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Phase I/II Study of CPT-11 plus UFT in Patients with Advanced/Recurrent Colorectal Cancer: Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG): Protocol 0102

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Objective: The primary objective of this study was to explore the efficacy and safety of combined chemotherapy with CPT-11 and UFT in patients with advanced/metastatic colorectal cancer.
Methods: Twenty-two patients with metastatic colorectal cancer were enrolled in the phase I trial and 35 patients (including eight patients treated at level 4 during phase I) were evaluated in the phase II trial. Treatment consisted of two 35-day cycles of combination chemotherapy with CPT-11 and UFT. During phase I, CPT-11 was administered on days 1 and 15 as an intravenous infusion over 90 min at four different dose levels, starting from a dose of 80 mg/m^2 (level 1). During phase II, the dose of CPT-11 was fixed at 150 mg/m^2 based on the results of the phase I study. UFT was administered orally at a fixed dose of 300 mg/m^2 on days 1–28, followed by a 1-week drug holiday, during each course (35 days).
Results: The maximum tolerated dose (MTD) of CPT-11 was determined to be 150 mg/m^2 during the phase I trial. The major toxicities detected during phase II in 35 patients receiving CPT-11 at this recommended dose were grade 3/4 neutropenia in nine patients (25.7%) and grade 3/4 anorexia in six patients (11.4%). No severe adverse events occurred. The overall response rate and the median overall survival time was 22.9% (8/35) and 23.9 months for all patients, respectively. For pre-treated patients they were 26.3% (5/19) and 25.1 months, respectively.
Conclusion: This combination of CPT-11 and UFT is considered to be both feasible and relatively safe. The response rate of the patients receiving CPT-11 at a dose of 150 mg/m^2 was comparable to that reported previously for 5-FU-based regimens coupled with CPT-11, and this regimen can probably be beneficial for patients with pre-treated advanced colorectal cancer on an outpatient basis.

Key words: colorectal cancer – chemotherapy – CPT-11 – UFT – oral fluoropyrimidine

INTRODUCTION

The 5-fluoropyrimidines have been key drugs in the treatment of metastatic colorectal cancer for over 50 years (1). With respect to the inhibition of thymidylate synthase (TS), which accounts for the major antitumor effect of 5-fluorouracil (5-FU), numerous studies on the combined administration of 5-FU and leucovorin (5-FU/LV) had been performed and a 5-FU/LV regimen was established as international standard chemotherapy for patients with advanced colorectal cancer in the 1990s (2–5). However, it has not necessarily contributed to prolongation of survival although combination with LV increased response rate (6).

More recently, newer drugs like irinotecan (CPT-11) and oxaliplatin have become available and are expected to contribute to an increase of therapeutic efficacy by combined use with 5-FU. CPT-11, a potent topoisomerase I inhibitor, is a derivative of camptothecin that was developed in Japan (7). It has been shown to be effective for various malignancies, including lung cancer, cervical cancer, ovarian cancer,

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breast cancer and malignant lymphoma, as well as for gastrointestinal tumors such as stomach cancer or colorectal cancer. The response rate to CPT-11 monotherapy as first-line or second-line treatment for colorectal cancer has been reported to be 15–32% (8–13). CPT-11 has also shown activity against 5-FU-resistant colorectal cancer (14,15). The efficacy of CPT-11 in combination with 5-FU (bolus administration or continuous infusion) and leucovorin was examined in several large-scale studies and finally the combination of CPT-11/5-FU/LV was established as first-line chemotherapy for advanced colorectal cancer (16,17). However, intravenous administration of 5-FU and leucovorin, especially by continuous infusion that has been shown to be most effective, is somewhat complex and inconvenient as outpatient therapy. If an alternative to continuous infusion of 5-FU could be developed with the same efficacy, it would be more convenient and beneficial for patients with colorectal cancer.

It is interesting to note in this context that evidence has been accumulating that various oral fluoropyrimidines, including tegafur/uracil (UFT), capecitabine and TS-1, may be as effective as intravenous 5-FU (18–20). Besides intravenous administration of 5-FU, oral 5-FU and its derivatives have long been used to treat cancer in Asian countries, including Japan. Despite previous criticism of the employment of oral fluoropyrimidines as a substitute for intravenous administration of 5-FU, especially in Western countries, the clinical usefulness of these oral drugs have been re-evaluated since the mid 1990s. Among several oral 5-FU derivatives, tegafur/uracil (UFT; Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) is a combined drug that contains tegafur and uracil at a molar ratio of 1:4. It has been widely used in Japan, where it has been demonstrated that UFT at doses of 300–600 mg/day is well tolerated and shows activity against various solid tumors (18). UFT was reported to have the same AUC as equimolar intravenous 5-FU and shows similar pharmacokinetics to those obtained with continuous infusion of 5-FU (21). This is considered to be due to the gradual conversion of UFT into 5-FU and inhibition of the 5-FU degrading enzyme, dihydropyrimidine dehydrogenase (DPD), by the uracil component of UFT (22). Because of these unique characteristics as a DPD-inhibitory fluoropyrimidine, UFT has been expected to become a substitute for intravenous 5-FU in various regimens. Ohtsu et al. performed a phase II study of combination of CPT-11 and infusional 5-FU without LV, and reported promising results with a response rate of 45% and lower toxicity (23). The Spanish TTD group reported that infusional 5-FU plus oxaliplatin without LV (FUFOX) was effective and well tolerated (24). Moreover, oral LV was not commercially available for colorectal cancer treatment in Japan at that time. Therefore, we designed this study to determine the maximum tolerated dose (MTD) of CPT-11 and to explore the preliminary therapeutic efficacy of a combination of CPT-11 and UFT in patients with advanced colorectal cancer. If CPT-11/UFT was as effective as CPT-11/5-FU/LV, while causing less toxicity, it could be better tolerated as first-line or second-line chemotherapy for colorectal cancer, especially when performed on an outpatient basis.

PATIENTS AND METHODS

Eligibility

Patients enrolled in this study were required to have histologically proven adenocarcinoma of the colon or rectum that was considered to be inoperable and to have at least one measurable metastasis (RECIST criteria). Patients also had to be older than 18 years and aged under 75 years, be expected to survive for more than 3 months after starting chemotherapy, have a performance status of 0–1 on the Eastern Cooperative Oncology Study Group (ECOG) scale, and have no problems with oral intake.

Other eligibility criteria included a white blood cell count of 4000–12 000/mm^3, a neutrophil count $>$2000/mm^3, a platelet count $>$100 000/mm^3, a hemoglobin $>$8.9 g/dl, AST and ALT $<$2.5 times the institutional upper limit of normal (ULN) total bilirubin $<$1.5 mg/dl, and creatinine $<$ the ULN.

Exclusion criteria included the following: previous CPT-11 treatment; concomitant treatment with other chemotherapy agents or radiation within the previous 2 weeks or failure to recover from adverse effects; interstitial pneumonia or pulmonary fibrosis causing chest X-ray changes or symptoms (or a history of these diseases); a fluid collection in a body cavity that needed treatment; concurrent active cancer originating from a site other than the colorectum or metachronous cancer that was untreated or had a disease free period $<$5 years (except carcinoma *in situ* or surgically treated skin cancer); infectious disease or intestinal paresis or obstruction; watery diarrhea; poorly controlled diabetes mellitus; uncontrolled medical conditions such as cardiac failure, hepatic failure, or renal failure; symptomatic brain metastasis; actual or potential pregnancy, breast-feeding status, or the intention to become pregnant in the near future; a past history of serious drug allergy; or any other condition that was judged to make the patient ineligible for this study by the responsible physician.

Pretreatment Evaluation and Dose Modification

Pretreatment evaluation included obtaining detailed medical history, performing physical examination and performing standard laboratory tests, including hematology (leucocyte and absolute neutrophil counts, platelet count and hemoglobin) and biochemistry (sodium, potassium, chloride, blood urea nitrogen, creatinine, alkaline phosphatase, total bilirubin, AST and ALT).

The criteria for starting day 1 of the first course were the eligibility criteria above. The criteria for administration of CPT-11 on day 15 of each course included a white blood cell count $>$3000/mm^3, a platelet count $>$100 000/mm^3, absence of fever ($>$38°C) caused by infection, no diarrhea

and no other non-hematological toxicities > grade 2. The criteria for the administration of CPT-11 on day 1 of the second and subsequent courses included a white blood cell count >3000/mm^3, a neutrophil count >2000/mm^3, a platelet count >100 000/mm^3, creatinine <1.5 mg/dl, absence of fever (>38°C) caused by infection, no diarrhea and no other non-hematological toxicities > grade 2. The criteria for administration of UFT on day 1 of each course included a white blood cell count >2000/mm^3, no diarrhea, no stomatitis > grade 1, no elevation of AST–ALT > grade 1 and no other non-hematological toxicities > grade 2. Dose modification for toxicity was performed as follows. If leucopenia (<1000/mm^3), thrombocytopenia (<20 000/mm^3), neutropenia (<1000/mm^3) associated with fever (>38°C) or infection, or non-hemaological toxicities > grade 3 occurred, the dose of CPT-11 was reduced by 20% for the subsequent course. In the case of stomatitis > grade 3, the dose of UFT was reduced by 60 mg/m^2/day.

Treatment

Protocol treatment consisted of two 35-day cycles of combination chemotherapy with CPT-11 and UFT. During the phase I study, CPT-11 was administered intravenously over 90 min at a starting dose of 80 mg/m^2 (level 1), followed by 100 mg/m^2 (level 2), 125 mg/m^2 (level 3), and 150 mg/m^2 (level 4). Dosing was performed on days 1 and 15. For the phase II study, the dose of CPT-11 was fixed at 150 mg/m^2 based on the results obtained during phase I. UFT was administered orally at a fixed dose of 300 mg/m^2 on days 1–28, followed by a 1-week rest during each course (35 days). In this study, UFT-E was used as tegafur/uracil (UFT). UFT-E is an enteric-coated granule of UFT and was developed for the purpose of mitigation of upper gastrointestinal toxicities of UFT. The previous study had shown that UFT-E had significantly lower occurrence of nausea and vomiting compared to UFT capsule (25). At least two courses of treatment were required for evaluation.

Trial Design

Phase I

This study was designed as a combined phase I/II study. Dose-limiting toxicities (DLT) during phase I were defined as grade 4 leucopenia, neutropenia, or thrombocytopenia, any grade 3/4 non-hematological toxicity (excluding nausea and vomiting), any non-hematological toxicity that resulted in skipping of the administration of CPT-11 on day 15 of the first course despite postponing treatment for up to 1 week, or reduced the administration period of UFT-E (28 days) to <14 days in the first course, or delayed administration of CPT-11 on day 1 of the second course. Cohorts of three to six patients were enrolled. If no DLT was observed, subsequent patients were treated at the next dose level of CPT-11. If one patient experienced DLT, the same dose level was used to treat a maximum of six patients. If two of the initial three or four out of six patients at a particular level experienced DLT, this dose level was defined as the maximum tolerated dose (MTD) and the preceding dose level was classified as the recommended dose of CPT-11 for this combined regimen. If MTD was not achieved at dose level 4, we defined the recommended dose of CPT-11 as 150 mg/m^2 because the maximum dosage of CPT-11 permitted and covered by medical insurance in Japan was 150 mg/m^2. An additional five patients were enrolled to receive this recommended dose for further confirmation and then it was used in the following phase II trial.

Phase II

In addition to the eight patients treated at dose level 4 in the phase I study, 27 patients were enrolled to receive the recommended dose of CPT-11 during the phase II study in order to assess the toxicity profile more accurately and predict the possible efficacy of this regimen.

Assessment of Toxicity and Response

Toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. Toxicities and laboratory abnormalities were assessed twice weekly during the first course of the phase I trial and during all courses of the phase II trial. Responses were evaluated according to the RECIST criteria. A complete or partial response required subsequent confirmation of the response after an interval of at least 4 weeks.

Statistical Analysis

The sample size for the study was calculated from an expected response rate of 30% and a minimum of 10% with α error of 0.05 and β error of 0.1. The required number of patients was estimated to be 32. Finally, we set it at 35 patients in order to allow for 10% of disqualified patients.

This trial was approved by the institutional review boards of all participating hospitals.

RESULTS

Patient Characteristics

Between July 2001 and February 2004, 49 patients were enrolled in this phase I/II study (22 patients in phase I and 27 in phase II). The characteristics of these patients are shown in Tables 1 and 2, respectively.

Phase I Trial

Toxicity

Twenty-two patients were enrolled in the phase I study. Among them, two patients dropped out because of a protocol

Table 1. Patient characteristics (phase I)

Sex	Male/Female	17/5
Age (median)	years	65.5 (38–74)
PS	0/1	21/1
Initial/recurrence		7/15
Histology	wel/mod/por/muc/unknown	6/12/0/3/1
Prior treatment	none/surg/chemo/surg + chemo	1/5/1/15
Metastatic sites	liver/lung/LN/other	3/12/8/9

PS, performance status; wel, well differentiated adenocarcinoma; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous carcinoma; surg, surgery; chemo, chemotherapy; LN, lymph node.

Table 2. Patient characteristics (phase II)

Sex	Male/Female	26/9
Age (median)	years	63 (46–74)
PS	0/1	34/1
Initial/recurrence		14/21
Histology	wel/mod/por/muc/unknown	14/17/1/2/1
Prior treatment	none/surg/chemo/surg + chemo	1/14/0/20
Metastatic sites	liver/lung/LN/other	14/17/10/8

*Including 8 patients treated at dose level 4 in phase I.

violation and refusal during the first course, respectively, and therefore 20 patients (dose level 1:4, dose level 2:6, dose level 3:3, dose level 4:7) were evaluated for toxicity and response. Hematological and non-hematological toxicities are listed in Tables 3 and 4, respectively. The only DLT was observed in one patient receiving dose level 2, who suffered from grade 4 neutropenia, and CPT-11 was well tolerated even at a dose of 150 mg/m^2 (dose level 4). Accordingly, the maximum tolerated dose (MTD) of CPT-11 was determined to be 150 mg/m^2 and another 27 patients were treated with this dose of CPT-11 during the phase II study.

Table 3. Hematological toxicities (phase I)

Grade	Level 1 ($n = 4$)				Level 2 ($n = 6$)				Level 3 ($n = 3$)				Level 4 ($n = 8$)			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Hemoglobin ↓	2	1			3								4	1		
Hypoglobulia					1				2				1			
Leukopenia	1				2	1	1		2				1	2		
Neutropenia	1				3			1(DLT)		2			1	1	2	
Thrombocytopenia					1											

DLT, Dose-limiting toxicities.

Table 4. Non-hematological toxicities (phase I)

Grade	Level 1 ($n = 4$)				Level 2 ($n = 6$)				Level 3 ($n = 3$)				Level 4 ($n = 8$)			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Stomatis													1			
Diarrhea	1				2	2			2				1			
Anorexia	2				4				1				5	2		
Nausea/vomiting	2				4				1				4	2		
Alopecia		1			2	2				1				1		
Fatigue	1				2				1				1	1		
Taste disturbance	1															
Stammering					1											
Constipation														1		
Abdominal pain						1							1	1		
AST/ALT ↑					2				1							
T-bil ↑					1											
Na ↓													1			
Cl ↑													1			
TP ↓					1				1				1			
Hyperglycemia													1			

AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-bil, total bilirubin; Na, sodium; Cl, chloride; TP, total protein.

Response

The response obtained at each dose level during the phase I trial is shown in Table 5. There were two partial responses (PR), with a response rate of 2/6 (33%) among patients receiving first-line therapy and 2/20 (10%) overall.

Phase II Trial

Toxicity

Twenty-seven patients were enrolled in the phase II study and a total of 35 patients (including eight patients given dose level 4 during phase I) were evaluated at a CPT-11 dose of 150 mg/m^2. The characteristics of these

Table 5. Response (phase I)

Dose level	CPT-11 dose (mg/m^2)	No. of patients treated	No. of patients evaluated	Response rate (%)
1	80	4	4	00.0 (0/4)
2	100	7*	6	16.7 (1/6)
3	125	3	3	00.0 (0/3)
4	150	8*	7	14.3 (1/7)
Overall		22	20	10.0 (2/20)

*No. 2-6, drop out (protocol violation); No. 4-4, dropout (patient refusal).
First-line response rate: 33.3% (2/6).
Overall response rate: 10.0% (2/20).

Table 6. Hematological toxicities (phase II)

Grade	Grade				Total		≥ Grade 3	
	1	2	3	4	No.	(%)	No.	(%)
Hemoglobin	18	6	1	0	25	(71.4)	1	(2.9)
Hypoglobulia	2	0	0	0	2	(5.7)	0	(0)
Leucopenia	4	12	1	0	17	(48.6)	1	(2.9)
Neutropenia	1	7	7	2	18	(51.4)	9	(25.7)
Thrombocytopenia	2	0	0	0	2	(5.7)	0	(0)

NCI-CTC, national cancer institute common toxicity criteria.
*Judged by NCI-CTC.

patients are shown in Table 2. The hematological and non-hematological toxicities that occurred during phase II are listed in Tables 6 and 7, respectively. There were no treatment-related deaths. The most common hematological toxicity was anemia (25/35, 71.4%), followed by neutropenia (18/35, 51.4%) and leucopenia (17/35, 48.6%). However, myelosuppression was comparatively mild, with grade 3–4 neutropenia occurring in nine patients (25.7%) and grade 3 anemia or leucopenia occurring in one patient each. The most common non-hematological toxicity was nausea/vomiting (25/35, 71.4%), followed by anorexia (24/35, 68.6%), diarrhea (13/35, 37.1%), alopecia (13/35, 37.1%) and fatigue (8/35, 22.9%). The grade 3 toxicities were anorexia in four patients (11.4%), diarrhea in two patients (5.7%), and nausea/vomiting in one patient (2.9%).

Table 7. Non-hematological toxicities (phase II)

Grade	Grade				Total		≥ Grade 3	
	1	2	3	4	No.	(%)	No.	(%)
Diarrhea	9	2	2	0	13	(37.1)	2	(5.7)
Abdominal pain	2	1	0	0	3	(8.6)	0	(0)
Nausea/vomiting	24	4	1	0	25	(71.4)	1	(2.9)
Anorexia	18	2	4	0	24	(68.6)	4	(11.4)
Constipation	0	1	0	0	1	(2.9)	0	(0)
Alopecia	6	7	–	–	13	(37.1)	–	–
Fatigue	5	2	1	0	8	(22.9)	0	(0)
Stomatitis	1	1	0	0	2	(5.7)	0	(0)
Taste disturbance	1	0	0	0	1	(2.9)	0	(0)
Neurologic—other	1	0	0	0	1	(2.9)	0	(0)
Itching	1	0	0	0	1	(2.9)	0	(0)
T-bill ↑	2	0	0	0	2	(5.7)	0	(0)
AST/ALT ↑	2	1	0	0	3	(8.6)	0	(0)

*Judged by NCI-CTC.

Table 8. Response (phase II)

	CR	PR	SD	NE	PD	Response rate (%)
Response	2	6	13	7	7	22.9 (8/35)
Prior chemotherapy (+)*	2	3	6	5	3	26.3 (5/19)
Prior chemotherapy (–)**	0	3	7	2	4	18.8 (3/16)

CR, complete response; PR, partial response; SD, stable disease; NE, not evaluable; PD, progressive disease.
*Recurrent cases less than 6 months after completion of adjuvant chemotherapy or advanced case that received one or more prior chemotherapy.
**Recurrent cases more than 6 months after completion of adjuvant chemotherapy or advanced case that received no prior chemotherapy.

Response and survival

The response to treatment during phase II is shown in Table 8. Two patients showed a complete response (CR). The measurable metastatic lesions of these two patients were lymph nodes and both patients had already received chemotherapy before the present study. Six patients achieved a partial response, including three patients with prior chemotherapy and three without it. Total response rate was 22.9% (8/35) and there was no difference in response rate in between two groups with or without prior chemotherapy (26.3% (5/19) versus 18.8% (3/16)). The median follow-up time was 16.4 months (3.5–43.4 months) and 19 deaths have occurred so far. The survival curve is shown in Fig. 1: median overall survival time was calculated to be 23.9 months and the 1-year survival rate was 67.2%.

Dose intensity

The number of courses given to 35 patients ranged from 1 to 8 (mean: 3.5 courses). The mean dose intensity of CPT-11

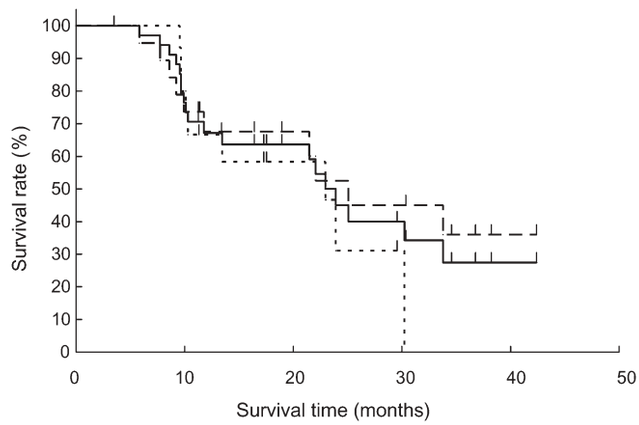

Figure 1. Survival curves of patients treated with a combination of CPT-11 and UFT (phase II). Solid line, survival curves of all patients (median survival time, 23.9 months); short dashed line, survival curves of patients without prior chemotherapy (median survival time, 23.0 months); dashed line, Survival curves of patients with prior chemotherapy (median survival time, 25.1 months).

was 51 mg/m^2/week and the relative dose intensity was 85%. Three patients required reduction of the dose of CPT-11 and administration was skipped on day 15 of treatment as a result of various toxicities in 11 patients during the second or subsequent course, as reflected in the data on dose intensity. The mean relative dose intensity of UFT was 85%.

DISCUSSION

The aim of this study was to determine the maximum tolerated dose of CPT-11 when administered in combination with UFT, an oral 5-FU derivative, to patients with advanced colorectal cancer. In addition, the activity and the toxicity profile of this regimen were assessed to determine its potential clinical usefulness.

During the phase I study, the recommended dose of CPT-11 was determined to be 150 mg/m^2. The phase II study was conducted with this dose of CPT-11, which showed that the combined regimen could be safely administered on an outpatient basis. There were no treatment-related deaths. Hematological toxicity was comparatively mild, with grade 3–4 neutropenia being seen in nine patients (25.7%) and grade 3 anemia or leucopenia only being detected in one patient each. The incidence of grade 3 non-hematological toxicity was anorexia occurred in four patients (11.4%), diarrhea occurred in one patient (2.9%) and no grade 4 non-hematological toxicities. Douillard et al.'s regimen, infusional 5-FU/LV plus CPT-11, is one of the standard chemotherapies and the incidence of common grade 3–4 toxicities were neutropenia (28.8%), leucopenia (20.4%), diarrhea (44.4%), nausea (7.4%) and vomiting (11.1%) (16). Our study showed that the toxicity profile of CPT-11 plus UFT was similar to that for the combination of CPT-11 and infusional 5-FU/LV, but was less severe. Thus, this regimen combining CPT-11 and UFT is considered to be feasible and safe for administration on an outpatient basis.

Total response rate, 22.9% (8/35), is fairly acceptable. However, the median overall survival time (25.1 months) and the 1-year survival rate (67.5%) of the patients with prior chemotherapy enrolled in phase II were comparable to the results obtained in previous studies on the combination of CPT-11 plus 5-FU in the second-line setting (26–29), and were quite promising.

As pointed out by Ho et al., the convenience and lower cost of oral 5-FU may be preferable for many patients, particularly those receiving palliative chemotherapy (21). A recent questionnaire study performed by Borner et al. compared oral with intravenous 5-FU treatment and revealed that most patients preferred the oral regimen because of the convenience of taking medication at home, less severe toxicity (less stomatitis or diarrhea), and a general preference for tablets over injections (30). Several treatment protocols that combine oral fluoropyrimidines (e.g. UFT with or without leucovorin, TS-1, or capecitabine) with CPT-11 or oxaliplatin have been utilized for patients with advanced colorectal cancer. Although there is promising data in the combination of capecitabine and oxaliplatin (24,31), as for the combination of capecitabine and CPT-11, any useful results have not been reported yet (32,33). Moreover, TS-1 or UFT/LV combined with CPT-11 are currently under investigation.

In conclusion, the present findings suggest that the combination of CPT-11 and UFT is a promising regimen with respect to safety and efficacy for patients who have advanced/metastatic colorectal cancer in the second-line setting. Considering the excellent safety profile of this regimen and no study comparing FOLFIRI and CPT-11, it could be a very good candidate for the second-line treatment after FOLFOX failure at present. Along with the importance of establishing a standard protocol that is proven to be the most effective for colorectal cancer, we hope that the most appropriate and convenient of several possible regimens will be selected for each patient in order to improve the quality of life.

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Conflict of interest statement

None declared.

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