reactions were evaluated according to the National Cancer Institute Common Criteria, version 2.0. The combination of capecitabine and irinotecan was given until there was disease progression or unacceptable toxicity.

Treatment was postponed if the ANC was <1,500 cells/mm^3 or platelets <100,000 cells/mm^3, or if there was persistent non-hematological toxicity of grade 2 or higher. Any patient who required more than 3 weeks for recovery from adverse reactions was taken out of the study. The dose of capecitabine and irinotecan was reduced by 20% in the cases of febrile neutropenia, grade 4 hematologic toxicity, and grade 3 or 4 non-hamatologic toxicity. In addition, the dose of capecitabine was adjusted for hand-foot syndrome (HFS) as follows: a 20% reduction for grade 2 and a 40% reduction for grade 3. All dose reductions were maintained for subsequent cycles.

Response evaluation

Response and progression were evaluated using RECIST (response evaluation criteria in solid tumors) [12] and assessed every two cycles. Patients were defined as responders if they had a complete response (CR) or partial response (PR) that was confirmed at least 4 weeks afterward. Patients were classified as achieving stable disease (SD) if there was neither disease progression nor a response to treatment.

In patients who had a confirmed response to therapy, the duration of response was defined as the interval between the initiation of treatment and the first observation of progressive disease (PD). Progression free survival (PFS) was defined as the time from treatment to either the first recording of disease progression or the date of death in patients with no evidence of disease progression. Survival was calculated from the date of patient randomization to the date of death or date of last follow-up. The primary endpoint of this study is the response rate and the secondary endpoints are the PFS response duration, over all survival and toxicity profiles.

Statistical analysis

According to optimal two-stage phase II design, the treatment program was designed to reject a response rate less

than 10% (P0) and to provide a statistical power of 80% in assessing the activity of the regimen in terms of a response rate of 30% (P1) for an α error less than 0.05. If one or fewer responses had been noted in the first ten eligible patients, patient enrollment would have stopped. Because several responses were observed, 19 additional patients were enrolled during stage 2, plus 10% to allow for losses, giving a total of 33 patients. Descriptive methods were used for the analysis of all the study variables. Continuous variables were expressed as means, standard deviations, medians, and ranges. Qualitative data were expressed as relative and absolute frequency distributions. Survival curves were estimated using the Kaplan–Meier method and the differences in survival between the groups were assessed by a log-rank test. Univariate and multivariate analyses were performed using Cox regression analysis model to identify prognostic factors and the risks associated with them.

Results

Patient characteristics

From December 2004 to April 2006, a total of 33 patients were enrolled, and 32 patients were evaluated for tumor response. One patient was excluded from the response evaluation because he underwent an operation for intestinal perforation after one cycle of chemotherapy. Patient characteristics are summarized in Table 1. The median age of 21 men (64%) and 12 women (36%) was 53 years (range 24–71 years) and the median ECOG performance status was 1 (range 1–2). The primary tumor site was the colon in 45% and the rectum in 55% of patients. The median number of cycles for the first-line chemotherapy was six (range 2–9) with a median relative dose intensity of 0.89. Nine patients had undergone prior curative resection of their primary tumor. While eleven (33%) patients presented with disease progression during prior therapy, 67% of the patients achieved the objective response or had at best SD with prior therapy. Furthermore, among patients who had a chemotherapy-free interval of at least 6 months, ten (31%) progressed. The main metastatic sites included liver ($n = 29$), lung ($n = 7$) and abdominal lymph nodes ($n = 7$).

Table 1 Patient characteristics

Number of patients	No. of patients	%
Number of enrolled patients	33	
Number of evaluated patients	32	
Evaluated for toxicity	33	
Age (years)		
Median (range)	53 (24–71)	
Sex		
Male	21	64
Female	12	36
ECOG performance status		
0	5	15
1	25	76
2	3	9
Primary site		
Colon	15	45
Rectum	18	55
Prior oxaliplatin-containing regimen		
Median cycle (range)	6 (2–9)	
Median relative dose intensity	0.89 (0.4–1.0)	
Previous surgery		
Curative	9	27
Palliative	17	52
None	7	21
Previous radiotherapy	7	21
Chemotherapy-free interval		
None	11	33
<6 months	12	36
≥6 months	10	31
Sites of metastases		
Liver	25	76
Lung	7	21
Abdominal LN	7	21
Peritoneum	2	6
Number of involved organs		
Single	24	73
Multiple	9	27

Treatment and dose intensity

A total of 33 patients received 198 cycles of treatment for which toxicity could be assessed (median 6, range 1–12 cycles). There were 40 total delayed weeks (8.9%) and the median delay week per cycle was one (range 1–3). In addition, dose modifications for capecitabine and irinotecan were required in 14 cycles (7.1%). Dose modifications or omissions of irinotecan at day 8 were needed in 15 cycles (7.6%). The cumulative percent of patients who received chemotherapy is shown in Fig. 1. In this study, 50% of patients finished six or more cycles of chemotherapy. The median relative dose intensities (RDI) of capecitabine and irinotecan were 0.94 (range 0.8–1) and 0.95 (range 0.58–1), respectively.

Efficacy

A total of 32 patients were evaluated for tumor response. The overall response rates are summarized in Table 2. The

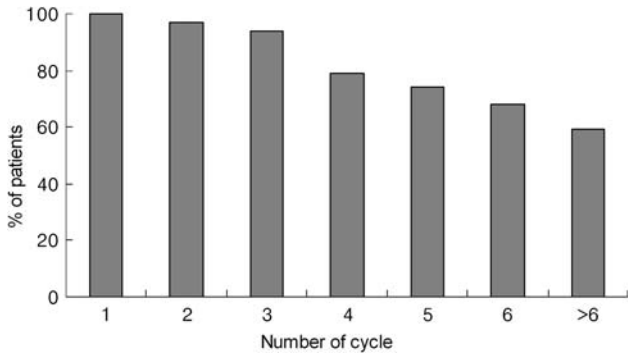

Fig. 1 Percentage of patients treated in each cycle

Table 2 Rates of radiological response in the intention-to-treat

Subgroup and Variable	No. of patients (n = 33)	%
Complete response (CR)	1	3.0
Partial response (PR)	10	30.3
Stable disease (SD)	12	36.4
Progressive disease (SD)	9	27.3
Not evaluated	1	3.0
Overall response rate	11	33.3
Disease control rate	23	69.7

median time to response was 2.2 months (range 1.5–2.9 months) and the median response duration was 6.7 months (range 3.9–9.5 months). The overall response rate (ORR) in intent-to-treat was 33.3% (95% CI, 21.5–58.3%), including one CR (3.0%) and ten partial remissions (30.3%). Twelve patients (36.4%) had disease stabilization and nine (27.3%) progressed. Moreover, the ORR was 44 and 17% in patients with response and progression in first-line chemotherapy, respectively (Table 3). For patients who progressed during, within 6 months of or over 6 months of first-line chemotherapy, the overall response rates were 20, 42, or 40%, respectively.

Table 3 Distribution of responses according to chemotherapy-free interval and response of first-line chemotherapy

	CR/PR		SD		PD	
	n	%	*N*	%	*n*	%
Chemotherapy-free interval						
None	2	20	4	40	4	40
<6 months	5	42	5	42	2	16
≥6 months	4	40	3	30	3	30
Response of first-line chemotherapy						
CR/PR	7	44	6	50	3	6
SD	3	30	3	30	4	40
PD	1	17	3	83	2	0

Survival

With a median follow up duration of 12 months (95% CI, 11.4–26.6), nine patients (27.3%) were still alive with metastatic disease at the conclusion of this study. The median PFS was 6.7 months for all patients (95% CI, 4.8–8.6 months) (Fig. 2), 3.1 months (95% CI, 1.4–4.8 months) for patients who progressed during first-line chemotherapy, 7.3 months (95% CI, 5.7–8.9 months) for patients who progressed within 6 and 8.4 months (95% CI, 5.6–11.2 months) in patients who progressed over 6 months (Fig. 3a).

The median OS was 13.4 months for all patients (95% CI, 11.0–15.8 months) (Fig. 2), 7.3 months (95% CI, 0.5–14.1 months) for patients who progressed during first-line chemotherapy, 21.7 months (95% CI, 9.0–34.3 months) for patients who progressed within 6 and 19.1 months (95% CI, 17.3–20.9 months) for patients who progressed over 6 months. The 1-year survival rate of all the patients was 55.4% (Fig. 3b).

When we compared the survival profile to the clinical parameters (age, ECOG performance status, site of the primary tumor, chemotherapy-free interval, relative dose intensity of prior chemotherapy, CEA, alkaline phosphatase, WBC count, hemoglobin) with Cox's proportional regression hazard model, only the chemotherapy-free interval was found to be significant for progression-free survival and overall survival ($P < 0.01$, both).

Toxicity

The hematologic and non-hematologic toxicities are summarized in Table 4. The most common grade 3 and 4 hematologic toxicity was neutropenia, which was found in 24% of patients. Grade 3 anemia and thrombocytopenia were documented in 3% of patients in both the groups. The most common non-hematologic toxicity was diarrhea, which was documented in 15% of patients. There was one case of

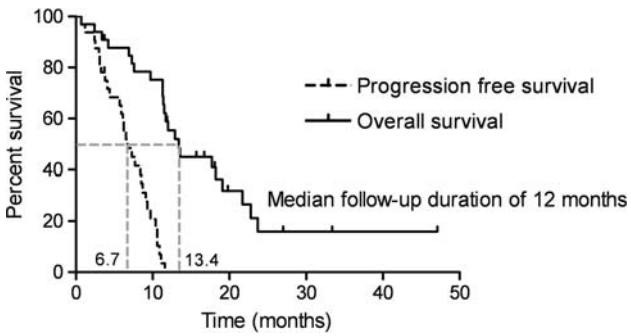

Fig. 2 Survival analysis in the study: progression-free survival and overall survival

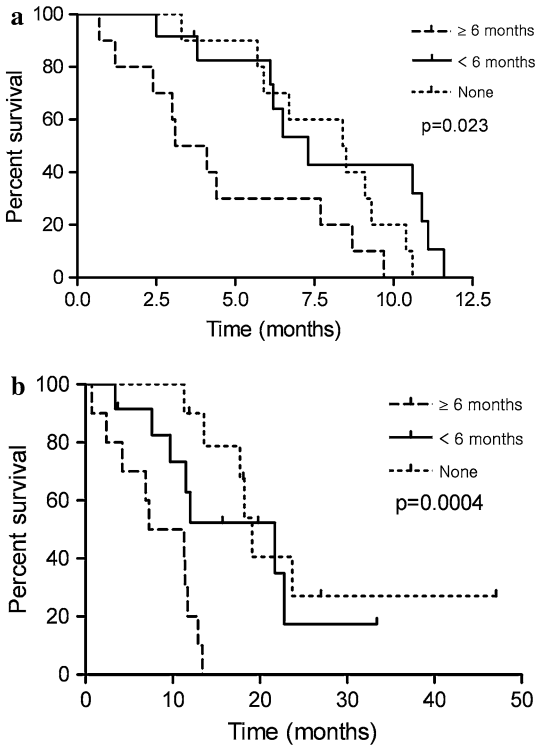

Fig. 3 Survival analysis in the study according to chemotherapy-free interval: **a** progression-free survival, and **b** overall survival

grade 3 hand-foot syndrome. However, there was no case of treatment-related mortality.

Discussion

In our study of the combination of capecitabine and irinotecan as a second-line treatment for MCRC patients who were previously treated with an oxaliplatin-based regimen, we observed a response rate of 33% and a median PFS of 6.7 months with an overall survival of 13.4 months. The median PFS and overall survival for patients who progressed within or over 6 months after first-line chemotherapy was significantly longer than for patients who progressed with first-line chemotherapy. Although the treatment options after failure of an oxaliplatin-based regimen are scarce, some phase II trials demonstrated a benefit from using irinotecan after failure of oxaliplatin. The reported response rate was in the range of 4–20% and progression free survival was in the rage of 4–9 months with overall survival of 11 months [13–15].

There were several phase II trials evaluating capectabine and weekly irinotecan regimen (capecitabine at 2,000–2,500 mg/m^2/day for 2 weeks plus irinotecan at 80–150 mg/m^2 on days 1 and 8) [11, 16–18]. Considering toxicities and ethnic difference, we used a 3-week dose schedule of capecitabine 2,000 mg/m^2/day for 2 weeks and of irinotecan 100 mg/m^2 on days 1 and 8.

Twice-daily oral administration of capecitabine enables chronic dosing that mimics a continuous infusion of 5-FU and provides a superior response rate and improved tolerability compared with 5-FU/LV (Mayo Clinic regimen) as a first-line therapy for MCRC [19, 20]. Preclinical studies have shown that co-administration of capecitabine and irinotecan can lead to supra-additive efficacy in xenograft models [21, 22]. In phase II trials, capecitabine in combination with irinotecan as a first-line treatment resulted in response rates of 29–52%, TTP of 7–9 months and OS of 17–24 months. Hofheinz et al. [23] used a combination regimen of irinotecan and capecitabine as a second-line treatment for advanced colorectal cancer after failure of a first-line infusional 24-h 5-fluorouracil/folinic acid. They have reported an objective response rate of 13%, a median time to progression of 3 months and a median overall survival of 15.7 months.

Our study treatment compared favorably with similar regimens of fluoropyrimidine and an irinotecan-containing combination as a second-line colorectal cancer treatment. In our study, two-thirds of patients demonstrated progression within or over 6 months after first-line treatment and

Table 4 The worst toxicities associated with treatment (per patients)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4 (%)
Hematological					
Neutropenia	39	24	21	3	24
Anemia	39	6	3	0	3
Thrombocytopenia	6	6	3	0	3
Non-hematological					
Nausea	52	24	3	0	3
Vomiting	21	12	3	0	3
Stomatitis	18	9	3	0	3
Diarrhea	36	27	12	3	15
Hepatotoxicity	6	6	0	0	0
Hand-foot syndrome	45	6	3	0	3

had a response rate of 40% while the other one-third who progressed during the first-line treatment had a 20% response rate. There were also statistically significant differences in PFS and OS between subgroups. The fact that the treatment was less effective in patients with an early progression or relapse was confirmed in the study of the GERCOR group [14]. In general, the performance status, WBC count, hemoglobin, alkaline phosphatase and site of the primary tumor were identified as prognostic factors [24]. However, our study reported the chemotherapy-free interval as a major prognostic factor. Although the issue of resistance to prior treatment remains poorly defined, especially according to the chemotherapy-free interval, the observed differences should not be overlooked due to the small sample size. In addition, it will be worth considering tailored therapy depending on chemotherapy-free interval if our findings are confirmed in larger studies.

The tolerability of the combination of capecitabine and irinotecan was fair and generally comparable with other studies. In phase III trial of weekly irinotecan in monotherapy (125 mg/m^2) as second-line treatment, grade 3/4 neutropenia and diarrhea occurred in 29 and 36% of patients, respectively [25]. The most frequent grade 3 adverse events with single-agent capecitabine in the second-line metastatic setting were HFS (13%) and diarrhea (26%), whereas there was no objective response and clinical benefits [26]. In a randomized GERCOR study, grade 3/4 neutropenia and diarrhea with FOLFIRI second-line was 31 and 12%, respectively. In a recent presentation by Borner et al. [27], capecitabine with weekly irinotecan in previously untreated patients with MCRC results in 34% grade 3/4 diarrhea and 5% grade 3/4 neutropenia. Interestingly, one Korean trial of oral capecitabine and weekly irinotecan as first-line chemotherapy showed that diarrhea was the main adverse event. However, no treatment-related mortality was observed on day 60 and grade 3/4 diarrhea was well controlled after a dose modification of irinotecan [18]. Compared with the high rate of grade 3/4 diarrhea reported in other clinical studies, the rate in our study was lower, but the severity and manageability of diarrhea was similar to the Korean study. The reason for the difference in the rate of diarrhea is because this study included patients who received chemotherapy as a second-line treatment and there might be a difference in the ethnic background of the patients. In addition, the reason why grade 3/4 neutropenia was common in our study may be due to the cumulative toxicity of bone marrow in second-line treatment.

Based on the results of this study, the combination of capecitabine and weekly irinotecan was as well tolerated and as effective as the alternative standard second-line regimens (e.g. FOLFIRI or irinotecan) for patients with progressive colorectal cancer following treatment with oxaliplatin and 5-FU/LV. Therefore, further phase III trials are required to clarify its utility in the treatment of metastatic colorectal cancer patients who have been pretreated with 5-fluorouracil and oxaliplatin. In addition, since targeted agents including bevacizumab, cetuximab, and oral tyrosine-kinase inhibitor of EGFR have now been added as chemotherapy drugs for metastatic colorectal cancer, it is worth investigating our regimen in combination with these targeted agents.

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References

1. Ries LA, Wingo PA, Miller DS, Howe HL, Weir HK, Rosenberg HM, Vernon SW, Cronin K, Edwards BK (2000) The annual report to the nation on the status of cancer, 1973–1997, with a special section on colorectal cancer. Cancer 88:2398–2424
2. Rougier P, Lepere C (2005) Second-line treatment of patients with metastatic colorectal cancer. Semin Oncol 32:S48–S54
3. Cunningham D, Pyrhonen S, James RD, Punt CJ, Hickish TF, Heikkila R, Johannesen TB, Starkhammar H, Topham CA, Awad L, Jacques C, Herait P (1998) Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 352:1413–1418
4. Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, Navarro M, Morant R, Bleiberg H, Wils J, Awad L, Herait P, Jacques C (1998) Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 352:1407–1412
5. Zalcberg J, Kerr D, Seymour L, Palmer M (1998) Haematological and non-haematological toxicity after 5-fluorouracil and leucovorin in patients with advanced colorectal cancer is significantly associated with gender, increasing age and cycle number. Tomudex International Study Group. Eur J Cancer 34:1871–1875
6. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, Shimma N, Umeda I, Ishitsuka H (1998) Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 34:1274–1281
7. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, Maroun J, Walde D, Weaver C, Harrison E, Burger HU, Osterwalder B, Wong AO, Wong R (2001) Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 19:2282–2292
8. Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, Bugat R, Findlay M, Frings S, Jahn M, McKendrick J, Osterwalder B, Perez-Manga G, Rosso R, Rougier P, Schmiegel WH, Seitz JF, Thompson P, Vieitez JM, Weitzel C, Harper P (2001) Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 19:4097–4106
9. Punt CJ (2004) New options and old dilemmas in the treatment of patients with advanced colorectal cancer. Ann Oncol 15:1453–1459
10. Jordan K GA, Kellner A et al. (2002) Randomized phase II trial of capecitabine plus irinotecan vs capecitabine plus oxaliplatin as first-line therapy in advanced colorectal cancer (ACRC): results of an interim analysis. Proc Am Soc Clin Oncol 21:103b

11. Bajetta E, Di Bartolomeo M, Mariani L, Cassata A, Artale S, Frustaci S, Pinotti G, Bonetti A, Carreca I, Biasco G, Bonaglia L, Marini G, Iannelli A, Cortinovis D, Ferrario E, Beretta E, Lambiase A, Buzzoni R (2004) Randomized multicenter Phase II trial of two different schedules of irinotecan combined with capecitabine as first-line treatment in metastatic colorectal carcinoma. Cancer 100:279–287
12. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
13. Mabro M, Artru P, Andre T, Flesch M, Maindrault-Goebel F, Landi B, Lledo G, Plantade A, Louvet C, de Gramont A (2006) A phase II study of FOLFIRI-3 (double infusion of irinotecan combined with LV5FU) after FOLFOX in advanced colorectal cancer patients. Br J Cancer 94:1287–1292
14. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 22:229–237
15. Vardakis NSJ, Kalbakis K (2000) Weekly irinotecan and leucovorin and 5-fluorouraci (AIO) schedule in pretreated patients with advanced colorectal cancer: preliminary results. Ann Oncol 11(suppl 4):57(abstr 249)
16. Burris HA, Kalman L, Bertoli L, Foulke R, Ranter L, Schwartzberg L, Weitber A, Lokich J (2004) Continuous flat-dose capecitabine plus weekly irinotecan: an alternative first-line treatment for metastatic colorectal cancer (MCRC). In: Proc Am Soc Clin Oncol GI Symposium (abstr 229)
17. Grothey A, Jordan A, Kellner O, Constantin O, Dittrich G, Kroening H, Mantovani H, Schlichting C, Forstbauer H, Schmoll H-J (2003) Randomized phase II trial of capecitabine plus irinotecan (CapIri) vs capecitabine plus oxaliplatin (CapOx) as first-line therapy of advanced colorectal cancer (ACRC). Proc Am Soc Clin Oncol 22:225 (abstr 1022)
18. Kim TW, Kang WK, Chang HM, Park JO, Ryoo BY, Ahn JS, Zang DY, Lee KH, Kang YK, Kim SR, Kim HK (2005) Multicenter phase II study of oral capecitabine plus irinotecan as first-line chemotherapy in advanced colorectal cancer: a Korean Cancer Study Group trial. Acta Oncol 44:230–235
19. Cassidy J, Twelves C, Van Cutsem E, Hoff P, Bajetta E, Boyer M, Bugat R, Burger U, Garin A, Graeven U, McKendric J, Maroun J, Marshall J, Osterwalder B, Perez-Manga G, Rosso R, Rougier P, Schilsky RL (2002) First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. Ann Oncol 13:566–575
20. Van Cutsem E, Hoff PM, Harper P, Bukowski RM, Cunningham D, Dufour P, Graeven U, Lokich J, Madajewicz S, Maroun JA, Marshall JL, Mitchell EP, Perez-Manga G, Rougier P, Schmiegel W, Schoelmerich J, Sobrero A, Schilsky RL (2004) Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised, phase III trials. Br J Cancer 90:1190–1197
21. Cao SHG, Rustum YM (2001) Enhanced antitumor activity of Xeloda by irinotecan in nude mice bearing human A253 and FaDu head and neck xenografts. Proc Am Assoc Clin Res 20:86
22. Patt YZ LJ, Diamandidis D, Eckhardt SG, Javle M, Justice GR, Keiser W, Lee F-C, Miller W, Lin E (2003) Capecitabine plus irinotecan (XELIRI) in first-line metastatic colorectal cancer (MCRC): update on a phase II trial. Eur J Cancer 1 (Supplement 5):S93 (abstract 304)
23. Hofheinz RD, Gnad-Vogt U, Wein A, Saussele S, Kreil S, Pilz L, Hehlmann R, Hochhaus A (2005) 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. Anticancer Drugs 16:39–45
24. Kohne CH, Cunningham D, Di CF, Glimelius B, Blijham G, Aranda E, Scheithauer W, Rougier P, Palmer M, Wils J, Baron B, Pignatti F, Schoffski P, Micheel S, Hecker H (2002) Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. Ann Oncol 13:308–317
25. Fuchs CS, Moore MR, Harker G, Villa L, Rinaldi D, Hecht JR (2003) Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. J Clin Oncol 21:807–814
26. Hoff PM, Pazdur R, Lassere Y, Carter S, Samid D, Polito D, Abbruzzese JL (2004) Phase II study of capecitabine in patients with fluorouracil-resistant metastatic colorectal carcinoma. J Clin Oncol 22:2078–2083
27. Borner MM, Bernhard J, Dietrich D, Popescu R, Wernli M, Saletti P, Rauch D, Herrmann R, Koeberle D, Honegger H, Brauchli P, Lanz D, Roth AD (2005) A randomized phase II trial of capecitabine and two different schedules of irinotecan in first-line treatment of metastatic colorectal cancer: efficacy, quality-of-life and toxicity. Ann Oncol 16:282–288