A randomized controlled Phase III trial comparing 2-weekly docetaxel combined with cisplatin plus fluorouracil (2-weekly DCF) with cisplatin plus fluorouracil (CF) in patients with metastatic or recurrent esophageal cancer: rationale, design and methods of Japan Clinical Oncology Group study JCOG1314 (MIRACLE study)

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Received 24 October 2014; Accepted 15 January 2015

Abstract

Chemotherapy with cisplatin plus fluorouracil is the current standard treatment for metastatic or recurrent esophageal cancer. We have developed a 2-weekly docetaxel combined with CF regimen and conducted a Phase I/II trial for metastatic or recurrent esophageal cancer (JCOG0807). Promising efficacy and safety were shown in JCOG0807, and we have commenced a Phase III trial in September 2014 to confirm the superiority of 2-weekly DCF to CF for patients with metastatic or recurrent esophageal cancer. A total of 240 patients will be accrued from 41 Japanese institutions over a period of 4 years. The primary end point is overall survival. The secondary end points are progression-free survival, response rate and proportion of adverse events. This trial has been registered in the UMIN Clinical Trials Registry as UMIN000015107 (http://www.umin.ac.jp/ctr/index.htm).

Key words: metastatic or recurrent esophageal cancer, 2-weekly DCF, Phase III
Introduction

Esophageal cancer is the fifth most common cause of cancer-related death for men and the eighth for women worldwide (1). In Japan, squamous cell carcinoma accounts for ~95% and adenocarcinoma accounts for only 1.6%. On the other hand, adenocarcinoma, which is sometimes caused by Barrett’s esophagus, accounts for >60% in western countries (2). Chemotherapy has been the standard treatment for metastatic or recurrent esophageal cancer regardless of its histological type, but the prognosis remains dismal. According to a comprehensive registry of esophageal cancer in Japan, in 2004, 5-year overall survival (OS) of patients with metastatic or recurrent esophageal cancer treated by chemotherapy alone was only 5.7% (3). The development of a new effective chemotherapy regimen is thus needed to improve the outcome of the metastatic or recurrent esophageal cancer treatment.

Over the past two decades, the two-drug combination of cisplatin plus fluorouracil (CF) has been regarded as a standard regimen for patients with esophageal cancer with distant metastases or recurrence. The Japan Esophageal Oncology Group (JEOG), one of the subgroups of the Japan Clinical Oncology Group (JCOG), has sequentially conducted four Phase II studies to explore an optimal fluorouracil-plus-platinum-based regimen for patients with metastatic or recurrent esophageal cancer (4–7). At present, the most commonly used fluorouracil-plus-platinum-based regimen in Japan is cisplatin (80 mg/m², Day 1) plus fluorouracil (800 mg/m², Days 1–5) every 4 weeks. The reports of CF therapy with this dose and schedule for metastatic or recurrent esophageal cancer have been limited to retrospective study (8), but safety and efficacy were similar to those in other reports using CF regimen with different dose and schedule (5–7,9–11). Thus, CF (cisplatin: 80 mg/m², Day 1; fluorouracil: 800 mg/m², Days 1–5) has been considered as the current standard treatment for metastatic or recurrent esophageal cancer in JEOG.

In most cases, metastatic or recurrent esophageal cancer patients who experienced failure with CF are given docetaxel as a subsequent therapy. However, the disadvantage of sequential use of docetaxel after CF is that patients sometimes miss the chance to receive docetaxel after the failure of CF due to severe adverse events caused by CF or due to poor performance status with disease progression. Based on this, a new concept of triplet combination therapy (docetaxel and CF) as the first-line treatment was planned expecting longer survival benefit. Recently, some groups have reported that the addition of docetaxel to CF (DCF) was effective for patients with gastric cancer and head and neck cancer (11,12). Taking these results into account, several studies evaluating the efficacy and safety of DCF regimen for metastatic or recurrent esophageal cancer have been reported (13–16). In these reports, the dose and schedule of DCF were as follows: docetaxel (50–70 mg/m², Day 1), cisplatin (60–70 mg/m², Day 1) and fluorouracil (600–800 mg/m², Days 1–5) every 3–4 weeks. Although these reports showed promising efficacy, they also report severe toxicities, particularly those related to myelosuppression. They showed febrile neutropenia at a rate of 10–21% and Grade 3–4 neutropenia at 44–90%. Thus, further improvement of the DCF regimen is considered to be needed to lessen the toxicity while maintaining the antimetastatic activity.

Divided doses of docetaxel combined with CF have been investigated in several studies and showed a safer toxicity profile especially for hematologic toxicities or febrile neutropenia (17–19), compared with the original DCF regimen (13–16). We, JEOG, have developed a 2-weekly DCF regimen in which docetaxel is administered twice every 4 weeks (Days 1 and 15). We conducted a Phase III trial to determine the recommended dose for Phase II (RDP2) in Phase I and to investigate the safety and efficacy of the 2-weekly DCF regimen for metastatic or recurrent esophageal cancer (JCOG0807) treatment (20). Our study showed that the RDP2 of docetaxel was 30 mg/m² in Phase I, and 2-weekly DCF (docetaxel: 30 mg/m², Days 1 and 15; cisplatin: 80 mg/m², Day 1; fluorouracil: 800 mg/m², Days 1–5; every 4 weeks) had promising efficacy with a response rate of 62% and a median OS of 11.1 months. As for safety, Grade 3–4 neutropenia was observed in 25.3% and febrile neutropenia in 0%, which was remarkably better than that for the original DCF regimen (13–16). Therefore, 2-weekly DCF regimen has been considered as the most promising treatment for metastatic or recurrent esophageal cancer in JEOG.

Against this background, we planned a multicenter randomized controlled Phase III trial to confirm the superiority of the 2-weekly DCF regimen over CF for patients with metastatic or recurrent esophageal cancer. In this Phase III trial, we modified the 2-weekly DCF regimen so as not to provide a limitation on the cumulative cisplatin dose, although JCOG0807 limited the cumulative cisplatin dose so as not to exceed 500 mg/m². This modification aims to maximize the dose of cisplatin, one of the key drugs for esophageal cancer. The influence of an excessive cisplatin dose on irreversible ototoxicity, nephrotoxicity and neurotoxicity has been reported (21,22), but there is little evidence of 500 mg/m² as the upper dose. Thus, we set no criteria regarding the total dose and cycles of cisplatin; instead, we determined to set strict off-treatment criteria to minimize the risks of neurotoxicity, nephrotoxicity and ototoxicity.

The JCOG Protocol Review Committee approved this study protocol in July 2014, and patient enrollment began in September 2014. Approval was obtained from the institutional review board prior to start of the study at each institution. This trial has been registered in the UMIN Clinical Trials Registry as UMIN000015107 (http://www.umin.ac.jp/ctr/index.htm).

Protocol Digest of JCOG1314

Objectives

The aim of this trial is to confirm the superiority of 2-weekly DCF to CF in terms of OS for patients with metastatic or recurrent esophageal cancer.

Study setting

A multi-institutional two-arm open-label randomized Phase III trial.

End points

The primary end point of Phase III is OS in all randomized patients. OS is defined as days from randomization to death from any cause, and it is censored at the last day when the patient is alive. The secondary end points are progression-free survival (PFS), response rate and proportion of adverse events. PFS is defined as days from randomization to progression or death from any cause, and it is censored at the last day when the patient is alive without any evidence of progression.

Eligibility criteria

Esophageal cancer is staged according to the UICC/AJCC seventh edition of the TNM Classification of Malignant Tumors (23). We exclude...
patients with dysphagia or stenosis because radiation-combined therapy is likely to be applied for these patients. We also exclude patients who received radiotherapy to lung within 52 weeks prior to the study to avoid the late-onset pneumonitis.

To be eligible for this study, patients must fulfill all of the following criteria:

(i) Primary tumor located at cervical esophagus, thoracic esophagus or esophago-gastric junction.
(ii) Histologically confirmed squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma or basaloid carcinoma (Siewert Type II/III adenosquamous carcinoma or adenocarcinoma is ineligible).
(iii) Unresectable or recurrent esophageal cancer with no indication for surgery, radiotherapy and chemoradiotherapy.
(A) In cases of unresectable esophageal cancer, all of the following conditions must be fulfilled:
1. Having a metastatic lesion except for #102 (deep cervical lymph nodes*) or #104 (supraclavicular lymph nodes*) lymph node metastases.
2. CT1–CT4a.
3. Dysphagia score ≤ 2 (being able to swallow semisolid foods) and no stenosis that an endoscope with a standard diameter can pass through.
(B) In cases of recurrent esophageal cancer, all of the following conditions must be fulfilled:
1. Having a metastatic lesion except for #102 or #104 metastases.
2. Dysphagia score ≤ 2.
(iv) Aged 20–75 years.
(v) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
(vi) No symptomatic bone or brain metastases.
(vii) No massive ascites/pleural effusion.
(viii) Measurable lesions not required.
(ix) As for previous therapy, either (A) or (B) in the following must be fulfilled:
(A) When pre-operative chemotherapy (CF or DCF) or post-operative chemotherapy (CF) has been given as previous therapy, all of the following four factors must be met:
1. Recurrence was detected more than 24 weeks after previous therapy was completed.
2. Previous therapy was not terminated due to adverse events or patient refusal.
3. Tumor response by previous therapy was not judged as disease progression.
4. Total prior dose of cisplatin ≤ 210 mg/m².
(B) When pre-operative chemoradiotherapy (CF-RT), concurrent chemoradiotherapy (CF-RT) or radiotherapy alone are given as previous therapy, all of the following five factors must be met:
1. More than 52 weeks after radiotherapy when lung is exposed to the radiation field.
2. No history of Grade 2–4 pneumonitis.
3. Previous therapy was not terminated due to adverse events or patient refusal.
4. Tumor response by previous therapy was not judged as disease progression.
5. Total dose of prior cisplatin ≤ 210 mg/m².
(x) Sufficient organ function.
(xi) Written informed consent.

Exclusion criteria
Patients fulfilling either of the following criteria are ineligible for this study:

(i) Synchronous or metachronous (within 5 years) malignancies except for carcinoma in situ or mucosal tumors curatively treated with local therapy.
(ii) Active infection requiring systemic therapy.
(iii) Pregnancy, possible pregnancy or breastfeeding.
(iv) Psychiatric disease.
(v) Patients requiring systemic steroid medication.
(vi) Under treatment with flucytosine, phenytoin or warfarin.
(vii) History of iodine allergy.
(viii) History of hypersensitivity to docetaxel, cisplatin or polysorbate 80.
(ix) Poorly controlled diabetes mellitus or routine administration of insulin.
(x) Severe pulmonary fibrosis or emphysema.
(xi) Poorly controlled hypertension.
(xii) Unstable angina within 3 weeks or with a history of myocardial infarction within 6 months.
(xiii) Positive HBs antigen or positive HIV antibody.

Randomization
After confirming that patients meet the eligibility criteria, registration is made by a web-based system to the JCOG Data Center. Patients are randomized to either arm A (CF) or arm B (2-weekly DCF) by a minimization method balancing the arms with institutions and the number of metastatic sites (1 vs. 2 or more). Institution is included as a stratification factor taking heterogeneity among hospitals (e.g. patient background) into account. The number of metastatic sites is also included because it was indicated as a prognostic factor in the previous Phase III/II trial of this study (JCOG0807) (20).

Treatment methods
Patients in the CF arm receive cisplatin (80 mg/m²), 2 h intravenous infusion on Day 1) and fluorouracil (800 mg/m², 24 h continuous intravenous infusion on Days 1–5), which is repeated every 4 weeks. Patients in the 2-weekly DCF arm receive docetaxel (30 mg/m², 1 h intravenous infusion on Days 1 and 15), cisplatin and fluorouracil (the same dose and schedule as those in the CF arm). Prophylactic antiemetics are given before the administration of cisplatin. When Grade 2 neuropathy or hearing impairment is observed, start of the next course is delayed. The course will start with a reduced dose of cisplatin when neuropathy or hearing impairment recovers to Grade 1 or 0 within 28 days. When creatinine clearance < 60 ml/min is observed, the dose of cisplatin is also reduced. The course will be repeated until progression of disease or intolerable toxicity is observed. In the 2-weekly DCF arm, even after docetaxel administration is terminated, chemotherapy with cisplatin and fluorouracil is continued as the treatment protocol. Primary G-CSF or antibacterial drug prophylaxis is not performed. Subsequent treatment with the completely same regimen as the other arm (crossover) is not allowed after termination of treatment protocol. Otherwise, any drugs can be used as a subsequent therapy.
Follow-up
All registered patients are followed-up for at least 1.5 years after patient accrual is completed. Enhanced neck, chest and upper abdominal computed tomography (CT) are performed every 8 weeks during treatment protocol. After termination of treatment protocol except for disease progression, enhanced neck, chest and upper abdominal CT are performed every 2 months.

Study design and statistical analysis
This randomized trial is designed to confirm the superiority of 2-weekly DCF to CF in patients with metastatic or recurrent esophageal cancer. The primary analysis is to be carried out at 1.5 years after accrual completion. Stratified log-rank test with the strata of the number of metastatic sites (1 vs. 2 or more) is used to test the superiority of the 2-weekly DCF arm in terms of OS. The hazard ratio between treatment arms and its confidence interval are estimated by the stratified Cox proportional hazard model with the strata of the number of metastatic sites (1 vs. 2 or more).

We assumed the median survival time with CF to be 8.0 months because the median survival time in previous reports about CF therapy for esophageal cancer patients was ~7–9 months. We expected a 3-month increase in the median survival time with 2-weekly DCF considering the additional toxicity by docetaxel. Following Schoenfeld and Richter’s method (23), the sample size was calculated as 115 patients per arm with a one-sided α level of 5%, power of 75%, an accrual period of 4 years, a follow-up period of 1.5 years and 212 expected events in total. The total sample size was set to 240 patients, assuming that a few patients will be lost to follow-up. All statistical analyses will be conducted at the JCOG Data Center.

Interim analysis and monitoring
We plan to conduct one interim analysis. The interim analysis will be conducted after half of the planned number of patients have been enrolled. The Lan-DeMets method with the O’Brien & Fleming type alpha spending function is used to adjust multiplicity of the interim analysis (26). The Data and Safety Monitoring Committee (DSMC) of the JCOG will review the interim analysis reports independently from the group investigators and group statistician. The trial will be terminated when the termination criteria for superiority or futility are met at the interim analysis or when treatment-related deaths are observed in >5% of patients of either arm.

In-house monitoring will be performed every 6 months by the JCOG Data Center to evaluate and improve study progress, data integrity and patient safety.

Participating institutions (from north to south)
Hokkaido University Hospital, Iwate Medical University, Tohoku University Hospital, Ibaraki Prefectural Central Hospital & Cancer Center, Tochigi Cancer Center, Saitama Cancer Center, National Cancer Center Hospital East, Chiba Cancer Center, Chiba University Graduate School of Medicine, Tokyo Dental College Ichikawa General Hospital, National Cancer Center Hospital, Tokyo Women’s Medical University, National Hospital Organization Tokyo Medical Center, Keio University Hospital, Showa University School of Medicine, Tokyo Medical and Dental University Hospital, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Toranomon Hospital, Tokai University School of Medicine, Kanagawa Cancer Center, Niigata Cancer Center Hospital, Niigata University Medical and Dental Hospital, Shizuoka General Hospital, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Kyoto University Hospital, Osaka University Graduate School of Medicine, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka National Hospital, Osaka City General Hospital, Osaka Medical College, Kobe University Graduate School of Medicine, Hyogo Cancer Center, Hiroshima University Hospital, Hiroshima City Asa Hospital, National Hospital Organization Shikoku Cancer Center, Kochi Health Sciences Center, National Kyushu Cancer Center, Kurume University School of Medicine, Kyushu University Hospital and Kumamoto University Medical School.

Funding
This study is supported by the National Cancer Center Research and Development Fund (26-A-4).

Conflict of interest statement
None declared.

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