8. Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. *N Engl J Med* 2008;358:1160–74.
9. Ciardiello F, Tortora G. A novel approach in the treatment of cancer: targeting the epidermal growth factor receptor. *Clin Cancer Res* 2001;7:2958–70.
10. Erbitux® (cetuximab). *Package Insert*. New York, NY: ImClone Systems Incorporated. Princeton, NJ: Bristol-Myers Squibb Company. (Revised: 01/2012).
11. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med* 2007;357:2040–8.
12. Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;26:2311–9.
13. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360:1408–17.
14. Siena S, Glynne-Jones R, Adenis A, et al. Reduced incidence of infusion-related reactions in metastatic colorectal cancer during treatment with cetuximab plus irinotecan with combined corticosteroid and antihistamine premedication. *Cancer* 2010;116:1827–37.
15. Wilke H, Glynne-Jones R, Thaler J, et al. Cetuximab plus irinotecan in heavily pretreated metastatic colorectal cancer progressing on irinotecan: MABEL Study. *J Clin Oncol* 2008;26:5335–43.
16. Ishiguro M, Watanabe T, Yamaguchi K, et al. A Japanese post-marketing surveillance of cetuximab (Erbitux®) in patients with metastatic colorectal cancer. *Jpn J Clin Oncol* 2012;42:287–94.

ANTICANCER RESEARCH *34*: 2029-2034 (2014)

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

YUSUKE SASAKI, TETSUYA HAMAGUCHI, TATSUHIRO ARAI, AYUMU GOTO, TAKASHI URA, KEI MURO, YASUHIDE YAMADA, KUNIAKI SHIRAO and YASUHIRO SHIMADA

Gastrointestinal Oncology Division, National Cancer Center Hospital, Tokyo, Japan

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.*

Correspondence to: Tetsuya Hamaguchi, Gastrointestinal Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel: +81 0335422511, Fax: +81 0335453567, e-mail: thamaguc@ncc.go.jp

Key Words: Colorectal cancer, FOLFIRI, irinotecan, Japanese patients, phase 1.

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

0250-7005/2014 $2.00+.40

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.

Acknowledgements

We are grateful to the participating patients and their families. We would like to thank Makiko Shinogi and Hiromi Orita (National Cancer Center Hospital) for administrative work.

References

1 Statistics of Cancer, Center for Information Services, National Cancer Center, Japan http://ganjoho.jp/public/statistics/pub/statistics01.html.

2 Petrelli N, Herrera L, Rustum Y, Burke P, Creaven P, Stule J, Emrich LJ and Mittelman A: A prospective randomized trial of 5-fluorouracil *versus* 5-fluorouracil and high-dose leucovorin *versus* 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. J Clin Oncol 5: 1559-1565, 1987.

3 Poon MA, O'Connell MJ, Moertel CG, Wieand HS, Cullinan SA, Everson LK, Krook JE, Mailliard JA and Tschetter LK: Biochemical modulation of fluorouracil: Evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol 7: 1407-1418, 1989.

4 Piedbois P, Buyse M, Rustum Y, Machover D, Erlichman C, Carlson RW, Valone F, Labianca R, Doroshow JH and Petrelli N: Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol *10*: 896-903, 1992.

5 Sobrero AF, Aschele C and Bertino JR: Fluorouracil in colorectal cancer – a tale of two drugs: implications for biochemical modulation. J Clin Oncol *15*: 368-381, 1997.

6 De Gramont A, Bosset JF, Milan C, Rougier P, Bouche O, Etienne PL, Morvan F, Louvet C, Guilot T, Francois E and Bedenne L: Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: A French Intergroup study. J Clin Oncol *15*: 808-815, 1997.

7 Hsiang YH, Lihou MG and Liu LF: Arrest of replication forks by drug-stabilized topoisomerase I-DNA cleavable complexes as a mechanism of cell killing by camptothecin. Cancer Res *49*: 5077-5082, 1989.

8 Kawato Y, Aonuma M, Hirota Y, Kuga H and Sato K: Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. Cancer Res *51*: 4187-4191, 1991.

9 Cunningham D, Pyrhönen S, James RD, Punt CJA, Hickish TF, Heikkila R, Johannesen TB, Starkhammar H, Topham CA, Awad L, Jacques C and Herait P: Randomised trial of irinotecan plus supportive care *versus* supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet *352*: 1413-1418, 1998.

10 Rougier P, Cutsem E Van, Bajetta E, Niederle N, Possinger K, Labianca R, Navarro M, Morant R, Bleiberg H, Wils J, Awad L, Herait P and Jacques C: Randomised trial of irinotecan *versus* fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet *352*: 1407-1412, 1998.

11 Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL and Miller LL: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 343: 905-914, 2000.

12 Rothenberg ML, Meropol NJ, Poplin EA, Custem E Van and Wadler S: Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. J Clin Oncol *19*: 3801-3807, 2001.

13 Douillard JY, Cunningham D, Roth AD, Navarro M, James PD, Karasek P, Jandik P, tveson T, Carmichael J, Alaki M, Gruia G, Awad L and Rougier P: Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomised trial. Lancet *355*: 1041-1047, 2000.

14 Andre T, Louvet C, Maindrault-Goebel F, Couteau C, Mabro M, Lotz JP, Gilles-Amar V, Krulik M, Carola E, Izrael V and de Gramont A: CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. Eur J Cancer *35*: 1343-1347, 1999.

15 Innocenti F, Undevia SD, Iyer L, Chen PX, Das S, Kocherginsky M, Karrison T, Janisch L, Ramirez J, Rudin CM, Vokes EE and Ratain MJ: Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict risk of severe neutropenia of irinotecan. J Clin Oncol *22*: 1382-1388, 2004.

16 Hoskins JM, Goldberg RM, Qu P, Ibrahim JG and Mcleod HL: UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. J Natl Cancer Inst *99*: 1290-1295, 2007.

17 Beutler E, Gelbart T and Demina A: Racial variability in the UDP-glucuronosyltransferase 1 (*UGT1A1*) promoter: A balanced polymorphism for regulation of bilirubin metabolism? Proc Natl Acad Sci USA *95*: 8170-8174, 1998.

18 Onoue M, Terada T, Kobayashi M, Katsura T, Matsumoto S, Yanagihara K, Nishimura T, Kanai M, Teramukai S, Shimizu A, Fukushima M and Inui K: *UGT1A1**6 polymorphism is most predictive of severe neutropenia induced by irinotecan in Japanese cancer patients. Int J Clin Oncol *14*: 136-142, 2009.

19 Minami H, Sai K, Saeki M, Saito Y, Ozawa S, Suzuki K, Kaniwa N, Sawada J, Hamaguchi T, Yamamoto N, Shirao K, Yamada Y, Ohmatsu H, Kubota K, Yoshida T, Ohtsu A and Saijo N: Irinotecan pharmacokinetics/pharamacodyanmics and *UGT1A* genetic polymorphisms in Japanese; roles of *UGT1A1**6 and *28. Pharmacogenet Genomics *17*: 497-504, 2007.

20 Akiyama Y, Fujita K, Nagashima F, Yamamoto W, Endo H, Sunakawa Y, Yamashita K, Ishida H, Mizuno K, Araki K, Ichikawa W, Miya T, Narabayashi M, Kawara K, Sugiyama M, Hirose T, Ando Y and Sasaki Y: Genetic testing for *UGT1A1**28 and *6 in Japanese patients who receive irinotecan chemotherapy. Ann Oncol *19*: 2089-2090, 2008.

21 Fukuoka M, Negoro S, Niitani H, Furue H, Hasegawa K, Hara Y, Hara N and Taguchi T: A phase I study of weekly administration of CPT-11 in lung cancer. Gan To Kagaku Ryoho *17*: 993-997, 1990.

22 Sakata Y, Shimada Y, Yoshino M, Kambe M, Futatsuki K, Nakao I, Ogawa N, Wakui A and Taguchi T: A late phase II study of CPT-11, irinotecan hydrochloride, in patients with advanced pancreatic cancer. CPT-11 Study Group on Gastrointestinal Cancer. Gan To Kagaku Ryoho *21*: 1039-1046, 1994.

23 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J Natl Cancer Inst *92*: 205-216, 2000.

24 Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C and de Gramont A: FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. J Clin Oncol *22*: 229-237, 2004.

25 Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, Crinò L, Benedetti G, Evangelista W, Fanchini L, Cortesi E, Picone V, Vitello S, Chiara S, Granetto C, Porcile G, Fioretto L, Orlandini C, Andreuccetti M and Masi G: Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: The Gruppo Oncologico Nord Ovest. J Clin Oncol *25*: 1670-1676, 2007.

26 Cutsem E Van, Köhne C-H, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J and Rougier P: Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med *360*: 1408-1417, 2009.

27 Muro K, Boku N, Shimada Y, Tsuji A, Sameshima S, Baba H, Satoh T, Denda T, Ina K, Nishina T, Yamaguchi K, Takiuchi H, Esaki T, Tokunaga S, Kuwano H, Komatsu Y, Watanabe M, Hyodo I, Morita S and Sugihara K: Irinotecan plus S-1 (IRIS) *versus* fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: A randomised phase 2/3 non-inferiority study (FIRIS study). Lancet Oncol *11*: 853-860, 2010.

28 Falcone A, Di Paolo A, Masi G, Allegrini G, Danesi R, Lencioni M, Pfanner E, Comis S, Del Tacca M and Conte P: Sequence effect of irinotecan and fluorouracil treatment on pharmacokinetics and toxicity in chemotherapy-naïve metastatic colorectal cancer patients. J Clin Oncol *19*: 3456-3462, 2001.

29 Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, André T, Chan E, Lordick F, Punt CJ, Strickland AH, Wilson G, Ciuleanu TE, Roman L, Van Cutsem E, Tzekova V, Collins S, Oliner KS, Rong A and Gansert J: Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol *28*: 4706-4713, 2010.

Received December 30, 2013
Revised February 2, 2014
Accepted February 3, 2014

J Cancer Res Clin Oncol (2015) 141:153–160
DOI 10.1007/s00432-014-1783-3

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

A phase 3 non-inferiority study of 5-FU/*l*-leucovorin/irinotecan (FOLFIRI) versus irinotecan/S-1 (IRIS) as second-line chemotherapy for metastatic colorectal cancer: updated results of the FIRIS study

Hirofumi Yasui · Kei Muro · Yasuhiro Shimada · Akihito Tsuji · Shinichi Sameshima · Hideo Baba · Taroh Satoh · Tadamichi Denda · Kenji Ina · Tomohiro Nishina · Kensei Yamaguchi · Taito Esaki · Shinya Tokunaga · Hiroyuki Kuwano · Narikazu Boku · Yoshito Komatsu · Masahiko Watanabe · Ichinosuke Hyodo · Satoshi Morita · Kenichi Sugihara

Received: 20 May 2014 / Accepted: 16 July 2014 / Published online: 9 August 2014

Abstract
Purpose The FIRIS study previously demonstrated non-inferiority of IRIS (irinotecan plus S-1) to FOLFIRI (5-fluorouracil/leucovorin with irinotecan) for progression-free survival as the second-line chemotherapy for metastatic colorectal cancer (mCRC) as the primary endpoint. The overall survival (OS) data were immature at the time of the primary analysis.
Methods Between 30 January 2006 and 29 January 2008, 426 patients with mCRC who failed in first-line chemotherapy were randomly assigned to receive either FOLFIRI or IRIS. After the primary analysis, the follow-up survey was cut off on 29 July 2010, and the final OS data were analysed.
Results With a median follow-up of 39.2 months, the median OS was 17.4 months in the FOLFIRI group and 17.8 months in the IRIS group [hazard ratio (HR) 0.900; 95 % confidence interval (CI) 0.728–1.112]. In the pre-planned subgroup of patients who received prior chemotherapy containing oxaliplatin, the median OS was

H. Yasui (✉)
Division of Gastrointestinal Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan
e-mail: h.yasui@scchr.jp

K. Muro
Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan

Y. Shimada
Division of Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo, Japan

A. Tsuji
Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan

S. Sameshima
Department of Surgery, Dokkyo Medical University Koshigaya Hospital, Koshigaya, Japan

H. Baba
Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

T. Satoh
Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Japan

T. Denda
Department of Gastroenterology, Chiba Cancer Center, Chiba, Japan

K. Ina
Department of Medical Oncology, Nagoya Memorial Hospital, Nagoya, Japan

T. Nishina
Department of Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan

K. Yamaguchi
Department of Gastroenterology, Saitama Cancer Center, Ina-machi, Kitaadachi-gun, Saitama, Japan

T. Esaki
Department of Gastrointestinal and Medical Oncology, National Kyushu Cancer Center, Fukuoka, Japan

S. Tokunaga
Department of Clinical Oncology, Osaka City General Hospital, Osaka, Japan

H. Kuwano
Department of General Surgical Science, Graduate School of Medicine, Gunma University, Maebashi, Japan

12.7 months in the FOLFIRI group and 15.3 months in the IRIS group (HR 0.755; 95 % CI 0.580–0.983).
Conclusions IRIS is non-inferior to FOLFIRI for OS as second-line chemotherapy for mCRC. IRIS can be an option for second-line chemotherapy of mCRC. (ClinicalTrials.gov Number: NCT00284258).

Keywords Colorectal cancer · FIRIS · Irinotecan · IRIS · S-1

Introduction

At present, the combination of 5-fluorouracil (5-FU)/leucovorin (LV) with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) is the mainstream chemotherapy for metastatic colorectal cancer (mCRC) worldwide (O'Neil and Goldberg 2008; National Comprehensive Cancer Network 2014a, b; Tournigand et al. 2004).

In Japan, FOLFOX or FOLFIRI is widely used as the first-line or second-line chemotherapy for mCRC. However, infusional 5-FU-based regimens such as FOLFOX or FOLFIRI are inconvenient because continuous infusion and implantation of an intravenous port system are required. In addition, their use is sometimes complicated by catheter-related infections and thrombosis. Replacement of infusional 5-FU with an oral anticancer drug may be convenient and reduce the burden on patients and healthcare professionals.

In Japan, oral S-1 has been widely used for the treatment of gastrointestinal cancers. In phase 2 studies of IRIS combining S-1 and irinotecan for mCRC, the response rates ranged from 52.5 to 62.5 %, and the median progression-free survival (PFS) was 7.8–8.6 months, suggesting that IRIS may have comparable efficacy to FOLFIRI as a first-line therapy (Goto et al. 2006; Komatsu et al. 2011; Tsunoda et al. 2009; Komatsu et al. 2010: Shiozawa et al. 2010).

The FIRIS study is a phase 3 randomised study to investigate the non-inferiority of IRIS to FOLFIRI, which is a standard second-line chemotherapy for mCRC after failure of fluoropyrimidine chemotherapy with or without oxaliplatin. In the primary analysis, the median PFS was 5.1 months in the FOLFIRI group and 5.8 months in the IRIS group [hazard ratio (HR) 1.077; 95 % confidence interval (CI) 0.879–1.319], demonstrating the non-inferiority of IRIS to FOLFIRI (Muro et al. 2010). Thereafter, in the ESMO Consensus Guidelines for management of patients with colon and rectal cancer, IRIS is listed in the table of the treatment options (Schmoll et al. 2012). However, the survival data of the FIRIS study were immature. In this paper, an updated analysis focusing on overall survival (OS) is reported.

Patients and methods

Study design and treatment

This randomised, open-label, phase 3 study of second-line chemotherapy for patients with mCRC was conducted at 40 institutions in Japan (see "Appendix"). The eligibility criteria and design were described in detail in a previous report (Muro et al. 2010).

The patients were centrally randomised to receive either FOLFIRI or IRIS using the minimisation method with stratification by institution, prior therapy (with oxaliplatin vs. without oxaliplatin), and performance status (PS; 0 vs. 1). In the FOLFIRI group, the patients received *l*-LV (200 mg/m^2) and irinotecan (150 mg/m^2) followed by a bolus injection of 5-FU (400 mg/m^2) on day 1, and then continuous infusion of 5-FU (2,400 mg/m^2) over 46 h, repeated every 2 weeks (4 weeks counted as one course). The dose of irinotecan (150 mg/m^2) given to the FOLFIRI group is the upper limit of the approved dose in Japan (Fuse et al. 2008). The IRIS group received irinotecan (125 mg/m^2) on days 1 and 15 and S-1 [40–60 mg/body, based on the body surface area (BSA): BSA < 1.25 m^2, 40 mg/body; 1.25 m^2 ≤ BSA < 1.5 m^2, 50 mg/body; BSA ≥ 1.5 m^2, 60 mg/body] twice daily for 2 weeks followed by 2 weeks of rest, based on the results of the phase 2 study (Goto et al. 2006). The treatment was continued until one of the following events occurred: disease progression (PD); unacceptable toxicity; or patient's refusal to continue treatment.

The primary objective of the study was to demonstrate the non-inferiority of IRIS to FOLFIRI for PFS.

N. Boku
Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan

Y. Komatsu
Department of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, Sapporo, Japan

M. Watanabe
Department of Surgery, Kitasato University School of Medicine, Sagamihara, Japan

I. Hyodo
Division of Gastroenterology, Tsukuba University Hospital, Tsukuba, Japan

S. Morita
Department of Biostatistics and Epidemiology, Yokohama City University Medical Center, Yokohama, Japan

K. Sugihara
Department of Surgical Oncology, Tokyo Medical and Dental University Graduate School, Tokyo, Japan

The secondary endpoints included OS, response rate, and safety. In addition, pre-planned subgroup analyses were performed.

The protocol of the study was approved by the institutional review board or ethics committee and was conducted in compliance with the Declaration of Helsinki and Japanese ethical guideline for clinical studies. Written informed consent was obtained from all patients participating in the study.

Study assessments

Physical examinations and laboratory tests were performed at baseline and repeated at least every 2 weeks during the treatment. Tumours were assessed at baseline (within 1 month before enrolment), 2, 3, and 4 months after enrolment, and every 2 months thereafter until progression. Progression was defined when any of the following three events occurred: (1) PD based on the response evaluation criteria in solid tumours (RECIST) version 1.0; (2) clinical progression judged by the investigator; or (3) death from any cause without progression. PFS was calculated from the date of randomisation to the date of the events described above.

OS was calculated from the date of randomisation to the date of death from any cause. Surviving patients, including those lost to follow-up, were censored at the date of last confirmation of survival. Toxicity was evaluated based on the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0).

Statistical analysis

The intent-to-treat (ITT) population consisted of all randomised patients, and the per-protocol set (PPS) population was defined as the ITT population excluding patients who violated protocols to a considerable extent, including major protocol inclusion/exclusion criteria or treatment protocols.

The primary endpoint of PFS was assumed to be 4 months in both groups. By defining a 1-month shorter PFS with IRIS than with FOLFIRI as the acceptance limit for non-inferiority, which was also the minimum difference detected by monthly image examinations, a non-inferiority margin of 1.333 was selected. After the required number of events was calculated with a one-sided α of 0.025 and a power of 80 %, a target sample size of 400 patients was selected.

For the primary endpoint of PFS and the secondary endpoint of OS, the HR for IRIS to FOLFIRI and its 95 % CI were calculated to show the non-inferiority of IRIS to FOLFIRI, respectively. Furthermore, Bayesian analyses were carried out to assess the robustness of these preliminary results. Post hoc analyses for posterior probabilities with log HR within the range of 1.333–1.15 (a stricter threshold) were performed (Spiegelhalter et al. 1994).

For the primary analysis, the collection of the primary endpoint PFS data was cut off on 31 December 2008 and the number of confirmed events was 389 (Muro et al. 2010). The final analysis was performed on 29 July 2010 (2.5 years after the last patient was enrolled, as pre-specified in the protocol).

Subgroup analyses were pre-planned to determine whether therapeutic efficacy interacted with sex, age, histological type, PS, and prior chemotherapy with or without oxaliplatin. PFS and OS were estimated using the Kaplan–Meier method. The 95 % CI for the median PFS and OS was calculated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982). All p values were two-sided. All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC, USA). This study is registered with ClinicalTrials.gov (Number: NCT00284258).

Results

Patient populations

A total of 426 patients from 40 institutions in Japan were enrolled from January 2006 to January 2008, and randomised to receive either FOLFIRI or IRIS ($n = 213$ in each group; Fig. 1). The PPS population consisted of 203 patients in the FOLFIRI group and 198 in the IRIS group. All patients who received a study treatment [FOLFIRI ($n = 211$) and IRIS ($n = 210$)] were included in the safety evaluation. The baseline characteristics were well balanced between the two groups, as previously reported (Muro et al. 2010).

Treatment

The median number of courses of the protocol treatment was 4.0 (range 1–27) and 4.0 (range 1–23) in the FOLFIRI and IRIS groups, respectively. The median dose intensity relative to the planned dose intensity was irinotecan 78.3 %, bolus 5-FU 76.9 %, and infusional 5-FU 81.5 % in the FOLFIRI group, and irinotecan 78.3 % and S-1 88.9 % in the IRIS group. Treatments were discontinued because of PD in 71.8 % of the FOLFIRI group ($n = 153$) and 67.1 % of the IRIS group ($n = 143$). Treatment discontinuation owing to adverse events was more frequently observed in the IRIS group ($n = 49$, 23.0 %) than in the FOLFIRI group ($n = 28$, 13.1 %). Overall, 179 (84.8 %) patients in the FOLFIRI group and 184 (87.6 %) patients in the IRIS group required at least one dose delay or dose reduction at some point during the treatment course.

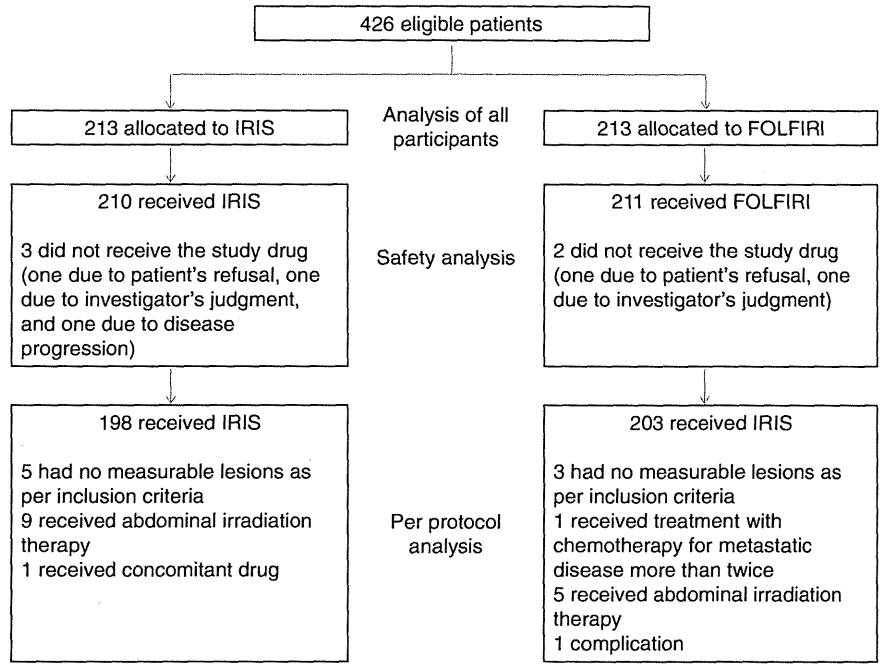

Fig. 1 Consort diagram. *IRIS* irinotecan plus S-1, *FOLFIRI* infusional 5-fluorouracil, folinic acid, and irinotecan

Third-line chemotherapy after failure of the protocol treatment in the second-line therapy was given to 168 (78.9 %) patients in the FOLFIRI group and 153 (71.8 %) patients in the IRIS group. In these patients, molecularly targeted agents were concomitantly used in 58 (27.2 %) patients (bevacizumab, 45; cetuximab, 17) in the FOLFIRI group and 52 (24.4 %) patients (bevacizumab, 38; cetuximab, 16) in the IRIS group, and no marked difference in the use of these agents was evident between the two groups (Table 1).

Table 1 Cancer treatment after discontinuation of the study treatment

Treatment	FOLFIRI *n* (%)	IRIS *n* (%)
No	45 (21.1)	60 (28.2)
Yes	168 (78.9)	153 (71.8)
Bevacizumab		
FOLFOX + bevacizumab	33 (15.5)	29 (13.6)
FOLFIRI + bevacizumab	19 (8.9)	12 (5.6)
5-FU/LV + bevacizumab	8 (3.8)	6 (2.8)
Cetuximab		
FOLFIRI + cetuximab	0 (0)	1 (0.5)
Irinotecan + cetuximab	16 (7.5)	13 (6.1)
FOLFOX	60 (28.2)	61 (28.6)
FOLFIRI	9 (4.2)	25 (11.7)
5-FU/LV	7 (3.3)	10 (4.7)
Irinotecan	8 (3.8)	20 (9.4)
S-1	35 (16.4)	7 (3.3)
Irinotecan + S-1	16 (7.5)	3 (1.4)
Operation	12 (5.6)	11 (5.2)
Radiation therapy	29 (13.6)	18 (8.5)
Other	48 (22.5)	45 (21.1)

FOLFIRI infusional 5-fluorouracil, folinic acid, and irinotecan, *IRIS* irinotecan plus S-1, *FOLFOX* 5-fluorouracil, LV, and oxaliplatin, *5-FU* 5-fluorouracil, *LV* leucovorin

Overall survival

As of 29 July 2010 when the data collection was finally cut off, 352 deaths (FOLFIRI, 178; IRIS, 174) were confirmed with a median follow-up of 39.2 months. A total of 125 censored cases resolved from the last cut-off that we reported. The median OS was 17.4 months in the FOLFIRI group and 17.8 months in the IRIS group (HR 0.900; 95 % CI 0.728–1.112; $p = 0.003$ for a non-inferiority margin of 1.333; Fig. 2a). In the PPS population, the median OS was 17.4 months in the FOLFIRI group and 17.4 months in the IRIS group (HR 0.905; 95 % CI 0.728–1.126). The Bayesian posterior probabilities that the HR of IRIS relative to FOLFIRI would be <1.333 and <1.15 were calculated to be >99.9 % and >98.7 %, respectively.

Progression-free survival

When the data collection was finally cut off, 412 events including an increase of 23 events from the primary analysis were confirmed. The median PFS was 5.1 months in the FOLFIRI group and 5.8 months in the IRIS group. In the ITT population, the HR for IRIS to FOLFIRI was

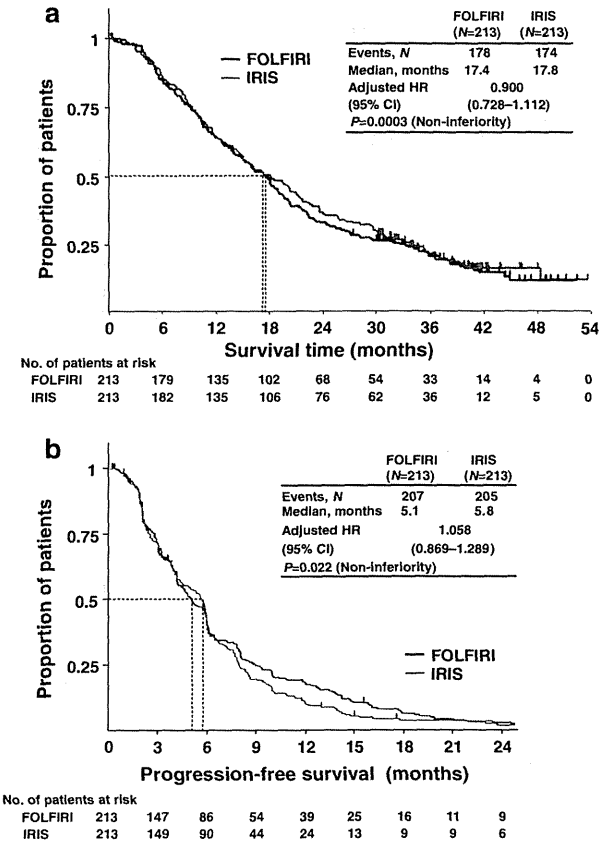

Fig. 2 OS (**a**) and PFS (**b**) in the intention-to-treat population. *IRIS* irinotecan plus S-1, *FOLFIRI* infusional 5-fluorouracil, folinic acid, and irinotecan, *HR* hazard ratio, *CI* confidence interval

1.058 (95 % CI 0.869–1.289; $p = 0.022$) and consistent with the primary analysis (Fig. 2b). In the PPS population, the median PFS was 5.1 months in the FOLFIRI group and 5.7 months in the IRIS group (HR 1.035; 95 % CI 0.843–1.271), being consistent with the primary analysis.

Subgroup analyses

Figure 3 shows the results of the subgroup analyses for OS. Except for the interaction of prior chemotherapy containing oxaliplatin (yes vs. no) and therapeutic effect, no interaction was observed between sex (male vs. female), age (<65 vs. 65–75 years), histological type (adenocarcinoma, well differentiated vs. moderately differentiated vs. poorly differentiated), or PS (0 vs. 1), and the therapeutic effect of IRIS was comparable to that of FOLFIRI.

In the subgroups of patients treated with FOLFIRI ($n = 128$) or IRIS ($n = 129$) who had received prior chemotherapy containing oxaliplatin, the median OS was 15.3 months in the IRIS group and 12.7 months in the FOLFIRI group (adjusted HR 0.755; 95 % CI 0.580–0.983), showing better survival in the IRIS group than in the FOLFIRI group (Fig. 4a). On the other hand, in the subgroups of patients treated with FOLFIRI ($n = 85$) or IRIS ($n = 84$) who had received prior chemotherapy without oxaliplatin, the median OS was more favourable in the FOLFIRI group than in the IRIS group (26.9 vs. 23.6 months; adjusted HR 1.229; 95 % CI 0.866–1.745) (Fig. 4b).

Safety

The results of the updated safety analysis were very similar to those previously reported (Muro et al. 2010). Briefly, specific adverse events were haematological toxicity (grade 3 or 4 neutropenia), which was observed in 52.1 % of the FOLFIRI group and 36.2 % of the IRIS group, and non-haematological toxicity (grade 3 diarrhoea), which was observed in 4.7 % of the FOLFIRI group and 20.5 % of the IRIS group. One treatment-related death from hypotension caused by shock was reported in the FOLFIRI group within 28 days after the end of the protocol treatment, while no treatment-related deaths were reported in the IRIS group.

Discussion

We conducted a phase 3 randomised study to compare FOLFIRI and IRIS as second-line chemotherapies for patients with mCRC. The primary analysis demonstrated the non-inferiority of IRIS to FOLFIRI for PFS as the primary endpoint. The secondary endpoints of OS and response rate were also equivalent between the two groups (Muro et al. 2010), but the data were immature with many cases censored at the primary analysis. In this updated analysis, data obtained 2.5 years after the end of the enrolment period (as pre-specified in the protocol) were included. The non-inferiority of IRIS to FOLFIRI for PFS as the primary endpoint was re-confirmed, and non-inferiority for OS was also demonstrated. In addition, the probabilities of HR < 1.333 and HR < 1.15, which are stricter non-inferiority margins for OS, were estimated to be >99.9 and >98.7 %, respectively, using Bayesian analyses. Our study results are highly robust.

When our study was started, FOLFOX was already one of the standard treatments worldwide, but oxaliplatin had just been launched and was rarely used in an adjuvant setting in Japan. Actually, 85 (39.9 %) patients in the FOLFIRI group and 84 (39.4 %) patients in the IRIS group had received prior chemotherapy without oxaliplatin. Most of these patients received prior chemotherapy in an adjuvant setting including tegafur-uracil with or without LV (27 patients in the FOLFIRI group and 32 in the IRIS group) or 5-FU/LV (11 patients in the FOLFIRI group and 7 in the IRIS group).

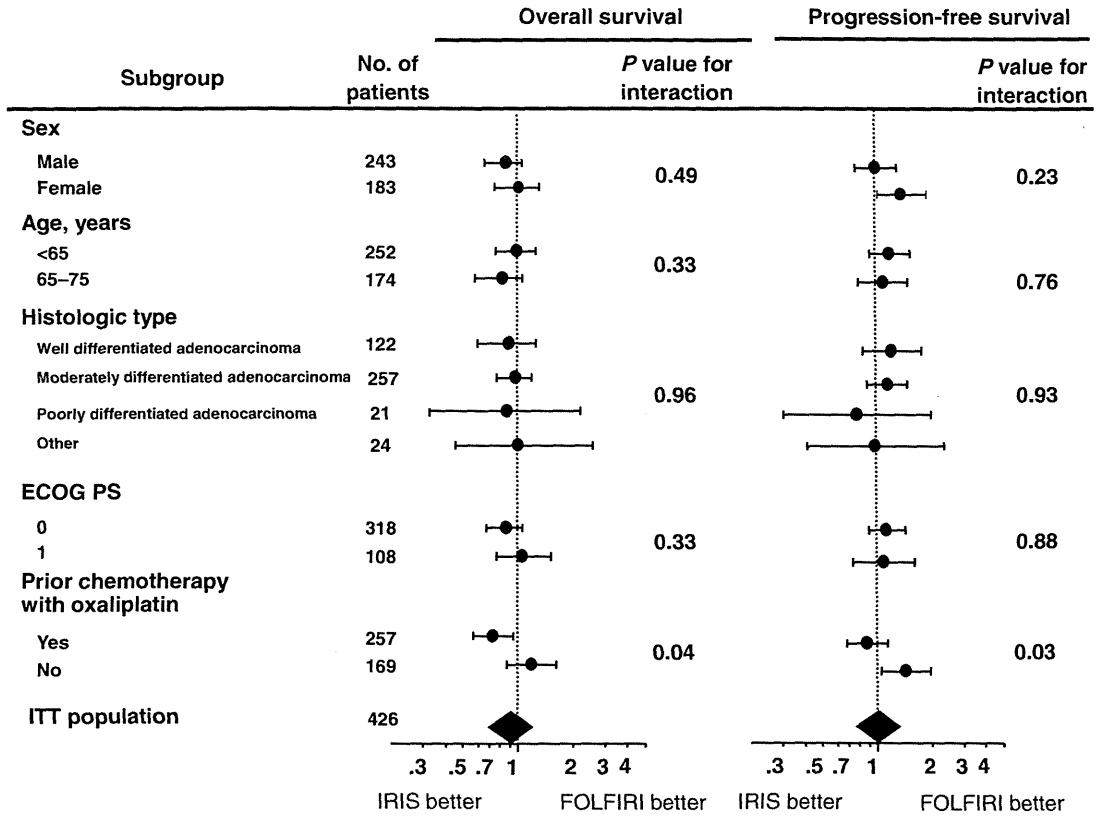

Fig. 3 Subgroup analyses of OS and PFS in the intention-to-treat (ITT) population. *IRIS* irinotecan plus S-1, *FOLFIRI* infusional 5-fluorouracil, folinic acid, and irinotecan

In the subgroup of patients who had received prior oxaliplatin, the adjusted HR for OS of IRIS to FOLFIRI was 0.755 (95 % CI 0.580–0.983), suggesting that IRIS might prolong the survival of patients who failed in first-line chemotherapy with oxaliplatin-containing regimens, compared with FOLFIRI. On the other hand, in the subgroup of patients who had received prior chemotherapy without oxaliplatin, the median OS was longer in the FOLFIRI group than in the IRIS group (adjusted HR 1.229; 95 % CI 0.866–1.745). Interactions between prior chemotherapy and therapeutic effects in the two groups may need to be considered.

There are some possible reasons for the interactions. Resistance to 5-FU/LV shared by patients receiving first-line FOLFOX and second-line FOLFIRI may be overcome to some extent by the dihydropyrimidine dehydrogenase (DPD) inhibitor contained in S-1. On the other hand, it is also speculated that cross-resistance to DPD inhibitory agents may be partly overcome by bolus 5-FU/LV in patients receiving FOLFIRI (Baba et al. 2012), considering the fact that many patients in the subset without prior oxaliplatin received adjuvant chemotherapy with DPD inhibitory agents as a prior therapy. However, further studies, including basic studies, are needed to clarify this finding.

In recent phase 3 trials of molecularly targeted agents used in second-line chemotherapy regimens, the median OS was reported to be 10.7–14.5 months in groups treated with anti-EGFR antibodies. The survival data in the present study seemed to be consistent with the survival data in these recent studies of molecularly targeted agents (Sobrero et al. 2008; Peeters et al. 2010).

In conclusion, this study has demonstrated that IRIS is non-inferior to FOLFIRI not only for PFS, but also for OS as second-line chemotherapy for mCRC. Thus, IRIS should be considered as a treatment option. In particular, IRIS may be a favourable regimen for patients previously treated with chemotherapy containing oxaliplatin. To further improve the outcome, future studies of both first-line and second-line therapies are warranted to evaluate IRIS in combination with molecularly targeted agents such as bevacizumab, cetuximab, and panitumumab.

Acknowledgments We thank all of the patients, their families, and the institutions involved in this study (see "Appendix"). The authors also thank Yuh Sakata, Yasuo Ohashi, and Nobuyuki Yamamoto for the Independent Data Monitoring Committee, and Atsushi Ohtsu, Yasuaki Arai, and Junji Tanaka for the Independent Central Review Committee for their contributions to this report. The authors dedicate this

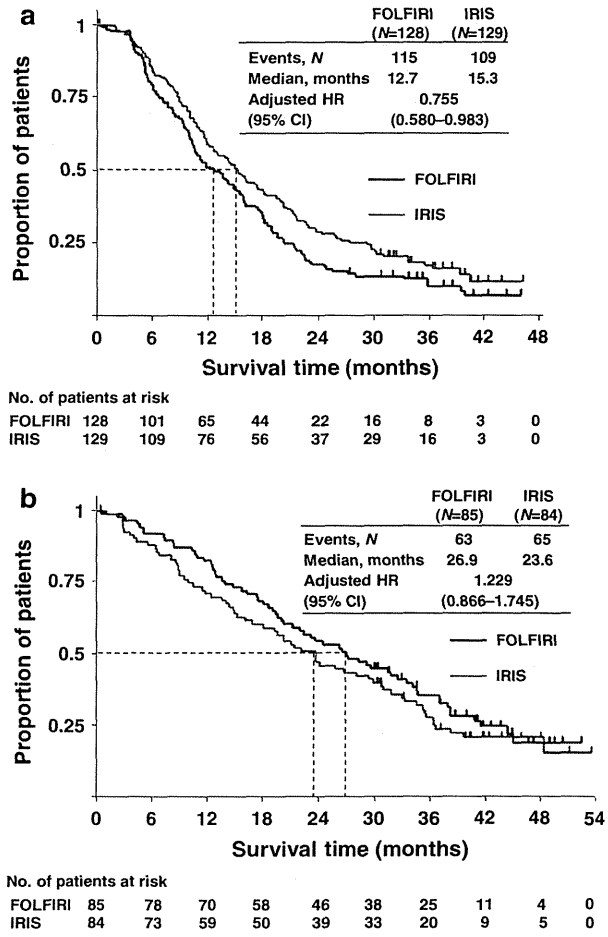

Fig. 4 Survival according to prior chemotherapy with oxaliplatin (**a**) or without oxaliplatin (**b**). *IRIS* irinotecan plus S-1, *FOLFIRI* infusional 5-fluorouracil, folinic acid, and irinotecan, *HR* hazard ratio, *CI* confidence interval

article to the memory of Prof. Hiroya Takiuchi, who contributed to the conception and design of this study. The senior academic authors designed the trial in cooperation with the study sponsors. The sponsors provided funding and organisational support, collected data, and performed analyses, but did not undertake any data interpretation. This report was written by the corresponding author (with additional input from the other authors), who had unrestricted access to the raw study data, gives assurance for the accuracy and completeness of the reported analyses, and had final responsibility for the decision to submit for publication. This work was funded by Taiho Pharmaceutical Co. Ltd., Japan, and Daiichi Sankyo Co. Ltd., Japan.

Conflict of interest The authors declare no conflict of interest.

Appendix (participating institutes): FIRIS Study Group

List of participating institutions in order of patient recruitment:

Shizuoka Cancer Center (Shizuoka, Japan); Aichi Cancer Center Hospital (Nagoya, Japan); National Cancer Center Hospital (Tokyo, Japan); Kochi Health Sciences Center (Kochi, Japan); Gunma Prefectural Cancer Center (Gunma, Japan); Kumamoto University Hospital (Kumamoto, Japan); Kinki University School of Medicine (Osaka, Japan); Chiba Cancer Center (Chiba, Japan); Nagoya Memorial Hospital (Nagoya, Japan); National Hospital Organization Shikoku Cancer Center (Matsuyama, Japan); Saitama Cancer Center (Saitama, Japan); Osaka Medical College Hospital (Takatsuki, Japan); National Kyushu Cancer Center (Fukuoka, Japan); Osaka City General Hospital (Osaka, Japan); Gunma University Graduate School of Medicine (Maebashi, Japan); Hokkaido University Hospital Cancer Center (Sapporo, Japan); National Hospital Organization Kyoto Medical Center (Kyoto, Japan); Keio University Hospital (Tokyo, Japan); Kansai Rosai Hospital (Hyogo, Japan); Tokyo Medical and Dental University (Tokyo, Japan); Osaka Medical Center for Cancer and Cardiovascular Diseases (Osaka, Japan); Aomori Prefectural Central Hospital (Aomori, Japan); Showa University Toyosu Hospital (Tokyo, Japan); Minoh City Hospital (Osaka, Japan); Saiseikai Kumamoto Hospital (Kumamoto, Japan); Toyama University Hospital (Toyama, Japan); National Hospital Organization Kagoshima Medical Center (Kagoshima, Japan); Tonan Hospital (Sapporo, Japan); Kanagawa Cancer Center (Yokohama, Japan); Niigata Cancer Center Hospital (Niigata, Japan); Saku Central Hospital (Nagano, Japan); Hyogo Cancer Center (Hyogo, Japan); Hiroshima University Hospital (Hiroshima, Japan); Tomakomai Nissho Hospital (Hokkaido, Japan); Aichi Cancer Center Aichi Hospital (Aichi, Japan); National Hospital Organization Nagoya Medical Center (Nagoya, Japan); Kobe University Hospital (Kobe, Japan); Yamagata Prefectural Central Hospital (Yamagata, Japan); Yokohama City University Hospital (Yokohama, Japan); and Kitasato University East Hospital (Kanagawa, Japan).

References

Baba H, Watanabe M, Okabe H et al (2012) Upregulation of ERCC1 and DPD expressions after oxaliplatin-based first-line chemotherapy for metastatic colorectal cancer. Br J Cancer 107:1950–1955

Brookmeyer R, Crowley J (1982) A confidence interval for the median survival time. Biometrics 38:29–41

Fuse N, Doi T, Ohtsu A et al (2008) Safety of irinotecan and infusional fluorouracil/leucovorin (FOLFIRI) in Japan: a retrospective review of 48 patients with metastatic colorectal cancer. Int J Clin Oncol 13:144–149

Goto A, Yamada Y, Yasui H et al (2006) Phase II study of combination therapy with S-1 and irinotecan in patients with advanced colorectal cancer. Ann Oncol 17:968–973

Komatsu Y, Yuki S, Fuse N et al (2010) Phase 1/2 clinical study of irinotecan and oral S-1 (IRIS) in patients with advanced gastric cancer. Adv Ther 27:483–492

Komatsu Y, Yuki S, Sogabe S et al (2011) Phase II study of combined treatment with irinotecan and S-1 (IRIS) in patients with inoperable or recurrent advanced colorectal cancer (HGCSG0302). Oncology 80:70–75

Muro K, Boku N, Shimada Y et al (2010) Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study). Lancet Oncol 11:853–860

National Comprehensive Cancer Network (2014a) NCCN Clinical Practice Guidelines in Oncology: Colon Cancer, version 3.2014. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed May 20 2014

National Comprehensive Cancer Network (2014b) NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer, version 3.2014. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed May 20 2014

O'Neil BH, Goldberg RM (2008) Innovations in chemotherapy for metastatic colorectal cancer: an update of recent clinical trials. The Oncol 13:1074–1083

Peeters M, Price TJ, Cervantes A et al (2010) Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 28:4706–4713

Schmoll HJ, Van Cutsem E, Stein A et al (2012) ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol 23:2479–2516

Shiozawa M, Akaike M, Sugano N et al (2010) A phase II study of combination therapy with irinotecan and S-1 (IRIS) in patients with advanced colorectal cancer. Cancer Chemother Pharmacol 66:987–992

Sobrero AF, Maurel J, Fehrenbacher L et al (2008) EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol 26:2311–2319

Spiegelhalter DJ, Freedman LS, Parmar MKB (1994) Bayesian approaches to randomized trials. J R Stat Soc 157:357–387

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

Tsunoda A, Yasuda N, Nakao K et al (2009) Phase II study of S-1 combined with irinotecan (CPT-11) in patients with advanced colorectal cancer. Oncology 77:192–196

Ann Surg Oncol (2015) 22:908–915
DOI 10.1245/s10434-014-4094-7

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – COLORECTAL CANCER

A Multicenter Phase II Trial of mFOLFOX6 Plus Bevacizumab to Treat Liver-Only Metastases of Colorectal Cancer that are Unsuitable for Upfront Resection (TRICC0808)

Hiroyuki Uetake, MD, PhD[1], Masamichi Yasuno, MD, PhD[2], Megumi Ishiguro, MD, PhD[1], Shingo Kameoka, MD, PhD[3], Yasuhiro Shimada, MD, PhD[4], Keiichi Takahashi, MD, PhD[5], Toshiaki Watanabe, MD, PhD[6], Kei Muro, MD, PhD[7], Hideo Baba, MD, PhD[8], Junji Yamamoto, MD, PhD[9], Nobuyuki Mizunuma, MD, PhD[10], Hiroshi Tamagawa, MD, PhD[11], Izumi Mochizuki, MD, PhD[12], Yusuke Kinugasa, MD, PhD[13], Takashi Kikuchi, PhD, DPhil[14], and Kenichi Sugihara, MD, PhD[15]

[1]Department of Translational Oncology, Graduate School, Tokyo Medical and Dental University, Tokyo, Japan; [2]Department of Surgery, Tokyo Metropolitan Hiroo Hospital, Tokyo, Japan; [3]Department of Surgery II, Tokyo Women's Medical University, Tokyo, Japan; [4]Division of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [5]Colorectal Surgical Division, Department of Surgery, Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, Tokyo, Japan; [6]Department of Surgical Oncology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [7]Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [8]Department of Gastroenterological Surgery, Graduate School of Medical Science, Kumamoto University, Kumamoto, Japan; [9]Department of Surgery, National Defense Medical College, Tokorozawa, Japan; [10]Gastroenterological Center, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [11]Department of Surgery, Osaka General Medical Center, Osaka, Japan; [12]Department of Surgery, Iwate Prefectural Central Hospital, Morioka, Japan; [13]Gastrointestinal Surgery Division, Shizuoka Cancer Center, Shizuoka, Japan; [14]Department of Statistical Analysis, Translational Research Informatics Center, Kobe, Japan; [15]Department of Surgery Oncology, Tokyo Medical and Dental University, Tokyo, Japan

ABSTRACT

Background. A phase II clinical trial was conducted on colorectal cancer patients with only liver metastases (focal diameter exceeds 5 cm or the number of liver metastases is ≥5; H2·H3) to evaluate the liver resection rate and safety after 6 cycles of mFOLFOX6+bevacizumab (BV) therapy.

Methods. mFOLFOX6+BV therapy was applied for 6 cycles to the patients with H2·H3 liver only metastasis. Hepatectomy was considered after the sixth cycle as a rule, and was performed if possible. The primary endpoint was the curative hepatectomy rate (R0 resection rate).

Results. Forty-six patients were registered and 45 patients were included in the efficacy analysis. Of the 19 patients rated as unresectable before therapy, 18 completed 6 cycles of mFOLFOX6+BV therapy and subsequently underwent hepatectomy (16 were R0-resected). Of the 26 initially unresectable patients, 6 underwent hepatectomy (4 were RO-resected). The overall R0 resection rate was 44.4% (20/45). Chemotherapy-associated grade 3 or higher adverse events included neutrophil decreased (17.4%) and leukocyte decreased (8.7%), fatigue (6.5%) etc. Only hypertension (6.5%) and venous thromboembolism (2.2%) were BV-associated grade 3 or higher adverse events. Among the 25 patients who underwent hepatectomy, intraoperative/postoperative complications included grade 3 wound infections (2 cases), biloma, delayed wound healing and intraperitoneal abscess (each 1 case).

Conclusions. In colorectal cancer patients with liver-only metastases, mFOLFOX6+ BV therapy yielded a high hepatectomy rate and a high percentage of initially unresectable and subsequently resectable cases. The chemotherapy associated adverse events and hepatectomy complications were both within acceptable ranges.

First Received: 25 February 2014;
Published Online: 3 December 2014

H. Uetake, MD, PhD
e-mail: h-uetake.srg2@tmd.ac.jp

Although the 5-year survival rate after stage I–III colorectal cancer curative resection is high (81 %), the 5-year survival rate for stage IV colorectal cancers is unsatisfactory (13 %),

which comprise 15–16 % of all colorectal cancers.[1] Liver metastases are observed in approximately 60 % of all stage IV colorectal cancer cases, and hepatic recurrence occurs in 9–13 % of all colorectal cancer cases after curative resection.[2]

Currently, hepatectomy is the most reliable and curative means of liver metastasis treatment and, thus, is the first-line treatment in cases with resectable liver metastases. In a domestic study of 763 cases of liver metastasis, factors at the time of hepatectomy adversely affecting prognosis after surgery for hepatic metastasis included residual tumor, extrahepatic metastasis, hepatic metastasis of degree H3 (maximum metastatic focal diameter >5 cm and number of metastases ≥5) stipulated by the Japanese classification of colorectal carcinoma,[3] number of metastases of four or more, pathology of hepatic metastasis of poorly differentiated adenocarcinoma, resection margin of <10 mm, and carcinoembryonic antigen value higher than normal preoperative and 1-month postoperative.[4]

To improve the prognosis of colorectal cancer patients, it is important to improve the liver metastasis treatment outcomes. Systemic chemotherapy for advanced/recurrent colorectal cancer has advanced markedly in recent years, following the clinical introduction of two powerful cytotoxic anti-cancer drugs (irinotecan and oxaliplatin[5]) and molecule-targeted drugs such as anti-vascular endothelial growth factor (VEGF)[6,7] and anti-epidermal growth factor receptor (EGFR) antibody preparations.[8–10] With these advances in systemic chemotherapy, the prognosis is expected to improve if perioperative chemotherapy is applied to resectable liver metastases of colorectal cancer to improve the curative resection rate by reducing the preoperative tumor size and suppressing preoperative micrometastasis.[11] When treating unresectable liver metastases of colorectal cancer, "conversion therapy" has been applied to reduce the tumor size and facilitate resection via preoperative chemotherapy.[12–16] Adam et al.[12] analyzed 2,047 cases of liver metastases of colorectal cancer and reported 5-year survival rates after hepatectomy for 335 initially resectable cases and 138 initially unresectable cases that became resectable after chemotherapy. The rates were 48 % for the former group and 33 % for the latter.[12]

We therefore conducted a phase II clinical study to evaluate the usefulness of preoperative chemotherapy in colorectal cancer patients with liver-only metastases in whom initial surgery seemed unsuitable (maximum metastatic focal diameter >5 cm or number of metastases ≥5; H2/H3[3]).

PATIENTS AND METHODS

Study Design

This was a multicenter single-arm phase II clinical study. The primary endpoint was the curative hepatectomy rate (R0 resection rate relative to the entire study population. Secondary endpoints were the hepatectomy rate, curative hepatectomy rate (R0 resection rate relative to all resected cases), percentage of initially resectable and subsequently unresectable cases, percentage of initially unresectable and subsequently resectable cases, hepatectomy safety, recurrence rate, and survival period.

The trial registration was as follows: University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) UMIN000010209.

Patients

This study was conducted in compliance with the Declaration of Helsinki and the Ethical Guidelines on Clinical Studies after its approval by the ethics committees of all participating facilities. Written consent was obtained from all patients before registration.

The following were major inclusion criteria:

1. Histopathologically established colorectal cancer (adenocarcinoma);
2. Underwent curative primary tumor resection ≥28 days before registration;
3. No distant metastases or recurrences, excepting liver metastases;
4. Maximum liver metastatic focal diameter >5 cm or number of liver metastases ≥5 (H2/H3);
5. No history of chemotherapy for colorectal cancer (noting that the history of postoperative adjuvant chemotherapy without oxaliplatin was acceptable if 3 months or more had passed after the final treatment);
6. No history of thermocoagulation or freezing therapy for liver metastasis (e.g., radiofrequency cauterization);
7. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–1; and
8. Age of 20–80 years.

All patients underwent baseline liver metastatic focal evaluations before initiating chemotherapy, using contrast-enhanced hepatic computed tomography (CT), superparamagnetic iron oxide-magnetic resonance imaging (SPIOMRI), or gadolinium ethoxybenzyl-magnetic resonance imaging (Gd-EOB-magnetic resonance imaging [MRI]).

Protocol Treatment

Each registered patient began to receive modified FOLFOX6 (mFOLFOX6) plus bevacizumab (BV) therapy within 2 weeks after registration. On day 1, bevacizumab (5 mg/kg), levohorinate (200 mg/m^2), 5-fluorouracil ([5-FU]; 400 mg/m^2), and oxaliplatin (85 mg/m^2) were rapidly injected intravenously, followed by a 46-hour continuous intravenous infusion of 5-FU (2,400 mg/m^2). Each cycle of

the treatment steps was repeated every 2 weeks. Before the start of each cycle, a physical examination by a physician and a blood test were performed and considered indispensable. Dose adjustments were made based on the adverse event grades in accordance with the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0.

After three treatment cycles, the first diagnostic imaging evaluation was performed. As a rule, diagnostic imaging evaluations used the same modality during the pretreatment evaluation. Antitumor efficacy was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0. For cases in which the diagnostic imaging evaluation after the third cycle was progressive disease (PD) or stable disease [(SD); tumor growth may make resection impossible], hepatectomy was performed if the metastasis was rated as resectable or the protocol treatment was discontinued if the metastasis was rated as unresectable. In cases rated as complete response (CR), partial response (PR), or SD, mFOLFOX6 plus BV therapy was applied for three additional cycles. During the sixth cycle, only mFOLFOX6 was administered (and BV was not used).

After the sixth cycle, the second diagnostic imaging evaluation was performed to determine whether hepatectomy would be possible. If deemed "resectable," hepatectomy was performed. If "unresectable," the protocol treatment was immediately discontinued. The following are major criteria for determining the possibility of hepatectomy after three cycles:

1. The liver metastatic focus is judged resectable without leaving any residual macroscopic tumor;
2. Residual hepatic function after resection can be preserved sufficiently (noting that residual liver volume after resection ideally would be 40 % or more of the cancer-free liver volume before resection; and in cases with hepatic dysfunction [e.g., alcoholic liver damage], the maximum residual liver volume is determined in accordance with each facility's criteria for indications of hepatectomy);
3. ECOG PS of 0–1; and
4. Other criteria for indications of hepatectomy at each participating facility are satisfied.

No restrictions were imposed on the procedures adopted for hepatectomy. Cases that underwent radiofrequency cauterization were considered R2 cases. Patients who underwent R0 hepatectomy were followed without further treatment until recurrence was detected. No rule was set regarding post therapy for cases that underwent R1 or R2 hepatectomy and those in which the protocol treatment was discontinued on the basis of an "unresectable" judgment.

Statistical Considerations

This study mainly concerns the examination of the null and alternative hypotheses about the primary endpoint. These hypotheses are written as follows:

The null hypothesis is that the true R0 resection rate is equal to 30 % or the threshold R0 resection rate. The alternative hypothesis is that the true R0 resection rate is higher than 30 %.

Assuming that the expected R0 resection rate and the threshold R0 resection rate are 45 and 30 %, respectively, we estimated that 64 subjects were required for analysis with a significance level of 5 % (one-tailed) and a power of 80 %. Considering the potential number of dropouts from this study, the targeted number of subjects for this study was decided to be 70.

For the evaluation of percentages and rates listed in the endpoints, except the recurrence rate and survival period, 95 % confidence intervals were used. The Kaplan–Meier curve shall evaluate the recurrence rate and survival period in the secondary endpoints.

We also used descriptive statistics to summarize the patient profiles and observations including background variables, pretreatment baseline liver metastasis status, chemotherapy implementation status, adverse event frequency and severity, responses to chemotherapy, status of hepatectomy implementation post hepatectomy complications, and rated responses to chemotherapy.

For the analysis of the endpoints, except the recurrence rate and survival period, data up to 9 months later than the registration were provided for the analysis. One- and 3-year data after the registration are being collected to calculate the recurrence rate and survival period and therefore the results are not reported in this paper.

Our data analysis was performed with SAS version 9.3 (SAS Institute Inc., Cary, NC)

RESULTS

Between April 2009 and October 2011, 46 patients were registered in this study at 25 domestic facilities and began to receive treatment. One patient was found to be ineligible after the start of treatment (history of hepatectomy) and was excluded from the efficacy analysis set (EAS), but included in the safety analysis set (SAS).

Patient Characteristics

Tables 1 and 2 summarized the patient background variables for the SAS ($n = 46$) and the baseline statuses of the liver metastatic foci in 46 patients. The median number of liver metastases was six, and this number differed significantly between the cases rated as resectable (five) and

TABLE 1 Patients characteristics (SAS, $n = 46$)

Gender	Male	27	(58.7 %)
	Female	19	(41.3 %)
Age, years	Median (range)	62.5 (39–80)	
Body surface area, m^2	Median (range)	1.6 (1.2–2.0)	
BMI	Median (range)	22.1 (15.9–29.0)	
PS	0	43	(93.5 %)
	1	3	(6.5 %)
Past history of liver diseases	(−)	44	
	(+)	2[a]	
Primary tumor location	Colon	32	(69.6 %)
	Rectosigmoid	7	(15.2 %)
	Rectum	7	(15.2 %)
Depth of primary tumor invasion (TNM 7th)	T1–T2	2	(4.4 %)
	T3	20	(43.5 %)
	T4	24	(52.1 %)
LN metastasis of primary tumor	N(−)	13	(28.3 %)
	N(+)	33	(71.7 %)

BMI body mass index, *LN* lymphnode, *PS* performance status, *SAS* safety analysis set

[a] Hepatitis B, liver resection

TABLE 2 Liver metastases (met) at baseline (SAS, $n = 46$)

	Assessment at baseline	Initially resectable ($n = 19$)	Initially unresectable ($n = 27$)	Total ($n = 46$)
Synchronous		15 (78.9 %)	24 (88.9 %)	39 (84.8 %)
Metachronous		4 (21.1 %)	3 (11.1 %)	7 (15.2 %)
Maximum diameter of liver met (cm)	Median (range)	5.3 (1.6–12.2)	5.7 (1.8–12.4)	5.5 (1.6–12.4)
No. of liver met	Median (range)	5 (1–10)	10 (1–23)	6 (1–23)
	1–4	8 (42.1 %)	5 (18.5 %)	13 (28.3 %)
	5–10	11 (57.9 %)	12 (44.4 %)	23 (50.0 %)
	≥11		10 (37.0 %)	10 (21.7 %)
Reason for initially unresectable	Insufficient remnant liver volume		24	
	Major vascular invasion		2	
	Others		1	

met metastasis, *No* number, *SAS* safety analysis set

those rated as unresectable before treatment (ten) ($p = 0.0137$).

Chemotherapy Delivery

Figure 1 outlines the EAS course of treatment ($n = 45$). All 45 patients included in EAS received mFOLFOX6 plus BV therapy. For one patient, the protocol treatment was discontinued at the end of the first cycle because of the patient's refusal. At the end of the third cycle, two cases were rated as PD. The protocol treatment for these cases was discontinued at that time. The other 42 patients continued to receive mFOLFOX6 plus BV therapy. After the fourth cycle, chemotherapy was terminated and hepatectomy was performed in one patient because of the patient's desire. The other 41 patients completed the six planned treatment cycles (chemotherapy completion rate, 91.1 %). The patient excluded from EAS completed six cycles of mFOLFOX6 plus BV therapy.

The number of patients who received each chemotherapy cycle and the relative dose intensities for each drug among the SAS ($n = 46$) are shown in Table 3. Each drug maintained a high-dose intensity (median, ≥90 %).

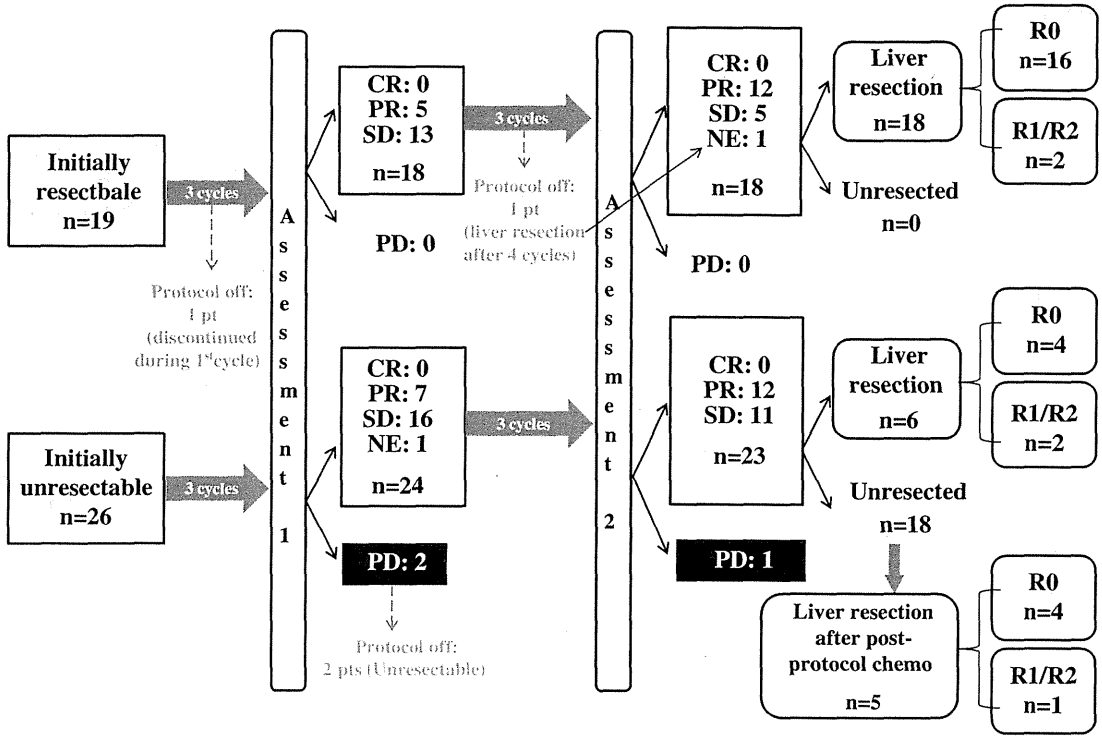

FIG. 1 Summary of treatment results (efficacy analysis set [EAS], $n = 45$). *CR* complete response, *NE* not evaluated, *PD* progressive disease, *PR* partial response, *SD* stable disease

TABLE 3 Relative dose intensity of chemotherapy (SAS, $n = 46$)

Median %	1st Cycle	2nd Cycle	3rd Cycle	4th Cycle	5th Cycle	6th Cycle
No. of pts. treated	46	45	45	43	42	42
BV	98.4	98.5	98.3	97.8	98.5	–
LV	96.9	97.4	96.8	96.1	97.3	98.1
L-OHP	94.4	95.3	93.8	93.7	94.3	95.3
5-FU iv	96.8	97.1	96.8	96.0	97.0	97.1
5-FU div	98.6	99.1	98.4	98.5	99.0	99.2

Dose intensity (mg/m^2/2 weeks) = total dose (/body/2 weeks)/duration (days) × 14 (days)

5-FU 5-fluorouracil, *BV* bevacizumab, *L-OHP* oxaliplatin, *LV* leucovorin, *No* number, *pts* patients, *SAS* safety analysis set

Adverse Chemotherapy-Associated Events

Table 4 shows the adverse events and their incidence rates during chemotherapy for SAS ($n = 46$). Deep vein thrombosis had an incidence of 2.2 % when analyzing BV-related grade 3 or higher adverse events. There were no chemotherapy-related deaths.

Responses to Chemotherapy

The best overall responses among the EAS ($n = 45$) were PR in 25 cases (55.6 %), SD in 17 cases (37.8 %), PD in two cases (4.4 %), and not evaluable (NE) in one case (2.2 %), with an overall response rate of 55.6 % (95 % CI 40.0–70.3 %). For the 19 initially resectable cases, the response rate was 68.4 % (26.3 and 63.2 % after the third and sixth cycles, respectively). For the 26 initially unresectable cases, the response rate was 46.2 % (26.9 and 46.2 % after the third and sixth cycles, respectively). PD was only observed in two of the 26 initially unresectable cases; both were rated this way because of the appearance of new lesions. Figure 2 graphically represents a waterfall plot analysis of the best overall responses of 44 of 45 patients that comprised the EAS, excluding one patient in whom the evaluation was omitted because of protocol treatment discontinuation during the first cycle. The median change in