Title	Planned Safety Analysis of the ACTS-CC 02 Trial: A Randomized Phase III Trial of S-1 With Oxaliplatin Versus Tegafur and Uracil With Leucovorin as Adjuvant Chemotherapy for High-Risk Stage III Colon Cancer
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Planned Safety Analysis of the ACTS-CC 02 Trial: A Randomized Phase III Trial of S-1 With Oxaliplatin Versus Tegafur and Uracil With Leucovorin as Adjuvant Chemotherapy for High-Risk Stage III Colon Cancer

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Abstract

To our knowledge, no phase III study has reported the safety of adjuvant chemotherapy with SOX (S-1 with oxaliplatin) in patients with colorectal cancer. We report the results of a planned safety analysis of the ACTS-CC 02 trial (Randomized phase III study of S-1/Oxaliplatin comparing Tegafur-Uracil/Leucovorin in the Adjuvant Chemotherapy of Stage IIIb Colorectal Cancer), which was a randomized phase III trial of SOX versus tegafur and uracil with leucovorin. The incidence of adverse events associated with SOX was acceptable.

Background: This trial was designed to verify the superiority of 6 months of postoperative adjuvant chemotherapy with SOX (S-1 with oxaliplatin) with UFT (tegafur and uracil) with LV (leucovorin) in terms of disease-free survival in patients with high-risk stage III colon cancer. We report the results of a planned safety analysis. **Patients and Methods:** Patients who underwent curative resection for high-risk stage III colon cancer (any T, N2, or positive nodes around the origin of the feeding arteries) were randomly assigned to receive either UFT/LV (300-600 mg/d UFT with 75 mg/d LV on days 1-28, every 35 days, for 5 cycles) or SOX (100 mg/m^2 of oxaliplatin on day 1 with 80-120 mg/d S-1 on days 1-14, every 21 days, for 8 cycles). Treatment status and safety were evaluated. **Results:** A total of 966 patients were enrolled, and 932 patients were included in safety analyses. The planned 6-month protocol treatment was received by 76.9% of the patients in the UFT/LV group and 65.8% of those in the SOX group. The overall

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incidence of any Grade adverse events (AEs) were 91.3% in the UFT/LV group and 98.7% in the SOX group, and those of Grade ≥ 3 AEs were 16.1% and 36.1%, respectively. As for Grade ≥ 3 AEs, leukopenia, neutropenia, thrombocytopenia, and sensory neuropathy were more common in the SOX group. The incidence of Grade ≥ 3 sensory peripheral neuropathy was 4.6% in the SOX group. **Conclusion:** The completion rate of adjuvant SOX and its incidence of AEs were acceptable in patients with colon cancer.

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Keywords: Adverse events, L-OHP, Oral fluorouracil, Sensory peripheral neuropathy, Tegafur/gimeracil/oteracil

Introduction

Postoperative adjuvant chemotherapy has been shown to improve outcomes in patients with stage III colon cancer and is considered the global standard treatment for this disease.

In Japan, convenient oral FU (fluoropyrimidine) preparations have been the treatment of choice. Two phase III studies of adjuvant chemotherapy with oral FUs in Japanese patients with stage III colon cancer (JCOG0205 [A Trial Comparing Adjuvant Oral UFT/LV to 5-FU/l-LV in Stage III Colorectal Cancer] and ACTS-CC [Adjuvant Chemotherapy Trial of S-1 for Colon Cancer 02]), most of whom underwent D3 lymph node (LN) dissection,[1] have reported good treatment outcomes. In the JCOG0205 study, which showed the noninferiority of UFT (tegafur and uracil) with LV (leucovorin) to intravenous bolus 5-FU (5-fluorouracil) with LV (5-FU/LV),[2] and the ACTS-CC study, which showed that S-1 is noninferior to UFT/LV[3]; the 5-year disease-free survival (DFS) rates were approximately 70%, and the 5-year overall survival rates were approximately 85%. Because the risk of recurrence and adverse events (AEs) associated with oxaliplatin, monotherapy with FUs is considered an option for adjuvant therapy in patients with stage III colon cancer.

However, stage III disease includes subgroups of patients with very poor outcomes. In the JCOG0205 study, the 5-year DFS rate was 90.4% in patients with stage IIIA disease, whereas it was 74.1% in patients with stage IIIB disease and 58.9% in those with IIIC disease. In such "high-risk" subgroups of patients with stage III disease, there is room for further improvement in outcomes. More aggressive regimens including oxaliplatin are expected to be effective. A subgroup analysis of the patients with stage II or III colon cancer who were enrolled in the MOSAIC (Multicenter International Study of Oxaliplatin/ 5FU-LV in the Adjuvant Treatment of Colon Cancer) study showed that oxaliplatin was beneficial in patients with N2 disease.[4] At present, 6 months of regimens combining FUs with oxaliplatin have been widely used in Western countries.[5-9] The Japanese Society for Cancer of the Colon and Rectum Guidelines 2016 have recommended 5-FU/LV, UFT/LV, capecitabine, and S-1 in addition to the oxaliplatin-based regimens of FOLFOX (infusional 5-FU/LV with oxaliplatin) and CapeOX (capecitabine with oxaliplatin).[10]

S-1 is an oral FU that combines tegafur (a prodrug of 5-FU) with gimeracil and oteracil potassium. Gimeracil more strongly inhibits dihydropyrimidine dehydrogenase than uracil in UFT, thereby more strongly suppressing 5-FU degradation. S-1 includes oteracil potassium to reduce gastrointestinal toxicity.[11] S-1 has the advantage of a lower incidence of hand-foot syndrome than capecitabine,[12] which is the most widely used oral FU in Western countries. We therefore focused on treatment with SOX (S-1 with oxaliplatin) as a new oxaliplatin-based regimen for adjuvant chemotherapy. As first-line treatment for metastatic colorectal cancer (mCRC), SOX has been shown to be noninferior to CapeOX,[13] and SOX with bevacizumab has been reported to be noninferior to infusional modified 5-FU/LV with oxaliplatin with bevacizumab.[14] However, the efficacy and safety of SOX as adjuvant chemotherapy for colorectal cancer remain to be confirmed.

We conducted the ACTS-CC 02 trial to validate the therapeutic usefulness of oxaliplatin-based adjuvant chemotherapy in patients with high-risk stage III colon cancer in Japan as well as to verify the efficacy and safety of adjuvant chemotherapy with SOX in patients with colon cancer. Patients in the control arm received UFT/LV, the regimen most commonly used for adjuvant chemotherapy in Japan. This randomized phase III study was designed to verify the superiority of SOX in terms of DFS.

Because no phase III study has reported the safety of adjuvant chemotherapy with SOX in patients with colorectal cancer, we now report the results of a planned safety analysis.

Patients and Methods

Patients

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with Japanese ethical guidelines for clinical studies. The study protocol was approved by the institutional review board of each participating institution. Written informed consent was obtained from all patients before enrollment.

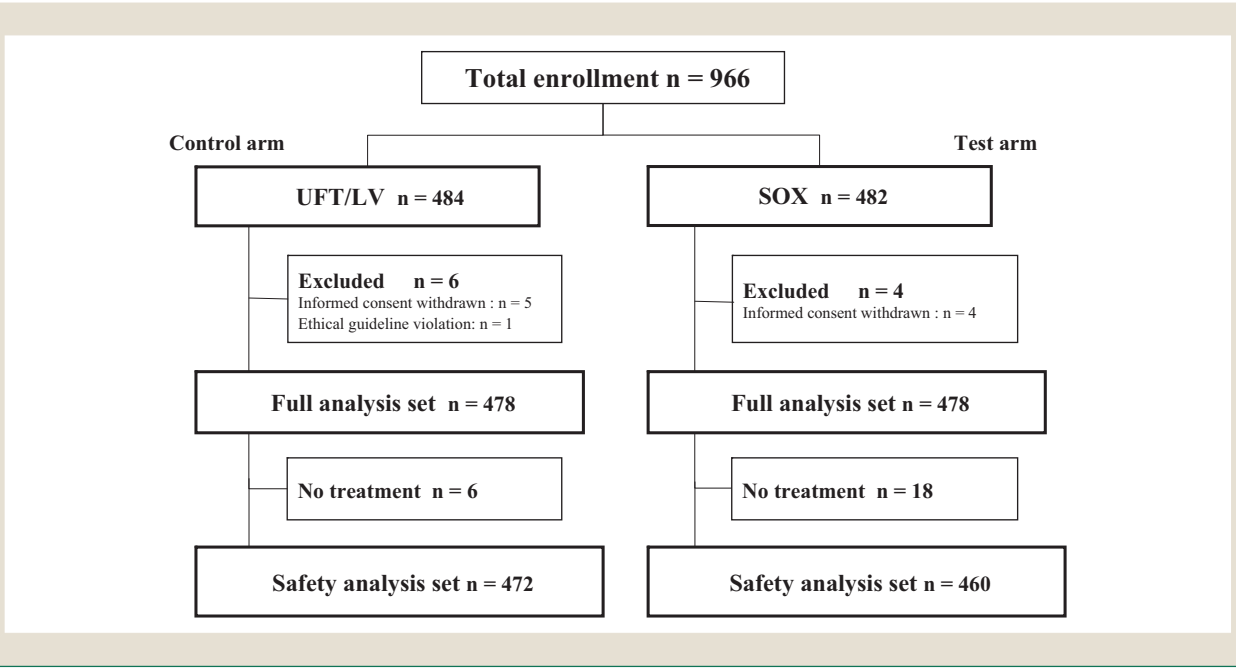
The main inclusion criteria were as follows: tumors located in the colon or the upper rectum, histologically confirmed high-risk stage III adenocarcinoma (any T, N2, or positive main LNs as defined below) after R0 resection, an age of 20 to 80 years, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, no previous chemotherapy or radiotherapy, adequate oral intake, preserved major organ functions, no other active malignancies, and no uncontrollable severe infection.

Main LNs are defined in the Japanese Classification of Colorectal Carcinoma, seventh edition as LNs around the origin of the feeding artery (ie, the ileocolic, right colic, middle colic, or inferior mesenteric artery; see Supplemental Figure 1 in the online version).[15]

Randomization and Masking

Participants were randomly assigned in a 1:1 ratio to receive either UFT/LV or SOX. Randomization was done centrally with the use of the minimization method and the following stratification factors: tumor location (colon or upper rectum), the number of

Figure 1 Consolidated Standards of Reporting Trials Diagram



Abbreviations: SOX = S-1 with oxaliplatin; UFT/LV = tegafur and uracil with leucovorin.

positive LNs (4-6 positive LNs, or ≥ 7 positive LNs or main LNs positive), and institution. The randomization sequence was generated by a team (EPS Corporation, Tokyo, Japan) independently of the trial sponsor and investigators, who used a validated computer system. Local investigators used a Web-based system for enrollment, which then automatically assigned patients to treatment groups. Participants, investigators, and data analysts were not masked to the treatment assignments because we compared an oral-based regimen with an infusional regimen.

Treatment

In the UFT/LV group, UFT (body surface area [BSA] < 1.17 m^2, 300 mg; BSA ≥ 1.17 m^2 to ≤ 1.49 m^2, 400 mg; BSA ≥ 1.50 m^2 to ≤ 1.83 m^2, 500 mg; BSA > 1.83 m^2, 600 mg) and LV (75 mg per patient) were orally administered daily in 3 divided doses (every 8 hours) for 28 consecutive days, followed by a 7-day rest. This 5-week treatment comprised 1 cycle. A total of 5 cycles (25 weeks) were delivered.

In the SOX group, S-1 (BSA < 1.25 m^2, 80 mg; BSA ≥ 1.25 m^2 to < 1.5 m^2, 100 mg; BSA ≥ 1.5 m^2, 120 mg) was orally administered twice daily from after dinner on day 1 to after breakfast on day 15, followed by a 7-day rest. Oxaliplatin (100 mg/m^2) was infused intravenously over the course of 2 hours on day 1 of each cycle. This 3-week treatment comprised 1 cycle. A total of 8 cycles (24 weeks) were delivered.

If the treatment schedule was delayed because of the withdrawal of drugs because of AEs in either treatment group, the protocol treatment was considered to be completed 6 months from the day of starting treatment. After completing the study treatment, patients were followed-up without any further treatment unless recurrence or secondary cancer developed.

The treatment was started within 8 weeks after surgery. At the initiation of each treatment cycle, patients were confirmed to meet all of the following criteria for starting treatment: white cell count ≥ 3.0 × 10^3/μL, neutrophil count ≥ 1500/μL, platelet count ≥ 75 × 10^3/μL, hemoglobin level ≥ 9.0 g/dL, serum aspartate aminotransferase (AST) level ≤ 100 U/L, serum alanine aminotransferase (ALT) level ≤ 100 U/L, serum total bilirubin level ≤ 2.0 mg/dL, serum creatinine level < 1.5 mg/dL, and Grade ≤ 1 anorexia, nausea, vomiting, diarrhea, mucositis, and stomatitis. In the SOX group, only S-1 was given to patients with Grade 3 sensory neuropathy, and treatment with SOX was not possible in patients with a creatinine clearance of < 60 mL/min. In patients who met the following criteria, treatment was restarted at a 1-level lower dose after recovery: white cell count < 2.0 × 10^3/μL, neutrophil count < 1000/μL, platelet count < 50 × 10^3/μL, hemoglobin level < 8.0 g/dL, serum AST level > 150 U/L, serum ALT level > 150 U/L, total bilirubin level > 2.5 mg/dL, or Grade ≥ 3 anorexia, nausea, vomiting, diarrhea, mucositis, or stomatitis. In the SOX group, however, even if the platelet count was between ≥ 50 × 10^3/μL and < 75 × 10^3/μL, only the dose of oxaliplatin was reduced by 1 level.

Evaluations

Adverse events, including the results of laboratory tests, were assessed at the initiation of each treatment cycle. Reporting the worst grade of the following AEs was mandatory: white cell count, neutrophil count, platelet count, hemoglobin level, serum AST level, serum ALT level, total bilirubin level, serum creatinine level, nausea, vomiting, diarrhea, anorexia, fatigue, rash, desquamation, pigmentation, mucositis, stomatitis, and sensory neuropathy. The contents and grades of AEs were evaluated according to the National

Table 1 Baseline Patient Characteristics (Safety Analysis Set)

	UFT/LV (n = 472)	SOX (n = 460)
Age		
Median (range)	66 (32-80)	65 (26-80)
Sex		
Male	252 (53.4)	253 (55.0)
Female	220 (46.6)	207 (45.0)
ECOG PS		
0	449 (95.1)	429 (93.3)
1	23 (4.9)	31 (6.7)
Tumor Location		
Right colon (C, A, T)	190 (40.3)	171 (37.2)
Left colon (D, S)	130 (27.5)	139 (30.2)
Rectosigmoid	90 (19.1)	85 (18.5)
Upper rectum[a]	62 (13.1)	65 (14.1)
Histological Type		
Papillary	10 (2.1)	3 (0.7)
Tubular	409 (86.7)	409 (88.9)
Poorly, mucinous, signet	53 (11.2)	48 (10.4)
Depth of Tumor Invasion		
T1	8 (1.7)	6 (1.3)
T2	16 (3.4)	20 (4.3)
T3	293 (62.1)	283 (61.5)
T4a	125 (26.5)	130 (28.3)
T4b	30 (6.4)	21 (4.6)
Lymphatic Invasion		
Negative	52 (11.0)	53 (11.5)
Positive	420 (89.0)	407 (88.5)
Venous invasion		
Negative	97 (20.6)	97 (21.1)
Positive	375 (79.4)	363 (78.9)
Scope of LN Dissection		
D2	56 (11.9)	32 (7.0)
D3	416 (88.1)	428 (93.0)
LNs Examined, n		
Median (range)	21 (0-96)	22 (0-107)
<12	62 (13.1)	47 (10.2)
≥12	410 (86.9)	413 (89.8)
LN Metastases (Stratification Factor), n		
Median (range)	5 (1-22)	5 (1-39)
4-6	283 (60.0)	274 (59.6)
≥7 or main LN positive	189 (40.0)	186 (40.4)
LN Metastasis		
N1a (1 positive LN)	1 (0.2)	4 (0.9)
N1b (2-3 positive LN)	17 (3.6)	22 (4.8)
N2a (4-6 positive LN)	317 (67.2)	305 (66.3)
N2b (≥7 positive LN)	137 (29.0)	129 (28.0)
Stage		
IIIA	6 (1.3)	6 (1.3)
IIIB	242 (51.3)	226 (49.1)
IIIC	224 (47.5)	228 (49.6)

Data are presented as n (%) except where otherwise stated.
Abbreviations: A = ascending colon; C = cecum; D = descending colon; ECOG = Eastern Cooperative Oncology Group; LN = lymph node; PS = performance status; S = sigmoid colon; T = transverse colon.
[a]Including patients in whom the lower edge of the tumor is in the upper rectum proximal to the peritoneal reflection.

Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

From the results of previous studies,[7,8] we estimated that the 3-year DFS rate would be 65% in the UFT/LV group and 71.5% in the SOX group in the present study. We therefore expected that the 3-year DFS rate would be 6.5 percentage points higher in the SOX group (hazard ratio, 0.78). We estimated that we would need to enroll a total of 1186 patients in 3 years to have a statistical power of 80% (2-sided α value of 0.05) to detect a difference between the groups after 3 years of follow-up. Taking into account dropout patients, we set the target number of patients at 1200. In this study, DFS was defined as the period from the day of enrollment in the study to the day of recurrence, the detection of cancer lesions other than recurrence, or the day of death, whichever came first.

Descriptive statistics such as means, SDs, and medians were calculated. Fisher exact test was used to compare the incidence of AEs between the treatment groups. P values of $< .05$ were considered to indicate statistical significance. The relative performance was defined as the ratio of the total drug dose actually administered to the patient to the total drug dose specified in the protocol. Patients who completed the protocol treatment were defined as those who completed the last dose of the planned protocol treatment (UFT/LV, 8 cycles; SOX, 5 cycles) or patients in whom 6 months had elapsed from the time of starting the protocol treatment. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC).

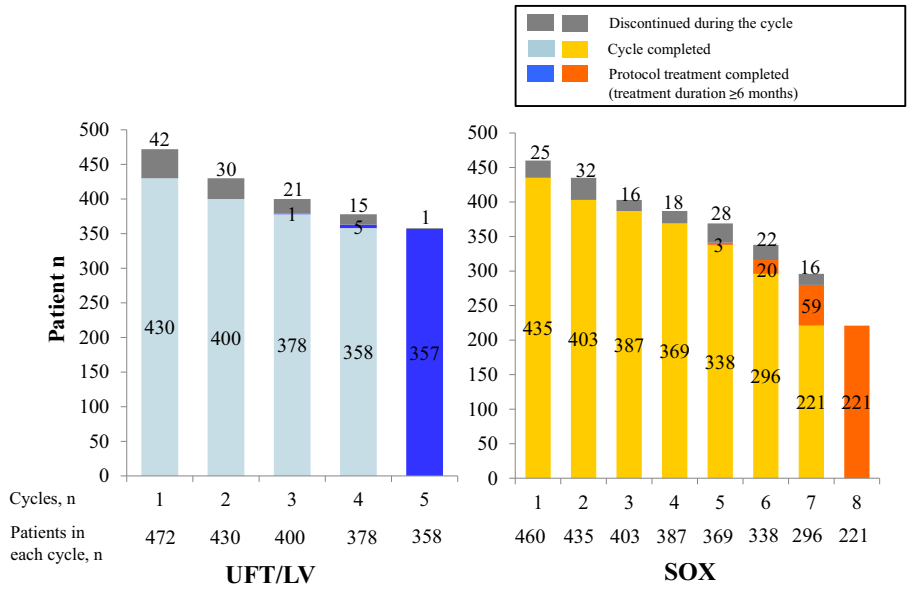
Results

Patient Characteristics

From April 2010 through October 2014, a total of 966 patients were enrolled at 260 institutions. Although we extended the enrollment period, the target number of patients was not attained. Patients who withdrew informed consent (9 patients), violated the Japanese ethical guidelines for clinical studies (1 patient), or who dropped out before receiving the protocol treatment (24 patients) were excluded, and the remaining 932 patients (472 in the UFT/LV group and 460 in the SOX group) were included in the safety analysis set (Figure 1).

The patient characteristics are shown in Table 1. The median age was 65 (range, 26-80) years, and 878 patients (94.2%) had

Figure 2 Treatment Status According to Cycle



Abbreviations: SOX = S-1 with oxaliplatin; UFT/LV = tegafur and uracil with leucovorin.

Table 2 Adverse Events (Safety Analysis Set)

	UFT/LV (n = 472)		SOX (n = 460)		
	Any	Grade ≥3	Any	Grade ≥3	
	n (%)	n (%)	n (%)	n (%)	*P* (Grade ≥3)
Patients With at Least 1 AE	431 (91.3)	76 (16.1)	454 (98.7)	166 (36.1)	
Laboratory Findings					
Leukopenia	111 (23.5)	0 (0.0)	271 (58.9)	5 (1.1)	.0290
Neutropenia	74 (15.7)	7 (1.5)	271 (58.9)	79 (17.2)	<.0001
Thrombocytopenia	76 (16.1)	3 (0.6)	324 (70.4)	13 (2.8)	.0111
Anemia	117 (24.8)	3 (0.6)	137 (29.8)	2 (0.4)	1.0000
Bilirubin	171 (36.2)	3 (0.6)	195 (42.4)	4 (0.9)	.7223
AST	141 (29.9)	10 (2.1)	278 (60.4)	3 (0.7)	.0904
ALT	141 (29.9)	14 (3.0)	184 (40.0)	4 (0.9)	.0296
Creatinine	34 (7.2)	2 (0.4)	33 (7.2)	0 (0.0)	.4995
Clinical Findings					
Stomatitis	58 (12.3)	4 (0.8)	101 (22.0)	4 (0.9)	1.0000
Nausea	85 (18.0)	4 (0.8)	190 (41.3)	9 (2.0)	.1715
Vomiting	30 (6.4)	0 (0.0)	53 (11.5)	4 (0.9)	.0590
Diarrhea	149 (31.6)	38 (8.1)	139 (30.2)	25 (5.4)	.1189
Anorexia	113 (23.9)	11 (2.3)	221 (48.0)	16 (3.5)	.3327
Fatigue	105 (22.2)	5 (1.1)	209 (45.4)	7 (1.5)	.5741
Rash/desquamation	49 (10.4)	2 (0.4)	48 (10.4)	1 (0.2)	1.0000
Hyperpigmentation	47 (10.0)	-	92 (20.0)	-	-
Peripheral sensory neuropathy	15 (3.2)	1 (0.2)	323 (70.2)	21 (4.6)	<.0001
Hand-foot syndrome	4 (0.8)	0 (0.0)	8 (1.7)	0 (0.0)	-

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SOX = S-1 with oxaliplatin; UFT/LV = tegafur and uracil with leucovorin.

Table 3 Incidence of Grade ≥ 3 Adverse Events Occurring During 6 Months of Treatment With Other Regimens Including Oxaliplatin

	ACTS-CC 02	XELOXA[7]	MOSAIC[8]	NSABP C-07[9]	JFMC41[18]	JFMC47[19]	
	(SOX: q3w; n = 460)	(CapeOX: q3w; n = 938)	(FOLFOX4: q2w; n = 1108)	(FLOX: q2w; n = 1200)	(mFOLFOX6: q2w; n = 828)	(mFOLFOX6: q2w; n = 158)	(CapeOX: q3w; n = 477)
Dose of Oxaliplatin	100 mg/m^2	130 mg/m^2	85 mg/m^2	85 mg/m^2	85 mg/m^2	85 mg/m^2	130 mg/m^2
Total Expected Dose of Oxaliplatin	800 mg/m^2	1040 mg/m^2	1020 mg/m^2	765 mg/m^2	1020 mg/m^2	1020 mg/m^2	1040 mg/m^2
Cumulative Dose of Oxaliplatin (Median)	625 mg/m^2	NA	810 mg/m^2	676 mg/m^2	672.5 mg/m^2	NA	NA
Patients With at Least 1 AE, %	36.1	55	NA	NA	NA	48.1	41.1
Neutropenia	17.2	9	41.1	NA	28.7	34.2	15.3
Thrombocytopenia	2.8	5	1.7	NA	1.7	0	5.5
Stomatitis	0.9	<1	2.7	NA	NA	0.6	0.8
Nausea	2	5	5.1	15.6	1.7	0.6	2.9
Vomiting	0.9	6	5.8	12.1	0.7	0.6	0.8
Diarrhea	5.4	19	10.8	38.1	2.1	0.6	5.5
Peripheral Sensory Neuropathy	22.4 (Grade 2/3)	11	12.4	30.4 (Grade 2/3)	5.8	36.1 (Grade 2/3)	36.7 (Grade 2/3)
Hand-Foot Syndrome	0.2 (Grade 2/3)	5	2.0	NA	NA	2.5 (Grade 2/3)	14.7 (Grade 2/3)

Abbreviations: ACTS-CC 02 = Randomized phase III study of S-1/Oxaliplatin comparing Tegafur-Uracil/Leucovorin in the Adjuvant chemotherapy of Stage IIIb colorectal cancer; CapeOX = capecitabine with oxaliplatin; FLOX = bolus 5-FU/LV with oxaliplatin; FOLFOX4 = infusional 5-FU/LV with oxaliplatin; JFMC41 = A tolerability study in Japan of Oxaliplatin, fluorouracil, and l-leucovorin for patients with stage II/III colon cancer(JFMC41-1001-C2: JOIN Trial); JFMC47 = A Randomized, Multicenter, Phase III Study to Compare 6 Months of either 5-Fluorouracil/l-leucovorin plus Oxaliplatin (mFOLFOX6) or Capecitabine plus Oxaliplatin (XELOX) with 3 Months of either mFOLFOX6 or XELOX as Adjuvant Chemotherapy in Patients with Completely Resected Stage III Colon Cancer (JFMC47-1202-C3: ACHIEVE Trial); mFOLFOX6 = infusional modified 5-FU/LV with oxaliplatin; MOSAIC = Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer; NSABP C-07 = Fluorouracil Plus Leucovorin With or Without Oxaliplatin in Treating Patients With Stage II or Stage III Colon Cancer; q2w = every 2 weeks; q3w = every 3 weeks; SOX = S-1 with oxaliplatin; XELOXA = A Study of Xeloda (Capecitabine) Plus Oxaliplatin in Patients With Colon Cancer.

an ECOG PS of 0. The baseline characteristics were well balanced.

Treatment Status

The median number of treatment cycles was 5 (range, 1-5) in the UFT/LV group and 7 (range, 1-8) in the SOX group. The mean and median relative performances were respectively 83.1% and 100.0% for UFT and 84.7% and 100.0% for LV in the UFT/LV group and 74.9% and 85.4% for S-1 and 73.6% and 81.3% for oxaliplatin in the SOX group. The mean and median cumulative doses of oxaliplatin in the SOX group were 569.3 mg/m^2 and 625.0 mg/m^2, respectively. The dose of oxaliplatin was reduced in 176 of the 460 patients in the SOX group.

Figure 2 shows the treatment status in each cycle. The 6-month protocol treatment was completed in 363 patients (76.9%) in the UFT/LV group and 303 patients (65.9%) in the SOX group. The main reasons for discontinuing the protocol treatment in the UFT/LV group (109 patients) and the SOX group (157 patients) were as follows: recurrence or secondary cancer in 20 patients (18.3%) and 17 patients (10.8%); difficulty in continuing treatment because of AEs in 33 patients (30.3%) and 45 patients (28.7%); treatment could not be resumed within 28 days after the last day of previous treatment in 20 patients (18.3%) and 38 patients (24.2%); and the patient requested treatment to be discontinued in 30 patients (27.5%) and 41 patients (26.1%), respectively.

Safety Profile

The incidence of AEs are shown in Table 2. Any Grade AEs occurred in 431 patients (91.3%) in the UFT/LV group and 454 patients (98.7%) in the SOX group. AEs of Grade $\geq$ 3 occurred in 76 patients (16.1%) in the UFT/LV group and 166 patients (36.1%) in the SOX group. In the SOX group, oxaliplatin-related sensory neuropathy of Grade 1 developed in 220 patients (47.8%), Grade 2 in 82 patients (17.8%), and Grade 3 in 21 patients (4.6%). No patient experienced Grade 4 sensory neuropathy.

Grade $\geq$ 3 leukopenia, neutropenia, thrombocytopenia, and peripheral sensory neuropathy occurred more frequently in the SOX group, whereas Grade $\geq$ 3 elevations of ALT were more common in the UFT/LV group. Febrile neutropenia did not develop in either group.

There was 1 treatment-related death: fulminant hepatitis developed in the second cycle in 1 patient in the UFT/LV group, and the patient died 14 days after the onset of fulminant hepatitis.

Discussion

We report the results of an interim safety analysis of a phase III study comparing SOX with UFT/LV as adjuvant therapy in patients with high-risk stage III colon cancer. The incidence of Grade $\geq$ 3 AEs in the 460 patients who received SOX was 36.1%, which was higher than the incidence in patients who received UFT/LV (16.1%), but was considered acceptable. The main cause of the difference in Grade $\geq$ 3 AEs was neutropenia.

We modified the dose of oxaliplatin used in our study to enhance the feasibility (continuity and completion) of adjuvant therapy. In phase I/II studies of SOX using oxaliplatin at a dose of 130 mg/m^2 in patients with mCRC, 27% of the patients had Grade $\geq$ 3 thrombocytopenia.[16] Therefore, the dose of oxaliplatin was set at 100 mg/m^2 in phase II studies of SOX for advanced gastric cancer. This dose was highly feasible and effective, and the incidence of Grade $\geq$ 3 thrombocytopenia was 13%.[17] On the basis of these results, the dose of oxaliplatin in the SOX group of our study was set at 100 mg/m^2. Furthermore, in our study, if the platelet count was between $\geq 50 \times 10^3$/mm^3 and $< 75 \times 10^3$/mm^3, only the dose of oxaliplatin was decreased by 1 level in the next cycle, and Grade $\geq$ 3 thrombocytopenia developed in only 2.8% of the patients.

The incidence of clinical symptoms such as diarrhea and anorexia in the SOX group in our study was lower than those in a previous study in which the dose of oxaliplatin was 130 mg/m^2 in patients with mCRC who received SOX.[14] The incidence of AEs in the SOX group was generally consistent with those reported for FOLFOX and CapeOX (ie, 2 other oxaliplatin-based regimens), and comparable results were obtained (Table 3).[7-9,18,19] The incidence of sensory neuropathy in the SOX group was 17.8% for Grade 2 and 4.6% for Grade 3. These incidence rates are similar to, or slightly lower than, the incidence rates of Grade 2 and Grade 3 sensory neuropathy reported for FOLFOX and CapeOX.[7-9,18,19] These results might also be attributed to the use of oxaliplatin in a dose of 100 mg/m^2. The completion rate of the 6-month protocol treatment with SOX was 65.9%, which is similar to the completion rates of the FOLFOX and CapeOX regimens in clinical trials performed in Japan (70% and 59%, respectively).[19]

The incidence rates of AEs in the UFT/LV group were similar to the reported incidence rates in previous reports.[2,3] Our results confirmed that liver dysfunction caused by UFT develops in a certain proportion of patients. The only Grade 3 or higher AE that was more common in the UFT/LV group than in the SOX group was elevated ALT levels. In the UFT/LV group, there was 1 treatment-related death. This patient was given UFT/LV without checking the result of laboratory tests at the start of the second cycle of treatment. This protocol violation might have led to the non-detection of early changes associated with liver damage and the development of fulminant hepatitis, resulting in death. UFT/LV has a very low incidence of serious AEs and is easy to use, but can cause severe liver dysfunction. Previous studies have reported that UFT-related liver dysfunction most commonly develops within 2 months after starting treatment. It is therefore mandatory to check liver function at the beginning of each cycle of UFT treatment.

Conclusion

The incidence of AEs associated with adjuvant SOX after colon cancer surgery was considered acceptable. The efficacy results will be available in 2018.

Clinical Practice Points

- In Japan, because of the risks of recurrence and the AEs associated with oxaliplatin, monotherapy with FUs is considered an option for adjuvant therapy in patients with stage III colon cancer.
- S-1 is an oral FU that has been already used in Japan in an adjuvant setting for gastric, pancreatic, and colorectal cancers.
- S-1 with oxaliplatin therapy has also been used to treat advanced gastric and colorectal cancers.
- We conducted the ACTS-CC 02 trial to validate the therapeutic usefulness of oxaliplatin-based adjuvant chemotherapy in

patients with high-risk stage III colon cancer in Japan and to verify the efficacy and safety of adjuvant chemotherapy with SOX in patients with colon cancer.

- In the planned safety analysis, the completion rate of adjuvant SOX and its incidence of AEs were acceptable in patients with high-risk colon cancer.
- Because no phase III study has reported the safety of adjuvant chemotherapy with SOX in patients with colorectal cancer, our results might provide valuable information for the optimal use of SOX regimens in clinical practice.

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Supplemental Data

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Supplemental Figure 1 Main Lymph Nodes (LNs) Defined in the Japanese Classification of Colorectal Carcinoma, Seventh Edition