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Clinical Trial Note

Phase II Study of Cisplatin and 5-Fluorouracil with Concurrent Radiotherapy in Advanced Squamous Cell Carcinoma of the Esophagus: a Japan Esophageal Oncology Group (JEOG)/ Japan Clinical Oncology Group Trial (JCOG9516)

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Background: In Japan, concurrent chemoradiotherapy is the standard treatment for unresectable esophageal cancer. The optimal combination of chemotherapeutic agents and radiotherapy dose remains controversial. The present study consists of a phase II trial of a cisplatin (CDDP)/5-fluorouracil (5-FU) infusion with concurrent radiotherapy in patients with unresectable, advanced esophageal cancer.
Methods: Between March 13, 1996, and April 28, 1998, 60 patients with advanced squamous cell carcinoma of the thoracic esophagus having either T4 tumor or distant lymph node metastasis (M1 Lym) were enrolled in this study. CDDP 70 mg/m^2 was administered on days 1 and 29, and 5-FU 700 mg/m^2/day was administered on days 1–4 and 29–32. Fractionated radiotherapy was performed on days 1–21 and 29–49; a total dose of 60 Gy was delivered at the rate of 2 Gy per fraction.
Results: The overall response rate of all the 60 registered patients was 68.3% (41/60), and the complete response rate was 15% (9/60). The median survival time was 305.5 days, and the 2-year survival rate was 31.5%. One toxicity-related death occurred. The major form of toxicity exceeding grade 2 was found to be myelosuppression; grade 4 toxicity was observed in five patients.
Conclusion: Based on the overall response rate, the results obtained from the present trial do not appear to be promising. However, it is currently suitable for the treatment of patients with unresectable, advanced esophageal cancer because of certain clinical advantages, a higher CR rate and a lower incidence of fistula formation. A phase II/III trial will be started in order to compare low-dose continual CDDP/5-FU infusion and concurrent radiotherapy with the results obtained in this study.

Key words: esophageal cancer – cisplatin – 5-fluorouracil – chemoradiotherapy – phase II study

INTRODUCTION

In Japan, the standard treatment for advanced esophageal cancer has not been established. Although surgery was performed on patients with locally advanced esophageal cancer, the outcome was not satisfactory due to high invasiveness and morbidity. Several clinical trials have been conducted to evaluate the efficacy and safety of radiotherapy and chemoradiotherapy, which could be more beneficial for the patients. Herskovic et al. (1) compared concurrent chemoradiotherapy (using 5-fluorouracil [5-FU] and cisplatin [CDDP] along with radiation) with radiation therapy alone in patients with locally advanced cancer of the thoracic esophagus (T1–3, N0–1, M0). They reported that the 2-year survival rate was 38% in the group that received chemoradiotherapy, and it was significantly higher than that observed in the group that received radiotherapy alone. As a result of this trial, concurrent chemoradiotherapy using 5-FU and CDDP has become a standard treatment for T1–3 disease. However, data regarding

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treatment of patients with more advanced disease are not available. We had previously conducted a phase II trial consisting of chemotherapy, using a combination of 5-FU and CDDP, followed by radiation therapy (sequential radiotherapy) in patients having T4 disease or distant lymph node metastasis (M1 Lym) and demonstrated that the response rate (RR) was 64.4% (2). Although the RR was found to be high in the group having a far advanced disease, it was felt that the concurrent chemoradiotherapy regimen would be more beneficial as compared with the sequential regimen because the radiosensitizing effect could be therapeutically more beneficial for the patients. Therefore, the present phase II trial (JCOG9516) was performed to evaluate the efficacy and safety of concurrent chemoradiotherapy.

Objective

The objective of this study was to evaluate the efficacy and safety of chemoradiotherapy regimen using CDDP/5-FU along with concurrent radiation therapy in order to determine whether this regimen merited further investigation by a phase III trial. The clinical hypothesis was that the above regimen would achieve a higher tumor response with acceptable levels of toxicity as compared to the former phase II trial that utilized a sequential regimen of CDDP/5-FU infusion and radiation therapy. The primary endpoint of this study was the observation of an overall response to this therapy. The secondary endpoints were concerned with the overall survival and toxicity.

SUBJECTS AND METHODS

Patients

Patients with histological proof of advanced squamous cell carcinoma (SCC) of the thoracic esophagus having T4 tumor or distant lymph node metastasis (M1 Lym) were considered to be eligible. Patients with esophagomediastinal fistula were included in this study, whereas those with esophagotracheal or esophagobronchial fistula and distant organ metastases were excluded. The other eligibility criteria were as follows: (i) age $\leqslant$75 years, (ii) performance status (PS) of 0–2 based on the classification criteria of the Eastern Cooperative Oncology Group, (iii) adequate renal (serum creatinine $\leqslant$1.2 mg/dl; BUN $\leqslant$25 mg/dl; creatinine clearance $\geqslant$60 ml/min), hepatic (total bilirubin $\leqslant$1.2 mg/dl; GOT $\leqslant$2.0 $\times$ normal value; GPT $\leqslant$2.0 $\times$ normal value), pulmonary (PaO_2 $\geqslant$70 mmHg) and bone marrow (Hb $\geqslant$10.0 g/dl; WBC $\geqslant$4000 /μl; platelets $\geqslant$100 000/μl) functions. Patients having other active synchronous carcinoma, concurrent uncontrolled medical illness, prior chemotherapy or radiation therapy for any neoplasms and pregnant or lactating women were excluded from the study. All patients provided written informed consent before registration in accordance with the policies of the JCOG. After assessment of the inclusion/exclusion criteria, the patients were centrally registered at the JCOG Data Center (JCOG DC); the orders were transmitted by telephone or fax.

Evaluation

Responses were assessed by barium esophagogram, computed tomography (CT) or magnetic resonance imaging (MRI) and esophageal endoscopy in accordance with the 'Guide Lines for Clinical and Pathologic Studies on Carcinoma of the Esophagus' 8th edition (3), issued by the Japanese Society for Esophageal Disease. A complete response (CR) was defined as a complete disappearance of all evidence of tumor without the appearance of new lesions for at least 4 weeks. A partial response (PR) was defined as a $\geqslant$50% reduction in the sum of the products of the two perpendicular diameters (SPD) of lesions that could be measured in two directions or a $\geqslant$30% reduction in the sum of the longest diameters of lesions that could be measured in one direction without the appearance of new lesions for at least 4 weeks. No change (NC) was defined as a <50% reduction and <25% increase in the SPD of lesions that could be measured in two directions or <30% reduction and <25% increase in the sum of the longest diameters of lesions that could be measured in one direction without the appearance of new lesions for at least 4 weeks. Progressive disease (PD) was defined as a $\geqslant$25% increase in the SPD of lesions that could be measured in two directions or in the sum of the longest diameters of lesions that could be measured in one direction or the appearance of new lesions. All responses (CR + PR) were reviewed and confirmed by X-rays, CT scan and endoscopic findings at regular JCOG meetings.

Statistical Analysis

Simon's two-stage minimax design (4) was used to investigate whether the overall response rate (CR + PR) was sufficient to proceed to phase III trials. The sample size was calculated based on an expected response rate of 80% and an acceptable lowest rate of 65%, with both alpha and beta error of 0.1; a total of 60 cases were required. In this design, when the number of responses exceeds 43 of 60 cases, this leads to the rejection of the hypothesis that true response rate is below 65%. Overall response rate was defined as the proportion of patients with CR or PR divided by the total number of registered patients. The confidence intervals for the response rate were based on the exact binomial distribution. Overall survival time was calculated from the date of registration to death due to any cause. Overall survival was estimated by the Kaplan–Meier method, and confidence intervals were based on Greenwoods' formula (5). The toxicity was graded based on the Japan Clinical Oncology Group Toxicity Criteria (6). All analyses were performed using SAS software version 6.12 (SAS Institute, Cary, NC) at the JCOG Data Center. The planned accrual period was 2 years, and the follow-up period was set as 2 years after the completion of the accrual.

Treatment

The treatment schedule is summarized in Fig. 1. CDDP 70 mg/m^2 was administered by slow drip infusion on days 1 and 29, and 5-FU 700 mg/m^2/day was administered by continuous

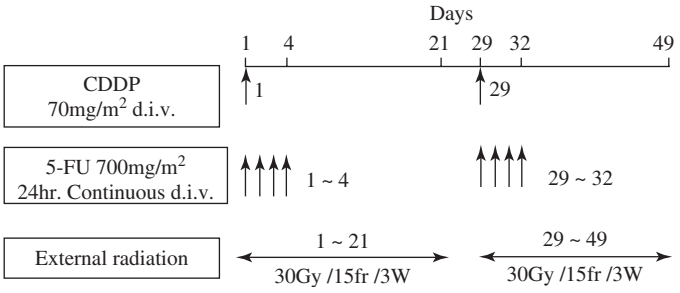

Figure 1. Treatment schedule. CDDP, cisplatin; 5-FU, 5-fluorouracil.

infusion for 24 h on days 1–4 and 29–32. Radiation was administered via a 6∼20 MV X-ray. Fractionated radiotherapy was performed on days 1–21 and 29–49, and a total dose of 60 Gy was delivered at the rate of 2 Gy per fraction (one fraction per day and five fractions per week). When the tumor was located in the upper or middle third of the thoracic esophagus, the treatment volume included the bilateral supraclavicular nodes as well as the mediastinum in a T-shaped pattern. When the tumor was located in the lower esophagus, the mediastinum and celiac axis lymph nodes were irradiated. However, in the celiac region, the dose was reduced to 46 Gy to avoid any adverse effect on gastrointestinal function. Oblique fields were used to spare the spinal cord after 40 Gy of radiation was delivered by anterior-posterior opposed pair portals. In the subsequent courses, the dose of CDDP was halved if creatinine level increased to ⩾1.3 mg/dl or creatinine clearance decreased to <60 ml/min, and terminated when the creatinine level increased to ⩾2.5 mg/dl or creatinine clearance decreased to <40 ml/min. Radiotherapy was suspended when the WBC count decreased to ⩽2000/μl or the platelet count decreased to ⩽50 000/μl and resumed when the WBC count recovered to ⩾3000/μl or the platelet count recovered to ⩾75 000/μl within 3 weeks, respectively. The study protocol was approved by the Clinical Trial Review Committee of JCOG and the institutional review board of each participating institution prior to the initiation of the study. The JCOG Data Center was in charge of the data management.

RESULTS

Between March 13, 1996 and April 28, 1998, a total of 60 patients from 15 institutions were registered in this study. The names of the 15 institutions, the number of registered patients from each institution and the names of the attending physicians are listed in Table 1. Among the 60 registered patients, there were 58 males and two females with a median age of 62 (range 45–74) years; no patients were found to be ineligible. The treatment was terminated in 14 patients for following reasons: disease progression in three patients, toxicities in seven patients, iatrogenic death in one patient, pulmonary tuberculosis in one patient, protocol violation in one patient and refusal of treatment by one patient. The characteristics of the patients and the target lesions are listed in Table 2.

Table 1. Names of the 15 institutions, number of registered patients in each institution and names of the attending physicians

Institution	No. of patients	Attending physicians	
Iwate Medical University	7	K. Ishida	T. Ynagisawa
National Cancer Center East	1	A. Ohtu	T. Ogino
Chiba University	1	K. Isono	T. Ariga
National Cancer Center	8	H. Watanebe	Y. Kagami
Tokyo Women's Medical College	8	H. Ide	T. Okawa
Keio University	8	N. Ando	H. Ito
Tokyo Medical Dental University	2	M. Endo	H. Shibuya
Tokai University	2	T. Mitomi	T. Omosato
Kanagawa Cancer Center	3	H. Koizumi	H. Yamashita
Niigata Cancer Center	7	O. Tanaka	M. Saito
Nigata University	4	T. Nishimaki	K. Sakai
Aichi Cancer Center	5	M. Shinoda	Y. Ito
Kyoto University	1	M. Imamura	Y. Nishimura
Shikoku Cancer Center	2	W. Takiyama	M. Kataoka
Kurume University	1	H. Yamana	M. Jo

Table 2. Patients' characteristics

Characteristic	$n = 60$
Sex	
Male	58
Female	2
Age (years)	
Median	62
Range	45–74
Target lesion (overlapped)	
Esophagus	60
Cervical lymph node	23
Mediastinal lymph node	33
Abdominal lymph node	13
Others	1

Table 3. Response rate and prognosis

No. of eligible patients	60/60 registered patients
Response rate	68.3% (9 CR + 32 PR/60 patients; 95% CI = 55.0–79.7%)
Median survival time	303.5 days (95% CI = 200–387 days)
2-year survival rate	31.5% (95% CI = 19.7–43.3%)

Forty-six (77%) patients completed the treatment regimen. Objective tumor responses observed among the 60 registered patients were as follows: 9 CR, 32 PR, 10 NC and 7 PD. Two patients could not be evaluated. The overall response rate (Table 3) was 68.3% (41/60, 95% confidence interval

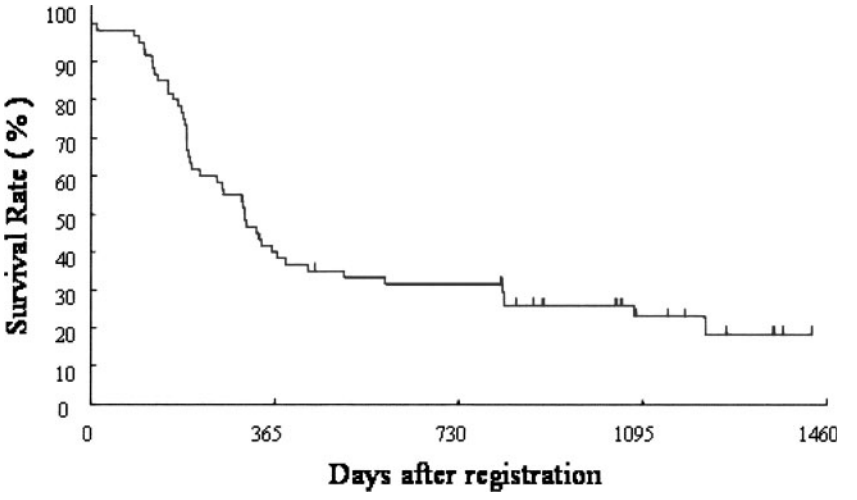

Figure 2. Overall survival among all patients ($n = 60$).

[CI] = 55.0–79.7). Forty-six patients out of a total of 60 died; 43 due to progressive disease, one due to iatrogenic cause and two due to other diseases. At the final follow up in May 2000, 13 patients remained alive, and one patient was lost to follow up. The overall survival curves for all patients are shown in Fig. 2. The median survival time (MST) was 305.5 days (95% CI = 200–387) and the 2-year survival rate was 31.5% (95% CI = 19.7–43.3). The toxicities observed in the patients are summarized in Table 4; hematologic toxicity was observed to be the dominant toxicity. Two iatrogenic deaths (3.3%) were observed either during or immediately following treatment. One patient died of hemorrhage from the tumor on day 6 following the first course, and this was considered to be an iatrogenic death. The other patient died due to sepsis from severe pulmonary infection, 26 days after the end of the treatment. Serious dyspnea was observed in one patient; this might be attributed to the radiation therapy. Grade 4 thrombocytopenia was observed in two patients.

Table 4. Toxicities: no. of cases ($n = 60$)

	Grade					% grade 4
	0	1	2	3	4	
Leukocyte	3	7	30	20	0	0
Neutrophil	14	12	27	5	0	0
Hemoglobin	16	12	28	4	–	0
Platelet	45	7	5	1	2	0
Total bilirubin	48	–	10	1	0	2.5
AST	33	17	7	3	0	0
ALT	32	17	5	6	0	0
PaO_2	23	32	2	0	0	0
Creatinine	52	8	0	0	0	0
Nausea/vomiting	1	27	18	3	–	0
Stomatitis	49	7	4	0	0	0
Diarrhea	50	6	3	1	0	0
Esophagitis	28	22	7	2	0	0
Dyspnea	57	1	0	1	1	1.7
Infection	46	10	3	0	1	1.7
Alopecia	58	2	0	0	0	0
Fever	29	23	8	0	0	0

DISCUSSION

There have been few reports on concurrent chemoradiotherapy for advanced esophageal cancer. Ohtsu et al. (7) reported a 3-year survival rate of 23% in 59 patients having T4 and/or M1 Lym esophageal cancer using definitive CT-RT consisting of 60 Gy irradiation along with CDDP and 5-FU. Furthermore, Nishimura et al. (8) initiated a prospective trial that aimed to evaluate the safety and efficacy of concurrent chemoradiotherapy using a protracted infusion of 5-FU and cisplatin in T4 esophageal cancer patients. They concluded that despite significant toxicity, which could result in the development or worsening of an esophageal fistula, their protocol appeared feasible and effective for the treatment of T4 esophageal cancer patient with or without fistula.

In the present study, the efficacy and safety of concurrent chemoradiotherapy was assessed using 5-FU and CDDP along with 60 Gy of radiotherapy in patients with advanced esophageal cancer in order to develop more effective treatment. The same concurrent chemoradiotherapy regimen used in the US study (1) was used in the present study. The overall tumor RR and CR rate were found to be 68.3 and 15%, respectively. From a statistical point of view, the overall tumor response rate was insufficient to reject the null hypothesis specified earlier in the protocol. One possible reason for this result was excessive expectation regarding the tumor response that could be achieved by this regimen; the expected RR appeared to be much higher than necessary. Although the efficacy of this regimen could not be demonstrated as planned, other efficacy endpoints, such as MST (305 days), 2-year survival rate (31.5%) and grade 4 toxicities (6.7%), were found to be better

than those in the previous study. Ishida et al. (2) investigated the efficacy and safety of sequential chemoradiotherapy in the same patients included in the present study and reported that the overall RR was 64.4%, CR rate was 8.9%, MST was 215 days, 2-year survival rate was 13.3% and life-threatening toxicities (grade 4) were observed in five patients (11%). Therefore, although not based on a direct comparison with sequential chemoradiotherapy, it is concluded that the concurrent regimen is more promising for the treatment of advanced esophageal cancer.

Other trials have used different combinations of chemotherapeutic agents and radiotherapy doses/methods with varying outcomes. John et al. (9) treated 21 patients with 5-FU, CDDP and Mitomycin C (MMC) along with local radiotherapy and reported that the 2-year survival rate was 29% and serious adverse events were observed in five patients (23.8%). Calais et al. (10) initiated a phase II trial that aimed to evaluate the feasibility of a combined treatment using 5-FU, CDDP and MMC chemotherapy and an external radiation dose of 60 Gy in patients with unresectable esophageal cancer and reported that the 3-year survival rate was 27% and WHO grade 4 toxicity rate was 7%. Gaspar et al. (11) conducted a trial of concurrent chemotherapy using 5-FU during both external beam radiation and brachytherapy in patients with potentially curable esophageal cancer and reported that the 1-year survival rate was 49%, MST was 11 months, life-threatening toxicities were observed in 24% patients and iatrogenic deaths occurred in 10% patients. These reports suggest that neither three-drug combination chemotherapy along with radiation nor concurrent chemoradiotherapy along with brachytherapy are more promising than our regimen. It is concluded that the two-drug combination of 5-FU and CDDP along with concurrent radiotherapy is effective and well tolerated. A phase II/III trial is being planned for comparing the regimen used in JCOG9516 and low-dose continuous CDDP/5-FU chemotherapy with radiotherapy (JCOG0303) in order to develop a more effective and less toxic concurrent chemoradiotherapy regimen.

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