Randomized phase III trial of gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer, the short-term safety and surgical results: Japan Clinical Oncology Group Study (JCOG0501)

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Abstract

Background The prognosis of patients with linitis plastica (type 4) and large (≥ 8 cm) ulcero-invasive-type (type 3) gastric cancer is extremely poor, even after extended surgery and adjuvant chemotherapy. Given the promising results of our previous phase II study evaluating neoadjuvant chemotherapy (NAC) with S-1 plus cisplatin (JCOG0210), we performed a phase III study to confirm the efficacy of NAC in these patients, with the safety and surgical results are presented here.

Methods Eligible patients were randomized to gastrectomy plus adjuvant chemotherapy with S-1 (Arm A) or NAC followed by gastrectomy + adjuvant chemotherapy (Arm B). The primary endpoint was the overall survival (OS). This trial is registered at the UMIN Clinical Trials Registry as C000000279.

Results From February 2007 to July 2013, 300 patients were randomized (Arm A 149, Arm B 151). NAC was completed in 133 patients (88%). Major grade 3/4 adverse events during NAC were neutropenia (29.3%), nausea (5.4%), diarrhea (4.8%), and fatigue (2.7%). Gastrectomy was performed in 147 patients (99%) in Arm A and 139 patients (92%) in Arm B. The operation time was significantly shorter in Arm B than in Arm A (median 255 vs. 240 min, respectively; $p=0.024$). There were no significant differences in Grade 2–4 morbidity and mortality (25.2% and 1.3% in Arm A and 15.8% and 0.7% in Arm B, respectively).

Conclusions NAC for type 4 and large type 3 gastric cancer followed by D2 gastrectomy can be safely performed without increasing the morbidity or mortality.

Keywords Linitis plastica · Neoadjuvant chemotherapy · Large type 3

Introduction

The incidence of gastric cancer has been decreasing, especially in the developed countries; however, it remains a major cause of cancer death and is the fifth commonest cancer in the world [1]. The treatment results for gastric

cancer have been gradually improving mainly due to the improvements in surgical techniques, especially lymph node dissection, and in perioperative treatments including chemotherapy. In Japan, adjuvant chemotherapy with 1-year S-1 is regarded as a standard treatment for Stage II and III gastric cancer after curative resection [2] based on the results of the ACTS-GC study [3].

However, despite a substantial increase in the survival rate, there remain several types of gastric cancer associated with an extremely poor survival such as those with extensive nodal disease or with scirrhous type cancer. The Japan Clinical Oncology Group (JCOG) has conducted several clinical trials targeting these cancer types to explore neoadjuvant

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chemotherapy [4–6]. The 3-year overall survival (OS) of these patients has been reported to be less than 15% in the historical data [7]. In Western countries, neoadjuvant chemotherapy (NAC) is considered to be a standard of care for locally advanced gastric cancer. However, when we started the treatment development of NAC for these extremely poor prognostic cohort, the evidence of NAC had not been demonstrated [8, 9] especially for scirrhous type of cancer [10]. So, the JCOG0210 trial was designed to evaluate the efficacy and safety of preoperative chemotherapy with S-1 + cisplatin (CDDP) (SP) followed by gastrectomy with D2/3 lymph node dissection for type 4 and large type 3 gastric cancer [5]. The completion rate of the protocol treatment, which was a primary endpoint of the JCOG0210 trial, was 73.5% (80% confidence interval [CI], 63.7–81.7%), which was much higher than the prespecified threshold of 45% ($p < 0.0001$). In addition, the rate of treatment-related death, which was another endpoint, was 2.0% (1/49), much lower than the prespecified threshold ($< 5\%$).

In the subsequent phase III trial (JCOG0501) targeting on large type 3 or type 4 gastric cancer, we attempted to prove superiority of the neoadjuvant S-1/CDDP followed by D2 gastrectomy over a control arm of upfront surgery. Postoperative adjuvant chemotherapy b7, L10-y S-1 for 12 months was offered to all patients after the first protocol amendment, which was conducted shortly after this trial started when another phase III trial proved efficacy of the postoperative treatment for Stage II/III gastric cancer. Patient enrollment has already been finished, and the short-term and safety results are reported in the present manuscript.

Methods

Patients

The eligibility criteria to this study were: (1) histologically proven adenocarcinoma of the stomach, (2) Bormann type 4 or large (≥ 8 cm) type 3, (3) no evidence of distant metastasis except localized peritoneal seeding around the stomach or positivity for peritoneal lavage cytology with laparoscopic confirmation, (4) no involvement of the esophagus ≥ 3 cm, (5) an age of 20–75 years, (6) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, (7) no history of chemotherapy or radiotherapy for any malignancy, (8) no history of surgery for gastric cancer except for endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), (9) no prominent bleeding from the primary tumor or gastrointestinal stenosis, (10) a sufficient oral intake, and (11) adequate organ function [white blood cell (WBC) count ≥ 3000 and $\leq 12,000/\text{mm}^3$; hemoglobin ≥ 9.0 g/dl; platelet (PLT) count $\geq 100,000/\text{mm}^3$;

AST and ALT ≤ 100 IU; total bilirubin ≤ 2.0 mg/dl; creatinine ≤ 1.5 mg/dl; creatinine clearance ≥ 60 ml/min]. Written informed consent was obtained from all of the patients.

Tumors were staged in accordance with the Japanese Classification of Gastric Carcinoma (2nd English edition) [11]. For confirming eligibility criteria, exploratory laparoscopy was mandatory to diagnose the presence or absence of peritoneal metastasis and to perform the peritoneal lavage cytology. If there was no cancer cell in the peritoneal lavage fluid, it was defined as CY0. If cancer cell was found in the lavage, it was defined as CY1. Peritoneal metastasis was classified as follows according to Japanese Classification of Gastric Carcinoma 12th edition: 4–7: P0 (no peritoneal metastasis), P1 (dissemination to the peritoneum adjacent to gastric cancer), P2 (a small number of distant metastases to the peritoneum), P3 (a large number of distant metastases to the peritoneum) [12].

After the second protocol amendment, patients with peritoneal metastases were eligible provided they were determined as P0CY1, P1CY0 or P1CY1 after the staging laparoscopy to accelerate the patient's enrollment. The sample size was unchanged, because the estimated prognosis of these patients was considered to be identical to that of originally eligible patients with P0CY0 stage by staging laparoscopy.

The exclusion criteria were: (1) synchronous or metachronous (within 5 years) other malignancy other than carcinoma in situ, (2) pregnancy or lactation, (3) treatment with a major tranquilizer, steroids, flucytosine, phenytoin, or warfarin, (4) lung fibrosis, interstitial pneumonitis, bowel obstruction, or ischemic heart disease.

Study design

This study was an open-label, randomized, phase III trial (JCOG0501) conducted by the Stomach Cancer Study Group in JCOG. Eligible patients were registered by telephone or fax to the JCOG Data Center. Patients were randomly assigned (1:1) to receive surgery plus postoperative adjuvant chemotherapy arm (Arm A) or NAC followed by surgery plus adjuvant chemotherapy arm (Arm B) using a minimization method with a random component to balance the arms on the basis of the institution, macroscopic type (large type 3 vs. type 4), clinical depth of invasion (T2–3 vs. T4), and clinical nodal status (N0 vs. N1 vs. N2). Patients and all investigators were unmasked to treatment assignment. The JCOG Data Center performed central monitoring to ensure data submission, patient eligibility, protocol compliance, safety, and on-schedule study progress and issued monitoring reports every 6 months.

The primary endpoint was the OS, defined as the time from random assignment to death from any cause or censored on the last date of contact for a surviving patient.

The secondary endpoints were as follows; Progression-free survival, defined as the time from random assignment to the first occurrence of disease progression, death from any cause, or the latest date at which a progression-free status was verified. The Proportion of the protocol completion in Arm B was defined as the proportion of the patients who completed NAC and achieved R0 resection with D2 or more lymph node dissection in all randomized patients. The proportion of R0 resection was defined as the proportion of the patients achieving R0 resection with D2 lymph node dissection among all randomized patients. Adverse events (AEs) associated with either gastrectomy or chemotherapy were separately evaluated by the Common Terminology Criteria for Adverse Events (version 3.0).

AEs were assessed at least monthly during NAC and post-operative chemotherapy via a verbal interview, physical examination, and blood tests, including a complete blood cell count and assessments of the liver and renal function, until disease progression. For follow-up, abdominal computed tomography (CT) was performed every 6 months, and measurements of carcinoembryonic antigen and carbohydrate antigen 19-9 were measured every 3 months until 3 years.

Treatment

Patients assigned to Arm A underwent a total or distal gastrectomy with D2 or more lymph node dissection, depending on the tumor location. Within 6 weeks after surgery, adjuvant chemotherapy with S-1 was given; initial 16 patients who were enrolled before the first amendment of the protocol and did not receive adjuvant chemotherapy. All curatively resected patients received oral S-1 80 mg/m² per day (80–120 mg/day total dose depending on the patient's body surface area as follows: < 1.25 m², 80 mg; 1.25–1.5 m², 100 mg; and > 1.5 m², 120 mg) on days 1–28 of every 6-week cycle. Treatment was discontinued in case of disease progression diagnosed clinically or by imaging, serious AE, treatment cycle was delay due to AE for longer than 3 weeks, requiring subsequent dose reduction after the second dose reduction due to AE, patient's refusal, or judgement by the attending physician for other reasons.

Patients assigned to Arm B received NAC with S-1 with CDDP before surgery. S-1 was given orally twice daily for the first three weeks of a 4-week course. The dose of S-1 administered each time was adjusted by body surface area same as above. CDDP was given as an intravenous infusion of 60 mg/m² on day 8 of each course as described previously [5]. Fourteen to Twenty days after the second course of chemotherapy, tumor resectability was assessed. The resection criteria were as follows: (i) R0 resection was deemed possible by gastrectomy with D2 or D3 (by the Japanese classification version 2) lymph node dissection,

where resectability was assessed comprehensively with CT scan, upper gastroenterological endoscopy and barium meal study, and (ii) sufficient organ function (WBC > 3000/mm³, PLT count > 100,000/mm³, arterial oxygen pressure in room air > 60 torr). Patients who fulfilled those criteria were subjected to surgery between 21 and 34 days after the last administration of chemotherapy. Surgery and adjuvant chemotherapy were same as Arm A.

Statistical analysis

This study was designed to confirm the superiority of Arm B compared with Arm A in terms of OS. The planned sample size was 300 (150 per arm), expecting a total of 276 deaths, to detect a 3-year survival difference by 10% (17.5% in Arm A vs. 27.5% in Arm B, which corresponded to a hazard ratio of 0.74), with a one-sided α of 5% and 80% statistical power. Follow-up for 3 years was planned after 5 years of patient accrual.

Protocol was amended on 13 February 2007 after publication of ACTS-GC trial [3] to add the adjuvant chemotherapy with S-1 for 1 year in both arms. At this time, a total of 16 patients had already been enrolled. The sample size was thus recalculated as 300 excluding these 16 patients already enrolled, based on a 3-year survival difference by 10.8% (25% in Arm A vs. 35.8% in Arm B, corresponding to the hazard ratio of 0.74) with a one-sided α of 5% and 80% statistical power. Full analysis set for efficacy and safety was all patients enrolled after this amendment.

Two interim analyses were planned, with adjustments for repeated comparisons using the Lan and DeMets method and the O'Brien-Fleming type α spending function [13]. The first and second interim analysis was planned when half and all of the planned sample size would be completed. Actually, the first interim analysis was performed on 17 September 2011 and the second interim analysis was performed on 15 March 2014. In both interim analyses, the Data and Safety Monitoring Committee of the JCOG recommended to continue this trial.

Fisher's exact test was used for comparison of categorical variables and Wilcoxon rank sum test was performed for continuous variables. Statistical analyses were performed by the JCOG Data Center using the SAS software program, version 9.4 (Cary, NC, USA). This study is registered with UMIN-CTR, number C000000279 (<https://upload.umin.ac.jp>).

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of Health, Labour and Welfare of Japan. The funders of the study had no role in the study design, data collection, analysis, interpretation, or writing of the report. The corresponding author had full access to all the data in the study after termination of the study and had the final responsibility regarding the decision to submit the findings for publication.

The study protocol was approved by the JCOG Protocol Review Committee and the institutional review board of each participating hospital before initiation of the study. This study was done in accordance with the international ethical recommendations stated in the Declaration of Helsinki, Japanese Ethical Guidelines for Clinical Research. This trial is registered at the UMIN Clinical Trials Registry as C000000279.

Results

Between 17 October 2005 and 19 July 2013, 316 patients were randomly assigned to Arm A (158 patients) or Arm B (158 patients) at 44 hospitals in Japan (Fig. 1). Two patients in Arm B were proved to be ineligible; one having malignant lymphoma as the final pathological diagnosis in the resected specimen and the other one having peritoneal metastasis diagnosed as P2 at the time of staging laparoscopy. These two patients were included in the safety analysis.

Excluding the initial 16 patients (9 patients in Arm A and 7 in Arm B), this safety analysis included 300 patients who were randomized after the first revision of the protocol (149 patients in Arm A and 151 patients in Arm B). In Arm

B, 4 patients did not receive NAC. Therefore, 147 patients received NAC and included in safety analysis of NAC. Two patients in Arm A and 8 patients in Arm B did not receive gastrectomy. As a result, 147 patients in Arm A and 139 patients in Arm B received per-protocol treatment and were included in the safety analysis for gastrectomy.

The patient characteristics were well balanced between the arms (Table 1). Type 3 accounted for one-third and remaining two-thirds were type 4 in both arms. cT3 (SE) and undifferentiated type of tumor were predominant in both arms. Peritoneal metastasis (P1) was found in the greater or lesser omentum, anterior lobe of the transverse mesocolon or pancreatic capsule in one patient in Arm A and in four patients in Arm B at the time of staging laparoscopy. In addition, a few peritoneal metastases other than the above-mentioned lesions in the upper abdominal cavity were found in one ineligible patient in Arm B. Peritoneal cytology was positive in 28 patients in Arm A and in 32 patients in Arm B.

Neoadjuvant chemotherapy

Of 151 patients eligible for efficacy analysis in Arm B, 4 patients did not receive NAC because of patient refusal in 1, acute cholecystitis in 1, liver dysfunction in 1, and miscellaneous reasoning in 1. As a result, 147 patients in Arm B who received NAC were included for this safety analysis. Among these 147 patients, NAC was terminated in the first course in 12 patients and during the second course in 2 patients, remaining 133 patients completed 2 courses of NAC. The reasons for termination of NAC were adverse

Fig. 1 The CONSORT flow-chart

Table 1 Patient characteristics

	Arm A <i>n</i> = 149	Arm B <i>n</i> = 151
Age (years)		
Median	62	64
Range	28–75	30–75
Gender		
Male	89	87
Female	60	64
PS		
0	141	149
1	8	2
Macroscopic type		
Type 3	58	55
Type 4	91	96
Tumor invasion		
cT1	0	0
cT2	28	17
cT3	118	128
cT4	3	6
Lymph node metastasis		
cN0	50	55
cN1	62	67
cN2	37	29
Histological type		
Differentiated	32	39
Undifferentiated	117	112
Esophageal invasion		
Absent	135	143
Present	14	8
Peritoneal metastasis ^a		
P0	148	146
P1	1	4
P2	0	1
P3	0	0
Peritoneal cytology		
CY0	121	119
CY1	28	32
cStage		
IA	0	0
IB	12	6
II	43	48
IIIA	41	40
IIIB	24	20
IV	29	37

^aAccording to the Japanese Classification of Gastric Cancer (12th edition)

events in 8, patients' refusal in 5, disease progression in 2, and others in 3.

Table 2 Toxicities of neoadjuvant chemotherapy

Toxicities	G1	G2	G3	G4	% Grade ≥ 3
Leukocytes	15	47	9	2	7.5
Hemoglobin	79	51	5	1	4.1
Platelets	87	10	1	0	0.7
Neutrocytes	39	37	37	6	29.3
Total bilirubin	14	5	0	0	0
AST	32	1	0	0	0
ALT	39	7	0	0	0
Creatinine	52	5	0	0	0
Nausea	49	23	8	0	5.4
Vomiting	13	10	4	0	2.7
Anorexia	43	36	17	0	11.6
Diarrhea	21	14	7	0	4.8
Stomatitis	14	2	2	0	1.4
Fatigue	42	17	4	0	2.7
Febrile neutropenia	–	–	1	0	0.7

Table 2 shows the adverse events of NAC in the 147 patients. Grade 3 or greater toxicities were observed in 30 patients (19.7%). Major adverse events were neutropenia, leucopenia, anemia, anorexia, nausea, vomiting, and diarrhea. Febrile neutropenia was observed in only 1 patient (0.7%).

Surgical resection

In Arm A, one patient did not undergo gastrectomy due to disease progression and one patient received NAC by refusal of upfront surgery. In Arm B, eight patients did not receive gastrectomy due to disease progression in five (2 before NAC and 3 during NAC), patient's refusal in 1, AEs in 1, and death due to other disease in 1. These patients were excluded from this safety analysis. The operative details were, therefore, evaluated in 147 patients in Arm A and 139 patients in Arm B (Table 3). The operation time was significantly shorter in Arm B than in Arm A. Blood loss was also tended to be smaller in Arm B than in Arm (A) The type of surgery and presence or absence of combined resection were not markedly different between the two arms. The incidence of blood transfusion was significantly higher in Arm (B) There were no severe complications during operation in either arm.

Morbidity and mortality

The operative morbidities are shown in Table 4. Any Grade 2 or greater morbidities were observed in 37 patients (25.2%) in Arm A and in 22 patients (15.8%) in Arm B ($p=0.058$). Similarly, Grade 3 or greater morbidities were observed in

Table 3 Operative details

	Arm A <i>n</i> = 147	Arm B <i>n</i> = 139	<i>p</i> value
Operation time (min)			
Median	255	240	0.024
Range	90–477	50–547	
Blood loss (ml)			
Median	420	330	0.124
Range	0–2600	0–4320	
Surgery			
Distal	21	16	
Total	123	117	
Bypass	2	0	
Laparotomy	1	6	
Combined resection			
Absent	22	28	
Present	125	111	
Spleen	112	96	
Gallbladder	55	40	
Pancreas	8	10	
Colon	6	5	
Others	13	3	
Blood transfusion			
RCC	9	20	0.045
FFP	1	4	0.203

RCC red cells concentrated, FFP fresh frozen plasma

Table 4 Operative morbidities

Morbidity	G1	G2	G3	G4	% Grade ≥ 3
Arm A (<i>n</i> = 147)					
Anastomotic leakage	0	2	1	1	1.4
Pancreatic fistula	7	12	4	0	2.7
Anastomotic stenosis	1	0	0	0	0
Abdominal abscess	–	1	10	0	6.8
Pyothorax	–	0	1	0	0
Wound infection	–	1	2	0	0
Pneumonia	–	1	0	0	0
Ileus	2	3	0	0	0
Arm B (<i>n</i> = 139)					
Anastomotic leakage	2	0	0	0	0.7
Pancreatic fistula	1	3	3	0	2.2
Anastomotic stenosis	0	0	0	0	0
Abdominal abscess	–	1	5	0	3.6
Pyothorax	–	0	0	0	0
Wound infection	–	1	0	0	0
Pneumonia	–	2	1	0	0.7
Ileus	0	4	2	0	1.4

16 patients (10.9%) in Arm A and in 9 patients (6.5%) in Arm B ($p=0.213$). The major complications (Grade 3 or greater) in Arms A and B included anastomotic leakage in 1.4% and 0.7%, pancreatic fistula in 2.7% and 2.2%, and abdominal abscess in 6.8% and 3.6%, respectively. Reoperation was done in 6 patients (4.1%) in Arm A and in 1 patient (0.7%) in Arm B ($p=0.121$). Two patients (1.3%) in Arm A died due to acute bacterial enteritis and strangulated intestinal obstruction, and 1 patient (0.7%) in Arm B died due to strangulated intestinal obstruction. Morbidity did not increase in Arm B.

Discussion

In this safety analysis, NAC for type 4 and large type 3 gastric cancer followed by D2 gastrectomy could be performed without reducing the chance of resection and increasing the morbidity or mortality.

In 147 patients assigned to the perioperative treatment arm, the planned 2 courses of NAC were completed in 133 patients (90%). No treatment-related death was observed. While neutropenia was the most frequent and common AE, the incidence of febrile neutropenia was as low as 0.7%. Among non-hematological toxicities, although anorexia, nausea, and diarrhea were relatively frequently observed, treatment could be continued with adequate dose interruption or dose modification in most of these patients. We had previously demonstrated the feasibility of the SP regimen in several phase II trials [5, 6]. The feasibility and safety of this SP regimen were again confirmed in the present large-scale phase III trial.

NAC using 5-fluorouracil + CDDP (FP) and epirubicin + CDDP + continuous infusion 5-fluorouracil (ECF) has been considered to be a standard regimen in the Western countries [14, 15]. However, the efficacy of docetaxel, oxaliplatin, fluorouracil, and leucovorin (FLOT) has recently been demonstrated, and FLOT is currently regarded as the standard treatment for NAC in fit patients [16–19]. Of note, though: FLOT is criticized for being quite toxic, with a 90-day mortality of up to 7% in potentially curable patients [20]. When compared with the results with FLOT [16], the severity of non-hematological toxicities with SP seems to be similar. However, the incidence of Grade 3 or higher neutropenia was 52% with FLOT and 29% with SP. In addition, febrile neutropenia was observed in 5% of patients with FLOT but in only 0.7% of SP. Although there exists a substantial racial difference, SP appears to more feasible than FLOT.

Regarding the influence of toxicity during NAC on the proportion for completing treatment including surgery, in Arm B, the proportion of the patients who received surgery as recommended by the protocol was as high as 88%. In

the FLOT4 study, planned surgery was performed in only 73% of those receiving ECF and in 80% of those receiving FLOT [16]. Thus, although we have to be careful about the difference of inclusion criteria and treatment intensities between these two trials, the SP regimen is considered to be a highly feasible treatment as NAC as compared with ECF or FLOT for locally advanced gastric cancer at least for Japanese patients.

Gastrectomy with D2 lymph node dissection is currently considered to be a global standard treatment for locally advanced gastric cancer [21]. However, there are concerns that preoperative treatment may make the surgery more difficult due to scar formation or edema. In the present study, operative time and blood loss were both shorter and smaller in Arm B than in Arm A. As the extent of surgery and the incidence of combined organ resection were similar between the two arms, the influence of NAC with SP regimen on surgery seems negligible. One point of note was the incidence of blood transfusion, which was significantly higher in Arm B than in Arm A. This may be due to existing anemia at the time of surgery due to myelosuppression by preoperative SP, as the amount of blood loss was rather smaller in Arm B than in Arm A.

The incidence of postoperative complications grade 3 or higher were quite low in both arms, and there were no marked differences between the two arms. In addition, no treatment-related death was observed in Arm B. NAC, therefore, appears to have no influence on the postoperative morbidity, which is consistent with the results of FLOT-4 and MAGIC studies, where the rate of surgical complications and mortality were 25% and 4% in the ECF group, and 12% and 2% in the FLOT group [18], while the morbidity and mortality were 45.3% and 5.9% in the surgery alone group, and 45.7% and 5.6% in the perioperative chemotherapy group in the MAGIC study [15]. Again, there were no significant differences in the morbidity or mortality due to preoperative chemotherapy.

In the present study, although more than 80% of the patients received total gastrectomy, the incidence of grade 3 or 4 anastomotic leakage was only 1.4% in Arm A and 0.7% in Arm B. Preoperative SP did not increase the incidence of anastomotic leakage. Furthermore, the quality of surgery in this trial appears to be quite high, as the rates of other major surgical complications, such as pancreatic fistula and intraabdominal abscess, were quite low (1.4% and 6.8% in Arm A and 2.2% and 3.6% in Arm B, respectively), and no marked difference was observed between the arms. These results suggest that preoperative chemotherapy does not increase the incidence of postoperative intraabdominal infectious complications.

Several limitations associated with the present study warrant mention. First, the subjects of the present study were all Japanese. It is, therefore, unclear whether or

not this preoperative SP regimen is feasible in Western patients. The dosage of S-1 may need to be reduced in Western patients due to the high incidence of diarrhea. However, SP with a reduced dose of S-1 demonstrated an increased safety and comparative efficacy to FP in metastatic gastric cancer in Western countries [22, 23]. SP is, therefore, suggested to be feasible even in Western patients. Second, docetaxel-containing regimens are regarded as the standard in Western countries, following the results of FLOT-4 [18, 19]. However, docetaxel was not included in the present study. We have previously performed a phase II trial investigating the safety and efficacy of preoperative docetaxel plus CDDP plus S-1 (DCS) in patients with extensive nodal disease [24]. The safety was similar to that of SP regimen. However, we failed to demonstrate any additional efficacy of docetaxel to SP. Whether or not adding docetaxel improves the efficacy against scirrhous type of cancer remains unclear. This issue should be further evaluated.

Conclusion

NAC for type 4 and large type 3 gastric cancer followed by D2 gastrectomy can be safely performed without increasing the morbidity or mortality. The efficacy of NAC with SP is expected to be demonstrated in the planned primary analysis.

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Compliance with ethical standards

Conflict of interest Author MT has received personal fees from Taiho, Ono, Chugai, Eli Lilly Japan, Bristol Myers Squibb, and Yakult Honsha outside the submitted work. Author MS received personal fees from Taiho, Chugai, Lilly, and Ono outside the submitted work. Author TS has received personal fees from Taiho. Author NB has received grant from Taiho, Ono and Bristol Myer-Squibb, and honorarium from Taiho, Ono, Chugai, Eli Lilly and Bristol Myer-Squibb. Author KN has received personal fees from Bayer, Chugai, Merck, and Eisai outside the submitted work. Author TY has received grants and personal fees from Taiho, Chugai, Yakult, personal fees from Ono, Bristol, Lilly, Terumo, Abbott, Johnson and Johnson, Covidien, Olympus, Nihon Kayaku, Daiichi Sankyo outside the submitted work. Author HK has received personal fees from Johnson & Johnson outside the submitted work.

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

Informed consent Informed consent was obtained from all patients for inclusion in the study.

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