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ORIGINAL ARTICLE

A Japanese multicenter phase II study of adjuvant chemotherapy with mFOLFOX6/CAPOX for stage III colon cancer treatment after D2/D3 lymphadenectomy

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Abstract

Purpose A phase II trial was conducted to investigate the benefit of oxaliplatin-based adjuvant chemotherapy in Japanese stage III colon cancer patients.

Methods Eligible patients were scheduled to receive 12 cycles of mFOLFOX6 or 8 cycles of CAPOX in adjuvant settings. The primary endpoint was the 3-year disease-free survival (DFS). Cox proportional hazards regression was performed to identify risk factors for a worse DFS.

Results A total of 130 patients, including 73 patients receiving mFOLFOX6 and 57 patients receiving CAPOX, were enrolled from 16 institutions between April 2010 and April 2014. The 3-year DFS was 82.2%, exceeding the expected primary endpoint of 81.7%. The 3-year DFS tended to be higher in patients receiving mFOLOFOX6 than in those receiving CAPOX (mFOLFOX6, 86.3%; CAPOX, 76.9%; $P=0.06$). The 3-year DFS rates did not differ markedly based on the risk stratification (T1/T2/T3 N1 vs. T4 or N2) indicated by the IDEA COLLABORATION study ($P=0.22$). In the multivariate analysis, stage IIIC ($P=0.046$) and early discontinuation ($P<0.01$) were identified as independent significant risk factors for a worse DFS.

Conclusion Our findings represent the first positive results in a Japanese phase II trial of adjuvant chemotherapy with mFOLFOX6/CAPOX. Early discontinuation within 2 months was an independent risk factor for a shorter DFS.

Keywords Stage III colon cancer · Adjuvant chemotherapy · mFOLFOX6 · CAPOX · Early discontinuation

Introduction

In Japan, D2 or D3 lymph node dissection is recommended as curative resection for T1–T4 colorectal cancer. D3 lymph node dissection is a surgical procedure used to remove paracolic, intermediate, and main lymph nodes as defined in the Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2016 for the treatment of colorectal cancer [1]. The procedures appear to closely resemble the concept of complete mesocolic excision (CME) proposed in Europe in recent years [2, 3]. As a result of the prevalence of standard lymph node dissection in Japan, the outcomes in patients with stage III colon cancer have been considerably favorable, despite postoperative adjuvant chemotherapy being a single treatment with 5-FU/leucovorin or oral fluoropyrimidines [4, 5].

In Europe and the United States, the inclusion of adjuvant chemotherapy with additional oxaliplatin in a 5-FU-based regimen for colon cancer treatment, e.g., oxaliplatin plus infusional 5-FU/LV (FOLFOX) and capecitabine plus oxaliplatin (CAPOX), has been introduced based on the results of several clinical trials. Subsequently, adjuvant chemotherapy with fluoropyrimidine derivatives and additional oxaliplatin for stage III colon cancer treatment has been recommended in the clinical guidelines in Europe, the United States [6, 7], and Japan [1].

Although the Japanese medical insurance system approved covering adjuvant therapy with FOLFOX in 2009 and CAPOX in 2011 based on the results of overseas phase

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III trials, in the Japanese guidelines for CRC treatment, they are merely listed as recommended drugs. Several phase III trials conducted with a single administration of fluoropyrimidines as adjuvant chemotherapy for stage III colon cancer patients in Japan demonstrated an excellent 3-year disease-free survival (DFS) of 72.5–77.8% with UFT/LV [4, 8, 9], 79.3% with 5-FU/LV [4], and 81% with capecitabine [10]. Because these results were similar to those of phase III trials with oxaliplatin-based regimens conducted in Europe and the United States [11–13], the benefit of oxaliplatin-based adjuvant chemotherapy in stage III colon cancer patients is viewed with skepticism among Japanese surgeons. Therefore, in clinical practice in Japan, this approach has not been applied to all patients with stage III colon cancer, especially in consideration of adverse events. This is one of the reasons that the accumulated prospective data of stage III colon cancer has not included treatment with oxaliplatin-based adjuvant chemotherapy in Japanese institutions performing D2/D3 dissection. Given this background, the present multicenter phase II study was initiated on April 2010. The differences in safety profiles between mFOLFOX6 and CAPOX in the trial have already been reported [14].

Recently, the results of a large-scale clinical trial evaluating the non-inferiority of 3-month administration over 6-month administration of CAPOX or FOLFOX to prove a reduction in neurotoxicity without the loss of the additional effect of oxaliplatin on the DFS were published [15]. Among low-risk patients, defined as those with histologically proven T1–T3N1 tumors, who were subsequently given CAPOX, 3-month administration proved to be non-inferior to 6-month administration in terms of the DFS. In contrast, in high-risk patients, defined as those with histologically proven T4 and/or N2 tumors, 3-month administration with either regimen did not prove non-inferior to 6-month administration. However, there have been few reports of prospective data on 6-month administration in Japan; therefore, the present phase II trial was conducted to explore the additional effect of oxaliplatin in stage III colon cancer patients.

In the present report, the study outcomes are presented mainly as those of the primary endpoint. In addition, risk factors for an unfavorable DFS were also analyzed.

Methods

This trial was registered with UMIN (UMIN ID: 000005427).

Study design

The study was designed as a phase II clinical study to demonstrate the efficacy of additional oxaliplatin on adjuvant chemotherapy with 5-FU/LV (mFOLFOX6) or capecitabine (CAPOX) for the treatment of patients with colon cancer who underwent curative resection based on the JSCCR guidelines. Furthermore, the safety of mFOLFOX6 therapy (12 cycles) and CAPOX therapy (8 cycles), with a focus on adverse reaction profiles, was observed [14]. The primary endpoint was the 3-year DFS. The secondary endpoints were adverse events (AEs), the therapy completion rate, and the 5-year overall survival (OS). The 5-year OS has not been calculated yet and was outside of the scope of this report.

The protocol was approved by the institutional review board in each hospital participating in this study.

Eligibility criteria

The eligibility criteria used have been described in a previous report [14]. In brief, among cases of histologically proven stage III colorectal adenocarcinoma in the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, or rectosigmoid, the patients were 20–80 years of age. All patients underwent potentially curative resection with D2 or D3 lymph node dissection without preoperative therapy. The patients were also assessed as having an Eastern Cooperative Clinical Oncology Group (ECOG) performance status 0 or 1 and a preserved major organ function. All patients participating in the study provided their written informed consent.

Study treatment

mFOLFOX6

mFOLFOX6 comprises the administration of l-LV (200 mg/m^2) and oxaliplatin (85 mg/m^2) via intravenous infusion over 2 h followed by rapid intravenous infusion (iv) of 5-FU (400 mg/m^2) and then slow infusion (civ) of 5-FU (2400 mg/m^2 over 46 h). This regimen was repeated every 2 weeks for 12 cycles.

CAPOX

CAPOX comprises the intravenous infusion of oxaliplatin (130 mg/m^2 over 2 h) on day 1 and oral administration of capecitabine (1000 mg/m^2 twice daily) from the evening of day 1 to the morning of day 15. This regimen was repeated every 3 weeks for 8 cycles.

Follow-up

The enrolled patients were followed up for at least 5 years after the completion of the scheduled treatment or until observation of disease relapse or the development of another malignancy or death. All patients were required to undergo a physical examination and routine laboratory tests,

including those for the tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), every 3 months for the first 3 years of follow-up and then once every 6 months for the subsequent 2 years. In addition, computed tomography of the chest, abdomen, and pelvis was scheduled every 6 months for surveillance.

Statistical analyses

The rationale for setting the sample size was described previously [14]. In brief, based on previous studies, the 3-year DFS rate was expected to be approximately 10% higher with FOLFOX than with 5-FU-based therapy. Because the JSCCR clinical guidelines published in 2009 [16] stated that patients with stage III colorectal cancer had a 3-year relapse-free survival rate of 73.2% after surgery, the threshold for the 3-year DFS rate was set at 73.2% in the present study. Including an additional 8.5%, the expected 3-year DFS rate was set at 81.7%. Using SWOG statistical tools (https://stattools.crab.org/) and assuming a threshold 3-year DFS of 73.2% and an expected 3-year DFS of 81.7% (one-sided $\alpha = 0.05$, $\beta = 0.2$), the required sample size was calculated to be 124 patients. Approximately 5% of patients were expected to drop out because of ineligibility, and the final planned sample size for this study was set at 130 patients.

The DFS rate was calculated using the Kaplan–Meier method. The difference in the DFS curves between subgroups was analyzed using the log-rank test. The risk factors in terms of the DFS were assessed via Cox univariate and multivariate analyses with stepwise selection. Chi square or Fisher's exact tests and the Mann–Whitney test were used to compare two groups. *P* values less than 0.05 were denoted to be statistically significant. All statistical analyses were performed using the SPSS software program for Windows, version 21 (SAS Institute, Cary, NC, USA).

Results

Patient background characteristics

A total of 132 patients from 16 hospitals were enrolled between April 2010 and April 2014 for the present study. Two patients were found to be ineligible for the protocol, leaving 130 patients assessed as eligible, including 73 patients receiving mFOLFOX6 and 57 receiving CAPOX. The cutoff date for follow-up was July 31, 2017. The median follow-up period for survival analyses was 52 months (range 10–89 months) or until the detection of relapse or development of other malignant diseases for the DFS or until death for OS.

The characteristics of the 130 eligible patients are shown in Table 1. The primary lesion was located in the proximal colon in one-third of the patients and in the distal colon in the other two-thirds. All cases were proven to have adenocarcinoma, including mucinous carcinoma in six cases. The tumor depth was T1–3 in 72.3% of patients and T4 in 27.7%, with a node status of N1 in 70.8% (N1a, 42 cases and N1b, 50 cases) and N2 in 29.2% (N2a, 18 cases and N2b, 20 cases). According to the risk classification based on the IDEA COLLABORATION [15], 68 patients were classified as low risk and 62 as high risk. Fifteen patients discontinued therapy at fewer than four cycles of mFOLFOX6 or fewer than three cycles of CAPOX and were classified as the early discontinuation group. There were no significant differences between patients treated with mFOLFOX6 and those treated with CAPOX in terms of the demographic and clinicopathologic factors examined.

The reasons for early discontinuation of treatment are shown in Table 2. The most frequent reason for early discontinuation was non-hematological grade 3 toxicity. The next most frequent reason was patient request. All six cases of patient request were associated with toxicity of less than grade 2 severity, including anorexia, fatigue and diarrhea, that did not meet the criteria for discontinuation. There were no patients who discontinued therapy early due to relapse.

The 3-year DFS

The DFS curves of all eligible patients are shown in Fig. 1. The 3-year DFS, which was the primary endpoint of the present study, was 82.2%, exceeding the expected 3-year DFS rate of 81.7%. Based on TNM staging, the 3-year DFS was found to be 100% in 9 stage IIIA patients, 86.3% in 95 stage IIIB patients, and 60.3% in 26 stage IIIC patients. The 3-year DFS in stage IIIC patients was significantly poorer than that in other stage patients ($P < 0.01$). Regarding the regimen, 73 patients receiving mFOLFOX6 and 57 receiving CAPOX demonstrated a 3-year DFS of 86.3% and 76.9%, respectively ($P = 0.06$). Based on the risk classification according to the IDEA COLLABORATION and regimen, no marked difference was noted between the regimens in low-risk patients with N1 and T3 or shallower invasion; however, in high-risk patients with N2 and/or T4, a significantly more favorable DFS was obtained with mFOLFOX6 than with CAPOX (82.5% vs. 67.2%, respectively, $P = 0.02$) (Fig. 2).

Risk factors for an unfavorable DFS (Table 3)

According to a univariate regression analysis, significant risk factors were the pathologic stage (stage IIIC vs. stage IIIA/IIIB), [hazard ratio (HR) 3.39; 95% confidence interval (CI) 1.57–7.31; $P < 0.01$), and duration of treatment (early discontinuation vs. non-early discontinuation or completion of scheduled cycles) (HR 4.55; 95% CI 2.0–10.0; $P < 0.01$). These factors and additional

Table 1 Patient characteristics

	All cases (n = 130)	mFOLFOX6 (n = 73)	CAPOX (n = 57)	*P*-value
Age[a]	65 (27–75)	64 (27–75)	65 (35–75)	0.35
Sex (male : female)	80 : 50	45 : 28	35 : 22	0.63
PS (0 : 1)[b]	127 : 3	71 : 2	56 : 1	>0.99
Primary tumor site				
Appendix	1	1	0	
Cecum	5	4	1	
Ascending colon	27	17	10	
Transverse colon	11	4	7	
Descending colon	12	5	7	
Sigmoid colon	38	19	19	
Rectosigmoid	36	23	13	0.63
Depth of invasion[c]				
T1	5	2	3	
T2	6	2	4	
T3	83	47	36	
T4a	32	20	12	
T4b	4	2	2	0.48
Type of histology[d]				
tub1	14	8	6	
tub2	104	57	47	
por	6	4	2	
muc	6	4	2	0.89
Lymph node metastasis[c]				
N1a	42	19	23	
N1b	50	30	20	
N2a	18	12	6	
N2b	20	12	8	0.30
Stage[c]				
IIIA	9 (6.9%)	3 (4.1%)	6 (10.5%)	
IIIB	95 (73.1%)	56 (76.7%)	39 (68.4%)	
IIIC	26 (20.0%)	14 (19.2%)	12 (21.0%)	0.32
Risk group				
Low-risk (T1-3/N1)	68 (52.3%)	33 (45.2%)	35 (61.4%)	
High-risk (T4 and/or N2)	62 (47.7%)	40 (54.8%)	22 (38.6%)	0.07
No. of lymph node dissection[a]	19 (3–67)	20 (3–67)	18 (1–49)	0.27
No. of lymph node metastasis[a]	2 (1–24)	2 (1–24)	2 (1–20)	0.04
Lymphatic invasion	107 (82.3%)	59 (80.8%)	48 (84.2%)	0.65
Venous invasion	102 (78.5%)	56 (76.7%)	46 (80.7%)	0.58
Medical history	31 (23.8%)	24 (32.9%)	7 (12.3%)	<0.01
Hypertension	16	15	1	
Diabetes mellitus	10	8	2	
Preoperative complications	14 (10.8%)	7 (9.6%)	7 (12.3%)	0.78
Perforation	4	2	2	
Colon obstruction	10	5	5	
Lymph node dissection[d]				
D2	12 (9.2%)	5 (6.8%)	7 (12.3%)	
D3	118 (90.8%)	68 (93.2%)	50 (87.7%)	0.36
Treatment cycles[a]				
mFOFLOX6 4cycles ≤ or CAPOX 3cycles ≤	115 (88.5%)	68 (93.2%)	47 (82.5%)	
mFOFLOX6 4cycles > or CAOX 3cycles >	15 (11.5%)	5 (6.8%)	10 (17.5%)	0.06
Preoperative CEA[a] (mg/mL)	4.1 (0.3–153)	4.1 (0.3–74.1)	3.6 (0.8–153)	0.81
Preoperative CA19-9[a] (U/mL)	12.7 (0.6–297)	12.7 (0.6–102)	13.0 (0.8–297)	0.52

[a]Median (range)

[b]ECOG performance status

[c]According to the 7th TNM classification

[d]According to the Japanese classification of colorectal carcinoma

Table 2 List of patients showing early treatment discontinuation

No	Age (years)	Gender	Location	Stage[a]	Risk classification[b]	Regimen	Number of cycles	Reason for discontinuation	Toxicity	Relapse
1	75	Female	Descending	IIIB	Low	CAPOX	2	Patient's request	Anorexia G2/peripheral neurotoxicity G2	No
2	70	Male	Rectosigmoid	IIIB	Low	CAPOX	2	Investigator's decision	Retroperitoneal hematoma G2	Yes
3	64	Male	Ascending	IIIB	Low	CAPOX	2	Toxicity	Diarrhea G3	Yes
4	71	Female	Sigmoid	IIIB	Low	CAPOX	1	Toxicity	Diarrhea G3/vomiting G3	No
5	69	Male	Sigmoid	IIIB	Low	CAPOX	1	Patient's request	Fatigue G1	No
6	72	Male	Descending	IIIB	Low	CAPOX	1	Toxicity	Fatigue G3	No
7	43	Male	Rectosigmoid	IIIB	Low	mFOLFOX6	1	Toxicity	Thrombosis G3	Yes
8	60	Female	Rectosigmoid	IIIC	High	mFOLFOX6	2	Patient's request	Anorexia G2	No
9	57	Male	Ascending	IIIB	Low	mFOLFOX6	1	Toxicity	Allergy G3	Yes
10	71	Female	Cecum	IIIB	High	mFOLFOX6	2	Investigator's decision	Retroperitoneal abscess	Yes
11	63	Female	Ascending	IIIB	Low	CAPOX	1	Toxicity	Peripheral neurotoxicity G3	Yes
12	74	Male	Ascending	IIIB	Low	CAPOX	2	Patient's request	Diarrhea G2	No
13	67	Female	Rectosigmoid	IIIB	Low	CAPOX	1	Patient's request	Anorexia G2	Yes
14	71	Female	Sigmoid	IIIB	Low	CAPOX	3	Patient's request	Fatigue G2	No
15	74	Female	Ascending	IIIC	High	mFOLFOX6	1	Toxicity	Tremor G3	Yes

[a]According to the 7th TNM classification

[b]According to the IDEA COLLABORATION

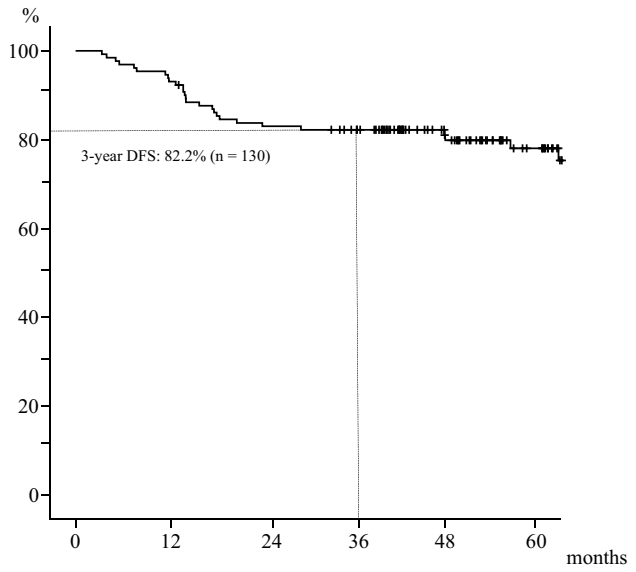

Fig. 1 Disease-free survival curves observed over a median of 59 months

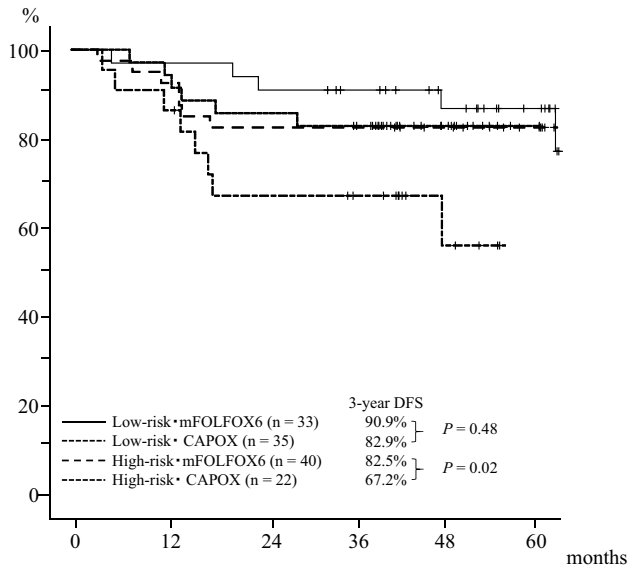

Fig. 2 Disease-free survival curves based on risk classification and regimen (——: low-risk mFOLFOXD6, – – – –: low-risk CAPOX, – – – –: high-risk mFOLFOX6, – – – –: high-risk CAPOX)

factors with $P < 0.1$, including type of treatment (CAPOX vs. mFOLFOX6) (HR 2.12; 95% CI 0.96–4.69; $P = 0.06$) and node status (N2 vs. N1) (HR 1.98; 95% CI 0.93–4.26; $P = 0.08$), were selected for the multivariate analysis with forward and backward selection. Regardless of the stepwise selection methods, stage IIIC (HR 3.55; 95% CI 1.64–7.68; $P = 0.0013$) and early discontinuation (HR 4.78; 95% CI 2.09–10.96; $P = 0.002$) were identified as significant independent risk factors for an unfavorable DFS.

Discussion

A phase II study of adjuvant chemotherapy was performed using an oxaliplatin-based regimen of mFOLFOX6/CAPOX for 6 months to treat stage III colon cancer following curative resection with standard lymph node dissection, as defined in the Japanese clinical guidelines [1]. The 3-year DFS was 82.2%, which exceeded the expected 3-year DFS of 81.7%. To our knowledge, the present report is the first of a prospectively designed clinical trial conducted in Japanese stage III colon cancer with oxaliplatin-based adjuvant chemotherapy where the DFS of stage III colon cancer patients was found to be greater than that reported in Europe and the United States, subsequently meeting the primary endpoint. As pointed out in European and US reports, the additional effects of adjuvant chemotherapy may be expected in not only high-risk patients but also low-risk stage III patients [17]. Our results may lead to a change in the perception of Japanese surgeons toward adjuvant chemotherapy for stage III colon cancer treatment, several of whom were skeptical of using oxaliplatin-based chemotherapy in practice at the initiation of the present study.

Our results showed that the DFS in patients receiving CAPOX tended to be inferior to that in patients receiving mFOLFOX6 despite the fact that there was no significant difference in the relative dose intensity (RDI) of oxaliplatin between the two treatment groups and that the RDI of 5-FU in the mFOLFOX6 group and that of capecitabine in the CAPOX group were considered equivalently high, as we previously reported [14]. Although we noted a slight trend toward early discontinuation in the CAPOX group ($P = 0.06$), neither CAPOX nor mFOLFOX6 showed any influence on the DFS in the multivariate analysis. Although the results of studies originally aimed at different endpoints should not be compared, our outcomes were equivalent or better than the DFS obtained after 6-month administration in the IDEA COLLABORATION study.

Nonetheless, treatment was discontinued because of AEs in 14 patients (19.2%) in the mFOLFOX6 group and 8 (14.0%) in the CAPOX group, as documented in our previous report [14], and in approximately 10% of cases, the early discontinuation of treatment was recorded as being due to non-hematological grade 3 toxicity or to patient request associated with grade < 2 toxicity. According to multivariate analyses for an unfavorable DFS, early discontinuation was an independent risk factor. A few reports have determined the incomplete administration of 5-FU-based regimens for adjuvant stage III colon cancer treatment to be a risk factor for a poorer prognosis compared with complete

Table 3 Risk factors for a poor DFS by univariate and multivariate analyses

	3-year DFS (%)	Univariate regression analysis			Multivariate regression analysis		
		HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
Age (years)							
< 70 (*n* = 96)	83.2	1					
≥ 70 (*n* = 34)	79.4	1.28	(0.56–2.92)	0.56			
Sex							
Male	81.1	1					
Female	84.0	0.80	(0.36–1.79)	0.58			
Primary tumor site							
Right side	83.9	1					
Left side	81.4	1.45	(0.61–3.45)	0.40			
Depth of invasion[a]							
T1–T3	85.1	1					
T4	74.6	1.39	(0.62–3.09)	0.43			
Type of histology[a]							
tub1, tub2	81.3	1					
por, muc	91.7	0.33	(0.04–2.40)	0.27			
Lymph node metastasis[a]							
N1	85.8	1					
N2	73.7	1.98	(0.93–4.26)	0.08			
Stage[a]							
IIIA, IIIB	87.5	1					
IIIC	60.3	3.39	(1.57–7.31)	< 0.01	3.55	(1.64–7.68)	0.0013
Risk group[b]							
Low risk	86.8	1					
High risk	73.7	1.62	(0.75–3.51)	0.22			
Lymphatic invasion							
Negative	78.3	1					
Positive	83.1	0.89	(0.34–2.34)	0.81			
Venous invasion							
Negative	78.6	1					
Positive	83.2	0.94	(0.38–2.32)	0.88			
Treatment							
mFOLFOX6	86.3	1					
CAPOX	76.9	2.12	(0.96–4.69)	0.06			
Treatment cycles							
mFOFLOX6 ≥ 4 cycles or CAPOX ≥ 3 cycles	86.9	1					
mFOFLOX6 < 4 cycles or CAPOX < 3 cycles	46.7	4.55	(2.0–10.0)	< 0.01	4.78	(2.09–10.96)	0.002
Preoperative CEA							
≤ 5.0 ng/mL (*n* = 70)	87.1	1					
> 5.0 ng/mL (*n* = 52)	76.9	1.42	(0.65–3.12)	0.38			
Preoperative CA19-9							
≤ 37 U/mL (*n* = 100)	83.9	1					
> 37 U/mL (*n* = 21)	76.2	1.30	(0.49–3.46)	0.60			

DFS disease-free survival, *HR* hazard ratio, *CI* confidence interval

[a]According to the 7th TNM classification

[b]According to IDEA COLLABORATION

administration [18–20]. However, no similar reports concerning oxaliplatin-based regimens have been published. Several reports have shown no marked difference in the prognosis between complete and incomplete administration in oxaliplatin-based adjuvant chemotherapy for stage III colon cancer [21, 22]. Furthermore, in analyses of 532 cases undergoing oxaliplatin-based regimens, dose reduction was not a significant risk factor for an inferior prognosis [23]. However, the above-mentioned studies included comparisons to a treatment period or dose of approximately two-thirds for 6-month treatment. There have been no previous reports showing that early discontinuation at < 2 months of treatment is a significant risk factor for an unfavorable DFS in patients undergoing oxaliplatin-based adjuvant chemotherapy. However, because our study included a limited number of cases, further studies with a larger number of cases are needed to verify whether or not early discontinuation is a definitive risk factor in terms of the DFS.

In summary, even though our trial was a single-arm phase II study performed with a limited number of cases, we consider the benefit of oxaliplatin-based adjuvant chemotherapy to be substantial in Japanese patients with stage III colon cancer undergoing D2 or D3 lymph node dissection. In addition, patients undergoing fewer treatment cycles had a significantly poorer DFS than those undergoing more treatment cycles and in a significant proportion of such patients, the reason for discontinuation was the patient's own desire to discontinue due to toxicity within one or two cycles. In other words, the prognosis of patients with 2 months of treatment or less might be very poor. Therefore, supportive therapy for toxicity is considered very important, at least for the first 3 months, with continuing treatment with additional oxaliplatin-based adjuvant chemotherapy for stage III colon cancer.

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Compliance with ethical standards

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