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ORIGINAL ARTICLE

Phase 2 trial of neoadjuvant docetaxel, oxaliplatin, and S-1 for clinical stage III gastric or esophagogastric junction adenocarcinoma

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Abstract

Background: Although perioperative treatment has been the standard of care for resectable gastric cancer in the West, postoperative adjuvant chemotherapy is still the standard in Japan. We conducted the first phase 2 trial to investigate the efficacy and safety of neoadjuvant docetaxel, oxaliplatin, and S-1 (DOS) chemotherapy for cStage III gastric or esophagogastric junction (EGJ) adenocarcinoma in Japan.

Methods: Eligibility criteria included cStage III adenocarcinoma of the stomach or EGJ. Patients received docetaxel (40 mg/m^2, day 1), oxaliplatin (100 mg/m^2, day 1), or S-1 (80 mg/m^2, days 1–14) during a 3-week cycle. After two or three cycles of DOS, patients underwent surgical resection. The primary endpoint was progression-free survival (PFS).

Results: Between June 2015 and March 2019, 50 patients were enrolled from four institutions. Of 48 eligible patients (37 gastric and 11 EGJ adenocarcinoma), 42 (88%) completed two or three DOS cycles. Grade 3–4 neutropenia and diarrhea occurred in 69% and 19% of patients, respectively, but there were no treatment-related deaths. R0 resection was achieved in 44 (92%) patients, and the pathological response rate (≥ grade 1b) was 63% (30/48). The 3-year PFS, overall survival, and disease-specific survival rates were 54.2%, 68.7%, and 75.8%, respectively.

Conclusion: Neoadjuvant DOS chemotherapy had a sufficient antitumor effect and tolerable safety profile in patients with gastric or EGJ adenocarcinoma. The survival benefit of a neoadjuvant strategy using our DOS regimen should be validated in phase 3 trials.

KEYWORDS
docetaxel, oxaliplatin, and S-1, esophagogastric junction tumor, gastroesophageal junction cancer, neoadjuvant treatment, preoperative chemotherapy

1 | INTRODUCTION

Gastric cancer is the fourth leading cause of cancer deaths and the fifth most common cancer worldwide.[1] Although surgical resection is the only cure for gastric cancer, many patients suffer from postoperative recurrence.[2-4] To improve the prognosis of patients with resectable gastric cancer, an application has been filed in Japan to use adjuvant chemotherapy with S-1, a fluoropyrimidine compound containing tegafur, gimeracil, and oteracil potassium, as a standard treatment for pathological stage (pStage) II or III gastric cancer.[5] In a Japanese phase 3 (START-2) trial, adjuvant chemotherapy using docetaxel plus S-1 (DS) resulted in significantly longer recurrence-free survival (RFS) compared with S-1 monotherapy in patients with pStage III gastric cancer.[6]

On the other hand, a perioperative treatment strategy has long been the standard of care for resectable gastric cancer in the West.[7,8] A German phase 3 (FLOT4) trial demonstrated that perioperative use of fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) was superior to fluorouracil or capecitabine plus cisplatin and epirubicin (ECF/ECX) in terms of progression-free survival (PFS) and overall survival (OS) in resectable gastric cancer.[9] Although neoadjuvant treatment may increase curative resection rates, some patients may lose the opportunity for radical resection due to progressive disease. Indeed, a recent Japanese phase 3 (JCOG0501) trial showed a significant increase in the R0 resection rate but no survival improvement after neoadjuvant chemotherapy using a doublet regimen of cisplatin plus S-1 (CS) in patients with type 4 or large type 3 gastric cancer.[10] However, a recent Korean phase 3 (PRODIGY) trial showed that neoadjuvant chemotherapy using a triplet regimen of docetaxel, oxaliplatin, and S-1 (DOS) with postoperative S-1 resulted in significantly longer PFS than postoperative S-1 alone in patients with clinical stage (cStage) II or III gastric cancer.[11] However, that trial has not yet shown an improvement in OS due to an insufficient follow-up period. Since there is inadequate evidence supporting neoadjuvant DOS chemotherapy, particularly in the East where the standard treatment is postoperative chemotherapy using S-1, we conducted the first phase 2 trial investigating the efficacy and safety of neoadjuvant DOS chemotherapy for cStage III gastric or esophagogastric junction (EGJ) adenocarcinoma in Japan.

2 | PATIENTS AND METHODS

2.1 | Patients

This trial was a phase 2, single-arm study conducted at four institutions in Japan. Eligibility criteria were histologically proven adenocarcinoma of the stomach or EGJ, cStage III according to the 14th edition of the Japanese Classification of Gastric Carcinoma (JCGC),[12] 20–79 years of age, amenable to R0 resection, Eastern Cooperative Oncology Group performance status score of 0 or 1, adequate oral intake, and adequate organ function as indicated by a neutrophil count ≥2000/mm^3, platelet count ≥100000/mm^3, hemoglobin ≥8.0 g/dL, both serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤100 IU/L, serum total bilirubin ≤1.5 mg/dL, and creatinine clearance (CCr) ≥60 mL/min. Patients with macroscopic (Borrmann) type 4 or large (≥8 cm) type 3 tumors, active tumor bleeding, a history of surgery for gastric cancer, or prior chemotherapy or radiation therapy for any other malignancies were excluded. Staging laparoscopy before enrollment was not required. All patients provided written informed consent before enrollment. The trial protocol was approved by the Institutional Review Boards of all participating institutions. This study was registered with UMIN Clinical Trials Registry, number UMIN000017652, and Japan Registry of Clinical Trials, number jRCTs051180086.

2.2 | Treatment

After enrollment, patients received docetaxel (40 mg/m^2) and oxaliplatin (100 mg/m^2) intravenously on day 1, and oral S-1 twice daily at a dose based on body surface area (<1.25 m^2, 40 mg; ≥1.25 to <1.5 m^2, 50 mg; ≥1.5 m^2, 60 mg) on days 1–14 of a 3-week cycle. The protocol recommended three cycles of neoadjuvant DOS chemotherapy, but surgery after two cycles was allowed. Each subsequent cycle was delayed until patient recovery, including a neutrophil count ≥2000/mm^3, platelet count ≥75,000/mm^3, hemoglobin ≥8.0 g/dL, AST ≤100 IU/L, ALT ≤100 IU/L, serum total bilirubin ≤2.0 mg/dL, creatinine ≤1.5 mg/dL, fever of grade 0, and the absence of other nonhematological adverse events ≥grade 2. Treatment with S-1 was suspended and the doses of docetaxel, oxaliplatin, and S-1 were reduced in the subsequent cycle if patients exhibited any of the following: neutrophil count <500/mm^3, platelet count <50,000/mm^3, total bilirubin >3.0 mg/dL, or creatinine >1.5 mg/dL; grade 2 nonhematological adverse events such as oral mucositis, palmar-plantar erythrodysesthesia syndrome, rash, allergic reaction, peripheral motor/sensory neuropathy, or hearing impaired; or grade 3 or higher nonhematological adverse events.

After two or three cycles of DOS chemotherapy, patients underwent surgical resection. The types of gastrectomy and reconstruction

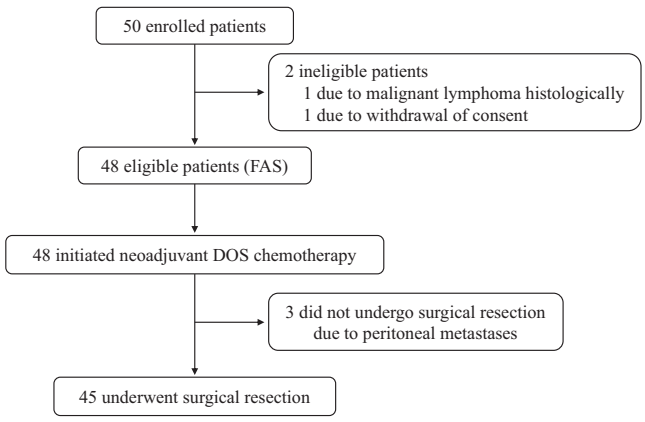

FIGURE 1 CONSORT flow diagram. DOS, docetaxel plus oxaliplatin plus S-1; FAS, full analysis set

TABLE 1 Patient characteristics

	n = 48
Age, y	
Median (range)	71 (45–79)
Sex	
Male	33 (69%)
Female	15 (31%)
Macroscopic type	
1	3 (6%)
2	17 (35%)
3	27 (56%)
5	1 (2%)
Location	
Stomach	37 (77%)
EGJ	11 (23%)
cT status	
T2	1 (2%)
T3	3 (6%)
T4	44 (92%)
cN status	
N0	1 (2%)
N1	16 (33%)
N2	20 (42%)
N3	11 (23%)
cStage[a]	
IIIA	21 (44%)
IIIB	18 (38%)
IIIC	9 (19%)

Abbreviation: EGJ, esophagogastric junction.

[a]TNM staging was based on the 14th edition of the Japanese Classification of Gastric Carcinoma (JCGC).

were not predetermined. In patients with ypStage II–IV disease after R0 resection, the study protocol recommended the use of adjuvant chemotherapy using S-1 during the first postoperative year.

2.3 | Outcomes

The primary endpoint of this trial was the 3-year PFS rate. The secondary endpoints were OS, PFS, response rate according to RECIST v. 1.1,[13] pathological response rate, R0 resection rate, and adverse events. PFS was calculated from the date of enrollment until the date of disease progression, recurrence, or death from any cause. OS was calculated from the date of enrollment until the date of death from any cause. Disease-specific survival (DSS) was calculated from the date of enrollment until the date of death from the current disease. Pathological response was evaluated according to the histological criteria of the JCGC.[12] Briefly, grade 0 means no evidence of treatment effect; grade 1a means viable tumor cells in more than 2/3 of the tumor area; grade 1b means viable tumor cells in 1/3 to 2/3 of the tumor area; grade 2 means viable tumor cells in less than 1/3 of the tumor area; and grade 3 means no viable tumor cells. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), v. 4.0. Postoperative morbidities were assessed according to the Clavien–Dindo classification.[14,15]

2.4 | Statistical analysis

In the ACTS-GC trial, the 3-year RFS rates after adjuvant S-1 chemotherapy were ~67% in pStage IIIA disease and ~50% in pStage IIIB disease, as defined by the 13th edition of the JCGC.[5] Since the

TABLE 2 Common adverse events

	Grade 1	Grade 2	Grade 3	Grade 4	% Grade 3-4
Neutropenia	2	7	17	16	69
Anemia	20	5	2	0	4
Thrombocytopenia	7	2	0	0	0
AST elevation	5	2	2	1	6
ALT elevation	7	3	1	1	4
Hyponatremia	19	–	6	0	13
Hypoalbuminemia	11	19	3	0	6
Malaise	22	3	0	0	0
Fatigue	9	3	1	0	2
Anorexia	12	20	3	0	6
Nausea	17	4	1	0	2
Diarrhea	9	10	9	0	19
Peripheral sensory neuropathy	13	1	0	0	0
Febrile neutropenia	–	–	6	0	13

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

TABLE 3 Pathological findings

	n = 45
Histological type[a]	
Differentiated	22 (49%)
Undifferentiated	20 (44%)
Adenosquamous carcinoma	1 (2%)
ypT status	
T0	2 (4%)
T1	7 (16%)
T2	5 (11%)
T3	17 (38%)
T4	14 (31%)
ypN status	
N0	11 (24%)
N1	11 (24%)
N2	12 (27%)
N3	11 (24%)
ypM status	
M0	43 (96%)
M1	2 (4%)
ypStage[a]	
I	9 (20%)
II	11 (24%)
III	21 (47%)
IV	2 (4%)
Residual tumor	
R0	44 (98%)
R1	1 (2%)

[a]TNM staging was based on the 14th edition of the Japanese Classification of Gastric Carcinoma (JCGC). Two patients were not assessed due to Grade 3 (ypT0).

ACTS-GC trial consisted only of patients who underwent R0 resection and were physically suitable for postoperative chemotherapy, we anticipated that the prognosis in the ACTS-GC trial would be better than that in this trial. We therefore assumed a threshold 3-year PFS rate of 50% and an expected rate of 65%. The required sample size was estimated to be 50 patients based on 80% power and a one-sided α of 0.1 using the SWOG single arm phase II design for survival outcome. We planned 4 years for accrual and 5 years for follow-up.

The primary analysis was based on the full analysis set (FAS), which consists of all eligible patients. Survival curves were estimated by the Kaplan–Meier method, and confidence intervals (CIs) for survival rates were calculated using Greenwood's formula. Statistical analyses were conducted using R, v. 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) or SPSS Statistics software program, v. 24 (IBM, Armonk, NY, USA).

3 | RESULTS

3.1 | Patient characteristics

Between June 2015 and March 2019, 50 patients were enrolled from four institutions (Figure 1). One patient was ineligible because histology revealed malignant lymphoma, and one withdrew consent for participation before treatment initiation. These two patients were excluded from the FAS. The characteristics of the 48 FAS patients are shown in Table 1. Thirty-seven patients (77%) had gastric cancer, while 11 (23%) had EGJ adenocarcinoma. Most patients (92%) had cT4 disease, and all but one were clinically node-positive. All patients were diagnosed as cStage III.

3.2 | Safety of neoadjuvant chemotherapy

Of the 48 FAS patients, eight (16.7%) and 34 (70.8%) completed two or three cycles of neoadjuvant DOS chemotherapy, respectively, whereas six (12.5%) discontinued chemotherapy after one cycle. The relative dose intensities (median [quartile]) of docetaxel, oxaliplatin, and S-1 were 91.7% (66.7%–100%), 90.0% (66.7%–100%), and 78.4% (50.6%–90.5%), respectively. Common (≥10%) adverse events based on CTCAE v. 4.0 are shown in Table 2. Grade 3–4 neutropenia occurred in 69% of patients. Among nonhematological toxicities, the most common grade 3–4 events were diarrhea (19%) followed by hyponatremia (13%) and febrile neutropenia (13%). Diverticulitis occurred in three patients (grade 3 in one, grade 2 in two). There were no treatment-related deaths. The response rate according to RECIST v. 1.1 in the 11 patients with measurable lesions was 72.7% (95% CI, 39.0%–94.0%).

3.3 | Surgical outcomes

After neoadjuvant DOS chemotherapy, 45 (94%) patients underwent surgical resection, whereas three (6%) did not, due to peritoneal metastases. Although one of the 45 resected patients resulted in R1 resection due to positive peritoneal lavage cytology; the remaining 44 patients achieved R0 resection. The R0 resection rate among the 48 FAS patients was 91.7% (95% CI, 80.0%–97.7%). Types of surgery were as follows: distal gastrectomy in 23 patients (51%), total gastrectomy in 18 (40%), proximal gastrectomy in three (7%), and subtotal esophagectomy in one (2%). The selected surgical approaches were open surgery in 24 (53%) patients and laparoscopic surgery in 21 (47%). Fifteen (33%) of 45 patients underwent combined resection of other organs. Grade II or higher postoperative morbidities occurred in 12 (27%) of 45 patients: anastomotic leakage in five (11%), surgical site infection in two (4%), bleeding in two (4%), pneumonia in one (2%), mediastinitis in one (2%), and ascites in one (2%). There were no hospital deaths.

TABLE 4 Pathological response

	Grade 0	Grade 1a	Grade 1b	Grade 2	Grade 3	NE[a]
Overall (n = 48)	2	13	18	10	2	3
Gastric adenocarcinoma (n = 37)	1	12	13	8	1	2
EGJ adenocarcinoma (n = 11)	1	1	5	2	1	1
Differentiated type (n = 23)	2	6	8	6	0	1
Undifferentiated type (n = 25)	0	7	10	4	2	2

[a]Three patients were not evaluable (NE) due to no surgical resection.

TABLE 5 Selected regimens of adjuvant chemotherapy in patients who underwent R0 resection

ypStage	Regimen of adjuvant chemotherapy	n = 44
ypT0 N0	None	1
ypT0 N2	S-1 monotherapy	1
ypStage I	None	5
	S-1 monotherapy	3
	Docetaxel plus S-1	1
ypStage II	None	4
	S-1 monotherapy	7
ypStage III	None	2
	S-1 monotherapy	14
	Docetaxel plus S-1	4
	Capecitabine plus oxaliplatin	1
ypStage IV	None	1

3.4 | Pathological findings

The pathological findings of the 45 patients who underwent surgical resection are shown in Table 3. Regarding the histological type of adenocarcinoma, 22 (49%) of 45 were differentiated and 20 (44%) were undifferentiated. One patient was diagnosed with adenosquamous carcinoma despite poorly differentiated adenocarcinoma in the biopsy specimen before neoadjuvant DOS chemotherapy. Two (4%) patients showed no residual cancer cells (ypT0). Nine (20%) and 11 (24%) patients regressed to ypStage I and II from cStage III, respectively. The overall pathological response rates (grades 3, 2, and 1b) according to the JCGC histological criteria in the 48 FAS patients were 62.5% (95% CI, 47.4%–76.1%) (Table 4). The rates did not differ significantly between gastric (59.5%) and EGJ (72.7%) adenocarcinoma or between the differentiated (60.9%) and undifferentiated (64.0%) types.

3.5 | Survival outcomes

Of the 44 patients who underwent R0 resection, 31 (70%) received adjuvant chemotherapy. The selected regimens were S-1 monotherapy in 25 (81%) patients, DS in five (16%), and capecitabine plus oxaliplatin in one (3%) (Table 5). At the 52-month median follow-up time for censored cases, 16 patients showed recurrence after surgical resection. The sites of first recurrence were as follows (five patients had multiple recurrence sites): lymph nodes in nine patients, peritoneum in five, bone in three, liver in two, stomach in two, and local in one. The 3- and 5-year PFS rates in the 48 FAS patients were 54.2% (95% CI, 41.8%–70.3%; 80% CI, 45.7%-64.2%) and 47.2% (95% CI, 34.1%-65.2%), respectively (Figure 2A). Five patients died from other diseases and did not exhibit tumor recurrence. If these patients were censored on the last day of follow-up, the 3- and 5-year PFS rates in the 48 FAS patients were 60.8% (95% CI, 48.2%–76.8%; 80% CI, 52.2%–70.8%) and 56.5% (95% CI, 42.9%–74.3%), respectively. The 3- and 5-year OS rates in the 48 FAS patients were 68.7% (95% CI, 56.8%–83.2%) and 59.9% (95% CI, 46.8%–76.7%), respectively (Figure 2B). The 3- and 5-year DSS rates were 75.8% (95% CI, 64.3%–89.3%) and 69.7% (95% CI, 57.0%–85.3%), respectively (Figure 2C).

4 | DISCUSSION

This phase 2 trial was the first to confirm the efficacy and safety of neoadjuvant DOS chemotherapy for cStage III gastric or EGJ adenocarcinoma in Japan. Both the response rate according to RECIST v. 1.1 and the histological response rate were higher than we expected. Although there were high incidences of neutropenia and diarrhea, the toxicities were almost always manageable. After neoadjuvant DOS chemotherapy, R0 resection was achieved in most patients with no mortality. Considering that all 48 cases in this study were cStage III and that they included 11 EGJ adenocarcinoma cases, the incidence of postoperative morbidities after neoadjuvant DOS chemotherapy was not high as compared with the data from the Japanese National Clinical Database (NCD).[16,17] Based on these findings, we conclude that neoadjuvant DOS chemotherapy is a promising treatment for cStage III gastric or EGJ adenocarcinoma.

Thus far, only one phase 3 trial (JCOG0501) of neoadjuvant CS chemotherapy for resectable gastric cancer has been conducted in Japan.[10] It showed that this treatment strategy was ineffective, possibly because docetaxel and oxaliplatin were not used. Docetaxel has been widely regarded as a key drug for the treatment of gastric cancer, ever since a landmark American phase 3 trial (V325) showed that adding docetaxel to cisplatin plus 5-FU (CF) significantly improved time-to-progression, OS, and response rate in patients with unresectable gastric cancer.[18] A German phase 3 trial (FLOT4)

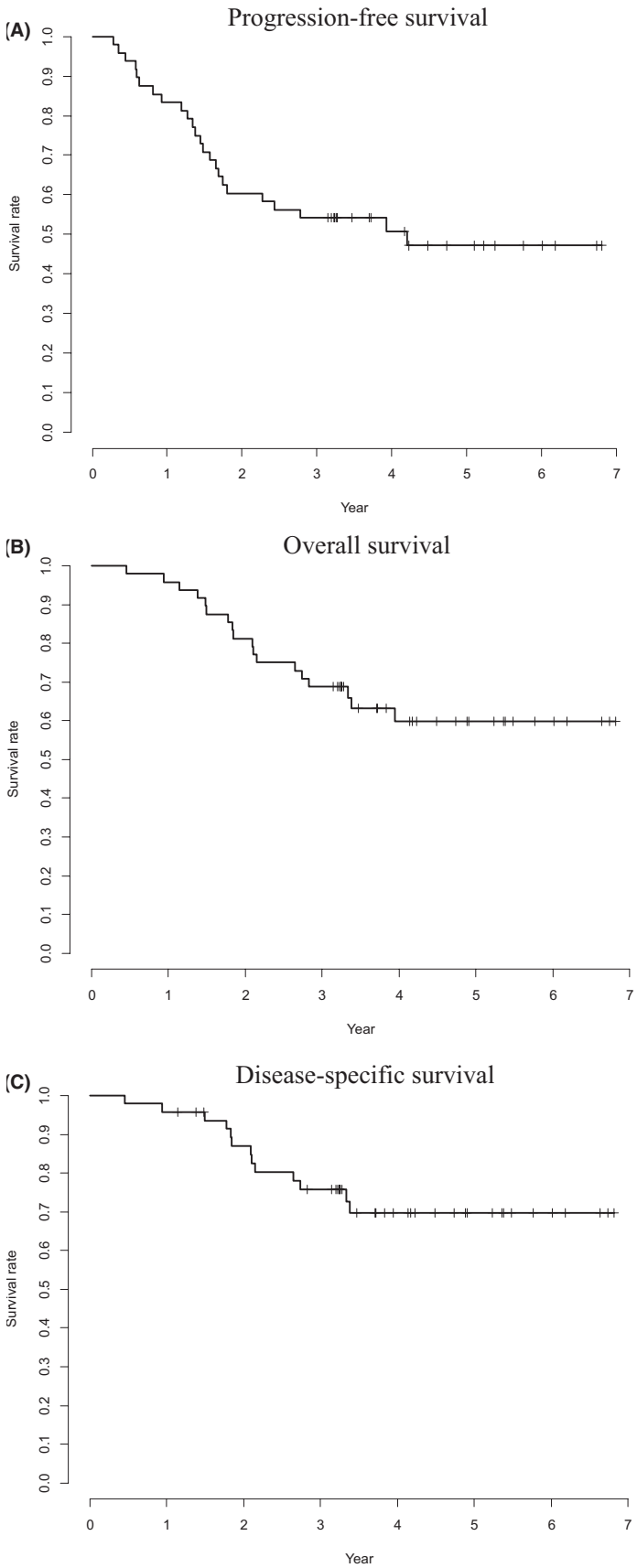

FIGURE 2 Kaplan–Meier progression-free survival (A), overall survival (B), and disease-specific survival (C) for all eligible patients (n = 48)

showed that, regarding OS and PFS in resectable gastric cancer, the new standard regimen FLOT, which includes both docetaxel and oxaliplatin, was superior to the conventional standard regimen ECF/ECX, which includes neither of these drugs.[9] However, a Japanese phase 3 trial (JCOG1013) showed no survival benefit of adding docetaxel to CS in patients with unresectable gastric cancer.[19] We

believe that this negative result was primarily due to the relatively low dose intensities of the drugs used (docetaxel, 10 mg/m^2/wk; cisplatin, 15 mg/m^2/wk; S-1, 280 mg/m^2/wk). Since our DOS regimen used much higher dose intensities (docetaxel, 13.3 mg/m^2/wk; oxaliplatin, 33.3 mg/m^2/wk; S-1, 373.3 mg/m^2/wk), the antitumor effect may have been much greater than that of the DCS regimen used in JCOG1013.

A Korean PRODIGY trial showed that neoadjuvant DOS chemotherapy improved PFS in cStage II–III gastric cancer.[11] The dose of docetaxel (40 mg/m^2) in our DOS regimen was slightly lower than that (50 mg/m^2) in the PRODIGY DOS regimen. In a previous phase 1 trial of the DS regimen in Japanese patients with unresectable gastric cancers, the recommended dose of docetaxel was determined to be 40 mg/m^2, because a dose of 50 mg/m^2 induced grade 3–4 neutropenia in 50% of patients, grade 2–4 anorexia and stomatitis in 33%, and grade 2–4 diarrhea and allergic reactions in 17%.[20] Since safety should be prioritized more highly than efficacy, particularly in the neoadjuvant setting for curable patients, we set the dose of docetaxel as 40 mg/m^2 in this phase 2 trial. Indeed, even with this relatively low dose, grade 3–4 neutropenia occurred in ~70% of patients, and grade 3–4 diarrhea, hyponatremia, and febrile neutropenia occurred in over 10% of patients. We therefore conclude that our dose should be used in subsequent trials, at least those involving Japanese patients.

Of the patients in our phase 2 trial, 23% had EGJ adenocarcinoma, compared to only 6% in the Korean PRODIGY trial.[11] This difference reflects the recent increase in the prevalence of EGJ adenocarcinoma in Japan.[21–24] We initially estimated the sample size based on the data of the ACTS-GC trial, which enrolled patients with pStage II-III gastric cancer. However, the prognosis of gastric adenocarcinoma is usually better than that of EGJ adenocarcinoma, even for the same TNM stage.[5,25] The high percentage of patients with EGJ adenocarcinoma in this trial might have led to the lower-than-expected survival rate. Our previous retrospective study that included only EGJ adenocarcinoma patients showed a high pathological response rate for neoadjuvant DOS chemotherapy,[26] suggesting that this is a promising treatment in this population.

This phase 2 trial had several limitations. First, this was a single-arm study with a small sample size. The superiority of neoadjuvant DOS chemotherapy should be validated further in phase III trials that use OS as the primary endpoint, because the Korean PRODIGY trial has not yet demonstrated a significant improvement in OS. Second, the relative dose intensities of DOS in our phase 2 trial were lower than expected. In particular, the median relative dose intensity of S-1 was below 80%. We hypothesize that the participating physicians were highly concerned about neutropenia. At our institution, most patients underwent inpatient neoadjuvant DOS chemotherapy from day 1 to 14 in each cycle, and received blood tests every other day between days 7 and 14 to check the neutrophil count. The frequent blood tests certainly contributed to identifying a high incidence of neutropenia and led to dose reductions in this trial. Third, this trial did not prescribe postoperative chemotherapy because there has been no evidence in Japan supporting adjuvant chemotherapy after neoadjuvant chemotherapy. Since our protocol recommended S-1 monotherapy for 1 year in cases of ypStage II–IV disease, only 70% of patients received adjuvant chemotherapy. The presence or absence of postoperative treatment might affect long-term patient survival.

In conclusion, neoadjuvant DOS chemotherapy had a sufficient antitumor effect and tolerable safety profile in patients with gastric or EGJ adenocarcinoma. Considering the high incidence of neutropenia and diarrhea, our dose of DOS seemed to be reasonable for neoadjuvant treatment. At this point there is minimal evidence supporting neoadjuvant DOS chemotherapy; this is particularly true in the East, where postoperative chemotherapy with S-1 is standard. As such, we should validate the survival benefit of this neoadjuvant strategy in phase 3 trials involving patients with resectable gastric or EGJ adenocarcinoma.

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

Y Kurokawa designed the study and wrote the protocol. Y Doki and H Eguchi chaired the study group. R Yoshioka was responsible for data management. T Shimokawa analyzed the data statistically. All authors except R Yoshioka, T Shimokawa, and H Eguchi recruited patients into the study. Y Kurokawa drafted the paper. All authors revised the paper, and approved the final version.

DISCLOSURE

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Conflict of Interest: Y. Kurokawa is an Associate Editor of the *Annals of Gastroenterological Surgery*, and has received research funding from Yakult Honsha and Taiho Pharmaceutical and lecture fees from Yakult Honsha, Taiho Pharmaceutical, and Nippon Kayaku. H. Eguchi has received research funding from Taiho Pharmaceutical and lecture fees from Taiho Pharmaceutical and Yakult Honsha. Y. Doki is an Editorial Board member of the *Annals of Gastroenterological Surgery*, and has received research funding from Yakult Honsha, Taiho Pharmaceutical, and Nippon Kayaku and lecture fees from Taiho Pharmaceutical. All remaining authors declare no conflicts of interest.

ETHICAL APPROVAL

This trial was approved by the Institutional Review Boards of Osaka University Hospital (nos. 14417, 18006) and all participating institutions. Informed consent was obtained from all individual participants included in the trial.

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