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ORIGINAL ARTICLE

Histological liver injury and surgical outcome after FOLFOX followed by a hepatectomy for colorectal liver metastases in Japanese patients

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Abstract
Background This study was performed to clarify the influence of preoperative chemotherapy on liver function and the correlation between histological hepatic injury and the postoperative outcome in patients with colorectal liver metastases who underwent a hepatic resection.
Methods Twenty-seven patients who underwent a hepatic resection for colorectal liver metastases were included. Fifteen patients with initially unresectable colorectal liver metastases who were able to undergo a tumor resection after FOLFOX (oxaliplatin plus fluorouracil and leucovorin, with a mean number of 7.7 cycles) were compared to 12 patients who underwent a hepatectomy with no preoperative chemotherapy. The postoperative mortality, morbidity, changes in liver function tests, and pathology of the resected liver were examined.
Results Preoperative FOLFOX therapy was significantly associated with the macroscopic appearance of oxaliplatin-associated blue liver ($p = 0.02$), and a tendency toward sinusoidal dilatation (33.3% in the FOLFOX group versus 8.3% in the no-chemotherapy group, $p = 0.056$). Preoperative liver function tests showed that the albumin and indocyanine green retention rate at 15 min (ICG-R15) test values were significantly worse after FOLFOX therapy; however, intraoperative events, postoperative liver function test values, and morbidity rates were similar in the two groups. There was no postoperative mortality in any of the patients.
Conclusions Although preoperative FOLFOX administration in patients with colorectal liver metastases caused macroscopic blue liver, microscopic sinusoidal dilatationin the liver parenchyma, and a significant decrease in liver function, there was no increase in the morbidity and mortality rates, in comparison to findings in patients without preoperative chemotherapy.

Keywords Colorectal liver metastases · Oxaliplatin · Fluorouracil and leucovorin (FOLFOX) · Sinusoidal dilatation · Hepatic resection · Postoperative morbidity

Abbreviations

FU	Fluorouracil
LV	Leucovorin
FOLFOX	Chemotherapy with oxaliplatin plus fluorouracil and leucovorin
FOLFIRI	Chemotherapy with CPT-11 plus fluorouracil and leucovorin
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
L-OHP	Oxaliplatin

Introduction

Liver metastases are among the most common metastases from colorectal cancer leading to death from this disease.

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Depending on the stage of the primary colorectal cancer, liver metastases occur in 20%–70% of the patients [1, 2]. A hepatic resection remains the only treatment that can yield 5-year survival rates of 20%–50% [3–6], if the liver metastases can be curatively resected in patients without nonresectable extrahepatic disease. Recently, various new therapeutic drugs have been introduced. These include irinotecan (CPT-11), a topoisomerase I inhibitor [7], and oxaliplatin, a platinum derivative with significant activity in colorectal cancer [8]. These drugs can yield high response rates of 34%–50% with a median survival of 15–19.5 months in patients with stage IV colorectal cancer [9, 10]. With such high response rates, 10%–13% of primary unresectable colorectal liver metastases can become resectable [11–13]. In Japan, a CPT-11-based regimen known as "FOLFIRI" (CPT-11 plus fluorouracil and leucovorin [LV]), or an oxaliplatin-based regimen ("FOLFOX"; oxaliplatin plus fluorouracil and LV) have became widely used for patients with metastatic colorectal cancer.

Of note, the widely used chemotherapeutic agents, 5-fluorouracil (5-FU) and its derivatives, as well as CPT-11, have been reported to induce steatosis of the liver [14, 15]. In addition, CPT-11 and oxaliplatin can be associated with liver injury [16–20]. Vauthey et al. [17] reported a close association between preoperative CPT-11 administration and steatohepatitis. Rubbia-Brandt et al. [20] and Karoui et al. [21] have suggested that an oxaliplatin-based regimen could induce sinusoidal obstruction.

The aim of this study was to clarify the influence of preoperative chemotherapy using FOLFOX on morphological changes in the liver parenchyma as well as changes in liver function and surgical outcome in Japanese patients with liver metastases from colorectal cancer.

Patients and methods

Patients

Between April 2005 and November 2007, forty-one patients underwent hepatic resection for liver metastases from colorectal carcinoma at the Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Japan. Seven patients who underwent a hepatic resection with a preoperative chemotherapy regimen other than FOLFOX within 6 months of the beginning of the study were excluded. Of the 22 patients who received FOLFOX, 2 patients who had a hepatectomy more than 4 months after the last FOLFOX cycle were excluded because sinusoidal dilatationdisappeared in the 4 months after the last chemotherapy cycle [20]. Also, 5 patients who had received FOLFOX followed by other chemotherapy were also excluded, to evaluate the effect of only FOLFOX on the postoperative course. Twenty-seven patients were therefore included in the present study (17 men and 10 women). The median age was 61 years (range, 39–83 years). The primary tumor location was the colon in 17 patients (60%) and the rectum in 10 patients (40%). Liver metastases were synchronous in 13 patients (52%). The preoperative mean carcinoembryonic antigen (CEA) value was 241 ng/ml ± 476 (range, 2.3–3157 ng/ml). Patients were classified into two groups; the FOLFOX group and the no-chemotherapy group. The liver metastases that were initially considered to be unresectable in all patients treated with FOLFOX subsequently became resectable after chemotherapy.

Protocol of systemic chemotherapy

The FOLFOX4 regimen administered before a hepatectomy included LV + 5-FU + oxaliplatin (FOLFOX4; day 1: oxaliplatin 85 mg/m^2, LV 100 mg/m^2, 5-FU 400 mg/m^2 bolus, 5-FU 600 mg/m^2 continuous infusion for 22 h. Day 2: LV 100 mg/m^2, 5-FU 400 mg/m^2 bolus, 5-FU 600 mg/m^2 continuous infusion for 22 h; and a repeat of this regimen every 2 weeks) [22].

Clinical assessments and the surgical procedure

All patients underwent pre- and postoperative assessments including liver function tests; blood counts; coagulation tests; and measurement of serum urea, creatinine, and electrolytes. The indocyanine green retention rate at 15 min (ICG-R15) and the ratio of liver to heart-plus-liver radioactivity of Tc- GSA (Garactosyl Serum Albumin) 15 min (LHL15) were evaluated preoperatively. Among the parameters of liver function, the most impaired values during the postoperative hospital days were analyzed (prothrombin time, albumin, total bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT]). The correlation between the number of FOLFOX cycles, as well as the total dose of oxaliplatin, and liver function damage was also evaluated.

The resectability of the hepatic lesions was assessed by abdominal ultrasound and chest and abdominal computed tomography (CT) scans after every three cycles. Unresectable liver metastases were defined as follows: when it was difficult to maintain a tumor-free margin during the resection of the entire tumor; when invasion to the entire hepatic vein was observed; when invasion to the bifurcation of the bilateral main Glissonian sheath was found; when invasion to the inferior vena cava behind the caudate lobe was observed; when invasion to the right or left Glissonian sheath and hepatic vein of another lobe was observed; and finally when resection of more than 65% of the liver parenchyma was required.

The tumor regression effect was evaluated by CT according to the Response Evaluation Criteria in Solid Tumors (RECIST). During the surgery, a complete examination of the liver was performed with intraoperative ultrasonography to determine the number and the location of the lesions and their anatomical relationship to the vascular system. Liver transection was performed using an ultrasonic dissector. Biliary and vascular pedicles were secured by ligation and clipping, and hemostasis of the cut surface of the liver was completed with a dissecting sealer (Valley Laboratories, Boulder, CO, USA) or a VIO soft coagulation system (ERBE; Elektromedizin, Germany). The duration of the surgery, the amount of blood loss, blood transfusion requirements (packed red cell units), the type of liver resection, and the vascular interruption time were recorded individually.

Pathology examination

Several samples of nontumorous tissue from the resected liver specimen were taken and fixed, paraffin-embedded, and stained with hematoxylin and eosin. The samples were blindly investigated by three pathologists (I.K., B.Y., and H.K.). A macroscopic blue liver was defined as a bluish discoloration of the surface of the liver with edema and a spongiform consistency [23]. The presence of sinusoidal dilatationwas recorded using the Rubbia-Brandt Score [20] as follows: 0, absent; 1, mild (centrilobular involvement limited to one-third of the lobular surface); 2, moderate (centrilobular involvement extending to two-thirds of the lobular surface); 3, severe (complete lobular involvement). Liver steatosis was graded from 0 to 3: absent ~5% (grade 0), 5%–33% of hepatocytes (grade 1), between 33% and 66% (grade 2), and more than 66% (grade 3). Steatohepatitis was evaluated using the nonalcoholic fatty liver disease (NAFLD) activity score (NAS): score 0 to 2, not NASH; 3 to 4, borderline NASH; and more than 5, NASH [24].

In addition, peliosis, hemorrhagic centrilobular necrosis, and regenerative nodular hyperplasia were evaluated as previously described [25]. The correlation between histological hepatic injury and the number of FOLFOX cycles, degree of pathological effects on the tumor, adverse effects, surgical insult, and postoperative morbidity were also evaluated.

Statistical analysis

Quantitative data were expressed as means ± SD. Comparisons between the groups were analyzed using the χ^2 test with the Yates correction, or Students' t test for quantitative and qualitative variables as appropriate, and comparisons of the pathological scores for steatosis, steatohepatitis, and sinusoidal dilatationbetween two groups were analyzed using the Mann–Whitney U-test. Correlations between the Rubbia-Brandt score and the vascular exclusion time, the number of cycles of chemotherapy, preoperative liver function, intraoperative blood loss, and postoperative days; as well as the correlations between the total dose of oxaliplatin and liver function damage were analyzed using the Spearman rank correlation. Statistical significance was recognized at a p value of 0.05 in all analyses. Statistical analyses were done using the StatView 5.0 software package (Abacus Concepts, Calabasas, CA, USA).

Table 1 Preoperative characteristics of patients with and without preoperative chemotherapy

Preoperative	Preoperative chemotherapy Group (n = 15)	No-chemotherapy Group (n = 12)	p value
Age, in years: median (range)	65 (53–81)	56 (39–79)	**0.038**
Sex (M/F)	10/5	7/5	0.953
BMI (kg/m^2)	24.1 ± 3.6	23.5 ± 2.4	0.616
WBC (/μl)	4640 ± 1861	5725 ± 1099	0.087
Hb (g/dL)	11.9 ± 1.8	12.2 ± 1.7	0.674
Plt (/μl)	18.3 ± 4.6	26.8 ± 10.8	**0.011**
Prothrombin time (%)	101.5 ± 11	109.2 ± 7.7	0.056
Albumin (g/dl)	3.8 ± 0.4	4.1 ± 0.3	**0.012**
Serum bilirubin (mg/dl)	0.7 ± 0.3	0.6 ± 0.2	0.661
AST (U/L)	26.4 ± 8.5	25.4 ± 16	0.684
ALT (U/L)	25.9 ± 12	25.3 ± 16	0.912
Preoperative ICG-R15 (%)	14.4 ± 6.3	6.8 ± 3.2	**0.001**
Asialo scintigraphy (LHL15)	0.933 ± 0.25	0.926 ± 0.31	0.034
No. of FOLFOX cycles	7.7 ± 2.1	–	
Duration of FOLFOX (months)	4.1 ± 1.2	–	
No. of days after last FOLFOX	37 ± 20 (median 30)	–	

Values are means ± SD

BMI body mass index, *Hb* hemoblobin, *Plt* platelets, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ICG-R15* indocyanine green retention rate at 15 min, *FOLFOX* chemotherapy with oxaliplatin plus fluorouracil and leucovorin

Results

Patients, tumors, and surgical procedures

The clinical characteristics of the 27 patients in the FOLFOX group ($n = 15$) and the no-chemotherapy group ($n = 12$) are summarized in Table 1. In the FOLFOX group, the median age of the patients was significantly higher, and platelet counts, serum albumin level, and ICG-R15 were significantly worse in comparison to those in the no-chemotherapy group (Table 1). The mean preoperative tumor size after FOLFOX was significantly smaller, and synchronous liver metastases were more frequent than in the no-chemotherapy group. The number of metastases was higher in the FOLFOX group (5.9 ± 5.6 vs. 2.4 ± 2.2), but the difference was not significant (Table 2).

Table 2 Preoperative characteristics of liver metastases in patients with and without preoperative chemotherapy

	Preoperative chemotherapy Group ($n = 15$)	No-chemotherapy Group ($n = 12$)	p value
Tumor size (mm)	34.6 ± 17	66.7 ± 43	0.013
Number of metastases	5.9 ± 5.6	2.4 ± 2.2	0.054
Primary site, colon/rectum	10/5	7/5	0.952
Synchronous/ metachronous	11/4	3/9	0.03
CEA (ng/ml) mean (range)	206.6 (1.2–2428)	285.4 (1.1–3157)	0.791

Values are means ± SD

CEA carcinoembryonic antigen

Table 3 Intraoperative parameters in patients with and without preoperative chemotherapy

	Preoperative chemotherapy Group ($n = 15$)	No-chemotherapy Group ($n = 12$)	p value
Resection type hemi liver/section/partial	3/7/5	5/2/5	0.210
Vascular interruption time (min)			
Total	21.0 ± 31	30.0 ± 33	0.453
Partial	58.9 ± 70	24.0 ± 60	0.185
Blood loss (mean ± SD) (ml)	435 ± 247	383 ± 458	0.714
No. of patients requiring blood transfusion (%)	15.4%	10.0%	0.999
Operative time (min)	501 ± 92	448 ± 180	0.323

Values are means ± SD

The liver resections included 7 right hepatectomies or more, 1 left hepatectomy, and 9 sectionectomies. Partial resections were performed in combination with wedge resections in 10 patients. Radiofrequency ablation (RFA) was additionally performed in three patients in the FOLFOX group, and in one in the no-chemotherapy group. Vascular interruption was performed during surgery in 22 of the 27 patients. No significant differences were observed between the two groups in the types of hepatic resection, vascular interruption times, operative times, blood loss, or the percentages of patients requiring blood transfusions (Table 3).

Pathological findings

The pathological examinations in the nontumorous liver are summarized in Table 4. The frequency of macroscopic "blue liver" was significantly higher in the FOLFOX group. No steatosis of more than grade 2 was observed in the patients in the FOLFOX group. There were no significant differences between the groups in the NAS scores for steatohepatitis. Steatohepatitis (NAS >5) was observed in only two patients (14%), who were in the no-chemotherapy group. Sinusoidal dilatation (Rubbia-Brandt Score >2) was seen in 5 of 15 patients (33.3%) in the FOLFOX group, and a tendency toward a higher score for sinusoidal dilatationwas observed in the FOLFOX group (Table 4; Fig. 1). No significant correlation was observed between the Rubbia-Brandt score and the vascular exclusion time, the number of cycles of chemotherapy, intraoperative blood loss, and the postoperative days; peliosis, hemorrhagic centrilobular necrosis, and regenerative nodular hyperplasia were not detected in either group.

Postoperative course

No significant difference was observed between the two groups in postoperative liver function test values (Table 5). There was no postoperative mortality. Postoperative complications occurred in two (1 aspiration pneumonia, 1 biliary fistula requiring drainage >1 month) of the 15 patients in the FOLFOX group and three (1 intestinal hemorrhage, 2 biliary fistula requiring drainage >1 month) of the 12 patients in the no-chemotherapy group (Table 6). There was no significant difference in the duration of postoperative hospital stay between the two groups.

Discussion

The use of preoperative chemotherapeutic agents has numerous theoretical benefits; however, the effects of these agents on the underlying liver parenchyma remain unclear.

Table 4 Pathological features of the nontumorous liver in patients with and without chemotherapy

	Preoperative chemotherapy Group ($n = 15$)	No-chemotherapy Group ($n = 12$)	p value
Macroscopic findings			
Blue liver (positive/negative)	**7/8**	**0/12**	**0.020**
Microscopic findings			
Steatosis; grade 0/1/2/3	9/6/0/0	8/2/2/0	0.768
NAFLD activity score (NAS) 0–2/3–4/5	9/6/0	10/0/2	0.302
Sinusoidal dilatation; Rubbia-Brandt classification 0/1/2/3	3/7/4/1	6/5/1/0	0.056
Hemorrhagic centrilobular necrosis	0	0	
Regenerative nodular hyperplasia	0	0	

Values are means ± SD

NAFLD nonalcoholic fatty liver disease

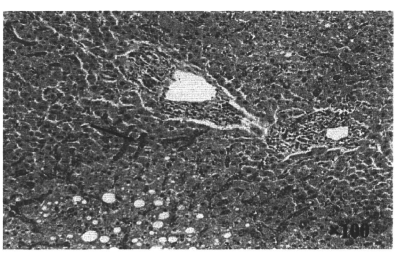

Fig. 1 Sinusoidal dilatation and congestion in a patient who received chemotherapy with oxaliplatin plus fluorouracil and leucovorin (FOLFOX). Only scattered macrovesicular steatosis is present. Compare the zone with sinusoidal dilatation (*arrow*) to the normal parenchyma in the *left lower quadrant*. H&E ×100

Table 5 Postoperative liver function in patients with and without chemotherapy

	Preoperative chemotherapy Group ($n = 15$)	No-chemotherapy Group ($n = 12$)	p value
Postoperative value[a] (mean ± SD)			
Prothrombin time (%)	64 ± 12	72 ± 16	0.158
Albumin (g/dl)	3.0 ± 0.4	3.2 ± 0.4	0.297
Total bilirubin (mg/dl)	1.4 ± 0.7	1.6 ± 0.8	0.505
AST (U/L)	798 ± 400	535 ± 405	0.105
ALT (U/L)	644 ± 403	509 ± 365	0.370
Prothrombin time (%)	64 ± 12	72 ± 16	0.158

Values are means ± SD

[a] The most impaired value of the postoperative hospital stay

Some reports have shown that preoperative chemotherapy had no influence on either liver function or the risk of liver resection [21, 26, 27]. In the present study there was no patient who could not undergo a hepatectomy because of liver injury after chemotherapy. However, the liver function values, including the serum albumin levels and ICG-R15 levels, were significantly worse in comparison to those in the no-chemotherapy group. The administration of FOLFOX may influence the preoperative laboratory data, although the total dose of oxaliplatin did not correlate with liver function damage.

It has recently been reported that new chemotherapeutic agents could cause pathological changes in the liver parenchyma, such as sinusoidal dilatation due to FOLFOX, and chemotherapy-associated steatohepatitis (CASH) due to FOLFIRI. Sinusoidal dilatation (Rubbia-Brandt score >grade 2) was observed in up to 63% of patients who received preoperative chemotherapy [28]. Karoui et al. [29] reported that sinusoidal dilatationwas present in 49% of patients in their chemotherapy group (only 25% in the control group, $p = 0.005$), although the result was not stratified by the type of chemotherapy regimen, and the correlation between the type of chemotherapeutic agent and the pathological changes was not evaluated. Vauthey et al. [17] demonstrated that a chemotherapeutic regimen with or without oxaliplatin was a key factor in the development of sinusoidal dilatation, but Aloia et al. [25] reported that 19% (10/52) of the patients administered an oxaliplatin-containing regimen showed sinusoidal alteration (vasodilatation and congestion), as opposed to a rate of 12% (2/17) of the patients who did not receive such a regimen. In the present study, blue liver was observed in 7 of the 15 patients in the FOLFOX group ($p = 0.02$). Sinusoidal dilatation (>grade 2) was detected in 5 of the 15 patients (33.3%) in the FOLFOX group, and the proportion of patients with high-grade sinusoidal dilatationwas greater in comparison with that in the no-chemotherapy group.

Recently, the efficacy of bevacizumab in combination with chemotherapy has been demonstrated, in the first BEAT study [30]. Furthermore, it was reported that

Table 6 Postoperative morbidity and mortality in patients with and without chemotherapy

	Preoperative chemotherapy Group ($n = 15$)	No-chemotherapy Group ($n = 12$)	p value
Postoperative events (%)			
Any complications	2 (13%)	3 (25%)	0.770
	Aspiration pneumonia (1)	Hemorrhage (1)	
	Bile leakage (1)	Bile leakage (2)	
Reoperation	0 (0%)	0 (0%)	
Postoperative hospital stay (mean ± SD) (days)	26 ± 28	18 ± 12	0.300
Postoperative mortality	0 (0%)	0 (0%)	

Values are means ± SD

bevacizumab improved the pathological response, while also protecting against hepatic injury including sinusoidal dilatation [31]. We also did not encounter sinusoidal dilatationin any patients (0 of 8 patients) after the administration of FOLFOX combined with bevacizumab (data not shown).

Venoocclusive disease (VOD) of the liver, including sinusoidal dilatation, is a clinical syndrome in patients with blood transplantation or bone marrow transplantation; the syndrome is a result of liver damage caused by pretransplant radiation and chemotherapy [29]. The clinical course of severe VOD frequently progresses with lethal results. However, as previously reported, oxaliplatin-containing chemotherapy causes sinusoidal dilatationwithout such severe complications [17, 25].

Blue liver and sinusoidal dilatationmay cause an increased amount of bleeding during a hepatic resection for colorectal liver metastases. Karoui et al. [29] reported that sinusoidal dilatation was detected in 49% of patients in their chemotherapy group, but there was no impact of the chemotherapy on the amount of intraoperative blood transfusion (3 ± 1.9 packed red cell units). Aloia et al. [25] reported that patients who received oxaliplatin-based chemotherapy before hepatic resection for colorectal liver metastases were more likely to receive intraoperative RBC transfusions. They did not address the relationship between sinusoidal dilatation (FU/LV 30%, FU/LV/L-OHP 19%) and oxaliplatin. Although the presence of surgical necrosis, hemorrhagic centrilobular necrosis, and regenerative nodular hyperplasia in the nontumor-bearing liver after systemic chemotherapy has been reported to be significantly related to oxaliplatin regimens, these pathological changes were not observed in either group in the present study. Perioperative transfusions are reported to be a risk factor for poor outcome after a liver resection for metastatic colorectal cancer [32]. In the present study, the mean blood loss in the FOLFOX group was 435 ml and the RBC transfusion rate was 15.4%; these findings were comparable to those in the no-chemotherapy group. No increased risk was encountered in regard to intraoperative blood loss and RBC transfusion due to preoperative FOLFOX administration. Recent advances in surgical techniques and perioperative management might reduce the risk of liver resections and contribute to better prognoses. In recent series of reports of hepatic resection for colorectal liver metastases, the postoperative mortality was less than 0–4% [33, 34]. Postoperative morbidity (including transient liver failure, hemorrhage, subphrenic abscess, and biliary fistula) occurs in 20%–40% of patients [33–37]. In the present study, the use of new devices (a dissecting sealer and a VIO soft coagulation system) during liver transection might have contributed to the reduced blood loss, and thus made it possible to perform safe liver resection despite the significant preoperative liver function damage.

Morbidity after a hepatectomy is correlated with the number of cycles of preoperative chemotherapy, but not with the type of chemotherapeutic agent [21]. A postoperative morbidity rate of 61.5% has been reported when more than 10 cycles of chemotherapy were administered. In the present study, an average of 7.7 cycles (range, 5–10 cycles) of FOLFOX were administered before the hepatic resections. Although three patients in the FOLFOX group received 10 cycles of chemotherapy, the postoperative liver function was approximately equal to that in the no-chemotherapy group, and no postoperative mortality was encountered. The mean number of FOLFOX cycles was less than that reported by Karoui et al. [29], and this difference may have contributed to the lower morbidity in our study (13%). In the present study, an average of 7.7 cycles of FOLFOX was administered to initially unresectable patients. We found that FOLFOX could be safely administered without any severe adverse effects to thus obtain a curative hepatic resection. We promptly performed the resection as soon as the tumors were determined to be resectable.

Recently, a correlation between sinusoidal injury and postoperative morbidity has been reported [38]. Sinusoidal injury was significantly associated with decreased liver functional reserve before a hepatectomy, and increased postoperative morbidity. The preoperative ICG-R15 values

were higher, and the number of postoperative hospital days tended to be longer in the oxaliplatin-based chemotherapy group in that study [38]. In contrast, no positive correlation between sinusoidal dilatationand morbidity was recognized in the present study. Scoggins et al. [39] reported the safety of preoperative chemotherapy for colorectal liver metastases in a large number of cases, and their findings were similar to those in a previous study; their study, however, included various chemotherapeutic regimens. In the present study, we attempted to clarify the effect of preoperative FOLFOX alone on the nontumoral hepatic parenchyma of patients with initially unresectable colorectal metastases in comparison to the findings in patients without any preoperative chemotherapy.

In contrast to FOLFOX, FOLFIRI administration caused steatohepatitis and it was also associated with an increase in the 90-day mortality after hepatic surgery [17]. Moreover, a higher curative resection rate was shown with the FOLFOX 6 first-line regimen than with FOLFIRI in the randomized GERCOR study [40]. From these results, we chose FOLFOX as the first-line therapy for unresectable colorectal liver metastases.

In conclusion, the FOLFOX regimen influenced the preoperative laboratory data, and caused gross blue liver and histological sinusoidal dilatationin the background liver; nevertheless, the surgical outcomes and postoperative mortality and morbidity rates in the FOLFOX group were equivalent to those in the no-chemotherapy group. FOLFOX can be safely administered as preoperative chemotherapy for Japanese patients with initially unresectable colorectal liver metastases.

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ORIGINAL ARTICLE

Phase II study of motesanib in Japanese patients with advanced gastrointestinal stromal tumors with prior exposure to imatinib mesylate

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Abstract
Purpose Motesanib (AMG 706) is a multitargeted anticancer agent with an inhibitory action on the human vascular endothelial growth factor receptor, the platelet-derived growth factor receptor, and the cellular stem-cell factor receptor (KIT). The aim of this single-arm phase II clinical study was to assess the efficacy and safety of single-agent motesanib in Japanese patients with advanced gastrointestinal stromal tumors with prior exposure to imatinib mesylate.
Methods All patients had experienced progression or relapse while undergoing with imatinib as 400 mg/day or higher. The patients were administered 125 mg of motesanib once daily. The primary endpoint was overall response. Efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumor, and safety was assessed according to the Common Terminology Criteria for Adverse Events (version 3).
Results Of 35 enrolled and treated patients, no patient showed a complete response, and one patient showed a partial response (PR). Seven had stable disease (SD) for at least 24 months, two of whom continued to have SD for more than 2 years. The median progression-free survival time was 16.1 weeks. Motesanib was well tolerated; commonly reported treatment-related adverse events were hypertension, diarrhea, and fatigue. Anemia was the only hematological toxicity that was reported.
Conclusions One patient showed PR, and seven patients showed SD more than 24 weeks. Motesanib was found to be safe and well tolerated. The observed toxicities were consistent with Phase I study findings.

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Keywords Motesanib · Angiogenesis inhibitor · Gastrointestinal stromal tumor (GIST)

Introduction

Gastrointestinal stromal tumor (GIST) is a rare stromal neoplasm that predominantly arises from the muscularis propria layers, representing the most common mesenchymal tumor of the gastrointestinal tract. Although the primary therapy for nonmetastatic GIST is surgical resection, there still remain unresectable cases of advanced or metastatic GIST. Unresectable GISTs are resistant to conventional chemotherapy and radiotherapy [1]. Before imatinib mesylate was introduced in clinical practice, the prognosis for patients with unresectable GIST was dismal, with a median survival period of 22 months [2].

The critical transforming and oncogenic mechanisms of GISTs are activating mutations in the stem-cell factor receptor, KIT tyrosine kinase [3]. About 5% of GISTs are caused by activating mutations of the platelet-derived growth factor receptor alpha (PDGFRA), and are independent of *c-kit* mutations [4]. The *c-kit* and PDGFRA mutations appear to be alternative and mutually exclusive oncogenic mechanisms in GIST.

Imatinib mesylate blocks the constitutively activated form of KIT in GISTs, and has dramatically improved the outcome for patients with unresectable GIST [5]. Treatment with imatinib mesylate results in partial response (PR) or stable disease (SD) in approximately 80% of patients with advanced or metastatic GIST [6], and the 2-year survival rate of these patients is reported to be 70% [7].

However, approximately 10–15% of advanced GIST patients will suffer a progressive disease (PD) despite treatment with imatinib mesylate. Many of the patients who initially responded to imatinib mesylate therapy experience tumor progression after an average of 2 years of treatment [7, 8].

Sunitinib is an orally administered receptor tyrosine kinase (RET) inhibitor that targets multiple kinases and is used as a second-line treatment for patients with imatinib-resistant or -intolerant GIST. A Phase III double-blind, placebo-controlled trial comparing sunitinib with placebo showed that the time to progression was significantly longer in the sunitinib group than in the placebo group (6.3 versus 1.5 months). Adverse reactions, though observed, were acceptable [9]. However, despite initial response or stabilization, the disease developed resistance in most patients after approximately 7 months. Because no therapies are available for patients with GIST once imatinib and sunitinib fail, there exists a need for alternative agents that block the signaling pathways in GIST cells.

Motesanib is a novel, synthetic, small molecule that strongly and selectively inhibits vascular endothelial growth factor receptors 1, 2, and 3, as well as the cellular KIT, the platelet-derived growth factor receptor (PDGFR), and the glial-derived nerve growth factor family ligand RET. The safety and pharmacokinetic (PK) profile of motesanib were evaluated in a Phase I, monotherapy, open-label, dose-finding study [10]. In this study, motesanib showed clinical activity in patients with advanced refractory solid tumors; SD was observed in a significant proportion of the patients, although the overall tumor response rate was low.

The above findings prompted us to conduct a Phase II study to evaluate the efficacy, safety, and PK of motesanib in Japanese patients with advanced GIST, after failure or withdrawal of imatinib mesylate due to resistance or intolerance.

Materials and methods

Patients

Japanese patients with pathologically confirmed advanced or metastatic GIST were eligible for this study if they met the following criteria; age $\geq$ 20 years; a proven KIT positive or activating mutation of PDGFR; prior imatinib mesylate therapy of 400 mg/day or more for at least 8 weeks; disease progression or relapse while on previous treatment with imatinib mesylate; at least one tumor lesion measurable by a computed tomographic (CT) scan or magnetic resonance imaging (MRI); an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; a life expectancy of more than 3 months; adequate organ functions as defined by: neutrophils $\geq 1.5 \times 10^3$ cells/mm^3, platelets $\geq 1.0 \times 10^4$ cells/mm^3, hemoglobin $\geq$9.0 g/dl, serum creatinine $\leq$2.0$\times$ upper limit of normal (ULN), urine protein quantitative value of $\leq$1+ on dipstick or 30 mg/dl in urinalysis, aspartate aminotransferase $\leq 2.5 \times$ ULN (5.0 $\times$ ULN in patients with liver metastasis), alanine aminotransferase $\leq 2.5 \times$ ULN (5.0 $\times$ ULN in patients with liver metastasis), alkaline phosphatase $\leq 2.5 \times$ ULN (5.0 $\times$ ULN in patients with bone or liver metastasis), and total bilirubin $\leq 2.0 \times$ ULN. This protocol was approved by the Institutional Review Board at each study site. All patients provided written informed consent.

Study design

This study was an open-label and multicenter Phase II clinical study. The primary endpoint was the objective response rate to a once daily oral treatment with 125 mg motesanib in patients with advanced GISTs who experienced disease progression or relapse while on imatinib mesylate treatment. (Sunitinib was not approved for imatinib-resistant

GIST until 2 years after their study was completed.) The secondary endpoints were duration of response, progression-free survival (PFS), time to response, overall survival, and PK profiles of motesanib in Japanese patients with advanced GISTs.

The dose was firstly reduced to 100 mg, and if need be, to 75 mg in the second time. If the grade 3 adverse event (AE) is not adequately controlled with appropriate supportive care or a grade 4 AE occurs, motesanib was withheld. Once the grade 3 or 4 AE has resolved to baseline or grade ≤ 1 for nonhematologic toxicities or baseline or grade ≤ 2 for hematologic toxicities, the dose was reduced by 25 mg and treatment was resumed. If treatment with motesanib was withheld for >21 days, the patient should be withdrawn from the treatment period and complete the end of study procedures. If a patient was receiving 75 mg and requires a dose reduction, treatment with motesanib was stopped and the patient should complete the end of study procedures.

Tumor evaluation was performed after 8 weeks and at every 8 weeks thereafter, by using the modified Response Evaluation Criteria in Solid Tumor (RECIST). A confirmation of tumor response was performed by using the modified RECIST at least 4 weeks after a complete response (CR) or PR was first documented. An appointed radiographic image reviewer who was independent of the study site or the study sponsor reviewed CT or MRI of all patients.

The severity of AEs was graded according to Common Toxicity Criteria for Adverse Events (CTCAE, version 3). Special attention was paid to cardiac function, hypertension, hypothyroidism, and cholecystitis. Laboratory assessments (serum chemistry, hematology, thyroid hormones, blood pressure, and electrocardiogram) were performed every 2 weeks.

Ten patients had the following PK parameters: maximum observed plasma concentration (C_{max}), terminal elimination half-life ($t_{1/2}$), area under the plasma concentration–time curve from time 0 to 24 h after dosing (AUC_{0-24}), concentration at 24 h after dosing (C_{24}), maximum plasma concentration time (t_{max}), the area under the plasma concentration versus time curve from 0 to infinity (AUC_{0-inf}), and apparent plasma clearance (CL/F). These PK parameters of motesanib were calculated by the standard noncompartmental model using WinNonlin software version 4.1e (Pharsight Corporation, Mountain View, CA, USA) and summarized according to the study day and history of gastrectomy using descriptive statistics. Individual plasma concentration–time profiles were summarized by history of gastrectomy.

Statistical analysis

Descriptive statistics are provided for each endpoint. The safety analysis population consisted of all patients who received at least one dose of motesanib. The objective response rate and its two-sided 95% confidence interval (95% CI) were calculated. The CI was constructed by the exact method described by Collett [10]. For a PFS, calculated as the number of days between the first dose of motesanib and the date when radiological evidence of disease progression is determined (date of CT scan/MRI), or death (regardless of cause), whichever comes first (date of PD or death minus date of first dose of motesanib), Kaplan–Meier curve (with two-sided 95% CI) was generated and its standard error was calculated using Greenwood's formula. Statistical analyses were performed using the SAS statistical software package (SAS Institute Inc., Cary, NC, USA) [11].

Results

Patient population

A total of 35 patients were enrolled and treated with motesanib between November 2005 and June 2006 at the following sites: Aichi Cancer Center Hospital, Osaka University Hospital, National Cancer Center Hospital, Hokkaido University Hospital, Niigata University Hospital, National Cancer Center Hospital East, National Hospital Organization Kure Medical Center, and Kumamoto University Hospital. One patient did not undergo baseline CT assessment. Hence, 34 patients were eligible for tumor response evaluation, and 35 for toxicity evaluation. Baseline demographic and clinical characteristics are summarized in Table 1. Of the 35 patients enrolled, 17 (49%) were female and the median age was 62.0 years (range 31–83 years). Every patient was diagnosed as having GIST with positive immunoreactivity for KIT protein. The most common primary sites of the tumor were the small intestine ($n = 17$) and the stomach ($n = 10$). The other sites of the tumor were the colon ($n = 2$) and the rectum ($n = 2$). All patients had received treatment with imatinib mesylate but not with other tyrosine kinase inhibitors. The mean time from the last imatinib treatment was 0.9 months (range 0.2–5.5 months).

Outcome measures

The tumor response as assessed by an independent radiographic image reviewer is shown in Table 2. No CR was observed among the 35 patients enrolled in this study. One patient (3%; 95% CI 0.1–14.9%) had a PR and seven patients (20%) demonstrated SD for at least 24 months, two of whom continued to have SD for more than 2 years. Twelve additional patients had SD lasting for 12 weeks or more. Thirteen patients experienced disease progression within 12 weeks. The patient with PR had a gastric GIST

Table 1 Baseline characteristics

	All patients ($N = 35$)
Sex, *n* (%)	
Female	17 (49)
Male	18 (51)
Age	
Median	62.0
Min, max	31, 83
Age group, *n* (%)	
<65 years	23 (66)
≥65 years	12 (34)
≥75 years	4 (11)
ECOG PS, *n* (%)	
0	24 (69)
1	9 (26)
2	2 (6)
Site of primary tumor at diagnosis, *n* (%)	
Small intestine	17 (49)
Stomach	10 (29)
Colon	2 (6)
Rectum	2 (6)

Table 2 Best tumor response per modified RECIST per independent review

	All patients ($N = 35$)
Patients with measurable disease at baseline	34 (97)
Response assessment, *n* (%)	
Confirmed CR	0 (0)
Confirmed PR	1 (3)
SD[a]	19 (54)
PD	13 (37)
Unevaluable[b]	1 (3)
Not done	1 (3)
Confirmed objective response (CR or PR)	1 (3)
95% CI[c]	0.1–14.9
Durable SD[d]	7 (20)

Full analysis set includes all patients who received at least one dose of motesanib

[a] Patients with a response assessment of PR or CR that is not subsequently confirmed at least 4 weeks later are included as SD

[b] Unevaluable includes patients with a response assessment of CR, PR, or SD prior to the scheduled first assessment of response without an additional assessment of response

[c] Binomial proportion with exact 95% CI

[d] Durable SD is defined as having a best response on study as SD with a duration of ≥24 weeks from study day 1

with spindle-cell type, exon 11 mutation, liver, and peritoneal metastases, and had initially responded to imatinib with SD as assessed by RECIST (Fig. 1). The median PFS

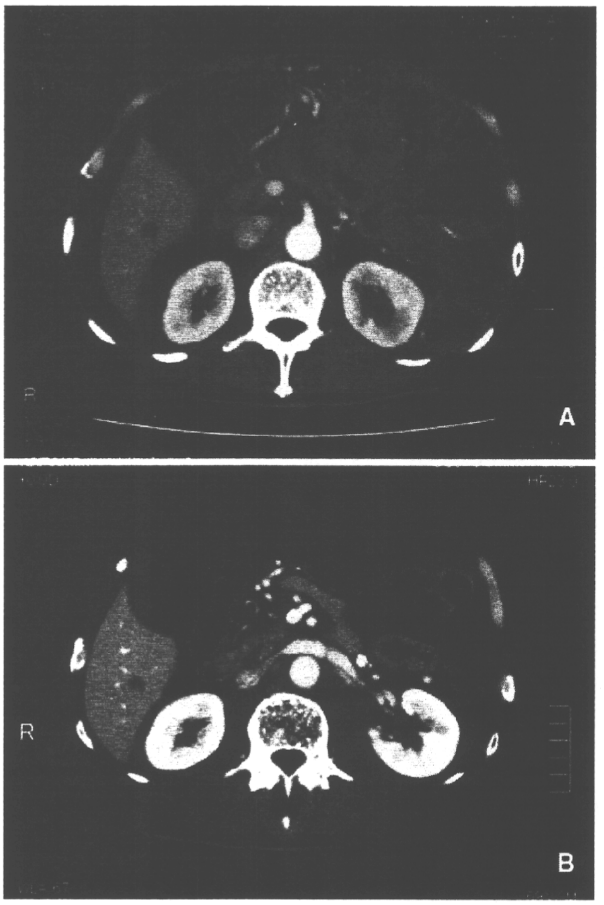

Fig. 1 A 68-year-old male with a primary GIST of the stomach and recurrent liver and peritoneal metastases. **a** Pre-treatment CT scan shows multiple low-density masses. **b** CT scan obtained after 3 months of treatment with once daily motesanib 125 mg shows that the multiple lesions have become significantly smaller and less dense

time of motesanib was 16.1 weeks (95% CI 8.4–32.0 weeks; Fig. 2).

Safety and tolerability

Table 3 summarizes treatment-related adverse events (TRAEs) (patient incidence ≥15%). The most frequent nonhematologic TRAEs included hypertension (63% of patients), diarrhea (51%), and fatigue (43%). Five patients (14%) experienced grade 3 hypertension and two patients (6%) experienced grade 3 fatigue. The only hematological toxicity was anemia (grade 2 in 3% of patients, grade 3 in 6% of patients, and grade 4 in 0% of patients). One patient (3%) experienced grade 4 hyperuricemia. No grade 5 TRAEs occurred.

Previous motesanib studies have reported an increased occurrence of cholecystitis in patients receiving motesanib,

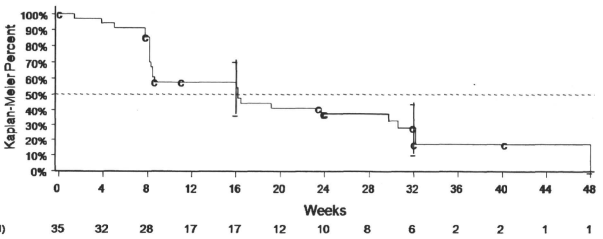

Fig. 2 Kaplan–Meier estimates of PFS

specifically at a dose of 75 mg twice daily continuously. The etiology of cholecystitis observed in patients receiving motesanib is unknown. Cholecystitis was not reported in this study. Gallbladder disorder was reported in three patients, specifically extended gallbladder or wall thickening, which was incidentally discovered in these patients on ultrasound sonography (US). The patients had not undergone US before starting motesanib treatment, nor were these disorders detected on routine CT scanning.

Figure 3 and Table 4 summarize the results of the intensive PK analyses. After a single-dose oral administration of 125 mg on day 1, motesanib was rapidly absorbed, with an overall median t_{max} of 0.75 h; a similar median t_{max} value (0.79 h) was observed after daily administration of motesanib on day 29. The mean C_{max}, AUC_{0-24}, and C_{24} were slightly lower on day 29 than on day 1, indicating that there was no accumulation after daily administration. The day 29 to day 1 mean ratios were 0.62, 0.71, and 0.80 for C_{max}, AUC_{0-24}, and C_{24}, respectively, for all evaluable patients.

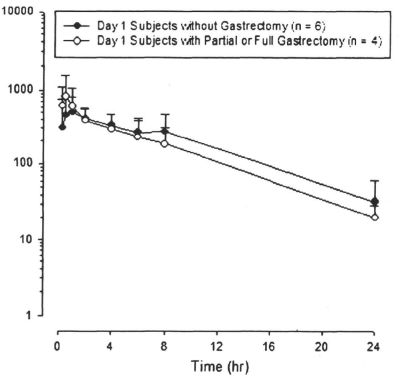

Fig. 3 Mean concentration–time profiles after oral administration of 125 mg of motesanib on day 1 in patients without gastrectomy and in patients with partial or full gastrectomy

Table 3 TRAE (15% or more of the patients)

Preferred term	Number of patients reporting TRAE, *n* (%), 35 (100)			All patients ($N = 35$)
	Grade 1/2	Grade 3	Grade 4	All grades
Anemia	1 (3)	2 (6)	0 (0)	3 (9)
Hypertension	17 (48)	5 (14)	0 (0)	22 (63)
Diarrhea	18 (51)	0 (0)	0 (0)	18 (51)
Fatigue	13 (38)	2 (6)	0 (0)	15 (43)
Headache	11 (31)	0 (0)	0 (0)	11 (31)
Weight decreased	11 (31)	0 (0)	0 (0)	11 (31)
Rash	10 (29)	0 (0)	0 (0)	10 (29)
Anorexia	5 (14)	4 (11)	0 (0)	9 (26)
Nausea	8 (23)	1 (3)	0 (0)	9 (26)
Blood thyroid-stimulating hormone increased	8 (23)	0 (0)	0 (0)	8 (23)
Dysphonia	8 (23)	0 (0)	0 (0)	8 (23)
Protein urine present	6 (17)	1 (3)	0 (0)	7 (20)
Dry skin	6 (17)	0 (0)	0 (0)	6 (17)
Vomiting	5 (15)	1 (3)	0 (0)	6 (17)

Table 4 Summary of PK parameters following oral administration of 125 mg motesanib on days 1 and 29

PK parameter	*N*	Day 1 Mean ± SD	Day 29 Mean ± SD	Day 29:Day 1 ratio Mean ± SD
All evaluable patients				
t_{max} (h)[a]	10	0.75 (0.25–2.0)	0.79 (0.50–4.0)	NA
C_{max} (ng/ml)	10	800 ± 439	488 ± 363	0.62 ± 0.20
AUC_{0-24} (μg h/ml)	9	3.87 ± 2.28	2.51 ± 2.10	0.71 ± 0.32
AUC_{0-inf} (μg h/ml)	9	4.14 ± 2.47	NA	NA
$t_{1/2,z}$ (h)	8	5.42 ± 1.51	4.27 ± 1.26	NA
CL/F (l/h)	9	41.1 ± 22.3	69.3 ± 31.8	NA
C_{24} (ng/ml)	9	27.6 ± 23.8	12.9 ± 15.4	0.80[b] ± 1.17
Evaluable patients with no prior gastrectomy				
t_{max} (h)[a]	6	1.0 (0.25–2.0)	1.0 (0.50–4.0)	NA
C_{max} (ng/ml)	6	692 ± 312	354 ± 193	0.53 ± 0.16
AUC_{0-24} (μg h/ml)	5	3.91 ± 2.43	1.93 ± 0.67	0.67 ± 0.39
AUC_{0-inf} (μg h/ml)	5	4.27 ± 2.73	NA	NA
$t_{1/2,z}$ (h)	4	5.20 ± 1.79	4.32 ± 1.89	NA
CL/F (l/h)	5	40.7 ± 24.5	71.5 ± 26.0	NA
C_{24} (ng/ml)	5	33.5 ± 31.1	16.6 ± 20.3	1.11[b] ± 1.57
Evaluable patients with partial or full gastrectomy				
t_{max} (h)[a]	4	0.50 (0.25–2.0)	0.50 (0.50–1.0)	NA
C_{max} (ng/ml)	4	962 ± 599	689 ± 492	0.75 ± 0.21
AUC_{0-24} (μg h/ml)	4	3.82 ± 2.45	3.23 ± 3.16	0.75 ± 0.25
AUC_{0-inf} (μg h/ml)	4	3.99 ± 2.49	NA	NA
$t_{1/2,z}$ (h)	4	5.63 ± 1.42	4.22 ± 0.38	NA
CL/F (l/h)	4	41.6 ± 22.9	66.4 ± 42.2	NA
C_{24} (ng/ml)	4	20.2 ± 9.2	8.37 ± 6.24	0.40 ± 0.16

Note: One patient did not have intensive sampling for day 29. This patient was excluded from the summary statistics

Parameters are presented to three significant figures when possible. Ratios are presented to two decimal places

Patients with elevated motesanib concentrations at 24 h post-dose were excluded from the C_{24}, $t_{1/2}$, AUC, and AUC-derived parameter summary statistics calculations, hence the reduced sample size for these parameters

t_{max} = the time the maximal plasma concentration was observed; C_{max} = the maximal observed plasma concentration after dosing; AUC_{0-24} = the area under the plasma concentration–time curve from time 0 to 24 h post-dose; AUC_{0-inf} = the area under the plasma concentration–time curve from time 0 to infinite time; $t_{1/2,z}$ = estimated terminal-phase half-life; CL/F = apparent clearance (AUC_{0-24} was used to estimate CL/F on day 29); C_{24} = the observed plasma concentration at 24 h after dosing; *NA* not applicable

[a] t_{max} is reported as a median (range) value, and is presented to two significant figures

[b] One patient had a C_{24} ratio of 3.84. The C_{24} ratio (mean ± SD) excluding this patient is 0.42 ± 0.30 for all patients and 0.43 ± 0.42 for patients without gastrectomy

For the patients who had partial or full gastrectomy ($n = 4$), day 1 C_{max} values were slightly higher (<2-fold) and AUC values were similar to those who had no gastrectomy. Means for C_{max} and AUC values on day 29 were higher compared with those who had no gastrectomy but not significant. Median t_{max} values occurred earlier in patients with gastrectomy on both days 1 and 29 (median t_{max} = 0.50 h with gastrectomy versus 1.0 h with no gastrectomy). C_{24} values on days 1 and 29 were lower in patients with gastrectomy compared with those who had no gastrectomy, though the mean $t_{1/2}$ values were similar (mean $t_{1/2,z}$ value = 4.22 versus 4.32 h, respectively).

Discussion

Although regression of thyroid cancer, renal cell carcinoma, and leiomyosarcoma was observed in the Phase I study of motesanib [12], objective tumor regression was observed in only one patient (3%) with GIST in this study. Motesanib administered as a single-agent was well tolerated, and a number of patients experienced prolonged stabilization of the disease. Seven (20%) did not exhibit disease progression for a minimum of 24 weeks, and the median PFS was 16.1 weeks. Serious hematological AEs (grade 3/4) were observed after sunitinib treatment in the Phase III trial. The incidence of grade

3/4 anemia, leukocytopenia, and neutrocytopenia was 4, 4, and 10%, respectively [9]. Anemia, leukocytopenia, and neutropenia were also reported as AEs for patients treated with imatinib; the incidence of grade 3/4 anemia, leukocytopenia, and neutropenia in a large Phase III study was 2.0, 1.4, and 4.8%, respectively [6]. The only hematological toxicity of motesanib was anemia (grade 2, 3%; grade 3, 6%). Despite long-term exposure to motesanib, hematological toxicities were mild. Motesanib may therefore present an alternative treatment option for patients who experienced neutrocytopenia or thrombocytopenia after treatment with imatinib or sunitinib.

To evaluate the potential effect of gastrectomy on motesanib disposition, the motesanib PK profiles from patients with a history of gastrectomy were compared with those who did not have prior gastrectomy. Median t_{max} values occurred earlier in patients with gastrectomy on both days 1 and 29, suggesting faster absorption in patients with a history of gastrectomy. Since gastrectomy impacts the gastric emptying rate and the absorption rate resulting in increase in C_{max}, these findings should be considered in the following clinical trials.

The current treatment options for patients with GIST after treatment failure with imatinib and sunitinib are limited to best supportive care and investigative therapies. This study shows that in Japanese patients with advanced GIST motesanib is well tolerated, and, although an objective tumor response was observed in only one patient, motesanib may have an impact on survival in a retrospective analysis. However, focusing on other clinically meaningful measures, such as the Choi criteria [13] that incorporating tumor density and small changes in tumor size as revealed by CT scanning, is more important than focusing on the tumor response rate, which may fail to identify a potentially effective therapy [14, 15]. Randomized, well-controlled studies with time to progression or survival as the primary endpoints of efficacy will be needed to identify agents for which a tumor regression effect is not anticipated. Results from such studies will help in making an informed decision of whether or not to continue the clinical development of such agents in GIST.

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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)

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Summary

Background **Fluorouracil and folinic acid with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) are widely used as first-line or second-line chemotherapy for metastatic colorectal cancer. However, infusional fluorouracil-based regimens, requiring continuous infusion and implantation of an intravenous port system, are inconvenient. We therefore planned an open-label randomised controlled trial to verify the non-inferiority of irinotecan plus oral S-1 (a combination of tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate; IRIS) to FOLFIRI as second-line chemotherapy for metastatic colorectal cancer.**

Methods **Between Jan 30, 2006, and Jan 29, 2008, 426 patients with metastatic colorectal cancer needing second-line chemotherapy from 40 institutions in Japan were randomly assigned by a computer-based minimisation method to receive either FOLFIRI (n=213) or IRIS (n=213). In the FOLFIRI group, patients received folinic acid (200 mg/m²) and irinotecan (150 mg/m²) and then a bolus injection of fluorouracil (400 mg/m²) on day 1 and a continuous infusion of fluorouracil (2400 mg/m²) over 46 h, repeated every 2 weeks. In the IRIS group, patients received irinotecan (125 mg/m²) on days 1 and 15 and S-1 (40–60 mg according to body surface area) twice daily for 2 weeks, repeated every 4 weeks. The primary endpoint was progression-free survival, with a non-inferiority margin of 1·333. Statistical analysis was on the basis of initially randomised participants. This study is registered with ClinicalTrials.gov, number NCT00284258.**

Findings **All randomised patients were included in the primary analysis. After a median follow-up of 12·9 months (IQR 11·5–18·2), median progression-free survival was 5·1 months in the FOLFIRI group and 5·8 months in the IRIS group (hazard ratio 1·077, 95% CI 0·879–1·319, non-inferiority test p=0·039). The most common grade three or four adverse drug reactions were neutropenia (110 [52·1%] of 211 patients in the FOLFIRI group and 76 [36·2%] of 210 patients in the IRIS group; p=0·0012), leucopenia (33 [15·6%] in the FOLFIRI group and 38 [18·1%] in the IRIS group; p=0·5178), and diarrhoea (ten [4·7%] in the FOLFIRI group and 43 [20·5%] in the IRIS group; p<0·0001). One treatment-related death from hypotension due to shock was reported in the FOLFIRI group within 28 days after the end of treatment; no treatment-related deaths were reported in the IRIS group.**

Interpretation **Progression-free survival with IRIS is not inferior to that with FOLFIRI in patients receiving second-line chemotherapy for metastatic colorectal cancer. Treatment with IRIS could be an additional therapeutic option for second-line chemotherapy in metastatic colorectal cancer.**

Funding **Taiho Pharmaceutical Co Ltd and Daiichi Sankyo Co Ltd.**

Introduction

The combination of fluorouracil and folinic acid with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) has been established as the standard first-line chemotherapy for metastatic colorectal cancer.[1] For second-line chemotherapy for patients resistant to fluorouracil, randomised comparative studies have shown that irinotecan monotherapy was effective.[2,3] Rougier and colleagues[4] showed comparable efficacy of FOLFIRI, FOLFOX, and irinotecan and oxaliplatin (IROX) in patients unresponsive to fluorouracil in a randomised phase 2 study.

Tournigand and colleagues[5] showed that, in patients with metastatic colorectal cancer who were randomly assigned to receive FOLFIRI or FOLFOX as first-line chemotherapy and then crossed over to receive the other as second-line chemotherapy, overall survival was similar in both groups. Consequently, initial treatment with FOLFOX and then second-line treatment with FOLFIRI or vice versa is recommended as standard therapy.[6] However, infusional fluorouracil-based regimens, requiring continuous infusion and implantation of an intravenous port system, are inconvenient and sometimes associated with catheter-related problems such as infection and thrombosis.

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S-1 is an oral fluoropyrimidine consisting of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate, in which tegafur is a pro-drug of fluorouracil, CDHP is a dihydropyrimidine dehydrogenase (DPD) inhibitor maintaining the serum concentration of fluorouracil, and potassium oxonate is an inhibitor of orotate phosphoribosyl transferase, reducing gastrointestinal toxicities. Response rates for monotherapy with S-1 are around 35% for colorectal cancer, and it is suggested that DPD inhibition in tumour cells might contribute to antitumour effects because S-1 has been effective against many solid tumours with high DPD expression.[7] Clinically, responses rates of 52·5–62·5% have been reported in phase 2 studies of irinotecan plus S-1 combination therapy, with median progression-free survival of 7·8–8·6 months for first-line treatment for metastatic colorectal cancer.[8–10] These results suggest that the efficacy of IRIS might be comparable to that of FOLFIRI and that IRIS might also be more convenient for both patients and medical facilities.

We did a phase 2/3 randomised study (FIRIS study) to verify the non-inferiority of IRIS to FOLFIRI in patients with metastatic colorectal cancer in whom first-line chemotherapy failed.

Methods

Patients

Inclusion criteria were histologically confirmed colorectal adenocarcinoma; unresectable metastatic disease; age 20–75 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; withdrawal from first-line chemotherapy due to toxicity or progressive disease, or relapse within 24 weeks after the final dose of preoperative or postoperative chemotherapy; no previous treatment with irinotecan; sufficient oral intake; adequate organ function (white blood cell count 3000–12 000 cells per μL, platelet ≥100 000 per μL, aspartate aminotransferase [AST] ≤100 IU/L, alanine aminotransferase [ALT] ≤100 IU/L, total bilirubin ≤25·7 μmol/L [≤15 mg/L], and creatinine ≤106·1 μmol/L [≤12 mg/L]); and no abnormal electrocardiographic findings within 28 days before enrolment. Exclusion criteria were pregnancy or lactation; second non-colorectal cancer; complications such as ileus, uncontrolled diabetes mellitus, or hypertension; severe diarrhoea; clinically evident gastrointestinal haemorrhage; and ascites or pleural effusion needing treatment.

The protocol of this study was approved by the institutional review board or ethics committee of each institution. The study was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all patients participating in the study.

Randomisation and masking

Investigators provided the patient's details to the central registration centre through a web-based registration system. After an eligibility check, patients were randomly assigned to receive FOLFIRI or IRIS at the central registration centre by a computer program, by use of a minimisation method with stratification by institution, prior therapy (with or without oxaliplatin), and performance status (0 or 1). Assignment of patients was concealed from the investigator. Treatment assignment was not masked from the investigators or patients.

Procedures

Our randomised, open-label, phase 2/3 study in patients with the second-line metastatic colorectal cancer was done in 40 institutions in Japan (mainly hospitals and medical centres). In the phase 2 portion, safety was assessed in patients treated with either FOLFIRI (30 patients) or IRIS (30). Additionally, the response rate in the first 50 patients in the IRIS group was assessed because IRIS is an unfamiliar regimen in Japan. An independent data and safety monitoring board reviewed our results (safety and efficacy in the phase 2 portion; safety in the phase 3 portion), and approved proceeding to the phase 3 portion. The final analysis was done by use of the combined data from phase 2 and 3 portions.

Patients in the FOLFIRI group received concurrent folinic acid (200 mg/m²) and irinotecan (150 mg/m²) and then a bolus injection of fluorouracil (400 mg/m²) on day 1 and subsequent continuous infusion of fluorouracil (2400 mg/m²) over 46 h, repeated every 2 weeks (4 weeks counted as one cycle). In the FOLFIRI group, the dose of irinotecan was 150 mg/m², the approved dose in Japan.[11] The IRIS group received irinotecan (125 mg/m²) on days 1 and 15 and S-1 (40 mg for patients with body surface area [BSA] <1·25 m²; 50 mg for patients with BSA 1·25<1·5 m²; 60 mg for patients with BSA ≥1·5 m²) twice daily for 2 weeks from days 1–14 and then a 2-week pause, on the basis of results of phase 2 studies.[12,13] We selected this regimen from several documented regimens of irinotecan and S-1 to match the regimen of FOLFIRI in the control arm. Regimens in which irinotecan is given every 2 weeks[12,13] and every 3 weeks are in clinical use in Japan.[8]

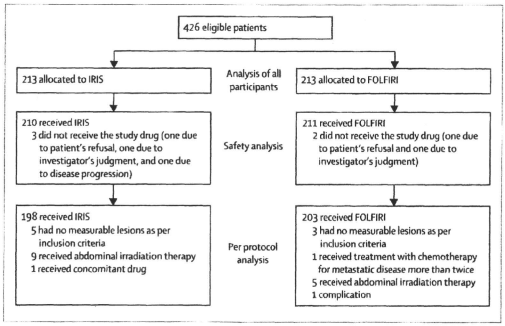

Figure 1: **Trial profile**

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In both FOLFIRI and IRIS groups, treatment was delayed until recovery if white blood cell count fell below than 3000 cells per μL, platelets fell below 100 000 per μL, AST or ALT were over 100 IU/L, total bilirubin was higher than 25·7 μmol/L, creatinine was higher than 106·1 μmol/L, the patient experienced diarrhoea of grade one or greater, or other non-haematological toxicities greater than grade two. If a patient experienced a grade four haematological or grade three or higher non-haematological toxicity, the dose was decreased by one level for the next course of treatment, and therapy was resumed.

Treatment was continued until progressive disease, unacceptable toxicity, or patient's refusal to continue treatment. Because molecularly targeted agents such as bevacizumab, cetuximab, and panitumumab were not approved in Japan at the start of our study, no restriction for such agents was specifically placed on treatment before or after the study.

Physical examination, electrocardiography, performance status, and laboratory tests were done at baseline and repeated at least every 2 weeks during treatment. Tumours were assessed at baseline (within 1 month before enrolment), and at 2, 3, and 4 months after enrolment, and thereafter every 2 months until progression. Progression was defined as progressive disease on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, clinical progression judged by the investigator, or death from any cause without progression.

Progression-free survival was counted from the date of randomisation to the date when the progressive disease was first confirmed by the investigator's assessment. For patients without documented progressive disease, data was censored on the date of the last tumour assessment with non-progression status. Overall survival was calculated from the date of randomisation to the date of death or confirmation of survival.

Toxicity was evaluated on the basis of the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Statistical analysis

The primary efficacy analysis was done with all randomised patients; we also did a per-protocol analysis in which patients in whom there was a major violation such as inclusion or exclusion criteria or protocol treatments were excluded. Safety was assessed in all patients who received at least one dose of the study drug.

The primary objective of our study was to show non-inferiority of IRIS to FOLFIRI for progression-free survival in the whole randomised population. On the basis of data from previous reports in patients with metastatic colorectal cancer who received second-line chemotherapy, median progression-free survival with both FOLFIRI and IRIS was assumed to be 4 months. The steering committee deemed that response assessment could not be repeated more frequently than once a month, so a difference in progression-free survival shorter than 1 month could not be detected precisely. Thus, progression-free survival with IRIS that was 1 month shorter than with FOLFIRI would be acceptable as a lower margin for inferiority, given the expected hazard ratio [HR] of 1·0. The 95% CI upper limit of the HR, calculated using Cox regression analysis with stratification factors other than institution, was prespecified as less than 1·333, meaning the null hypothesis was that median progression-free survival with IRIS would be 1 month shorter than with FOLFIRI. Because 379 events were needed to show non-inferiority with a two-sided α of 0·05 and a power of 80%, a target sample size of 400 patients was required.

Secondary endpoints were overall survival, response rate, and toxicity. Subgroup analyses were done to establish whether therapeutic efficacy was affected by sex, age, histological type, performance status, and prior chemotherapy with or without oxaliplatin. Progression-free and overall survival were estimated using the Kaplan-Meier method. The 95% CI for median progression-free and overall survival was calculated using the method of Brookmeyer and Crowley.[14] All p values were two-sided. All statistical analyses were done with SAS version 8.2. This study is registered with ClinicalTrials.gov, number NCT00284258.

Role of the funding source

The funding source had no role in the study design, data collection, data analysis, or interpretation. All authors had access to all of the data. The corresponding author had final responsibility for decision to submit for publication.

	FOLFIRI (n=213)	IRIS (n=213)
Sex		
Male	123 (57·7%)	120 (56·3%)
Female	90 (42·3%)	93 (43·7%)
Age (years)	63·0 (32–75)	61·0 (29–75)
ECOG performance status		
0	160 (75·1%)	158 (74·2%)
1	53 (24·9%)	55 (25·8%)
Histological type		
Well differentiated	62 (29·1%)	60 (28·2%)
Moderately differentiated	124 (58·2%)	133 (62·4%)
Poorly differentiated	13 (6·1%)	8 (3·8%)
Other	13 (6·1%)	11 (5·2%)
Undetermined	1 (0·5%)	1 (0·5%)
Previous chemotherapy with oxaliplatin		
Yes	128 (60·1%)	129 (60·6%)
No	85 (39·9%)	84 (39·4%)
Number of metastatic sites		
One	92 (43·2%)	88 (41·3%)
Two or more	120 (56·3%)	124 (58·2%)

Data are number (%) or median (range). FOLFIRI=folinic acid, fluorouracil, and irinotecan. IRIS=irinotecan and S-1. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline patient characteristics**

Results

426 patients from 40 institutions in Japan were enrolled in the study from Jan 30, 2006, to Jan 29, 2008, and randomised either to the FOLFIRI or IRIS group (213 patients in each; figure 1). Of the per-protocol population, 203 patients were in the FOLFIRI group and 198 were in the IRIS group; reasons for exclusion are shown in figure 1. All patients who received study treatment (211 patients in the FOLFIRI group and 210 patients in the IRIS group) were included in the safety evaluation. Baseline characteristics were well balanced between the two groups (table 1).

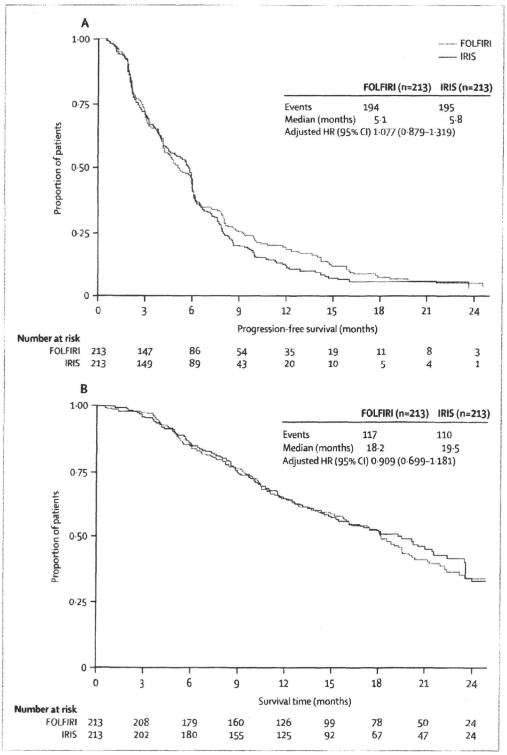

Figure 2: **Progression-free survival (A) and overall survival (B)**
FOLFIRI=infusional fluorouracil, folinic acid, and irinotecan. IRIS=irinotecan plus S-1. HR=hazard ratio.

The mean number of cycles of protocol treatment was 4·7 (range 1–20) for FOLFIRI and 4·9 (1–23) for IRIS. Median relative dose intensities to the planned dose were almost identical: irinotecan 78·3%, bolus fluorouracil 76·9%, and infusional fluorouracil 81·5% in the FOLFIRI group, and irinotecan 78·3% and S-1 88·9% in the IRIS group. Treatments were discontinued because of disease progression in 68·5% (146 patients) in the FOLFIRI group and in 66·2% (141) in the IRIS group, adverse events in 10·8% (23) and in 16·9% (36), and patient's refusal 1·9% (four) and 6·1% (13). 179 patients in the FOLFIRI group and 184 patients in the IRIS group needed a dose delay or dose reduction. Treatment after the trial (ie, treatment after failure of second-line regimen) was given to 159 (74·6%) patients in the FOLFIRI group and 147 (69·0%) in the IRIS group. As third-line treatment, an oxaliplatin-containing regimen was given to 58 (27·2%) patients in the FOLFIRI and 63 (29·6%) in the IRIS group. Molecularly targeted agents as treatments after the trial were used in 24 patients in the FOLFIRI group and 16 in the IRIS group.

As of Dec 31, 2008, collection of progression-free and overall survival data was cut off, with 389 confirmed events (194 FOLFIRI and 195 IRIS). Median follow-up was 12·9 months (IQR 11·5–18·2). Median progression-free survival was 5·1 months in the FOLFIRI group and 5·8 months in the IRIS group. In the entire randomised population, the HR of progression-free survival in the IRIS group compared with the FOLFIRI group was 1·077 (95% CI 0·879–1·319, p=0·039). Similar results were seen in the per protocol population: median progression-free survival was 5·1 months in the FOLFIRI group and 5·7 in the IRIS group (HR 1·050, 95% CI 0·851–1·294).

The data on overall survival are preliminary because of short follow-up. 117 of the 213 patients in the FOLFIRI group and 110 of the 213 patients in the IRIS group died due to any cause. Median overall survival in the entire randomised population was 18·2 months in the FOLFIRI group and 19·5 months in the IRIS group (HR 0·909, 95% CI 0·699–1·181; figure 2). In the per protocol population, median overall survival was 18·1 months in the FOLFIRI group and 19·3 months in IRIS group (HR 0·896, 95% CI 0·685–1·172).

The overall response rate was 16·7% (one patient had a complete response, 28 patients had a partial response) of 174 patients with evaluable response data in the FOLFIRI group and 18·8% (one patient had a complete response, 33 patients had a partial response) of 181 in the IRIS group.

Figure 3 shows the results of subgroup analyses of progression-free survival. Although no interaction was identified between sex, age, histological type, or performance status and therapeutic effects of IRIS compared with FOLFIRI, a statistically significant interaction was noted between prior chemotherapy (with or without oxaliplatin) and therapeutic effects (p=0·030). In the subgroup of patients receiving prior chemotherapy with oxaliplatin, median progression-free survival was

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5·7 months in the IRIS group and 3·9 months in the FOLFIRI group (adjusted HR 0·876, 95% CI 0·677–1·133), whereas in patients without prior oxaliplatin treatment it was 6·0 months and 7·8 months, respectively (HR 1·490, 95% CI 1·079–2·059). A similar tendency was noted in the overall survival (figure 4).

Table 2 lists major adverse events. In the two groups, the incidences of adverse events were not markedly different from those previously reported, and none of the adverse events were unexpected. Significantly more patients in the FOLFIRI group experienced grade three or four neutropenia than did those in the IRIS group (110 [52·1%] of 211 patients in the FOLFIRI group *vs* 76 [36·2%] of 210 in the IRIS group; p=0·0012); 33 (15·6%) of patients in the FOLFIRI group and 38 (18·1%) in the IRIS group experienced leucopenia (p=0·5178). The most common non-haematological toxicities were diarrhoea (10 [4·7%] in the FOLFIRI group *vs* 43 [20·5%] in the IRIS group; p<0·0001), anorexia (11 [5·2%] *vs* 23 [11·0%]; p=0·0329), nausea (nine [4·3%] *vs* four [1·9%]; p=0·2593), fatigue (seven [3·3%] *vs* 18 [8·6%]; p=0·0242), and febrile neutropenia (two [0·9%] *vs* 10 [4·8%]; p=0·0205), all at grade three (table 2). One treatment-related death from hypotension due to shock was reported in the FOLFIRI group within 28 days after the end of treatment; no treatment-related deaths were reported in the IRIS group.

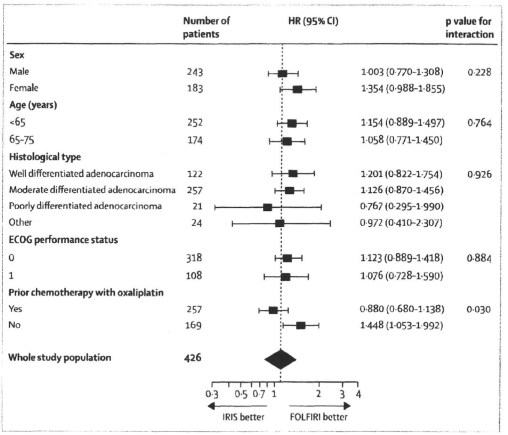

Figure 3: **Subgroup analysis of progression-free survival**
HR=hazard ratio.

Discussion

Our randomised study, comparing FOLFIRI and IRIS as second-line chemotherapy for patients with metastatic colorectal cancer, shows the non-inferiority of IRIS to FOLFIRI. Similar results were obtained in both the entire randomised population and in the more conservative per-protocol analysis. Response rates and overall survival were equivalent between the groups. To our knowledge, this is the first phase 3 trial that shows non-inferiority of oral fluoropyrimidine plus irinotecan therapy to FOLFIRI. From the point of convenience, there has been substantial demand for replacing infusional fluorouracil-based regimens with oral fluorouracil agents. Our study was not designed to collect specific data on working hours of clinicians or the quality of life of patients. However, unlike FOLFIRI, IRIS does not contain infusional fluorouracil and thus does not require a long infusion process, reducing the inconvenience to both patients and clinicians. Additionally, no infuser pump is needed, providing a great advantage to patients. Randomised studies comparing FOLFOX with capecitabine plus oxaliplatin (XELOX) in patients with metastatic colorectal cancer showed that XELOX was non-inferior to FOLFOX.[15,16] By contrast, Fuchs and colleagues[17] reported that progression-free survival with capecitabine plus irinotecan (CapeIRI; 5·8 months) was clearly inferior to that with FOLFIRI (7·6 months) as the first-line chemotherapy for metastatic colorectal cancer, and CapeIRI was associated with a higher incidence of gastrointestinal toxicities and hand-foot syndrome, resulting in discontinuation for reasons other than disease progression.

In our study, the incidence of grade three or worse diarrhoea, fatigue, febrile neutropenia, and anorexia were significantly higher in the IRIS group than the FOLFIRI group. In general, oral fluorouracil-derivative drugs have been shown to be associated with a higher incidence of diarrhoea.[15,17–19] This might also be applicable to S-1. It might be attributable to 2-week treatment with S-1 in IRIS compared with 2-day treatment with fluorouracil in FOLFIRI. However, there was no significant difference in the number of courses or dose intensity between groups. It is thought that all adverse events could be controlled by supportive care, treatment interruptions, or dose reduction, with little effect on treatment continuity. Of note, in the IRIS group, grade four diarrhoea was not detected and fewer of the patients enrolled towards the end of the study experienced grade three diarrhoea.

The incidence of fluorouracil-induced diarrhoea, especially by oral fluoropyrimidines, has been shown to be higher in non-Asian patients than Asian patients.[17,18,21] We speculate that IRIS therapy might also be less feasible in non-Asian patients; therefore, the optimum dose of S-1 in IRIS should be clarified for this population. The reported incidence of hand-foot syndrome due to fluoropyrimidine derivatives containing DPD inhibitors, such as S-1, was low in both Japanese and western trials.[22] In our study, grade three hand-foot syndrome, which is frequently noted with capecitabine-based regimens both in Japanese and non-Asian patients, was not noted in the IRIS group.