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Clinical Trial Results

A Phase II Study of Perioperative Capecitabine Plus Oxaliplatin Therapy for Clinical SS/SE N1-3 M0 Gastric Cancer (OGSG 1601)

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Trial Information

- **ClinicalTrials.gov Identifier:** UMIN000021641, jRCTs051180109
- **Sponsor(s):** Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG)
- **Principal Investigator:** Masahiro Goto
- **IRB Approved:** Yes

Lessons Learned

- Perioperative capecitabine and oxaliplatin (CapeOx) therapy showed favorable efficacy with sufficient pathological response. Small sample size limited the statistical power of this result.
- Perioperative CapeOx therapy showed good feasibility.
- Further studies with larger sample size are required to validate this novel approach.

Abstract

Background. D2 gastrectomy followed by adjuvant S-1 is the standard therapy for patients (pts) with stage III gastric cancer (GC) in Japan; however, the outcome is not satisfactory. We examined the efficacy of perioperative capecitabine and oxaliplatin (CapeOx) in pts with GC.

Methods. The eligibility criteria included confirmed clinical T3 (SS)/T4a(SE) N1-3 M0 GC according to the Japanese Classification (JCGC; 3rd English Edition). Three cycles of neoadjuvant CapeOx (NAC; capecitabine, 2,000 mg/m^2 for 14 days; oxaliplatin, 130 mg/m^2 on day 1, every 3 weeks) were administered, followed by five cycles of adjuvant CapeOx (AC) after D2 gastrectomy. The primary endpoint was the pathological response rate (pRR) according to the JCGC (≥grade 1b).

Results. Thirty-seven pts were enrolled on CapeOx. An R0 resection rate of 78.4% (n = 29) and a pRR of 54.1% (n = 20, p = .058; 90% confidence interval [CI], 39.4–68.2) were demonstrated. Among 27 pts who initiated AC, 21 (63.6%) completed the treatment. Grade 3–4 toxicities during NAC included neutropenia (8%), thrombocytopenia (8%), and anorexia (8%) and during AC included neutropenia (37%), diarrhea (4%), and anorexia (4%).

Conclusion. Perioperative CapeOx showed good feasibility and favorable efficacy with sufficient pathological response, although statistical significance at .058 did not reach the commonly accepted cutoff of .05. The data obtained using this novel approach warrant further investigations. ***The Oncologist*** 2019;24:1–9

Discussion

The present study is the first to demonstrate the efficacy and safety of perioperative capecitabine plus oxaliplatin (CapeOx) in clinical T3(SS)/T4a(SE) N1-3 M0 gastric cancer

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Table 1. Surgical complications (n = 33)

Surgical complications	I	II	IIIa	IIIb	Iva
Ileus	0	1 (3.0)	0	1 (3.0)	0
Paralytic ileus	0	1 (3.0)	0	0	0
Weight loss	1 (3.0)	0	0	0	0
Intraabdominal abscess	0	0	1 (3.0)	0	0
Anastomotic leakage	0	0	1 (3.0)	0	0
Pancreatic fistule	0	1 (3.0)	0	0	0

Clavien-Dindo criteria.

(GC). Importantly, the pathological response of CapeOx was evaluated via independent central review by pathologists. Perioperative CapeOx showed acceptable feasibility and favorable efficacy with sufficient pathological response as demonstrated by a pathological response rate (pRR) value of 54.1% (n = 20), including 2.7% (n = 1) complete response (90% confidence interval [CI], 39.4%–68.2%; p = .058).

The pRR was set as the primary endpoint in this study, given that resectable GCs rarely have measurable lesions, although the RECIST criteria is the current gold standard for the evaluation of tumor response. The pathological response, grade Ib or greater according to Japanese classification of gastric carcinoma (JCGC), has been adopted as the best surrogate endpoint for overall survival (OS) for GC in this setting [1]. Furthermore, a pathological response of grade Ib or greater according to JCGC predicted the survival [2]. Thus, a pathological response equivalent to or higher than grade Ib according to the JCGC criteria was determined as the primary endpoint. Previously, pilot phase II studies evaluating two or four cycles of neoadjuvant S-1 plus cisplatin therapy for locally advanced GC demonstrated a pRR of 40%–55%, but the target lesions were limited to bulky lymph nodes or CY metastasis [3, 4]. These values are similar to the pRR obtained in the present study; however, the small sample size in this study may account for the lower limit of the 90% CI (39.4).

With regard to safety, both neoadjuvant and adjuvant CapeOx therapies showed good tolerability. In the neoadjuvant treatment, the hematologic and nonhematological toxicities were comparable with neoadjuvant S-1 plus oxaliplatin (SOX) [5]. In addition, the major complications of surgery were comparable to neoadjuvant SOX, where the incidences of grade IIIb complication of postoperative ileus, grade IIIa intraabdominal abscess, and grade IIIa anastomotic leakage were found in 3% of patients (Table 1) [5]. In the adjuvant CapeOx phase, fewer incidences of nonhematological toxicities, such as diarrhea, anorexia, vomiting, and fatigue, were noted when compared with the J-CLASSIC trial, a phase II trial of adjuvant CapeOx therapy conducted for pathological stage III GC in Japan. This discordance is possibly due to the starting dose of the adjuvant perioperative CapeOx regimen, which was adjusted according to the last dose of the neoadjuvant CapeOx or the body surface area after gastrostomy, whichever was lower, making the adjuvant CapeOx therapy more feasible even after gastrectomy.

In conclusion, perioperative CapeOx treatment showed good feasibility and favorable efficacy with sufficient pathological response. Nevertheless, further studies with larger sample size are required to validate this novel approach.

Trial Information	
Disease	Gastric cancer
Disease	Advanced cancer
Stage of Disease/Treatment	Neoadjuvant
Prior Therapy	None
Type of study – 1	Phase II
Type of study – 2	Single arm
Primary Endpoint	Pathological response rate
Secondary Endpoint	3-year recurrence-free survival rate
Secondary Endpoint	Percentage completion of the protocol treatment
Secondary Endpoint	Relative dose intensity (RDI) of neoadjuvant chemotherapy
Secondary Endpoint	RDI of adjuvant chemotherapy
Secondary Endpoint	3-year overall survival rate
Secondary Endpoint	Percentage completion of adjuvant chemotherapy
Secondary Endpoint	Overall response rate
Secondary Endpoint	Safety
Secondary Endpoint	Surgical complications

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Additional Details of Endpoints or Study Design

The primary endpoint was a pRR classified according to the 3rd English Edition JCGC [6] as follows: grade 0, the tumor was not affected; grade 1a, less than one-third of the tumor was affected; grade 1b, one- to two-thirds of the tumor was affected; grade 2, greater than or equal to two-thirds was affected; and grade 3, no residual tumor [7]. A pathological response was defined as grade 1b or greater. The pathological response for the tumor was evaluated via independent central review by pathologists according to the JCGC and Becker regression criteria [8].

The secondary endpoints were the percent completion of the protocol treatment, RDI of neoadjuvant chemotherapy, RDI of adjuvant chemotherapy, 3-year OS rate, 3-year RFS rate, percent completion of adjuvant chemotherapy, overall response rate (RR) [9], and safety. RDI was defined as the dose received divided by the planned dose. The OS was defined as the number of days from enrollment to death due to any cause and was censored at the last day of the patient's life. RFS was defined as the number of days from enrollment to the date of recurrence of the original GC or death. RR was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). Adverse events were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0), and surgical complications were evaluated using the Clavien-Dindo criteria.

OGSG1601 was a multicenter phase II study conducted to evaluate the efficacy and safety of perioperative CapeOx therapy. The sample size was 34 patients, which was calculated on the hypothesis that the expected pRR was 65% and the threshold was 40%, with a one-sided α of 0.05 and a β of 0.1, according to exact *p* value methods. The total sample size was set at 37 patients to account for deviation. All statistical analyses were conducted at the Osaka Gastrointestinal cancer chemotherapy Study Group (OGSG) Data Center. Statistical analyses were conducted with R, version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Investigator's Analysis	Correlative endpoints not met but clinical activity observed

Drug Information

Drug 1	
Generic/Working Name	Capecitabine
Dose	2,000 mg/m^2
Route	Oral (po)
Schedule of Administration	Day 1–14, every 3 weeks Three cycles of neoadjuvant chemotherapy and five cycles of adjuvant chemotherapy were administered
Drug 2	
Generic/Working Name	Oxaliplatin
Trade Name	
Company Name	Yakult Honsha Co., Ltd.
Dose	130 mg/m^2
Route	Intravenooous
Schedule of Administration	Day 1, every 3 weeks We planned three cycles of NAC and five cycles of adjuvant therapy.

Patient Characteristics

Number of Patients, Male	28 (75.7%)
Number of Patients, Female	9 (24.3%)
Stage	
cT factor	
3 (SS)	14 (37.8)
4a (SE)	23 (62.2)
cN factor	
1	20 (54.1)
2	15 (40.5)
3	2 (5.4)
Clinical stage	
IIB	9 (24.3)
IIIA	13 (35.1)
IIIB	13 (35.1)
IIIC	2 (5.4)

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Age	Median (range): 65 (38–81)
Number of Prior Systemic Therapies	Median (range): not collected
Performance Status: ECOG	0 — 29 (78.4%) 1 — 8 (21.6%)
Other	
Baseline characteristics of patients	*n* (%)
Tumor Location	
Upper third	11 (29.7)
Middle third	12 (32.4)
Lower third	14 (37.8)
Macroscopic type	
1	1 (2.7)
2	6 (16.2)
3	29 (78.4)
4	0 (0)
5	1 (2.7)
Cancer Types or Histologic Subtypes	Tubular adenocarcinoma, 17 (45.9%); poorly differentiated, signet ring, or mutinous adenocarcinoma, 20 (54.1%)

Primary Assessment Method

Title	New assessment/pathological response
Number of Patients Enrolled	37
Number of Patients Evaluable for Toxicity	37
Evaluation Method	JCGC, Becker regression criteria
Outcome Notes	
Pathological response	*n* (%)
JCGC	
Grade 0	0 (0)
Grade 1a	13 (35.1)
Grade 1b	8 (21.6)
Grade 2	11 (29.7)
Grade 3	1 (2.7)
No surgery	4 (10.8)
pRR	54.1% (90% CI, 39.4–68.2)
Becker regression criteria	
Grade 1a	1 (2.7)
Grade 1b	2 (54.1)
Grade 2	16 (43.2)
Grade 3	14 (37.8)
No surgery	4 (10.8)
pRR	19 (51.4) (95% CI:34.4–68.1)

Pathological response was classified according to the 3rd English Edition JCGC: grade 0, the tumor was not affected; grade 1a, less than one-third of the tumor was affected; grade 1b, one- to two-thirds of the tumor was affected; grade 2, greater than or equal to two-thirds was affected; and grade 3, no residual tumor. A pathological response was defined as grade 1b or greater.
Becker regression criteria included the following categories: grade 1a, complete regression; grade 1b, subtotal regression; <10% residual tumor; grade 2, partial regression; 10–50% residual tumor; grade 3, minor or no regression; >50% residual tumor. A pathological response was defined as grade 2 or greater.
Abbreviations: JCGC; Japanese classification of gastric carcinoma, pRR; pathological response rate.

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Adverse Events

	Neoadjuvant chemotherapy (*n* = 37), *n* (%)					Adjuvant chemotherapy (*n* = 27), *n* (%)				
Event	**G1**	**G2**	**G3**	**G4**	**G3–4**	**G1**	**G2**	**G3**	**G4**	**G3–4**
Leukopenia	8 (22)	6 (16)	2 (5)	0 (0)	2 (5)	5 (14)	8 (22)	0 (0)	0 (0)	0 (0)
Neutropenia	6 (16)	8 (22)	2 (5)	1 (3)	3 (8)	3 (11)	7 (26)	9 (33)	1 (4)	10 (37)
Anemia	10 (27)	5 (14)	1 (3)	0 (0)	1 (3)	11 (41)	4 (15)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	8 (22)	2 (5)	2 (5)	1 (3)	3 (8)	12 (44)	2 (7)	0 (0)	0 (0)	0 (0)
Febrile neutropenia	-	-	0 (0)	0 (0)	0 (0)	-	-	0 (0)	0 (0)	0 (0)
Nausea	7 (19)	7 (19)	1 (3)	0 (0)	1 (3)	7 (26)	4 (15)	0 (0)	0 (0)	0 (0)
Vomiting	5 (14)	1 (3)	0 (0)	0 (0)	0 (0)	4 (15)	0 (0)	0 (0)	0 (0)	0 (0)
Stomatitis	2 (5)	1 (3)	1 (3)	0 (0)	1 (3)	2 (7)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	7 (19)	4 (11)	3 (8)	0 (0)	3 (8)	9 (33)	3 (11)	1 (4)	0 (0)	1 (4)
Anorexia	6 (16)	10 (27)	3 (8)	0 (0)	3 (8)	5 (14)	9 (33)	1 (4)	0 (0)	1 (4)
Fatigue	6 (16)	4 (11)	1 (3)	0 (0)	1 (3)	4 (15)	5 (14)	0 (0)	0 (0)	0 (0)
Peripheral neuropathy	14 (38)	3 (8)	0 (0)	0 (0)	0 (0)	9 (33)	8 (22)	0 (0)	0 (0)	0 (0)
Hand foot syndrome	3 (8)	2 (5)	0 (0)	0 (0)	0 (0)	2 (7)	2 (7)	0 (0)	0 (0)	0 (0)

Source: CTCAE Ver. 4.0.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Correlative endpoints not met but clinical activity observed

Gastric cancer (GC) is the third most common cause of cancer-related deaths, both worldwide [10] and in Japan [11]. For patients with localized GC, gastrectomy with D2 lymphadenectomy (D2 gastrectomy) is the present standard of care [6, 12–14]. However, more than half of patients with GC experience recurrence, even after complete macroscopic resection. Various treatment strategies have been explored over the past four decades to control postsurgical relapse [15–17]. In Japan, prolonged overall survival (OS) and relapse-free survival (RFS) following adjuvant S-1 monotherapy were seen in patients with stage II or III GC in one study when compared with the observations of another ACTS-GC trial [15], in which the tumors were staged according to the Japanese Classification of GC (JCGC; second English Edition) [18]. However, the efficacy of S-1 is limited, with a 5-year OS rate of 67.1% in patients with stage IIIA disease and 50.2% in patients with stage IIIB disease. Furthermore, the treatment benefits of S-1 during stages IIIA or IIIB appear to be lower than that in stage II, as suggested by ACTS-GC [15]. Thus, the treatment for patients with stage III disease needs further improvement [15]. Subsequently, in the CLASSIC trial conducted in Korea, the adjuvant capecitabine and oxaliplatin (CapeOx) regimen demonstrated significant survival benefits over surgery alone, with 5-year OS rates of 70% and 66% for stages IIIA and IIIB, respectively [16]; hence, this therapy was considered as a standard of care for stage III GC in Japan [19]. Recently, the superiority of S-1 plus docetaxel (66%) to S-1 (50%) for 3-year RFS (hazard ratio, 0.632; 99.99% CI, 0.400–0.998; p = .001) was also reported [20]. However, postoperative adjuvant therapy has the limitation of drug compliance for more toxic regimens. In contrast, neoadjuvant strategies allow for intensive chemotherapy because the general condition of most preoperative patients is good. Stage III GCs have a poor prognosis due to which neoadjuvant chemotherapies are currently being developed; clinical T3/T4 N1-3 M0 is adopted for the eligibility criteria in neoadjuvant trials instead of stage III, given that it is difficult to identify stage III accurately by preoperative imaging examination alone [21]. In contrast, perioperative chemotherapy has been the standard of care for resectable GC in Europe, based on the results of the MAGIC trial, where the survival benefits of three cycles of perioperative chemotherapy with epirubicin, cisplatin, and infused fluorouracil were superior to that of surgery alone [17]. Based on these findings, we conducted a phase II study to evaluate the efficacy and safety of perioperative CapeOx in clinical T3(SS)/T4a(SE) N1-3 M0 GC.

The pathological response at each histological type was 58.8% at differentiated tumors (tubular adenocarcinoma, n = 17) and 50.0% at poorly differentiated tumors (poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma, n = 20). The pRR was higher in differentiated tumors when compared with the undifferentiated tumors. The low expression levels of dihydropyrimidine dehydrogenase (DPD), related to fluoropyrimidine metabolism, was reported as a predictive marker of capecitabine [22]. Evidence suggests that differentiated GC are associated with low DPD, whereas the undifferentiated types have high DPD levels. Taken together, these findings indicate that the discrepancies in pRR between the histological types is likely due to differences in the levels of DPD expression. Further studies are required to evaluate this association.

So far, the more intensive triplet regimens, such as docetaxel, oxaliplatin, and S-1 (DOS) and docetaxel, oxaliplatin,

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fluorouracil, and leucovorin (FLOT), have demonstrated high rates of complete regression (14.6% and 16%, respectively), with considerably high incidence of severe neutropenia (65.8% and 52%, respectively) [23, 24]. Given the severe toxicities, these regimens are likely to be suitable for only selected patients with GC, underscoring the importance of the development of a highly efficacious treatment strategy with fewer toxicities, such as the perioperative CapeOx therapy.

Patients generally experience loss of appetite and decreased food intake after gastrectomy, resulting in severe toxicities following adjuvant chemotherapy, thereby influencing compliance with such treatment [25–27]. In the present study, the relative dose intensity (RDI) of adjuvant CapeOx was maintained regardless of the surgical technique used and was comparable to the RDI of previously reported adjuvant CapeOx trials (Table 2) [19, 28]. The eligibility criteria in these past studies included patients who were in good condition with adequate oral intake after surgery [18, 28]. However, further studies about the relation between RDI and OS are warranted.

Regarding treatment delivery (Fig. 1), overall, two patients discontinued the neoadjuvant therapy; one because of severe toxicity, and the other because of deterioration of Parkinson's disease. In addition, two patients did not undergo surgery; one did not meet criteria of surgery because of grade 3 enteritis, whereas disease progression was observed in the other patient during neoadjuvant CapeOx. As a result, 33 patients (89.2%) completed the planned three cycles of neoadjuvant CapeOx and underwent gastrectomy. Eventually, R0 resection was achieved in 29 patients (78.4%), whereas R1 and R2 resections were achieved in 3 patients and 1 patient, respectively. After R0 surgical resection, 27 out of the 29 patients (73.0%) received adjuvant CapeOx, whereas the remaining two patients could not be treated by this regimen because one patient did not meet the protocol criteria because of grade 3 enteritis and the other refused adjuvant therapy because of toxicity. Six patients did not complete the adjuvant CapeOx therapy because of the following reasons: grade 4 neutropenia; grade 2 anorexia and fatigue; grade 2 allergic reaction; nausea and vomiting; refusal to continue with treatment; and other reasons. Therefore, the completion rate of the adjuvant CapeOx therapy was 63.6%, wherein 21 out of 33 patients underwent gastrectomy (95% CI, 45.1–79.6). The completion rate of the protocol treatment was 56.8% (21 out of 37 eligible patients; 95% CI, 39.5–72.9).

The present study has several limitations. First, this trial was a single-arm study performed in a limited number of patients. Second, survival data of perioperative CapeOx therapy are not currently available. Third, in this trial, staging laparoscopy was not regulated; hence, peritoneal cytology or metastasis was not completely excluded before enrollment. Three patients achieved R1 resection, although the presence of peritoneal cytology or metastasis during enrollment was not evaluated in these patients (Table 3). Follow-up data including final analysis of OS are awaited.

Perioperative CapeOx therapy showed good feasibility and favorable efficacy with sufficient pathological response. Nevertheless, further studies with a larger sample size are required to validate this novel approach.

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Figure and Tables

Table 2. ypStage (*n* = 33)

ypStage	*n* (%)
T factor	
1a(M)	3 (9.1)
1b(SM)	5 (15.2)
2(MP)	6 (18.2)
3(SS)	11 (33.3)
4a(SE)	8 (24.2)
N factor	
0	17 (51.5)
1	8 (24.2)
2	3 (9.1)
3	5 (15.2)
M factor	
0	30 (90.9)
1	3 (9.1)
P1	1 (3.0)
CY1	2 (6.1)
ypStage	
IB	4 (12.1)
IIA	9 (27.3)
IIB	5 (15.2)
IIIA	3 (9.1)
IIIB	3 (9.1)
IV	3 (9.1)

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Table 3. Relative dose intensity

Relative dose intensity	NC (*n* = 37), %	AC (*n* = 27), %	AC with total gastrectomy (*n* = 13), %	AC with distal gastrectomy (*n* = 14), %
Capecitabine	90.5	80.9	82.4	79.6
Oxaliplatin	91.9	65.1	62.3	67.8

Abbreviations: AC, adjuvant chemotherapy; NC, neoadjuvant chemotherapy.

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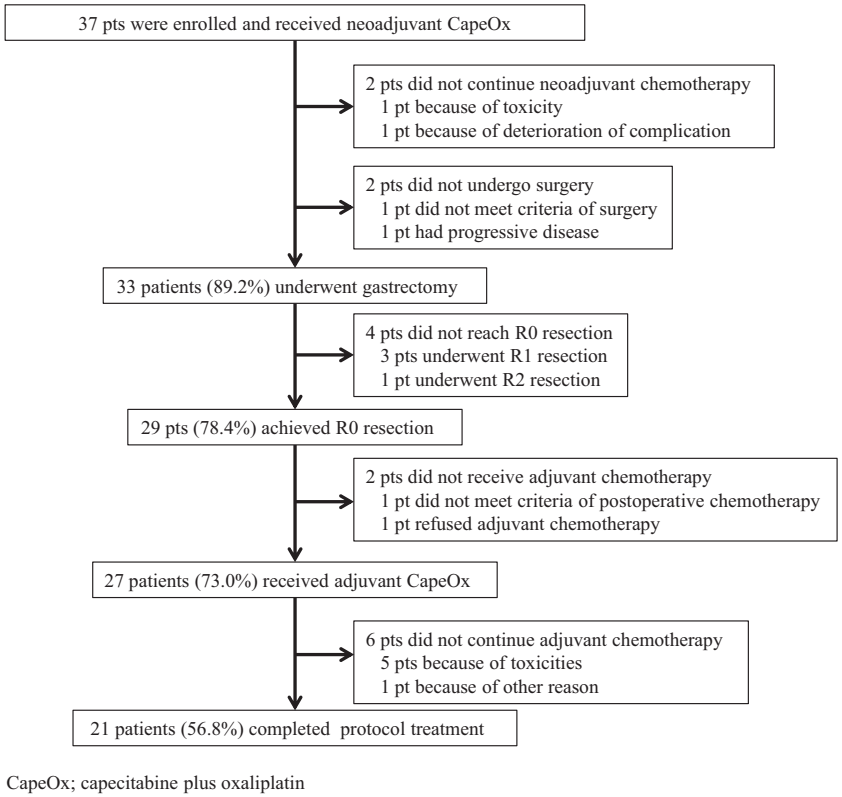

Figure 1. Flow chart showing treatment delivery.
Abbreviations: CapeOx, capecitabine plus oxaliplatin; pt, patient.