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ORIGINAL ARTICLE

Neoadjuvant docetaxel, oxaliplatin and S-1 (DOS) combination chemotherapy for patients with resectable adenocarcinoma of esophagogastric junction

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Abstract

Backgrounds Since the prognosis of patients with adenocarcinoma of the esophagogastric junction (AEG) remains poor, more intensive treatments, including neoadjuvant chemotherapy (NAC), should be developed. We retrospectively examined whether neoadjuvant docetaxel, oxaliplatin, and S-1 (DOS) combination chemotherapy resulted in a favorable clinical response and acceptable toxicity in patients with AEG.

Methods This retrospective cohort study included 36 consecutive patients with cStage IIB–IV AEG (Siewert types I–III). Regarding stage IV disease, patients with resectable distant lymph node metastasis (M1-LYM) were eligible. Patients underwent three 3-week cycles of docetaxel (40 mg/m^2) and oxaliplatin (100 mg/m^2) on day 1 plus oral S-1 (80–120 mg according to body surface area) from day 1 to 14. Surgical resection was performed within 2–4 weeks after completion of NAC.

Results Three cycles of neoadjuvant DOS were completed in 28 (78%) patients. Grade 3–4 neutropenia, anorexia, and diarrhea were observed in 26 (72%), 7 (19%), and 4 (11%) patients, respectively. Febrile neutropenia occurred in six (17%) patients. There were no treatment-related deaths. R0 resection was achieved in 35 (97%) patients, and postoperative morbidities of Clavien–Dindo grade III or higher were observed in 6 (17%) patients. Pathological complete response was observed in 11 (31%) of 36 patients. Pathological response rates of grade ≥ 2 and grade ≥ 1b were 47 and 72%, respectively. Two-year progression-free and overall survival rates were 60.1 and 81.2%, respectively.

Conclusions Neoadjuvant DOS therapy for AEG produced high pathological response rates with an acceptable safety profile, and may be a promising treatment strategy.

Keywords Neoadjuvant chemotherapy · Preoperative DOS · Gastroesophageal junction cancer · EGJ · Siewert classification

Introduction

While adenocarcinoma of the esophagogastric junction (AEG) is common in Western countries, there has also been a gradual increase in the incidence of AEG in Asian countries [1–3]. In Japan, this trend is considered to be caused by a decreased prevalence of *Helicobacter pylori* infection and an increased prevalence of obesity, the latter of which results in gastroesophageal reflux disease that can induce Barrett's esophagus and finally AEG [4, 5]. The clinicopathological characteristics of AEG are still being explored, and a great deal of research has recently focused on the extent of favorable lymph node metastasis and optimal surgical treatment [6, 7]. However, the prognosis of patients with AEG remains poor, and therefore more intensive treatments, including neoadjuvant chemotherapy (NAC), should be developed [6, 8].

For resectable gastric cancer, the survival benefit of NAC was first confirmed in Western countries by the MAGIC trial, which used perioperative epirubicin and cisplatin as well as continuous 5-fluorouracil (ECF) [9]. On the other hand, adjuvant chemotherapy is the standard therapy in Asian countries, where the regimen for pStage II disease is either 1 year of S-1 monotherapy or 6 months of capecitabine plus oxaliplatin (CAPOX), and that for pStage

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III disease is either 6 months of S-1 plus docetaxel (DS) followed by 6 months of S-1 monotherapy, or 6 months of CAPOX [10–12]. Recently, a German phase 2/3 trial (FLOT4) demonstrated that a new perioperative regimen consisting of continuous 5-FU plus leucovorin, oxaliplatin, and docetaxel (FLOT) was superior to the ECF regimen in terms of overall and disease-free survival [13]. In a recent Korean phase 3 trial (PRODIGY), the addition of preoperative docetaxel, oxaliplatin, and S-1 (DOS) resulted in a significant improvement in progression-free survival (PFS) compared with conventional adjuvant S-1 treatment for cStage II–III gastric cancer patients [14]. Thus, a neoadjuvant strategy using docetaxel, oxaliplatin, and fluorouracil could be a new standard for locally advanced gastric cancer in both the East and the West.

Patients with AEG comprised about half of those (398/716) in the aforementioned FLOT4 trial, whereas only 5.6% of those (27/484) in the PRODIGY trial. Thus, the efficacy and safety of neoadjuvant DOS for AEG patients have not been adequately confirmed. Furthermore, the dose of DOS (docetaxel 50 mg/m^2, oxaliplatin 100 mg/m^2, S-1 80 mg/m^2) in the PRODIGY trial may have been toxic, because a previous Japanese phase 1 trial showed that 50 mg/m^2 of docetaxel with 80 mg/m^2 of S-1 (DS) was not acceptable, even without oxaliplatin, due to a high incidence of neutropenia in advanced gastric cancer patients [15]. Therefore, in this study we reduced the dose of docetaxel from 50 to 40 mg/m^2 and retrospectively examined whether our DOS regimen resulted in a favorable clinical response and acceptable toxicity in patients with AEG.

Patients and methods

Patient population

This retrospective cohort study included 36 consecutive patients with locally advanced AEG who were treated with neoadjuvant DOS therapy at Osaka University Hospital between June 2015 and October 2020. Patients were eligible if they had histologically confirmed AEG and were regarded as having cStage IIB–IV disease as assessed by endoscopic examination and contrast computed tomography (CT) scanning before treatment. AEG was classified into three subtypes according to the Siewert classification [16]. Tumor staging was based on the 8th Edition of the Union for International Cancer Control (UICC) TNM Classification of Malignant tumors; tumors with Siewert type I or II were staged using the esophageal scheme, whereas those with Siewert type III were staged using the stomach scheme [17]. As for stage IV disease, patients with resectable distant lymph node metastasis (M1-LYM) were eligible, while those with other M1 disease were not. This study was approved by the institutional review board of Osaka University Hospital (No. 21440).

Treatments and preoperative examinations

Patients received docetaxel (40 mg/m^2) and oxaliplatin (100 mg/m^2) intravenously on day 1, with oral S-1 twice a day 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) from day 1 to 14 for three 3-week cycles. During each cycle, S-1 was discontinued if patients had a neutrophil count < 500/mm^3, platelet count < 50×10^3/mm^3, AST or ALT > 100 IU/L, total bilirubin > 3.0 mg/dL, creatinine > 1.5 mg/dL, or non-hematological toxicity of grade 2 or higher.

Three cycles of chemotherapy were planned, followed by radical surgery. A maximum of six cycles of chemotherapy were allowed for pStage IV disease. CT scans that included the chest and the whole abdomen were carried out after cycles 1 and 3 to evaluate the tumor response. If tumor progression was confirmed after cycle 1, NAC was discontinued and surgical resection was planned. Esophagogastroduodenoscopy was carried out after cycle 3. Surgical resection was performed within 2–4 weeks after completion of NAC. Generally, subtotal esophagectomy plus upper gastrectomy was chosen for AEG patients with esophageal involvement over 3 cm or clinical node-positive disease in the upper or middle mediastinal field, while lower esophagectomy plus proximal or total gastrectomy was chosen for other AEG patients. Regarding adjuvant chemotherapy, S-1 monotherapy was basically considered for patients after R0 resection with NAC, but that depended on the patient's condition and physician's choice.

Evaluations

PFS was defined as the time from the date of NAC initiation to the date of disease progression, relapse, or death from any cause. In this study, non-resection or non-curative resection, including R1 or R2 resection, was defined as disease progression. Overall survival (OS) was defined as the time from the date of NAC initiation to the date of death from any cause. Toxicities and adverse events were reported using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0. The severity of postoperative complications was evaluated according to the Clavien–Dindo classification system [18, 19]. All resected specimens were examined by pathologists, and tumor regression grade after chemotherapy was quantified according to the Japanese classification of gastric carcinoma regression criteria [20].

Statistical analysis

Clinicopathological characteristics and laboratory data were compared using the χ^2 test for categorical variables and the Mann–Whitney *U* test for continuous variables. Cumulative survival was plotted by the Kaplan–Meier method and statistically analyzed with the log-rank test. *P* values < 0.05 were considered statistically significant. Statistical analyses were performed using the SPSS statistical package, version 22.0 (SPSS, Chicago, IL, USA) and JMP Pro, version 14.

Results

Baseline characteristics of the 36 patients are shown in Table 1. The tumor location was Siewert type I in 10 patients (28%), type II in 22 (61%), and type III in four (11%). Half of the patients had the differentiated histological type. All but one patient had cStage III–IV disease. Nine had M1 lesions (25%), all of which were paraaortic lymph node metastases, and one of these patients had simultaneous cervical lymph node metastases. Twenty-five (69%) of 36 patients received three cycles of NAC. On the other hand, eight patients (23%) underwent fewer than three cycles, and three (9%) underwent more than three cycles. The relative dose intensity was 95% for docetaxel, 95% for oxaliplatin, and 76% for S-1.

Adverse events during NAC are shown in Table 2. Those regarding blood parameters were only evaluated based on blood test results on days 7, 14, and 21 of each cycle. The most common grade 3–4 hematological toxicity was neutropenia ($n = 26$; 72%), and febrile neutropenia occurred in six patients (17%). Granulocyte-colony stimulating factor (G-CSF) was administered during 26 of the 104 courses overall (25%). Regarding non-hematological toxicities, grade 3 adverse events included anorexia ($n = 7$; 19%), diarrhea ($n = 4$; 11%), and nausea ($n = 1$; 3%).

The details of surgical outcomes for 35 patients are summarized in Table 3. Since one patient did not undergo surgical resection due to liver metastases detected by CT scan after cycle 3 of NAC, the R0 resection rate was 97% (35 of 36 patients). Among the 35 R0 patients, subtotal and lower esophagectomy were performed in 23 (66%) and 12 (34%) patients, respectively. Postoperative complications (grade III or higher) according to the Clavien–Dindo classification occurred in six patients (17%); these included pneumonia, internal hernia, chylothorax, and difficulty expectorating sputum in one patient each with subtotal esophagectomy, and abdominal abscess and bleeding in one patient each with lower esophagectomy plus proximal gastrectomy. There was no treatment-related mortality.

Pathological findings of resected specimens are shown in Table 4. Fourteen patients (40%) were diagnosed with ypStage 0–I, indicating the possibility of significant downstaging by NAC. A grade 3 pathological complete response (pCR) was observed in 11 (31%) of 36 patients. Pathological responses of grade ≥ 2 and grade ≥ 1b occurred in 17 (47%) and 26 (72%) of 36 patients, respectively.

Table 1 Patient characteristics

		(*n* = 36)
Age, years	Median (range)	69 (39–83)
Sex	Male	29 (81%)
	Female	7 (19%)
Siewert type	I	10 (28%)
	II	22 (61%)
	III	4 (11%)
Histological type	Differentiated	20 (56%)
	Undifferentiated/others	16 (44%)
cT status	T2	1 (3%)
	T3	31 (86%)
	T4	4 (11%)
cN status	N0	7 (19%)
	N1	13 (36%)
	N2	11 (31%)
	N3	5 (14%)
cM status	M0	27 (75%)
	M1 (LYM)	9 (25%)
cStage	IIB	1 (3%)
	III	19 (53%)
	IV	16 (45%)

Table 2 Adverse events based on CTCAE v4.0 criteria

	G1	G2	G3	G4	G3/4 (%)
Anemia[a]	6	5	1	0	1 (3%)
Neutropenia[a]	0	4	17	9	26 (72%)
Thrombocytopenia[a]	3	4	1	0	1 (3%)
AST elevation[a]	10	0	0	0	0 (0%)
ALT elevation[a]	12	1	0	0	0 (0%)
Hyponatremia[a]	7	0	0	0	0 (0%)
Hypokalemia[a]	2	0	0	0	0 (0%)
Hypoalbuminemia[a]	18	4	0	0	0 (0%)
Malaise	17	0	0	0	0 (0%)
Fatigue	6	0	0	0	0 (0%)
Anorexia	14	7	7	0	7 (19%)
Nausea	9	1	1	0	1 (3%)
Diarrhea	10	5	4	0	4 (11%)
Stomatitis	3	0	0	0	0 (0%)
Neuropathy	0	1	0	0	0 (0%)
Febrile neutropenia	–		6	0	6 (17%)

AST aspartate aminotransferase; *ALT* alanine aminotransferase

[a]These adverse events were evaluated based on blood test results only on day 7, 14, and 21 of each cycle

Table 3 Surgical outcomes

		(*n* = 35)
Surgery	Subtotal esophagectomy + upper gastrectomy	23 (66%)
	Lower esophagectomy + proximal gastrectomy	7 (20%)
	Lower esophagectomy + total gastrectomy	5 (14%)
Approach	Minimally invasive surgery	23 (66%)
	Open surgery	12 (34%)
Operation time (min)	Median (range)	508 (262–883)
Intraoperative blood loss (mL)	Median (range)	170 (0–2270)
Morbidity (C–D[a] grade ≥ III)	Any	6 (17%)
	Abdominal abscess	1 (3%)
	Bleeding	1 (3%)
	Internal hernia	1 (3%)
	Pneumonia	1 (3%)
	Chylothorax	1 (3%)
	Difficulty in sputum expectoration	1 (3%)
Mortality		0 (0%)

[a]*C–D* Clavien–Dindo classification

Table 4 Pathological findings

		(*n* = 35)
ypT status	T0	11 (31%)
	T1	3 (9%)
	T2	3 (9%)
	T3	17 (49%)
	T4	1 (3%)
ypN status	N0	19 (54%)
	N1	8 (23%)
	N2	2 (6%)
	N3	6 (17%)
ypM status	M0	33 (94%)
	M1 (LYM)	2 (6%)
ypStage	0	11 (31%)
	I	3 (9%)
	II	6 (17%)
	III	10 (29%)
	IV	5 (14%)
Pathological response	Grade 1a	9 (26%)
	Grade 1b	9 (26%)
	Grade 2	6 (17%)
	Grade 3	11 (31%)

The details of the 11 patients with pCR are shown in Table 5. pCR was observed in every Siewert type, but was more frequent in the differentiated type (*n* = 7) than in the undifferentiated type (*n* = 3). As for tumor stage, pCR was achieved even in highly advanced AEG with distant lymph node metastases (*n* = 4). No recurrence was observed during the follow-up period, although this period was short in this cohort.

Of 35 patients who underwent R0 resection, 24 (69%) received adjuvant chemotherapy, including S-1 monotherapy (*n* = 20, 57%) or fluorouracil-based combined chemotherapy (*n* = 4, 11%). At the median follow-up time of 30.0 months (range, 2.0–77.5 months), the 2-year PFS and OS rates in all 36 patients were 60.1% and 81.2%, respectively (Fig. 1).

Discussion

Our study revealed that neoadjuvant DOS combination chemotherapy for patients with resectable advanced AEG was well tolerated and had a favorable clinical response. There was no treatment-related mortality, and surgery-related morbidity was acceptable. The R0 resection rate was 97%. The pCR rate (31%) of neoadjuvant DOS was much higher than the rates of other regimens used for AEG or gastric cancer. No patients with pCR developed recurrence during the follow-up period, which suggests a favorable prognosis.

As for the effect of NAC, the pCR rate in patients with gastric cancer was reported to be 5.6% with S-1 plus oxaliplatin (SOX) and 10.4% with DOS [14, 21]. These data suggest that the addition of docetaxel in the NAC setting is effective against gastric cancer. Moreover, the recent Japanese E-SOX trial investigating the effect of neoadjuvant SOX therapy against AEG reported a pCR rate of 18.0% [22]. Although care should be taken when comparing the results of different studies, even those using the same SOX regimen, a higher pCR rate might be obtained against AEG than against gastric cancer. In the FLOT4 trial, where half of the eligible patients had AEG and the other half had gastric cancer, the pCR rate with neoadjuvant FLOT therapy in the

Table 5 The details of patients with pathological CR

No	Siewert type	Histological type	cTNM stages	No. of cycles	Adjuvant chemotherapy	Prognosis
1	I	Differentiated	cT3 N0 M0	3	–	No recurrence (5.2 years)
2	I	Undifferentiated	cT3 N1 M0	3	–	No recurrence (5.2 years)
3	II	Differentiated	cT3 N1 M0	3	–	No recurrence (4.7 years)
4	II	Undifferentiated	cT3 N3 M0	2	S-1	No recurrence (4.5 years)
5	II	Differentiated	cT3 N3 M1(LYM)	3	S-1	No recurrence (3.2 years)
6	II	Others[a]	cT2 N0 M0	3	–	No recurrence (2.3 years)
7	III	Differentiated	cT4 N2 M1(LYM)	6	–	No recurrence (2.2 years)
8	I	Differentiated	cT3 N1 M0	2	–	No recurrence (2.1 years)
9	I	Differentiated	cT3 N3 M1(LYM)	3	–	No recurrence (1.7 years)
10	I	Undifferentiated	cT3 N1 M0	3	S-1	No recurrence (1.4 years)
11	II	Differentiated	cT3 N2 M1(LYM)	4	S-1	No recurrence (1.2 years)

[a]Adenocarcinoma with enteroblastic differentiation

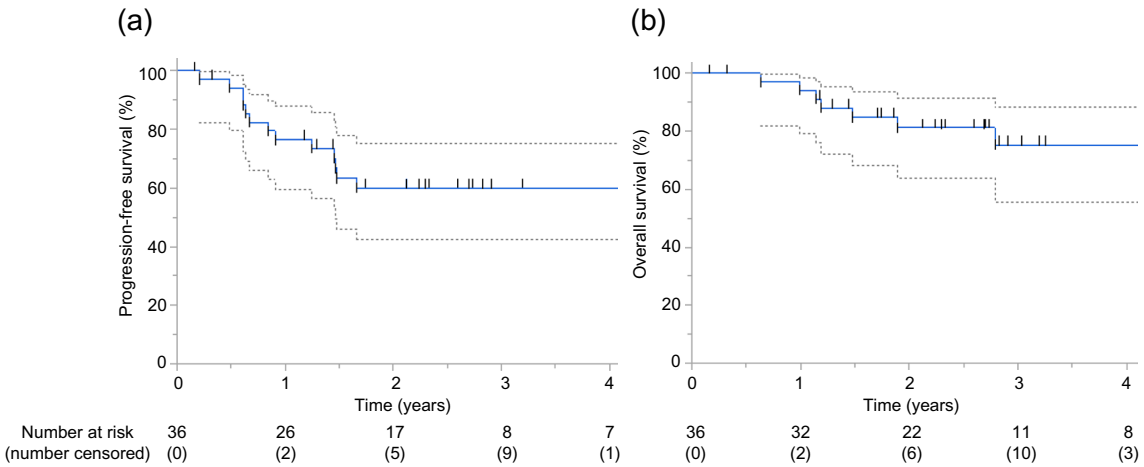

Fig. 1 Kaplan–Meier progression-free survival (**a**) and overall survival (**b**) in 36 patients

phase 2 part was 16% [23]. The hazard ratio (HR) of death for AEG was smaller than for gastric cancer in the FLOT4 trial [13], which suggested that neoadjuvant chemotherapy might be more effective for AEG than for gastric cancer. Further research will be needed to determine the appropriate NAC regimen for AEG.

It is unclear why AEG is more chemosensitive than gastric cancer. According to comprehensive molecular characterization of gastric adenocarcinoma based on data from The Cancer Genome Atlas, gastric cancer can be divided into four types; most AEG cases are classified as the chromatin instability type with intestinal histology, and only a few are the microsatellite instability (MSI) type [24]. In the FLOT4 trial, perioperative FLOT therapy had a better therapeutic effect than perioperative ECF/ECX therapy, with a HR for death of 0.746 for the intestinal type and 0.852 for the diffuse type [13]. In the PROGIDY trial, the addition of preoperative DOS improved PFS, with a HR of 0.38 for the intestinal type and 0.81 for the diffuse type [14]. A high therapeutic effect was observed for tumors with intestinal histology, which may be one of the reasons for the high therapeutic effect of NAC in AEG. Moreover, recent studies suggested that MSI-high gastric cancers were resistant to chemotherapy [25, 26]. The fact that there are relatively few MSI-high AEG cases may be related to the favorable effect of chemotherapy. Since the R0 resection rate is critically important for the prognosis of AEG, the response of NAC could be an essential biomarker for prognosis. Thus, neoadjuvant DOS combination chemotherapy is expected to have a survival benefit for resectable advanced AEG.

As for the dose of the triplet chemotherapy regimen in this study, S-1 was used at 373 mg/m^2/week, oxaliplatin at 33 mg/m^2/week, and docetaxel at 13 mg/m^2/week. Although a docetaxel dose of 16 mg/m^2/week as used

in the PROGIDY trial may be acceptable, we followed the results of a previous Japanese phase 1 trial of S-1 plus docetaxel for advancer gastric cancer showing the recommended dose of docetaxel was not 16 mg/m^2/week but 13 mg/m^2/week [15]. In the FLOT4 trial, 5-FU was used at 186 mg/m^2/week, oxaliplatin at 42.5 mg/m^2/week, and docetaxel at 25 mg/m^2/week. The dose of docetaxel was lower with the DOS regimen than with the FLOT regimen, which may be due to the fact that Asian patients have a low tolerability for docetaxel [27]. This ethnic difference is why docetaxel has been used at 13 mg/m^2/week in Japan instead of at 25 mg/m^2/week like the FLOT4 trial [11, 28]. On the other hand, the activity of fluorouracil may be higher in the DOS regimen compared to the FLOT regimen, which may have been why the response was maintained even when the dose of docetaxel was reduced. One of the most common side effects observed with DOS combination therapy was myelosuppression. In this study, grade 3 or higher neutropenia occurred in 72% of patients, and febrile neutropenia in 17%, which was safely treated with G-CSF and antibiotics. In the previous studies, neutropenia was observed in 51% of patients with FLOT, 8–10% with SOX, and 11% with DOS, and febrile neutropenia was observed in 2% of patients with FLOT and 9.2% with DOS [13, 14, 21]. The incidence of toxicity in this study was higher than that in the PRODIGY trial, likely because we performed weekly monitoring to capture the nadir absolute neutrophil count. Despite the high incidence of myelosuppression toxicity, high R0 resection rate (97%) and no treatment-related death indicated the safety of this combination chemotherapy in the neoadjuvant setting. To maintain a high response rate with a sufficiently high chemotherapy dose, it is mandatory to strictly manage side effects.

The study had several limitations. First, it was a retrospective cohort study with small sample size performed at a single institution; thus, no final conclusions can be made. Given the high efficacy and acceptable toxicity of the DOS chemotherapy regimen, the superiority of the DOS chemotherapy regimen compared to other NAC regiments should be validated in a large-scale prospective trial. Second, this study did not prescribe adjuvant treatment after R0 resection. Adjuvant chemotherapy was administered to 69% of R0 patients, including single-agent S-1 to 57% of patients and fluorouracil-based combined chemotherapy to 11%. In the PRODIGY trial, 77% (204/266) of patients allocated to the neoadjuvant DOS group received adjuvant S-1 monotherapy, while in the FLOT4 trial, 60% (213/356) of patients allocated to the FLOT group started postoperative FLOT. These data indicate that neoadjuvant DOS for AEG patients did not interfere with the initiation of adjuvant chemotherapy.

Conclusions

In conclusion, neoadjuvant DOS chemotherapy is expected to result in a high pCR rate and an acceptable safety profile. Since this was a small-scale, retrospective study, future prospective studies are needed to clarify the efficacy of neoadjuvant DOS therapy in patients with resectable advanced AEG.

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Declarations

Conflict of interest Yukinori Kurokawa and Yuichiro Doki have received research funding and lecture fees from Taiho Pharmaceutical and Yakult Honsha outside of the submitted work.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed consent Written informed consent was obtained from all patients before treatment. Consent to participate in this retrospective study was not considered necessary.

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