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

Shuichi Hironaka,1 Yasuhiro Tsubosa,2 Junki Mizusawa,3 Takayuki Kii,4 Ken Kato,5 Takahiro Tsuchima,2 Keisoh Chin,6 Akihisa Tomori,7 Tatsuya Okuno,8 Toshikatsu Taniki,9 Takashi Ura,10 Hisayuki Matsushita,11 Takashi Kojima,12 Yuichiro Doki,13 Hitoshi Kusaba,14 Kazumasa Fujitani,15 Koichi Taira,16 Shiko Seki,17 Tsutomu Nakamura,18 Yuko Kitagawa19 and Japan Esophageal Oncology Group/Japan Clinical Oncology Group

1Clinical Trial Promotion Department, Chiba Cancer Center, Chiba; 2Division of esophageal surgery, Shizuoka Cancer Center, Shizuoka; 3JCOG Data Center, Multi-institutional Clinical Trial Support Center, National Cancer Center, Tokyo; 4Cancer Chemotherapy Center, Osaka Medical College, Osaka; 5Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo; 6Department of Gastroenterology, Cancer Institute Hospital, Tokyo; 7Department of Gastroenterology, Saku Central Hospital, Nagano; 8Division of Gastroenterology, Department of Internal Medicine, Graduate School of Medicine, Kobe University, Kobe; 9Department of gastroenterological and general surgery, Kochi Health Sciences Center, Kochi; 10Department of Clinical Oncology, Aichi Cancer Center, Nagoya; 11Department of Surgery, Tochigi Cancer Center, Utsunomiya; 12Gastrointestinal Oncology Division, National Cancer Center Hospital East, Kashiwa; 13Gastroenterological Surgery, Osaka University, Osaka; 14Department of Medicine and Biosystemic Science, Kyushu University, Fukuoka; 15Department of Surgery, Osaka National Hospital, Osaka; 16Division of Clinical Oncology, Osaka City General Hospital, Osaka; 17Department of Surgery, National Hospital Organization Tokyo Medical Center, Tokyo; 18Department of Gastroenterological Surgery, Tokyo Women’s Medical University, Tokyo; 19Department of Surgery, Keio University School of Medicine, Tokyo, Japan

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

Correspondence
Shuichi Hironaka, Clinical Trial Promotion Department, Chiba Cancer Center, 666-2 Nitona cho Chuo-ku Chiba-shi, Chiba 260-8717, Japan. Tel: +81-43-264-5431; Fax: +81-43-265-9515; E-mail: shironaka@ta2.so-net.ne.jp.

Funding Information
National Cancer Center Research and Development Fund; Ministry of Health, Labour and Welfare of Japan.

Received May 21, 2014; Revised July 10, 2014; Accepted July 14, 2014

Cancer Sci 105 (2014) 1189–1195
doi: 10.1111/cas.12486

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/m² [dose level (DL)1] or 40 mg/m² [DL]2) with a 3 + 3 design in phase I, on days 1 and 15) in combination with fixed-dose CF (80 mg/m² cisplatin, day 1; 800 mg/m² 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.1–3 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.4–6 The JCOG has carried out four phase II studies including esophageal cancer patients with distant metastases or recurrence since the late 1980s.5–6 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/m² docetaxel) compared with CF therapy for gastric cancer in the palliative phase and head and neck cancer in the induction phase.17–19 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, adenocarcinoma, 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/m². 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/m², 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/m² 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/m² cisplatin had been given before, cisplatin was given for five cycles; if 100–180 mg/m² 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/m² (DL1) to 40 mg/m² (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 the six patients experienced a 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 during 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 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 enrollment, 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%), hypotension (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   | –      |

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

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/m² in phase I, and this triplet therapy had 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. 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. 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 esophageal cancer, including a small number of esophageal cancers, have been reported. However, 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. However, the incidence of febrile neutropenia with a weekly DCF regimen has been shown to be <6%. 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/m² without G-CSF support, and that of the 3-weekly DCF regimen included docetaxel 75 mg/m² 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 antitumor 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. Cisplatin-containing regimens have been reported to induce hyponatremia in 4–10% of cases, and it was reported that hyponatremia might be associated with severe hematological toxicity in gastric cancer. Although it was unclear whether adding 2-weekly docetaxel to CF induces hyponatremia, 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 limited to Japanese esophageal cancer patients. Almost all the enrolled patients had squamous cell carcinoma of the thoracic esophagus. Patients with esophageal...
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.③4 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,③5 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

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

| Adverse Event       | 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.
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. 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 ≥ 40% RR. Moreover, Crosby et al. 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.

Acknowledgments

The authors are grateful to the members of the Japan Clinical Oncology Group’s Data Center and Operations Office for their support in preparing the manuscript (Dr. Hiroshi Katayama), data management (Ms. Hiromi Katsuki), and oversight of the study management (Dr. Haruhiko Fukuda). This study was supported by the National Cancer Center Research and Development Fund (23-A-16, 23-A-19, and 26-A-4) and Grants-in-Aid for Cancer Research (20S-3 and 20S-6) from the Ministry of Health, Labour and Welfare of Japan.

Disclosure Statement

Yuko Kitagawa has received research funding from Pfizer Co., Ltd. The other authors have no conflict of interest.

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

References

1 Jemal A, Bray F, Center MM et al. Global cancer statistics. CA Cancer J Clin 2011; 61: 69–90.
2 DeVita VT, Lawrence TS, Rosenberg SA. DeVita, Hellman, and Rosenberg’s Cancer: Principles & Practice of Oncology, 8th edn. 2008: Wolters Kluwer/Lippincott Williams & Wilkins, 2008: 1032–5.
3 Iizuka T, Kakegawa T, Ida H et al. Phase II evaluation of combined cisplatin and vindesine in advanced squamous cell carcinoma of the esophagus: Japanese Endoscopy Oncology Group Trial. Jpn J Clin Oncol 1991; 167–9.
4 Iizuka T, Kakegawa T, Ide H et al. Phase II evaluation of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus: a Japa-nese Endoscopy Oncology Group Trial. Jpn J Clin Oncol 1992; 172–6.
5 Hayashi K, Ando N, Watanabe H et al. Phase II evaluation of protracted infusion of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus: a Japan Endoscopy Oncology Group (JEOG) Trial (JCOG9407). Jpn J Clin Oncol 2001; 31: 419–23.
6 Kato K, Muro K, Ando N et al. A phase II study of nedaplatin and 5-fluorouracil in metastatic squamous cell carcinoma of the esophagus: The Japan Clinical Oncology Group (JCOG) Trial (JCOG9905-DI). Esophagus 2014; 11: 183–188.
7 Van Cutsem E, Mosseynenko VM, Tjulandin S et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006; 24: 4991–7.
8 Posner MR, Hershko DM, Stoller RG et al. Random assignment multicenter phase II study of modified docetaxel, cisplatin, fluorouracil (mDCF) with growth factor support (GCSF) in metastatic gastroesophageal adenocarcinoma (GE). J Clin Oncol 2010; 28: abstract 4014.
9 Vermerken JB, Remenar E, van Herpen C et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007; 357: 1695–704.
10 Ison DH. Docetaxel, cisplatin, and fluorouracil in gastric cancer: does the punishment fit the crime? J Clin Oncol 2007; 25: 3188–90.
11 Ajani JA, Phan A, Ho L et al. Phase I/II trial of docetaxel plus oxaliplatin and 5-fluorouracil (D-FOX) in patients with untreated, advanced gastric or gastroesophageal cancer. J Clin Oncol 2007; 25: abstract 4612.
12 Lorenzen S, Hentrich M, Haberl C et al. Split-dose docetaxel, cisplatin and leucovorin/fluorouracil as first-line therapy in advanced gastric cancer and adenocarcinoma of the gastroesophageal junction: results of a phase II trial. Ann Oncol 2007; 18: 1673–9.
13 Tebbutt NC, Cummings MM, Sourjina T et al. Randomised, non-comparative phase II study of weekly docetaxel with cisplatin and 5-fluorouracil or cetuximab in oesophagogastric cancer: the AGITG ATTAX trial. Br J Cancer 2010; 102: 475–81.
14 Shah MA, Shibata S, Stoller RG et al. Random assignment multicenter phase II study of modified docetaxel, cisplatin, fluorouracil (mDCF) with growth factor support (GCSF) in metastatic gastroesophageal adenocarcinoma (GE). J Clin Oncol 2010; 28: abstract 4014.
15 Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92: 205–16.
16 Japan Esophageal Society. Japanese Classification of Esophageal Cancer, tenth edition: part II and III. Esophagus 2009; 6: 71–94.
17 Green SJ, Dahlberg S. Planned versus attained design in phase II clinical trials. Stat Med 1992; 11: 853–62.
18 Takahashi H, Arimura Y, Yamashita K et al. Phase I/II study of docetaxel/cisplatin/fluorouracil combination chemotherapy against metastatic esophageal squamous cell carcinoma. J Thorac Oncol 2010; 5: 122–8.
19 Tamura S, Imano M, Takiuchi H et al. Phase II study of docetaxel, cisplatin and 5-fluorouracil (DCF) for metastatic esophageal cancer (OGSG 0403). Anticancer Res 2012; 32: 1403–8.
20 Overman MJ, Kazmi SM, Jhamb J et al. Weekly docetaxel, cisplatin, and 5-fluorouracil as initial therapy for patients with advanced gastric and esophageal cancer. Cancer 2010; 116: 1446–53.
21 Roth AD, Fazio N, Stupp R et al. Docetaxel, cisplatin, and fluorouracil: docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol 2007; 25: 3217–23.
22 Berghmans T. Hyponatremia related to medical anticancer treatment. Support Care Cancer 1996; 4: 341–50.
23 Boku N, Ohtsu A, Nagashima F et al. Retrospective study of hyponatremia in gastric cancer patients treated with a combination chemotherapy of 5-fluorouracil and cisplatin: a possible warning sign of severe hematological toxicities? Jpn J Clin Oncol 2001; 31: 382–7.
24 Ando N, Kato H, Igaki H et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol 2012; 19: 68–74.
25 Nakamura K, Kato K, Igaki H et al. Three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU (DCF) versus radiotherapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer (JCOG1109, NExT study). Jpn J Clin Oncol 2013; 43: 752–5.
26 Lorenzen S, Schuster T, Porschen R et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2009; 20: 1667–73.
27 Crosby T, Hurt CN, Falk S et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. Lancet Oncol 2013; 14: 627–37.
28 Sobin LH, Wittekind Ch (eds): International Union Against Cancer (UICC): “TNM classification of malignant tumors.” 6th ed. New York: Wiley; 2002.
29 Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events, Version 3.0. 2003 Mar. Available from URL: http://ctep.cancer.gov