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ORIGINAL ARTICLE

# Combination chemotherapy of biweekly irinotecan (CPT-11) plus tegafur/uracil (UFT) and leucovorin (LV) for patients with metastatic colorectal cancer: phase I/II study in Japanese patients

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**Abstract**
*Purpose* We aimed to evaluate the safety and efficacy of combination chemotherapy with biweekly irinotecan (CPT-11) plus oral tegafur/uracil (UFT) and leucovorin (LV) in patients with previously untreated metastatic colorectal adenocarcinoma in phase I/II setting.
*Patients and methods* We recruited 37 patients with histologically proven metastatic colorectal adenocarcinoma. UFT (300 mg/m$^2$ per day) and LV (75 mg/day) were administered orally on days 1–21. CPT-11 was administered intravenously on day 1 and 15, at an initial dose of 60 mg/m$^2$, stepping up to 150 mg/m$^2$ in a traditional phase I fashion. The treatment was repeated every 4 weeks. After patients enrolled into a phase II portion, the efficacy and toxicity of this regimen were also assessed.
*Results* The recommended dose of CPT-11 was determined to be 150 mg/m$^2$. Although one patient had a pulmonary embolism after 60 mg/m$^2$ of CPT-11, the treatment was well tolerated in general. The overall objective response rate was 37.8% (14/37; 95% CI, 22.5–55.2) in all patients. Median progression-free survival was 226 days (95% CI, 133–276).
*Conclusions* Biweekly CPT-11 plus UFT and LV had a reasonable safety profile with manageable toxicity, and had a promising activity in patients with metastatic colorectal cancer. Further trials are indicated based on the promising results observed in this study.

**Keywords** Chemotherapy · Irinotecan · Leucovorin · Metastatic colorectal cancer · UFT

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## Introduction

Intravenous administration of 5-fluorouracil (5-FU) and leucovorin (LV) is a widely accepted systemic treatment for colorectal cancer patients. In most chemotherapy for patients with advanced metastatic colorectal cancer (mCRC), 5-FU/LV is administered with a bolus injection or continuous infusion. Irinotecan (CPT-11) is the topoisomerase I inhibitor and has shown consistent efficacy for mCRC [7, 22, 24]. The FOLFIRI regimen is combination chemotherapy of biweekly irinotecan and 5-FU/LV and is widely used as first-line chemotherapy for mCRC in the world [5, 9, 27].

Tegafur/uracil (UFT) is an oral third-generation fluoropyrimidine. This drug is composed of 1-(2-tetrahydrofuryl)-5-fluorouracil [ftorafur (FT) or tegafur] and uracil at a molar ratio of 1:4. Tegafur is a 5-FU prodrug synthesized by Hiller in 1967, which is converted by cytochrome P450 hepatic isoenzymes (CYP2A6) to 5-FU, while uracil is a modulator of 5-FU catabolism [15, 26]. Uracil prevents 5-FU degradation by competing with 5-FU as a substrate of the dihydropyrimidine dehydrogenase (DPD), which is the primary catabolic enzyme of 5-FU [12, 16].

The antitumor activity of UFT was enhanced by simultaneous administration with oral leucovorin (LV) [21]. Three

large phase III studies revealed that UFT/LV had equivalent efficacy and a more favorable toxicity profile than conventional 5-FU/LV in metastatic [2, 10] and adjuvant settings [18]. Thereafter, these results were extrapolated to Japanese patients based on the results of the Joint United States and Japan Study of UFT/LV [25].

Combination chemotherapy of CPT-11 and UFT/LV seems to become an attractive option in the treatment of mCRC. Several previous studies evaluated the feasibility and efficacy of this combination chemotherapy as first-line chemotherapy. The regimens of these studies had the weekly or triweekly CPT-11 schedule [1, 8, 20, 28].

The aim of this study was to determine the recommended dose of biweekly CPT-11 in combination with UFT/LV and to evaluate safety and efficacy as first-line chemotherapy for Japanese mCRC patients in phase I/II setting.

## Patients and methods

### Patients

Between 2004 and 2007, all patients were recruited from the Departments of Surgery, Keio University and Hiratsuka City Hospital. Eligibility criteria were determined as follows: histologically proven metastatic adenocarcinoma of the colon or rectum with measurable disease, no prior chemotherapy for metastatic disease, age $\geq$20 and $\leq$75 years, ECOG performance status 0–2, life expectancy $\geq$3 months, adequate hematological and biochemical parameters, defined as a leukocyte count of $\geq$4,000–12,000 $mm^{-3}$, neutrophil count $\geq$2,000 $mm^{-3}$, platelets $\geq$100,000 $mm^{-3}$, hemoglobin $\geq$9.0 g/dl, serum bilirubin level $\leq$1.5 mg/dl, serum transaminases $\leq$2.5 $\times$ upper limit of normal (ULN), serum creatinine $\leq$ULN, and normal electrocardiogram. All patients provided written informed consent. This study was performed according to the guidelines of the Declaration of Helsinki as amended in Edinburgh, Scotland, October 2000, and the protocol was approved by ethics committees in each institution.

### Study design

This study is a phase I/II study. The study was conducted as an open label, non-randomized, dose-finding study using dose escalation of CPT-11 with a fixed dose of UFT/LV, and a small phase II portion.

UFT was administrated at a dose of 300 $mg/m^2$ per day, and LV was administrated at a dose of 75 mg/day given orally on days 1–21, followed by a 7-day rest, repeated every 28 days as one cycle. The daily dose of both UFT and LV were divided into three doses administered 8 h apart and taken together, along with water. Patients were instructed to avoid food consumption between 1 h before and 1 h after each dose. CPT-11 was administrated as an i.v. infusion over 90 min on day 1 and 15. Six dose levels of CPT-11 were tested ranging from 60 to 150 $mg/m^2$ (Table 1). No intrapatient dose escalation was allowed. We routinely administered 5-HT3 antagonists and steroid for 30 min before infusion of CPT-11.

The endpoints were defined as the maximum tolerated dose (MTD) and recommended dose (RD) of CPT-11 in phase I portion. After patients enrolled into a small phase II portion, the efficacy and toxicity of this regimen were also assessed.

Dose escalation proceeded according to the planned dose escalation schedule (Table 1). At least three patients were entered at each dose level and dose escalation was permitted if no dose-limiting toxicity was encountered in the first cycle. If one of three patients at a given dose developed any dose-limiting toxicity (DLT), three more patients were entered at the same dose. If one of the resulting six patients had DLT, the dose could be increased to the next level; if two or more patients had DLT, that dose level was deemed the MTD. When DLT occurred in two or all three patients in the initial three patients, that level was also considered as the MTD. The MTD was thus defined as the dose at which >33% patients experienced DLTs during the first cycle. DLT was defined as any of the following experienced during the first cycle; grade 4 hematological toxicity and grade 3 or 4 non-hematological toxicity.

Treatment was discontinued for disease progression, unacceptable toxicity, delay of >14 days in instituting the next cycle of treatment, or at the investigators' discretion or the patients' request. Protocol specified dose reductions and delays were based on previous cycle toxicity utilizing both hematological nadirs and hematological/biochemical parameters on the day following treatment. In this study, UFT dose was reduced by 100 mg/day and CPT-11 dose was reduced by 20%, when grade 3 or more toxicity occurred in the previous treatment cycle.

### Evaluation

Toxicity was evaluated biweekly during treatment in accordance with National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2. Response was evaluated by computed tomography every two cycles during treatment. RECIST criteria were used to determine the response.

### Statistics

Statistical analyses were performed using the JMP software version 6 (SAS Institute, Inc., Cary, NC, USA). Kaplan–Meier estimations were used for the calculation of progression-free survival (PFS) and overall survival (OS).

**Table 1** Dose level of irinotecan and patient characteristics

| | Dose level of irinotecan | | | | | |
|---|---|---|---|---|---|---|
| | Level 1 | Level 2 | Level 3 | Level 4 | Level 5 | Level 6 |
| CPT-11 (mg/m$^2$) | 60 | 80 | 100 | 120 | 140 | 150 |
| No. of patients | 6 | 6 | 3 | 3 | 6 | 13 |
| Age (years) | | | | | | |
| Median | 71.5 | 61.5 | 63 | 59 | 58 | 58 |
| Range | 57–73 | 36–65 | 47–71 | 56–69 | 29–72 | 40–72 |
| Sex | | | | | | |
| Female | 2 | 2 | 1 | 0 | 3 | 5 |
| Male | 4 | 4 | 2 | 3 | 3 | 8 |
| Performance status | | | | | | |
| 0 | 6 | 6 | 3 | 3 | 6 | 10 |
| 1 | 0 | 0 | 0 | 0 | 0 | 3 |
| Primary sites | | | | | | |
| Colon | 5 | 4 | 2 | 1 | 4 | 10 |
| Rectum | 0 | 2 | 0 | 1 | 2 | 2 |
| Colorectal | 1 | 0 | 1 | 1 | 0 | 1 |
| Metastatic lesion | | | | | | |
| Liver | 3 | 4 | 2 | 1 | 4 | 8 |
| Lung | 5 | 2 | 1 | 2 | 0 | 6 |
| Lymph node | 1 | 0 | 0 | 0 | 1 | 5 |
| Others | 1 | 1 | 0 | 1 | 2 | 1 |

## Results

### Patient characteristics

A total of 37 Japanese patients were enrolled in this study at two institutions. All received at least one cycle study treatment and were analyzed for toxicity. Patient characteristics are shown in Table 1. There were 24 men and 13 women with a median age of 60 years (range 29–73). Thirty-six patients had metastatic lesions; 22 patients had metastasis to the liver, 16 patients to the lung, 7 patients to the lymph nodes, and 3 patients to the peritoneum. Among the 37 patients, 13 had ≥2 metastatic sites synchronously. In all, 15 patients had received previous adjuvant chemotherapy with fluoropyrimidine such as UFT alone or UFT/LV.

### Treatment exposure and toxicity results

A total of 228 chemotherapy cycles were administered to the 37 patients, with a median number of six cycles per patient (range 1–20) during the study. The mean actual relative dose intensities of both CPT-11 and UFT for up to six cycles were 0.96 and 0.96 at level 1 ($n = 6$), 0.96 and 0.96 at level 2 ($n = 6$), 0.97 and 0.98 at level 3 ($n = 3$), 0.91 and 0.94 at level 4 ($n = 3$), 0.96 and 0.96 at level 5 ($n = 6$), and 0.86 and 0.93 at level 6 ($n = 13$), respectively.

Table 2 shows the adverse events recorded during the first cycle. DLTs were experienced at level 1, 2, 5 and 6. Grade 4 pulmonary embolism developed in one of six at 60 mg/m$^2$ of CPT-11 (level 1), and grade 3 fatigue developed in one of six at 80 mg/m$^2$ (level 2) and in one of six at 140 mg/m$^2$ of CPT-11 (level 5), respectively. At 150 mg/m$^2$ of CPT-11 (level 6), one of six patients developed grade 3 diarrhea with grade 3 fatigue, but did not reach the MTD even at this dose level. Therefore, seven additional patients were entered into this dose level as the phase II portion of the study. Finally, grade 3 diarrhea as a DLT was observed in 3 out of 13 patients (23.1%), thus this dose was confirmed as the RD.

Table 3 shows the adverse events by patient recorded in at least 5% during all study cycles. Grade 3 neutropenia occurred in 3 patients (8.1%), while grade 3 anorexia occurred in 10 patients (27%), grade 3 nausea in 11 patients (29.7%), grade 3 fatigue in 3 patients (8.1%), and grade 3 diarrhea in 5 patients (13.5%).

### Efficacy results

Partial response was seen in 14 of the total of 34 patients evaluated for response. Overall objective response rate was 37.8% (14/37; 95% CI, 22.5–55.2) in all patients. Stabilization of disease lasting for at least 8 weeks was observed in 17 patients (45.9%), whereas progressive disease was apparent in 3 patients (8.1%) (Table 4).

Analysis of Kaplan–Meier survival curves revealed that the overall median PFS for all patients was 226 days (95%

**Table 2** Adverse events reported during first cycle

| | Level 1 | | Level 2 | | Level 3 | | Level 4 | | Level 5 | | Level 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CPT-11 (mg/m$^2$) | 60 | | 80 | | 100 | | 120 | | 140 | | 150 | |
| No. of patients | 6 | | 6 | | 3 | | 3 | | 6 | | 13 | |
| NCI-CTC grade | All | 3/4 | All | 3/4 | All | 3/4 | All | 3/4 | All | 3/4 | All | 3/4 |
| Hematological | | | | | | | | | | | | |
| Leukopenia | 1 | 0/0 | 1 | 0/0 | 0 | 0/0 | 1 | 0/0 | 0 | 0/0 | 2 | 1/0 |
| Neutropenia | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 | 1 | 1/0 |
| Anemia | 3 | 0/0 | 1 | 0/0 | 0 | 0/0 | 2 | 0/0 | 2 | 0/0 | 1 | 0/0 |
| Non-hematological | | | | | | | | | | | | |
| Alopecia | 0 | – | 1 | – | 0 | – | 0 | – | 2 | – | 1 | – |
| Anorexia | 4 | 1/0 | 1 | 1/0 | 2 | 0/0 | 2 | 1/0 | 2 | 1/0 | 10 | 1/0 |
| Nausea | 4 | 1/0 | 3 | 1/0 | 2 | 0/0 | 2 | 1/0 | 2 | 1/0 | 9 | 2/0 |
| Vomiting | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 | 1 | 0/0 | 1 | 0/0 | 4 | 1/0 |
| Diarrhea | 2 | 0/0 | 2 | 0/0 | 1 | 0/0 | 1 | 0/0 | 3 | 0/0 | 6 | 3/0 |
| Skin reaction | 1 | 0/0 | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 | 1 | 0/0 | 1 | 0/0 |
| Stomatitis | 0 | 0/0 | 0 | 0/0 | 1 | 0/0 | 0 | 0/0 | 0 | 0/0 | 3 | 0/0 |
| Fatigue | 2 | 0/0 | 1 | 1/0 | 1 | 0/0 | 0 | 0/0 | 0 | 0/0 | 3 | 1/0 |
| Neuropathy | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 | 1 | 1/0 | 1 | 0/0 |
| Fever | 0 | 0/0 | 1 | 0/0 | 1 | 0/0 | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 |
| Liver dysfunction | 0 | 0/0 | 2 | 0/0 | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 | 1 | 0/0 |
| Dysgeusia | 2 | – | 0 | – | 0 | – | 1 | – | 0 | – | 2 | – |
| Dysosmia | 1 | – | 0 | – | 0 | – | 1 | – | 0 | – | 1 | – |
| Pulmonary embolism | 1 | 0/1 | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 |

CI, 133–276 days) (Fig. 1). Five patients have died, but the median survival time had not yet been reached at a median follow-up period of 364 days (range 56–1,272 days).

## Discussion

We set out to determine the safety and efficacy of biweekly CPT-11 plus UFT/LV every 28-day cycle in Japanese patients with mCRC.

In early 2000, the IFL regimen (weekly CPT-11 and bolus 5-FU/LV) was proved to have anticancer activity [23]. Thereafter, many phase II or III studies for advanced and metastatic colorectal cancer patients revealed that CPT-11 combined with cytotoxic agents had adequate cytotoxic effect. Combination chemotherapy regimens such as FOLFOX or FOLFIRI have been standard chemotherapy as first-line treatment for mCRC patients [5, 9, 13, 17, 27]. However, these regimens need 46 h of continuous 5-FU infusion and are very troublesome. There is hope that combination chemotherapy with oral fluoropyrimidines will become a well-tolerated treatment by replacing complicated continuous infusion and with more convenient oral intake. Therefore, in our regimen, infusion of 5-FU/LV was replaced by oral UFT/LV, which has the potential to minimize adverse effects and be more convenient to the patient.

The profile of adverse effects in this study was acceptable. Most hematological and non-hematological adverse events were generally mild or moderate, although one patient had pulmonary embolism at level 1. The patient additionally experienced grade 3 appetite loss and this condition seemed to be strongly associated with pulmonary embolism, but the patient recovered with oxygen administration. The most frequent grade 3 adverse events were nausea and anorexia, which were seen in 29.7 and 27.0%, respectively. The incidence of grade 3 diarrhea was 13.5% and all diarrhea cases were controlled by administration of loperamide. In our study, grade 3 neutropenia was seen in only 8.1%. All toxicities were reversible and manageable with appropriate intervention including treatment interruption or dose reduction of CPT-11 or UFT or both, despite the fact that upper gastrointestinal toxicities were relatively frequent. No cases of febrile neutropenia or toxic deaths were reported. In previously reported studies combining CPT-11 and fluoropyrimidines including UFT/LV, the incidence of neutropenia was 10–28.8% [1, 5, 8, 9, 19, 27]. The incidence of severe neutropenia in our study was relatively lower than that of those reports. In this study, the planned maximum escalated dose of CPT-11 was limited to 150 mg/m$^2$, because the Japanese maximum legally permissible dose of irinotecan to 150 mg/m$^2$ in biweekly dosing, although the dose given even in the RD was lower than the

**Table 3** Adverse events (AE) reported in at least 5% during all cycles (per patient)

| | Level 1 | | Level 2 | | Level 3 | | Level 4 | | Level 5 | | Level 6 | | All patients | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CPT-11 (mg/m$^2$) | 60 | | 80 | | 100 | | 120 | | 140 | | 150 | | AE % | |
| No. of patients | 6 | | 6 | | 3 | | 3 | | 6 | | 13 | | 37 | |
| NCI-CTC grade | All | 3/4 | All | 3/4 | All | 3/4 | All | 3/4 | All | 3/4 | All | 3/4 | All | 3/4 |
| Hematological | | | | | | | | | | | | | | |
| Leukopenia | 1 | 0/0 | 2 | 0/0 | 1 | 0/0 | 2 | 0/0 | 3 | 0/0 | 7 | 1/0 | 43.2 | 2.7 |
| Neutropenia | 0 | 0/0 | 0 | 0/0 | 1 | 0/0 | 1 | 0/0 | 1 | 1/0 | 5 | 2/0 | 21.6 | 8.1 |
| Anemia | 3 | 0/0 | 6 | 0/0 | 3 | 0/0 | 3 | 0/0 | 4 | 0/0 | 4 | 0/0 | 62.1 | 0.0 |
| Thrombocytopenia | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 | 1 | 0/0 | 0 | 0/0 | 2 | 0/0 | 8.1 | 0.0 |
| Non-hematological | | | | | | | | | | | | | | |
| Alopecia | 1 | – | 6 | – | 2 | – | 1 | – | 6 | – | 7 | – | 62.2 | – |
| Anorexia | 5 | 1/0 | 5 | 2/0 | 3 | 0/0 | 3 | 1/0 | 4 | 2/0 | 10 | 4/0 | 81.1 | 27.0 |
| Nausea | 6 | 1/0 | 5 | 2/0 | 3 | 1/0 | 3 | 1/0 | 4 | 1/0 | 10 | 5/0 | 83.8 | 29.7 |
| Vomiting | 1 | 0/0 | 4 | 1/0 | 2 | 0/0 | 2 | 0/0 | 4 | 0/0 | 6 | 2/0 | 51.4 | 8.1 |
| Diarrhea | 4 | 0/0 | 6 | 1/0 | 3 | 0/0 | 1 | 0/0 | 5 | 0/0 | 9 | 4/0 | 75.7 | 13.5 |
| Constipation | 1 | 0/0 | 2 | 0/0 | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 | 4 | 0/0 | 18.9 | 0.0 |
| Skin reaction | 3 | 0/0 | 6 | 0/0 | 2 | 0/0 | 2 | 0/0 | 2 | 0/0 | 7 | 1/0 | 59.5 | 2.7 |
| Stomatitis | 4 | 0/0 | 5 | 1/0 | 3 | 0/0 | 1 | 0/0 | 1 | 0/0 | 6 | 1/0 | 54.1 | 5.4 |
| Fatigue | 4 | 0/0 | 3 | 1/0 | 1 | 0/0 | 0 | 0/0 | 2 | 1/0 | 4 | 1/0 | 37.8 | 8.1 |
| Neuropathy | 1 | 0/0 | 4 | 0/0 | 0 | 0/0 | 1 | 0/0 | 2 | 0/0 | 1 | 0/0 | 24.3 | 0.0 |
| Fever | 0 | 0/0 | 2 | 0/0 | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 | 0 | 0/0 | 5.4 | 0.0 |
| Liver dysfunction | 1 | 0/0 | 3 | 0/0 | 0 | 0/0 | 1 | 0/0 | 2 | 0/0 | 5 | 0/0 | 32.4 | 0.0 |
| Dysgeusia | 2 | – | 3 | – | 2 | – | 2 | – | 2 | – | 2 | – | 35.1 | – |
| Dysosmia | 2 | – | 4 | – | 0 | – | 1 | – | 0 | – | 1 | – | 21.6 | – |

**Table 4** Response rate by CPT-11 dose level

| Dose level | *n* | CR | PR | SD | PD | NE | Response % |
|---|---|---|---|---|---|---|---|
| Level 1 | 6 | 0 | 1 | 3 | 1 | 1 | 16.6 |
| Level 2 | 6 | 0 | 3 | 3 | 0 | 0 | 50.0 |
| Level 3 | 3 | 0 | 0 | 2 | 1 | 0 | 0.0 |
| Level 4 | 3 | 0 | 0 | 3 | 0 | 0 | 0.0 |
| Level 5 | 6 | 0 | 2 | 3 | 1 | 0 | 33.3 |
| Level 6 | 13 | 0 | 8 | 3 | 0 | 2 | 61.5 |
| Total | 37 | 0 | 14 | 17 | 3 | 3 | 37.8 |

95% CI of the response in 37 patients was 22.5–55.2%

*CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable

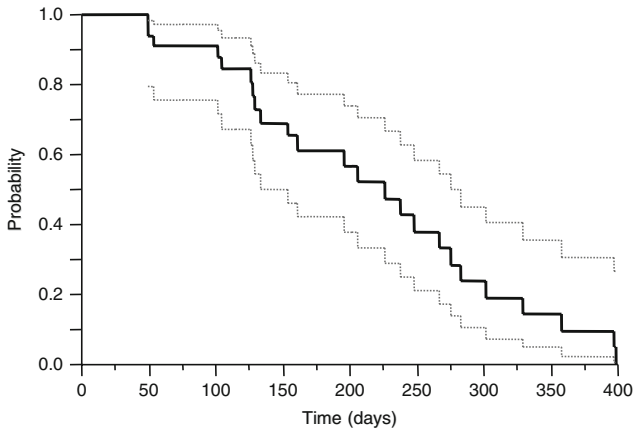


**Fig. 1** Progression-free survival in all 37 patients. The median progression-free survival was 226 days (95% CI, 133–276 days)

previous studies containing CPT-11 every 2 weeks in the Western countries [5, 9, 27]. This may, in part, explain the low myelosupression profile of our regimen even in the RD or near RD.

The previous phase II studies evaluated different schedules of triweekly CPT-11 plus UFT/LV (TEGAFIRI) and showed overall response rates of 30–42% and median PFS of 5.5–8 months [1, 8]. The FOLFIRI regimen yielded overall response rates of 31–56%, with median PFS of 6.7–8.5 months [5, 9, 27]. Similarly, our study regimen also presented a relatively high overall response rate of 37.8% and similar median PFS of 226 days (7.5 months) to TEGAFIRI or FOLFIRI regimen, despite including the patients given a lower dose of CPT-11 than the RD.

Several different schedules of CPT-11 combined with UFT/LV were reported: weekly or triweekly in combination with UFT/LV as mentioned above. Overall, the adverse effect profiles of these two schedules were similar but our schedule appeared to have favorable therapeutic ratio, especially regarding lower myelosupression.

Cohen et al. [4] reported that bi-weekly CPT-11 plus UFT regimen (without leucovorin) revealed unfavorable toxicity (grade 3 diarrhea of 28%) in a meeting abstract. Given that the dosage of CPT-11 (160 mg/m$^2$) and UFT (250 mg/m$^2$ per day) was not intensive, in addition, leucovorin was not combined with UFT, the high incidence of severe diarrhea was hard to be explained. Different dosing of UFT, twice daily in their study versus three times daily in ours, or ethnic difference of drug metabolizing enzymes might lead to these discordant results [25].

New strategies, particularly inhibition of angiogenesis and epidermal growth factor receptors, have been developed and new combination chemotherapy using these molecular targeting agents are now achieving better efficacy [6, 11, 14]. Little is known about the efficacy and safety profile of combination chemotherapy using oral fluoropyrimidines and these molecular targeting agents except capecitabine plus oxaliplatin (XELOX) with bevacizumab at this time [3]. In the future, combination chemotherapy of CPT-11 plus UFT/LV and molecular targeting agent may become recognized also as a first line regimen of choice for advanced mCRC.

In conclusion, the recommended dose of biweekly CPT-11 was 150 mg/m$^2$, when combined with 300 mg/m$^2$ of UFT and 75 mg/body of LV on days 1–21 every 28-day cycle. In addition, the results of this study revealed that the regimen had a reasonable safety profile with manageable toxicity, and had a promising activity. Although its efficacy needs to be further evaluated in a randomized phase II or III study, the regimen seemed to be a good alternative candidate to FOLFIRI for patients with advanced metastatic colorectal cancer. To confirm the efficacy and safety of this regimen, we are carrying out a multicenter randomized phase II study (UMIN000000951).

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