Phase I Study of Combination Therapy with Irinotecan, Leucovorin, and Bolus and Continuous-infusion 5-Fluorouracil (FOLFIRI) for Advanced Colorectal Cancer in Japanese Patients

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Abstract. *Background: Irinotecan, leucovorin, and bolus and continuous-infusion 5-fluorouracil administered every two weeks (FOLFIRI regimen) is active in patients with metastatic colorectal cancer. However, the efficacy and toxicity of this regimen in Japanese patients with metastatic colorectal cancer remain unknown. Patients and Methods: We investigated the maximum tolerated dose, dose-limiting toxicity, and recommended dose at Step 1. Twenty-one patients with metastatic colorectal cancer were enrolled in Step 1. At the five dose levels, fixed doses of bolus 5-fluorouracil (400 mg/m^2) and leucovorin (200 mg/m^2) were administered in combination with escalating doses of irinotecan from 120-180 mg/m^2 with 46-h continuous infusion of 5-fluorouracil 2000-3000 mg/m^2 every two weeks. In Step 2, an additional 24 patients received the recommended doses determined in Step 1, and safety and antitumor efficacy were evaluated in terms of tumor response. Results: No dose-limiting toxicities were observed at dose levels 1-4. Four out of eight patients experienced a dose-limiting toxicity at level 5; therefore, this level was considered the maximum tolerated dose. Consequently, the recommended doses were determined to be 180 mg/m^2 of irinotecan and 2,400 mg/m^2 of 5-fluorouracil in continuous i.v. infusion. At this level (FOLFIRI-180), National Cancer Institute common terminology criteria grade 3-4 neutropenia, leukopenia, and vomiting were common but manageable. Other hematological and non-hematological toxicities were mild. Seven out of 23 response-assessable patients achieved an objective response (response rate=30%). Conclusion: This FOLFIRI-180 regimen is manageable and effective in Japanese patients with metastatic colorectal cancer.*

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Colorectal cancer is a major cause of death in Japan; it is the greatest cause of death due to malignant tumors in women and the third greatest in men (1). Furthermore, the incidence and mortality of colorectal cancer is increasing. In 2009, more than 42,000 patients died due to colorectal cancer in Japan.

Fluorouracil (5-FU) remains the most frequently used agent to treat metastatic colorectal cancer. The modulation of leucovorin (LV) increases the antitumor activity of 5-FU (2-4). Pre-clinical data suggest bolus 5-FU acts *via* a different mechanism (namely inhibition of RNA synthesis) from that of infusional 5-FU (namely thymidylate synthase inhibition) (5). The LV5FU2 regimen, which combines bolus and infusional 5-FU administration, is superior to bolus 5-FU in terms of response rate and time-to-tumor progression (6).

Irinotecan inactivates topoisomerase I, thereby inhibiting cell division (7, 8). Irinotecan exhibits antitumor efficacy against metastatic colorectal cancer when used as a second-line treatment after the failure of fluorouracil (9, 10). Saltz *et al*. reported that irinotecan at 125 mg/m^2 and bolus 5-FU at 500 mg/m^2 plus LV at 20 mg/m^2 administered weekly for four weeks every six weeks is superior to 5-FU/LV alone in terms of response rate and overall survival (11). However, the North Central Cancer Treatment Group (N9741) and Cancer and Leukemia Group B (C89803) clinical trials demonstrated that patients treated with irinotecan plus bolus 5-FU/LV had higher rates of treatment-related death (2.5-3.5%) due to high rates of severe neutropenia, vomiting, and diarrhea (12). On the other hand, Douillard *et al*. performed a randomized study involving 387 patients with advanced colorectal cancer who received infusion once weekly or every two weeks (13). In both regimens, fluorouracil was administered by continuous infusion (24 or 44 h). The irinotecan group exhibited a significantly higher response rate (49% *vs*. 31%, $p<0.001$) and

better overall survival (median=17.4 *vs.* 14.1 months, p=0.031) than the non-irinotecan group. In light of these results, irinotecan plus infusional 5-FU/LV has become a first-line chemotherapy regimen for patients with metastatic colorectal cancer. This bi-weekly regimen has been modified to include LV at 400 mg/m^2 and irinotecan at 180 mg/m^2, followed by 5-FU at 400 mg/m^2 in *i.v.* bolus and 5-FU at 2,400–3,000 mg/m^2 given as a 46-h *i.v.* infusion (14).

Irinotecan is metabolized by carboxylesterase to form SN-38, which is an active metabolite. SN-38 is subsequently conjugated by UDP-glucuronosyltransferase 1A1 (UGT1A1) to yield an inactive form. Irinotecan toxicity is significantly associated with *UGT1A1* gene polymorphisms, especially *UGT1A1*28* (15, 16). However, these polymorphisms exhibit large interethnic variation (17). The frequency of *UGT1A1*28* is low in Asians, including Japanese, and high in Caucasians. In addition to genetic variants of *UGT1A1*6*, variations in *UGT1A1*28* are associated with the occurrence of severe irinotecan-induced neutropenia in Asians (18, 19). *UGT1A1*6* is not found in Caucasians. Thus, homozygosity for *UGT1A1*28* or *UGT1A1*6* and heterozygosity for both *UGT1A1*28* and *UGT1A1*6* are associated with severe irinotecan-related toxicity in Japanese patients. The combined frequency of patients with high-risk alleles is 10.1% (20). Therefore, the suitable dose of irinotecan in Japanese patients may be different from that in others.

However, at present, irinotecan at 150 mg/m^2 bi-weekly must be used for colorectal cancer because of prior approval by the Japanese Ministry of Health, Labor, and Welfare on the basis of the results of a previous study in Japan (21, 22); this FOLFIRI dose is different from those used in Western countries.

The primary objective of the present study was to identify the maximum tolerated dose (MTD) and decide upon the recommended dose (RD) for the FOLFIRI regimen in Japanese patients.

Patients and Methods

Eligibility. The eligibility criteria were as follows: histologically-confirmed metastatic colorectal cancer, age between 20 and 75 years, Eastern Cooperative Oncology Group (ECOG) performance status less than 2, adequate organ function defined as white blood cell count ≥4,000/mm^3 and ≤12,000/mm^3, platelet count ≥10×10^4/mm^3, total bilirubin ≤1.1 mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤100U/l, serum creatinine ≤1.1 mg/dl, and no history of chemotherapy containing irinotecan. Prior chemotherapy that did not include irinotecan was required to have ended at least four weeks before study entry. Written informed consent was obtained from each patient. The exclusion criteria were as follows: evidence of any active infection, severe uncontrolled comorbidities, substantial pooling of pleural effusion and ascites, brain metastases, and fresh bleeding from the gastrointestinal tract; chronic diarrhea; pregnant and breast-feeding women; and prior radiotherapy to the abdomen.

Treatment plan. Irinotecan was supplied in 5-ml vials containing 100 mg drug and administered in 250 ml dextrose over 90 min. l-LV was administered as a 2-h *i.v.* infusion concurrent with the start of irinotecan administration, followed by 5-FU in *i.v.* bolus and 5-FU in a continuous 46-h *i.v.* infusion. All patients received premedication with antiemetic drugs. 5-hydroxytryptamine 3 receptor antagonist *i.v.* and dexamethasone at 8 mg *i.v.* were administered before irinotecan. Treatment was given every two weeks; one course consisted of four weeks.

Dose-escalation schedule. Fixed doses of l-LV (200 mg/m^2) and 5-FU in *i.v.* bolus (400 mg/m^2) were administered together with escalating doses of irinotecan from 120-180 mg/m^2 and 5-FU continuous infusion from 2,000-3,000 mg/m^2. Three patients were initially enrolled at each dose level; if none of them experienced a dose-limiting toxicity (DLT), then three additional patients were enrolled at the next dose level. If one patient experienced a DLT, the dose level was expanded to at least six patients. The MTD was defined as the dose at which more than two out of three, or three out of six patients experienced a DLT. The dose level below the MTD was considered the RD for further studies (Step 1). If the RD was determined, toxicity and efficacy were evaluated in an additional 20 patients at the same dose (Step 2).

Pre-treatment evaluation and follow-up. Pre-treatment evaluation included complete medical history and physical examination, complete blood cell (CBC) count, serum chemistry including electrolytes, liver and renal function tests, tumor markers (carcinoembryonic antigen and carbohydrate antigen 19-9), chest X-ray, and abdominal computed tomographic (CT) scans. During treatment, clinical toxicities, physical examination, CBC count, and serum chemistry were assessed weekly during the first four weeks and biweekly thereafter. Chest X-ray and CT scans were performed every eight weeks. During the follow-up period, four weeks after the end of treatment, physical examination, CBC count, serum chemistry, chest X-ray, and CT scans were evaluated.

Toxicity and response evaluation. Toxicities were graded according to the National Cancer Institute – Common Toxicity Criteria (NCI-CTC) criteria. A DLT was defined was any grade 3 or higher non-hematological toxicity (except nausea, vomiting, anorexia, fatigue, constipation, and abnormal serum sodium), grade 4 neutropenia lasting more than five days, febrile neutropenia, or thrombocytopenia of grade 4 or grade 3 if associated with bleeding during the first cycle.

After treatment initiation, patients were permitted to proceed with therapy if the WBC count was ≥3,000/mm^3, platelet count was ≥10×10^4/mm^3, and they had recovered from any non-hematological toxicities of grade 2 or higher. In case of a DLT during the first cycle, treatment was continued at the dose level immediately below as soon as the DLT had resolved.

Tumor response was assessed by CT scans every four treatment cycles (*i.e.* every eight weeks). Response was classified according to Response Evaluation Criteria in Solid Tumors (23).

Results

Patients' characteristics. In Step 1, a total of 21 patients were enrolled between April 2003 and February 2004. In Step 2, an additional 24 patients were enrolled and received RDs determined in Step 1. Detailed clinical data are summarized in

Table I. *Patients' characteristics*.

	Step 1	%	Step 2	%	Total	%
No. of patients	21		24		45	
Gender						
male	12	57	12	50	24	53
female	9	43	12	50	21	47
Age, years						
Median	61		59		61	
Range	46-71		29-70		29-71	
ECOG performance status						
0	14	67	21	87	35	78
1	7	33	3	13	10	22
Disease status						
Metastases	14	67	17	71	31	69
Recurrence after curative resection	7	33	7	29	14	31
Previous chemotherapy	16	76	16	67	32	71
Adjuvant chemotherapy	7	33	7	29	14	31
Histological differentiation						
Well	12	57	4	17	16	36
Moderate	8	38	16	66	24	53
Por	0	0	4	17	4	9
Muc	1	5	0	0	1	2
Sites of disease						
Liver	16	50	14	58	30	67
Lung	10	31	8	33	18	40
Lymph node	5	16	12	50	17	38
Other	1	3	3	13	4	9

ECOG, Eastern Cooperative Oncology Group; Por, poorly; Muc, mucinous.

Table I. The median patient age was 61 years (range=29-71 years); 24 (53%) were men, and 21 (47%) were women. All 45 patients showed good ECOG performance status scores of 0 or 1 at study entry. Thirty-five patients had metastatic disease at initial diagnosis, and 10 had recurrent colorectal cancer. The most common sites of metastatic disease were the liver (67%) and lungs (40%). Thirty-two patients (71%) received prior chemotherapy, mostly 5-FU-based chemotherapy; 14 (31%) patients received adjuvant chemotherapy. Sixteen (36%), 24 (53%), 4 (9%), and 1 (2%) patient had well-differentiated, moderately-differentiated, poorly-differentiated, and mucinous adenocarcinoma, respectively.

Toxicity and RD. Median follow-up time for toxicity was six months after initiation of treatment. In Step 1, patients were treated at five different dose levels (Table II). No DLTs were observed at dose levels 1-4 (Table III). The most commonly observed toxicities were leukopenia, neutropenia, nausea, diarrhea, anorexia, alopecia, and fatigue. No patient experienced febrile neutropenia. Although all patients received prophylactic anti-emetic therapy, NCI-CTC grade 1 or 2 nausea was observed in 54% of patients over all cycles. One patient experienced NCI-CTC grade 4 neutropenia and grade 3 anorexia during the first cycle (dose level 1), but all patients were able to continue treatment. No significant changes in serum bilirubin or hepatic enzymes (*i.e*. AST and ALT) were observed. Out of the eight patients who entered level 5, four exhibited DLTs; three had to delay the second treatment course by eight or more days due to leukopenia (2/3) or fatigue (1/3), while the other patient experienced NCI-CTC grade 3 diarrhea. On the basis of these results, the MTD was defined as dose level 5, and the RDs for irinotecan and 5-FU in continuous *i.v.* infusion were determined to be 180 and 2400 mg/m^2, respectively.

Table II. *Dose-escalation scheme and incidence of dose-limiting toxicity (DLT)*.

Dose level	CPT-11 (mg/m^2)	5-FU continuous (mg/m^2)	5-FU bolus (mg/m^2)	l-LV (mg/m^2)	No.of patients	DLT
1	120	2000	400	200	4	Not observed
2	150	2000	400	200	3	Not observed
3	150	2400	400	200	3	Not observed
4	180	2400	400	200	3	Not observed
5	180	3000	400	200	8	Reached

CPT-11, Irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin.

At Step 2, toxicity was evaluated in a total of 27 patients including 3 treated at dose level 4 in Step 1 (Table IV). The most common grade 3 and 4 toxicities were neutropenia (48%), leukopenia (19%), and vomiting (11%). Two patients (7%) experienced febrile neutropenia, and five required granulocyte colony-stimulating factor. Grade 3 diarrhea occurred in only 1 patient (3%). Other hematological or non-hematological toxicities, particularly anemia, nausea, anorexia and alopecia, were mild and did not exceed grade 2.

There were no treatment-related deaths within 30 days of treatment initiation. However, two patients discontinued chemotherapy during the first course because of toxicity (febrile neutropenia and nausea, respectively).

Patients had good relative dose intensities of irinotecan (88.9%), although the doses of irinotecan and 5-FU in continuous *i.v.* infusion were reduced in 8 out of 27 patients (29%). The reasons for dose reduction included prolonged neutropenia in 4 patients, vomiting in 3, and diarrhea in 1.

Treatment outcomes. The objective responses at each dose level in Step 1 are summarized in Table V. Seven out of 16 patients who could be assessed for a response achieved an objective response, resulting in an overall response rate of 44%. However three patients receiving the RD (level 4) did not show a response, although two had stable disease.

In Step 2, all patients were administered at least one treatment course. Twenty-three patients could be assessed for response; three complete responses and four partial responses were observed, resulting in an objective response rate of 30%

Table III. *Frequency of toxicities at each dose level (Step 1).*

Dose level	1 (n=4)				2 (n=3)				3 (n=3)				4 (n=3)				5 (n=8)				Total
Grade of adverse event (NCI-CTCAE version 3.0)	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	
Hematological																					
Leukopenia	0	1	1	0	0	0	0	0	1	1	0	0	0	1	0	0	1	4	2	0	12
Neutropenia	0	0	1	1	0	0	1	0	0	1	1	0	0	1	1	0	0	2	3	3	15
Anemia	0	2	0	0	0	0	0	0	1	0	0	0	2	1	0	0	4	0	0	0	10
Thrombocytopenia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Non-hematological																					
Nausea	2	1	0	0	0	1	0	0	1	0	0	0	2	0	0	0	4	2	0	0	13
Vomiting	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	3	1	0	0	6
Anorexia	2	0	1	0	0	1	0	0	1	0	0	0	1	1	0	0	5	1	0	0	13
Diarrhea	1	1	0	0	1	0	0	0	1	1	0	0	0	0	0	0	5	2	0	0	12
Stomatitis	1	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	1	0	0	0	5
Alopecia	3	0	0	0	1	0	0	0	2	0	0	0	2	0	0	0	2	2	0	0	12
Fatigue	1	1	0	0	3	0	0	0	2	0	0	0	1	0	0	0	5	0	1	0	14
Constipation	1	2	0	0	0	2	0	0	1	1	0	0	0	0	0	0	1	1	0	0	9
Bilirubin	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
AST/ALT	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	3	0	0	0	5

Data are expressed as numbers of patients with the listed grade of toxicity as their maximum. NCI-CTC, National Cancer Institute common toxicity criteria. AST, aspartate transaminase; ALT, alanine transaminase.

(Table VI). No major differences in tumor response were found between patients with no prior exposure to chemotherapy and pre-treated patients, except those treated with adjuvant chemotherapy. There were only three cases (13%) of progressive disease.

Discussion

This phase I dose-escalation study was performed to determine the MTDs and RDs of irinotecan and 5-FU for FOLFIRI therapy for advanced colorectal cancer in Japanese patients. The RD for irinotecan was 180 mg/m^2, while that for 5-FU in continuous *i.v.* infusion was 2,400 mg/m^2 administered on day 1 of 2-week cycles. The RDs were almost the same as those reported previously. Furthermore, safety and anti-tumor efficacy were evaluated in additional patients in Step 2. It is difficult to compare the present results with those of other studies directly administering FOLFIRI therapy. However, the incidence of grade 3 or higher neutropenia (48%) was more frequent in the present trial, while the incidence of diarrhea (3%) was less frequent. According to previous clinical trials, grade 3-4 neutropenia and diarrhea were observed in 24-52% and 4-14% of patients receiving FOLFIRI therapy, respectively (24-27). Interestingly, even though no patients experienced a DLT at the RD in Step 1, irinotecan and 5-FU doses were reduced in 8 out of 27 patients and treatment was discontinued in two patients in Step 2. However, most patients recovered rapidly from toxicities. The dose intensity of irinotecan at this level was maintained at about 90% throughout the study.

Falcone *et al*. reported that the schedule of irinotecan followed by 5-FU infusion is less toxic than the reverse schedule (28). In their study, the MTDs were 300 mg/m^2 for 5-FU followed by irinotecan and 450 mg/m^2 for irinotecan followed by 5-FU. DLTs, mainly neutropenia and diarrhea, were observed only when 5-FU preceded irinotecan. Plasma pharmacokinetics analysis revealed that the area under the curve of SN-38 decreased by 40.1% in the irinotecan followed by 5-FU group. In addition, genetic polymorphisms of *UGT1A1*, which is related to irinotecan metabolism, may affect the likelihood of patients developing severe neutropenia (15, 16, 18). The risk of toxicity was higher among patients receiving moderate and high doses of irinotecan. Although *UGT1A1* genotypes were not analyzed in the present trial, ethnic variability in the gene polymorphisms may affect the differentiation of toxicities. Therefore, *UGT1A1* genotypes should be evaluated before the initiation of treatment regimens including irinotecan at 180 mg/m^2.

Although therapeutic efficacy was not the main interest of the present phase I study, patients treated at dose levels below the RD exhibited high response rates in Step 1 (six out of 10 patients). In Step 2, the objective response rate was 30% at the RD level. Responses were observed in four out of 11 chemotherapy-naïve patients (36%) and three out of 12 pre-treated patients (25%). Previous phase III trials administering

Table IV. *Incidence of toxicities (Step 2).*

Grade of adverse event (NCI-CTCAE version 3.0)	All events	%	Grade≥3	%
Hematological				
Leukopenia	25	93	5	19
Neutropenia	22	81	13	48
Anemia	16	59	1	3
Thrombocytopenia	3	11	0	0
Febrile neutropenia	2	7	2	7
Non-hematological				
Nausea	18	67	2	7
Vomiting	9	33	3	11
Anorexia	18	67	2	7
Diarrhea	9	33	1	3
Stomatitis	12	44	0	0
Alopecia	20	74	0	0
Fatigue	13	48	1	3
Constipation	4	15	0	0
Bilirubin	7	26	0	0
AST/ALT	11	41	0	0

Data are expressed as numbers of patients with the listed grade of toxicity as their maximum. NCI-CTC, National Cancer Institute common toxicity criteria. AST, Aspartate transaminase; ALT, alanine transaminase.

Table V. *Objective tumor response in evaluable patients (Step 1).*

Dose level	CR	PR	SD	PD	ORR (%)
1 (n=4/4)	0	1	1	2	25
2 (n=3/3)	0	3	0	0	100
3 (n=3/3)	0	2	1	0	67
4 (n=3/3)	0	0	2	1	0
5 (n=3/8)	0	1	2	0	33
Total (n=16)	0	7	6	3	44

n=Evaluable/Total patients, ORR, overall response rate.

Table VI. *Objective tumor resoponse (Step 2).*

	n	CR	PR	SD	PD	ORR (%)
Overall	23	3	4	13	3	30
Prior chemotherapy						
No	11	1	3	6	1	36
Yes	12	2	1	7	2	25

ORR, Overall response rate.

FOLFIRI therapy as a first- and second-line chemotherapy for patients with advanced colorectal cancer report response rates from 38-56% (24-26) and 4-16%, respectively (27, 29). In the present trial, the tumor response rate was comparable between patients pre-treated with 5-FU-based chemotherapy and those without prior exposure to chemotherapy.

In conclusion, the RDs of irinotecan and continuous 5-FU infusion in the FOLFIRI regimen in Japanese patients with colorectal cancer are 180 and 2,400 mg/m^2, respectively. These doses are consistent with those in Western countries and global trials. This FOLFIRI regimen is well-tolerated, and toxicities were manageable in Japanese patients.

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