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ORIGINAL ARTICLE

A phase II study of irinotecan in combination with doxifluridine, an intermediate form of capecitabine, in patients with metastatic colorectal cancer

Takeshi Kato · Hideyuki Mishima · Masakazu Ikenaga · Kouhei Murata · Hideyuki Ishida · Mutsumi Fukunaga · Hirofumi Ota · Shusei Tominaga · Tadashi Ohnishi · Masahiro Amano · Kimimasa Ikeda · Masataka Ikeda · Mitsugu Sekimoto · Junichi Sakamoto · Morito Monden

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Abstract The purpose of this study was to examine the efficacy of a combination treatment of sequential irinotecan and doxifluridine, an intermediate of capecitabine, evaluated by the response rate and safety in patients with metastatic colorectal cancer. In all, 60 metastatic colorectal cancer patients with measurable disease were enrolled. The schedule of the treatment consisted of a 90 min intravenous (IV) infusion of irinotecan 150 mg/m^2 for on days 1 and 15, and 600–1,000 mg/body of oral doxifluridine on days 3–14 and 17–28. Cycles were repeated every 35 days. A median of three cycles of the combination therapy (range 1–14 cycles) was administered. A total of 57 patients (95%) completed at least two cycles of the therapy without any dose reductions. There was one complete response and 23 partial responses with an overall response rate of 40% [95% confidence interval (CI): 28–53%]. A total of 19 patients had stable disease, 43(72%) achieved disease control. The median time to progression was 5.9 months and the median overall survival was 20.5 months. Ten (17%) and 17 (28%) patients developed Grade 3–4 leukopenia and neutropenia, respectively. Grade 3–4 fatigue was observed in 7(12%) patients, nausea in five (8%), vomiting in four (7%), and diarrhea,in three (5%) patients. No treatment-related deaths were noted during the study. From these results, the combination of sequential irinotecan and doxifluridine is considered to be an effective, easy-to-administer regimen with acceptable tolerability.

Keywords Combination chemotherapy · Colorectal cancer · Irinotecan · Doxifluridine · Phase II clinical trials

T. Kato (✉)
Minoh City Hospital 5-7-1 Kayano,
Minoh City, Osaka 562-8562, Japan
e-mail: takeshi_kato@maple.city.minoh.lg.jp

T. Kato · H. Mishima · M. Ikenaga · K. Murata · H. Ishida · M. Fukunaga · H. Ota · S. Tominaga · T. Ohnishi · M. Amano · K. Ikeda · M. Ikeda · M. Sekimoto · M. Monden
Multicenter Clinical Study Group of Osaka,
Colorectal Cancer Treatment Group, Suita, Osaka, Japan

M. Ikeda · M. Sekimoto · M. Monden
Graduate School of Medicine,
Department of Surgery, Osaka University,
Suita, Osaka, Japan

J. Sakamoto
Graduate School of Medicine,
Social Life Science, Young Leaders' Program,
Nagoya University, Nagoya, Aichi, Japan

Introduction

Colorectal cancer is one of the most frequently diagnosed malignancies in Japan. Surgical resection had been considered to be a therapy that offers a potential cure to patients with colorectal cancer. However, in spite of the curative resection, a considerable number of patients experience relapses of the disease and eventually die. In this regard, systemic chemotherapy aims to improve quality of life and prolong survival in patients with relapse and/or distant metastases.

5-Fluorouracil (5-FU) was developed approximately 50 years ago [10] and it has still been the key drug for the treatment of metastatic colorectal cancer. 5-FU has low oral bioavailability and prolonged infusion of the agent is the optimal administration method to exert high anti-tumor

activity. The combination of leucovorin (LV) with 5-FU significantly improved tumor response rates and time to progression compared to 5-FU alone [1].

Recent clinical study results showed significant activity of new cytotoxics, such as irinotecan and oxaliplatin, in monotherapy treatment for metastatic colorectal cancer. The addition of irinotecan or oxaliplatin to 5-FU/LV in randomised Phase III trials has shown high anti-tumor activity in patients with metastatic colorectal cancer [5, 6, 8, 21].

Although combination chemotherapy has been an important strategy in the treatment of metastatic colorectal cancer, some disadvantages accompany the treatment. First, higher treatment-related mortality and increased toxicity were observed, particularly when irinotecan is combined with bolus 5-FU/LV [13, 20]. Second, continuous infusion 5-FU/LV regimens require the use of implantable access devices and pumps, and sometimes have a negative influence on the patient's quality of life. For this reason, oral chemotherapy may represent one of the more convenient and acceptable treatments. Furthermore, some studies show that patients with advanced disease prefer oral chemotherapy rather than intravenous chemotherapy, provided that their efficacy remains the same [2, 14].

Doxifluridine is an oral fluoropyrimidine that was designed to generate 5-FU preferentially at the tumor site, via an enzymatic process that exploits the significantly higher activity of thymidine phosphorylase (TP) in tumors, compared with healthy tissue [11, 12]. Doxifluridine, which is an intermediate of capecitabine, has been shown to be effective in patients with colorectal cancer [17, 18]. Combining capecitabine instead of infusional 5-FU/LV with irinotecan or oxaliplatin is a rational alternative in terms of the practicability of the treatment. Phase II studies of capecitabine in combination with irinotecan or oxaliplatin have shown promising activity and a favorable safety profile in patients with metastatic colorectal cancer [4, 19]. When we started this study, oxaliplatin and capecitabine had not been approved in Japan, hence we chose irinotecan and doxifluridine in the present clinical trial for advanced colorectal cancer.

Irinotecan and doxifluridine both proved effective in colorectal cancer; however they can induce diarrhea. Preclinical and clinical Phase I studies have demonstrated the optimal dosing schedule [16]. According to the result of the previous study, we determined that irinotecan and doxifluridine would be better administered sequentially in order to protect from gastrointestinal toxicity. Based on the results of the Phase I trial, we decided to conduct a Phase II study to estimate the efficacy of a sequential irinotecan and doxifluridine combination regimen in patients with metastatic colorectal cancer.

Patients and methods

Patient eligibility

Patients with histologically confirmed recurrent or metastatic colorectal carcinoma were eligible for the study. Patients were required to have unresectable and measurable disease according to the Response Evaluation Criteria in Solid Tumor (RECIST) and aged between 20 and 74 years; Eastern Cooperative Oncology Group performance status (PS) $\leq$1; a life expectancy of at least three months; adequate bone marrow function, i.e., a neutrophil count $\geq$2,000 per μl, platelets $\geq$100,000 per μl and hemoglobin $\geq$8.0 g/dl; adequate hepatic function with serum bilirubin $\leq$1.5 mg/dl; glutamic oxaloacetic transaminase values (GOT) and glutamic pyruvic transaminases (GPT) $\leq$2 times the upper normal limit in the absence of hepatic metastases or $\leq$5 times the upper normal limit in the presence of metastasis; and adequate renal function with a creatinine value $\leq$1.5 mg/dl. Concurrent uncontrollable serious disease was not allowed in the eligibility criteria.

Exclusion criteria consisted of large amounts of ascites or pleural effusion, brain metastases, serious complications and any active malignancies (except for carcinoma-in-situ). Patients were excluded from the study if they had previously received more than two chemotherapy regimens or radiation therapy for advanced disease, or had a history of prior therapy with irinotecan.

The study was performed in accordance with the Helsinki Declaration. The study was previously approved by the Ethics Committees of each individual participating Institution. All patients provided written informed consent prior to entering this trial.

Treatment

The trial was conducted in 16 centers. Patients were registered before starting treatment in the coordinating center. Patients received 150 mg/m^2 per day of irinotecan on days 1 and 15, given as a 90 min IV infusion in 500 ml of normal saline or dextrose. Doxifluridine was administered orally three times daily, after every meal, on days 3–14 and 17–28. The daily dosages of doxifluridine were assigned on the basis of BSA: 600 mg (3 cap); <1.48 m^2, 800 mg (4 cap); 1.48–1.91 m^2, 1,000 mg (5 cap); >1.91 m^2. Each cycle of chemotherapy was given every 5 weeks if the patient's blood count had returned to normal and non-hematological toxicities had been resolved. Treatment was repeated for at least two cycles and was continued until disease progression or unacceptable toxicity was detected, or upon withdrawal of consent by the patient. The prophylactic use of anti-emetics was allowed. No prophylactic administration

using granulocyte colony-stimulating factor or diarrhea remedies was allowed.

Treatment was delayed until the neutrophil count had recovered to =1,500 per μl, the platelet count to =75,000 per μl, serum bilirubin to =1.5 mg/dl, serum creatinine to =2.0 mg/dl, and when there was no diarrhea = Grade 2 or infection. If toxicity required a dosing delay of more than 3 weeks, the patient would be withdrawn from the study for toxicity. If patients experienced Grade 3 toxicity or patients required a dosing delay of more than 2 weeks, the CPT-11 dose given was reduced to 120 mg/m^2. If patients experienced Grade 4 toxicity, the CPT-11 dose was reduced to 100 mg/m^2. If patients required a dosing delay of more than 3 weeks, the protocol treatment was stopped.

Evaluation procedures

Before initiating chemotherapy, all patients were assessed by physical examinations, PS assessment, routine hematology and biochemistry analyses, carcinoembryonic antigen (CEA) levels, and ECG. Radiological examinations (chest X-ray, CT scan and MRI of abdominal and thoracic measurable lesions) were performed within 2 weeks before the onset of treatment to serve as a baseline for serial evaluation of the patients' disease. Complete blood cell counts with platelet and differential counts were obtained weekly during chemotherapy. Serum chemistry and physical examination were repeated at least twice every cycle. All adverse reactions were recorded before each biweekly dose of chemotherapy. Radiological tumor parameter assessment and CEA levels were obtained every cycle and at the end of treatment. Tumor response was assessed according to RECIST criteria and confirmed at least 4 weeks later by the same evaluation. Progression-free survival (PFS) was determined by the interval from the date of registration to the date when disease progression was first documented, or to death due to any cause or to the last contact date. Overall survival (OS) was measured from the date of registration to death due to any cause or to the last contact date. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria, version 2. For toxicity analysis, the worst data for each patient across all cycles were used.

Sample size and statistical considerations

The primary end point was response rate (RR), and the secondary objectives were OS, PFS and toxicity profiles. Dose intensity was calculated by dividing the actual dose of irinotecan given in each cycle by the dose originally scheduled for each patient.

Fifty-five patients were required for a single-stage Phase II trial, assuming that the expected RR would be 30% and the minimum acceptable RR 15% ($\alpha = 0.030$, $\beta = 0.190$). With 10% added for expected ineligible cases, a total of 60 patients were required.

OS and PFS were calculated using the Kaplan–Meier product-limit method from the date of registration. The 95% confidence intervals (95% CI) were also calculated. All analyses were performed using SAS for Windows, version 8.02 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

During the period between February 2003 and June 2004, a total of 60 patients were enrolled. All of the patients were assessable for efficacy and toxicity. Baseline patient characteristics are shown in Table 1. Patient ages ranged from 28 to 74, with a median age of 64 years; 87% of patients had a PS of zero and the others had a PS of one. There were 29 patients with colon carcinoma and 31 with rectal carcinoma as the primary tumor site. Twenty-three patients (38.3%) had synchronous metastatic diseases at first diagnosis, and the remaining 37 patients had recurrent metastatic diseases after surgery. Patients generally had distant metastases, with the most frequent distant sites including liver, lungs and peritoneal lymph nodes. A total of 30 patients (50%) had taken prior adjuvant chemotherapy with 5-FU derivatives.

Table 1 Patient characteristics

Characteristic	Number	%
Age (years) (mean and range)	64	28–74
Sex		
Male	37	62
Female	23	38
ECOG performance status		
0	52	87
1	8	13
Primary site		
Colon	29	48
Rectum	31	52
Metastatic site		
Liver	31	52
Lung	13	22
Lymph node	15	25
Others	6	10
Number of metastatic sites		
1	54	90
2	6	10
Previous adjuvant chemotherapy	30	50
Previous chemotherapy	11	18

Eleven patients (18%) had received prior chemotherapy with 5-FU derivatives for advanced disease, but terminated at least 4 weeks before registration into this study.

Treatment summary

A median of three cycles of combination therapy (range 1–14 cycles) was administered. A total of 57 patients (95%) completed at least two cycles of therapy without any dose reductions. The average dose intensity of irinotecan corresponded to 90%, and was maintained at more than 80% for seven cycles.

Response and survival

Response data are listed in Table 2. One patient obtained a complete response and 23 had a partial response. The overall RR achieved was 40% (95% CI: 28–53%), which was superior to the expected RR of 30%. Taking into account the 19 patients who had stable disease, 43 patients (72%) achieved disease control, defined as response or stable disease. Chemo-naïve patients had a good response rate (49.9%) compared to patients receiving second line therapy (29.3%).

With a median follow-up duration of 17.0 months, the median PFS was 5.9 (95% CI: 4.7–7.2) months. The median OS was 20.5 (95% CI: 14.3–31.3) months, and the one-year survival rate was 65% (Fig. 1). Chemo-naïve patients had slightly better survival (20.5 months) and PFS (6.0 months) compared to patients receiving second line therapy (19.5, 5.1 months, respectively). However, the differences were not significant.

Follow up treatment

For patients' refractory the irinotecan/doxifluridine regimen, mainly FOLFOX, hepatic arterial infusion (HAI), and some other regimens were adopted. The long survival rates obtained after progression may be related with the follow up regimens.

Table 2 Tumor response in 60 patients

Results	Number of patients	%
Complete response	1	2
Partial response	23	38
Stable disease	19	32
Progressive disease	14	23
Not evaluable	3	5
Overall response rate	40% (95% CI: 28–53%)	
Response rate according to receiving prior chemotherapy		
Yes		27
No		43

Toxicity

Toxicity assessments were available for all patients who received treatment. The incidence of the main toxic effects is listed in Table 3 as the maximum grade seen per patient. Ten (17%) patients developed grade 3 or 4 leukopenia, 17 (28%) developed neutropenia and one (2%) developed anemia. The most common Grade 3 or 4 non-hematological adverse events were fatigue (12%). Grade 3 or 4 nausea was seen in 5 (8%), vomiting in 4 (7%) and anorexia in 4 (7%) patients. Diarrhea at any grade was observed in 37% of patients, with Grade 3 or 4 in only 3 (5%) patients. No treatment-related deaths occurred during the study.

Discussion

The clinical efficacy of combination therapy with irinotecan and 5-FU is well established by phase III studies, showing that the addition of intravenous 5-FU/LV significantly improved anti-tumor activity and OS, compared to 5-FU/LV alone in patients with previously untreated metastatic colorectal cancer [6, 21]. Combination therapy with irinotecan and 5-FU, however, also resulted in increased toxicity such as diarrhea and neutropenia [13, 20], while it has been suggested that continuous infusion with 5-FU in combination with irinotecan may be a safer option than bolus 5-FU [15].

Doxifluridine, an oral fluoropyrimidine that converted to 5-FU predominantly in tumors [11, 12], is an intermediate form of capecitabine. Replacement of infused 5-FU/LV with oral doxifluridine is expected to be more efficacious and also reduce the toxicity of irinotecan and 5-FU combination therapy. Irinotecan in combination with doxifluridine might ameliorate the inconvenience and potential complications associated with the intravenous access required with infusional regimens. The primary toxicity of doxifluridine is gastrointestinal complications [17], which is the same as that for irinotecan [22]. On this point, the results of the preclinical study in the murine models suggested that the augmentation of gastrointestinal toxicity for the sequential dosing regimen, doxifluridine administered after intervals of a few days following the injection of irinotecan, was mild compared with that for the simultaneous dosing regimen [16]. Thus, we chose the sequential dosing regimen in which doxifluridine was administered two days after the administration of irinotecan. The hatus between irinotecan and doxifluridine (two days) could have alleviated the diarrhea commonly seen with the capecitabine-irinotecan regimen (simultaneous administration).

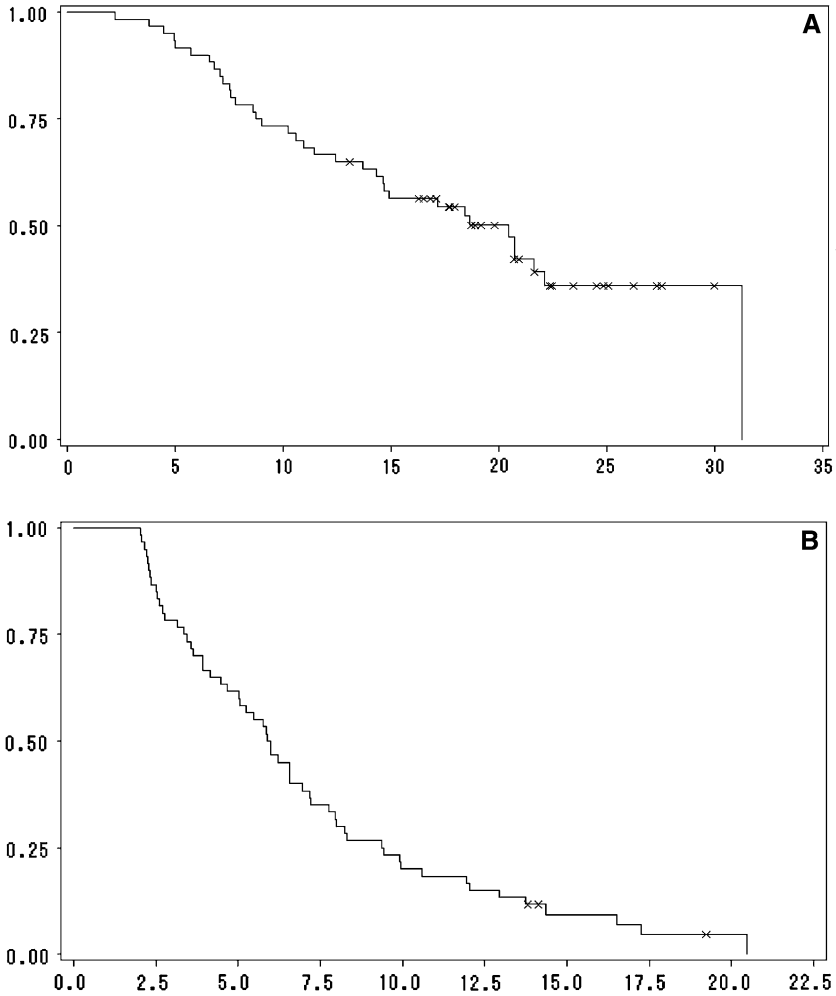

Fig. 1 Kaplan–Meier curves for overall survival and progression-free survival (total subjects = 60 patients). **a** Overall survival, death = 35 patients, median survival time = 20.5 months. **b** Progression free survival, progression/death = 57 patients, median PFS time = 5.9 months

In the present study, the sequential irinotecan and doxifluridine combination regimen was well tolerated, with fatigue the most frequently observed non-hematological toxicity. Grade 3–4 diarrhea occurred in only three patients (5%). This incidence was similar to that (5%) reported for 800 mg doxifluridine alone and slightly lower than that (13%) reported for 150 mg/m^2 irinotecan q2w alone. Compared to Phase II or III studies with irinotecan in combination with infusional 5-FU/LV regimens and oral fluoropyrimidines such as capecitabine, the incidence of Grade 3–4 diarrhea of 5% in our study is obviously lower than the 44% reported in the study by Douillard et al. [6], the 13% in the study by Tournigand et al. [23], and the 19% in the study with capecitabine by Rea et al. [19]. In addition, the average dose intensity of irinotecan corresponded to 90%, and was being maintained at more than 80% over seven cycles. Patient's informed consent for chemotherapy is essential in limiting the impact of toxicity, and clear instructions should be provided on the management of side effects, e.g., diarrhea, and the importance of seeking professional medical advice in case of severe complications.

The combination of irinotecan and doxifluridine is highly effective. The response rate and median survival time are comparable to the results for combinations of 5-FU and irinotecan in randomized studies: Saltz et al. (bolus 5-FU) reported 39% and 14.8 months [21]; Douillard et al. (infusional 5-FU), 41% and 17.4 months [6]; and Tournigand et al. (infusional 5-FU) 56% and 21.5 months [23], respectively. Besides efficacy, oral doxifluridine offers an advantage over infusional 5-FU/LV in terms of convenience. The response rates and time to progression in this study were similar to capecitabine and irinotecan [3, 7]. The median overall survival also seems to be closer to FOLFIRI [20] than other previously reported oral fluoropyrimidine regimens.

This trial has demonstrated that combining irinotecan and doxifluridine is an effective and well-tolerated regimen for patients with metastatic colorectal cancer when irinotecan is administered IV on days 1 and 15 in combination with doxifluridine administered on days 3–14 and 17–28 every 5 weeks. It produced an overall RR of 40% (95% CI: 28–53), a median PFS of 5.9 months (95% CI: 4.7–7.2) and a median OS of 20.5 months (95% CI: 14.3–31.3). With

Table 3 Maximum toxicity per patient (60 enrolled patients)

	NCI-CTC grade			All grades (%)
	G3	G4	≥G3 (%)	
Hematologic				
Neutropenia	12	5	17 (29)	30 (50)
Leukopenia	9	1	10 (17)	27 (45)
Anemia	0	1	1 (2)	1 (2)
Thrombocytopenia	0	0	0 (0)	1 (2)
AST	0	0	0 (0)	1 (2)
ALT	0	0	0 (0)	1 (2)
Non-hematologic				
Fatigue	6	1	7 (12)	36 (60)
Alopecia	–	–	–	30 (50)
Nausea	4	1	5 (8)	28 (47)
Diarrhea	3	0	3 (5)	22 (37)
Vomiting	3	1	4 (7)	12 (20)
Anorexia	4	0	4 (7)	7 (12)
Dysgeusia	0	0	0 (0)	3 (5)
Neuropathy	0	0	0 (0)	1 (2)
Abdominal pain	0	0	0 (0)	1 (2)
Headache	0	0	0 (0)	1 (2)
Rash	0	0	0 (0)	1 (2)
Stomatitis	0	0	0 (0)	1 (2)
Epigastralgia	0	0	0 (0)	1 (2)
Dehydration	1	0	1 (2)	1 (2)

respect to time to progression in this study (median PFS = 5.9 months), it is longer than 5FU/LV or capecitabine alone [24]. It is slightly shorter than a combination of CAPIRI or CAPOX [9]. The relatively shorter progression free survival could be related to inclusion of second line therapy patients whose PFS was 5.1 months. Besides, 72% of patients achieved stable disease and, overall, the regimen produced good symptom resolution.

In conclusion, the present study confirmed the potential efficacy of the sequential irinotecan and doxifluridine regimen without augmentation of gastrointestinal toxicity. We expect that combining irinotecan with doxifluridine would be more preferable than a combination of irinotecan and infusional 5-FU/LV with regard to the convenience of oral administration of doxifluridine and practicability with similar efficacy and less toxicity.

Since capecitabine is not approved for mCRC in Japan, We performed the preliminary examinations of irinotecan combination therapy with doxifluridine, a precursor substance of capecitabine, which has already been approved and utilized as a chemotherapeutic agent in Japan. We are planning to conduct an examination evaluating a capecitabine and irinotecan combination compared with doxifluridine and irinotecan, as soon as capecitabine is approved in Japan.

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References

1. Advanced Colorectal Meta-Analysis Project (1992) Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 10:896–903
2. Borner MM, Schoffski P, de Wit R et al (2002) Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a randomised crossover trial in advanced colorectal cancer. Eur J Cancer 38:349–358
3. Borner MM, Bernhard J, Dietrich D et al (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
4. Cassidy J, Tabernero J, Twelves C et al (2004) XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. J Clin Oncol 22:2084–2091
5. de Gramont A, Figer A, Seymour M et al (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938–2947
6. Douillard JY, Cunningham D, Roth AD et al (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 355:1041–1047
7. Fuchs C, Marshall J, Mitchell E et al (2006) A randmized trial of first-line irinotecan/fluoropyrimidine combinations with or without celecoxib in metastatic colorectal cancer (BICC-C). J Clin Oncol Proc ASCO 24:18s
8. Giacchetti S, Perpoint B, Zidani R et al (2000) Phase III multicenter randomised trial of oxaliplatin added to chronomodulated fluorouracil–leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 18:136–147
9. Grothey A, Jordan K, Kellner O et al (2004) Capecitabine/irinotecan (CapIri) and capecitabine/oxaliplatin (CapOx) are active second-line protocols in patients with advanced colorectal cancer (ACRC) after failure of first-line combination therapy: results of a randomized phase II study. J Clin Oncol Proc ASCO 22:14s
10. Heidelberger C, Chaudhuri NK, Danneberg P et al (1957) Fluorinated pyrimidines: anew class of tumor-inhibitory compounds. Nature 179:663
11. Ishitsuka H, Miwa M, Takemoto K, Fukuoka K, Itoga A, Maruyama HB (1980) Role of uridine phosphorylase for antitumor activity of 5'-deoxy-5-fluorouridine. Gann 71:112–123
12. Kono A, Hara Y, Sugata S, Karube Y, Matsushima Y, Ishitsuka H (1983) Activation of 5'-deoxy-5-fluorouridine by thymidine phosphorylase in human tumors. Chem Pharm Bull (Tokyo) 31:175–178
13. Ledermann JA, Leonard P, Seymour M (2001) Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. N Engl J Med 345:145–146
14. Liu G, Franssen E, Fitch MI, Warner E (1997) Patient preferences for oral versus intravenous palliative chemotherapy. J Clin Oncol 15:110–115
15. Meta-Analysis Group in Cancer (1998) Toxicity of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. J Clin Oncol 16:3537–3541
16. Mishima H, Kato T, Yanagisawa M et al (2005) Sequential treatment with irinotecan and doxifluridine: Optimal dosing schedule in murine models and in a phase I study for metastatic colorectal cancer. Chemotherapy 51:32–39

17. Niitani H, Kimura K, Saito T et al (1985) Phase II study of 5'-deoxy-5-fluorouridine (5'-DFUR) on patients with malignant cancer: Multi-institutional cooperative study (in Japanese). Jpn J Cancer Chemother 12:2044–2051
18. Ota K (1988) Multicentre cooperative phase II study of 5'-deoxy-5-fluorouridine in the treatment of colorectal cancer. J Int Med Res 16(suppl 2):19B–20B
19. Rea DW, Nortier JWR, Ten Bokkel Huinink WW et al (2005) A phase I/II and pharmacokinetic study of irinotecan in combination with capecitabine as first-line therapy for advanced colorectal cancer. Ann Oncol 16:1123–1132
20. Rothenberg ML, Meropol NJ, Poplin EA, Van Cutsem E, Wadler S (2001) Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. J Clin Oncol 19:3801–3807
21. Saltz LB, Cox JV, Blanke C et al (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 343:905–914
22. Shimada Y, Yoshino M, Wakui A et al (1993) Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. J Clin Oncol 11:909–913
23. Tournigand C, André T, Achille E et al (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 22:229–237
24. Van Cutsem E, Hoff PM, Harper P et al (2004) Oral capecitabine vs intravenous 5-floorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised, phase III trials. Br J Cancer 90:1190–7