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ORIGINAL ARTICLE

Neoadjuvant docetaxel, oxaliplatin, and S-1 therapy for patients with large type 3 or type 4 gastric cancer: short-term outcomes of a multicenter, phase II study (OGSG1902)

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Abstract

Background Large type 3 (≥ 8 cm) and type 4 gastric cancers (GCs) have poor prognoses and necessitate multidisciplinary treatment. A multi-institutional phase II study (OGSG1902) was conducted to assess the efficacy and safety of neoadjuvant chemotherapy (NAC) with docetaxel, oxaliplatin, and S-1 (DOS) in these patients.

Methods Patients with large type 3 or type 4 GC without distant metastasis, except for positive peritoneal cytology (CY), were enrolled. Patients received three courses of neoadjuvant DOS therapy (docetaxel 40 mg/m^2 and oxaliplatin 100 mg/m^2 on day 1 via intravenous infusion, and S-1 80 mg/m^2 orally for 14 days, repeated every 3 weeks) followed by gastrectomy. After R0 resection, adjuvant docetaxel/S-1 therapy was administered for 1 year.

Results From October 2019 to February 2022, 48 patients were enrolled. NAC was completed in 91.7% of patients. The R0 resection rate was 89.6%. The pathological response rate (Grade 1b–3) was 66.7%. Among patients with measurable lesions, the response rate was 50.0%. The CY-negative conversion rate was 80.0%, and the protocol completion rate was 45.8%. Grade 3 or 4 adverse events during NAC, including neutropenia and appetite loss, occurred in 37.5% of patients. Major postoperative complications (Clavien–Dindo Grade IIIa or higher) were observed in 2.1% of patients.

Conclusions NAC with DOS for large type 3 or type 4 GC followed by gastrectomy demonstrated promising efficacy, high pathological response rates, and an acceptable toxicity profile. Further evaluation of long-term survival outcomes is ongoing.

Keywords Stomach neoplasms · Adenocarcinoma · Scirrhous · Neoadjuvant therapy · Oxaliplatin

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Introduction

Gastric cancer (GC) ranks as the fifth most common and the third leading cause of cancer-related deaths globally [1], with the highest age-adjusted incidence and mortality rate among gastroenterological malignancies in Japan [2]. Macroscopic type 4 GC known as linitis plastica has a particularly poor prognosis [3], and the prognosis of type 3 GC deteriorates with increasing tumor size [3]. Large type 3 GC (diameters > 8 cm) shares many characteristics with type 4 GC, including patient age, histology, and progression patterns [4].

For these cancers with poor prognosis, surgery with postoperative adjuvant chemotherapy is insufficient for satisfactory outcomes, prompting studies on neoadjuvant chemotherapy (NAC). The Japan Clinical Oncology Group (JCOG) conducted a phase II study with neoadjuvant S-1 plus cisplatin (SP) (JCOG0210) for large type 3 or type 4 GC, reporting a feasible treatment with a 3-year overall survival (OS) rate of 24.5% [5]. Based on JCOG0210, a phase III trial (JCOG0501) tested neoadjuvant SP therapy against standard upfront surgery followed by adjuvant S-1 for large type 3 or type 4 GC [6, 7]. This trial had a favorable R0 resection rate of 73.9% but failed to demonstrate a survival benefit for neoadjuvant SP. The 3-year OS rates were 60.9% for neoadjuvant SP therapy and 62.4% for the standard treatment, and the hazard ratio (HR) was 0.916 (95% confidence interval [CI] 0.679–1.236).

In Korea, a phase II study of neoadjuvant DOS (docetaxel 50 mg/m^2 day 1, oxaliplatin 100 mg/m^2 day 1, and S-1 80 mg/m^2) chemotherapy, administered every 3 weeks and followed by surgery and adjuvant S-1, for stage cT3–4 N0 or cT2–4 N + GC, showed all patients completed three NAC courses [8]. The R0 resection rate was 97.6%, and the pathological complete response rate of the primary lesion was 19.5%. An Osaka University research group reduced the docetaxel dose to 40 mg/m^2 due to neutropenia concerns [9]. They reported sufficient antitumor effects and tolerable safety in a phase II trial of neoadjuvant DOS for clinical stage (cStage) III gastric or esophagogastric junction adenocarcinoma. DOS therapy is expected to achieve better pathological responses than dual-drug therapy and may become an essential therapeutic strategy in future GC treatment.

In postoperative adjuvant chemotherapy, the JACCRO GC-07 (START-2) study for pathological stage (pStage) III GC showed the superiority of docetaxel plus S-1 (DS) therapy over S-1 monotherapy, with 3-year relapse-free survival rates of 66% and 50%, respectively, according to an interim analysis (HR: 0.632, 99.99% CI: 0.400–0.998, P < 0.001) [10]. Based on these findings, DS therapy is the standard adjuvant chemotherapy for pStage III in Japan, while S-1 is the standard for pStage II as established by the ACTS-GC trial [11]. However, no established standard exists for adjuvant therapy following neoadjuvant chemotherapy. Considering DS therapy's superior efficacy and manageable toxicity, we selected it as the adjuvant regimen for this study.

The Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) conducted a phase II study to confirm the efficacy and safety of neoadjuvant DOS and adjuvant DS for large type 3 or type 4 GC (OGSG1902) [12]. OS is considered the gold standard endpoint in clinical trials; however, it requires an extended follow-up period. In clinical trials employing neoadjuvant chemotherapy, a surrogate endpoint for OS had not yet been established at the time this study was designed. We selected 3-year progression-free survival (PFS) as the primary endpoint, drawing on the Korean phase III PRODIGY trial [13, 14]. Patient enrollment has been completed, and while the primary endpoint remains 3-year PFS, short-term outcomes are also of significant clinical interest. Therefore, we are reporting these interim findings ahead of the final analysis.

Methods

Patients

Eligibility criteria were as follows: (1) histologically confirmed adenocarcinoma of the stomach, (2) large type 3 (≥ 8 cm) or type 4 GC, (3) no evidence of distant metastasis except for positive peritoneal lavage cytology confirmed via laparoscopy, (4) no esophageal involvement ≥ 3 cm, (5) age 20–80 years, (6) Eastern Cooperative Oncology Group performance status of 0 or 1, (7) no prior history of chemotherapy or radiotherapy for any malignancy, (8) human epidermal growth factor receptor negative or unexamined, (9) adequate oral intake, with or without prior bypass surgery, and (10) adequate organ function: neutrophil count ≥ 1500/mm^3; hemoglobin concentration ≥ 8.0 g/dL (No transfusion within 14 days before registration date); platelet (PLT) count ≥ 100,000/mm^3; aspartate and alanine transaminase concentrations ≤ 100 IU; total bilirubin concentration ≤ 2.0 mg/dL; and creatinine clearance ≥ 50 mL/min. All patients provided written informed consent. Tumors were staged in accordance with the Japanese Classification of Gastric Carcinoma (JCGC; 2nd English edition).

Staging laparoscopy and peritoneal lavage cytology were performed before enrollment to identify the peritoneal metastasis. The absence of cancer cells in lavage fluid was CY0; presence was CY1.

Exclusion criteria included the following: (1) synchronous or metachronous (within 5 years) malignancies other than carcinoma in situ; (2) infectious disease

requiring systemic treatment (body temperature > 38.0 °C); (3) pregnancy or lactation; (4) severe mental illness; (5) unstable angina within 3 weeks or myocardial infarction within 6 months before registration; (6) continuous systemic corticosteroid or immunosuppressant treatment; (7) treatment with flucytosine, phenytoin, or warfarin; (8) poorly controlled valve disease or dilated or hypertrophic cardiomyopathy; (9) positive for hepatitis B surface antigen; (10) interstitial pneumonia, pulmonary fibrosis, or severe emphysema on chest computed tomography (CT); (11) poorly controlled hypertension or diabetes; or (12) patients deemed unsuitable for the study by their physicians.

Study design

This multicenter, open-label, single-arm, phase II study was conducted across 16 institutions and was designed to evaluate the efficacy and safety of DOS therapy as NAC followed by gastrectomy with D2 dissection and adjuvant DS therapy. Protocol completion was defined as the successful completion of 1 year of adjuvant chemotherapy. Eligible patients were registered via fax to the OGSG Data Center. This study followed the Declaration of Helsinki and the Japanese Clinical Trials Act. The protocol was approved by the Certified Review Board and was registered in the Japan Registry of Clinical Trials on October 11, 2019 (jRCTs 051190060).

The primary endpoint was 3-year PFS, the interval from registration to an event. Secondary endpoints were assessed in the full analysis set and included the following: PFS time; OS time, from registration to death from any cause or last contact for a surviving patient; pathological response rate evaluated according to the JCGC; response rate based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [15]; completion rate of NAC; R0 resection rate; completion rate of surgery; protocol treatment completion rate; negative conversion rate of positive peritoneal lavage cytology; adverse event (AE) occurrence rate; and nutritional evaluation.

AEs associated with either gastrectomy or chemotherapy were evaluated separately using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, as provided by the JCOG [16]. AEs were assessed at least monthly during NAC and adjuvant chemotherapy via verbal interviews, physical examinations, and blood tests, including complete blood counts and evaluations of liver and renal function, until disease progression. Follow-ups included abdominal CT every 6 months and tests for carcinoembryonic antigen and carbohydrate antigen 19–9 levels every 3 months for up to 3 years.

Table 1 Patient characteristics

	N = 48
Age (years), median (range)	66 (44–79)
Sex	
Male	29 (60.4%)
Female	19 (39.6%)
ECOG PS	
0	38 (79.2%)
1	10 (20.8%)
Main location	
Upper third	17 (35.4%)
Middle third	21 (43.8%)
Lower third	10 (20.8%)
Macroscopic type	
3	21 (43.8%)
4	27 (56.2%)
Histological type	
Differentiated	8 (16.7%)
Undifferentiated	40 (83.3%)
Signet-ring cell component	
Present	26 (54.2%)
Absent	22 (45.8%)
Esophageal invasion	
Absent	41 (85.4%)
Present (within ≤ 3 cm)	7 (14.6%)
cT	
T2	1 (2.1%)
T3	9 (18.7%)
T4a	35 (72.9%)
T4b	3 (6.3%)
cN	
N0	15 (31.3%)
N1	13 (27.1%)
N2	15 (31.3%)
N3	5 (10.4%)
Peritoneal cytology	
CY0	38 (70.2%)
CY1	10 (29.8%)
cStage	
I	1 (2.1%)
IIB	12 (25.0%)
III	24 (50.0%)
IVA	1 (2.1%)
IVB	10 (20.8%)

ECOG PS Eastern Cooperative Oncology Group performance status; *cT* clinical stage relating to tumors; *cN* clinical stage relating to nodes; *cStage* clinical stage

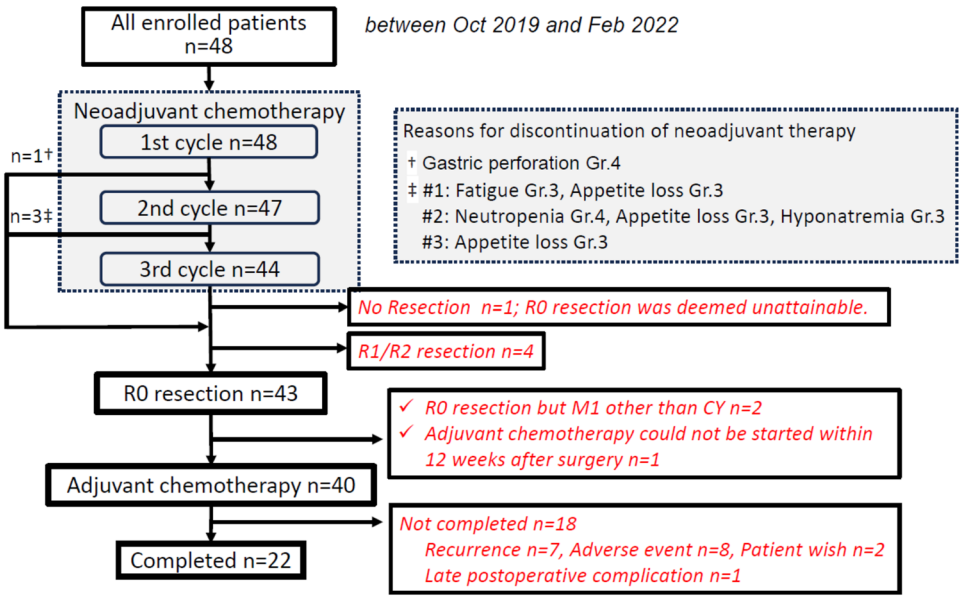

Fig. 1 CONSORT diagram

Treatment

Neoadjuvant DOS chemotherapy

The neoadjuvant DOS chemotherapy protocol has been previously described in detail [12]. Briefly, docetaxel (40 mg/m^2) and oxaliplatin (100 mg/m^2) were both administered intravenously, on day 1 of a 21-day cycle. S-1 was administered orally twice a day at a dose based on body surface area (< 1.25 m^2, 80 mg; ≥ 1.25 to < 1.5 m^2, 100 mg; ≥ 1.5 m^2, 120 mg/day) on days 1–14. Patients received three courses before surgery. The criteria for initiating each cycle of neoadjuvant chemotherapy included Grade 0–1 appetite loss, and treatment was delayed if patients had Grade ≥ 2 appetite loss until recovery to Grade 1 or lower.

Surgery

After confirming that R0 resection was possible by image evaluation after the final course of neoadjuvant chemotherapy, gastrectomy with ≥ D2 lymph node dissection was performed within 56 days (recommended within 28 days) from the last administration of S-1 in the final course. For patients with direct invasion into adjacent organs, combined resection was performed if feasible. This included esophagectomy when necessary. If R0 resection was impossible or if distant metastases including peritoneal metastases (P1), hepatic metastases (H1), or positive peritoneal cytology (CY1) were found during surgery, the protocol treatment was discontinued.

Adjuvant DS chemotherapy

The adjuvant DS chemotherapy protocol based on the START-2 study [10] has also been previously described in detail [12]. Briefly, docetaxel (40 mg/m^2) was administered intravenously on day 1 of a 21-day cycle, starting from the second course. S-1 was administered orally twice a day at a dose based on body surface area (< 1.25 m^2, 80 mg; ≥ 1.25 to < 1.5 m^2, 100 mg; ≥ 1.5 m^2, 120 mg/day) on days 1–14, beginning from the first course.

Statistical analysis

The null hypothesis posited a 3-year PFS rate of 45%, given the NAC group's 47.7% rate in JCOG0501. The expected rate was set to 60% due to additional neoadjuvant DOS therapy and a 16% DS therapy increase in relapse-free survival over S-1 in START-2 [10]. To achieve 80% power at a one-sided α level of 0.05, with a threshold 3-year PFS of 45%, we estimated 44 patients were needed over a 2-year registration and 3-year follow-up. Accounting for dropouts, 46 patients were targeted for enrollment.

The full analysis set (FAS) included eligible NAC-started patients. Background data were summarized as frequency and proportion for categorical variables, and the median and range for continuous ones. The 95% confidence intervals (CIs) for binomial outcomes used Clopper–Pearson exact method. Analyses were conducted at the OGSG Data Center using R software (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Between October 2019 and February 2022, 48 patients were enrolled from 16 institutions in Japan. The characteristics

Table 2 Adverse events during neoadjuvant chemotherapy (n = 48)

Toxicities	Grade*				Grade 3–4 (%)
	1	2	3	4	
Laboratory findings					
Leucopenia	5	15	8	2	20.8
Neutropenia	3	10	13	5	37.5
Febrile neutropenia	0	0	0	1	2.1
Anemia	19	8	2	0	4.2
Thrombocytopenia	7	0	0	0	0.0
Hyperbilirubinemia	1	2	1	0	2.1
Hypoalbuminemia	15	13	3	0	6.3
Aspartate aminotransferase increased	9	2	2	0	4.2
Alanine aminotransferase increased	10	1	2	0	4.2
Creatinine increased	4	0	0	0	0.0
Hyperkalemia	4	0	0	0	0.0
Hypokalemia	9	2	0	0	0.0
Hypernatremia	3	0	0	0	0.0
Hyponatremia	15	2	1	1	4.2
γ-glutamyltranspeptidase increased	0	0	1	0	2.1
Alkaline phosphatase increased	1	0	0	0	0.0
Objective findings					
Nausea	6	8	5	0	10.4
Vomiting	6	4	0	0	0.0
Oral mucositis	3	2	0	0	0.0
Diarrhea	12	8	6	0	12.5
Constipation	7	0	0	0	0.0
Abdominal pain	3	1	1	0	2.1
Appetite loss	7	11	18	0	37.5
Fatigue	18	10	1	0	2.1
Acneiform eruption	1	0	0	0	0.0
Fever up	5	0	0	0	0.0
Skin hyperpigmentation	4	0	0	0	0.0
Dysgeusia	9	3	0	0	0.0
Paronychia	1	0	0	0	0.0
Peripheral sensory neuropathy	11	4	0	0	0.0
Alopecia	8	10	0	0	0.0
Peripheral motor neuropathy	0	1	0	0	0.0
Palmar/plantar redness dysesthesia syndrome	2	0	0	0	0.0
Upper respiratory tract infection	0	1	1	0	2.1
Urinary tract infection	1	1	0	0	0.0
Visual abnormalities	0	1	0	0	0.0
Gastric perforation	0	0	0	1	2.1
Thromboembolism	0	1	0	0	0.0
Malaise	0	1	0	0	0.0
Hyperglycemia	0	1	0	0	0.0
Wound infection	0	1	0	0	0.0
Colitis	0	1	0	0	0.0

* CTCAE: version 5.0

of all 48 eligible patients are summarized in Table 1. The median age was 66 years (range, 44–79), and 29 patients (60.4%) were men. Twenty-one patients (43.8%) had type 3 GC, and 27 (56.2%) had type 4 GC. Clinical T4a tumors, node-positive status, and undifferentiated histological type were predominant. Signet ring cell component was identified

Table 3 Postoperative complications (n = 47)

	Clavien–Dindo Grade					≥ III (%)
	I	II	IIIa	IIIb	IVa	
Intra-abdominal abscess	0	2	0	0	0	0
Incisional infection	0	1	0	0	0	0
Dumping syndrome	0	1	0	0	0	0
Hyponatremia	1	0	0	0	0	0
Empyema	0	0	1	0	0	2.1
Ascites	1	0	0	0	0	0

in 26 patients (54.2%). Peritoneal cytology was positive in 10 patients (29.8%). cStage III disease was observed in 24 patients (50.0%), and cStage IV disease in 11 patients (22.9%).

A flow diagram summarizing patient enrollment and treatment is provided in Fig. 1.

Neoadjuvant chemotherapy

All patients underwent neoadjuvant DOS chemotherapy. Four patients in total discontinued treatment. One patient discontinued treatment before the second course because of gastric perforation. Three other patients discontinued treatment before the third course because of AEs, including fatigue (Grade 3) and appetite loss (Grade 4) in one patient; neutropenia (Grade 4), appetite loss (Grade 3), and hyponatremia (Grade 3) in the second patient; and appetite loss (Grade 3) in the third patient. The remaining 44 patients completed three courses of neoadjuvant DOS therapy. The completion rate of NAC, defined as the percentage of patients who completed all three planned courses, was 91.7% (44/48, 95% CI 80.0–97.7%).

The chemotherapy-related AEs in the 48 patients who received at least one course of DOS therapy are summarized in Table 2. The most frequent toxicity of any grade was appetite loss, which was observed in 36 patients (75.0%), followed by neutropenia and hypoalbuminemia in 31 (64.6%), leukopenia in 30 (62.5%), and anemia and fatigue in 29 (60.4%). The most common Grade 3 or 4 hematological toxicity was neutropenia, which was reported in 18 patients (37.5%). One patient (2.1%) developed febrile neutropenia. The most frequent Grade 3 or 4 nonhematological toxicity was appetite loss, which was observed in 18 patients (37.5%), requiring intravenous infusion or enteral nutrition. No serious AEs requiring hospitalization or chemotherapy-related deaths were reported.

Surgical procedures and complications

Forty-seven patients underwent gastrectomy following neoadjuvant DOS therapy. One of the 48 patients did not undergo gastrectomy because the R0 resection was deemed unattainable. The surgical approaches included open surgery in 28 patients (59.6%), laparoscopic surgery in 16 (34.0%), and robotic surgery in 3 (6.4%). Total gastrectomy was performed in 32 patients (68.1%), and distal gastrectomy in 15 (31.9%). No patients underwent pancreatoduodenectomy. Combined resections involved the gallbladder in 17 patients (36.2%), spleen in 10 (21.3%), colon in four (8.5%), and pancreas in two (4.3%). Omentectomy was performed in 10 (21.3%). Lymphadenectomy was classified as D2 in 39 patients (83.0%) and D2 + in eight (17.0%). Reconstruction methods included Roux-en-Y in 38 patients (80.9%), Billroth-I in four (8.5%), and other methods in five (10.6%). The median operation time was 352 min (interquartile range: 266–421 min), and the median blood loss was 181 mL (interquartile range: 40–421 mL).

R0 and R1 resections were achieved in 43 and three patients, respectively. Positive surgical margins were observed in one patient and positive peritoneal cytology in two patients. The R0 resection rate was 89.6% (95% CI: 77.3–96.5%) among all 48 eligible patients.

As summarized in Table 3, postoperative complications occurred in seven patients (14.9%). Clavien–Dindo (C–D) Grade IIIa or higher complications were reported in one patient (2.1%): empyema. None of the patients required reoperation, and there were no in-hospital deaths or deaths within 30 days of surgery.

Pathological findings

The pathological findings are presented in Table 4. Six patients were staged pathologically as M1, primarily because of positive peritoneal cytology in two patients, macroscopic peritoneal nodules in one patient, small bowel metastasis in one patient, para-aortic lymph node metastasis in one patient, and posterior mediastinal lymph node metastasis in one patient. After neoadjuvant DOS therapy, the number of patients with positive peritoneal cytology decreased from 10 to two, which resulted in a CY-negative conversion rate of 80% (95% CI: 44.4–97.5%).

A pathological response of the primary tumor graded as ≥ 1b was observed in 66.7% of patients (32/48, 95% CI: 51.6–79.6%), including one patient (2.1%) who achieved

Table 4 Pathological findings

	n = 47
ypT	
T0	1 (2.1%)
T1a	1 (2.1%)
T1b	1 (2.1%)
T2	5 (10.6%)
T3	17 (36.1%)
T4a	19 (40.4%)
T4b	3 (6.4%)
ypN	
N0	12 (25.5%)
N1	10 (21.3%)
N2	6 (12.8%)
N3	18 (38.3%)
NX	1 (2.1%)
P	
P0	46 (97.9%)
P1	1 (2.1%)
CY	
CY0	45 (95.7%)
CY1	2 (4.3%)
ypM	
M0	41 (87.2%)
M1	6 (12.8%)
Lymphatic invasion	
Ly0	16 (34.0%)
Ly1a	18 (38.3%)
Ly1b	5 (10.6%)
Ly1c	7 (14.9%)
Vascular invasion	
V0	22 (46.8%)
V1a	15 (31.9%)
V1b	7 (14.9%)
V1c	2 (4.3%)
ypStage	
IA	2 (4.3%)
IB	3 (6.4%)
IIA	9 (19.1%)
IIB	3 (6.4%)
IIIA	8 (17.0%)
IIIB	11 (23.4%)
IIIC	4 (8.5%)
IV	6 (12.8%)
Pathological response	
Grade 0	2 (4.3%)
Grade 1a	13 (27.7%)
Grade 1b	15 (31.9%)
Grade 2	16 (34.0%)
Grade 3	1 (2.1%)

ypT yield or post-therapy pathological stage relating to tumors; *ypN* yield or post-therapy pathological stage relating to nodes; *ypM* yield or post-therapy pathological stage relating to metastasis; *ypStage* yield or post-therapy pathological stage

a complete response (Table 5). When analyzed separately by macroscopic tumor type, the response rates were 66.7% (14/21) for type 3 tumors and 66.7% (18/27) for type 4 tumors. The comparison of response rates between differentiated and undifferentiated types was limited by the small number of differentiated cases (n = 8), making trend analysis challenging. When stratified by the presence or absence of a signet ring cell component, the response rates were 57.7% (15/26) in patients with signet ring cell carcinoma and 77.3% (17/22) in those without.

Adjuvant chemotherapy

Protocol completion, which included NAC, R0 gastrectomy, and adjuvant chemotherapy for more than 1 year, was achieved in 45.8% of the patients (22/48, 95% CI 31.4–60.8). The AEs associated with adjuvant DS therapy are summarized in Table 6. Grade 3 or 4 AEs included neutropenia (40.0%), leukopenia (30.0%), appetite loss (22.5%), anemia (12.5%), and febrile neutropenia (10.0%). No treatment-related deaths were observed.

Discussion

In this phase II study, we evaluated the feasibility, safety, and short-term efficacy of neoadjuvant DOS therapy followed by gastrectomy and adjuvant DS therapy in patients with large type 3 or type 4 GC. Of the 48 patients, 91.7% completed the planned three courses of DOS therapy. AEs during DOS therapy were predominantly hematological, with Grade 3 or 4 neutropenia observed in 37.5% of patients. R0 resection was achieved in 89.6%. Postoperative complications occurred in 14.9% of patients, with C–D Grade ≥ IIIa complications observed in only 2.1%. Evaluation of the pathology revealed a high pathological response rate (Grade ≥ 1b) of 66.7%, including a complete pathological response in 2.1%. Notably, the CY-negative conversion rate reached 80%, which supports the potential efficacy of the neoadjuvant approach in this high-risk population.

The JCOG0501 trial [6, 7], a phase III study of neoadjuvant SP therapy for large type 3 or type 4 GC, reported an NAC completion rate of 88.1%, with Grade 3 or 4 AEs such as neutropenia (29.3%). Gastrectomy was associated with 7.9% of the C–D Grade ≥ IIIa complications, and the R0 resection rate was 74.2%. The pathological response rate was 51.0%, with a pathological complete response rate of 2%. Compared with JCOG0501, our study had a higher NAC completion rate (91.7%), higher R0 resection rate (89.6%), and better pathological response (66.7%), although JCOG0501 included patients with peritoneal metastasis (3.3%). The incidence of Grade 3 or 4 neutropenia was higher in our study (37.5%) than in JCOG0501 but

Table 5 Pathological response of neoadjuvant chemotherapy

		n	No resection	Grade					Grade ≥ 1b		Grade ≥ 2	
				0	1a	1b	2	3	n (%)	p-value	n(%)	p-value
All		48	1	2	13	15	16	1	32 (66.7)	-	17 (35.4)	-
Macroscopic type	3	21	0	1	6	7	7	0	14 (66.7)	1.000	7 (33.3)	1.000
	4	27	1	1	7	8	9	1	18 (66.7)		10 (37.0)	
Histology	Differentiated	8	0	0	1	5	2	0	7 (87.5)	0.240	2 (25.0)	0.694
	Undifferentiated	40	1	2	12	10	14	1	25 (62.5)		15 (37.5)	
Signet-ring cell component	Present	26	1	1	9	7	7	1	15 (57.7)	0.221	8 (30.8)	0.551
	Absent	22	0	1	4	8	9	0	17 (77.3)		9 (40.9)	

was manageable. The incidence of surgical complications of C–D Grade ≥ IIIa (2.1%) was lower than in JCOG0501. These results suggest that neoadjuvant DOS therapy provides a favorable balance of high efficacy and manageable toxicity for large type 3 or type 4 GC.

After a phase III study (FLOT4) in Germany showed that FLOT was superior to epirubicin, cisplatin, and fluorouracil or capecitabine in terms of both OS and PFS in resectable GC, FLOT is now the standard regimen for perioperative chemotherapy in Western countries [17]. On the other hand, DOS has attracted attention as a promising regimen in East Asia. In the PRODIGY trial, neoadjuvant DOS resulted in a significant improvement in PFS and OS compared with upfront surgery for cT2–3N1 or cT4 GC, with an NAC completion rate of 89.9% and Grade 3 or 4 neutropenia observed in 12.6% of patients [13, 14].

In Japan, the JCOG1704 trial, which assessed the efficacy of neoadjuvant DOS using the Osaka University regimen (docetaxel 40 mg/m^2) for GC with bulky nodal involvement or para-aortic node metastases, reported an NAC completion rate of 98%, a pathological response rate (grade ≥ 1b) of 65%, pathological complete response rate of 24%, and Grade 3 or 4 neutropenia in 24.4% of patients [18]. In JCOG1704, differentiated-type cases accounted for 70% of the cohort, whereas undifferentiated-type cases comprised 83% in our study, with a high prevalence (54%) of cases containing a signet-ring cell carcinoma component. Despite these differences, the observed pathological response rate of 66.7% in our study was comparable to that of JCOG1704.

The prognosis and chemoresistance of signet-ring cell carcinoma have been debated, and concerns have been raised about the efficacy of perioperative chemotherapy for such tumors [19, 20]. Voron et al. conducted a retrospective cohort study involving 1,799 cases and reported that signet-ring cell carcinoma was identified as an independent predictor of poor outcome and exhibited lower sensitivity to chemotherapy [21]. In our study, the pathological response rate was 77.3% in patients without signet-ring cell component, whereas it was much lower at 57.7% in those with signet-ring cell component. This substantial difference underscores the need for more potent and targeted treatment options for signet-ring cell gastric carcinoma, which appears to be less responsive to NAC. We additionally compared pathological response rates across subgroups based on age, sex, performance status, tumor location, cT, cN, CY, and cStage. However, no specific characteristics of good responders were identified (data not shown).

The present study showed a significantly higher CY-negative conversion rate of 80% compared with a previous report showing a rate of 44.3% following SP therapy [22]. In clinical practice in Japan, gastrectomy with D2 lymphadenectomy followed by S-1 monotherapy is a widely accepted strategy for GC patients with CY1. However, the prognosis was still poor, with a 5-year OS rate of 26% [23]. Conversion surgery with R0 resection following NAC for CY1 showed prolongation of survival [22, 24]. The DOS regimen may represent a more promising therapeutic approach for CY1 cases.

A randomized phase II trial, JCOG2204, is currently ongoing to evaluate the efficacy of FLOT versus DOS therapy as neoadjuvant chemotherapy for large type 3 or type 4 gastric cancer. The primary endpoint of this trial is the pathological response rate, and the results are highly anticipated. However, since JCOG2204 includes P1a cases and differs in adjuvant chemotherapy, direct survival analysis comparisons may not be valid.

We acknowledge the limitations of this study despite its promising results. First, this was a nonrandomized, single-arm phase II study, which may have introduced selection bias and thus limits the generalizability of the findings. Second, the relatively small sample size of 48 limited the statistical power and meant that we may not have captured all potential AEs. Third, although we report promising short-term efficacy and safety for this study, longer follow-up data are needed to assess the full impact of this therapy on OS and PFS.

Table 6 Adverse events during adjuvant chemotherapy (n = 40)

Toxicities	Grade*				Grade 3–4 (%)
	1	2	3	4	
Laboratory findings					
Leucopenia	5	7	9	3	30.0
Neutropenia	2	5	7	9	40.0
Febrile neutropenia	0	0	1	3	10.0
Anemia	18	9	5	0	12.5
Thrombocytopenia	12	1	0	0	0.0
Hyperbilirubinemia	6	1	1	0	2.5
Hypoalbuminemia	19	4	0	0	0.0
Aspartate aminotransferase increased	11	1	3	0	7.5
Alanine aminotransferase increased	7	2	2	0	5.0
Creatinine increased	2	1	0	0	0.0
Hyperkalemia	5	0	0	0	0.0
Hypokalemia	9	1	1	0	2.5
Hypernatremia	4	0	0	0	0.0
Hyponatremia	5	0	0	0	0.0
Serum amylase increased	0	0	0	1	2.5
Hyperglycemia	0	1	0	0	0.0
Chronic kidney disease	0	1	0	0	0.0
Objective findings					
Nausea	12	2	1	0	2.5
Vomiting	4	1	0	0	0.0
Oral mucositis	8	1	1	0	2.5
Diarrhea	16	5	2	0	5.0
Constipation	8	1	0	0	0.0
Abdominal pain	4	2	2	0	5.0
Appetite loss	15	7	7	2	22.5
Fatigue	17	8	3	0	7.5
Acneiform eruption	2	1	0	0	0.0
Fever up	5	1	0	0	0.0
Ecchypapuloid skin rash	1	1	0	0	0.0
Lacrimation	7	3	0	0	0.0
Skin hyperpigmentation	6	0	0	0	0.0
Dysgeusia	9	3	0	0	0.0
Peripheral sensory neuropathy	10	2	0	0	0.0
Alopecia	10	5	0	0	0.0
Peripheral motor neuropathy	1	0	0	0	0.0
Palmar/plantar redness dysesthesia syndrome	8	3	1	0	2.5
Urinary tract infection	0	0	1	0	2.5
Visual abnormalities	0	1	0	0	0.0
Lower extremity edema	1	0	0	0	0.0
Eyelid dysfunction	0	1	0	0	0.0
Muscle spasms	1	0	0	0	0.0
Hematuria	1	0	0	0	0.0
Fatigue	0	1	0	0	0.0
Limb edema	2	1	0	0	0.0
Small bowel obstruction	0	0	1	0	2.5
Renal dysfunction	0	1	0	0	0.0
Kidney stone	0	1	0	0	0.0
Vertebral fracture	0	1	0	0	0.0

Table 6 (continued)

Toxicities	Grade*				Grade 3–4 (%)
	1	2	3	4	
Nail changes	1	0	0	0	0.0
Nail infection	1	0	0	0	0.0
Palpitation	1	0	0	0	0.0
Pulmonary infection	0	0	1	0	2.5
Dry skin	1	0	0	0	0.0
Epistaxis	1	0	0	0	0.0
Edema	1	0	0	0	0.0
Anastomotic stenosis	0	1	0	0	0.0

* CTCAE: version 5.0

Conclusions

In this multi-institutional phase II study, neoadjuvant DOS therapy followed by gastrectomy and adjuvant DS therapy demonstrated promising feasibility, safety, and short-term efficacy in patients with large type 3 or type 4 GC. The high completion rate of NAC and favorable pathological response rates suggest that neoadjuvant DOS therapy may offer significant clinical benefits. The primary endpoint, 3-year PFS, will be analyzed and reported upon completion of the follow-up period.

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Author contributions Study concept: RT, SE, and TY. Study design: RT, SE, TY, TK, KF, DS, YK, TT, TSh, and TSa. Acquisition of data: RT, SE, HM, TO, JK, NT, TM, HF, and YS. Statistical analysis of data: TSh. Analysis and/or interpretation of data: RT, SE, TY, HM, JK, YK, TT, TSh, and TSa. Drafting the manuscript: RT and SE. Revising the manuscript critically for important intellectual content: All authors. All authors approved the final version of the manuscript.

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Declarations

Conflict of interest The authors declare their financial interests/personal relationships, which may be considered as potential competing interests. Disclosures provided by the authors are disclosed in Supplementary text 3.

Research involving human and animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent All patients provided written informed consent.

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