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ORIGINAL ARTICLE

Neoadjuvant chemoradiotherapy with docetaxel, cisplatin, and 5-fluorouracil for esophageal cancer

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Abstract
Purpose We aimed to evaluate the safety, tolerability, and efficacy of combination preoperative chemoradiotherapy as first-line treatment in patients with advanced esophageal cancer.
Methods We performed a phase I dose-escalation trial of docetaxel at 25–40 mg/m^2 in four planned dose levels in 3–6 patient cohorts on days 1, 15, 29, and 43 administered in combination with cisplatin (70 mg/m^2 on days 1 and 29) and 5-fluorouracil (70 mg/m^2/day on days 1–4 and 29–32) and concurrent radiation therapy (40 Gy). The tumors were resected during weeks 10–13.
Results This study included 7 patients with esophageal cancer. The dose-limiting toxicity was observed at a biweekly docetaxel dose of 30 mg/m^2 when patients developed grade 3 febrile neutropenia, grade 4 thrombocytopenia, and grade 4 pain/esophagus, resulting in a maximum tolerated dose of 25 mg/m^2. Grade 3/4 hematological toxicity was observed in 71% of the patients and grade 3/4 non-hematological toxicity in 57%. The overall tumor response rate was 86% (complete, 57% and partial, 29%). All patients underwent surgery, and there were no deaths as a result of postoperative complications.
Conclusions This preoperative chemoradiotherapy regimen using triplets is feasible but results in moderate toxicity. It is noteworthy that this regimen was associated with a high rate of pathological complete remission.

Keywords Esophageal cancer · Chemoradiotherapy · Docetaxel · Cisplatin · 5-Fluorouracil

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Introduction

Esophageal cancer is the sixth leading cause of cancer deaths in Japanese men. An estimated 12,000 individuals die due to esophageal cancer every year [1]. The incidence of esophageal adenocarcinomas is increasing in Western Europe and the United States, whereas esophageal squamous cell carcinomas are the most commonly encountered type of esophageal cancer in Japan. Most patients with newly diagnosed carcinoma of the esophagus present with locally advanced disease. Since the incidence of locoregional and distant failure is high, considerable interest has been generated in combining local and systemic therapy. Preoperative chemoradiotherapy and surgery are potentially curative for patients with locoregional disease, and this treatment is probably superior to surgery alone [2–4]. However, prognosis for these patients remains poor. In an effort to improve treatment results, newer combinations of chemotherapy with radiotherapy have been evaluated.

5-Fluorouracil and cisplatin (CF) are the most commonly used agents in combination chemotherapy and radiotherapy. A V325 phase III study on gastric cancer demonstrated that adding docetaxel to CF significantly improved the time to progression, survival, and overall response rate as compared to treatment with CF alone [5]. A randomized trial of squamous cell carcinoma of the head and neck illustrated the advantages of combining docetaxel, cisplatin, and 5-fluorouracil as induction

chemotherapy compared to cisplatin and 5-fluorouracil, when followed by chemoradiotherapy [6]. On the basis of these studies, it was hypothesized that a preoperative therapy consisting of a chemotherapy combining docetaxel, cisplatin, and 5-fluorouracil, followed by radiotherapy, could significantly improve the prognosis of patients with localized esophageal cancer. The present work is a phase I clinical trial designed to evaluate the safety and efficacy of this neoadjuvant chemotherapy. The primary end point was dose-limiting toxicity (DLT) during chemoradiation. Secondary objectives were feasibility and efficacy of the neoadjuvant chemoradiotherapy.

Methods

Eligibility

Previously untreated patients with histological proof of squamous cell carcinoma of the thoracic esophagus or gastroesophageal junction (GEJ), with clinical T2–T3 N0–3, and M0 (including supraclavicular or celiac lymph node involvement) disease according to the American Joint Committee on Cancer (AJCC), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 were eligible to participate in this study.

The patients were required to have measurable disease by radiological or endoscopic evaluation at the time of enrollment. Other eligibility criteria included age $\leq$75 years, adequate organ function (white blood cell count [WBC], $\geq$3,000/μL; platelet count, $\geq$100 $\times$ 109/L; serum bilirubin, $\leq$1.5 $\times$ the upper limit of normal (UNL); serum, AST/ALT less than 1.5 $\times$ the UNL; alkaline phosphatase, $<$2.5 $\times$ the UNL; and serum creatinine, $\leq$1.2 mg/dL; or calculated creatinine clearance, $\leq$60 mL/min). The exclusion criteria included history of hypersensitivity to docetaxel, cisplatin (CDDP), 5-fluorouracil (5-FU), or polysorbate 80; infection with fever elevation; peripheral neuropathy $>$grade 1; any other serious preexisting medical illnesses; pregnancy or lactation; and prior invasive malignancy within 5 years. This study was approved by the Institutional Ethics Committee, and all the patients provided their written informed consents prior to the enrollment.

Treatment plan

Radiation therapy

External beam radiotherapy was given at 5 fractions per week for 4 weeks (total dose, 40 Gy) [7]. Radiotherapy was delivered using 10-MV X-rays. A computed tomography (CT) simulator was used for three-dimensional treatment planning. The radiation field for upper thoracic tumors included the region from the supraclavicular, cervical, and mediastinal lymph nodes to the carina. The field for mid-thoracic or lower thoracic tumors included the cervical, mediastinal, and perigastric lymph nodes, and the supraclavicular fossa was included if the cervical nodes tested positive. The field for GEJ tumors included the mediastinal (lower than subcarinal), perigastric, and celiac lymph nodes. The primary tumor was included with a craniocaudal margin of 2–3 cm.

Concurrent chemotherapy

During radiotherapy, all patients received intravenous docetaxel (days 1, 15, 29, and 43), CDDP (days 1 and 29), and 5-fluorouracil (days 1 thorough 4 and days 29–32), as shown in Fig. 1. Initial dose levels were influenced by dose levels reported as a phase I trial of definitive chemoradiotherapy by Higuchi et al. [8]. They used docetaxel (20–40 mg/m^2) and an infusion of cisplatin (40 mg/m^2) on day 1 plus a continuous infusion of 5-fluorouracil (400 mg/m^2/day) on days 1–5, administered every other week and recommend the following dosage for phase II studies of DCF plus radiotherapy: docetaxel 35 mg/m^2, cisplatin 40 mg/m^2, and 5-fluorouracil 400 mg/m^2/day with 61.2 Gy of concurrent radiotherapy. We reduced the dose with respect to neoadjuvant chemoradiotherapy. We used a conventional dose-escalation schema with the primary end point of defining the DLT of docetaxel that can be delivered with CDDP, 5-fluorouracil, and radiotherapy, as shown in Table 1. Steroids and antiemetic premedication were administered to all the patients.

Definition of dose-limiting toxicities (DLTs): The following toxicities (according to the Common Terminology Criteria for Adverse Events (version 3.0) of the National Cancer Institute) that occurred during chemoradiotherapy or before surgery were defined prospectively as DLTs:

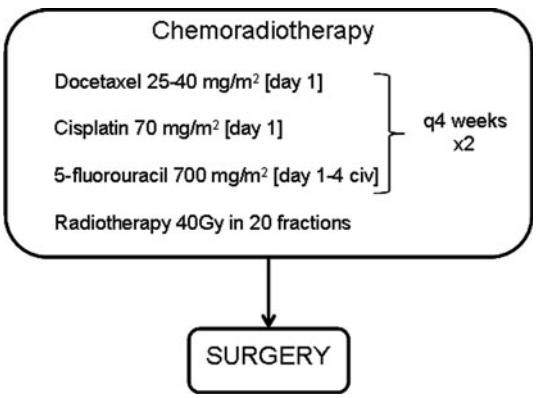

Fig. 1 A schematic showing the treatment and the dosage of different drugs

Table 1 Chemotherapy dose levels

	Docetaxel (mg/m^2) Day 1, 15	Cisplatin (mg/m^2) Day 1	5-FU (mg/m^2/day) Days 1–4
Level 1	25	70	700
Level 2	30	70	700
Level 3	35	70	700
Level 4	40	70	700

(1) grade 4 neutropenia or leucopenia (persisting for 5 days or longer); (2) grade 4 thrombocytopenia; (3) grade 3 or 4 febrile neutropenia; (4) other grade 3 or 4 non-hematological toxicity, except for grade 3 esophagitis, nausea, vomiting, anorexia, and diarrhea within 3 days, dyspepsia, hyperglycemia, and abnormalities of sodium, potassium, and calcium; (5) omission of chemotherapy >1 week; (6) interruption of radiotherapy for >1 week.

Dose-escalation schema

At least three patients were enrolled at each level. If no DLT was observed, the next dose level was opened for enrollment. If DLT was observed in one or two patients, then up to three additional patients were enrolled. Intrapatient dose escalation was not permitted. If 3 or more patients experienced DLTs, the dose escalation was stopped and that dose was regarded as the maximum tolerated dose (MTD). The recommended dose (RD) for the phase II study of docetaxel was determined to be one dose level below the MTD.

Suspended criteria of chemoradiotherapy: In the case of toxicity, no dose modification was allowed in this study. If hematological toxicity ≥grade 3 occurred, administration of the chemotherapy was delayed until the platelet count was $\geq 10 \times 10^4/mm^3$, and absolute neutrophils were $\geq 2 \times 10^3$. Radiotherapy continued despite chemotherapy interruptions. Radiotherapy, together with chemotherapy, was suspended if the patient experienced grade 4 esophagitis until improvement to grade 2.

Surgery

Patients were underwent definitive surgical resection from weeks 10–13. The patients in whom the primary tumor was located in the upper or middle thoracic esophagus underwent transthoracic esophagectomy (involving laparotomy, right thoracotomy, and cervical anastomosis) with three-field lymph node dissection (thoracic, abdominal, and cervical). Those whose primary tumor was located in the lower thoracic or abdominal esophagus underwent transthoracic esophagectomy with two-field lymph node dissection. Reconstruction was usually carried out via a gastric tube through the posterior mediastinal or retrosternal route.

Definition of response

The tumors, nodes, and metastases were staged according to the International Union against Cancer criteria [9]. Clinical staging was carried out using results of endoscopy, endoscopic ultrasound, barium swallow, computed tomography scanning of the abdomen and thorax, and positron-emission tomography.

The Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used to evaluate the responses in all the patients. The final response category assigned to the patients represented the best response obtained during treatment. All the patients were reassigned into stages 3–4 weeks after completing combined therapy (week 9) using results of CT scans, endoscopy and, where available, endoscopic ultrasound and positron-emission tomography. Histopathological response, a secondary end point, was based on the pathological findings after esophagectomy. Pathological complete remission (pCR) was defined as the complete disappearance of the tumor on histological examination.

Monitoring procedures and follow-up

During treatment, patients were reviewed weekly, and their weight, patient performance status (PS), and physical examination were measured, and acute toxicities were recorded. Biochemical analysis and creatinine clearance were measured weekly from blood samples obtained from the patients every week.

After active treatment, the patients were examined (including CT scan) every 3 months for the first year, every 4 months in the next year, and then every 6 months in the next 3 years. Endoscopic examination was carried out annually.

Results

Patients

Between December 2009 and November 2010, we enrolled 7 patients with esophageal cancer into this study. Patient characteristics are summarized in Table 2. There were 5 male and 2 female subjects of ages ranging from 38 to 71 years (median, 61 years). The PS was 0 in all cases. Of these, 5 patients had stage IIIA esophageal cancer and 2 had stage IIIB esophageal cancer. All the patients had squamous cell carcinoma.

Table 2 Patient characteristics

Age (year)	
Median	61
Range	38–71
Gender (*n*, %)	
Male	5 (71.4)
Female	2 (28.6)
ECOG performance (*n*, %)	
0	6 (85.7)
1	1 (14.3)
AJCC TNM stage (*n*, %)	
IIIA	5 (71.4)
IIIB	2 (28.6)
Histological type (*n*, %)	
Squamous cell	7 (100)

ECOG Eastern Cooperative Oncology Group, *AJCC* American Joint Committee on Cancer

Treatment delivery and toxicity

All the patients were evaluated for toxicity weekly during radiotherapy and concurrent chemotherapy. The adverse effects of the treatment are summarized in Table 3. The patients completed planned radiotherapy without any treatment interruptions. Hospitalization and intravenous fluids were required in the case of 4 patients with grade 3 esophagitis.

Among the 3 patients who were administered level 1 docetaxel, none had DLTs. Of the 3 patients who were administered level 2 docetaxel, 2 had DLT. One patient in dose level 2 experienced grade 3 febrile neutropenia. This event caused a delay in chemotherapy; however, radiotherapy was completed without any interruption. Despite the use of opioids, 1 patient at dose level 2 experienced severe pain due to esophagitis after the completion of radiotherapy. Since the pain resulted in the patient becoming confined to bed, we deemed it as grade 4 pain and DLT. However, these symptoms disappeared after approximately 2 weeks of central venous nutrition. Therefore, a fourth patient was treated. This additional patient had grade 4 thrombocytopenia. Therefore, DLT occurred in 3 of the 4 patients, and the level 2 dose was designated as the MTD and the level 1 dose was designated as the RD for phase II studies. One patient who was administered level 2 docetaxel had grade 4 hyponatremia and was diagnosed with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), but this patient recovered after water restriction, and Na supplements were applied.

All the patients underwent definitive surgical resection during weeks 10–13. Four patients underwent transthoracic esophagectomy with three-field lymph node dissection and 3 underwent transthoracic esophagectomy with two-field lymph node dissection. Infections were the predominant complication of surgery (Table 4) and occurred in 3 patients (43%). One patient (14%) developed anastomotic leakage, which was resolved with conservative measures. There were no deaths at 30 days after the surgery. Furthermore, there was no in-hospital mortality during the 6-month follow-up, and there were no treatment-related deaths.

Response

All the 7 patients are included in the response analyses (Table 5). Complete pathological response was seen in 3 patients and partial response in 4 patients with an overall response rate of 86%. One patient had progressive disease. Complete tumor resection with microscopically clear

Table 3 Common toxicities (NCI-CTC version 3)

	Level 1 ($n = 3$)			Level 2 ($n = 4$)			Overall ($n = 7$)		
	Any	G3	G4	Any	G3	G4	Any	G3	G4
Leukopenia	3	2	0	4	3	0	7	5	0
Neutropenia	3	1	0	4	3	0	7	4	0
Anemia	3	0	0	4	1	0	7	1	0
Thrombocytopenia	1	0	0	2	1	1[a]	3	1	1
Febrile neutropenia	0	0	0	1	1[a]	0	1	1	0
Creatinine	1	0	0	1	0	0	2	0	0
Anorexia	3	1	0	4	0	0	7	1	0
Nausea	3	0	0	4	0	0	7	0	0
Vomiting	0	0	0	0	0	0	0	0	0
Esophagitis	3	2	0	4	2	0	7	4	0
Pain/esophagus	3	2	0	3	1	1[a]	6	3	1
Diarrhea	1	0	0	0	0	0	1	0	0
Fatigue	3	0	0	2	1	0	5	1	0

[a] Three patients in dose level 2 experienced dose-limiting toxicity

Table 4 Post-operative complications (within 30 days of surgery) in patients undergoing resection

Complications	Thoracic surgery ($n = 7$)
Postoperative infection	2
Anastomotic leakage	1
Anastomotic stricture	1
Recurrent nerve paralysis	2
Recurrent nerve paralysis	3
Pneumonia	1
Re-operation	0

Anastomotic leakage: The condition resolved with conservative treatment

There were no deaths as a result of postoperative complications during the study

margins (R0 resection) was achieved in 6 of the 7 patients (86%).

Discussion

Gebski et al. [10] conducted a recent meta-analysis of neoadjuvant chemoradiotherapy for resectable esophageal cancer; they reported that a significant survival benefit was evident for preoperative chemoradiotherapy and suggested that evidence-based treatment be used for esophageal cancer. Tepper et al. [4] used chemotherapeutic agents—100 mg/m^2 cisplatin and 1,000 mg/m^2/for 4 days 5-fluorouracil with radiotherapy (50.4 Gy total dose)—and reported favorable results for neoadjuvant chemoradiation followed by surgery. In particular, the 5-year survival was 16% (95% CI, 5–33%) in the surgery-alone group versus 36% (95% CI, 21–57%) in the neoadjuvant chemoradiation group. In addition, the use of neoadjuvant chemoradiation did not appear to increase operative mortality, and the preoperative therapy was associated with manageable toxicity.

Because the achievement of pCR in the primary tumor after preoperative CRT is a positive long-term outcome [11, 12], regimens of new drug combinations containing docetaxel, paclitaxel, and/or other molecular target agents have been tested to achieve higher rates of pCR and improve survival benefit of preoperative chemoradiation for resectable esophageal cancer [13].

In this study, to improve the therapeutic effect of standard cisplatin plus 5-FU concurrent chemoradiotherapy, we focused on docetaxel incorporation into the therapy, which has been extensively used with radiation for the treatment of patients with non-small lung cancer and head and neck cancer [14, 15]. Although not powered to demonstrate improvements in cancer outcomes, this study shows that the addition of docetaxel to the current preoperative chemotherapy plans combining cisplatin and 5-FU provides a high response rate. Pathological CR rate of 43% compares favorably with other chemoradiotherapy studies using cisplatin and 5-FU [3, 4].

Esophagitis was the most frequent toxicity in this study. Hospitalization was required in 2 of 3 level 1 patients and 2 of 4 level 2 patients who experienced grade 3 esophagitis.

Spigel et al. [16] used a triplet regimen consisting of oxaliplatin, docetaxel, and capecitabine in combination with radiation therapy. Grade 3 esophagitis occurred in 20% of all cases. Day et al. [17] conducted a phase I trial of cisplatin and docetaxel concurrent with 50 Gy radiotherapy. In this trial, grade 3 radiation esophagitis was found to be the most common acute toxicity (37.5%). In our study, regional lymph nodes were included in the clinical target volume (CTV) as a prophylactic irradiation field for patients with no clinical evidence of lymph nodes metastases, which was larger than the irradiation field used in previous trials. This increased irradiation field could be attributed to the occurrence of esophagitis, which was the most commonly encountered adverse event.

In radiotherapy, there is no clear consensus about the CTV, especially regarding inclusion of regional lymph nodes in the CTV when there is no clinical evidence of lymph node metastases of esophageal cancer.

A recent publication has suggested that the 5-year survival improves with the number of lymph nodes removed and that this effect is observed for the removal of over 40

Table 5 Histopathological response and clinical course

Patient no.	Dose level	Stage	Clinical response		Pathological response		Status (month)
			Primary	LN	Primary	LN	
1	1	IIIB (T3N2)	PR	PR	CR	CR	ADF (18)
2	1	IIIA (T3N1)	PR	PR	PR	CR	AWD (17)
3	1	IIIB (T3N2)	PR	PR	CR	PR	ADF (17)
4	2	IIIA (T3N1)	CR	CR	CR	CR	ADF (14)
5	2	IIIA (T3N1)	CR	CR	CR	PR	ADF (11)
6	2	IIIA (T3N1)	PD	NC	PD	NC	AWD (10)
7	2	IIIA (T3N1)	CR	PR	CR	CR	ADF (6)

AWD alive with disease, *ADF* alive and disease free, *CR* complete response, *PR* partial response, *NC* no change, *PD* progressive disease

nodes [18]. Another study showed that the total number of surgically resected lymph nodes is independently associated with the overall and disease-free survival in esophageal cancer [19, 20]. We believe that neoadjuvant chemoradiotherapy aims to resect not only primary tumors but also lymph nodes and surrounding tissues with microscopically clear margins that may be potentially involved, and neoadjuvant chemoradiotherapy is associated with improved lymphadenectomy. Therefore, regional lymph nodes were included as a prophylactic irradiation field in the CTV.

In this trial, the 3 agents—docetaxel, cisplatin, and 5-fluorouracil—were found to be well tolerated when combined with radiation in patients with potentially resectable esophageal cancer. The antitumor efficacy, as demonstrated by the high pathological response rate, was also extremely encouraging. Moreover, it is noteworthy that there was no indication of increased operative mortality and morbidity in our trial.

A phase II study in esophageal cancer using the doses found in this study (25 mg/m^2 docetaxel on days 1, 15, 29, and 43; 70 mg/m^2 cisplatin on days 1 and 29; 700 mg/m^2/day 5-FU on days 1–4 and 29–32; and 40 Gy radiotherapy) is currently underway at our institution.

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