Risk factors for FN, mucositis and esophagitis of combination chemotherapy with docetaxel, cisplatin, and 5-fluorouracil for esophageal cancer

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Abstract

Background

Addition of docetaxel to cisplatin plus 5-fluorouracil (DCF regimen) for treatment of esophageal carcinoma can improve the clinical outcome, but it is associated with increased toxicity. The risk factors for severe toxicities associated with DCF treatment remain unknown.

Methods

We retrospectively reviewed the data of esophageal cancer patients who received DCF between July 2009 and April 2014 at the National Cancer Center Hospital. Docetaxel 70 mg/m²/day (day 1), cisplatin 70 mg/m²/day (day 1), and continuous infusion of 5-fluorouracil 750 mg/m²/day (days 1–5) were administered every 3 weeks. The risk factors for severe adverse events were explored.

Results

We included 100 patients with a median age of 63 years (range: 37–76), among whom 81 were men, and 44 and 55 had performance status scores of 0 and 1, respectively. A total of 96 patients had squamous cell carcinoma, while 4 had adenocarcinoma. A total of 1, 12, 64, and 23 patients had clinical stages I, II, III, and IV, respectively. DCF was used as neoadjuvant therapy in 69 patients, induction before chemoradiotherapy in 23, and palliative in 8. Approximately 45 patients experienced grade 4 hematological adverse events, while 40 developed grade ≥ 3 non-hematological adverse events: anorexia, 12%; mucositis, 6%; and esophagitis, 2%. Multivariate analysis showed a significant association between dysphagia score >2 ($P = 0.022$) and febrile neutropenia, and between platelet count $\leq 27,500/\mu\text{l}$ and grade >3 mucositis and/or esophagitis ($P = 0.007$).

Conclusion

During DCF therapy, patients with dysphagia or decreased platelet count should be carefully managed.

Trial registration: Not applicable

Background

Esophageal cancer is one of the most aggressive malignant diseases with a poor survival outcome. According to the Global Cancer Observatory, esophageal cancer is the seventh most commonly occurring cancer in men, and the 13th most commonly occurring cancer in women; with over 500,000 new cases in 2018¹. The disease is common in East Asia: in Japan, 22,400 patients diagnosed with esophageal cancer, and 11,300 died of esophageal cancer in 2012². The Japan Clinical Oncology Study Group (JCOG9907) compared between preoperative chemotherapy and postoperative chemotherapy with cisplatin and 5-fluorouracil (5-FU) (CF) followed by surgery for stage II/III esophageal squamous cell

carcinoma (ESCC), showing that the preoperative CF resulted in 55% of overall survival at 5 years, which is significantly higher than that of postoperative chemotherapy³.

In Japan, neoadjuvant chemotherapy with CF followed by surgery is the current standard therapy for locally resectable disease. However, the efficiency of neoadjuvant CF therapy is currently limited since the clinical response rate, and the pathological complete response (pCR) rates are relatively lower (33.7% and 5%, respectively) than those of neoadjuvant chemoradiotherapy (70%–80% and 40%–50%, respectively)^{4,5}. For many years, systemic chemotherapy with CF has been the standard treatment for metastatic or recurrent esophageal cancer, resulting in modest efficacy with a median survival time of 7–9 months^{6–9}. Therefore, there is room for further improvements adding to chemotherapy with CF for both neoadjuvant and metastatic treatment settings.

In recent years, triplet chemotherapy with docetaxel in addition to CF (DCF) for the treatment of head and neck, esophageal, and gastric cancers showed better patient outcome^{10–13}. In the neoadjuvant setting for ESCC patients, DCF therapy showed promising activity with a response rate of 64.3% and a pCR rate of 17%¹⁴. A three-arm randomized controlled clinical trial (JCOG1109) has been conducted to compare DCF, chemoradiotherapy with CF, and CF in the neoadjuvant setting¹⁵. Furthermore, DCF showed promising efficiency in patients with metastatic and recurrent esophageal cancer in the JCOG0807 trial¹². A randomized controlled clinical trial (JCOG1314) is currently underway¹⁶. Even though several studies have shown promising results of DCF, severe adverse events were often observed during treatment with DCF such as neutropenia, anorexia, and febrile neutropenia (FN). In the V325 study, a phase III analysis compared DCF with CF for advanced gastric cancer; FN was reported in 12% of the CF arm and 29% of the DCF arm. The incidence rates of grade 3–4 neutropenia were 57% in the CF arm and 82% in the DCF arm¹³. These severe toxicities are important issues for esophageal carcinoma patients in poor medical condition due to impaired oral intake. Here, we aimed to explore the risk factors for severe toxicities leading to reduced dose-intensity associated with DCF treatment in esophageal cancer patients.

Methods

Patients

This study included patients who were newly diagnosed with esophageal or gastroesophageal junctional cancer and treated at least one cycle of DCF between July 2009 and April 2014 at the National Cancer Center Hospital. From this cohort, patients who lack data on adverse events in the medical records, whose schedule or dosage of DCF in the first cycle were modified, with neutrophil count of $<1,500 \mu\text{l}$, with hemoglobin (Hb) level of $<9 \text{ g/dl}$, or with serum creatinine level of $\geq 1.2 \text{ mg/dl}$ before the initiation of DCF were excluded. The study was approved by the National Cancer Center Institutional Review Board (2017-229). In this retrospective study, patients' consent was obtained by opt-out manner.

Treatment

DCF consisted of docetaxel 70 mg/m²/day (drip infusion, day 1), cisplatin 70 mg/m²/day (drip infusion, day 1), and 5-fluorouracil 750 mg/m²/day (continuous infusion, days 1–5) in one cycle, repeated every 3 weeks¹⁴. Prophylactic treatment for chemotherapy-induced nausea and vomiting was administered using 5-hydroxy tryptamine₃ antagonist, neurokinin-1 inhibitor, and dexamethasone. If granulocyte colony-stimulating factor (G-CSF) was used for the treatment of FN during the first cycle, G-CSF was used for prophylaxis if necessary. Oral antibiotics were administered between days 5 and 15 as prophylactic treatment. The subsequent treatment cycles could be delayed, or doses were reduced by up to 20% if either grade 4 hematological and/or grades 3–4 non-hematological adverse events occurred in the previous treatment cycle.

Assessment

Data on patients' baseline characteristics and adverse events were obtained from the electronic medical records. DCF treatment was completed in two or three cycles in the neoadjuvant and induction settings, but was discontinued when disease progression and unacceptable toxicities occurred in the palliative setting. In this study, the adverse events developing within the first three cycles were evaluated in accordance with the Common Terminology Criteria for Adverse Events version 4.02. Dysphagia score was defined as follows: 0, able to eat a normal diet; 1, unable to swallow certain solids; 2, able to swallow semisolid food; 3, able to swallow liquids only; and 4, unable to swallow liquids.

Statistics

The odds ratios of patient background divided into two categorical groups for each adverse event was calculated using logistic regression models with Firth's bias reduction method. Confidence intervals (CI) (95%) and P values were derived by performing the Wald chi-square test. The IBM SPSS statistics 23.0 (IBM, Chicago, IL, USA) software package and SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA) were used for statistical analyses.

Results

Baseline characteristics

A total of 111 patients were included in this study. Of them, 7 with dose reduction of DCF in the first cycle and 4 who lacked data on adverse events were excluded. Finally, 100 patients were included in this study, whose baseline characteristics are shown in **Table 1**. Approximately 87% of the patients had stage III or IV, and 99% of them had PS score of 0–1. Adenocarcinoma accounted for only 2%. A total of 76 patients (76%) received three courses of DCF, while the treatment in 21 (21%) patients were discontinued after receiving two courses of DCF.

Treatment profile

Figure 1 shows the clinical course of the patients in this study. DCF treatment was discontinued in six patients (6%) in the first cycle due to the occurrence of grade 3 non-hematological toxicities (grade 3 fatigue, 2; grade 3 anorexia with grade 3 fatigue, 1; grade 3 syncope, 1; grade 3 encephalopathy, 1; and disease progression associated with patient refusal due to continuous grade 2 fatigue, 1). The dose of any drug was reduced in 40 (40%) and 43 (43%) patients in the second and third cycles, respectively. The main reasons for discontinuation after the second cycle of DCF were as follows: planned surgery (n=8: 8%) and planned chemoradiotherapy (n=5: 5%). The relative dose intensities during the first three cycles of docetaxel, cisplatin, and 5-FU were 86%, 85%, and 86%, respectively. Most of the adverse events causing dose-reduction of DCF were FN and mucositis or esophagitis. Prophylaxis antibiotics were administered in 92 patients (92%).

Adverse events

Approximately 99% of the patients experienced some hematological or non-hematological adverse events during the first three cycles (**Tables 2 and 3**). Forty patients developed grade ≥ 3 non-hematological adverse events: including anorexia (12%), mucositis (6%), and esophagitis (2%). Forty-five patients developed grade 4 hematological adverse events. Seventeen patients experienced FN (FN). One patient died in the third treatment cycle due to pneumonia.

Risk factors for adverse events

In univariate analysis, dysphagia score ≥ 2 was associated with FN ($P = 0.011$). In the multivariate analysis using sex, age, PS, dysphagia score, creatinine clearance (CCr), and blood cell count as covariates, dysphagia score ≥ 2 was a statistically significant risk factor of FN (odds ratio (OR): 4.150 (95% CI: 1.23–14.03), $P = 0.022$). Male gender and lower Ccr (<80 mg/mL) have a tendency for risk of FN (**Table 4**). Approximately 31% of the patients with a dysphagia score ≥ 2 (11/36) and 25% (12/48) with lower CCr developed FN. The lower platelet count ($\leq 275,000/\mu\text{L}$) increased the risk of grade 3–4 mucositis or esophagitis with significance (OR: 14.769 [95% CI, 2.09–104.43], $P = 0.007$) (**Table 5**). Lower neutrophil count and hemoglobin level increased the risk for grade 3–4 stomatitis and esophagitis. The incidence of grade 3–4 mucositis or esophagitis was reported in 11.3% (7/62) of the patients with lower platelet count ($\leq 275,000/\text{uL}$) before initiation of chemotherapy and in 2.6% (1/38) of the patients with higher platelet count.

Discussion

This report focuses on the risk of severe adverse events associated with DCF treatment for esophageal cancer, mainly targeting on squamous cell carcinoma. We conducted this retrospective study to identify the patients receiving DCF therapy who required more support or modification. Several studies have been conducted to investigate the efficiency and safety of platinum-containing triplet chemotherapies for solid tumors. Most of the studies on cisplatin-based triplet regimens for non-small cell lung carcinoma concluded that triplet chemotherapy reduced the tolerability, largely due to an increase in hematological

toxicities^{17,18}. Meanwhile, trials of gastroesophageal cancer indicated that triplet procedures, with adequate dosing and scheduling, have promising results and are well tolerated by the patients^{19,20}. Together, these data reveal that the adverse events of a triplet chemotherapy treatment may be manageable if it is provided as a supportive treatment.

This study showed the group at risk for FN. Worse dysphagia score and lower CCr were correlated with the incidence of FN, while lower platelet count was correlated with mucositis. Dysphagia is one of the most frequent symptoms occurring in patients with ESCC. The degree of dysphagia was correlated with the risk of aspiration leading to aspiration pneumonia. Dysphagia might cause FN through aspiration pneumonia. Our study also indicated that lower CCr (<80mg/mL) have a tendency of risk for FN. Although CCr correlates with the risk of neutropenia in some drugs, for example, carboplatin, no correlation was found between the level of CCr and grade 4 neutropenia in this analysis (data not shown). Lower CCr seems to reflect the patient's nutritional status including fluid intake, which may be one of the causes of FN.

There are two essential points to consider before introducing DCF: (i) the prevention of severe adverse events and (ii) the selection of patients.

Several methods have been used to prevent the adverse events. Among them, prophylactic antibiotics were used to prevent FN. A previous meta-analysis of randomized clinical trials revealed that prophylactic antibiotics in the course of intensive chemotherapy reduced the number of patients with infections²¹. Although a previous phase II study reported that preoperative DCF led to grade 3/4 neutropenia (83%), anorexia (7%), and stomatitis (5%)¹⁴, FN was reduced to 3% by prophylactic use of antibiotics on days 5–15 in all patients. In our analysis, most of the patients – except those who cannot take drugs orally – received prophylactic antibiotics. The substantial difference in the incidence of FN (3% for phase II vs 17% for this study) might be caused by the differences in the background of the patients who had more advanced cases. For example, only patients with resectable disease were enrolled in the phase II trial, while 17% of T4 patients were enrolled in this analysis although dysphagia score was not reported. Recently, the risk factor of FN during DCF therapy was reported in a retrospective manner, where dysphagia score at diagnosis was the independent predictive factor for FN and severe diarrhea²². Although the relationship of diarrhea and dysphagia score was unclear in our study, further advanced T stage and severe dysphagia may increase the risk for inspiration pneumonia and lower nutritional status. Dysphagia score may reflect these factors and was an independent risk factor for FN in our study.

To reduce the incidence of neutropenia and non-hematological toxicity associated with docetaxel, the divided dose of docetaxel was evaluated in previous clinical trials^{23,24}. A phase I/II clinical trial, JCOG0807, of biweekly DCF for metastatic cancer reported that the common grade 3-4 adverse events were neutropenia (25%), anemia (36%), hyponatremia (29%), anorexia (24%), and nausea (11%)¹². No FN was reported among 53 patients. The response rate was 62%, and the overall survival of the metastatic patients in this study was 11.1 months; patients received 30 or 40 mg/m² of docetaxel on days 1 and 15, which indicate that administering docetaxel in two doses might have reduced the incidence of

hematological adverse events without reducing the efficacy. However, no pathological efficacy data reported the use of divided dose of docetaxel in neoadjuvant triplet regimen.

One more solution is the use of G-CSF as prophylactic treatment. In this study, 5 (5%) patients used G-CSF after the onset of FN, while none of the patients received G-CSF as prophylactic treatment. The prophylactic use of G-CSF is recommended when the risk of FN is 20% or higher^{25, 26}. Based on the ASCO guidelines, the DCF regimen should be administered together with a prophylactic drug in patients with risk factors of FN. Due to the higher cost of G-CSF, patients who really benefit should be strictly selected. Results of our analysis indicated that the patients who had dysphagia, and/or lower CCr, may have a risk of FN superior to 20%. For these patients, prophylactic use of G-CSF might be adequate to prevent FN and to keep the dose intensity of DCF. Another issue is the timing of G-CSF administration. Usually, G-CSF is usually administered 24 h after the discontinuing the administration of chemotherapeutic drugs, but this might eliminate the effect of G-CSF. A previous report for day 5 administration of Peg-G-CSF showed that it does not reduce the incidence of grade 3/4 neutropenia associated with DCF therapy, because the nadir of DCF mainly appears at days 7 to 10. The investigators concluded that earlier administration of peg-G-CSF is more suitable for patients receiving the DCF regimen, and clinical trials should be conducted for further investigation²⁷.

Mucositis and esophagitis are common adverse events in patients receiving chemotherapy containing 5-FU and docetaxel. Based on the results of clinical trials of ESCC, gastric cancer, and head and neck cancer, 4.6%–21% of grade 3-4 stomatitis was reported during the course of DCF^{10, 11, 13, 14}. Risk factor of mucositis induced by chemotherapy and chemoradiotherapy was reported in many articles²⁸⁻³⁰. The risk factors have been attributed to both therapy and patient characteristics and varied across cancer types and treatment regimens. With regard to the therapeutic factor, intensive chemotherapy, radiotherapy, and radiation were major the risk factors. Meanwhile, the patients' factor is more complex, and the individual differences are more intense; however, age, gender, nutritional status, comorbidities, dentition, neutrophil count, hemoglobin, and others have been reported.

Results of our analysis indicated that lower platelet count is the risk factor of severe stomatitis, and the potential of lower neutrophil count and anemia. For the patients with these risk factors, the prophylactic use of oral hygiene or topical therapy might be considered during DCF therapy. However, the exact cut-off level of the risk factors should be evaluated in another study using a larger sample size, since this is a limitation of our study.

There were also other limitations in this retrospective analysis. This study was conducted in a single institution, and the patients' purpose of receiving DCF varied. Moreover, blood examination was conducted in an unscheduled time point. Further analysis might be needed in a larger prospective cohort, such as a phase III trial of neoadjuvant DCF regimen¹⁵.

Conclusion

DCF chemotherapy is safe and its toxicity is controllable in most patients. During DCF therapy, patients with dysphagia or a decreased platelet count should be carefully managed.

Abbreviations

5-FU: 5-fluorouracil

CCr: creatinine clearance

DCF: docetaxel to cisplatin plus 5-fluorouracil

ESCC: esophageal squamous cell carcinoma

FN: febrile neutropenia

pCR: pathological complete response

Declarations

- Ethics approval and consent to participate

This study was approved by institutional review board of National Cancer Center (Number: 2017-229), and took a consent by opt-out manner because this analysis is retrospective one.

- Consent for publication

Not applicable.

- Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

- Competing interests

There are no competing interests.

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- Authors' contributions

Each author is expected to have made substantial contributions to the conception, and KK and SY for design of the work; **and KN for** the acquisition, analysis, **and KK, SY, NB and KN for** interpretation of

data; **and KK and SY** for have drafted the work or substantively revised it. All authors have read and approved the manuscript.

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Tables

Due to technical limitations, table 1 to 5 is only available as a download in the Supplemental Files section.

Figures

*Including one patient with palliative surgery

CRT: Chemoradiotherapy, Chemo: Chemotherapy, BSC: Best supportive care

Figure 1

Schematic representation of the treatment course

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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