Neoadjuvant Chemotherapy with Docetaxel, Cisplatin and S-1 for Resectable Advanced Esophageal Cancer

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Abstract. *Background/Aim:* Although the efficacy is limited, standard therapy for Stage II/III esophageal cancer in Japan includes neoadjuvant chemotherapy with cisplatin plus 5-fluorouracil. A phase II trial was conducted on patients with resectable advanced esophageal cancer obtaining neoadjuvant chemotherapy with docetaxel, cisplatin plus S-1 (DCS). *Patients and Methods:* A total of 40 patients were enrolled, each treated by the following DCS regimen: docetaxel 40 mg/m², cisplatin 60 mg/m² on day 1, and S-1 80 mg/m² on days 1-14, repeated every four weeks, for a maximum of three cycles. *Results:* Clinical response rate was 76% and the pathological response rate (Grade 2/3) was 33%. Hematological toxicities of Grade 3/4 were leukopenia 50%, neutropenia 68%, and febrile neutropenia 18%. *Conclusion:* Neoadjuvant chemotherapy with DCS is a feasible therapeutic strategy for patients with advanced thoracic esophageal squamous cell carcinoma.

Prognosis of esophageal squamous cell carcinoma (ESCC) is poor compared to that of other types of gastrointestinal cancers (1-3). Multidisciplinary management, including chemoradiotherapy (CRT) or chemotherapy with surgery, is therefore required. In western countries, neoadjuvant CRT has been the standard treatment for locally advanced esophageal cancer (4). Meanwhile, in eastern Asia, neoadjuvant chemotherapy (NAC) has been preferred compared to neoadjuvant CRT because local control was considered to be achieved by radical esophagectomy and microscopic metastasis was controlled by systemic chemotherapy.

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According to the Japan Clinical Oncology Group (JCOG) 9907 study, the standard therapy in Japan for Stage II/III advanced esophageal cancer is NAC with cisplatin (CDDP) plus 5-fluorouracil (5-FU) (CF) (5). However, the reported clinical response rate is 38% and the pathological response rate is 22%, and efficacy was not observed in cStage III and cT3. More effective regimens are therefore urgently desired and some triplet regimens have been recently developed (6, 7). Docetaxel plus CF (DCF) regimen is one potential candidate for ESCC (8-10). We also conducted a Phase II trial of NAC with modified DCF in order to provide good efficacy (11). The modified DCF regimen showed good efficacy, as the clinical response rate was 43% and pathological response rate was 40%. However, the modified DCF regimen was associated with incidence of high-grade toxicity. Incidences of grade 3/4 neutropenia and febrile neutropenia (FN) were 56% and 20%, respectively. Although it was a retrospective study, modified DCF regimen did not show a survival benefit compared to the CF regimen. In addition, a long hospital stay was necessary for pre-operative chemotherapy. In order to develop a new regimen with a high response rate and overcome some of these problems, we undertook a phase II trial of NAC with Docetaxel/CDDP/S-1 (DCS) for resectable advanced esophageal cancer.

DCS regimen has never been used for esophageal cancer, so this is the first report of the regimen being used in this way. Among several DCS regimen, the one used in phase II trials for gastric cancer was adopted in this study (JCOG1002) (12).

Patients and Methods

Patients. Study participants were patients diagnosed with esophageal cancer at the Wakayama Medical University Hospital (WMUH) in Wakayama, Japan, between October 2014 and October 2016. Eligible patients met the following criteria: 1) pathologically confirmed squamous cell carcinoma of thoracic esophagus, 2) planned curative resection with two-field or three-field lymph node dissection, 3) clinical stage IB, II, III or IV (M1 lymph node metastasis confined to the supraclavicular lymph nodes), 4) aged

between 20 and 75 years with an Eastern Cooperative Oncology Group performance status of 0-1, 5) no serious major organ dysfunction, as indicated by a leukocyte count of 4,000-12,000 mm³, neutrophil count of $\geq 2,000$ mm³, hemoglobin of ≥ 8.0 g/dl, platelet count of $\geq 100,000$ mm³, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of > 100 IU/l, total bilirubin of ≤ 1.5 mg/dl, creatinine of ≤ 1.2 mg/dl and creatinine clearance > 60 ml/min, 6) no prior chemotherapy and radiotherapy. This study was conducted according to a protocol reviewed and approved by the Ethical Committee on Human Research at WMUH. All participants gave written informed consent before entry into the study. The study protocol was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000017153).

Preoperative chemotherapy. DCS chemotherapy comprised an infusion of docetaxel 40 mg/m² and CDDP 60 mg/m² on day 1, and S-1 80 mg/m² taken orally on days 1-14, followed by two weeks of rest (12) (Figure 1). DCS regimen was repeated every four weeks up to a maximum of three cycles or until toxicity became unacceptable, the patient refused treatment, or disease progression was observed. The subsequent chemotherapy cycle was delayed until patient recovery, which included the following parameters: neutrophil count of $\geq 1,500$ /mm³, hemoglobin concentration of ≥ 8.0 g/dl, platelet count of $\geq 75,000$ /mm³, AST and ALT < 100 IU/l, total bilirubin of < 2.0 mg/dl, and creatinine of < 1.5 mg/dl. Non-hematological adverse events were required to be grade 0 or grade 1. Granulocyte colony-stimulating factor (G-CSF) was given once a day when the neutrophil count was below 500/ μ l or FN (fever $\geq 38^{\circ}\text{C}$ and neutrophil count $< 1,000$ / μ l) was observed. The protocol did not allow the use of prophylactic G-CSF and antimicrobial therapy during chemotherapy. For FN, grade 4 neutropenia or grade 3 or 4 thrombocytopenia, total bilirubin of > 3.0 mg/dl, creatinine > 1.5 mg/dl or grade 3 non-hematological adverse event, the DCS chemotherapy dose was reduced in docetaxel (35 mg/m²), CDDP (50 mg/m²) and S-1 (65 mg/m²) in the subsequent cycle after recovery.

Response and toxicity. Pathological response was evaluated and graded according to the histological criteria of the Japanese classification of esophageal cancer, tenth edition: Grade 0, no recognizable cytological or histological therapeutic effect; Grade 1a, viable cancer cells accounting for 2/3 or more tumor tissue; Grade 1b, viable cancer cells accounting for 1/3 or more, but less than 2/3, of tumor tissue; Grade 2, viable cancer cells account for less than 1/3 of tumor tissue, while other cancer cells are severely degenerated or necrotic; Grade 3, no viable cancer cells are evident (13). Postoperative complications were redefined as higher than grade II according to the Clavien-Dindo classification (14). Mortality was defined as any death within 30 days after surgery.

Surgery and follow-up. Patients underwent esophagectomy and mediastinal dissection with extensive lymph node dissection (15). At our institution, patients were treated with thoracoscopy-assisted esophagectomy in the left-lateral decubitus position or thoracoscopically in the prone position. Patients were then repositioned to a supine position and abdominal lymph node dissection and gastric conduit reconstruction using either open laparotomy or hand-assisted laparoscopic surgery were performed. A 4-cm wide gastric conduit was created using linear stapler. Using retrosternal or posterior mediastinal routes, the gastric conduit was pulled up to the neck after the thoracic and abdominal procedures. On

the left cervical side, esophagogastric anastomosis was performed. All surgeries were supervised by two senior esophageal surgeons.

Adjuvant therapy was not performed. Patients' general conditions were checked and blood tests were performed every three months. They underwent CT scan and upper gastrointestinal endoscopy every six months.

Study design and statistical analysis. The primary endpoint of this trial was histopathological tumor response. In this study, the pathological response was defined as $> \text{grade 2}$. Secondary endpoints were the curative resection rate (TMN R0 resection) (16), clinical response rate (complete response or partial response), postoperative complications, and two-year survival rate.

The pathological response of previous CF therapy was between 11-22% (5, 11), and that of previous DCF therapy was between 26-63% (8-11). The efficacy of DCS therapy was assumed to be equivalent to DCF therapy. The planned sample size of this phase II study was 40 patients, which is the number of patients necessary to confirm the null hypothesis that the 95% confidence interval of the pathological response rate (40%) would be less than 19% under conditions of an α error of 0.05 and a β error of 0.2. All statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, NY, USA) statistical software program. Data were expressed as the mean $\pm$ standard deviation or the median and ranges. Recurrence-free survival and overall survival were calculated from the date of registration. Survival curves were computed by means of the Kaplan-Meier method. $p < 0.05$ was considered statistically significant.

Results

Patient characteristics. During the trial period, 58 patients were scheduled to undergo NAC for thoracic esophageal cancer, 18 patients were excluded from the study because they did not meet the inclusion criteria ($n=9$) or refused to participate ($n=9$). All 40 remaining patients were registered in this study (Figure 2). Of these, most underwent surgery, but one patient who eventually refused operation ultimately underwent CRT. Table I shows patient demographics and tumor characteristics. All patients had locally advanced ESCC of thoracic esophagus. The rates of cT3 and cStageIII/IV were 85% and 88%, respectively. Of 40 enrolled patients, 36 patients (90%) received three cycles (Figure 2). Dose reductions were required once for 23 patients (57%) and twice for one patient (3%) during NAC.

Clinical response and down-staging. Of 30 patients who had evaluable lesions, one patient had complete response, 22 patients had partial response, five patients had stable disease, and two patients had progressive disease (Table II). Clinical response rate was 76%. To assess down-staging, we compared the clinical stage before chemotherapy with pathological stage after chemotherapy. The rate of down-staging was 32%.

Pathological response. There was complete response (grade 3) in four patients, grade 2 in nine patients, grade 1b in eight patients, grade 1a in 15 patients, and grade 0 in three

Figure 1. NAC-DCS regimen. The DCS regimen was repeated every four weeks up to a maximum of three cycles or until toxicity became unacceptable, if the patient refused treatment, or if disease progression was observed. NAC: Neoadjuvant chemotherapy; DCS: docetaxel, cisplatin and S-1; i.v.: intravenous infusion; Doc: docetaxel; Cisplatin: CDDP.

patients. The pathological response rate (primary endpoint) was 33% (80% confidence interval 23.4-42.7%, 95% confidence interval 18.2-47.8%) (Table II). The null hypothesis was rejected (one-sided $p=0.021$)

Surgical details and postoperative complications. R0 resection was achieved in 33 patients (85%) (Table II). There were no reoperations. No mortality occurred during this trial.

Adverse events. Overall adverse events observed during chemotherapy are shown in Table III.

Grade 3/4 hematological toxicities included leukopenia (50%), neutropenia (68%), FN (18%), thrombocytopenia (5%), anemia (13%), hyponatremia (23%), and hypokalemia (5%). Grade 3 or grade 4 non-hematological adverse events included anorexia (23%) and diarrhea (15%). All toxicities were manageable. Median time of onset with Grade 3/4 neutropenia was day 11 (range=day 8-15) from the start of each cycle. Median time of recovery after administration of G-CSF was one day (range=1-4 days). There were no chemotherapy-related deaths.

Survival. The one-year and two-year recurrence-free survival (RFS) rates were 74% and 56%, respectively (Figure 3a). One-year and two-year overall survival (OS) rates were 90% and 71%, respectively (Figure 3b). At the time of analysis, the median follow-up period was 28 months.

Discussion

This phase II study was designed to evaluate the safety and efficacy of NAC-DCS for advanced esophageal cancer. It is

Table I. Patient characteristics (n=40).

	Values
Age (years), median (range)	68 (45-75)
Gender (male/female)	35/5
Location	
Ut	3 (8%)
Mt	27 (68%)
Lt	10 (25%)
Tumor depth*	
cT1	0
cT2	6 (15%)
cT3	34 (85%)
cT4	0
Lymph node metastases*	
cN0	4 (10%)
cN1	21 (53%)
cN2	15 (38%)
cN3	0
M category*:	
cM0	33 (83%)
cM1	7 (18%)
cStage*	
IA	0
IB	0
IIA	2 (5%)
IIB	3 (8%)
IIIA	15 (38%)
IIIB	13 (33%)
IIIC	0
IV**	7 (18%)

*Tumor-Node-Metastasis (TMN) Classification of the International Union Against Cancer (UICC), 7th edition. **All patients were diagnosed as stage IV because of M1 (non-regional lymph node; only supraclavicular lymph nodes). Ut: Upper third thorax; Mt: middle third thorax; Lt: lower third thorax.

Figure 2. Treatment summary. CRT: Chemoradiotherapy.

Figure 3. Kaplan-Meier estimates of recurrence-free survival (a) and overall survival (b). Two-year recurrence-free survival was 51.9%. Two-year overall survival was 68.2%.

the first to report the results of DCS regimen for ESCC. NAC with DCS provided high clinical and pathological responses among patients with ESCC.

The results of V-325 or FLOT-4 trial indicated the docetaxel-containing triplet regimen had stronger anti-tumor efficacy in gastric and esophagogastric junction cancer (6, 7). DCF regimen

has been expected as one alternative regimen to CF regimen. Some retrospective studies and phase II trials of neoadjuvant DCF regimen for ESCC have reported promising efficacy (8-11). In the NAC-DCS regimen, the clinical response and pathological response rates were 76% and 33%, respectively. It is highly active and similarly to a previous phase II study of

Table II. Clinical and histopathological tumor response, pathological stage, and operative results.

	Values
Clinical response, n (%)*	(n=30)
CR	1 (3%)
PR	22 (73%)
SD	5 (17%)
PD	2 (7%)
CR + PR	23 (76%)
Pathological stage	(n=39)
pT	
0	5 (13%)
1	6 (15%)
2	20 (51%)
3	8 (20%)
4a	0
pN	
0	11 (28%)
1	15 (38%)
2	10 (26%)
3	3 (8%)
pM	
0	33 (85%)
1	6 (15%)
pStage	
0	3 (8%)
IA	4 (10%)
IB	1 (3%)
IIA	1 (3%)
IIB	3 (8%)
IIIA	13 (33%)
IIIB	5 (13%)
IIIC	3 (8%)
IV	6 (15%)
Residual tumor	
R0	33 (85%)
R1/2	6 (15%)
Pathological response, n (%)	(n=39)
Grade 0	3 (8%)
Grade 1a	15 (39%)
Grade 1b	8 (21%)
Grade 2	9 (23%)
Grade 3	4 (10%)
Grade 2 + grade 3	13 (33%)
Operative details	(n = 39)
Right thoracotomy/thoracoscope	0/39
Lymph node dissection, 3-/2- field	28/11
Reconstruction organ (stomach/ileocolic)	34/5
Operation time (min)	477 (330-689)
Blood loss (ml)	90 (25-1000)
Postoperative complications, n (%)**	(n=39)
Anastomotic leakage	5 (13%)
Pneumonia	1 (3%)
Vocal cord paralysis	3 (8%)

*Response Evaluation Criteria in Solid Tumors version 1.0. **Clavien-Dindo classification of >grade 2. CR: Complete response; PR: partial response; SD: stable diseases; PD: progressive diseases.

Table III. Toxic effect of DCS therapy according to National Cancer Institute Common Toxicity Criteria; Version 4.0.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4 (%)
Hematological					
Leukopenia	4	8	18	2	50
Neutropenia	2	7	16	11	68
Febrile neutropenia	0	0	7	0	18
Thrombocytopenia	17	5	2	0	5
Hemoglobin	17	16	5	0	13
AST	5	0	2	0	5
ALT	6	1	0	0	0
Creatinine	2	0	0	0	0
Hyponatremia	20	-	9	0	23
Hypokalemia	19	0	2	0	5
Non-hematological					
Anorexia	19	7	9	0	23
Diarrhea	6	8	6	0	15
Alopecia	20	15	-	-	0

DCS: Docetaxel, cisplatin and S-1; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

NAC-DCF regimens (8-11). No phase III randomized controlled trials have investigated NAC with DCF, so its survival benefit has not been confirmed. In a recent randomized phase II trial of NAC with DCF *versus* adriamycin with CF (ACF), two-year RFS and OS rates for DCF *vs.* ACF were 64% *versus* 43% and 79% *versus* 66% (17). NAC with DCF is a promising regimen for resectable advanced ESCC. In our NAC-DCS regimen, two-year RFS and OS rates were 56% and 71%, respectively. Despite the fact that more advanced cases in our study (Stage III/IV: 88%) were included compared with the JCOG9907 study (Stage III/IV: 50%), these survival rates were similar to the JCOG9907 study (two-year PFS and OS rates were 57% and 73%) (5). On the other hand, the use of triplet regimen containing S-1 in NAC setting for ESCC has been reported only once (18). It used docetaxel (35 mg/m²), nedaplatin (40 mg/m²) and S-1 (twice-daily dose of 80 mg/m²/day, two-weeks on, two-weeks off). NAC was performed for two cycles. Clinical response and pathological response rates were 83% and 44%, respectively. Triplet regimen containing S-1, such as in our study, may retain anti-tumor effect, even if the dose of docetaxel is reduced.

The most frequent toxicity of DCS was myelosuppression. In this study, the rates of Grade 3/4 neutropenia and FN were 68% and 18%. However, the rate of grade 3/4 neutropenia was lower than the rates of previously reported DCF therapies and FN was similar (8-11). In a recent randomized phase II study, the incidence of Grade 3/4 neutropenia and FN by NAC with DCF was reportedly very high (90%) (19). The DCS regimen in this study used the same regimen as in the JCOG1002 study for gastric cancer, but toxicity in this study was higher than in the JCOG 1002 study (Grade 3/4

neutropenia and FN is 40% and 6%) (12). The reason is unclear, but it may be related to differences in the general condition of patients and the variety of cancer. In our NAC-DCS, myelosuppression also occurred at high frequency as well as in the case of DCF regimen, but improved rapidly (median one day) after administration of G-CSF and did not necessarily delay surgery. Thus, careful monitoring for myelosuppression could ensure safe completion of the DCS regimen. In addition, DCS did not increase postoperative complications compared to previous CF regimen (5, 11).

The limitation of this study was its small sample size and that it was a single-arm phase II trial. The JCOG recently launched a three-arm randomized controlled trial to confirm the superiority of DCF and CRT with CF as preoperative therapy for locally advanced ESCC (20), however there are no phase III trials of the triplet regimen containing S-1 for ESCC.

In conclusion, NAC-DCS regimen was feasible and gave good response for advanced thoracic ESCC and might improve prognosis. Further studies should investigate the survival benefit of the use of a triplet regimen including S-1 by a randomized controlled trial.

Conflicts of Interest

The Authors declare no conflict of interest. No funding was sought for the study.

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This trial was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN000017153).

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