Phase II Study of Docetaxel, Cisplatin and 5-Fluorouracil (DCF) for Metastatic Esophageal Cancer (OGSG 0403)

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Abstract. *Background: The aims of this multiple-institution phase II study were to evaluate the efficacy and tolerability of docetaxel, cisplatin and 5-fluorouracil (DCF) for the therapy of patients with metastatic squamous cell carcinoma of the esophagus (SCCE). Patients and Methods: Eligible patients included those with previously untreated SCCE, score of ECOG 0-2 and adequate organ function. Patients received 60 mg/m^2 docetaxel and 70 mg/m^2 cisplatin on day 1, and 600 mg/m^2 5-fluorouracil on days 1-5 every four weeks. Results: Twenty-nine (22 male, 7 female) patients with metastatic SCCE (M1a: 20, M1b: 9) were enrolled. Three cases achieved complete response and seven a partial response. In addition to these patients, three patients achieved good response and underwent surgical resection, giving an overall response rate of 34.5% (95% Confidene Interval=17.9-54.3) in confirmed cases and 44.8% (95% CI=26.4-64.3) in unconfirmed cases. Grade 3 or 4 hematological toxicities were as follows: leukopenia in 15 patients (52%), neutropenia in 22 patients (76%) and febrile neutropenia in 6 patients (21%), while grade 3 or 4 non-hematological toxicities were relatively rare. Conclusion: This DCF regimen was well tolerated; the results of this study provide information on the potential of DCF for treatment of patients with metastatic SCCE.*

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Key Words: Metastatic esophageal cancer, docetaxel, cisplatin, fluorouracil, combination chemotherapy.

Squamous cell carcinoma of the esophagus (SCCE) is a disease with one of the highest mortality rates and is often diagnosed at a late stage with metastatic spread. For patients with locally advanced esophageal cancer, surgery with or without chemotherapy, or combined modality treatment with chemoradiotherapy with or without surgery, is considered to be a standard treatment. On the other hand, for patients with metastatic esophageal cancer, chemotherapy is generally indicated except for cases where radiation therapy is applied for local disease control. However, the optimal chemotherapeutic regimen for metastatic esophageal cancer remains to be established. In the 1990s, in both Japan and the Western countries, combination therapy with 5-fluorouracil (5-FU) and cisplatin was regarded as the standard chemotherapy for advanced esophageal cancer. In Western countries, the overall response rate (ORR) to 5-FU and cisplatin (FP) regimen is reported to be 27% to 42% (1-4). In a randomized phase II study of FP *versus* cisplatin alone, ORR and median survival times (MST) in an FP group and a group treated with cisplatin alone were 35% and 19%, and 33 weeks and 28 weeks, respectively; however, FP treatment induced severe side-effects and cannot be recommended for patients with advanced SCCE (3).

On the other hand, in a phase II study for patients with advanced or recurrent esophageal cancer conducted in Japan, FP treatment produced a response rate of 35.9% and a median survival time of 9.2 months for responders and 5.3 months for non-responders (5). In addition, FP with daily continuous infusion of cisplatin for patients with advanced SCCE led to an ORR of 33.3% and an MST of 201.5 days, as well as a one-year survival rate of 27.8%. However, this treatment was not associated with higher response or lower

toxicity than those seen with high-dose bolus or multibolus treatment regimens (6).

To improve the prognosis of patients with advanced esophageal cancer, a more intensive and feasible regimen of chemotherapy is required.

For advanced head and neck cancer or gastric cancer, chemotherapy using FP combined with docetaxel was reported to achieve better outcomes than FP treatment (7-9). In a randomized phase III trial for advanced gastric cancer that compared therapy of docetaxel, cisplatin and 5-FU (DCF) every three weeks with FP every four weeks, the median time to tumor progression (TTP) and the median overall survival (OS) were reported to be significantly higher with DCF every three weeks (10).

However, there have been few reports of DCF chemotherapy specifically confined to advanced SCCE (11).

Therefore, the aims of this phase II study were to evaluate the efficacy and tolerability of DCF in the treatment of metastatic esophageal cancer.

Patients and Methods

Eligibility criteria. This study was conducted according to a protocol reviewed and approved by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG), and reviewed and approved by the Institutional Review Board (IRB) of each participating institution. Written informed consent was obtained from each patient before entry in the study.

The eligibility criteria of this study were as follows: i) histologically proven SCCE; ii) stage IVa disease with N4 lymph node metastasis (distant lymph node metastasis) or IVb according to the Japanese Classification of Esophageal Cancer (12) (stage IV of the TNM classification (13)); iii) metastatic disease that was uni-dimensionally measureable according to the Response Evaluation Criteria in Solid Tumors (RECIST (14)); iv) age of 20-75 years; v) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2; vi) no previous treatment for cancer including surgery, chemotherapy and radiotherapy; vii) life expectancy of more than three months; and viii) adequate organ function including a leukocyte count of between 4,000 mm^3 and 12,000 mm^3, a neutrophil count of over 2,000 mm^3, a platelet count of over 100,000 mm^3, hemoglobin of over 9.0 g/dl, aspartate aminotranferase (AST) and alanine aminotransferase (ALT) levels within 2.5 times the upper limits of their normal ranges, a serum bilirubin level under 1.5 mg/dl, and a serum creatinine level of under 1.2 mg/dl or creatinine clearance of at least 60 ml/min/body.

Exclusion criteria were as follows: i) congestive heart failure; ii) interstitial pneumonia or lung fibrosis; iii) liver cirrhosis or active hepatitis; iv) symptomatic brain metastasis; v) infection or suspected infection with fever; vi) synchronous malignancy; and vii) pregnancy. Patients with a prior history of surgery, chemotherapy and radiotherapy were also excluded.

Study design. The administration schedule began with 5-FU at 600 mg/m^2, which was continuously infused from day 1 to 5. Docetaxel at 60 mg/m^2 was intravenously infused for 60 to 120 minutes on day 1 and cisplatin at 70 mg/m^2 was infused for 120 minutes, immediately after docetaxel.

Premedication of dexamethasone was administered before docetaxel administration, and cisplatin hydration was given according to each investigator's routine practice. Dose-modification criteria were defined in this protocol. Treatment continued in the absence of disease progression, or request by the patient or doctor to discontinue therapy, unacceptable toxicity, or serious systemic allergic reaction to any of the study drugs. This regimen comprised one course and was repeated every four weeks. Dose-limiting criteria for docetaxel were defined as follows: either grade 4 leukopenia or neutropenia continuing for more than five days; grade 3 or greater neutropenia with pyrexia over 38˚C; grade 3 or greater thrombocytopenia; and non-hematological toxicity of grade 3 or greater except for nausea, vomiting, fatigue, and anorexia. Dose-limiting criterion for cisplatin was defined as ≥grade 2 toxicity of creatinine. When dose-limiting toxicity (DLT) for docetaxel developed, its dose was reduced to 40 mg/m^2. When DLT for cisplatin developed, its dose was reduced to 50 mg/m^2. The primary endpoint was ORR and the secondary endpoints were tolerability, OS and progression-free survival (PFS).

We judged the anticancer effects in accordance with RECIST, whereas for safety assessment, we followed the NCI-Common Toxicity Criteria v2.0 (15).

Follow-up. Patients underwent hematological tests and assessments of clinical symptoms at least once every course of chemotherapy. The presence of relapse was determined by imaging studies, including ultrasonography, computed tomography (CT) and gastrointestinal endoscopy. Patients underwent thoracic and abdominal CT at three or four weeks after the start of chemotherapy, and CT was again performed more than four weeks later in order to evaluate the efficacy of the treatment, when complete response (CR) or partial response (PR) was achieved.

Statistical analysis. The calculation of the sample size for the study was based on an expected response rate of 55% and a threshold response rate of 35%, using a two-sided alpha error of 0.05 and a beta error of 0.20. The planned sample size was 45 patients, allowing for a 10% drop-out rate. An interim analysis was planned after the first 20 patients were enrolled. If there were some problems in feasibility, the trial was to be stopped. All enrolled patients were included in the intention-to-treat analysis of efficacy. OS was measured from the start of treatment until the time of death; OS was estimated using the Kaplan-Maier method and the 95% confidence interval (95% CI) for median survival was estimated by the Brookmeyer-Crowley method. Statistical analysis was carried out using R software version 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

This protocol was registered at the UMIN Clinical Trials Registry (UMIN000000821) on 7 September 2007.

Results

Patients' characteristics. This trial was stopped before the planned number of patients had been enrolled because the registration of cases lagged far behind the plan. Twenty-nine patients from five institutions were enrolled in this study between July 2004 and February 2009. These included 22 males and seven females, with a median age of 61 (range, 38-73) years. All patients had metastatic disease; 23 had

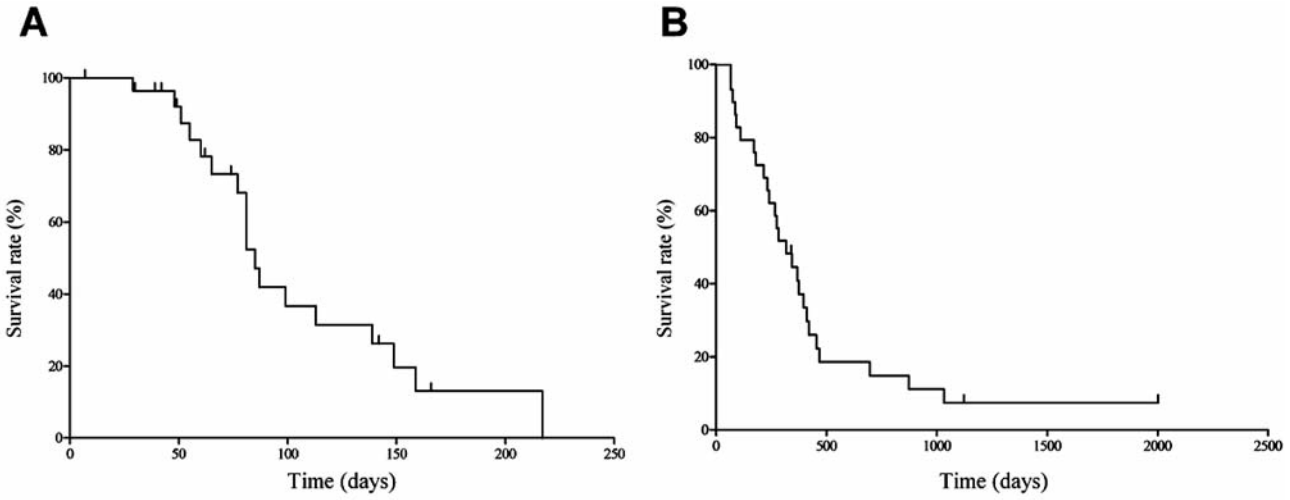

Figure 1. *Progression-free (PFS) and overall survival (OS). A: PFS was analyzed by the Kaplan-Meier method. The median PFS was 85 days (95% Confidene Interval=81-159 days). B: OS by the Kaplan-Meier method. The median survival time was 318 days (95% CI=240-421 days) and the one-year survival rate was 44.6% (95% CI=29.6-67.0%).*

metastasis to a distant lymph node, which was the most common site of the metastases, five had lung metastasis, one had liver metastasis and two had metastasis to other distant organs. Overall, 20 patients had M1a disease and nine patients had M1b disease. The demographic and clinicopathological characteristics of these patients are listed in Table I.

Efficacy. Three cases of CR and seven cases of PR were confirmed, while three cases achieved a good response, which allowed surgical resection before confirmation of PR, giving an ORR of 34.5% (95% CI=17.9-54.3%) in confirmed cases and 44.8% (95% CI=26.4-64.3%) including unconfirmed cases.

Because all response cases were cases with distant lymph node metastasis, the response rate for lymph nodes in confirmed cases was 53% (10/19 cases). On the other hand, there were no responders among patients with hematogenous metastases, such as lung and liver metastases.

The median PFS for all patients was 85 (95% CI=81-159) days. The median survival was 318 (95% CI=240-421) days and the one-year survival rate was 44.6% (95% CI: 29.6-67.0%) (Figure 1).

Toxicity. Toxicity data are summarized in Table II. Grade 3 or 4 leukopenia occurred in 15 patients (52%), grade 3 or 4 neutropenia occurred in 22 patients (76%), including 6 patients (21%) with febrile neutropenia, and no cases of grade 3 or 4 thrombocytopenia occurred. Non-hematological toxicities of grade 3 or more involved anorexia in 17% of cases, diarrhea in 7%, and nausea, fatigue and alopecia in 3% each. Grade 4 non-hematological toxicities of anorexia, fatigue and nausea occurred in one case each.

Table I. *Patients' baseline characteristics*[1].

Characteristic	No. of patients
Gender	
Male	22
Female	7
Age (years)	
Median	61
Range	38-73
Performance status (ECOG2))	
0	25
1	4
2	0
Primary tumor site	
Upper thoracic	6
Middle thoracic	12
Lower thoracic	8
Two sites	2
Three sites	1
Primary tumor (T)	
T1	0
T2	5
T3	18
T4	6
Nodal stage (N)	
N0	1
N1	28
Distant metastasis (M)	
M1a	20
M1b	9
Site of metastasis (overlapping)	
Lung	5
Lymph nodes	23
Liver	1
Other	2

[1]According as the Japanese Classification of Esophageal Cancer (ref.12). ECOG: Eastern Cooperative Oncology Group.

Table II. *Toxic effects of DCF therapy according to National Cancer Institute Common Toxicity Criteria; Version 2.0.*

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	G3-4 (%)
Hematological					
Leukopenia	2	8	13	2	52
Neutropenia	2	1	5	17	76
Thrombocytopenia	12	2	0	0	0
Hemoglobin	12	10	1	0	3
AST	0	0	1	0	3
ALT	1	0	0	1	3
Creatinine	1	0	1	0	3
Gastrointestinal					
Stomatitis	2	1	0	0	0
Anorexia	6	4	4	1	17
Nausea	12	2	0	1	3
Vomiting	6	1	0	0	0
Diarrehea	8	2	2	0	7
Fatigue	8	4	0	1	3
Alopecia	17	4	-	-	-
Febrile Neutropenia	-	-	5	1	21

AST: Aspartate aminotransferase, ALT: alanine aminotransferase.

Four patients had dose reductions of docetaxel at the second course of chemotherapy due to febrile neutropenia. Grade 3 and 4 neutropenia at the second course of chemotherapy (25 patients) occurred in eight (32%) and five patients (20%), respectively. The results regarding reasons for leaving the protocol are shown in Table III.

No treatment-related deaths occurred within 30 days of completion of this regimen.

Discussion

This DCF regimen appears to be well tolerated, with manageable hematological toxicities and limited non-hematological toxicities, and seems more effective for metastatic esophageal cancer than the standard FP regimen (1-4), with a response rate of 44.8% including unconfirmed patients, because of surgical resection.

Recently, reported clinical studies of DCF therapy for advanced or metastatic esophageal cancer as first-line chemotherapy are summarized in Table IV (16-20). Although differences in these study subjects preclude direct comparison, the response rate lies between 34% and 83.3% which indicates considerable variability. Three of the studies that had moderate response rates under 50% included two studies on heterogeneous patient populations, with both adenocarcinoma of gastric, gastroesophageal and esophageal sites and SCCE, while the third of these was our study. On the other hand, three studies with promising response rates over 50% were phase II studies on metastatic and/or unresectable SCCE. The DCF regimen might achieve a more favorable outcome for patients with SCC than for those with adenocarcinoma of the esophagus. In fact, in some clinical trials for advanced gastric cancer and adenocarcinoma of the gastroesophageal junction, the ORR was reported to range from 37% to 43% (9, 21). In four studies that included patients with stage III and IV advanced SCCE, only our study did not include patients with stage III disease, which might have caused the lower response rate in our study to some extent.

Table III. *Reasons for leaving the protocol.*

Reason	No. of cases
Disease progression	16
Toxicity	5
Patient's refusal	4
Surgical resection+	3
Other disease	0
Other	1

+Three cases underwent surgical resection after two courses of chemotherapy before the confirmation of partial response.

The dosages were selected for our combination regimens with reference to earlier phase I studies for head and neck cancer reported at the 41st Annual Meeting of the Japan Society of Clinical Oncology in 2003, as reported by Kamei *et al* (abstract only in Japanese).

We calculated the dosages in terms of mg/m^2/week to compare the quantities of the drugs used in these studies. In these DCF regimens, docetaxel was used in the range of 15-23.3 mg/m^2/week, cisplatin was in the range of 17.5-23.3 mg/m^2/week and 5-FU in the range of 750-1400 mg/m^2/week. With respect to the dosages of the three drugs in these DCF regimens, the dosages in our study might have been low for metastatic stage IV esophageal cancer, which would explain why our DCF schedule did not reach the expected response rate of 55%.

The major toxicity of DCF was myelosuppression, such as leukopenia and neutropenia. As shown in Table IV, in patients treated with the DCF regimen, grade 3 or 4 neutropenia and febrile neutropenia were observed in the ranges of 10 to 90%, and 0% to 21%, respectively. The hematological toxicity did not seem to be related to the dose intensity of the three drugs, but may depend on the cancer stage or condition of the patients such as PS and/or nutritional condition (22, 23), because neutropenia of grade 3 or 4 occurred as the second most frequent toxicity and febrile neutropenia occurred as the most frequent toxicity in our study, in which low dose intensities of these drugs were used compared with those in other studies.

DCF is a promising and tolerable regimen for patients with advanced esophageal cancer and seems more effective

Table IV. *Clinical studies of DCF therapy for advanced or metastatic esophageal cancer as first line chemotherapy.*

Reference (first author), year	Phase	Target	No. cases (stage III/IV)	Regimen	Dose intensity (mg/m^2/ week)	Response Rate (%)	MST	Neutropenia grade 3/4 (%)	Febrile neutropenia (%)
Takahashi (16) 2010	I/II	Metastatic SCC	39 (5/34)	DOC 50 mg/m^2 Day 1 CDDP 70 mg/m^2 Day 1 5-FU 700 mg/m^2 Day 1-5 (c.i.v)/3 wks	DOC: 16.6 CDDP: 23.3 5-FU: 1166.6	66.6	390 D	43.6	12.8
Overman (17) 2010	Retro-spective	Esophagus Gastric GEJ	30 (SCC: 17) 28 37	DOC 20 mg/m^2 Day 1, 8, 15, 22, 29, 36 CDDP 20 mg/m^2 Day 1, 8, 15, 22, 29, 36 5-FU 350 mg/m^2 Day 1, 8, 15, 22, 29, 36/8 wks	DOC: 15 CDDP: 15 5-FU: 262.5	34	5.3 M	4	0
Tebbutt (18)+ 2010	II	Esophagus Gastric GEJ	11 (SCC: 2) 26 13	DOC 30 mg/m^2 Day 1, 8 CDDP 60 mg/m^2 Day 1 5-FU 200 mg/m^2 (c.i.v)/ 3wks×8 courses	DOC: 20 CDDP: 20 5-FU: 1400	47	11.2M	10	6
Osaka (19) 2011	II	Unresectable SCC	30 (5/25)	DOC 60 mg/m^2 Day 1 CDDP 60 mg/m^2 Day 1 5-FU 800 mg/m^2 Day 1-5 (c.i.v)/3-4wks×2 courses	DOC: 20-15 CDDP: 20-15 5-FU: 1333.3-1000	Primary: 83.3 LN: 72.4 Distant: 72.0	271 D	Leukopenia 33.3	-
Yamasaki (20) 2011	I/II	Advanced/ recurrent SCC	40 (18/21 +rec:1)	DOC 70 mg/m^2 Day 1 CDDP 70 mg/m^2 Day 1 5-FU 700 mg/m^2 Day 1-5 (c.i.v) /3wks ×2 courses	DOC: 23.3 CDDP: 23.3 5-FU: 1166.6	72.5 Primary:79.4 LN: 71.5 Distant: 100	- (One-year survival rate: 74.6%)	90	10
Current study	II	Metastatic SCC	29 (0/29)	DOC 60 mg/m^2 Day 1 CDDP 70 mg/m^2 Day 1 5-FU 600 mg/m^2 Day 1-5 (c.i.v)/ 4wks	DOC: 15 CDDP: 17.5 5-FU: 750	44.8 34.5 (confirmed cases)	318 D	76	21

+Only results with DCF regimen are indicated in this table, those for docetaxel and capecitabine regimen are excluded. MST: Median survival time, D: days, M: months, SCC: squamous cell carcinoma, GEJ: gastro-esophageal junction, DOC: docetaxel, CDDP: cisplatin, 5-FU: 5-fluorouracil, LN: lymph node.

for metastatic esophageal cancer than the standard FP regimen. Because this triplet regimen seems effective for metastasis to lymph nodes in particular, it might be used as a neoadjuvant chemotherapy for patients with lymph node metastases. On the other hand, our DCF regimen had little effect on hematogenous metastases. Since some toxicity of our treatment occurred, such as febrile neutropenia in 21% of cases, the dose intensity cannot easily be increased for patients with metastatic esophageal cancer. It should be taken into consideration that appropriate treatment dose and schedule and sufficient systemic support such as enteral nutrition support (23), may be required for these patients.

Further prospective study of alternative administration schedules of these active chemotherapeutic agents in advanced and metastatic esophageal cancer should be planned according to the site of metastasis.

Conflict of Interest

The Authors declare that they have no conflict of interest with regards to any part of this study.

Acknowledgements

We are indebted to the physicians and all of the clinical study teams at the participating institutions. We also thank Dr Toshio Shimokawa and Dr Yukinori Kurokawa for their scientific and statistical advice and Ms Akiko Hotta and Ms Hiroko Maruyama for their excellent secretarial assistance at the OGSG data center.

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Received Ferbuary 20, 2012
Revised March 11, 2012
Accepted March 12, 2012