

Phase I Dose-Escalation Study of Docetaxel, Cisplatin, and 5-Fluorouracil Combination Chemotherapy in Patients With Advanced Esophageal Carcinoma

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A dose-escalation study of docetaxel (DOC), cisplatin (CDDP), and 5-fluorouracil (5-FU; DCF combination regimen) was performed to determine the maximum-tolerated dose (MTD), recommended dose (RD) and dose-limiting toxicities (DLT) in advanced esophageal carcinoma. Eighteen patients with esophageal carcinoma were enrolled and received DCF combination therapy at different dose levels. DLTs included febrile neutropenia and oral mucositis. DLT occurred in 2 out of 6 patients at level 2 and 3. The study proceeded to level 4, according to the protocol. The level 4 dose was defined as the MTD and the level 3 dose was defined as the RD. The RD for DCF combination chemotherapy for advanced esophageal carcinoma in the present study was 70 mg/m² DOC plus 70 mg/m² CDDP on day 1 plus 700 mg/m² 5-FU on days 1–5 at 4-week intervals. This regimen was tolerable and highly active. A phase II study has been started.

Key words: Docetaxel – Cisplatin – Fluorouracil – Esophagus – Phase I

Locally advanced esophageal carcinoma is often refractory to current therapeutic approaches, and its prognosis is grim.^{1,2} Patients with unresectable or inoperable disease are usually treated with chemotherapy or chemoradiotherapy.^{3,4} Although

various chemotherapy regimens are available, esophageal cancer carries a very poor prognosis, with a survival time of less than 8.1 months with current chemotherapies used singly or in combination with 5-fluorouracil (5-FU), vindesine, mitomy-

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cin, docetaxel (DOC), paclitaxel, cisplatin (CDDP), irinotecan, vinorelbine, or capecitabine.⁵ 5-FU and CDDP combination therapy (PF) is regarded as standard,⁶ for which the median survival time is reported to be 9.2 months for responders and 5.3 months for nonresponders.⁷

In recent years, a new combined chemotherapeutic regimen consisting of DOC, CDDP, and 5-FU (DCF) has received much attention for the treatment of esophageal cancer.⁸ The DCF regimen exploits the strong clinical effects of each component. However, there are few reports describing the use of a combination of DOC, CDDP, and 5-FU (DCF) for esophageal carcinoma.⁹ Therefore, we conducted a phase I clinical trial of a DCF regimen in patients with advanced esophageal carcinoma. Our aim was to determine the recommended dose (RD), maximum tolerated dose (MTD), and dose-limiting toxicity (DLT) of DCF combination chemotherapy for patients with esophageal carcinoma. Secondary objectives were to assess treatment-related toxicity and efficacy.

Patients and Methods

This open-label, prospective, phase I study was conducted at Dokkyo Medical University Hospital, Tochigi, Japan. The institutional review board of Dokkyo Medical University approved this study, and all patients gave written informed consent before enrollment.

Patients aged 20 to 75 years with a measurable target lesion pathologically confirmed as squamous cell carcinoma (SCC) or adenocarcinoma, which was surgically unresectable or recurrent, were eligible. They also had to have an ECOG performance status of 0, 1, or 2, a life expectancy of >12 weeks, and adequate liver, bone marrow, renal, and cardiovascular function (serum bilirubin ≤ 1.5 mg/dL; neutrophil count, $2000/\text{mm}^3$; serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 1.5 times the upper limit of normal; alkaline phosphatase (ALP) 2.5 times the upper limit of normal, platelet count $>10 \times 10^4/\text{mm}^3$; hemoglobin 9.5 g/dL; and creatinine 1.2 mg/dL. The last chemotherapeutic treatment had to be at least 4 weeks before trial enrollment. Patients were excluded for the following reasons: known sensitivity to DOC, CDDP, 5-FU, or polysorbate 80; presence of other severe diseases, including malignant hypertension, severe heart failure, liver failure, and liver cirrhosis; inadequately controlled diabetes mellitus or bleeding disorders; current infectious disease

with fever; presence of motor paralysis, peripheral neuropathy, or severe edema; pleural effusion or cardiac effusion needing treatment; presence of multiple primary cancers; pregnancy, or breast feeding; presence of interstitial pneumonia on chest X-rays or CT, or pulmonary fibrosis; known psychosis or neurologic manifestations, or patients considered unlikely to fully cooperate in the study; and patients deemed inappropriate for the study by the investigator for any other reason. All the participants had to sign an informed consent, which was approved by the Medical Ethics Committee of Dokkyo Medical University.

The primary objectives of this phase I study were to determine the MTD and toxicity of escalating doses of DOC, CDDP, and 5-FU in patients with advanced esophageal carcinoma. The secondary objective was to obtain preliminary data regarding the clinical response. At least 3 patients were entered at each dose level. All 3 patients at a given dose level completed the first cycle of treatment without DLT before further patients were enrolled in the next dose level. In the absence of DLT, the next dose level was explored. Doses were escalated in sequential groups of three patients until the MTD was established or the highest intended dose level was reached. If any of the 3 patients experienced DLT, an additional 3 patients were treated at the same dose level. If 3 or more of the 6 patients at a given dose level experienced DLT, the dose level was defined as the MTD. The level one step below was set as the RD for further evaluation in a phase II study.

The DCF regimen consisted of an adequate dose of DOC, which was infused over 1 hour on day 1, followed by an adequate dose of CDDP, which was infused over 1 hour on day 1, and an adequate dose of 5-FU, which was administered by continuous infusion on days 1 through 5. Supportive therapy for treatment and prophylaxis for expected side effects was performed. All patients were premedicated with aprepitant, 150 mg, intravenously and palonosetron hydrochloride, 0.75 mg, intravenously. Hypersensitivity reactions were treated with prophylactic use of dexamethasone, 10 mg, intravenously, which was infused 1 hour before the administration of DOC. Diuretics were added at the discretion of the treating physician. Appropriate hydration was given before and after the CDDP infusion. Prophylactic antibiotics were not given.

Tumor size and new lesions were assessed by CT, endoscopy, and FDG-PET after 2 courses. Tumor stage was classified according to the seventh edition

Table 1 Dose escalation schema

Dose level	Docetaxel, mg/m ²	Cisplatin, mg/m ²	5FU, mg/m ²
1	60	60	600
2	60	70	700
3	70	70	700
4	70	80	800

of the tumor-node-metastasis (TNM) classification system developed by the International Union against Cancer (UICC). Standard clinical measurements and radiologic examination were used to assess tumor response according to response evaluation criteria in solid tumors (RECIST version 1.1).

Toxicity was evaluated and scored according to the Common Terminology Criteria for Adverse Events (NCI CTC AE) version 4.0. The dose-escalation plan is shown in Table 1. The patient's full medical history and biochemistry profiles were assessed before starting each treatment cycle. Complete blood count and biochemistry were determined every week in all treatment cycles. If grade 4 neutropenia occurred, the complete blood count was repeated daily during the treatment cycle to determine its duration.

DLT was defined as grade 3/4 febrile neutropenia, grade 4 neutropenia or grade 4 leukopenia lasting >5 days, grade 4 thrombocytopenia, any grade 3 to 4 nonhematologic toxicity with the exceptions of nausea, vomiting, diarrhea, general fatigue, and alopecia.

A minimum of 3 patients were enrolled at each dose level. If no excessive toxicity was observed after the first 2 treatment cycles, the dose was escalated in successive cohorts. If a DLT was observed in 1 or 2 patients at that dose level, further patients were enrolled to receive that dose. The recommended dose (RD) was defined as the dose level below the maximum tolerated dose (MTD) in which DLTs were observed in ≥ 3 patients from a cohort of 3 to 6 patients.

Results

Patient characteristics

Between February 2010 and March 2012, 18 patients were entered into the study. The cohort included 16 men and 2 women, aged 45 to 72 years (mean age, 63.6 years). Their demographic and clinical characteristics are summarized in Table 2. All patients had an ECOG performance status of 0 to 1.

Table 2 Characteristics of patients

Characteristic	
Total	18
Age, years	
Median	63.6
Range	45–72
Sex	
Males	16
Females	2
Performance status	
0–1	18
Histology	
Squamous cell carcinoma	16
Adenocarcinoma (por)	2
Site of primary disease	
Ce	1
Ut	0
Mt	11
Lt	6
TNM	
T	
T3	16
T4	2
N	
N0	0
N1	3
N2	2
N3	13
M	
M0	12
M1	6
Stage	
IIIA	2
IIIB	2
IIIC	8
IV	6
Prior therapy	
Surgery	4
Chemoradiation	8
First treatment	6

All 18 patients were fully evaluated for toxicity. Table 3 summarizes the incidence of toxic events that occurred at each dose level. Only 2 patients developed grade 3 or grade 4 leukopenia and neutropenia at each level, but myelosuppression lasted not longer than 5 days when treated by granulocyte-colony stimulating factor (G-CSF). Grade 3 febrile neutropenia occurred in 2 patients at levels 2 and 3. Grade 3 hyponatremia occurred in 1 patient at level 1 and in 3 patients at level 3.

Mucositis oral occurred in 1 patient at level 2 and 3, which was considered a DLT. Therefore, 3 patients were added to dose level 2 and 3. The additional patients experienced no toxicity.

At level 4, two patients developed grade 3 leukopenia, 1 patient developed grade 3 neutrope-

Table 3 Hematologic and nonhematologic toxicity

	CTCAE ver.4 common toxicity criteria											
	Dose level											
	1 (n = 3)			2 (n = 6)			3 (n = 6)			4 (n = 3)		
	1-2	3	4	1-2	3	4	1-2	3	4	1-2	3	4
Anemia	0	0	0	3	0	0	3	0	0	1	0	0
Leukopenia	1	2	0	0	3	1	1	2	1	1	2	0
Neutropenia	1	1	1	0	0	3	0	4	1	0	1	2
Thrombocytopenia	0	0	0	3	1	1	3	0	0	2	0	0
Febrile neutropenia	0	0	0	0	2	0	0	2	0	0	0	0
Nausea/loss of appetite	1	2	0	0	4	0	0	3	1	0	0	0
Diarrhea	0	2	0	0	2	0	0	3	0	0	0	0
Mucositis oral	0	0	0	0	1	0	1	1	0	0	0	0
Acute kidney injury	0	0	0	0	0	0	1	1	0	0	0	0
Colitis	1	0	0	0	0	0	1	0	0	0	0	0
Hyponatremia	0	1	0	0	3	0	0	0	0	2	0	0
Colonic hemorrhage	0	0	0	0	0	0	1	0	0	0	0	0
Stomach pain	0	0	0	0	0	0	1	0	0	0	0	0

nia, and 2 patients developed grade 4 neutropenia, which did not meet the criteria of DLT. The study could be extended to level 4 according to the protocol. The level 4 dose defined the MTD, and the level 3 dose was adopted as the RD.

Although response to therapy was not the endpoint of this study, patients who had completed at least 2 cycles of chemotherapy were evaluated for radiographic response. At dose level 1, 2 patients had partial response (PR), and 1 patient had stable disease (SD). At dose level 2, 3 patients had PR, 1 patient had progressive disease (PD), with lung metastasis, and 2 patients had SD. At dose level 3, five patients had PR. One patient had SD. At dose level 4, two patients had PD, consisting of uncontrolled ascites with carcinomatous peritonitis and lymph node metastasis. One patient had SD. The treatment response rate was 11/18 (61.1%).

Discussion

PF therapy is standard chemotherapy in esophageal carcinoma, but in a recent report, patients with SCC of the head and neck who received induction chemotherapy using DCF achieved significantly longer survival than patients who received PF induction chemotherapy.^{10,11} More trials with DCF therapy in esophagus carcinoma have been reported.^{8,9,12,13} DOC is a semisynthetic taxoid derived from the European yew tree, *Taxus baccata*. The taxanes enhance polymerization of tubulin into stable microtubule formation and inhibit their

tubulin depolymerization by blocking the cell cycle in metaphase, anaphase, and interphase.¹⁴ This inhibition may improve the efficacy of drugs such as CDDP, which are active in all phases of the cell cycle via direct DNA damage. Furthermore, the taxanes increase programmed cell death, and DOC appears to be more potent than paclitaxel in inhibiting angiogenesis.¹⁵ Response rates of 20 to 30% were obtained in phase II studies of DOC (70–100 mg/m²) for advanced and recurrent esophageal SCC.^{16,17} CDDP and 5-FU combination therapy is a standard protocol for patients with unresectable esophageal carcinoma and advanced esophageal carcinoma after surgery.^{7,18}

This study was designed to evaluate the safety and determine the RD for DOC, CDDP, and 5-FU used in combination (DCF) for advanced esophageal carcinoma. Based on the dose level tested, the RD for DOC, CDDP, and 5-FU was 70 mg/m² (day 1), 70 mg/m² (day 1), and 700 mg/m² (day 1–5), respectively, at 4-week intervals. In this study, we set up the highest intended dose, level 4 as DOC 70 mg/m², CDDP 80 mg/m², and 5-FU 800 mg/m². This quantity is the recommended dose for single-agent DOC and PF therapy for esophageal carcinoma in Japan.^{16,18} This highest dose level 4 for DCF combination therapy is appropriate.

The primary hematologic toxicity was myelosuppression. At all dose levels, grade 3/4 leukocytopenia and neutropenia was 11/18 (61.1%) and 12/18 (66.7%), respectively. Four patients developed febrile neutropenia (FN), but FN was managed by adequate supportive care, antibiotics, and G-CSFs.

There were no dropouts. Fortunately, FN did not develop at the level 4 dose, but 2 patients had myelosuppression lasting no longer than 5 days. Moreover, 2 patients had FN at level 2 and 3 doses. The RD was set at the level 3 dose, which is safe and ethically appropriate. Yamasaki *et al* reported that the major toxicity of DCF, repeated every 3 weeks at a dose of DOC 70 mg/m², CDDP 70 mg/m², and 5-FU 700 mg/m², was myelosuppression and that the frequencies of grade 3/4 leukopenia and neutropenia in a phase II study were 72.5% and 90%, respectively.⁹ Ando *et al* reported toxicity with PF therapy when repeated every 3 weeks after surgery within 2 months. The dose levels were CDDP 70 mg/m² and 5-FU 700 mg/m². The side effects were leukocytopenia and neutropenia in 4% and 18%, respectively.¹⁹ We compared side effects between the present study and the previous report of PF. In our study, some patients had the worse side effect, myelosuppression, but it was tolerated by the patients and there was no chemotherapy-related death.

In summary, the RD for DCF combination chemotherapy for advanced esophageal carcinoma in the present study was 70 mg/m² DOC plus 70 mg/m² CDDP on day 1 plus 700 mg/m² 5-FU on days 1 through 5 at 4-week intervals. This regimen was associated with relatively minor side effects and was administered safely at the RD. A phase II study is now under way to confirm these findings in a larger cohort.

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The authors declare that they have no conflict of interest.

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