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Original

Efficacy and Safety of Preoperative DCF Therapy for Resectable Squamous Cell Carcinoma of the Esophagus

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Introduction: DCF therapy [docetaxel (DOC) + cisplatin (CDDP) + 5-fluorouracil (5FU)(FP therapy)] is reported to be effective for squamous cell carcinoma (SCC) of the esophagus, but conclusive data are unavailable and this regimen is not clearly mentioned in the Guideline for Diagnosis of Esophageal Carcinoma. We compared preoperative DCF therapy with preoperative FP therapy in this study.

Materials and Methods: Twenty-seven patients with cStage 2/3 thoracic esophageal carcinoma (excluding T4 disease and R2 resection) underwent preoperative DCF therapy at our hospital from 2010 to January 2015. They were retrospectively compared with 22 patients receiving preoperative FP therapy from 2000 to 2009 to assess efficacy and safety.

Results: DCF therapy achieved clinical and histological response rates of 62.9 % and 70.4 %, respectively. Grade 3/4 neutropenia occurred in 22 patients. Postoperative complications included suture leakage in 2 patients and intestinal obstruction, pneumonia, arrhythmia, and liver dysfunction in 1 patient each. The response rates to FP therapy were 63.6 % and 68.2 %, respectively. Grade 3 neutropenia occurred in 5 patients. Postoperative complications were suture leakage in 1 patient and respiratory complications in 6 patients.

Conclusion: DCF therapy may be an acceptable option for esophageal cancer, but further investigation is required.

Key Words: esophageal carcinoma, neoadjuvant, chemotherapy, DCF, FP

Introduction

Multidisciplinary therapy is performed for esophageal carcinoma, including various combinations of surgery, chemotherapy, and radiation therapy[1)2)]. At present, FP therapy [cisplatin (CDDP) + 5-fluorouracil (5FU)][1)~3)] combined with surgery is the standard treatment[4)~6)]. Other regimens have also been reported, such as FP therapy[7)] with Adriamycin or nedaplatin + 5FU[8)]. In the 1990s, the efficacy of preoperative adjuvant therapy was first reported[6)], and FP therapy became the standard adjuvant treatment for patients with resectable squamous cell carcinoma (SCC) of the esophagus.

In recent years, DCF therapy [docetaxel (DOC) added to FP therapy] has been reported to be effective for adenocarcinoma of the stomach[9)10)] and for intracranial and cervical SCC of the head and neck [11)]. Efficacy of DCF therapy for esophageal SCC has also been studied in Japan[12)13)], but conclusive results have not been reported and this regimen is not clearly mentioned in the Guideline for Diagnosis for Esophageal Carcinoma[9)]. We have performed preoperative DCF therapy at our hospital since 2010, and we compared the results with those of preoperative

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Table 1 Chemotherapy regimens

DCF		
DOC	70 mg/m^2	Day 1
CDDP	70 mg/m^2	Day 1
5-FU	700 mg/m^2	Days 1-5
		2 courses with a 3-4 week interval
FP		
CDDP	80 mg/m^2	Day 1
5-FU	800 mg/m^2	Days 1-5
		2 courses with a 3-4 week interval

Both groups were scheduled to receive 2 courses.
DCF: docetaxel (DOC) combined with cisplatin (CDDP) + 5-fluorouracil (5FU), DOC: docetaxel, CDDP: cisplatin, 5-FU: 5-fluorouracil, FP: cisplatin (CDDP) + 5-fluorouracil (5FU).

FP therapy in the present study.

Materials and Methods

Twenty-seven patients with thoracic esophageal carcinoma underwent preoperative DCF therapy at our hospital from 2010 to January 2015 (DCF group). They were retrospectively compared with a historical control group of 22 patients who underwent preoperative FP therapy at our hospital from 2000 to 2009 (FP group) to assess efficacy and safety. Patients of both groups were in clinical Stages 2/3, excluding T4 disease and R2 resection (surgery with incomplete tumor resection) according to the Japanese Classification of Esophageal carcinoma.

DCF group: DOC 70 mg/m^2 on day 1, CDDP 70 mg/m^2 on day 1, 5-FU 700 mg/m^2 on days 1-5.

FP group: CDDP 80 mg/m^2 on day 1, 5-FU 800 mg/m^2 on days 1-5 (Table 1).

Each group was scheduled to receive 2 courses with a 3-4 week interval. The antitumor effect and adverse events were documented in accordance with RECIST 1.0[14] and NCI-CTC (ver.2)[15], respectively. In both groups, we reduced the dosage for the first course by about 10 % in patients with low activity (performance Status (PS) =1), those over 70 years old, and those with diabetes mellitus, serum creatinine $>$ 1.5 mg/dL, or no oral intake. The tumor response was determined by esophagoscopy, CT scanning, and upper gastrointestinal contrast radiography in accordance with the Japanese Guidelines for clinical and pathologic studies on carcinoma of the esophagus[16]. Postoperative transfusion was performed when hemoglobin (Hb) was predicted to fall below 9 g/dl[17]. Febrile neutropenia (FN) was assessed and treated based on the Guidelines for antimicrobial use[18] issued by The Japanese Association for Infectious Diseases and Japanese Society of Chemotherapy. Statistical Analysis: Student's *t*-test was used for analysis of continuous variables. For univariate analysis, the chi-square test, Fisher's exact test or the Wilcoxon test was performed, as appropriate. JMP® Pro 11.2.0 (SAS Institute Inc., USA) was employed for statistical analysis. This study has been approved by the research ethics committee of Tokyo Women's Medical University (No.3797).

Results

The DCF group showed significantly deeper tumor invasion than the FP group, but no other significant demographic differences were observed between the two groups (Table 2).

The clinical effect of DCF therapy was SD and PR in 10 and 17 patients, respectively, with the clinical response rate being 62.9 %. Postoperative assessment revealed that the histological effect was Grade 0, 1a, 1b, 2, and 3 in 1, 7, 12, 5, and 2 patients, respectively, with a histological response of grade 1 b or better in 70.4 %. In the FP group, the clinical effect was SD and PR in 8 and 14 patients, respectively, with a clinical response rate of 63.6 %. The histological effect was Grade 0, 1a, 1b, 2, and 3 in 1, 6, 6, 7 and 2 patients, respectively, and the histological response rate was 68.2 % (Table 3).

As for the surgical approach, right thoracotomy was performed in both groups, except in 1 patient from the DCF group who underwent left thoracotomy. The average time from the day of finishing chemotherapy until the day of surgery was 35.7 days in the DCF group and 32.4 days in the FP group, showing no significant difference. Operating time was 396 minutes in the DCF group and 352 minutes in the FP group, and this was significantly different (p=0.015). No significant difference of blood loss was observed. In the DCF group, perioperative blood transfusion was required in 22 patients (81.5 %). Postoperative complications noted in DCF group were suture leakage in 2 patients (7.4 %) and

Table 2 Characteristics of the two groups

	FP	DCF	p value	Test
n	22	27		
Period	2000-9	2010-15/Jan.		
Men	21	24	0.617	chi-square
Age (mean ± SD, years)	59.8 ± 9.5	63.8 ± 7.5	0.156	Wilcoxon
Age range (years)	38-75	47-77		
Comorbidities (No. of patients)	8	15	0.084	chi-square
Location: Ut/Mt/Lt	2/15/5	5/11/11	0.536	Fisher's exact
Depth T1b/2/3	3/5/14	3/1/23	0.015	chi-square
Clinical Stage 2/3	5/17	9/17	0.414	chi-square
No. of chemotherapy courses (1/2)	4/18	11/16	0.123	chi-square
Tumor histology				
well/mod/por/adenoscc/basoloid	2/12/8/0/0	4/16/2/1/2	0.076	Fisher's exact
Pathological stage 0/1/2/3/4	0/3/5/9/5	3/4/5/10/5	0.668	Fisher's exact

There was a significant difference in the depth of tumor invasion.
FP: cisplatin (CDDP) + 5-fluorouracil (5FU), DCF: docetaxel (DOC) combined with cisplatin (CDDP) + 5-fluorouracil (5FU).

Table 3 Results of preoperative chemotherapy

	FP (n = 22)	DCF (n = 27)	p value	Test
Clinical response = PR	14	17	0.961	chi-square
Clinical response rate	63.6%	62.9%		
Pathological response				
Grade 0/1a/1b/2/3	1/6/6/7/2	1/7/12/5/2	0.762	Fisher's exact
Pathological response rate ≧ Grade 1b	68.2 %	70.4 %	0.869	chi-square
Adverse events				
Hematological: Grade 3/4	5/0	11/10	<0.0001	Wilcoxon
Nadir neutrophil count: /dL	1,647 ± 605*	698 ± 508*	<0.0001	Wilcoxon
Decrease of hemoglobin: g/dL (until surgery)	2.3 ± 1.5*	2.7 ± 1.4*	0.151	Wilcoxon
Non-hematological ≧ Grade 3	6	12	0.215	chi-square
Renal dysfunction ≧ Grade 3	0	0	0.727	chi-square
Non-hematological adverse events (some patients are reported more than once)				
Appetite loss ≧ Grade 3	6	10		
Febrile neutropenia	0	5		
Diarrhea	1	3		
Stomatitis	1	2		
Liver dysfunction	0	1		
Alopecia	0	27		

There were no significant differences between the two groups, except for the frequency of grade 3/4 neutropenia and alopecia.
FP: cisplatin (CDDP) + 5-fluorouracil (5FU), DCF: docetaxel (DOC) combined with cisplatin (CDDP) + 5-fluorouracil (5FU), *mean ± SD.

intestinal obstruction, pneumonia, arrhythmia, and liver dysfunction in 1 patient (3.7 %) each. In the FP group, perioperative blood transfusion was performed in 13 patients (59 %), while there was postoperative suture leakage in 1 patient (4.5 %) and respiratory complications in 6 patients (27.2 %). Blood transfusion was performed at a higher rate in the DCF group than the FP group, but a significant difference was not observed. It was mainly performed for prophylaxis because of comorbidities in about half of the patients or because of the postoperative decline of Hb due to infusion of fluid, although Hb

Table 4 Results of surgery

	FP (n=22)	DCF (n=27)	p value	Test
Operating time (min)	352.5±95*	396±75.5*	0.015	Wilcoxon
Hemorrhage (ml)	887±1,321*	475±289*	0.191	Wilcoxon
Blood transfusion	59.0 %	81.5 %	0.084	chi-square
ICU stay (days)	7.2±6.0*	4.9±0.8*	0.315	Wilcoxon
Duration of SIRDS (days)	4.2±6.4*	1.8±1.6*	0.097	Wilcoxon
Postoperative complications	9	9	0.584	chi-square
Hospitalization period (days)	32.4±24.7*	41.7±95.7*	0.338	Wilcoxon
Interval from chemotherapy to operation (days)	32.4±7.7*	35.7±5.2*	0.093	Student's t
Surgical complications (some patients are reported more than once)				
Suture leakage	1	2		
Respiratory disease	5	2		
Recurrent laryngeal nerve paralysis	3	2		
Cardiac complications	0	1		
Ileus	0	1		
Liver dysfunction	1	1		

The operating time was longer in the DCF group. There were no significant differences of postoperative complications between the two groups.

FP: cisplatin (CDDP)+5-fluorouracil (5FU), DCF: docetaxel (DOC) combined with cisplatin (CDDP)+5-fluorouracil (5FU), SIRDS: systemic inflammatory response syndrome, *mean±SD.

Table 5 Actual dosages of chemotherapy delivered

	FP (n=22)	DCF (n=27)	p value	Test
Dose of CDDP (mg/m^2)	76.1±3.05*	54.6±9.64*		
Average dosage ratio	95 %	75 %		
No. of courses (1/2)	4/18	11/16	0.081	chi-square
Reasons for 1 course	Stable disease: 3 Refusal: 1	Stable disease: 3 Refusal: 2 Neutropenia: 5 Renal dysfunction: 1		
Pathological response rate (in patients receiving 1 course)	0%	63.6%	0.051	chi-square

The histological response rate was higher in patients receiving 1 course of DCF therapy compared with those given 1 course of FP therapy.

FP: cisplatin (CDDP)+5-fluorouracil (5FU), DCF: docetaxel (DOC) combined with cisplatin (CDDP)+5-fluorouracil (5FU), CDDP: cisplatin, *mean±SD.

spontaneously returned to about 10 g/dl after chemotherapy in many patients. There were no significant differences of postoperative complications and postoperative hospital stay between the two groups (Table 4).

We compared the two groups with respect to the drug dosages administered. In the FP group, the average dose of CDDP administered was 76.1 mg/m^2, which was 95 % of the scheduled dose. In the DCF group, the mean dose of CDDP was 54.6 mg/m^2, which was approximately 80 % of the scheduled dose (Table 5) because of the dose reduction criteria (both groups had the same average doses of 5-FU and DOC).

With respect to adverse events, grade 3 and grade 4 neutropenia occurred in 11 and 10 patients from the DCF group (77.8 %), respectively, while grade 3 neutropenia affected 5 patients (22.7 %) and there was no grade 4 neutropenia in the FP group. Hb showed no significant difference, but was lower in the DCF group. In both groups, renal dysfunction of grade 3 or more not observed. Febrile neutropenia occurred in 5 patients (18.5 %) from the DCF group.

In the DCF group, 11 patients (40.7 %) did not receive the second course due to grade 4 neutropenia, no tumor response, and patient refusal. A histological effect of grade 1b or better and histological re-

sponse rate of 63.6 % were documented in these patients, which were not significantly different from the results obtained in the FP group or in patients who received 2 courses of DCF therapy. In the FP group, 4 patients (18.2 %) did not receive the second course due to inability to tolerate oral food intake leading to patient refusal or due to renal dysfunction (< Grade 2). The histological effect was grade 1 a in all 4 of them. The dose was reduced in 4 patients from the DCF group because of renal dysfunction (< Grade 2) and FN, but no patient required dose reduction in the FP group. Among adverse events due to DOC, alopecia occurred in almost all patients from the DCF group.

Discussion

Kelsen et al[2] reported on the efficacy of FP therapy for advanced esophageal cancer. In Japan, the 5-year recurrence-free survival rate was reported to be higher with FP therapy than with surgery alone[5]. Based on this report, postoperative FP therapy became the standard treatment for patients with lymph node metastasis and local progression. Then preoperative chemotherapy became the standard treatment after its efficacy was demonstrated by a Japan Clinical Oncology Group (JCOG) clinical trial (9907), which compared preoperative and postoperative chemotherapy for Stage 2/3 esophageal carcinoma, although efficacy was not demonstrated in stage 3 disease[6]. It was reported that the prognosis is improved if patients respond to preoperative chemotherapy[19], although the prognosis is generally poor for esophageal cancer patients with metastasis to 3 lymph node regions[20][21]. Muro et al[22] reported a response rate of 15.8 % with DOC monotherapy as second-line therapy for recurrent esophageal carcinoma. However, severe adverse events were documented, including FN in 18 %, suggesting that careful monitoring and countermeasures were needed. A response rate of 36 % was obtained with postoperative FP therapy in a multicenter study[5]. At our hospital, the clinical and histological response rates to FP therapy were 63.6 % and 68.2 %, and efficacy was demonstrated. The clinical response rate was 62.9 %, which was lower than reported[23]. There is also a report that the response rate was 50 % after the first course of DCF as second-line therapy[12].

Our study suggested that superior tumor regression was achieved in the DCF group compared with the FP group, although simple comparison cannot be done because this was a single-center study. As for adverse events, grade 3/4 neutropenia was observed in 81.3 % of the DCF group, which was significantly more frequent than in the FP group, and FN occurred in 18.5 % of the DCF group. There was a high incidence at low doses, so the risk of FN is anticipated to increase with dose escalation and measures such as prophylactic granulocyte-colony stimulating factor (G-CSF)[24] are considered to be necessary. In this study, the actual dose of CDDP delivered was about 80 % of the scheduled dose in the DCF group, and neutropenia was observed in spite of dose adjustment. Yamasaki et al[25] performed a Phase II Study of DCF therapy using a similar regimen to ours, and reported a response rate of 72.5 %, grade 3/4 neutropenia in 90 %, and FN in 10.5 %. Their response rate was slightly higher than ours, but the results were similar with respect to adverse effects.

Kuderer et al[26] performed a meta-analysis, which showed that prophylactic G-CSF significantly lowered the risk of FN irrespective of tumor type, age, and other factors, and also reduced early death including death attributable to infection. Considering that antibiotics and G-CSF were initiated on the day after completion of chemotherapy in a Phase III study of prophylaxis during chemotherapy for lung small cell carcinoma[27][28], prophylactic administration of G-CSF for three days from around day 7 could be expected to reduce the risk of FN[13]. In the present study, non-hematologic toxicities included anorexia, nausea, vomiting, diarrhea, and stomatitis, twelve patients had grade 3/4 of the toxicities (44 %) with DCF therapy, but improvement was prompt. Nausea/vomiting is considered to increase dose-dependently, although it can be mitigated by antiemetic medications[29]. Since DCF therapy has an important role in the management of esophageal carcinoma, countermeasures for adverse events are considered to be essential for continuation of treat-

ment. In recent years, a Guideline for Optimum Antiemetic Medications[29] has been published and countermeasures are being taken, but further improvement is needed.

There was a significant difference of operating time between the 2 groups, but it was considered to have been greatly influenced by different surgeons performing the procedures. There were no significant differences of the interval between completion of chemotherapy and operation, hemorrhage, and perioperative complications. In both groups, surgery was performed safely with no fatal complications suspected to be attributable to chemotherapy. Although the incidence of neutropenia was high in the DCF group, the neutrophil count recovered to the normal range with G-CSF treatment. It was reported that the decrease of the neutrophil count was greater with DCF as second-line therapy, but recovery was prompt and only 2 out of 32 patients experienced prolonged neutropenia[12].

With respect to perioperative complications, the incidence of respiratory complications was reported to be 15-20 % even with surgery alone due to the characteristics of esophageal surgery[20]. At our hospital, the rate of such complications tended to be slightly higher in the FP group and the incidence was lower in the DCF group. Blood transfusion was more frequent in the DCF group than in the FP group. Hb was slight lower in the DCF group, but there was no significant difference. While there have been no reports on the standards for blood transfusion in patients receiving preoperative chemotherapy, the usefulness of autologous perioperative transfusion after preoperative chemo-radiation therapy has been studied[17)30].

In recent years, new regimens have been developed, but treatment is not effective in many cases regardless of the regimen and the dosage. Patients with esophageal cancer can achieve long-term survival if treatment is very effective, but useful predictive markers of efficacy are unknown. Thus, the effect of treatment is only revealed after evaluation. With regard to the number of courses, 11 patients (40.7 %) only received 1 course in the DCF group, but their response rate was 63.6 %, which was equivalent to that of patients who received 2 courses. Considering the relative dose intensity, it may be more effective to increase the dose, but FN could be predicted to occur more often. Prophylactic G-CSF and antibiotics seem to be effective for FN, while further treatment was also refused due to loss of appetite, nausea, and vomiting, which could be prevented with optimum antiemetic medications. Thus, countermeasures for adverse events are essential to improve both therapeutic efficacy and patient QOL. Although the dosages used in this study were reduced, the response rate was equivalent to that at a higher dosage. By taking the countermeasures mentioned above, DCF therapy could be performed safely according to the scheduled regimen.

Conclusion

Although severe adverse events sometimes occurred during DCF therapy, these should be preventable by careful management. Therefore, DCF therapy is considered to be an acceptable option, but further investigation will be required.

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根治切除可能食道癌に対する術前 DCF 療法の有効性および安全性の検討

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〔緒言〕近年食道癌化学療法において Docetaxel（DOC）/Cisplatin（CDDP）/5-fluorouracil（5FU）療法（DCF 療法）が行われているが，食道癌治療ガイドラインでは明記されていないため，今回術前 FP 療法群と臨床病理学的項目について比較検討を行った．

〔対象と方法〕cStage 2/3（T4 症例，R 2 切除症例は除く）進行胸部食道癌に対し，当院で 2010 年より術前 DCF 療法を行った 27 症例を対象とし，2000 年～2009 年まで当院で術前 FP（CDDP/5-FU）療法を施行した 22 例と比較検討，その安全性と有効性を Retrospective に検討を行った．

〔結果〕DCF 群では臨床奏効率 62.9%，組織学的奏効率 70.4% であった．有害事象は Grade 3 以上の好中球低下は 22 例であった．術後合併症は縫合不全 2 例，腸閉塞 1 例，心肺合併症 3 例，肝障害 1 例であった．FP 群では臨床奏効率は 63.6%，組織学的奏効率 68.2% であった．有害事象では Grade 3 以上の好中球低下 5 例であった．術後合併症は縫合不全 1 例，肺合併症 6 例であった．

〔結論〕術前化学療法の一つとして許容できるものとして考えられたが，今後さらなる検討が必要である．