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Phase I/II trial of 2-weekly docetaxel combined with cisplatin plus fluorouracil in metastatic esophageal cancer (JCOG0807)

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Key words

Chemotherapy, DCF therapy, metastatic esophageal cancer, phase I/II, 2-weekly docetaxel

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We carried out a phase I/II trial of adding 2-weekly docetaxel to cisplatin plus fluorouracil (CF) therapy (2-weekly DCF regimen) in esophageal cancer patients to investigate its safety and antimetastatic activity. Patients received 2-weekly docetaxel (30 mg/m^2 [dose level (DL)1] or 40 mg/m^2 [DL2] with a 3 + 3 design in phase I, on days 1 and 15) in combination with fixed-dose CF (80 mg/m^2 cisplatin, day 1; 800 mg/m^2 fluorouracil, days 1–5) repeated every 4 weeks. The primary endpoint was dose-limiting toxicity (DLT) in phase I and central peer review-based response rate in phase II. At least 22 responders among 50 patients were required to satisfy the primary endpoint with a threshold of 35%. Sixty-two patients were enrolled in phase I and II. In phase I, 10 patients were enrolled with DLT of 0/3 at DL1 and 2/7 in DL2. Considering DLT and treatment compliance, the recommended phase II dose was determined as DL1. In phase II, the response rate was 62% ($P < 0.0001$; 95% confidence interval, 48–75%); median overall survival and progression-free survival were 11.1 and 5.8 months, respectively. Common grade 3/4 adverse events were neutropenia (25%), anemia (36%), hyponatremia (29%), anorexia (24%), and nausea (11%). No febrile neutropenia was observed. Pneumonitis caused treatment-related death in one patient. The 2-weekly DCF regimen showed promising antimetastatic activity and tolerability. A phase III study comparing this regimen with CF therapy is planned by the Japan Clinical Oncology Group. This study was registered at the UMIN Clinical Trials Registry as UMIN 000001737.

Esophageal cancer constitutes a global health problem, with between 400 000 and 500 000 new cases diagnosed annually, and it is the fifth most common worldwide cause of cancer-related death in men and the eighth in women.[1] The incidence of esophageal adenocarcinomas predominantly affecting the lower esophagus and gastroesophageal junction has increased substantially in the last decades, especially in Europe and the USA, whereas the majority of esophageal cancers worldwide are of the squamous cell carcinoma type, the most common histological type in Japan.

Surgery, radiation therapy, and chemotherapy are the major treatments for esophageal cancer. For two decades, chemotherapy, especially the two-drug combination of cisplatin plus fluorouracil has been regarded as a standard regimen to treat patients with esophageal cancer with distant metastases or recurrence.[2] The JCOG has carried out four phase II studies including esophageal cancer patients with distant metastases or recurrence since the late 1980s.[3–6] In these studies, the RR of combination chemotherapy with platinum plus fluorouracil was approximately 35% and the median OS was 6.7–8.9 months. Because these results are unsatisfactory, a new active regimen is needed to improve the outcome for metastatic esophageal cancer patients.

In the past decades, three phase III studies showed a prolongation of OS by adding docetaxel to CF therapy (3-weekly DCF regimen with 75 mg/m^2 docetaxel) compared with CF therapy for gastric cancer in the palliative phase and head and neck cancer in the induction phase.[7–9] Although a study using

a 3-weekly DCF regimen improved clinical outcomes even in palliative chemotherapy for advanced gastric cancer, it was also associated with severe toxicity, particularly those related to myelosuppression, and showed a 29% incidence of febrile neutropenia or neutropenic infection.[7] Thus, this high incidence of treatment-related toxicity limits the applicability of the 3-weekly DCF regimen in all gastric cancer patients, particularly in elderly patients or those with a poor PS.[10]

To minimize the toxicity associated with the 3-weekly DCF regimen while maintaining antitumor activity, divided doses of docetaxel combined with CF has been investigated, and several phase II studies have been carried out recently in patients with advanced gastric cancer.[11–14] These results showed that the tolerability profile could be markedly improved when docetaxel was given weekly or 2-weekly, even in the palliative chemotherapy phase. We postulated that 2-weekly docetaxel might provide palliative benefit with good tolerability, even in metastatic esophageal cancer patients. Therefore, we carried out a phase I/II trial to determine the RP2D in phase I and to investigate the safety and efficacy of the 2-weekly DCF regimen for metastatic esophageal cancer.

Materials and Methods

Patients. Eligible patients were aged 20–75 years with histologically confirmed stage IVB[28] or recurrent esophageal squamous cell carcinoma, adenosquamous carcinoma, and adenocarcinoma. Patients with metastases limited only to cervical or para-aortic lymph nodes were excluded. Other inclusion criteria were: ECOG PS of 0–1; having at least one measurable metastatic lesion; clinical T stage between cT1 and cT3; no histologically confirmed adenocarcinomatous invasion of the esophagogastric junction; no indication for palliative or definitive chemoradiotherapy; no history of palliative chemotherapy or chemoradiotherapy; no dysphagia or insufficient oral intake; and adequate bone marrow, hepatic, and renal functions. If patients recurred after receiving neoadjuvant or adjuvant chemotherapy with CF therapy, the confirmed recurrence must have occurred ≥6 months after the last dose, with no evidence of serious toxicity, and the total dose of prior cisplatin must have been <180 mg/m^2. The final requirements were no brain metastasis and no moderate or severe coelomic fluid retention.

Patients were excluded if they had: uncontrolled diabetes mellitus; synchronous or metachronous malignancies diagnosed within the past 5 years; serious drug hypersensitivity to docetaxel, cisplatin, fluorouracil, and polysorbate 80; active infection; continuous dose of steroids; motor paralysis or peripheral neuropathy; edema; interstitial pneumonitis; or psychiatric disease.

Study design. This was a multicenter, single-arm, phase I/II trial of the 2-weekly DCF regimen in patients with advanced or recurrent esophageal cancer. This trial was carried out in accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by the JCOG Protocol Review Committee and the institutional review boards of the participating institutions. All patients provided written informed consent before study entry. The trial was registered at the UMIN Clinical Trials Registry under registration number 000001737.

Treatment and dose escalation. Docetaxel was given as a 1-h i.v. infusion on days 1 and 15 followed by cisplatin 80 mg/m^2, given as a 2-h i.v. infusion on day 1 of each cycle. Prophylactic antiemetics were given before the cisplatin dose. Concurrently, fluorouracil 800 mg/m^2 was given as a 24-h continuous i.v. infusion on days 1–5. This regimen was repeated every 4 weeks. If cisplatin had not been given before, cisplatin was given for six cycles; if ≤100 mg/m^2 cisplatin had been given before, cisplatin was given for five cycles; if 100–180 mg/m^2 cisplatin had been given before, cisplatin was given for four cycles. Even after cisplatin treatment was terminated, chemotherapy with docetaxel and fluorouracil was continued until disease progression or unacceptable toxicity developed.

In phase I, patients received increasing doses of docetaxel, that is, from 30 mg/m^2 (DL1) to 40 mg/m^2 (DL2), given on days 1 and 15 in combination with CF. At least three patients at each DL were monitored for DLT throughout the first cycle. If none experienced a DLT at DL1 during the first cycle, the next cohort of patients was treated at DL2. If none experienced a DLT at DL2, the RP2D was considered as DL2. If only one or two of three patients at each DL experienced any DLT, an additional three patients were enrolled at the same DL. After that, if only one or two of the six patients experienced DLT at DL1, the next cohort was started at DL2. If only one or two of six patients experienced DLT at DL2, RP2D was considered as DL2. However, if three or more of the six patients experienced DLT at DL2, RP2D was considered as DL1. Finally, RP2D was determined by considering not only DLT during the first cycle but also serious adverse events in the second cycle or later. No intrapatient dose escalation was permitted.

Dose-limiting toxicity. Dose-limiting toxicities were defined as follows: grade 4 neutropenia or leukocytopenia lasting for ≥5 days even if using G-CSF; grade 3/4 infection; grade 4 thrombocytopenia; any grade 3/4 non-hematologic toxicity (except for grade 3 nausea, vomiting, or anorexia, grade 3/4 electrolyte abnormalities, and grade 3 diarrhea that is improved within 3 days by antidiarrheal agent); grade 2 leukoencephalopathy or esophageal fistula; >7 days prolongation of day 15 docetaxel administration in the first cycle because of toxicity; >14 days prolongation of starting the second cycle because of toxicity; and discontinuation of fluorouracil because of toxicity.

Efficacy and safety assessment. Tumor assessment using computed tomography scans was carried out within 28 days before study entry and repeated every 4 weeks. Response Evaluation Criteria in Solid Tumors version 1.0 was used to evaluate treatment responses.[15] In patients with primary lesions, endoscopic evaluation and evaluation of tumor markers, such as serum carcinoembryonic antigen and squamous cell carcinoma antigen, were mandatory. Primary tumor response was evaluated by endoscopy according to the criteria of the 10th edition of the Japanese Society for Esophageal Diseases.[16] If endoscopic examination or tumor marker evaluation were not carried out, the response was considered "not evaluable." After confirmation of complete response or partial response, response evaluation was determined every 8 weeks.

Toxicity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.[29] Patients' symptoms and general condition were observed periodically. Physical examinations, complete blood cell counts with differential counts, and serum chemical laboratory tests were carried out at least once a week during the DLT evaluation period.

Statistical analysis. In phase I, the primary endpoint was DLT and the secondary endpoints were toxicity and RR. Subsequently, in phase II, the primary endpoint was RR by central peer review and the secondary endpoints were OS, PFS, and toxicity. Progression-free survival was defined as the time from the date of registration to the date of the first documentation

of disease progression (by imaging methods or clinical judgment) or death. Overall survival was defined as the time from the date of registration to the date of death due to any cause. Both OS and PFS were estimated by the Kaplan–Meier method. All efficacy analyses were carried out in all eligible patients and all safety analyses were carried out in all treated patients.

On the basis of a Southwest Oncology Group two-stage design,[17] to test the hypothesis that the expected value of 50% and threshold value of 35% with one-sided interim alpha of 2% for futility and final alpha of 10% with 80% power, 52 patients, including patients treated with RP2D in phase I and II, were required in this study. All the statistical analyses were carried out using SAS software version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patients. Between February 2009 and June 2011, a total of 62 patients were enrolled in this study. In phase I, no DLT was observed at DL1 (docetaxel 30 mg/m^2). At DL2 (docetaxel 40 mg/m^2), one patient among the first three patients had a DLT (grade 3 fatigue). An additional three patients were enrolled, among whom one patient refused protocol treatment in the first cycle due to an adverse event that was not regarded as DLT. According to the protocol, this patient was judged as non-evaluable for DLT, and one more patient was enrolled. Among the additional four patients, at DL2, one DLT (grade 3 alanine aminotransferase increase) was observed. In total, two DLTs were observed at DL2 during the first cycle. Moreover, one patient treated at DL1 experienced a serious adverse event, which was grade 4 depressed level of consciousness due to hyperammonemia after the first cycle, and four of 7 patients at DL2 refused to continue protocol treatment because of toxicity in the first or later cycles. On the basis of the results of phase I, the RP2D was determined to be DL1.

Fifty-two patients were then enrolled in phase II of the trial. Three patients enrolled at DL1 of phase I and the subsequent 52 patients in phase II were analyzed. Two patients were considered ineligible after treatment initiation, as one had hepatocellular carcinoma, which had been diagnosed as hepatic metastasis at the time of enrolment, and another had a basaloid carcinoma. Thus, 53 patients were analyzed for efficacy (RR, PFS, and OS) and 55 patients for safety (Fig. 1).

Patient characteristics are provided in Table 1. The majority of patients were male with an ECOG PS of 0 and histologically squamous cell carcinoma. Approximately 20% of patients had received prior adjuvant chemotherapy and around 40% of patients had lymph node metastasis with two or more metastatic sites.

Exposure to chemotherapy. The median number of treatment cycles was five (range, 1–26) among 55 patients. Reasons for discontinuation of treatment included disease progression (67.3%), adverse events (21.8%), and treatment converting to definitive chemoradiotherapy because of remarkable efficacy (1.8%), as well as identification of hepatocellular carcinoma, mentioned previously (1.8%).

Efficacy. Fifty-three patients could be evaluated for efficacy. Of those, 33 achieved a confirmed response, all of which were partial responses, and eight had stable disease (Table 2). The RR was 62% ($P < 0.0001$; 95% CI, 48–75%), which indicated that the primary endpoint was met. With a median follow-up period for censored patients of 15.6 months, median PFS and OS were 5.8 months (95% CI, 4.6–7.4 months) and 11.1 months (95% CI, 9.4–13.8 months), respectively (Fig. 2).

Safety. Fifty-five patients could be evaluated for safety analysis. Table 3 lists the adverse events and the proportion of patients experiencing adverse events during the treatment. The common grade 3/4 adverse events were anemia (36%), hyponatremia (29%), neutropenia (26%), anorexia (24%), nausea (11%), and leukopenia (9%). No patient had febrile neutropenia. Treatment-related death confirmed by the Data and Safety Monitoring Committee was observed in one patient (2%). The cause of death in this patient was pneumonitis, which occurred during subsequent chemotherapy with docetaxel alone, 91 days after the last date of protocol treatment. The association between protocol treatment and pneumonitis was considered as possible.

Subsequent therapy. Forty patients (72.7%) received subsequent therapy after protocol treatment. Chemotherapy was carried out in 30 patients (54.5%), radiotherapy in 5 patients (9.1%), chemoradiotherapy in 8 patients (14.5%), and surgery

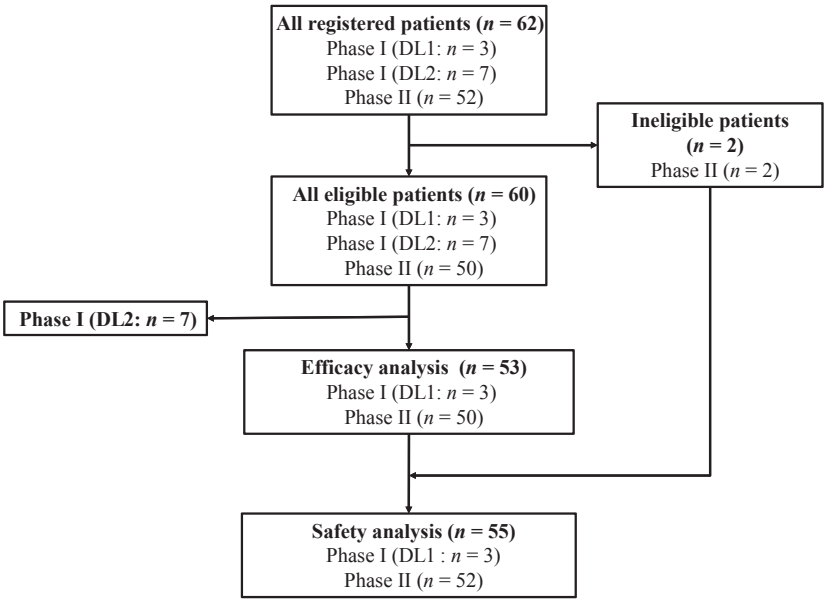

Fig. 1. Flowchart of a phase I/II trial of adding 2-weekly docetaxel to cisplatin plus fluorouracil therapy in esophageal cancer patients.

Table 1. Baseline characteristics of esophageal cancer patients (n = 55) who participated in a phase I/II trial of adding 2-weekly docetaxel to cisplatin plus fluorouracil

Characteristic	No.	%
Sex		
Male	49	89.1
Female	6	10.9
Age, years		
Median	61	
Range	44–75	
ECOG PS		
0	39	70.9
1	16	29.1
Advanced/recurrent disease		
Advanced	41	74.5
Recurrent	14	25.5
Histology		
Squamous cell carcinoma	52	94.5
Adenosquamous carcinoma	2	3.6
Basaloid carcinoma	1	1.8
Primary lesion location		
Upper	3	5.5
Middle	25	45.5
Lower	27	49.1
Prior adjuvant chemotherapy		
Absent	43	78.2
Present	12	21.8
No. of metastatic sites		
1	33	60.0
≥2	22	40.0
Site of distant metastasis		
Organ	32	58.2
Lymph node only	23	41.8

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Table 2. Overview of response rate in esophageal cancer patients (n = 53) treated with cisplatin plus fluorouracil and additional 2-weekly docetaxel, by central peer review

Response	Response rate		95% CI
	No.	%	
Total no. of patients	53	100	
ORR (CR or PR)	33	62.3	48–75
CR	0	0.0	–
PR	33	62.3	–
SD	8	15.1	–
PD	9	17.0	–
Not evaluable	3	5.7	–

–, Not applicable; CI, confidence interval; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

in 3 patients (5.5%); other therapy was carried out in 5 patients (9.1%). The breakdown of chemotherapy was listed in Table 4.

Discussion

To our knowledge, this is the first phase I/II trial of the 2-weekly DCF regimen for metastatic esophageal cancer. This study shows that the RP2D of docetaxel is 30 mg/m^2 in phase I, and this triplet therapy has promising activity with an RR of 62% and a median OS of 11.1 months in phase II. Previous studies showed that the RR of doublet therapy with platinum and fluorouracil was <40% and median OS was <9 months.[4–6] On the basis of these results, the 2-weekly DCF regimen has promising efficacy with high RR and improved OS for metastatic esophageal cancer.

Two studies of phase II trials with the 3-weekly or 4-weekly DCF regimens have been reported for metastatic esophageal cancer.[18,19] Takahashi *et al.*[18] reported that the RR was 66.6% with the 3-weekly DCF regimen, and Tamura *et al.*[19] reported that the RR was 34.5% with the 4-weekly DCF regimen for advanced or recurrent esophageal cancer. In addition, a couple of retrospective and prospective studies, investigating weekly docetaxel combined with CF for esophagogastric cancer, including a small number of esophageal cancers, have been reported. Overman *et al.*[20] described a retrospective study that showed an RR of 34%, although only 32% patients had esophageal cancer and 18% had squamous cell carcinoma. Tebbutt *et al.*[13] also reported a phase II study, which showed that the RR was 47%; in this study, however, 29% patients had esophageal cancer and only 4% had squamous cell carcinoma. Considering these results, the 2-weekly DCF regimen might be highly effective and may have comparable efficacy with other schedules of DCF regimens even for metastatic esophageal cancer.

With regard to safety, high incidence of febrile neutropenia has been a major problem with the 3-weekly and 4-weekly DCF regimens, and its incidence with these regimens was 12.8–21% in previous studies for esophageal cancer.[18,19] However, the incidence of febrile neutropenia with a weekly DCF regimen has been showed to be <6%.[13,20] In our study, no febrile neutropenia was observed without prophylactic G-CSF support. Shah *et al.*[14] reported a randomized phase II study of the modified DCF regimen *versus* the 3-weekly DCF regimen for metastatic gastroesophageal adenocarcinoma. The schedule of the modified DCF regimen included 2-weekly docetaxel 40 mg/m^2 without G-CSF support, and that of the 3-weekly DCF regimen included docetaxel 75 mg/m^2 with G-CSF support. As a result, the incidence of febrile neutropenia was lower with the modified DCF regimen (6%) than with the 3-weekly DCF regimen (17%), and the RR was higher with the modified DCF regimen (52%) than with the 3-weekly DCF regimen (34%). Therefore, the addition of docetaxel at an interval of 2 weeks to the CF regimen might decrease the incidence of febrile neutropenia while maintaining its antimetastatic efficacy, and it could be an appropriate triplet regimen for metastatic esophageal cancer.

In our study, grade 3/4 hyponatremia was observed in approximately 30% patients, although this adverse event was not mentioned in previous reports with DCF regimens for esophageal or gastric cancer.[7,12–14,18–21] Cisplatin-containing regimens have been reported to induce hyponatremia in 4–10% of cases,[22] and it was reported that hyponatremia might be associated with severe hematological toxicity in gastric cancer.[23] Although it was unclear whether adding 2-weekly docetaxel to CF induces hyponatoremia, this event would not be a neglectable adverse event. A careful observation would be required when using platinum-containing regimens such as the 2-weekly DCF regimen.

Our study was limited to Japanese esophageal cancer patients. Almost all the enrolled patients had squamous cell carcinoma of the thoracic esophagus. Patients with esophageal

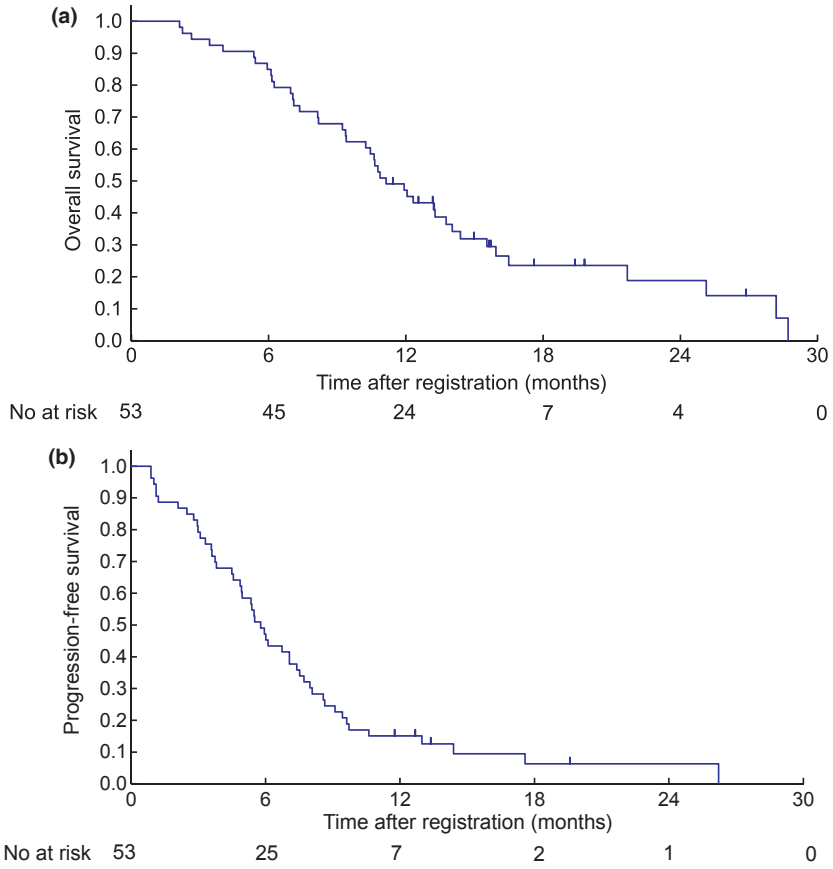

Fig. 2. Kaplan–Meier estimates of overall survival (a) and progression-free survival (b) in a phase I/II trial of esophageal cancer patients treated with 2-weekly docetaxel added to cisplatin plus fluorouracil therapy.

Table 3. Adverse events observed in esophageal cancer patients (n = 53) treated with cisplatin plus fluorouracil and additional 2-weekly docetaxel

	All grades		Grade 3/4	
	No.	%	No.	%
Leukocytopenia	46	83.6	5	9.1
Neutropenia	47	85.5	14	25.5
Hemoglobin	53	96.4	20	36.4
Thrombocytopenia	10	18.2	1	1.8
Febrile neutropenia	0	0.0	0	0.0
Nausea	44	80.0	6	10.9
Vomiting	11	20.0	0	0.0
Anorexia	53	96.4	13	23.6
Diarrhea	25	45.5	3	5.5
Constipation	25	45.5	0	0.0
Fatigue	45	81.8	3	5.5
Stomatitis	21	38.2	0	0.0
Creatinine	34	61.8	3	5.5
AST	30	54.5	2	3.6
ALT	27	49.1	2	3.6
Hyponatremia	42	76.4	16	29.1
Any infection	9	16.4	3	5.5
Pneumonitis	1	1.8	1	1.8

ALT, alanine aminotransferase; AST, aspartate transaminase.

Table 4. Agents used in chemotherapy and chemoradiotherapy subsequent to a phase I/II trial of adding 2-weekly docetaxel to cisplatin plus fluorouracil in esophageal cancer patients

Subsequent therapy (multiple choices allowed)	No.	%
Chemotherapy	30	54.5
5-FU	9	16.4
CDDP	4	7.3
CDGP	7	12.7
Docetaxel	11	20.0
Vindesine	4	7.3
Others	12	21.8
Chemoradiotherapy	8	14.5
5-FU	7	12.7
CDDP	4	7.3
CDGP	1	1.8
Docetaxel	1	1.8

CDDP, cisplatin; CDGP, nedaplatin; 5-FU, 5-fluorouracil.

cancer with adenocarcinoma invading the gastroesophageal junction were excluded, because, in Japan, these patients tend to be treated as having gastric cancer. Patients treated with the CF regimen as neoadjuvant or adjuvant therapy with a recurrence of 6 months or more after the last dose of CF were eligible, because, in Japan, the standard of care for resectable esophageal cancer is neoadjuvant CF therapy followed by surgery.[24] Although neoadjuvant chemoradiotherapy is a standard of care for resectable esophageal cancer in the USA, this therapy is only now under clinical trial in Japan,[25] and patients under this therapy did not participate in this study. In addition, >50% of the patients were treated with chemotherapy, and approximately 10% patients were treated

with chemoradiotherapy or radiotherapy after completion of the study. The high proportion of patients receiving subsequent treatment can be a reason why this study showed better efficacy than previous studies.

Recently, a triplet regimen with cetuximab, which targets the epidermal growth factor receptor, in combination with CF has also been investigated in patients with esophageal cancer. Lorenzen *et al.*[26] reported a randomized phase II study of cetuximab plus CF *versus* CF alone for metastatic esophageal squamous cell carcinoma. The confirmed RR was 19% in triplet therapy and 13% in doublet therapy; thus, the cetuximab treatment did not meet the primary objective of a $\geq$ 40% RR. Moreover, Crosby *et al.*[27] reported a phase II/III study of chemoradiotherapy with or without cetuximab. Unfortunately, this study also did not show the superiority of cetuximab plus chemoradiotherapy over chemoradiotherapy. These results indicate the difficulty of adding cetuximab to standard-dose CF therapy or chemoradiotherapy, because of increasing toxic effects, which might be caused partly by inappropriate drug doses. It was unclear whether the reasons for the negative results of these clinical trials were the increased adverse events and/or ineffectiveness of cetuximab itself. Therefore, when adding a new drug to a standard dose of chemotherapy, a dose-finding study would be needed to investigate the efficacy and tolerability in a phase II study, similar to our study.

In conclusion, adding 2-weekly docetaxel to a fixed-dose of CF therapy showed promising activity and tolerability for metastatic esophageal cancer, especially with no febrile neutropenia. Therefore, this regimen might deserve additional investigation. However, the possibility of patient selection bias and increased treatment options might result in improved efficacy and safety, because previous phase II studies with doublet therapy were carried out approximately 10 years before. To further investigate the benefits of our study, a randomized phase III trial (JCOG1314) comparing the 2-weekly DCF regimen with the CF regimen, which was considered as a standard of care for metastatic esophageal cancer, is planned in our group.

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Disclosure Statement

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Abbreviations

CF	cisplatin plus fluorouracil
CI	confidence interval
CR	complete response
DCF	docetaxel plus CF
DL	dose level
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
G-CSF	granulocyte colony-stimulating factor
JCOG	Japan Clinical Oncology Group
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PS	performance status
RP2D	recommended phase II dose
RR	response rate
SD	stable disease
UMIN	University Hospital Medical Information Network

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