Concurrent FP (5-fluorouracil, cisplatin) Chemoradiotherapy for Patients with Esophageal Cancer

Min Ok Kim, M.D.¹, Eui Sil Hong, M.D.₁, Ji Young Chai, M.D.₁, Joung Muk Leem, M.D.₁, Il Young You, M.D.₁, Won Dong Kim, M.D.₁, Woo Yoon Park, M.D.₁, Seung Taik Kim, M.D.₁ and Ki Hyeong Lee, M.D.₁

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Purpose: The outcomes of a surgical approach for patients with an esophageal carcinoma remain unsatisfactory despite its high complication rates. We conducted a phase II trial, using combined FP (5-fluorouracil and cisplatin) chemotherapy and concurrent radiotherapy, as a definitive therapy for patients with esophageal cancer.

Materials and Methods: Patients with histologically proven esophageal cancer were enrolled onto this study. The treatment consisted of four courses of chemotherapy and six and a half weeks of radiotherapy. The patients received chemotherapy in weeks 1, 5, 12 and 16 (5-fluorouracil 1,000 mg/m² on days 1 to 4 and cisplatin 75 mg/m² on day 1). Radiotherapy was administered at a dose of 59.4 Gy, in five 1.8 Gy fractions a week.

Results: A total of 22 eligible patients entered the study. Of the 19 evaluable patients, a complete response occurred in 7 (37%), and a partial response in 8 (42%). After a median follow-up of 35 months, the overall survival rate was 32% at three years and the median survival was 11 months. Fourteen (64%) received planned dose of radiotherapy and 13 (59%) received more than three courses of chemotherapy. However, there was no difference in three-year survival rates between the patients that received less than three courses of chemotherapy and those that received three or more courses (31% vs. 32%). The major treatment related toxicity was mucositis, which developed in every patient, with grades III or IV in thirteen (59%) patients. During the treatment, the patients lost, on average, 3.8% of their body weight. The mean hospital stay was 23 days, with a total duration of treatment of 74 days.

Conclusions: Concurrent FP chemoradiotherapy was effective as a definitive therapy for patients with esophageal cancer. The major toxicity was mucositis. Although the treatment was relatively feasible, a randomized trial of reduced courses of chemotherapy is warranted.

Key Words: Esophageal neoplasm, Concurrent chemotherapy and radiotherapy

INTRODUCTION

Esophageal carcinomas represent the third most common cancer among the gastrointestinal malignancies, following gastric and colorectal carcinomas, both worldwide and in Korea (1,2). With the exception of early stage diseases, the prognosis remains very poor, despite aggressive surgical approaches (3). Furthermore, the abundant mucosal and submucosal lymphatics, and the lack of serosal coats, make the tumor cells spread easily, which hinder the earlier detection of this cancer.

Traditionally radiotherapy has been used as the primary therapy for the unresectable, locally advanced diseases, or as a palliation for a metastatic disease. Although it has a lesser degree of complications and mortality rates related with the treatment, the cure rates with radiotherapy alone are lower than with surgical resection (4–6). In an effort to improve the local and distant disease control using radiotherapy, various combinations and schedules of chemotherapeutic agents are being tested combined with radiotherapy. Among these, FP (5-FU, cisplatin) is one of the most active regimens in neoadjuvant, or palliative, settings for metastatic diseases (7–9). Furthermore, each drug of this regimen is known to have its own radiosensitizing activities (10,11).

This study was performed to determine the effectiveness, toxicities and feasibility of concurrent FP chemoradiotherapy in patients with esophageal carcinomas.

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This study was performed to determine the effectiveness, toxicities and feasibility of concurrent FP chemoradiotherapy in patients with esophageal carcinomas.
MATERIALS AND METHODS

1) Patients

The eligibility requirements included: the presence of a pathologically confirmed carcinoma of the esophagus, including the gastroesophageal junction, regardless of the metastases in local lymph nodes and clinically limited to the locoregional areas (T 1, 2 or 3; any nodal stage; and no distant metastasis). During patient accrual, the American Joint Committee (AJC) staging system was revised, without affecting the eligibility for inclusion into this trial (12). The clinical stages for all the patients presented are based on the revised AJC system. The clinical stage was evaluated by a complete medical history, physical examination, complete blood count, chemical screening, chest x-ray, computed tomography of the chest and upper abdomen, gastrofiberscopy and ultrasonography of the liver, and an isotope bone scan, if there are any symptoms that suggest bony involvement or abnormalities in serum calcium or alkaline phosphatase levels. All patients were at least 18 years of age; had adequate hepatic, renal and bone marrow reserves; and an ECOG status of 0 to 2. Patients were excluded if they had distant metastases, had previously undergone any treatment for the current tumor or previously had another primary cancer. The written informed consent of all the patients was required.

2) Chemotherapy

Cisplatin, at a dose of 75 mg per square meter of body surface area, was given as a rapid intravenous infusion on day 1, following prehydration. 5-fluorouracil was administered, at a dose of 1,000 mg per square meter of body-surface area, as a continuous intravenous infusion from day 1 to day 4 of each cycle. The cycle was repeated, beginning on days 1, 28, 77 and 105. Patients were required to be hospitalized for chemotherapy. All patients were treated prophylactically with the antiemetic agents, ondansetron or granisetron, both before and after the cisplatin infusion. The dose for each drug was adjusted according to the complete blood count and chemical data obtained just before each cycle. The dose of 5-fluorouracil was reduced by 25% if there was a grade 1 leukopenia or thrombocytopenia, and the dose of cisplatin was reduced by 50% if there was a grade 3 increase in the serum creatinine level, according to the WHO classification system. If there was any grade II, or severe, toxicities in the bone marrow or renal function, the chemotherapy was delayed for at least one week until they had recovered.

3) Radiotherapy

The irradiation field included the macroscopic tumor and enlarged lymph nodes, if any, surrounded by 5-cm proximal and distal margins and a 2-cm radial margin. Radiotherapy was begun on the first day of the first cycle of chemotherapy, and was delivered for six and a half week. During the course, five daily fractions of 1.8 Gy were delivered per week. The total delivered dose was 59.4 Gy; with three weekly booster doses of 2 Gy each delivered intraluminally. The booster doses were encouraged, but not mandatory. The radiotherapy was delivered at an outpatient clinic.

4) Evaluation for clinical response

The clinical restaging procedures included all the studies that had shown abnormal finding prior treatments, and were performed 3 to 4 weeks after the completion of all treatments, or at the last treatment in those that did not complete the planned treatment.

In contrast to metastatic diseases, which frequently have bidimensionally measurable lesions, those confined to the esophagus usually provide only unidimensional lesions (3), and in such a cases the WHO criteria for tumor responses following chemotherapy or radiotherapy are applicable only for those with a complete response. In this study, a complete response was defined as the complete disappearance of all clinical evidence of disease that persisted for more than 4 weeks, which was exactly the same as in WHO criteria. A partial response was defined as a decrease in the maximum esophageal wall thickness of more than 50%, with no evidence of progression or development of new lesions. Progressive diseases were defined as an increase in wall thickness of more than 25%, or any development of new lesions. A stable disease was defined as any changes in the esophageal wall thickness that did not fit into the partial improvement or progressive diseases.

5) Statistical analyses

Survival was measured from the date the treatment began to the date of death, or the most recent follow-up visit; the response duration was measured from the date that the response was declared to the date that the progression was confirmed, or the last visit without progression; and the time to progression from the date the treatment began to the date of the progression, or the last visit without progression. Estimates of all median durations are based on the Kaplan-Meier method.

RESULTS

1) Demographic data

Between October 1995 and April 2001, 22 eligible patients, with cancer of esophagus, were recruited. The patients’ characteristics are presented in Table 1. The tumor histology represented a squamous carcinoma in all cases, and all the patients were male, with only 4 cases older than 70 years.

The median length of follow-up the patients was 35.3 months, ranging from 3.5 to 69 months. The median follow-up, for the patients who were still alive at the most recent follow-up visit, was 19.3 months, ranging from 3.5 to 69 months.

2) Treatment-related toxicity

The hematological toxicity was relatively mild in all patients. Of the 57 evaluable cycles of chemotherapy, grades I or II neutropenia developed in 20 (35%) cycles, and grade III in 2 (4%). There were no episodes of treatment-related systemic infection or death. The major adverse effect of the treatment was mucositis. All patients had grade II, or more severe, mucositis, and 13 (59%) had grades III or IV toxic reactions that required a liquid diet or intravenous alimentation, as defined by the WHO criteria.
3) Response to treatment

Nineteen (86%) patients could be evaluated after the completion of their treatment. A complete response occurred in 7 (37%) patients, a partial improvement in 8 (42%), with an overall response rate of 79%. Of the 3 patients that could not be evaluated, 2 had subjective improvement of difficulties in swallowing. The median duration of the response, for the responders, and the time to progression, for all the patients, were 3 (95% confidence interval, 2.3−3.5) and 5.8 (95% C.I., 4.5−7.1) months, respectively.

4) Compliances with treatments and overall feasibility

The overall feasibility was evaluated by the weight changes during the treatment, the requirement for a hospital stay and the compliance with the treatment. Of the 22 patients, 13 (59%) had more than three cycles of chemotherapy and 9 (41%) received all four cycles (Table 2). Of the 13 patients not completing all the planned chemotherapy, 3 were due to a progression of the disease. The main reason for the completion of fewer than four cycles was from choice on the part of the physician or the patient. The mean (±SD) total delivered dose of radiation was 53±18 Gy. Fourteen (64%) patients received radiation of more than 59.4 Gy, with only 8 completing the four planned courses of chemotherapy.

The body weights were measured just before each treatment began, and 3 to 4 weeks after the last treatment in each patient. Overall, the mean (±SD) change in body weight during the treatment was a loss of 3.8±6.9% of the initial body weight. The mean changes in the body weight during the treatment, for patients who had grade II, III and IV mucositis, were 0.5, 3.3 and 7.1%, respectively (p=0.145). The body weights of the partial responders and nonresponders were reduced, on average, by 6.3 and 9.4%, respectively, compared with that of the complete responders, which increased by 1.2%.

The median number of admission was 4 (range, 1~7) and the mean (±SD) total duration of treatment, with the exception of the initial evaluation period, was 74±49 days. The mean (±SD) duration of hospital stay was 23±14 days.

5) Survival

After a median follow-up of 35 months, 12 patients had died and 2 were lost to follow-up. The median survival for all patients was 11 months (95% C.I., 3.2~19) (Fig. 1). The overall 1- and 3-year survivals were 49 and 32%, respectively. The median survival and the three-year survival rates for the patients with clinical stage II were 16.5 months and 38%, respectively, and those for the patients with stage III were 11.1 months and 26%, respectively (p=0.07) (Fig. 2). Of notes, whereas the median survival for the patients with grade III or

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<td>Evaluable for survival</td>
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<td>Sex (M/F)</td>
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<th>Table 2. Ability to deliver planned dose of treatment</th>
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<td>Chemotherapy</td>
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<td>Received all four cycles</td>
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<td>Radiotherapy</td>
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Fig. 1. Overall survival of all registered patients.

Fig. 2. Survival of patients according to the clinical stage.
IV mucositis was 8.4 months, that for the patients with grade II mucositis has not yet been reached (p=0.0027). However, there was a marginally significant correlation between the grades of mucositis and the clinical stages (p=0.06).

Survival analyses, according to compliance with the chemotherapy, showed that the median survival for patients who received three or more cycles of chemotherapy was 16.5 months, compared with 8.3 months for those that received less that three cycles. However, the three year survival rates for both groups were almost identical (32.5 and 31.1%).

**DISCUSSION**

In this study, it was found that 37% of patients who received the combined FP chemoradiotherapy had a complete clinical response, with 32% still alive after three years. These results were in accordance with those of recent trials investigating the role of the combined chemotherapy and radiotherapy as a definitive treatment, which showed three-year survival rates in the range of 25 to 35% (13 ~ 15).

The chemotherapies were delivered concurrently with the radiotherapy. Generally, chemotherapy combined with radiotherapy can be sorted into neoadjuvant and concurrent chemotherapy, according to the timing of the delivery, although trials using purely neoadjuvant chemotherapy prior to the radiotherapy, or sequential chemoradiotherapy, have been relatively rare with esophageal cancers (16,17). A recent follow-up result for the RTOG 85 ~ 01 trial, which used a similar treatment schedule to our study, showed a three-year survival rate of 30% for the combination arm, which was similar to our trial (32%) (18). Other trials, using neoadjuvant followed by concurrent chemotherapy with radiotherapy, have also shown similar 3-year survival rates (19,20). Of these, Minsky et al. reported results from 45 patients that received a modified RTOG 85 ~ 01 regimen, where the chemotherapy was somewhat more dose intensive, delivered before instead of after, the radiotherapy followed by concurrent chemoradiotherapy (20). With a median follow-up of 59 months and a three-year survival rate of 30%, which was exactly the same as for the RTOG 85 ~ 01. This result suggests that the benefit of chemotherapy, combined with radiotherapy, could be primarily attributable to the concurrent therapy, and the timing of the additional chemotherapy might be out of question. Lee et al. treated 43 patients with a similar regimen to our trial, but delivered maintenance chemotherapy after the completion of the radiotherapy for the patients who had not attained a complete response (21). The two and five-year survival rates were 39 and 18%, respectively, which were in similar ranges to our results.

In this trial, the median survival for the patients who received three or more courses of chemotherapy was almost double that of those that received less than three courses (16.5 vs. 8.3 months). However, the three-year survival rates for both groups were almost identical, suggesting the shorter median survival was not attributable to less chemotherapy. Instead, the patients with a poorer prognosis tended to receive lesser courses of chemotherapy. The further benefits of extended courses of chemotherapy, after completion of the radiotherapy, should therefore be seriously doubted, and a randomized trial comparing these reduced courses of chemotherapy is warranted. Moreover, in locally advanced non-small cell lung cancer, for which the combined modality treatments are being most extensively tested, the two courses of concurrent chemotherapy, without additional chemotherapy, have shown the best results (22,23).

In this trial, none of the patient underwent a salvage esophagectomy following the completion of the chemoradiotherapy. The role of surgery, following the combined modality treatment, still remains questionable (24). To our knowledge, there have, as yet, been no well designed randomized studies, which tested whether surgery, in addition to chemoradiotherapy, improves the outcome. Moreover, the operative or hospital mortalities, after multimodality treatment, are still very high, even in the more recent trials (25). The problem with surgical resection following chemoradiotherapy is not confined to esophageal cancers. In our opinion, it is a very important issue to be determined as soon as possible, as multimodality treatment are rapidly replacing surgical resection as the definitive therapies in relatively common tumors, such as non-small cell lung and head and neck cancers, where surgery has previously been considered the standard primary therapy.

The overall feasibility of the treatment was determined in terms of changes in the body weight and the total duration of hospital stay, in addition to the compliance with the treatment. Patients are more familiar with their weight changes than with the toxicity grades of mucositis. It is hypothesized that the major reason for the loss of weight is due to the decrease in oral intake, primarily related to the gastrointestinal mucosal toxicities. On average, about a 4% weight loss was observed during treatment. The weight losses were relatively tolerable in many patients, but were unacceptably severe (near 10 percent) to the patients that showed no response. Interestingly, the median survival for patients with more severe mucositis was significantly shorter than that of those with milder mucositis (8.4 months vs. not reached). However, because the grades of mucositis correlated with the clinical stages, with marginal significance (p=0.06), the decreased survival seemed to be due to the more advanced diseases among patients with more severe mucositis. There was no association between the grades of mucositis and the delivered number of chemotherapy cycles or dose of irradiation (data not presented). The hospital stays were in an acceptable range. The mean hospital stay was 23 days, which was slightly longer than the 17 days calculated as being necessary for an average of 2.8 cycles of chemotherapy.

**CONCLUSION**

Concurrent FP chemoradiotherapy provides a moderate chance of long term survival for patients with esophageal cancer. The major toxicity was mucositis. Although there were no treatment related deaths, a significant portion of the patients did not complete the planned treatment. Randomized trials, for shortening the duration of the chemotherapy, are warranted.

**REFERENCES**

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