Phase II Study of Neoadjuvant Chemotherapy With S-1 Plus Oxaliplatin for Gastric Cancer Clinical T4 or N2-3

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Abstract

Background: In Japan, the standard treatment for stage II or III gastric cancer is D2 gastrectomy followed by administration of S-1 for one year. However, patients with stage III disease have unsatisfactory survival rates. The purpose of this study was to evaluate the efficacy and safety of neoadjuvant chemotherapy consisting of S-1 and oxaliplatin for advanced gastric cancer.

Methods: Patients with cT4 or cN2–3 gastric cancer were scheduled to receive two courses of chemotherapy (130 mg/m² oxaliplatin on Day 1, 80 mg/m² S-1 per day twice daily for 14 days) followed by surgery. The primary endpoint was the R0 resection rate. The secondary endpoints were rates of completion of protocol treatment, pathological response, and adverse events; and 3-year overall survival, 5-year overall survival, and 5-year recurrence-free survival.

Results: Between May 2016 and March 2019, 30 patients were enrolled in the study, all of whom completed the protocol treatment. The R0 resection rate (primary endpoint) was 93.3% (95% confidence interval: 77.9–99.2). The pathological response rate was 63.3%. Grade 3–4 toxicities included anemia (3.3%), anorexia (6.7%), and fatigue (3.3%). Relative dose intensities were 91.2% and 94.2% for S-1 and oxaliplatin, respectively.

Conclusions: Neoadjuvant S-1 and oxaliplatin is highly effective, achieving an acceptable R0 resection rate with relatively few severe toxicities and good compliance.

Trial registration information:

Registry name: A prospective intervention study on the availability of preoperative SOX therapy for T4 or N2-3 gastric cancer

Trial ID: UMIN: UMIN000024656

URL: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000028365

Introduction

Gastric cancer is the fifth most common cancer and the second leading cause of all cancer deaths worldwide [1]. In Japan, the standard treatment for stage II or III gastric cancer (GC) is D2 gastrectomy followed by administration of S-1 for one year, this being based on the results of the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) [2]. However, at 67.1% and 50.2%, the 5-year overall survival (OS) rates in patients with stage IIIA and IIIB disease, respectively [2], have been unsatisfactory. Therefore, new treatment strategies for stage III GC are needed.

Impaired gastric function causes weight loss, and erratic food intake, resulting in deterioration in performance status, which can hinder administration of intensive combination chemotherapy after gastrectomy. Neoadjuvant chemotherapy has several benefits over postoperative chemotherapy,

including reduction in tumor volume, eradication of micrometastases, evaluation of sensitivity to chemotherapy, and better compliance than with more intensive chemotherapy [3]. In Japan, several Phase II studies have demonstrated that cisplatin and S-1 (CS), a standard regimen for metastatic gastric cancer, is also effective as neoadjuvant therapy for advanced gastric cancer [4, 5]. However, cisplatin frequently causes febrile neutropenia, nausea, and impairment of renal function, prejudicing compliance with, and efficacy of, chemotherapy. Oxaliplatin, a third-generation platinum compound, was developed to improve tolerability and ease of administration of platinum derivatives [6]. A randomized phase III study of S-1 and oxaliplatin (SOX) as first line chemotherapy for advanced GC demonstrated that SOX is safer than, and almost as effective as, CS [7]. In Japan, SOX is now regarded as a standard first line chemotherapy regimen for unresectable GC. However, the usefulness of SOX as neoadjuvant chemotherapy has not been adequately investigated. We conducted this study to examine the efficacy and safety of neoadjuvant SOX for cT4 or N2–3M0 advanced gastric cancer. In this first report clarified the short-term results including R0 resection rate which was a primary endpoint.

Patients And Methods

Study design and cohort

This single-arm, prospective, phase II study was conducted by Tokyo Women's University, the participating centers being Tokyo Women's Medical University Hospital (Shinjuku-ku, Tokyo, Japan) and Tokyo Women's Medical University, Yachiyo Medical Center (Yachiyoshi, Chiba, Japan). The study was approved by the Institutional Review Board of Tokyo Women's Medical University and conducted in accordance with the Helsinki Declaration. It was registered with the University Hospital Medical Information Network Clinical Registry (UMIN-CTR; ID: UMIN000024656). All enrolled patients provided written informed consent.

The eligibility criteria were as follows: (1) histologically proven gastric adenocarcinoma; (2) clinical T4a/4b(SE/SI) gastric carcinoma or more than three enlarged (major axis ≥ 10 mm) lymph nodes on computed tomography; (3) no distant metastases detected by thoracic/abdominal/pelvic computed tomography (CT), no non-curable factors identified by staging laparoscopy other than positive lavage cytology (cM0); (4) no esophageal invasion > 3 cm; (5) age 20–80 years; (6) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; (7) adequate oral intake and absence of intestinal obstruction or active bleeding from primary lesion; (8) adequate bone marrow function (white cell count $3,000/\text{mm}^3$ – $12,000/\text{mm}^3$; neutrophil count $\geq 1,500/\text{mm}^3$; platelet count $\geq 100,000/\text{mm}^3$; hemoglobin ≥ 8.0 g/dL), adequate liver function (serum bilirubin concentration ≤ 2.0 mg/dL; and serum transaminase ≤ 100 IU/L), adequate renal function (serum creatinine ≤ 1.5 mg and creatinine clearance ≥ 60 mL/min); and (9) written informed consent. The exclusion criteria were as follows: (1) synchronous or metachronous (within 5 years) malignancies; (2) peripheral sensory neuropathy Grade ≥ 2 ; (3) severe drug hypersensitivity; (4) presence of serious complications; (5) infections requiring systemic treatment; (6) history of unstable angina pectoris or myocardial infarction within 12 months before registration; (7)

interstitial pneumonia, pulmonary fibrosis, or severe emphysema; (8) uncontrolled mental illness; (9) receiving treatment with flucytosine, phenytoin, or warfarin; (10) receiving continuous systemic corticosteroid or immunosuppressant treatment; and (11) pregnancy. Staging laparoscopy was mandatory and all patients were confirmed as having no peritoneal dissemination before being enrolled in this study.

Neoadjuvant SOX chemotherapy

Patients were scheduled to receive two courses of neoadjuvant chemotherapy with oxaliplatin (130 mg/m²) by intravenous infusion on Day 1 and oral S-1 (twice daily) for 14 days, repeated every 3 weeks. The dosage of S-1 was 80 mg/day for body surface area (BSA) < 1.25m², 100 mg/day for BSA from 1.25 m² < 1.5 m², and 120 mg/day for BSA ≥ 1.5m². After completion of two courses, an abdominal CT scan and endoscopy were performed to evaluate the response.

Surgery and adjuvant chemotherapy

Tumors were resected 2–6 weeks after completion of the second course of chemotherapy. Gastrectomy with D2 lymphadenectomy was performed in accordance with the Japanese Gastric Cancer Treatment guidelines [8]. Distal gastrectomy was performed provided a satisfactory proximal resection margin could be achieved. If not, total gastrectomy was performed. The criteria for resection after neoadjuvant chemotherapy were as follows: (1) R0 resection by gastrectomy with D2 lymph node dissection considered possible on the basis of findings on comprehensive CT scanning and upper gastroenterological endoscopy; and (2) adequate organ function (white cell count > 3000/mm³, platelet count < 100,000/mm³). Patients who fulfilled these criteria underwent surgery between 21 and 49 days after the last dose of S-1. Administration of S-1 for 1 year following gastrectomy was recommended, but not mandatory, in patients in whom R0 resection was achieved. If R0 resection was not achieved, protocol treatment was terminated.

Statistical analysis

The primary endpoint was the R0 resection rate and the secondary endpoints the 3-year OS, 5-year OS, 5-year recurrence-free survival, rate of completion of protocol treatment, pathological response rate (pRR), and rates of adverse events. Disease stage, extent of lymph node dissection, and histologic type were assessed in accordance with the standards defined by the Japanese Gastric Cancer Association [9]. Pathological response was graded by the institutional pathologists in each center in accordance with the Japanese classification of gastric carcinoma, third English edition [9] as follows: Grade 0 (no evidence of effect); Grade 1a (viable tumor cells remain in more than two-thirds of the tumor); Grade 1b (viable tumor cells remain in more than one-third but less than two-thirds of the tumor); Grade 2 (viable tumor cells remain in less than one-third of the tumor); and Grade 3 (no viable tumor cells). In this study, a pathological response was defined as Grade 1b or higher. Toxicity and adverse events were classified in accordance with the Common Toxicity Criteria of the National Cancer Institute (NCI-CTC) version 4.0. Intra- and postoperative complications were graded in accordance with the Clavien–Dindo classification [10].

Calculation of required sample size

Prior to this trial, the R0 resection rate of pT4 or pN2 gastric cancers in patients who underwent upfront surgical resection in our institute was 66.2%. We therefore added 20% to the threshold to set the expected R0 resection rate at 86.2%. This provided a required sample size of 27 patients with one-sided testing at the 5% significance level with a power of 80%.

Results

Patient characteristics

Between May 2016 and March 2019, 30 patients were enrolled in the study; a flow diagram is presented in Fig. 1. Table 1 shows patient and tumor characteristics. The median age was 71 years and the male:female ratio 23:7. Most included patients were in good general condition (86.7% with performance status 0). Fifteen (50.0%) patients had histologically proven intestinal adenocarcinomas and 15 (50.0 %) had diffuse adenocarcinomas. Twenty-three patients (76.7%) had T4 tumors and 25 (83.3%) had N+ disease, including N2 bulky masses (20.0%, 6/30).

Table 1
Patient (*n* = 30) and tumor characteristics

	Value
Age (years)	71.0 (48–80)
Sex (male: female)	23:7
ECOG performance status 0/1	26/4
Cancer type	
Bulky N2 lymph nodes	6
Type 4/Type 3	3/17
Histological type	
Intestinal/diffuse	15/15
Tumor depth	
cT3/cT4a/cT4b	7/23/0
Lymph node metastases	
cN0/cN1/cN2/cN3	5/10/14/1
cStage	
IIB	6
IIIA	16
IIIB	8
IIIC	0
^a The median is given, with the range in parentheses	
^b Including one patient having both a large type3 tumor and a bulky N2 lymph node	

Neoadjuvant chemotherapy

This treatment was initiated in all 30 patients, all of whom completed the specified two courses. Table 2 shows the toxicity profile during this regimen. No patient had Grade 3 febrile neutropenia. One patient (3.3%) had Grade 3 anemia. Grade 3 non-hematologic toxicities comprised anorexia and fatigue in two patients (6.7%) and nausea and vomiting in one (3.3%). There were no treatment-related deaths. The relative dose intensities of S-1 and oxaliplatin were 91.2% and 94.2%, respectively.

Table 2
Adverse events during neoadjuvant chemotherapy

Event, N(%)	Grade 1/2	Grade 3/4
Hematologic		
Leucopenia	7 (23.3%)	0
Neutropenia	11 (36.6%)	0
Anemia	26 (86.7%)	1 (3.3%)
Thrombocytopenia	21 (70.0%)	0
Febrile neutropenia	N/A	0
Non-hematologic		
Anorexia	19 (63.3%)	2 (6.7%)
Fatigue	14 (46.7%)	1 (3.3%)
Nausea	12 (40.0%)	1 (3.3%)
Diarrhea	12 (40.0%)	0
Vomiting	2 (6.7%)	1 (3.3%)
Dysesthesia	18 (60.0%)	0
Peripheral neuropathy	0	0
Dysgeusia	4 (13.3%)	0
Oral mucositis	5 (16.7%)	0
Hyperpigmentation	7 (23.3%)	0
Alopecia	1 (3.3%)	0
Watering eyes	1 (3.3%)	0
Constipation	1 (3.3%)	0
Maculo-papular rash	2 (6.7%)	0
Thromboembolic event	1(3.3%)	0
Injection site reaction	6 (20.0%)	0
High serum creatinine	10 (33.3%)	0
High aspartate aminotransferase	16 (53.3%)	0
High alanine aminotransferase	12 (64.3%)	0
Hypoalbuminemia	29 (96.7%)	0

Event, N(%)	Grade 1/2	Grade 3/4
Hypokalemia	12 (40.0%)	0
Hyperkalemia	6 (20.0%)	0
Hyponatremia	16 (53.3%)	0
Hypernatremia	2 (6.7%)	0

Surgical findings and pathological stage

The 30 study patients, all of whom had completed chemotherapy, underwent surgery, the median interval between last dose of S-1 and surgery being 24.5 days (range 14–41 days). The surgical findings are summarized in Table 3. Twelve patients underwent total gastrectomy, the remaining 18 undergoing distal gastrectomy. The mean number of retrieved lymph nodes was 39 (18–74). Resection with curative intent was performed on all 30 patients, achieving R0 resection (the primary endpoint) in 28 of them (93.3%; 95% confidence interval:77.9–99.2) and R1 resection in the remaining two. R1 resection was attributable to a microscopically cancer-positive proximal margin in one patient and positive peritoneal washing cytology (CY1) in the other. Operative morbidities are itemized in Table 4. Grade 3 or greater morbidities occurred in seven patients (23.3%), the major complications being anastomotic leakage in 6.7% and pancreatic fistula in 6.7%. There were no reoperations or treatment-related or in-hospital deaths.

Table 3
Surgical variables in the 30 study patients

Values ^a	
Gastrectomy	
Distal	18 (60%)
Total	12 (40%)
Lymph node dissection	
D2	100 (100%)
Operation time (min) ^a	280 (173–465)
Blood loss (mL) ^a	394 (51–1986)
^a Values provided as median (range)	

Table 4
Operative morbidities in the 30 study patients

	Grade ^a				Grade 3–4 (%)
	1	2	3	4	
Pancreatic fistula		1	2		6.7
Abdominal infection			1		3.3
Anastomotic leakage			2		6.7
Anastomotic stricture		1			
Small intestinal obstruction		1	3		10.0
Splenic infarction		1			
Postoperative hemorrhage		1			
Wound infection	2				
Lung infection			2		6.7
^a Clavien–Dindo Criteria for Adverse Events, version 2.0					

Pathological responses (Grade 1b–3) were identified in 19 (63.3%) patients, two (6.7%) of whom had no residual disease (Grade 3) (Table 5).

Table 5
Pathological findings in the 30 study patients

	Values
Tumor depth	
ypT0	2 (6.7%)
ypT1a	4 (13.3%)
ypT1b	2 (6.7%)
ypT2	6 (20.0%)
ypT3	11 (36.7%)
ypT4	5 (16.7%)
Lymph node metastases	
ypN0	15 (50.0%)
ypN1	4 (13.3%)
ypN2	8 (26.7%)
ypN3a, ypN3b	3 (10.0%)
ypStage	
IA	3 (10.0%)
IB	6 (20.0%)
IIA	5 (16.7%)
IIB	6 (20.0%)
IIIA	5 (16.7%)
IIIB	0 (0.0%)
IIIC	2 (6.7%)
IV	1 (3.3%)
Median number of retrieved lymph nodes ^a	39 (18–74)
Peritoneal disease	
Yes	1 (3.3%)
M category	

^a, presented as number (range)

	Values
M0	29 (96.7%)
ypM1	1 (3.3%)
Resection achieved	
R0	28 (93.3%)
R1	2 (6.7%)
Pathological response	
Grade 0	1 (3.3%)
Grade 1a	10 (33.3%)
Grade 1b	4 (13.3%)
Grade 2	13 (43.3%)
Grade 3	2 (6.7%)
^a , presented as number (range)	

Discussion

In this study, the R0 resection rate was 93.3%, which is superior to the expected primary endpoint of 86.2% and met the primary endpoint. The pathological response rate was 63.3%. Furthermore, chemotherapy-related adverse events and postoperative complications were within manageable and acceptable limits.

The standard treatment for stage III gastric cancer is upfront gastrectomy followed by adjuvant chemotherapy, this regimen being based on the results of the ACTS-GC trial [2]. However, the recurrence rate is still high and the 5-year OS low, being 50.2–63.1% [2]. Some clinicians have attempted to administer combination adjuvant chemotherapy. However, post-gastrectomy patients characteristically have weight loss and inadequate food intake, which prejudices compliance with chemotherapy. Therefore, when intensive chemotherapy is indicated, compliance may potentially be better with neoadjuvant chemotherapy than with postoperative adjuvant chemotherapy, making the former an attractive option for patients with resectable advanced gastric cancer.

JCOG0405, a Phase II study of neoadjuvant CS in patients with gastric cancer and bulky lymph nodes or para-aortic lymph node metastases, reported favorable outcomes, the R0 resection rate being 82% and the 3-year and 5-year survival rates 59% and 53%, respectively [5]. However, the JCOG0501 trial, a phase III study that investigated the efficacy of neoadjuvant chemotherapy with CS in patients with Type 4 or

large Type 3 (> 8 cm in maximum diameter) gastric cancers [11], failed to demonstrate that patients who received neoadjuvant CS had better OS than those who underwent upfront surgery [12].

One of the problems of preoperative CS combination therapy is its low completion rate as a result of severe toxicities. The rate of completion of scheduled neoadjuvant chemotherapy was 88% in both JCOG 0405 and JCOG 0501 [5, 11]. Therefore, a feasible regimen that is equally effective is needed. In this study, we selected the combination regimen of SOX for neoadjuvant treatment of gastric cancer, the G-SOX trial having demonstrated non-inferiority of OS after SOX compared with CS for unresectable advanced gastric cancer [7], along with less toxicity. One advantage of the SOX regimen is that abundant intravenous hydration to protect renal function is unnecessary [7]. Thus, patients can receive neoadjuvant SOX on an outpatient basis. Honma et al. and Satake et al. reported that neoadjuvant chemotherapy with SOX for locally advanced gastric cancer [13, 14] is feasible, has acceptable toxicity, and is effective, achieving a pathological response rate of 83–85.7%. However, long-term outcomes have not been reported.

Previous studies have found that Grade 3 or more adverse hematological events, such as leukemia, neutropenia, anemia, and thrombocytopenia, occur in 19–29.3% of patients receiving preoperative CS combination chemotherapy, and that adverse non-hematological events, such as nausea, anorexia, and diarrhea, occur in 11.6–15% of such patients [5, 11]. These severe toxicities may delay the timing of surgery and prejudice prognosis. In our study, only three patients (9.9%) had Grade 3 or more adverse events: one of these patients had adverse hematological effects and the other two had adverse non-hematological events. There were no chemotherapy-related deaths. Additionally, all patients completed the planned two courses of neoadjuvant chemotherapy with SOX and underwent surgery. The minimal toxicity of our regimen may have contributed to the high relative dose intensity (91.2 % for S-1 and 94.2% for oxaliplatin) and favorable R0 resection rate in this study. In the JCOG0501 trial, only 68% of the patients underwent the planned surgery [11]. The low frequency of adverse events and high rate of completion of planned chemotherapy in our study suggest that SOX may be more useful than CS.

A subgroup analysis of the G-SOX trial found that, in patients aged 70 years or more, Grade 3 or worse adverse events occurred less frequently in those receiving SOX therapy than in those receiving CS therapy, indicating that SOX is an effective and feasible treatment for older individuals with advanced gastric cancer [15]. In the present study, more than half of the enrolled patients were aged 70 years or more (median age: 72), the median age being higher than it was in JCOG0405 (63) or JCOG0501(64) [5, 11]. In Japan, the proportion of older individuals is rapidly increasing; accordingly, the need to treat older persons is also increasing [16]. The SOX regimen appears to be more suitable than CS for older patients, both for treatment of unresectable tumors and in the neoadjuvant setting.

A Grade 1b or greater pRR according to the Japanese classification of gastric carcinoma (JCGC) is reportedly the one of the best surrogate endpoints for OS after neoadjuvant chemotherapy for advanced gastric cancer [17, 18]. Previous pilot Phase II studies evaluating two or four courses of neoadjuvant CS therapy for locally advanced gastric cancer have demonstrated pRRs of 47–51% [5, 11]. In our study, the

pRR was 63.3%, which is comparable to that reported for CS. Although we do not yet have long-term survival data, our findings suggest that long-term survival after SOX may be comparable with that after CS.

It is possible that tumor progression during long-term neoadjuvant chemotherapy may result in patients foregoing the opportunity to undergo curative resection [19]. Prolonged administration of neoadjuvant chemotherapy to patients who do not respond to it may lead to lower complete resection rates and a worse prognosis. The optimal duration of neoadjuvant chemotherapy is yet to be established. Yoshikawa et al. demonstrated that two versus four courses of neoadjuvant chemotherapy are equivalent in terms of pathological response rate and OS [20]. Although in the present study only two courses of chemotherapy were administered over 6 weeks, acceptable R0 resection rates and pRR were achieved.

In conclusion, neoadjuvant chemotherapy with SOX is feasible and effective in patients with advanced gastric cancer, yielding a high R0 resection rate and acceptable pRR. Analysis of long-term survival data is awaited.

Declarations

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Conflict of interest

HK received a scholarship grant from Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan)

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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1

Flowchart of study