Phase II Study of Combined Chemotherapy with Docetaxel, CDDP and 5-FU for Highly Advanced Esophageal Cancer

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Abstract. *Advanced esophageal cancer with widespread metastasis to lymph nodes or other organs is difficult to treat and has an extremely poor prognosis. A new combined chemotherapy of docetaxel with cisplatin (CDDP) and 5-fluorouracil (5-FU) (DPF therapy) was performed and its efficacy and safety were examined. Among those hospitalized between May 2003 and October 2009, 30 patients with stage III or stage IV unresectable, untreated advanced esophageal squamous cell carcinoma which had invaded other organs were enrolled in this study. The regimen of DPF therapy was as follows: a set of intravenous drips of 60 mg/m^2 of docetaxel (day 1), 60 mg/m^2 of CDDP (day 1) and 800 mg/m^2 of 5-FU (days 1-5) was administered twice at an interval of 3 to 4 weeks. Antitumor effects, adverse reactions and treatment outcomes were then examined. The patients included 26 men and 4 women aged 40 to 73 years (average age, 58.1 years), and the performance status (PS) was 1 in 18 cases and 2 in 12 cases. The main location of the esophageal cancer was the upper/middle/lower thoracic esophagus in 7/14/9 cases, respectively. Clinical stage was III in 5 cases and IV in 25. The effective rate of DPF therapy was 83.3% for the primary lesion (complete response, CR: 4 cases, partial response, PR: 21 cases), 72.4% for lymph node metastasis (CR: 3 cases, PR: 18 cases) and 72.0% for distant organ metastasis (CR: 3 cases, PR: 15 cases). The observed adverse reactions of grade 2 or higher of National Cancer Institute-Common Toxicity Criteria (NCI-CTC) included anemia (16.7%), leukopenia (73.3%), liver dysfunction (20.0%), anorexia (16.7%), stomatitis (33.3%), esophagitis (16.7%), alopecia (16.7%) and diarrhea (26.7%). The therapy completion rate was 96.7% and the therapy-related death rate was 3.3%. Treatments given after the completion of the DPF therapy were surgery in 6 cases, chemotherapy such as additional DPF in 12, chemoradiation in 4, esophageal stent placement in 1, and no treatment in 7. The patients' median survival time was 271 days, the 1-year survival rate was 41.9% and the 5-year survival rate was 13.3%. DPF therapy can be used as a standard chemotherapy for advanced esophageal cancer in view of its strong antitumor effect and relatively safe outcome.*

Esophageal cancer is a highly malignant gastrointestinal cancer that readily progresses to widespread metastasis to lymph nodes and easily infiltrates the trachea and great vessels. Better treatment outcomes of esophageal cancer have been obtained by improved diagnostic technologies such as dye-spraying endoscopy, surgical skills such as three-field lymphadenectomy, and perioperative management. Because esophageal cancer is generally more sensitive to anticancer drugs than other gastrointestinal carcinomas, various multidisciplinary treatments have been attempted and chemoradiation has long been established as a standard treatment for esophageal cancer because it is highly effective and can be performed relatively safely. Moreover, treatment outcomes comparable to those of surgery have been reported (1). However, as in the case of surgery, chemoradiation mainly provides localized treatment, and treatment outcomes of cases for which radical surgery is impossible, such as cancer infiltrating into other organs, distant lymph node metastasis and metastasis to other organs, are still poor. In these cases, systemic chemotherapy is usually adopted, and many regimens have been reported using cisplatin (CDDP) as a key drug. At present, the combined use of 5-fluorouracil (5-FU) and CDDP (FP therapy) is an internationally adopted standard treatment for esophageal cancer (2-4) since a synergistic effect of this combination was proved in basic tests (5). Favorable effective rates of 50% for locally advanced esophageal cancer and 35% for distant metastasis have been shown (6), and better results than with CDDP alone have been reported (7). However, FP therapy patients

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seldom achieve a complete response (CR) and their mean survival time (MST) is 6 to 10 months, which is unsatisfactorily short; moreover, the outcome for stage IV disease or recurrent cancer is particularly poor. Several other treatments have been attempted such as leucovorin (LV) or folic acid (FA) in combination with FP therapy (8, 9); nedaplatin, a derivative of CDDP, in combination with 5-FU therapy (10); nedaplatin and adriamycin in combination with 5-FU therapy (11); and a combination of oxaliplatin (L-OHP), 5-FU and LV (12); but none have provided better effects than FP therapy. Furthermore, no effective treatment has been established for patients who are nonresponsive to FP therapy.

Taxane anticancer drugs including docetaxel are now considered to be potentially effective against esophageal cancer since, in combination with FP, favorable results for metastatic gastric cancer and unresectable advanced head and neck cancer have been reported (13-15). Docetaxel blocks cell division by accelerating the polymerization of and inhibiting the depolymerization of microtubules; this mechanism is different from those of other anticancer drugs and therefore docetaxel exhibits less cross resistance to conventional chemotherapies such as 5-FU and CDDP (16). In addition, docetaxel action is considered to be independent of p53, an advantage for esophageal cancer in which *p53* gene mutation is very common. Docetaxel also had a stronger antitumor effect than paclitaxel, another taxane anticancer drug, on esophageal cancer cell lines (17). Therefore, a phase II study of combined chemotherapy with docetaxel, 5-FU and CDDP (DFP therapy), as a new treatment for highly advanced esophageal cancer, was performed and its efficacy and safety were examined. Although there are several reports on docetaxel-based combined chemotherapy for esophageal cancer, phase II data of DPF therapy for esophageal cancer are available only for adenocarcinoma. Therefore, this is the first report on DPF therapy for esophageal squamous cell carcinoma.

Patients and Methods

Patients. Among those hospitalized in our Department between May 2003 and October 2009 with stage III or IV unresectable, previously untreated advanced esophageal cancer which had invaded other organs, 30 patients who satisfied the following conditions were enrolled in this study: disease pathologically diagnosed as esophageal cancer; having an evaluable lesion(s); aged between 20 and 80 years; assessed as Grade 0-2 performance status (PS) (Eastern Cooperative Oncology Group scale); without serious complications; functioning vital organs: leukocytes >4,000/mm^3, neutrophils >2,000/mm^3, Hb >9.0 g/dl, platelets >10×10^4/mm^3, total bilirubin: within the normal range, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) < normal value×1.5, alkaline phosphatase (ALP) < normal value×2.5, serum creatinine < normal value×1.5 and patient's written informed consent provided.

Approval of study. The study was performed after obtaining approval from the Medical Ethics Committee of Tokyo Medical University.

Combined chemotherapy with docetaxel, CDDP and 5-FU. Intravenous drips of 60 mg/m^2 of docetaxel (day 1), 60 mg/m^2 of CDDP (day 1) and 800 mg/m^2 of 5-FU (days 1-5) constituted one cycle and this cycle was administered twice at an interval of 3 to 4 weeks. Administration was stopped under the following conditions: serious adverse reactions manifested; clear progression of the disease observed or a doctor otherwise judged that medication should be stopped. After completion of the second administration, chemotherapeutic efficacy was evaluated by diagnostic imaging such as esophagography, esophagoscopy, computed tomography (CT) and magnetic resonance imaging (MRI).

Evaluation of chemotherapy. Clinicopathological factors were analyzed based on the TNM (International Union Against Cancers, UICC) classification method (18). The radiological effects were evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST) and Japanese guidelines for clinical and pathological studies on esophageal carcinoma (19). Toxicity grading was based on the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 3.0 (20). Clinical efficacy (effective rate, CR or PR), evaluated about 3-4 weeks after completion of the treatment, adverse reactions and prognosis were examined. Actual survival rates were calculated by the Kaplan-Meier method.

Results

Patient characteristics. As shown in Table I, the majority of the patients were men, the mean age was 58.1±5.2 and the PS was 1 or 2. The histological type was squamous cell carcinoma in all cases. Most of the cases were T3 or T4, N1 and M1 and the clinical stage was stage III or stage IV.

Clinical efficacy (effective rate). The clinical efficacy is shown in Table II. A complete response (CR) was shown in 4 of the primary lesions, PR in 21, stable disease (SD) in 2, and 3 patients were not assessable (NA). Lymph node metastases showed CR in 3 cases, PR in 18 and SD in 5 with 3 NA. Distant organ metastases showed CR in 3 cases, PR in 15, SD in 6 and 1 NA. The effective rates (CR plus PR) for the primary lesions, metastatic lymph nodes and distant organ metastases were 83.3%, 72.4% and 72%, respectively, and progressive disease (PD) was not observed at all.

Adverse reactions. Toxicities of Grade 2 or higher included leukopenia in 22 cases (73.3%), anemia in 5 (16.7%) and thrombocytopenia in 2 (6.7%) (Table III). Stomatitis occurred in 10 cases (33.3%), esophagitis in 5 (16.7%), diarrhea in 8 (26.7%), liver dysfunction in 6 (20.0%) and anorexia in 5 (16.7%) while nausea or vomiting in 2 (6.7%) and alopecia in 5 (16.7%) did not exceed Grade 2. The therapy completion rate was 96.7% and the therapy-related death rate was 3.3%.

Table I. *Patient characteristics*.

Number of patients	30
Gender: male/female	26/4
Age (years, mean±SD)	58.1±5.2 (40~73)
Performance status: 1/2	18/12
Tumor location: Upper/middle/lower	7/14/9
Clinical T factor: T1/T2/T3/T4	1/1/12/16
Clinical N factor: N0/N1	1/29
Clinical M factor: M0/M1	5/25
Clinical stage: III/IV	5/25

Table II. *Radiological evaluation of primary lesion, metastatic lymph node and distant organ response*.

	Primary lesion (n=30)	Lymph node (n=29)	Distant organ (n=25)
Radiological evaluation			
Complete response (CR)	4 (13.3%)	3 (10.3%)	3 (12.0%)
Partial response (PR)	21 (70.0%)	18 (62.1%)	15 (60.0%)
Stable disease (SD)	2 (6.7%)	5 (17.2%)	6 (24.0%)
Progressive disease (PD)	0 (0%)	0 (0%)	0 (0.0%)
Not assessable (NA)	3 (10%)	3 (10.3%)	1 (4.0%)
Effective rate (CR+PR/ total number of cases)	83.3%	72.4%	72.0%

Table III. *Adverse reactions (Grade 2 or higher)*.

	Grade 2	Grade 3/4	Total
Leukopenia	12 (40.0%)	10 (33.3%)	22 (73.3%)
Anemia	4 (13.4%)	1 (3.3%)	5 (16.7%)
Thrombocytopenia	1 (3.3%)	1 (3.3%)	2 (6.7%)
Anorexia	4 (13.4%)	1 (3.3%)	5 (16.7%)
Nausea, vomiting	2 (6.7%)	-	2 (6.7%)
Stomatitis	6 (20.0%)	4 (13.4%)	10 (33.3%)
Esophagitis	2 (6.7%)	3 (10.0%)	5 (16.7%)
Diarrhea	6 (20.0%)	2 (6.7%)	8 (26.7%)
Liver dysfunction	4 (13.4%)	2 (6.7%)	6 (20.0%)
Alopecia	5 (16.7%)	-	5 (16.7%)

Treatment after DPF therapy. Treatments given after the completion of DPF therapy were surgery in 6 cases (esophagectomy through right thoracotomy: 5 cases; esophagectomy without thoracotomy: 1 case), chemotherapy in 12 (DPF therapy: 9 cases 1-6 cycles; nedaplatin/docetaxel: 3 cases), chemoradiation in 4 (DPF therapy + radiation: 3 cases; nedaplatin/docetaxel + radiation: 1 case), esophageal stent placement in 1 case and no treatment in 7 cases.

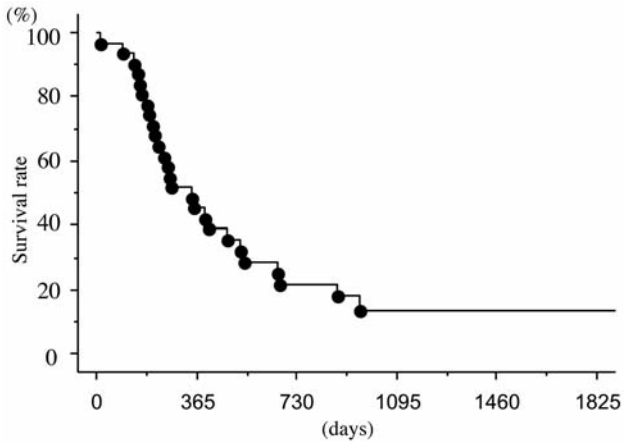

Figure 1. *Actual survival curve of DPF therapy. The median survival time was 271 days, the 1-year survival rate was 41.9% and the 5-year survival rate was 13.3%.*

Prognosis. The median survival time was 271 days, the 1-year survival rate was 41.9% and the 5-year survival rate was 13.3% (Figure 1). The causes of death were the original disease in 23 cases and death related to the therapy in one.

Discussion

Docetaxel is produced by partial chemical modification of the precursor 10-deacetyl baccatin III, extracted from the leaves of the European yew tree. Response rates of 20 to 30% have been clinically obtained in phase II studies using docetaxel (70 to 100 mg/m^2) for advanced and recurrent esophageal squamous cell carcinoma (21, 22). Agents that have been combined with docetaxel for esophageal cancer include irinotecan (23), vinorelbine (24), capecitabine (25) and irinotecan/CDDP (26), and all these combinations have been reported to be effective.

Most esophageal carcinomas in Japan are, as in the case of head and neck cancer, squamous cancer. Higher CR and overall effective rates than those obtained by FP therapy for advanced head and neck squamous cancer have recently been reported using DPF therapy (14, 15) and DPF plus high-dose LV therapy (27). Randomized controlled trials of FP therapy and DPF therapy as induction chemotherapy for radiation showed that DPF therapy was significantly better for the extension of progression-free survival (PFS) and overall survival (OS) (28), while in advanced esophageal cancer, good overall response rate, PFS and OS were shown (13). DPF therapy has been reported to be highly effective for resectable esophageal cancer (29) and is considered to be

effective for gastric cancer and head and neck cancer. However, there have been no reports of DPF therapy for unresectable esophageal cancer.

In the present study, the level of docetaxel, CDDP and 5-FU administration was based on various trials. In Japan, the dose normally adopted in FP therapy for esophageal cancer is 80 mg/m^2 of CDDP (day 1) and 800 mg/m^2 of 5-FU (days 1-5) (30), with CDDP dose reduction for cases with liver dysfunction. Adverse reactions were observed in 37% of cases administered docetaxel at 70 mg/m^2 in phase II trials in Japan for esophageal cancer, and when the dose was reduced to 60 mg/m^2, its effectiveness was still confirmed (21). Docetaxel at 60 mg/m^2 has been reported to be effective not only for head and neck cancer, including squamous cancer, but also non-small cell lung cancer, gastric cancer and breast cancer (31-36). Posner *et al*. (14) performed DPF therapy on head and neck cancer with a dose of 75 mg/m^2 of docetaxel (day 1), 75 or 100 mg/m^2 of CDDP (day 1) and 1,000 mg/m^2 of 5-FU (days 1-4) and obtained favorable results, with an effective rate of 93% and a CR of 40%, but adverse reactions such as neutropenia (95%) and stomatitis (30%) were observed. For head and neck cancer and gastric cancer, the dose for DPF therapy employed in phase III randomized controlled trials with FP therapy was 75 mg/m^2 of docetaxel (day 1), 75 mg/m^2 of CDDP and 1,000 mg/m^2 of 5-FU (days 1-5) (13, 28). In Japan, Tsukuda *et al*. (37) in a phase I trial for head and neck cancer reported that the maximum tolerated dose was reached at 70 mg/m^2 of docetaxel (day 1), 70 mg/m^2 of CDDP (day 4) and 750 mg/m^2 of 5-FU (days 1-5).

Because the esophageal cancer examined in the present study was very advanced, the dose of CDDP was reduced by 25% to 60 mg/m^2 (day 1) and the dose of 5-FU was set at 800 mg/m^2 (days 1-5) without reduction compared to the dose of conventional FP therapy, taking renal toxicity and gastrointestinal toxicity into consideration. Moreover, 60 mg/m^2 of docetaxel (day 1), the dose evaluated to be sufficiently effective, was added, taking bone marrow toxicity into consideration. The adverse reactions were within the permissible range, with 33.3% Grade 3 or higher leukopenia, 13.4% stomatitis and 10.0% esophagitis: the therapy completion rate was 96.7%, and one therapy-related death occurred. The overall effective response rate ranged from 83.3% for the primary lesions to 72.0% for distant organ metastases. The outcome was also favorable, with a median survival time of 271 days and a 5-year survival rate of 13.3%.

In summary, the combined chemotherapy using docetaxel, CDDP and 5-FU for advanced esophageal cancer involved relatively minor adverse reactions, was administered safely and was also highly effective for advanced esophageal cancer. Further study with more case examples through multicenter studies as well as randomized controlled trials in combination with current standard treatments, such as FP therapy and chemoradiation, will be needed to validate the effectiveness of DPF therapy.

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Conflict of Interest

The Authors declare that they have no conflict of interest with regard to any part of this study.

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