Pre-operative Chemoradiation Therapy with 5-Fluorouracil and Low-dose Daily Cisplatin for Esophageal Cancer: A Preliminary Report

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Background: A combination of chemotherapy and radiotherapy (chemoradiation therapy; CRT) has recently been developed to improve the survival of esophageal cancer patients. However, the optimal choice of chemotherapeutic agents and their doses, as well as chemotherapy and radiotherapy regimens, remain unclear.

Methods: Based on recent advances in knowledge on the radiosensitizing and biochemical modulation effects of chemotherapeutic agents, we have recently developed concurrent CRT which consisted of continuous 5-fluorouracil (5FU) administration (600 mg/m²/day, days 1–5) combined with a low dose of daily cisplatin administration (10 mg/m²/day, days 1–5, and 5 or 10 mg/m²/day, days 8–12 and 15–19) before each fraction of radiation (2 Gy each). To evaluate the efficacy and safety of our concurrent CRT, 10 esophageal cancer patients received one or one and a half courses of the CRT.

Results: All patients tolerated and completed a full course of the CRT. The effectiveness of the CRT on the primary tumor included pathologically or endoscopically complete responses in three patients (30%), partial response in five (50%), no response in two (20%) and tumoral downstaging (T-classification) in five (50%). Grade 2 and Grade 3 toxicity, seen in six patients, did not affect surgical operation. No patients showed CRT-related deaths. Eight patients (80%) underwent resection with no operative mortality. Of these, two patients (25%) showed pathologically or endoscopically complete responses, and four (50%) showed partial response. Three patients died of cancer after resection. The two inoperable patients showed a pathologically complete response and partial response, respectively. They were relieved of their cancer-related complaints and were living without hospitalization at the time of this analysis.

Conclusions: These results suggest that the concurrent CRT based on the theoretical backgrounds is effective and has acceptable toxicities with maintaining its efficacy for the treatment of esophageal cancer patients.

Key words: esophageal cancer – chemoradiation therapy – biochemical modulation – radiosensitizing effect

INTRODUCTION

Esophageal cancer remains one of the most aggressive types of cancer, and is already an advanced, invasive and distant metastatic disease at the time of presentation (1). Although many attempts toward the improvement of survival times of esophageal cancer patients, such as adjuvant or neoadjuvant therapies, have been carried out, the results of these single-modality treatments have not been satisfactory (2–6). On the other hand, a combination of chemotherapy and radiotherapy (chemoradiation therapy; CRT) has recently been developed and reported as an effective treatment modality for operable as well as non-operable esophageal cancer patients (7–13). However, the optimal choice of chemotherapeutic agents and their doses, as well as the schedules of chemotherapy and radiotherapy, remain unresolved. The rationale of CRT is the radiosensitizing and biochemical modulation effects of chemotherapeutic agents. In addition, recent advances in knowledge on CRT have proved that biochemical modulation effects between 5-fluorouracil (5FU) and cisplatin are...
effective, and that the maximum radiosensitizing effects are achieved by daily cisplatin administration before each fraction of radiation (14–17). In consideration of these advances, we have developed a concurrent CRT whose essential ideas are a continuous 5FU infusion and a low dose of daily cisplatin before each fraction of radiation (18). Subsequently, we have recently reported a case of complete response of advanced esophageal cancer receiving the neoadjuvant CRT (18). Based on these experiences, we investigated the efficacy and safety of the CRT by application of the therapy to advanced esophageal cancer patients. In this report, we demonstrate both a high response rate to the primary site without affecting surgical operation in operable patients, and a good palliation and improvement of quality of life in inoperable patients. In addition, we demonstrate no post-operative mortality and no treatment-related deaths due to the CRT. These benefits are due to the relatively lower doses of chemotherapy and radiotherapy without any decrease in their efficacies, which can be supported by the theoretical backgrounds of radiosensitizing and biochemical modulation effects of chemotherapeutic agents.

PATIENTS AND METHODS

EVALUATION SYSTEM OF PRE- AND POST-CRT

The clinical staging work-up included a barium roentgenogram, upper gastrointestinal endoscopy, and computed tomography (CT) scan of the thoracic and upper abdomen. Chest X-ray, complete blood count (CBC) with platelets, and serum analyses of liver and renal function were also routine. Magnetic resonance imaging and bronchoscopy were performed, if necessary. Tumor size was determined by the length of the lesion at endoscopy or barium roentgenogram. Tumor location, macroscopic and microscopic depth of invasion of the primary tumor, lymph node and distant metastases, and stage grouping of the tumor followed the TNM classification (19). All patients received parenteral alimentation regardless of the degree of dysphagia before treatment. Toxicity of the CRT was defined according to the WHO system (20).

PATIENTS AND TUMOR CHARACTERISTICS

Between October 1996 and November 1997, 10 esophageal cancer patients received the CRT in Showa General Hospital (Table 1). Informed consent was obtained from all patients. All patients were male, with a mean age of 58.6 years (range 51–71). Five patients had stage III (T3N1M0 or T4 anyN M0) and five had stage IV (anyT anyN M1) disease. Four patients showed a T4 tumor with either tumor extension into the bronchus (two patients) or thoracic aorta (two patients). Five patients showed an M1 tumor due to distant lymph node metastases around the abdominal aorta (two patients), supraclavicular (two patients) and neck (one patient). No patients had distant organ metastases. The chief complaints of the patients included dysphagia in eight patients and epigastralgia in one patient. One patient suffered from dysphagia, cough and fever due to obstructive pneumonia subsequent to the tumor invasion of the left main bronchus. The mean length of the tumor was 8.6 cm (range 3–21 cm). There were no patients with cancer of the cervical esophagus.

Table 1. Patient and tumor characteristics

<table>
<thead>
<tr>
<th>Factors</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (range)</td>
<td>58.6 (51–71)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>10/0</td>
</tr>
<tr>
<td>Mean tumor length (cm) (range)</td>
<td>8.6 (3–21)</td>
</tr>
<tr>
<td>Location of tumor</td>
<td></td>
</tr>
<tr>
<td>Upper/middle/lower</td>
<td>0/1/3</td>
</tr>
<tr>
<td>Any of two locations</td>
<td>5</td>
</tr>
<tr>
<td>All locations</td>
<td>1</td>
</tr>
<tr>
<td>T-classification</td>
<td></td>
</tr>
<tr>
<td>T3/T4</td>
<td>6/4</td>
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<tr>
<td>N-classification</td>
<td></td>
</tr>
<tr>
<td>N0/N1</td>
<td>2/8</td>
</tr>
<tr>
<td>M-classification</td>
<td></td>
</tr>
<tr>
<td>M0/M1</td>
<td>5/5</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>III/IV</td>
<td>5/5</td>
</tr>
<tr>
<td>Chief complaint</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>8</td>
</tr>
<tr>
<td>Epigastralgia</td>
<td>1</td>
</tr>
<tr>
<td>Dysphagia, cough, fever</td>
<td>1</td>
</tr>
</tbody>
</table>

DEFINITION OF RESPONSE TO THE CRT

After the CRT, evaluation of clinical response was performed through upper gastrointestinal endoscopy, barium roentgenogram and CT scan. CRT responses of the primary site (T-classification) and lymph node metastases (N- and M-classification) were evaluated independently. A complete response (CR) was defined as 100% regression of all visible tumors at the primary site. A partial response (PR) was defined as a ≥50% reduction in the tumor, and no change (NC) was defined as a ≤50% reduction in the tumor. Progressive disease (PD) was defined as a ≥25% enlargement of the tumor, or the appearance of a new tumor which had not been observed before the CRT. Furthermore, CR was divided into two categories: pathologically complete response (pCR) and endoscopically or radiologically complete response (eCR). The pCR was defined as having no histological evidence of disease in the resected specimens of the operable patients or in the biopsy specimens of the inoperable patients. The eCR was defined as 100% regression endoscopically or radiologically of all visible tumors, but a histological persistence of disease in the resected specimens of the operable patients or in the biopsy specimens of the inoperable patients.

TREATMENT

The protocol of the CRT has been reported previously (18). In brief, one course of the chemotherapy schedule consisted of 5FU (600 mg/m² in continuous 24 h infusion) for five days (days 1–5), and the concurrent administration of radiation (2 Gy given 15 times, in five fractions a week) and cisplatin (10 mg/m² given
daily, days 1–5, and 5 or 10 mg/m²/day, days 8–12 and 15–19, one hour before radiation) for three weeks beginning at day 1. The length of the radiation field included points at least 3 cm distant from the proximal and distal edges of the tumor, and the width of the radiation field included a mediastinal septum which sufficiently covered the tumor. CT scan was used before treatment to confirm the radiation field. A parallel-opposing anterior and posterior pair of fields was performed in all patients. The dose of cisplatin in the second and third weeks could be reduced to 5 mg/m² according to patient status. When one or one and a half courses of the CRT were completed, the patients were re-evaluated for therapeutic response by the examinations described above. The median total doses of 5FU, cisplatin and radiation were 4625 mg (range 4250–7200 mg), 176 mg (range 140–425 mg) and 30 Gy (range 30–50 Gy), respectively. The actual median duration of CRT and the median actual interval from the end of CRT to surgery were 22 days (range 21–49 days) and 21 days (range 17–37 days), respectively. The surgical procedure comprised total esophagectomy with a right thoracotomy and laparotomy with regional lymph node dissection three weeks later from the completion of the CRT. Sampling of the distant metastatic lymph nodes was added, if necessary. The gastrointestinal tract was reconstructed by means of a gastric tube pulled up through the retrosternal or mediastinal route.

RESULTS

RESPONSE

Table 2 summarizes the conclusive responses of the CRT. The pCR and eCR rate of the primary site was 30% (3/10) with a 50% (5/10) PR rate. Tumoral downstaging (T-classification) was observed in five patients (50%). Of these, two patients showed a change from T4 to T0 or T3, and three patients showed a change from T3 to T0, T1 or T2. Eight patients underwent esophagectomy (resection rate 80%). Seven of them underwent R0 resection (no residual cancer) and one of them underwent R2 resection (macroscopic residual cancer). In patients who underwent surgery, the pCR or eCR rate of the primary site was 25% (2/8), and four patients (50%) showed PR. One of these patients underwent palliative resection and the other seven patients underwent complete removal of any gross residual disease. Two patients were diagnosed as inoperable. One showed a pCR in the primary site and was free from dysphagia, but had progression of distant lymph node metastases at the cervical region. Another showed a PR with a persistent but minor invasion of the tumor to the left main bronchus. This patient experienced dramatic relief of the obstructive pneumonia, which was his chief complaint before the CRT. In comparison with the response of the primary tumor, the response of the lymph nodes to the CRT was less effective for only one patient showing PR (Table 2).

SURVIVAL

There were no deaths during the month following surgery. Three patients later died of esophageal cancer; two patients (R0 resection) died of bone marrow metastases three months and 18 months after resection, respectively; the other patient (R2 resection) succumbed to an extension of residual cancer five months after resection. The remaining seven patients were alive at the time of analysis. The mean and median follow-up times of these patients from the commencement of the CRT were 14.4 and 14 months, respectively (range 12–19 months). The two patients who did not undergo resection were also alive at the time of analysis without hospitalization 14 and 16 months after beginning the CRT.

TOXICITY

The CRT was well tolerated, and all patients completed the full course. Hematological toxicities of grade 1, grade 2 and grade 3 were observed in four, three and three patients, respectively. Renal toxicities of grade 1 and grade 2 were observed in three and two patients, respectively (Table 3). Two patients who showed Grade 3 leukopenia (WBC < 2000/ml) required granulocyte colony stimulating factor (G-CSF) administration before surgical operation. In addition, one patient who showed Grade 3 decreased hemoglobin level (hemoglobin < 8.0 g/dl) required a blood transfusion before surgical operation. However, there were no severe toxicities which affected surgical operation. Chemotherapy-related nausea, vomiting and stomatitis were not severe problems in any of the patients. There were no CRT-related deaths. Stricture of the irradiated esophagus was not observed.

<table>
<thead>
<tr>
<th>Degree*</th>
<th>Number (%) of patients (resection 8/non-resection 2)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Hematological</td>
</tr>
<tr>
<td>Grade 0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3 (30)</td>
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</tbody>
</table>

*The degree of toxicity was classified according to the WHO system.
DISCUSSION

In many cases, esophageal cancer is already advanced at the time of presentation, and has been documented as a highly invasive and distant metastatic disease (1). Because surgical efforts alone have not been able to improve survival times of esophageal cancer patients over the last two decades, a variety of therapies, such as chemotherapy, radiotherapy, as well as combined pre-operative CRT, have been attempted. However, post-operative chemotherapy or post-operative radiotherapy have not improved survival times of esophageal cancer patients (2,3). In addition, recent randomized trials have proved that resection rates and survival times of esophageal cancer patients cannot be improved by pre-operative radiotherapy (4) or by pre-operative chemotherapy (5,6) as compared with those of patients undergoing only surgery.

On the other hand, CRT has been developed over the last decades and demonstrated to be an effective treatment modality for operable (7–10) as well as inoperable esophageal cancer patients (11–13). In these previous trials, the two-year survival rates and median survival times of the pre-operative chemoradiation group were 30–65% and 10–37 months, respectively, which were better than those of the surgery-only group (22–33% and 7–17 months, respectively). In inoperable esophageal cancer patients, the two-year survival rate ranged from 29 to 47%, median survival ranged from 11 to 12 months, and endoscopically complete response rate ranged from 56 to 87%. However, in these clinical trials, the optimal choice of chemotherapeutic agents and their doses, as well as chemotherapy and radiotherapy regimens, have not been precisely established. 5FU and cisplatin seem to be more common, but mytomycin C (11,12) has occasionally appeared in the chemoradiation protocols. The schedules of chemotherapy and radiotherapy have included 5FU infusion associated with bolus or weekly cisplatin administration, combined with concurrent radiotherapy for only several days or sequential radiotherapy. In this respect, we have recently reported a complete response case of advanced esophageal cancer by neoadjuvant CRT, which was characterized by continuous 5FU administration combined with daily low-dose cisplatin administration before each fraction of radiation (18). This experience prompted us to perform this chemoradiation protocol to subsequent advanced esophageal cancer patients. The rationale and keys to this protocol are as follows: (i) cytotoxic effects by continuous 5FU administration were superior to bolus 5FU administration (21); (ii) cisplatin enhanced the cytotoxicity of 5FU (biochemical modulation) (14); (iii) 5FU could act as a radiation sensitizer and continuous 5FU administration with radiation was more effective (22,23); (iv) cisplatin administration prior to radiation maximized the radiosensitizing effects (15,16); (v) daily low-dose cisplatin before each fraction of radiation was most effective (17); (vi) daily low-dose cisplatin had the same antitumor effects as bolus larger dose cisplatin (16); (vii) low-dose cisplatin enabled daily concurrent CRT without increasing the toxicities (18,24). These investigations give credence to the possibility of relatively lower doses of radiation and chemotherapeutic agents without decreasing their efficacy, if combined appropriately. Because continuous 5FU administration was common during the first several days as a radiosensitizer in the previous reports (600–1000 mg/m²) (7–10), and on the basis of recent advances in knowledge on CRT as described above, we developed this concurrent CRT and evaluated its efficacy.

In the present study, several benefits and efficacies could be demonstrated. A high overall response rate (80%) was observed with a 30% pCR or eCR rate for the primary tumor. In the operable patients, the response rate was 75% (6/8), with a pCR or eCR rate of 25% (2/8). Two patients were unfortunately diagnosed as inoperable; however, we found this CRT protocol to provide good palliation and quality survival in these patients without stricture of the irradiated esophagus. In addition, freedom from dysphagia or obstructive pneumonia was achieved in these patients by tumor regression in the esophagus or left main bronchus. Four of the five patients who showed tumoral downstaging (T-classification) were able to undergo resection of the tumor. With regard to survival, we cannot comment on the survival benefits of the chemoradiation protocol because of still insufficient follow-up data; however, it should be noted that the longest survival time was 18 months. Furthermore, the two non-operable patients are also still alive at the time of analysis without hospitalization 14 and 16 months from their beginning the CRT. Moreover, it should be emphasized that there was no post-operative mortality nor CRT-related deaths in the present study, because some clinical trials have reported relatively higher post-operative mortality (3–11%) (8–10), or treatment-related complications or deaths (2–12%) (10–12) which sometimes have required hospitalization (11) or which sometimes have resulted in death (10,12). The acceptable toxicities of our CRT are due to the relatively lower dose of radiation or daily lower dose of cisplatin which can be supported by the above theoretical backgrounds of radiosensitivity and biochemical modulation effects of these agents. Therefore, our concurrent CRT, which was based on its rationale, was effective and safe, and we conclude that this CRT can be recommended for the treatment of advanced esophageal cancer patients.

Fink et al. (1) reviewed several recent publications and compared the effectiveness of CRT with surgery and that of CRT alone. In this review, the local recurrence rates were higher (14–72%) in the studies of CRT alone as compared with those in the studies of CRT with surgery (0–36%). Furthermore, it should be noted that CRT alone (25,26) resulted in higher rates of local recurrence (14–47%) than CRT with surgery (0–2%) (27,28), even among the resectable esophageal cancer patients. These results suggest the necessity of surgical resection for local tumor control after CRT. On the other hand, in the present study, the response of the distant lymph node metastases seems to be less effective as compared to the response of the primary tumor. The same observations were reported by Fink et al. (1), who pointed out that the rate of distant failures was higher than the rate of local failures after the CRT with or without surgical resection. Therefore, control of distant metastases remains one of the general problems of the CRT. In the future, the supportive use of G-CSF to increase the dose intensity of chemotherapy per treatment, or another application of biochemical modulation to
5FU and cisplatin, such as leucovorin (24,29) or interferon (30) (dual or triple biochemical modulation), to intensify the effect of chemotherapy may be the most promising approach for solving these problems.

References