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Early results of multicenter phase II trial of perioperative oxaliplatin and capecitabine without radiotherapy for high-risk rectal cancer: CORONA I study

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Abstract

Backgrounds: Perioperative introduction of developed chemotherapy into the treatment strategy for locally advanced rectal cancer (LARC) may be a promising option. However, the most prevalent treatment for high-risk LARC remains preoperative chemoradiotherapy (CRT) in Western countries.

Patients and methods: A phase II trial was undertaken to evaluate safety and efficacy of perioperative XELOX without radiotherapy (RT) for patients with high-risk LARC. Patients received 4 cycles of XELOX before and after surgery, respectively. Primary endpoint was disease-free survival.

Results: We enrolled 41 patients between June 2012 and April 2014. The completion rate of the preoperative XELOX was 90.3%. Twenty-nine patients (70.7%) could start postoperative XELOX, 15 of these patients (51.7%) completed 4 cycles. Allergic reaction to oxaliplatin was experienced by 5 patients (17.2%) during postoperative XELOX. One patient received additional RT after preoperative XELOX. Consequently, the remaining 40 patients underwent primary resection. Major complications occurred in 6 of 40 patients (15.0%). Pathological complete response (pCR) rate was 12.2%, and good tumor regression was exhibited in 31.7%. N down-staging (cN+ to ypN0) and T down-staging were detected in 56.7% and 52.5%, respectively. Clinical T4 tumor was a predictor of poor pathological response ($p < 0.001$).

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Conclusions: We could show the favorable pCR rate after preoperative XELOX alone. However, the T and N down-staging rate was likely to be insufficient. When tumor regression is essential for curative resection, the use of preoperative CRT is likely to be recommended. For patients with massive LN metastasis, the additional Bev to NAC might be a promising option.

Keywords: Rectal cancer; Perioperative chemotherapy; Neoadjuvant treatment

Introduction

Preoperative chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC) significantly reduces local failure but does not improve survival.[1,2] To improve survival, not only an improvement in local control but also a decrease in distant metastasis is extremely important. Perioperative introduction of developed chemotherapy into the treatment strategy for LARC may be a promising option.[3–8] The NCCN guidelines adopted the strategy of induction chemotherapy in August 2014. Induction chemotherapy followed by CRT and surgery has been noted on their home page as an option for LARC.[9]

Several studies to evaluate the safety and efficacy of neoadjuvant chemotherapy (NAC) alone have been attempted in Western countries and Japan.[10–13] A pilot study from Memorial Sloan-Kettering Cancer Center reported preliminary results of NAC alone in 32 patients with intermediate-risk rectal cancer, which included stage II/III LARC but excluded diseases with cT4, a threatened circumferential resection margin, or requiring abdominoperineal resection.[10] This study evaluated the efficacy of neoadjuvant FOLFOX (oxaliplatin + fluorouracil [FU] + leucovorin) + bevacizumab (Bev) without radiotherapy (RT) followed by total mesorectal excision (TME) and showed excellent short-term results. Although additional RT was planned for non-responders to NAC, all patients responded to NAC, and all underwent R0 resection without additional RT. The pathological complete response (pCR) rate was 32%. Based on these promising short-term results, a large randomized phase II/III study (PROSPECT trial: NCT01515787) comparing preoperative conventional CRT with neoadjuvant FOLFOX alone for intermediate-risk rectal cancer is ongoing in the United States. Another large randomized phase II trial (BACCHUS trial: NCT01650428) comparing neoadjuvant FOLFOX + Bev with FOLFOXILI (oxaliplatin + irinotecan + FU + leucovorin) + Bev is being performed in the UK.[14] However, the most prevalent treatment for high-risk LARC remains preoperative CRT in Western countries.

In addition, several trials evaluating the safety and efficacy of NAC alone for high-risk LARC have been conducted in Japan.[11–13] We performed the N-SOG03 trial, which evaluated the safety and efficacy of neoadjuvant XELOX (capecitabine and oxaliplatin) + Bev, and showed satisfactory short-term results with a completion rate of 84.4% and pCR rate of 13.3%.[12] In that trial, a high rate of Bev-related toxicity such as anastomotic leakage was a serious problem. Therefore, we conducted the current prospective study to confirm the safety and efficacy of perioperative XELOX alone in patients with high-risk LARC. Although the primary endpoint of this study was disease-free survival (DFS), this report showed the results of an interim analysis of safety and short-term outcomes.

Patients and methods

Patients

A multicenter phase II trial was undertaken to evaluate the safety and efficacy of perioperative XELOX for patients with LARC. Baseline assessment included clinical examination, total colonoscopy, chest and abdominopelvic computed tomography, and pelvic magnetic resonance imaging (MRI). Lymph nodes (LNs) >5 mm were considered positive. Eligibility was evaluated in accordance with the classification by the Japanese Society for Cancer of Colon and Rectum,[15] and all patients were additionally staged using the seventh edition of the International Union Against Cancer TNM classification. Eligible patients had high-risk rectal cancer and were candidates for R0 resection. High-risk rectal cancer was defined by MRI findings; that is, a cT3 $\geq$ tumor located in the low rectum, a tumor extending to within 1 mm of or beyond the mesorectal fascia, a tumor extending 5 mm or more into peripheral fat, a cT4 tumor, or a tumor with a positive LN.

Perioperative chemotherapy

Oxaliplatin (130 mg/m^2) was administered on day 1 and capecitabine was given orally at a dose of 2000 mg/m^2/d, which was divided into 2 split daily doses for 14 days followed by 7 days of rest. This regimen was repeated every 3 weeks and was administered for 4 cycles before and after surgery, respectively. Postoperative XELOX was started within 56 days after surgery. Relative dose-intensity (RDI) was calculated as the actual dose-intensity divided by the planned dose-intensity and multiplied by 100. Adverse events were assessed according to the Common Toxicity Criteria of the National Cancer Institute (version 3.0).

Surgery

Preoperative reevaluation of the tumor was the same as the pretreatment evaluation. Objective response was assessed on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[16] Complete response and partial response was regarded as objective responses. TME or tumor-specific mesorectal excision with bilateral autonomic nerve preservation was basically performed 2–8 weeks after the completion of chemotherapy. A tumor located at or below the peritoneal reflection was an indication for lateral pelvic LN dissection according to the Japanese guidelines.[15] For patients requiring extended resection to achieve R0 resection, combined resection of the autonomic nerve, pelvic vessels and/or adjacent organs was at the surgeons' discretion, although recommendations were given by the multidisciplinary team. For patients with consequent R1/2 resection or non-resection, subsequent therapy was not stipulated and was decided by each clinician.

Pathological assessment

Resected specimens were subjected to conventional processing. Grades of histological regression were assessed according to the tumor regression grade (TRG) proposed by Dworak et al.[17] Patients were divided into 2 groups according to the regression grade: responders (TRG 3/4) and non-responders (TRG 0–2).

Endpoints and statistical analysis

The primary endpoint of this study was disease-free survival DFS. Secondary endpoints were overall survival, local recurrence-free survival, objective response rate, R0 resection rate, pathological response rate, RDI, and rate of the adverse events. Calculation of the sample size was based on an expected 3-year DFS of 70% and a threshold 3-year DFS of 50%, using a 2-sided alpha error of 0.05 and a statistical power of 80%. The planned sample size was 40 patients, allowing for a 10% dropout rate.

We evaluated the short-term outcome of this study. Variables were compared by the Chi-squared test and a value of $p < 0.05$ was considered to be statistically significant. Statistical analysis was done using SPSS software version 20.0 (IBM Japan Ltd., Tokyo, Japan).

This trial was registered in the UMIN Clinical Trials Registry (www.umin.ac.jp/ctr/) as 000008316.

Results

We enrolled 41 patients (30 males and 11 females; median age of 63 years) at 9 participating hospitals between June 2012 and April 2014. The baseline clinical characteristics of the 41 patients are summarized in Table 1. The median body mass index was 21.1 kg/m^2. The depth of the tumors was cT3 in 61.0% of the patients, cT4a in 12.2% and cT4b in 26.8%, and 75.6% of the patients were judged to have clinically positive LNs, including lateral LNs in 9.8% of the patients.

Table 1
Baseline characteristics of 41 patients.

	No.	%
Gender		
Male	30	73.2
Female	11	26.8
Age (years)		
Median	63	
Range	37–79	
ECOG performance status		
0	39	95.1
1	2	4.9
BMI (kg/m^2)		
<20	14	34.2
20≤, <24	15	36.6
≥24	12	29.2
Median	21.1	
Range	15.4–28.1	
Tumor size (mm)		
Median	46	
Range	14–120	
Distance from the AV (cm)		
<5	23	56.1
5≤, <9	15	36.6
≥9	3	7.3
Median	4.5	
Range	0–12	
Clinical T stage		
T3	25	61.0
T4a	5	12.2
T4b	11	26.8
Clinical N stage		
N0	10	24.4
N1	15	36.6
N2	16	39.0
Lateral LN metastasis		
Absent	37	90.2
Present	4	9.8
Baseline CEA level (ng/ml)		
≤5.0	14	34.2
5.1–30	21	51.2
>30	6	14.6
Median	7.7	
Range	1.2–129.8	
Histological grade		
Well differentiated	13	31.7
Moderately differentiated	24	58.5
Poorly differentiated	4	9.8

ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; AV, anal verge; LN, lymph node; CEA, carcinoembryonic antigen.

Table 2 shows treatment exposure and the incidence of adverse events during perioperative chemotherapy. During the preoperative period, grade 3/4 toxicity was experienced by 10 of 41 patients (24.4%). The completion rate of the scheduled 4 cycles of preoperative XELOX was 90.3%. Reasons for withdrawal were pancytopenia (n = 3) and allergic reaction (AR) to oxaliplatin during the 2nd cycle

Table 2
Treatment exposure and incidence of adverse events during chemotherapy.

Treatment exposure	Preoperative XELOX (n = 41)		Postoperative XELOX (n = 29)	
	No.	%	No.	%
Number of cycles				
4	37	90.3	15	51.7
3	3	7.3	6	20.7
2	1	2.4	6	20.7
1	0		2	6.9
Dose reductions	11	26.8	12	41.4
Delayed cycles	17	41.5	17	58.6
RDI (mean ± SD, %)				
Capecitabine	94.1	±0.5	87.9	±0.5
Oxaliplatin	92.7	±0.5	80.4	±0.5
Adverse events[a]	Any grade (%)	≥G3 (%)	Any grade (%)	≥G3 (%)
Leukopenia	36.6	0	41.4	3.4
Neutropenia	39.2	2.4	48.3	10.3
Anemia	39.2	0	55.2	0
Thrombocytopenia	63.4	14.6	75.9	0
Febrile neutropenia	0	0	3.4	3.4
AST	61.0	0	65.5	3.4
ALT	46.3	2.4	34.5	3.4
Total bilirubin	14.6	0	31.0	0
Nausea	26.8	2.4	17.2	0
Vomiting	4.9	2.4	6.9	0
Fatigue	29.3	2.4	17.2	3.4
Diarrhea	4.9	2.4	10.3	3.4
Appetite loss	48.8	4.9	48.3	0
Hand-foot syndrome	29.3	0	10.3	0
Peripheral neuropathy	84.4	3.1	82.8	3.4
Allergy	2.4	0	17.2	0

[a] National Cancer Institute Common Toxicity Criteria, version 3.0.; RDI, relative dose-intensity; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

(n = 1). The mean RDIs of capecitabine and oxaliplatin were 94.1% and 92.7%, respectively. Twenty-nine patients (70.7%) started postoperative XELOX, of whom 15 (51.7%) completed 4 cycles of XELOX. The main reasons why postoperative chemotherapy did not started were R2 resection (n = 3) patients' refusal (n = 2), postoperative complications (n = 2), and local progression during the preoperative period (n = 2). During the postoperative period, grade 3/4 toxicity was experienced by 6 of those 29 patients (20.7%). AR to oxaliplatin was experienced by 5 patients (17.2%). The mean RDIs of capecitabine and oxaliplatin for 29 patients were 87.9% and 80.4%, respectively.

Surgical and pathological results are shown in Table 3. The preoperative evaluation of the objective response showed that 24 of the 41 patients (58.5%) were responders. However, 3 patients were judged to have progressive disease, because of local progression (n = 2) or newly developed liver metastasis (n = 1). They underwent primary tumor resection without additional RT or chemotherapy. Another patient was judged to have stable disease, but permanent colostomy was recommended. He hoped for sphincter-preservation and received additional RT at an outside institution. Consequently, the remaining 40 patients underwent primary resection. On laparotomy, 1 patient was found to have diffuse peritoneal dissemination and received only primary resection (R2 resection). As to pathological findings of the entire cohort, the R0 resection rate was 90.2%, pCR rate was 12.2%, and good tumor regression was exhibited in 31.7%.

Table 4 shows the relationship between clinical stage at baseline and the pathological staging. N down-staging (cN+ to ypN0) and T down-staging were detected in 17 of 30 patients (56.7%) and in 21 of 40 patients (52.5%), respectively. Six of 11 patients (54.5%) with a cT4b tumor remained ypT4b. Table 5 showed the results of the univariate analysis of factors affecting the pathological response. A clinical T4 tumor was a predictor of poor pathological response ($p < 0.001$).

Discussion

To improve survival after rectal resection, the suppression of distant metastasis is essential. Although adjuvant developed chemotherapy is likely to improve survival,[18] the low induction rate after curative surgery is a serious problem.[5,19] The introduction of developed chemotherapy during the preoperative period might be a promising alternative method. Various approaches, such as induction chemotherapy,[5–7] consolidation chemotherapy,[8] and concomitant use of chemotherapy with RT,[3,4] have been attempted worldwide. NAC alone is another novel approach to intermediate-risk LARC, which may take the place of conventional CRT.[10] However, the basis of standard treatment for high-risk LARC remains preoperative CRT in Western countries. In this study, we evaluated the safety and efficacy of perioperative XELOX alone for high-risk LARC and achieved a pCR rate equivalent to that after conventional CRT, which was reported to be 10–18%.[20–24]

In Japan, NAC alone for high-risk LARC has been gradually accepted in clinical practice even though clear evidence of its efficacy has been lacking. Reasons for its acceptance are as follows. First, upfront surgery is the Japanese standard and is recommended in guidelines.[15] Second, the efficacy of oxaliplatin-based adjuvant chemotherapy remains unclear after upfront surgery, and use of the oral FU is not unusual in daily practice.[25] The use of developed chemotherapy in a neoadjuvant setting is expected to not only bring favorable local results but also have a systemic effect, and could be a promising alternative method for treatment of high-risk LARC in Japan. The rationale is to shift part of oxaliplatin-based adjuvant chemotherapy to the preoperative period. However, there are still many problems to be resolved in this treatment approach including determining the preferred chemotherapy regimen, the optimal chemotherapy period, and whether a targeted drug is required.

In this trial, the half of adjuvant chemotherapy was shifted to the preoperative period, because to shift the total

Table 3
Surgical and pathological results (n = 41).

	No.	%
Objective response (RECIST)		
Complete response	1	2.4
Partial response	23	56.1
Stable disease	14	34.2
Progressive disease	3	7.3
Operative procedures (n = 40)		
Low anterior resection	18	45.0
Intersphincteric resection	7	17.5
Hartmann	1	2.5
Abdominoperineal resection	12	30.0
Total pelvic exenteration	2	5.0
Lateral lymph node dissection (n = 40)		
Bilateral	20	50.0
Unilateral	5	12.5
No	15	37.5
Approach (n = 40)		
Open	19	47.5
Laparoscopic	21	52.5
Postoperative complications (n = 40)		
Any complications	18	45.0
Major complications[a]	6	15.0
Ileus	7	17.5
Anastomotic leakage	3/25	12.0
Wound sepsis	2	5.0
Bleeding	1	2.5
Pelvic sepsis	0	0
Residual tumor classification (local)		
R0	37	90.3
R1	2	4.9
R2	1	2.4
NA	1	2.4
Tumor regression grade		
4 (pCR)	5	12.2
3	8	19.5
2	11	26.8
1	12	29.3
0	4	9.8
NA	1	2.4
ypStage		
pCR	5	12.2
I	7	17.1
II	14	34.1
III	12	29.3
IV	2	4.9
NA	1	2.4

[a] ≥Grade 3 according to the Clavien–Dindo classification; RECIST, Response Evaluation Criteria in Solid Tumors; NA, not available; pCR, pathological complete response.

chemotherapy was considered to prolong excessively the period of neoadjuvant treatment. In this sandwich treatment, the exposure to adjuvant chemotherapy is interesting and important point. The EORTC 22921 trial showed that, although 73% of the patients could start planned adjuvant FU, only 66% could complete 4 cycles of chemotherapy after preoperative RT. The GCR-3 trial showed that the scheduled 4 cycles of adjuvant XELOX could be completed in 54% of the patients after CRT and oxaliplatin. We expected that omission of preoperative RT would decrease the systemic stress in patients and increase the exposure to adjuvant chemotherapy. Although the induction rate of adjuvant XELOX after NAC alone was 70.7%, only 36.6% of patients completed the scheduled 4 cycles. The exposure to adjuvant chemotherapy after NAC alone was similar to that after CRT.

Table 4
Relationship between baseline and pathological staging (n = 40).

Clinical stage (baseline)	Pathological stage					
	ypCR	ypT1	ypT2	ypT3	ypT4b	ypN+
cT3 (n = 25)	5	2	5	11	2	
cT4a (n = 4)			1	3		
cT4b (n = 11)		1	2	2	6	
cN0 (n = 10)						1
cN+ (n = 30)						13
Total (n = 40)	5	3	8	16	8	14

AR to oxaliplatin might be a reason of low completion rate of adjuvant chemotherapy. In this trial, an AR to oxaliplatin was experienced in 17.2% of patients during the postoperative period, although the rate was only 2.4% during the preoperative period. The incidence of any grade AR to oxaliplatin was reported to be 3.3–17%.[26–30] It depends on simply the cumulative dose of oxaliplatin. However, Mori et al. pointed out that an oxaliplatin-free interval was a risk factor for AR.[28] In that study, the incidence of

Table 5
Factors affecting the pathological response.

	Total n = 40	Pathological responder n = 13	Pathological non-responder n = 27	p Value[a]
Tumor size				0.090
≤50 mm	26	11	15	
>50 mm	14	2	12	
Clinical T stage				<0.001
cT4	15	0	15	
≤cT3	25	13	12	
Clinical N status				1.000
cN0	10	3	7	
cN (+)	30	10	20	
Baseline CEA level				0.722
≤5.0 ng/ml	13	5	8	
>5.0 ng/ml	27	8	19	
Histological grade				0.242
Differentiated	37	11	26	
Non-differentiated	3	2	1	
Preoperative XELOX				0.284
4 cycles	36	13	23	
≤3 cycles	4	0	4	
RDI of preoperative oxaliplatin				0.154
≥80%	35	13	22	
<80%	5	0	5	
RDI of preoperative capecitabine				0.284
≥80%	36	13	23	
<80%	4	0	4	

[a] Responder vs. non-responder; CEA, carcinoembryonic antigen; RDI, relative dose-intensity.

ARs in patients who received stop-and-go FOLFOX was 41%. Interestingly, most ARs were observed during the 2nd or 3rd cycle of the reintroduction phase. The CCOG-0704 study also showed the high incidence (33.3%) of any grade AR during the reintroduction phase.[29] In our study, 4 of the 5 patients with an AR were observed during the 2nd or 3rd cycle in the postoperative period. The rest period for oxaliplatin in this treatment strategy might promote the incidence of AR.

Preoperative use of Bev is expected to increase tumor response and improve survival. We retrospectively showed that the preoperative use of Bev inhibited microvessel density in tumor tissue, and achieved better clinical and pathological response compared with chemotherapy alone.[31] However, Bev-related delayed wound healing is a serious problem for surgeons.[32] Our previous study suggested that preoperative Bev seemed to increase Bev-related postoperative major complications such as anastomotic leakage.[12] In this trial, we omitted Bev; nevertheless, the pCR rate was 12.2%, and good tumor regression was exhibited in 31.7% of patients. These results were equivalent to those of our previous trial using XELOX + Bev (pCR rate, 13.3%; good tumor regression, 36.7%). Moreover, the rate of anastomotic leakage in patients who underwent sphincter-preserving surgery decreased to 12% compared with our previous study (25%). This result suggested that neoadjuvant chemotherapy alone without Bev did not necessarily increase the postoperative anastomotic leakage.

Despite the favorable pathological response to XELOX alone, the rate of N down-staging (56.7%) was inferior to that in the previous reports of regimens including Bev (79–83%).[12,13] A survival benefit associated with the preoperative use of Bev has not been shown yet. Additionally, large randomized trials failed to show the survival benefit of Bev in an adjuvant setting for colonic cancer.[33,34] However, regimens that include Bev might increase the cytotoxic effect on LN metastasis. Therefore, we should carefully investigate the long-term effect of the preoperative use of Bev. The low T down-staging rate was another important point. Chua et al. reported that induction XELOX followed by CRT achieved an excellent T down-staging rate (100%) even in T4 disease.[6] Potency of local control by NAC alone might be inferior to that with RT. Although, obvious cT4b disease is actually an indication for combined resection, we must take this fact into consideration when we select organ-preserving surgery especially for patients with initially T4b-suspected disease. More intensive chemotherapy or additional RT is likely to be preferred in such a situation.

Conclusion

We could show the favorable pCR rate after preoperative XELOX alone for LARC. However, the T and N down-staging rate was likely to be insufficient. When tumor regression is essential for curative resection, the use of preoperative CRT is likely to be recommended. For patients with massive LN metastasis, the additional Bev to NAC might be a promising option. For cN2 tumor, the efficacy of additional Bev to NAC should be investigated in the future clinical trial.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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