Neoadjuvant Chemotherapy (FAP) for Advanced Esophageal Cancer

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Abstract. *This study was performed to assess the usefulness and safety of neoadjuvant chemotherapy utilizing the FAP regimen consisting of 5-fluorouracil, cisplatin and adriamycin for the treatment of highly advanced esophageal cancer. Twenty-seven patients with Stage III or more advanced esophageal cancer were enrolled in the study. The patients generally received two cycles of FAP. The response rate was as high as 55.6% and the resectability rate as high as 85.2%. All adverse events reported were mild in intensity. The histological effect was assessed as follows: Grade 1 in 18 patients, Grade 2 in 3 patients and Grade 3 (a pathological complete response) in 2 patients. All patients with nonresectable tumors died within 6 months, whereas of the 5 patients who responded with Grade 2 or better histological effects, all survived without recurrence for a follow-up period up to 60 months. The results of this study therefore showed the usefulness and safety of FAP therapy, which is considered to be a treatment method worth aggressively trying for highly advanced esophageal cancer in which a curative resection can hardly be expected.*

Owing to recent improvements in both surgical techniques and perioperative management, the surgical treatment of esophageal cancer has become increasingly conducted utilizing a three-field lymphadenectomy, thereby yielding improved therapeutic outcomes (1-3). However, it is still difficult to achieve a curative resection by surgical treatment alone in patients with advanced malignancies, and the therapeutic results in such patients have not been gratifying. Therefore, neoadjuvant FP chemotherapy consisting of cisplatin (CDDP) and 5-fluorouracil (5-FU) has been used at our Department as a multidisciplinary treatment for Stage III or more advanced cancer of the esophagus (4, 5). In addition, we have also recently been performing three-drug combination chemotherapy with the FP regimen plus adriamycin (ADM), called FAP chemotherapy, intended for a further improvement in the response, the respectability and the survival rates. This report presents the results of FAP chemotherapy with respect to its usefulness and safety.

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Patients and Methods

Patients. The study population comprised 27 patients with cStage III or more advanced esophageal cancer who were admitted to this hospital for surgery and received FAP therapy between December 2001 and June 2006. There were 23 men and 4 women, with a mean age of 65.1 years. The tumors measured 6.3 cm in their longer diameter on average, and were, according to macroscopic classification, mostly Type 2 and Type 3. The majority of tumors were cStage III. The histological type of the tumor was squamous cell carcinoma in all patients (Table I). The macroscopic classification and staging described herein were made in accordance with the Japanese Society for Esophageal Diseases, ninth edition (6).

Treatment and evaluation. ADM was administered intravenously at 25 mg/m^2/day on day 1, 5-FU at 500 mg/m^2/day by intravenous infusion from days 1 to 5, and CDDP at 20 mg/person/day by intravenous drip from days 1 to 5, followed by a drug-free period to complete a 3-week cycle. The patients generally received two cycles of the FAP therapy and, if the tumor was judged to be resectable, then surgical intervention was undertaken (Figure 1). Observation variables included the number of cycles performed, tumor response, response rate, resectability rate, histological effect of anticancer agents based on resected tissue specimens according to the Japanese Society for Esophageal Diseases, ninth edition (6), adverse events were graded using the Common Terminology Criteria for Adverse Events v 3.0 (7), and the cumulative survival rate (summarized for overall population and by tumor response, operative radical curability, and histological effect). The survival rate was calculated using the Kaplan-Meier plot and evaluated using the Wilcoxon test.

Table I. *Patient characteristics (27 cases).*

Gender	
Male/Female	23/4
Age (years)	
Mean (range)	65.1 (32-77)
Tumor diameter (cm)	
Mean (range)	6.3 (3.0-9.0)
Macroscopic type	
Type 1	2
Type 2	10
Type 3	13
Type 4	2
Clinical stage	
III	22
IVa	5
Histological type	
Squamous cell carcinoma	27

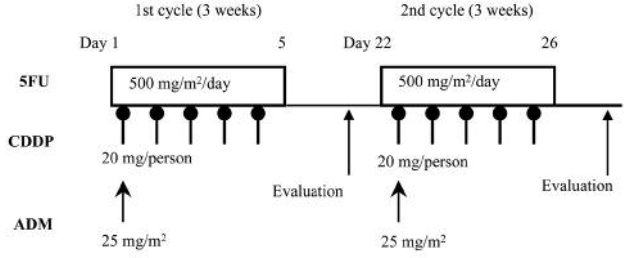

Figure 1. *Treatment schedule.*

Results

FAP therapy was given in one cycle in 7 patients, 2 cycles in 19 patients and 3 cycles in 1 patient. The tumor response after completion of the last cycle was a complete response (CR) in 1 patient, a partial response (PR) in 15 patients, and no change (NC) in 11 patients. No tumor was rated as progressive disease (PD). The response rate was 55.6%. Twenty-three patients excluding the 4 NC cases underwent surgical treatment, with a resectability rate of 85.2%. Of these 23 patients, there were 9 whose lesions had been strongly suspected to be Stage T4 prior to the therapy, and a curative resection could therefore hardly be expected in these patients. The histological effect of anticancer agents based on the resected tissue specimens was Grade 1 in 18 patients, Grade 2 in 3 patients and Grade 3 in 2 patients, and there were 2 cases (7.4%) rated as a pathological complete response (Table II).

The adverse events reported during the study were as follows: Grade 2 leukopenia in 5 patients, Grade 3 leukopenia in 2 patients, Grade 3 thrombocytopenia in 1 patient, and Grade 3 myelosuppression in 3 patients (13.0%). There were two patients in whom bone marrow suppression recurred after achieving postoperative stabilization of their general condition. Regarding gastrointestinal symptoms, 8 events developed Grade 2 symptoms, and none had any renal disorders. No noticeable complications attributable to FAP chemotherapy were noted during the preoperative course (Table III).

When the therapeutic responses were assessed in terms of the cumulative survival rate, the overall 5-year survival rate was 49.7% (Figure 2). The cumulative survival rate according to the tumor response for the 16 patients achieving CR or PR tended to be more gratifying, though marginally not statistically significant, than that for the 11 patients whose

Table II. *Results of FAP therapy.*

	No. of cases
Frequency	
1 cycle	7
2	19
3	1
Resection (curability)	
Absolute curative	16
Relative curative	7
Non-resection	4
Resectability rate	85.2%
Tumor response	
CR	1
PR	15
NC	11
PD	0
Response rate	55.6%
Histological criteria (Grade)	
3	2
2	3
1	18
0	0

CR: complete response, PR: partial response, NC: no change, PD: progressive disease.

Table III. *Adverse events.*

	Grade			
	1	2	3	4
Bone marrow				
Leukopenia	5	5	2	0
Hemoglobin	7	0	0	0
Platelets	2	0	1	0
Gastrointestinal				
Stomatitis	9	0	0	0
Nausea	13	3	0	0
Anorexia	18	5	0	0
Renal failure	0	0	0	0
Alopecia	9	0	0	0

Common Terminology Criteria for Adverse Events v3.0 (7).

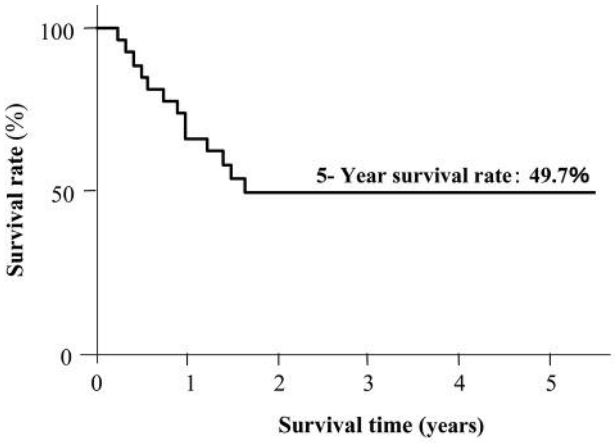

Figure 2. *Survival curve of all patients.*

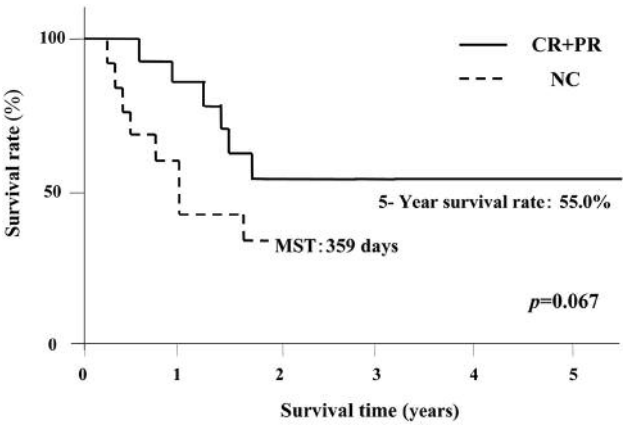

Figure 3. *Survival curve in relation to tumor response.*

tumor responses were NC (p=0.067) (Figure 3). Regarding the survival rate by curability, the 5-year survival rate was 65.0% for 16 patients, which was rated as absolute curative resection and significantly better in comparison to other groups (p<0.001). Of 7 patients with relative curative resection, none achieved a 5-year survival and the mean survival time (MST) was also unfavorable (550 days). For the 4 patients with nonresectable tumors, the MST was as short as 120 days, and all these patients died within 6 months, thus showing a grave outcome (Figure 4). As for the survival rate by histological effect, results are remarkably gratifying for 3 Grade-2 patients and 2 Grade-3 patients, who are all recurrence-free and are still alive, for follow-up periods ranging up to 60 months at the time of writing. For 18 Grade-1 patients, in contrast, the MST was not favorable (590 days). This variable was very unfavorable for the four patients with nonresectable tumors as mentioned above (Figure 5).

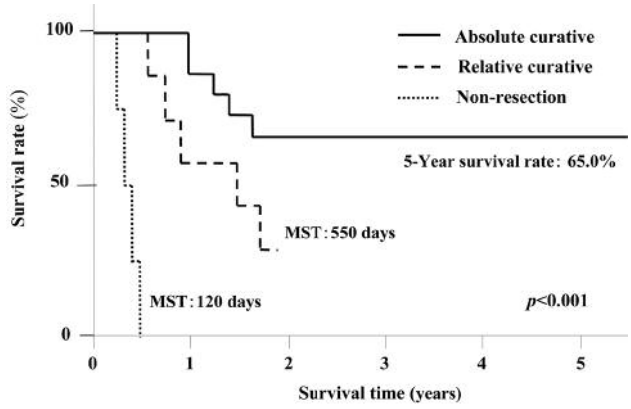

Figure 4. *Survival curve in relation to curability.*

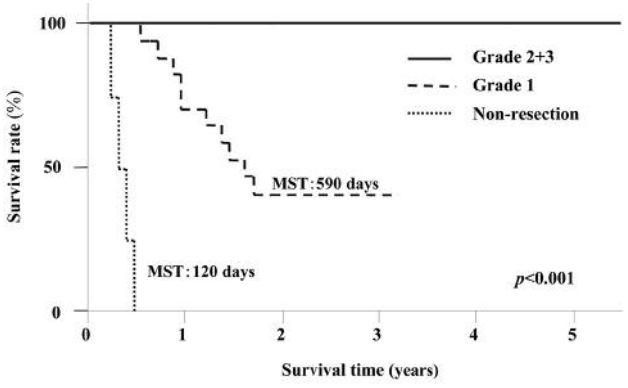

Figure 5. *Survival curve in relation to histological effect.*

Discussion

In the surgical treatment of advanced esophageal cancer, the survival rate has improved following the introduction of three-field lymphadenectomy (1-3), but in patients with highly advanced cancer, surgical therapy alone does not suffice and multidisciplinary treatment is needed. In view of this, combination therapy with 5-FU and CDDP (FP therapy) has been performed as neoadjuvant chemotherapy for advanced malignancies of the esophagus at this Department since 1994. However, although the responders had a favorable prognosis, PD cases still accounted for approximately 10%; thereby not necessarily resulting is highly gratifying therapeutic outcomes (4, 5).

Since December 2001, therefore, 3-drug combination therapy with ADM added (FAP therapy) has been used at this Department in an attempt to improve both the response and resectability rates (8). A remarkably high usefulness of such neoadjuvant chemotherapies based on the FAP therapy regimens has been reported, with a response rate as high as

Table IV. *Neoadjuvant chemotherapy for esophageal cancer.*

Regimen	No. of cases	Resection rate (%)	Response rate/CR (%)	Survival rate (%)	Author
CDDP/5-FU	26	38	42/0	17 (5 years)	Kies *et al.* (26)
CDDP/5-FU	35	77	57/7	54 (3.5 years)	Hilgenberg *et al.* (27)
CDDP/5-FU	70	81	66/7	31 (5 years)	Carey *et al.* (28)
CDDP/5-FU	32	56	66/11	–	Ajani *et al.* (12)
CDDP/5-FU	49	88	–/0	39.8 (3 years)	Hosoya *et al.* (29)
CDDP/5-FU/VDS	57	100	40/0	35.2 (4 years)	Okuma *et al.* (30)
CDDP/5-FU	32	100	34/0	–	Minamide *et al.* (13)
CDDP/5-FU/LV	44	100	63/2	28.5 (4 years)	Ide *et al.* (31)
CDDP/5-FU/ADM	27	85.2	55.6/7	49.7 (5 years)	Present study

75% for primary lesions and a Grade-3 histological effect rate as high as 40% for lymph node metastases (9-11). The results in the present series were similarly favorable, thus showing a response rate of 55.6%, a resectability rate of 85.2% and an overall 5-year survival rate of 49.7%.

Generally, the purpose of neoadjuvant chemotherapy is to achieve contraction of the primary neoplastic lesion as well as to control lymph node metastasis and local and systemic micrometastases, with subsequent down-staged surgical resection, in anticipation of improvement in long-term results. Neoadjuvant chemotherapy is advantageous over postoperative chemotherapy in that i) histopathological examinations of resected tissue specimens allow for sensitivity tests of target tissues for chemotherapeutic agents, ii) a higher attainment rate can be obtained than with postoperative chemotherapy, iii) it provides a better drug delivery to target tissues, and iv) it reduces intraoperative cancer cell dissemination. On the other hand, neoadjuvant chemotherapy has the following disadvantages: i) it may stimulate the acquisition of drug resistance, ii) the tumor may further grow in non-responders, thereby making a resection infeasible or worsening the prognosis, and iii) it may raise the risk of postoperative complications (12-14). Among patients who have received the FAP therapy as a neoadjuvant chemotherapy at this Department, nevertheless, no PD case has been noted to date, nor any increased incidence of postoperative complications; little or no disadvantage has been clinically observed.

Several randomized comparative studies have been conducted in Western countries in patients treated by surgical procedures alone and those receiving neoadjuvant chemotherapy combined with surgical treatment in order to verify the usefulness of neoadjuvant chemotherapy in terms of therapeutic outcome (15-18). Some of these studies demonstrated the effectiveness of neoadjuvant chemotherapy, but conclusions derived from meta-analyses of the data including these studies are controversial, so that the usefulness of neoadjuvant chemotherapy has yet to be verified (19-24). According to the Japanese Guidelines for Treatment of Esophageal Cancer, no sufficient basis exists for recommending neoadjuvant chemotherapy in patients with a resectable tumor of the esophagus, so that its recommendability is graded as C (25). However, most of the therapy regimens used in these reported cases and the Japanese Guidelines are based on FP therapy, and the cancer of the esophagus is adenocarcinoma in most of the cases reported in Western countries, where operative procedures tend to differ greatly from those in Japan. Therefore, these reported study results and the Guidelines do not necessarily seem to be entirely applicable to the present status in Japan.

The results of neoadjuvant chemotherapy using the FAP regimen at this Department in comparison to those reported from other medical institutions are shown in Table IV. No noticeable differences are seen in the resectability rate or response rate, but the 5-year survival rate was 49.7% at this Department, being more favorable than those reported from other institutions (12, 13, 26-31). Furthermore, the 5-year survival rate for patients attaining CR or PR was as good as 55% and that for those in whom an absolute curative resection was feasible was also as good as 65%. No death was noted among patients achieving a Grade 3 or Grade 2 histological effect. Moreover, the FAP therapy was safely practicable because all adverse events reported were mild in intensity as mentioned above. Although the present study was performed in a retrospective manner, the results indicate the usefulness of the FAP therapy undertaken at this Department as a neoadjuvant chemotherapy. The prognosis was very poor, nevertheless, in non-responders with nonresectable tumors rated as NC. For such non-responders, neoadjuvant chemotherapy entails problems such as a loss of time, a progression of the disease and the wasting of an opportunity to perform alternative therapies. It is therefore urgently necessary to develop a simple method to determine in advance a cancer patient's susceptibility to chemotherapy.

Conclusion

The use of neoadjuvant chemotherapy using the FAP regimen in patients with advanced esophageal cancer in which a curative resection can hardly be expected is considered to be a useful treatment option that is clearly worth trying since it has been demonstrated to yield a high response rate, good resectability and survival rates while, in addition, it can also be safely performed.

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