3–4 non-hematological toxicity. Other dose adjustments are made on an individual patient basis. Treatment is discontinued if the tumor progresses, severe toxicity occurs or at the patient's request. There is no set maximum number of courses.

Cetuximab PK Analysis

Blood samples for PK analysis are taken in five patients at day 1 (end of infusion), day 15 (pre-dose and end of infusion) and day 29 (pre-dose). PK parameters are calculated according to standard non-compartmental methods.

Follow-up

Physical examination, safety evaluation and laboratory tests are performed prior to starting treatment and biweekly thereafter. Responses are evaluated every 8 weeks or earlier if there are indications of treatment failure due to toxicity. All eligible subjects are included in the assessment of efficacy and safety. Non-evaluable subjects are only added into the efficacy assessment data set as 'not evaluable'. The following dates are recorded: (i) date of starting treatment, (ii) date achieving best tumor response, (iii) date of disease progression, (iv) final date assessing survival and (v) date of death.

Study Design and Statistical Methods

A one-stage design employing binomial probability is used to determine the sample size. A patient receiving at least one chemotherapy study dose is considered evaluable for response. The response rate threshold is defined as 5%, and the expected response rate is set at 25%, since the response rate in the BOND-1 study was 22.9% (2). The sample size of this trial is 25 patients (α- and β-error probabilities, 0.05 and 0.2, respectively). Considering an ~10% drop-out rate, 30 patients are required for this study. Progression-free survival is measured from the date of entry into the trial to the time when progression or death without evidence of progression occurs. The median survival time is estimated from the date of study entry to the date of death or last follow-up visit using Kaplan–Meier methodology.

PARTICIPATING INSTITUTIONS (FROM NORTH TO SOUTH)

Hokkaido University Hospital, Aichi Cancer Center Hospital, Nagoya Kyoritsu Hospital and Osaka Medical College.

Conflict of interest statement

None declared.

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REPORT

PHASE II STUDY OF CHEMORADIOTHERAPY WITH 5-FLUOROURACIL AND CISPLATIN FOR STAGE II–III ESOPHAGEAL SQUAMOUS CELL CARCINOMA: JCOG TRIAL (JCOG 9906)

KEN KATO, M.D.,* KEI MURO, M.D.,*† KEIKO MINASHI, M.D.,‡ ATSUSHI OHTSU, M.D.,‡ SATOSHI ISHIKURA, M.D.,§ NARIKAZU BOKU, M.D.,¶ HIROYA TAKIUCHI, M.D.,‖ YOSHITO KOMATSU, M.D.,** YOSHINORI MIYATA, M.D.,†† AND HARUHIKO FUKUDA, M.D. § GASTROINTESTINAL ONCOLOGY STUDY GROUP OF THE JAPAN CLINICAL ONCOLOGY GROUP (JCOG).

*Gastrointestinal Oncology Division, National Cancer Center Hospital, Tokyo; †Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Aichi; ‡Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Chiba; §Clinical Trials and Practice Support Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo; ¶Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-gun, Shizuoka; ‖Cancer Chemotherapy Center, Osaka Medical College Hospital, Takatsuki, Osaka; **Department of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, Sapporo, Hokkaido; ††Department of Internal Medicine, Saku Central Hospital, Nagano, Japan

Purpose: In this Phase II study, we evaluated the efficacy and toxicity of chemoradiotherapy (CRT) with cisplatin (CDDP) and 5-fluorouracil (5-FU) for Stage II–III esophageal squamous cell carcinoma (ESCC).
Patients and Methods: Patients with clinical Stage II–III (T1N1M0 or T2–3N0–1M0) thoracic ESCC were enrolled between April 2000 and March 2002. Chemotherapy comprised two courses of protracted infusion of 5-FU (400 mg/m^2/day) on Days 1–5 and 8–12, and 2-h infusion of CDDP (40 mg/m^2) on Days 1 and 8; this regimen was repeated every 5 weeks. Concurrent radiotherapy involved 60-Gy irradiation (30 fractions) for 8 weeks with a 2-week break. Responders received two courses of 5-FU (800 mg/m^2/day) on Days 1–5 and CDDP (80 mg/m^2) on Day 1. Final analysis was conducted in March 2007. Survival and late toxicities were monitored for 5 years.
Results: The characteristics of the 76 patients enrolled were as follows: median age, 61 years; male/female, 68/8; performance status 0/1, 59/17 patients; Stage IIA/IIB/III, 26/12/38 patients. Of the 74 eligible patients, 46 (62.2%) achieved complete response. Median survival time was 29 months, with 3- and 5-year survival rates of 44.7% and 36.8%, respectively. Acute toxicities included Grade 3/4 esophagitis (17%), nausea (17%), hyponatremia (16%), and infection without neutropenia (12%). Late toxicities comprised Grade 3/4 esophagitis (13%), pericardial (16%) and pleural (9%) effusion, and radiation pneumonitis (4%), causing 4 deaths.
Conclusions: CRT is effective for Stage II–III ESCC with manageable acute toxicities and can provide a nonsurgical treatment option. However, further improvement is required for reduction in late toxicity. © **2010 Elsevier Inc.**

Esophageal squamous cell carcinoma, Chemoradiotherapy, Long-term toxicity, Salvage surgery.

INTRODUCTION

Esophageal cancer, a highly virulent malignancy, was responsible for 11,182 deaths in Japan in 2005, accounting for 3.4% of the country's total cancer deaths (1), with 35–40% of the patients diagnosed with Stage II–III disease. When this study was planned, the standard treatment for Stage II–III esophageal squamous cell carcinoma (ESCC) in Japan was esophagectomy with three-field lymph node dissection, followed by postoperative chemotherapy; the 5-year survival rate is reported to be 36.8–61% (2–4), with a high morbidity rate.

Chemoradiotherapy (CRT) has proved effective against resectable/unresectable ESCC. The Radiation Therapy Oncology Group (RTOG) trial 85-01 demonstrated the superiority of CRT with cisplatin (CDDP), 5-fluorouracil (5-FU), and concurrent irradiation (50.4 Gy) over radiotherapy alone (64 Gy) in patients with T1–3N0–1M0 esophageal cancer (5), in which the final outcome showed a 5-year survival rate of 26% in the CRT arm compared with 0% in the

Reprint requests to: Ken Kato, M.D., Ph.D., Gastrointestinal Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel: (+81) 3-3542-2511; Fax: (+81) 3-3542-3815; E-mail: kenkato@ncc.go.jp

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radiation-alone arm (6). Therefore, CRT is recognized as the standard noninvasive treatment for patients with localized esophageal cancer who opt for nonsurgical treatment.

CRT was introduced in Japan in the early 1990s as a treatment for potentially unresectable locally advanced ESCC. In a Phase II trial, 18 of 54 (33%) patients with clinical T4 and/or M1 lymph node ESCC, who received CDDP/5-FU with concurrent 60-Gy irradiation, achieved complete response (CR) with a 3-year survival rate of 23% (7). Since then, CRT has been clinically indicated for patients with resectable ESCC who refuse surgical resection. In a retrospective analysis, 55 patients with T1–3NanyM0 ESCC, who received CRT with CDDP, 5-FU, and concurrent 60-Gy irradiation, showed a CR of 70% and a 5-year survival rate of 46%, suggesting comparable outcomes with surgery (8). However, the results were retrospective. Thus, we conducted a Phase II study to evaluate the efficacy and toxicity, particularly the long-term outcome, of CRT for Stage II–III ESCC.

PATIENTS AND METHODS

Eligibility

The eligibility criteria were as follows: pathologically confirmed thoracic ESCC; clinical Stage II–III excluding T4 (T1N1M0 or T2–3N1–0M0: International Union Against Cancer [UICC] 1997); Eastern Cooperative Oncology Group (ECOG) performance status (PS), 0 or 1; and age, 20–70 years. Patients who had previously undergone therapy for esophageal cancer or chemotherapy/radiotherapy for other malignancies and who previously had had other active malignancies were excluded. All the patients had to meet the following laboratory criteria within 14 days before registration: leukocytes $\geq$3,000/mm^3; platelet count $\geq$100,000/mm^3; hemoglobin level $\geq$10 g/dL; aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leq 2 \times$ the upper normal limit at the institution; total bilirubin $\leq$1.5 mg/dL; serum creatinine $\leq$1.2 mg/dL; creatinine clearance $\geq$50 mL/min; $PaO_2 \geq$70 mm Hg; and no major electrocardiogram abnormalities. Written informed consent was obtained from all the patients. The study protocol was approved by the JCOG Clinical Trial Review Committee and institutional review boards of the participating institutions.

Chemotherapy

Chemotherapy comprised two courses of protracted infusion of 5-FU (400 mg/m^2/day) on Days 1–5 and 8–12, and 2-h infusion of CDDP (40 mg/m^2) with adequate hydration and antiemetic coverage on Days 1 and 8; this regimen was repeated every 5 weeks. Responders additionally received two courses of 5-FU (800 mg/m^2/day) on Days 1–5 and CDDP (80 mg/m^2) on Day 1 (Fig. 1), repeated every 4 weeks. No further treatment was administered to patients with CR until disease progression. Additional chemotherapy courses were optional for patients with visible disease.

Administration of both chemotherapy agents was discontinued until toxicity improved to $\leq$Grade 2. The doses were reduced by 25% in the subsequent course after at least one of the following toxicities was observed: leukocytes <1,000/mm^3; platelet count <30,000/mm^3; total bilirubin >2.0 mg/dL; serum creatinine $\geq$2.0 mg/dL; Grade 3/4 stomatitis; or Grade 3/4 esophagitis. Total parenteral nutrition was provided as necessary. Treatment was terminated when disease progression was observed, patients refused to continue, or recovery from toxicity delayed the initiation of the second course by >3 weeks from the planned schedule.

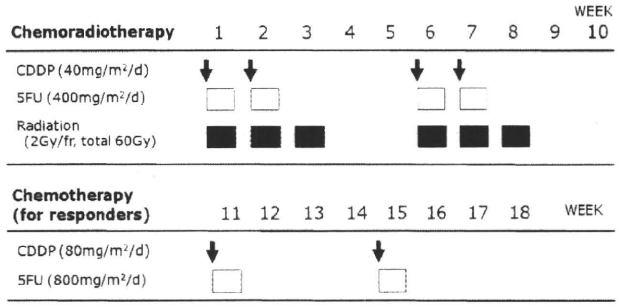

Fig. 1. Protocol scheme.

Radiotherapy

Radiotherapy was delivered using megavoltage ($\geq$6 MV) x-rays; a total dose of 60 Gy was administered in 30 fractions. A 2-week break was provided after 30-Gy irradiation, and radiotherapy was resumed on Day 36 with the second chemotherapy course. The clinical target volume (CTV) for 60-Gy irradiation included the primary tumor plus a 5-cm craniocaudal margin, and the metastatic lymph nodes plus a 1-cm margin. Planning target volume was defined as CTV plus 5- to 20-mm margins for uncertainty. Elective nodal irradiation (40 Gy) of mediastinal and perigastric lymph nodes for all cases, cervical lymph nodes for an upper thoracic primary tumor, and celiac lymph nodes for a lower thoracic primary tumor was also performed. Three-dimensional computed tomography (CT) or X-ray simulation was performed, allowing two-dimensional anterior–posterior opposed fields and bilateral oblique boost. Heterogeneity-uncorrected doses were used.

Assessments

Esophagoscopy and CT were carried out after each course to assess the response. Primary tumor response was evaluated by endoscopy using the modified criteria of the Japanese Society for Esophageal Diseases (9). Complete response of lymph node metastasis was defined as the disappearance of all visible lymph node metastases on the CT or size reduction to $\leq$1 cm for $\geq$3 months after the completion of treatment. Overall CR was declared by an attending physician when CR at both a primary tumor and a lymph node was obtained without the appearance of a new lesion. Complete response was confirmed by reassessment at $\geq$4 weeks after the first assessment. Complete response cases were centrally reviewed, and CR was confirmed by extramural review of the CT scan and images of endoscopy.

Acute toxicities were assessed weekly during CRT and every 2 weeks during additional chemotherapy for 90 days after the completion of CRT. Toxicities were evaluated based on the National Cancer Institute Common Toxicity Criteria (version 2.0). Late toxicity, which first occurred 90 days after CRT initiation, was assessed using the RTOG/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.

Statistical methods

The primary endpoint was overall survival (OS), which was defined as the time from the date of registration to that of death resulting from any cause, and it was censored at the date of the last follow-up for survivors. Progression-free survival (PFS) was defined as the time from the date of registration to that of disease progression or death resulting from any cause, and it was censored at the date of the last visit for patients without progression. Based on the JCOG 9204 trial results (2), in which the 3-year survival rate was 61% for esophagectomy with adjuvant chemotherapy, we initially calculated the sample size expecting a 3-year survival rate of 60%, with a threshold of 45%. With the alpha and beta error levels set at 0.05 and 0.2, respectively, the required number of eligible patients was 68. We finally decided on a sample size of 76, including ineligible patients. The planned accrual and follow-up periods after registration was closed were 1 and 2 years, respectively. For early termination of this study, an interim analysis was planned once 50% of the patients were accrued. A CR point estimate of <60% at the interim analysis would result in early termination of the study.

The JCOG 9204 had enrolled patients based on the pathologic stage after surgery, whereas we enrolled patients based on the clinical stage diagnosed from CT scans. Therefore, this study might include patients with more advanced stages than those in the JCOG 9204. Thus, the protocol was amended to recalculate the sample size from the expected 50% 3-year survival rate and a threshold of 35% in December 2000. The required sample size was 67. The target sample size remained unchanged. The second amendment in February 2007 prolonged the follow-up period to 5 years after the last enrollment to evaluate late toxicity. These amendments were approved by the Data and Safety Monitoring Committee of JCOG.

Secondary endpoints included CR rate, PFS, and acute and late adverse events. Time-to-event distribution was estimated using the Kaplan-Meier method, and confidence intervals (CIs) were calculated using Greenwood's formula. All analyses were performed using SAS Version 9.1.3 software (SAS Institute, Cary, NC, USA) at the JCOG Data Center, with the final analysis conducted in March 2007.

RESULTS

Patient characteristics

Seventy-six patients, whose characteristics are summarized in Table 1, were accrued between April 2000 and March 2002. The median age was 61 years (range, 39–70). Fifty-nine (78%) and 17 (22%) patients showed ECOG PS of 0 and 1, respectively. Fifty-two patients had T3 disease, and 50 had N1 disease. The clinical stages (UICC-TNM) were IIA for 26 patients, IIB for 12 patients, and III for 38.

Table 1. Patient characteristics

Characteristic	Patients (n = 76)	(%)
Male	68	89.4
Female	8	10.6
Age (y)		
Range	39–70	
Median	61	
Performance status		
0	59	77.6
1	17	22.4
Tumor location		
Upper	3	3.9
Middle	44	57.9
Lower	29	38.2
T factor		
T1	8	10.5
T2	16	21.1
T3	52	68.4
N factor		
N0	26	34.2
N1	50	65.8
Stage		
IIA	26	34.2
IIB	12	15.8
III	38	50.0

Response

Two patients were excluded from the efficacy analysis because of inadequate liver function and T4 disease diagnosed after registration (Fig. 2). Of the 74 eligible patients, 46 achieved CR, resulting in a CR rate of 62.2% (95% CI, 50.1–73.2). The confirmed CR rate in 23 patients with T1–2 disease was 78.3% (95% CI, 56.3–92.5), and that in 51 patients with T3 disease was 54.9% (95% CI, 40.3–68.9).

Survival

There were 49 deaths in the final analysis, and all except 5 patients were followed up for >5 years. The median survival time was 2.4 years (Fig. 3); the 3- and 5-year survival rates were 44.7% (90% CI, 35.2–53.8) and 36.8% (95% CI, 26.1-47.5), respectively. The lower limit of 90% CI for the 3-year survival rate exceeded the threshold of 35%, and the

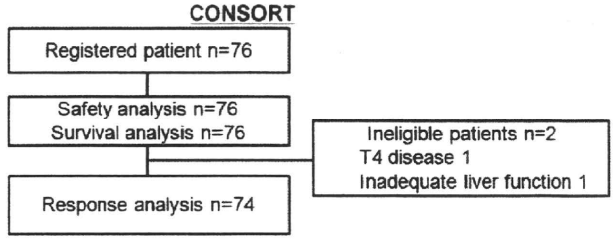

Fig. 2. Consolidated Standards of Reporting Trials diagram.

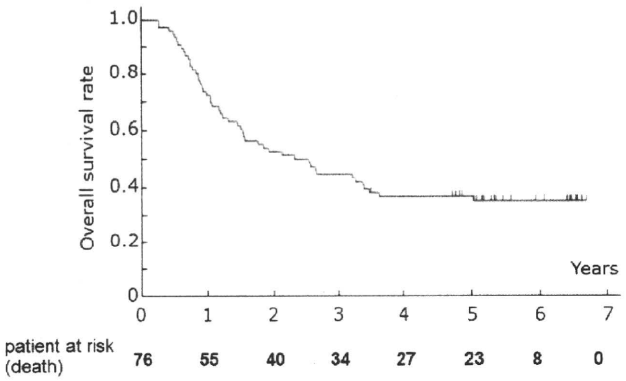

Fig. 3. Overall survival of the 76 patients enrolled in the study.

null hypothesis was rejected ($p = 0.019$). The median PFS was 1 year; the 3- and 5-year PFS rates were 32.9% and 25.6%, respectively (Fig. 4).

Acute toxicity

Data of adverse events for all 76 patients occurring within 90 days after CRT completion are shown in Table 2. Grade 4 leukopenia, neutropenia, anemia, and thrombocytopenia were observed in 1.3%, 1.3%, 2.6%, and 0% of the patients, respectively, whereas Grade 3/4 esophagitis, nausea, infection without neutropenia, and hyponatremia were observed in 17%, 17%, 12%, and 16% of the patients, respectively.

Fifty-three (69.7%) patients completed the 2-course CRT and 2-course additional chemotherapy. Seventy-two (95%) patients received the full dose (60 Gy) of radiation. The treatment protocol was terminated in 23 patients because of disease progression ($n = 10$), toxicity ($n = 11$), patient refusal ($n = 1$), and other reasons ($n = 1$). One early death occurred from esophageal perforation caused by disease progression 21 days after CRT completion. A relationship between early death and the treatment protocol was considered unlikely by the Data and Safety Monitoring Committee.

Late toxicity

Late toxicity data are shown in Table 3. Grade 3–4 late toxicities included pleural (9%) and pericardial (16%) effusion, stenosis, or esophageal fistula (13%), and radiation pneumonitis (4%). Four (5.3%) patients possibly died of treatment-related late toxicity at 3.1, 8.5, 21.3, and 27.8 months after registration. The cause of death were pneumonitis ($n = 2$), pericarditis ($n = 1$), and pleural effusion ($n = 1$). There was no evidence of residual or recurrent disease in these patients. The proportion of any Grade 3/4 late toxicity was 30.1% after 5 years from the initiation of chemoradiation.

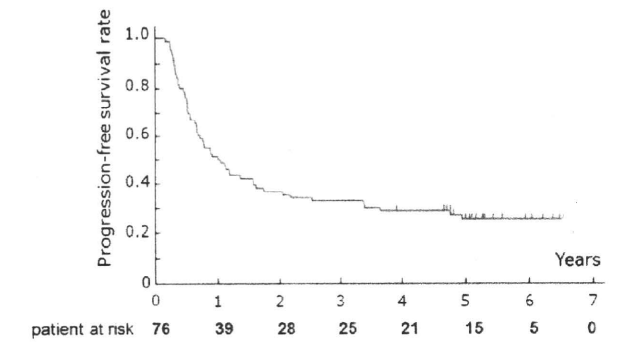

Fig. 4. Progression-free survival rate of the 76 patients enrolled in the study.

Salvage treatment

Twenty-six (34.2%) patients had residual disease or locoregional recurrence without distant metastasis after CRT. Because of inadequate conditions or patient refusal, 7 and 5 patients received chemotherapy and the best supportive care, respectively; the remaining 14 patients received unplanned curative-intent salvage therapy. Eleven patients underwent salvage esophagectomy for residual ($n = 4$) and recurrent ($n = 7$) disease, and the remaining 3 patients underwent endoscopic treatment such as endoscopic mucosal resection (EMR) or argon plasma coagulation. The characteristics of the patients who underwent salvage surgery are described in Table 4.

The median time to salvage surgery after CRT initiation was 13.9 months (range, 4.0–22.7). Six patients underwent esophagectomy with two- or three-field lymph node dissection, 3 patients underwent simple esophagectomy, and 1 underwent only lymphadenectomy; 1 patient could not undergo any resection because of extensive lymph nodes metastasis detected at thoracotomy. Reconstruction was performed using a gastric tube in 7 patients who had R0 resection. There was no operative mortality or hospital death. The median survival time and 3-year survival rate for these 10 patients who received salvage esophagectomy was 16.7 months and 40% (95%C.I: 12.3%–67.0%), respectively.

Of the 3 patients who underwent endoscopic treatment, 1 had mediastinal lymph node metastasis 3 months after argon plasma coagulation, 1 died of surgery-related complication of the pharynx detected 1 year after EMR, and 1 survived for >5 years with no evidence of disease.

DISCUSSION

From the results, CRT for Stage II–III ESCC showed a CR rate of 62.2% (95% CI, 50.1–73.2), a 3-year survival rate of 44.7% (90% CI, 35.2–53.8), and a 5-year survival rate of 36.8% (95% CI, 26.1–47.5). The 3-year survival rate, which is the primary endpoint of this study, met the decision criteria.

Clinically, it is very important to know whether definitive CRT can achieve survival comparable with surgery plus postoperative adjuvant chemotherapy. In this regard, there were several differences in the background between the present study and JCOG 9204 (2) described in Statistical Methods. The study conducted after JCOG 9204, which compared preoperative and postoperative adjuvant chemotherapy comprising the administration of 5-FU and CDDP to Stage II–III esophageal cancer patients (JCOG 9907) (10), could be a reference for this study, because the patients were registered before surgery based on the clinical stage. In the recently

Table 2. Toxicity (n = 76)

Toxicity	NCI-CTC Version 2.0				
	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)
Leukocytes	5	34	32	1	43
Neutrophils	17	31	19	1	26
Hemoglobin	13	35	15	2	22
Platelets	15	13	4	0	5
Dysphagia, esophagitis	29	14	13	0	17
Nausea	25	20	13	–	17
Vomiting	16	6	0	0	0
Diarrhea	10	5	1	0	1.3
Stomatitis/pharyngitis	15	9	6	0	8
Radiation dermatitis	18	4	0	0	0
Febrile neutropenia	–	–	1	0	1.3
Infection without neutropenia	7	8	8	1	12
Hyponatremia	40	–	11	1	16
AST	35	4	3	0	3.9
ALT	43	7	2	1	3.9
Creatinine	15	13	1	0	1.3

Abbreviations: NCI-CTC Version 2.0 = National Cancer Institute Common Toxicity Criteria Version 2.0; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

published results of JCOG 9907, the preoperative chemotherapy arm was highly superior to the postoperative chemotherapy arm in terms of OS. The 5-year survival rate of the postoperative chemotherapy arm in JCOG 9907 did not differ significantly from that in the present study, that is, 38.4% and 36.8%, respectively (10). By contrast, the 5-year survival rate of the preoperative chemotherapy arm in JCOG 9907 was 60.1%, although further follow-up is needed to verify the data. CRT may produce comparable outcomes with surgery plus postoperative adjuvant chemotherapy; however, surgery after preoperative chemotherapy is considered to be superior to CRT. Nevertheless, CRT is one of the treatment options for patients with Stage II and III ESCC because of its apparent advantage of preserving the esophagus, which may provide better quality of life.

Chemoradiotherapy achieves prolonged survival with possibly more late toxicity. Late toxicity after thoracic radiotherapy has been reported in patients with esophageal cancer, lung cancer, and Hodgkin's lymphoma (11–13). Some reports have described that long-term toxicity after CRT results in serious, life-threatening complications. In a previous study, 2 of 78 patients with CR after CRT died of myocardial infarction, and 8 (10.2%) died of pericardial or pleural effusion (14) Late toxicity after CRT against ESCC has not yet been investigated in detail, and early reports of trial outcomes generally seem to underestimate the risk of late toxicity in long-term survivors (15). In the present study, the incidence of ≥Grade 3 late toxicity was similar to that reported in a previous study (14). Most of these events occurred several years after CRT. It is considered that reduction in radiation dose, careful observation, and control of late toxicity may improve post-CRT survival. RTOG 94-05 demonstrated that a higher irradiation dose (64.8 Gy) in CRT was not advantageous with regard to survival and local control, compared with the standard dose (50.4 Gy) (16). One of the reasons was the low tolerability of the high-dose arm because of toxicity. Whereas decreasing the irradiation dose in radiotherapy is essential for reducing late toxicity, the radiation volume is also

Table 3. Late toxicity (n = 76)

Late toxicity	RTOG/EORTC late radiation morbidity scoring scheme					
	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)	≥Grade 4 (%)
Pleural effusion (nonmalignant)	24	5	7	0	9	0
Esophagus-related (dysphagia, stenosis, fistula)	11	4	4	6	13	8
Pericardial effusion	6	5	9	3	16	4
Radiation pneumonitis	33	6	2	1	4	1.3
Skin-related	3	0	0	0	0	0
Spinal cord—related	3	0	0	0	0	0

Abbreviation: RTOG/EORTC: radiation therapy oncology group/european organization for research and treatment of cancer.
four (5.3%) patients possibly died of treatment-related late toxicity: pericarditis (n = 1), pleural effusion (n = 1), and pneumonitis (n = 2).

Table 4. Characteristics and outcomes in patients who underwent salvage surgery

Characteristic	Patients (n = 11)	Characteristic	Patients (n = 11)
Male	11	Residual/Recurrent	4 /7
Female	0		
Age (y)		Surgical curability	
Range	46–70	R0	7
Median	59	R1 + R2	4
Tumor location			
Upper	0	Operative mortality or hospital death	0
Middle	6		
Lower	5	Relapse after surgery	8
Clinical stage*		No relapse	3
IIA	5		
IIB	0		
III	6		

* Clinical stage at the time of registration.

important. In this study, late toxicity might have been caused by the extended volume of irradiation, which corresponds to the dissected area in extended surgery. In the near future, three-dimensional conformal radiotherapy, which was not mandatory in this study, or other methods based on advanced technology such as intensity-modulated radiotherapy and proton therapy, may have potential advantages over conventional two-dimensional radiotherapy in terms of reduced doses for the heart. A clinical trial with these latest radiotherapy techniques is required (17).

Salvage treatment—*e.g.*, salvage surgery (18–20) or salvage EMR (21)—has recently been reported to have therapeutic potential for patients with local failure of CRT. In our study, one-third of the patients did not achieve CR, and 50% of the remaining patients had recurrence after achieving CR. For the latter, salvage treatment should be indicated, if applicable. Mucosal disease can be removed by EMR, and locoregional residual or recurrent disease can be curatively resected by surgery. It has been reported that 6–34% of patients undergo salvage esophagectomy after definitive CRT (22, 23). Although a high rate of hospital deaths (6–33%) is observed compared with that after surgery without preoperative therapy, some patients achieve long-term survival with a 5-year survival rate of 25–35% (24–26). In the present study, 11 (14.5%) patients underwent salvage esophagectomy and 7 had R0 resection. There was no operative mortality or hospital death. The limitations of salvage surgery include patient tolerance, capability of medical staff, and early detection of residual or recurrent disease; however, salvage esophagectomy can achieve long-term survival. Some patients benefit from salvage surgery after definitive CRT; therefore, this procedure is worth further investigation.

Neoadjuvant CRT has recently been recognized as a standard therapy for resectable esophageal cancer in Western countries. According to CALGB 9781, CRT followed by surgery prolonged survival (median survival time, 4.48 vs. 1.79 years) compared with surgery alone in the treatment of esophageal cancer (27). However, most participants in CALGB 9781 had esophageal adenocarcinoma. Meta-analysis has revealed the survival benefit of neoadjuvant CRT in patients with esophageal adenocarcinoma (28). According to FFCD 9102, which included 90% patients with squamous cell carcinoma, surgery after neoadjuvant CRT (40 Gy) and continuation of CRT to 60 Gy without surgery had the same impact on survival and quality of life for responders as induction CRT (29). The results of a randomized trial from Germany, in which 172 ESCC patients randomly received CRT with or without additional surgery, indicated equal efficacy of surgery and CRT. The median survival times were 16.4 months and 14.9 months, respectively, and the 2-year survival rates were 39.9% and 35.4% with and without surgery, respectively (30). This suggests that CRT, which can preserve organ function, is equally effective as surgery for responders. For nonresponders, salvage surgery can be a therapeutic option. Importantly, which types of patients are benefited by salvage surgery or how the surgical procedure is performed after CRT should be prospectively evaluated. We are planning a Phase II trial of CRT for resectable ESCC, followed by salvage surgery for residual or recurrent disease.

CONCLUSION

Chemoradiotherapy is effective for Stage II–III ESCC with manageable acute toxicities and can provide a noninvasive treatment option. However, further improvement is required for reduction in late toxicity.

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ORIGINAL ARTICLE

A phase II study of paclitaxel by weekly 1-h infusion for advanced or recurrent esophageal cancer in patients who had previously received platinum-based chemotherapy

Ken Kato · Makoto Tahara · Shuichi Hironaka · Kei Muro · Hiroya Takiuchi · Yasuo Hamamoto · Haruhiko Imamoto · Norihito Amano · Taku Seriu

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Abstract
Purpose To evaluate the efficacy and safety of weekly paclitaxel (Taxol®) in patients with advanced or recurrent esophageal cancer.
Methods Fifty-three patients with recurrent or advanced esophageal cancer who had previously received platinum-based chemotherapy were treated with paclitaxel 100 mg/m^2 once weekly by 1-h infusion on days 1, 8, 15, 22, 29, and 36 of a 49-day cycle. Fifty-two patients were evaluable for efficacy and 53 for safety. Forty-one (77%) patients had recurrent, and 12 (23%) had advanced disease. Most patients (52/53) had squamous cell carcinoma, and one had adenocarcinoma.
Results A median of 2 cycles was delivered (range 1–8). The overall response rate was 44.2% (23/52; 95% confidence interval (CI) 30.5, 58.7%), with 4 patients (7.7%) achieving complete response. The median duration of response was 4.8 months, and median overall survival was 10.4 months. The most common Grade 3 or 4 adverse events were neutropenia (52.8%), leukopenia (45.3%), anorexia (9.4%), and fatigue (9.4%). Adverse events resulted in treatment discontinuation in 34.0% of patients and dose reductions in 43.4%. There were no treatment-related deaths.
Conclusions Weekly paclitaxel demonstrated efficacy and manageable toxicity in patients with advanced or recurrent esophageal cancer and may be a treatment option for this population.

Keywords Esophageal cancer · Paclitaxel · Phase II study · Weekly infusion

K. Kato (✉)
Gastrointestinal Oncology Division,
National Cancer Center Hospital, Tsukiji 5-1-1,
Chuo-ku, Tokyo 104-0045, Japan
e-mail: kenkato@ncc.go.jp

M. Tahara
Department of Gastrointestinal Medicine,
National Cancer Center Hospital East,
Kashiwanoha 6-5-1, Kashiwa, Chiba 277-8577, Japan

S. Hironaka
Gastrointestinal Oncology Division,
Shizuoka Cancer Center,
1007 Shimonagakubo Nagaizumi Sunto-gun,
Shizuoka 411-8777, Japan

K. Muro
Department of Clinical Oncology,
Aichi Cancer Center Central Hospital,
1-1 Kanakoden, Chikusa-ku Nagoya,
Aichi 464-8681, Japan

H. Takiuchi
Department of Gastrointestinal Medicine,
Osaka Medical College, Daigaku-cho 2-7,
Takatsuki, Osaka 569-8686, Japan

Y. Hamamoto
Division of Clinical Oncology, Tochigi Cancer Center,
Yonan 4-9-13, Utsunomiya, Tochigi 320-0834, Japan

H. Imamoto
Department of Surgery, Kinki University,
Onohigashi 377-1, Osakasayama,
Osaka 589-8511, Japan

N. Amano · T. Seriu
Research and Development, Bristol-Myers K.K,
Nishishinjuku 6-5-1, Shinjuku-ku,
Tokyo 163-1328, Japan

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Introduction

Esophageal cancer constitutes a global health burden, with between 400,000 and 500,000 new cases diagnosed annually [1, 2]. It is the eighth most common cancer worldwide and ranks sixth as a cause of cancer death [2]. The overall incidence of esophageal cancer appears to be rising, principally due to an increase in the incidence of adenocarcinoma of the lower third of the esophagus in western countries [3–5]. This may be due to increasing rates of obesity, gastro-esophageal reflux, and Barrett's esophagus in those countries. However, the majority of esophageal cancers worldwide are squamous cell carcinomas, which is the most common histological type in Japan. Surgery, radiation therapy, and chemotherapy are the major treatment modalities for esophageal cancer. For operable patients, surgery is the first choice of treatment in Japan. The 5-year survival rate with surgery alone is 31–55% [6–8], comparable to results obtained in the United States and Europe. However, local resection is still far from satisfactory, due to the rate of surgery-related death and the negative effect on quality of life that can follow surgery [6–8]. In addition, local resection alone rarely results in complete recovery, since esophageal cancer spreads rapidly into the adjacent structures such as trachea or bronchus [9]. Chemotherapy, specifically the combination of cisplatin and 5-fluorouracil (5-FU), is considered the first-line standard regimen for non-surgical therapy for esophageal cancer. This regimen is active, demonstrating a response rate of 36% for advanced or recurrent squamous cell esophageal cancer [10]. However, no treatment is established for patients who fail therapy with this regimen.

Paclitaxel has shown anti-tumor activity against esophageal cancer as a single agent, in combination with chemotherapy, and administered with concurrent radiotherapy for locally advanced disease [11–15]. Combination therapy has been shown to achieve good response rates even for metastatic disease, but has been associated with high rates of toxicity, including myelosuppression, gastrointestinal toxicity, and neurotoxicity [14]. Identifying an optimal dose and schedule for paclitaxel therapy is key to minimizing toxicity while maintaining anti-tumor activity. Weekly administration of paclitaxel for breast and ovarian cancer has been shown to be associated with acceptable toxicity levels [16–18]. In addition, the use of a 1-h infusion schedule has been shown to result in less hematologic toxicity compared to a 24-h infusion schedule [19, 20].

Ilson et al. [21] recently showed that paclitaxel 80 mg/m^2 administered by weekly 1-h infusion was well tolerated and showed modest activity in advanced esophageal cancer. A phase I trial in Japan studied weekly paclitaxel for solid tumors, in which paclitaxel was administered weekly over 1 h for 6 weeks followed by a 1-week break. Paclitaxel dose was escalated from 80–120 mg/m^2 with no dose limiting toxicity observed. Peripheral neuropathy developed in all six patients who received 120 mg/m^2/week and four patients discontinued treatment [22]. A dose of 120 mg/m^2 was therefore set as the maximum acceptable dose (MAD) and 100 mg/m^2 recommended for phase II studies. We therefore evaluated the efficacy and safety of paclitaxel 100 mg/m^2/week in patients with advanced or recurrent esophageal cancer who were previously treated with platinum-based chemotherapy.

Patients and methods

This open-label, phase II, multicenter single-stage study was conducted at 12 participating centers in Japan. Eligible patients were adults of at least 20 years of age (no upper limit) with histologically confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the esophagus, and who had received at least one regimen of platinum-based chemotherapy. Patients were required to have advanced (stage IV) or recurrent (after chemotherapy, surgery or radiotherapy) disease. Previous platinum-based chemotherapy could have occurred in the adjuvant or neoadjuvant setting, or in combination with radiotherapy. Patients had either failed or progressed (stage IV) following platinum-based therapy, or had discontinued due to toxicity. Patients were required to have measurable disease, defined as a lesion that could be measured in at least one dimension, for which the longest diameter was either $\geq$20 mm as assessed by conventional computed tomography (CT) or magnetic resonance imaging (MRI) scan or $\geq$10 mm as assessed by spiral CT scan. Measurable lesions were required to be outside the primary lesion prior to previous chemotherapy. Further, criteria included an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and a life expectancy of $\geq$2 months. Patients were required to have had adequate recovery from prior systemic therapy as follows: $\geq$4 weeks post-radiation therapy; $\geq$4 weeks post-chemotherapy and surgical therapy; $\geq$2 weeks post-treatment with fluorouracil (5-FU and TS-1) or biologic response modifiers (in the absence of bone marrow toxicity, 2 weeks was considered sufficient to wash out fluorouracil); $\geq$4 weeks post other study medication. Other requirements included adequate functioning of major organ systems as indicated by the following laboratory parameters: neutrophils $\geq$2,000/μL; platelets $\geq$100,000/μL; hemoglobin $\geq$9 g/dL; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels $<$2.5 $\times$ upper limit of normal (ULN) as defined by local laboratory or $\leq$5 $\times$ ULN for patients with metastatic disease; total bilirubin $\leq$1.5 mg/dL; and serum creatinine $\leq$1.5 mg/dL.

Patients were excluded if they had active infection, uncontrolled comorbidities (e.g. serious cerebrovascular disorders, hypertension, diabetes mellitus, severe infection, or active gastric ulcer), acute inflammatory disease, interstitial pneumonia or pulmonary fibrosis, symptomatic metastases of the central nervous system, neuropathy grade ≥2 by National Cancer Institute common toxicity criteria (NCI-CTC) version 2.0, or body cavity fluid retention requiring treatment. Financial support was provided by Bristol-Myers K.K. (Shinjuku, Tokyo, Japan). The study was conducted in compliance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and Articles/Notifications of the Ministry of Health, Labour and Welfare in Japan. Written informed consent was obtained from all patients.

Treatment plan

Patients received paclitaxel once weekly by intravenous infusion on Days 1, 8, 15, 22, 29, and 36, after which treatment was suspended until Day 49 to allow recovery of decreased white blood cells and neutrophil count. Administration for 6 consecutive weeks was based on the tolerated number of consecutive paclitaxel dosages determined in previous dose-dense studies in patients with metastatic breast cancer [23]. On the treatment day, all patients were premedicated 30–60 min prior to therapy with dexamethasone 8 mg intravenously (i.v.), ranitidine 50 mg i.v., and diphenhydramine 50 mg orally. Paclitaxel (Taxol®, Bristol-Myers K.K., Tokyo) 100 mg/m^2 was administered intravenously over 1 h. Dose reductions in increments of 20 mg/m^2 to a minimum of 60 mg/m^2 were made if patients developed >Grade 4 neutropenia, febrile neutropenia, platelets <20,000/μL, ≥Grade 3 non-hematologic toxicity, and ≥Grade 2 neuropathy, arthralgia, or myalgia. One cycle of treatment was defined as 49 days, and one or more cycles of treatment were to be administered. Chemotherapy was continued until tumor progression, unacceptable toxicity, or until the patient refused treatment. The response rates and toxicities were evaluated by an independent safety and efficacy assessment committee. Responses were assessed by CT and/or MRI scans every 4 weeks. Toxicities were evaluated every week according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 2.0.

Statistical analysis

The primary efficacy end points were response rate and safety. Response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) [24], and toxicity was graded according to NCI-CTC version 2.0. Secondary endpoints were duration of response and median time to progression (TTP). This study set the threshold response rate at 5% and the expected response rate at 15% to demonstrate that the response rate is not less than 5%. Under these conditions, the number of fully evaluable patients required to reject the hypothesis that a true response rate is lower than a threshold response rate with an α of 0.05 (one-tailed) and a β of 0.2 was determined to be 52. With 6 or more partial responders and/or complete responders observed out of a total of 52 evaluable patients, the hypothesis that a true response rate is below a set threshold will be rejected. All patients with measurable disease who received at least one dose of study medication, except those who were misdiagnosed and did not have esophageal cancer, were included in the efficacy analysis. All patients who received at least one dose of study medication were included in the safety analysis. Baseline demographics and disease characteristics were summarized using descriptive statistics for all patients who received at least one dose of study medication. Response rate was defined as total number of responders, including complete and partial responders, divided by the response-evaluable patients. Response rate was also calculated using the total number of treated patients as the denominator. A two-sided 95% confidence interval was calculated for the response rate. Observed responses were confirmed by an external independent review committee. Duration of overall response, overall survival, and time to progression was summarized using the Kaplan–Meier product-limit method for all responders among response-evaluable patients.

Results

Study population

Fifty-six patients were enrolled in the study between June 2006 and July 2007. Three patients were withdrawn prior to receiving any study medication, because their hemoglobin values had dropped below 9.0 g/dL between screening and baseline. Fifty-three patients received at least one dose of paclitaxel. One patient was excluded from the efficacy analyses, because it was found that the target lesion was not a metastatic esophageal tumor. All 53 patients were evaluable for safety.

Baseline characteristics are shown in Table 1. Fifty-two of 53 patients had squamous cell carcinoma. In prior treatment regimens, twenty-five (47.2%) patients had undergone surgery and 34 patients had undergone radiotherapy, including chemoradiation therapy in 30 patients. Three patients received other therapies: 1 immunotherapy plus thermotherapy, 1 NK cell therapy, and 1 photodynamic therapy. Seven patients (13.2%) had received prior

Table 1 Baseline characteristics

Characteristic	No. of patients $N = 53$	%
Male	46	86.8
Female	7	13.2
Median age (range), years	65.0 (47–76)	
<65 years	24	45.3
≥65 years	29	54.7
Performance status		
0	28	52.8
1	25	47.2
Smoking history		
Smokers	5	9.4
Non-smokers	2	3.8
Previous smokers	46	86.8
Advanced/recurrent disease		
Recurrent	41	77.4
Advanced	12	22.6
Stage IVa	1	1.9
Stage IVb	10	18.9
Stage IIa*	1	1.9
Adenocarcinoma	1	1.9
Squamous cell carcinoma	52	98.1
Primary lesion location		
Cervical plus upper thoracic esophagus	3	5.7
Upper thoracic esophagus	8	15.1
Upper plus middle thoracic esophagus	2	3.8
Middle thoracic esophagus	29	54.7
Lower thoracic esophagus	8	15.1
Abdominal esophagus	3	5.7
Prior treatment**		
Neoadjuvant chemotherapy	7	13.5
Post-operative adjuvant chemotherapy	14	26.9
Chemoradiation therapy	30	57.7
Chemotherapy for residual or recurrent lesion	12	23.1
Surgery	24	46.2
Radiotherapy	34	65.4
Other therapy	3	5.8
Reasons for prior chemotherapy failure**		
Disease progression	25	48.1
Recurrence	5	9.6
Adverse events	1	1.9
Other***	26	50.0
Treatment-free interval**· ****		
≦6 months	39	75.0
>6 months	13	25.0

* Patient excluded from the efficacy analyses, because it was found that the target lesion was not a metastatic esophageal tumor

** Stage IIa patient (*) was excluded from the count

*** Completed planned course of therapy

**** Duration from last day of prior treatment therapy

neoadjuvant chemotherapy, and 14 (26.4%) had received adjuvant chemotherapy. Most of the prior chemotherapy regimens were a combination of a platinum agent and a fluoropyrimidine. The number of patients who failed prior therapy due to disease progression was 25/52 (48%), while 1/52 (1.9%) failed due to toxicity (Table 1).

The median number of cycles delivered was 2 (range 1–8), and the median number of administrations was 10 (range 1–42). In this study, all patients received paclitaxel at an initial dose of 100 mg/m^2—if a patient experienced a severe adverse event, dosage was reduced to 80 mg/m^2 and then to 60 mg/m^2. The median time to the first dose reduction was 84 days and the median dose intensity was 78.5 mg/m^2/week (range: 39.8–100 mg/m^2/week), which was >90% of expected dosing. The median total duration of treatment was 3 months (range: 0.2–14.0). After the initial dose of 100 mg/m^2, the dose was reduced to 80 mg/m^2 in 23 patients (43.4%) and reduced further to 60 mg/m^2 in 7 patients (13.2%).

Table 2 Response to therapy (RECIST criteria)

Response						Response rate (%)	95% CI
CR	PR	SD	PD	NE	Total		
4	19	14	8	7	52	44.2	(30.5, 58.7)

Characteristic	Response					Total	Response rate (%)
	CR	PR	SD	PD	NE		
PS							
0	2	13	7	1	4	27	55.6
1	2	6	7	7	3	25	32.0
Histology							
Adeno	0	1	0	0	0	1	100.0
SCC	4	18	14	8	7	51	43.1
Advanced/recurrent							
Recurrent	4	16	10	6	5	31	48.8
Stage IV	0	3	4	2	2	11	27.3
Prior treatment							
Chemoradiation							
−	1	8	6	5	2	22	40.9
+	3	11	8	3	5	30	46.7
Chemotherapy							
CDDP+ 5-FU (+ADM)	3	17	14	7	6	47	42.6
TFI							
≦6 months	2	13	10	8	6	39	38.5
>6 months	2	6	4	0	1	13	61.5

PS performance status (ECOG), *Adeno* adenocarcinoma, *SCC* squamous cell carcinoma, *CDDP* cisplatin, *5-FU* fluorouracil, *ADM* adriamycin, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *TFI* Treatment-free interval

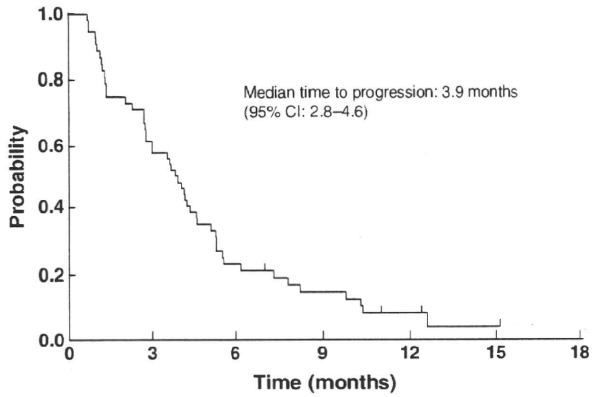

Fig. 1 Time to progression curve for patients with esophageal cancer treated with weekly paclitaxel and who had received prior platinum therapy. The median follow-up time of patients was 3.9 months, with a median time to progression of 3.9 months (95% CI: 2.8, 4.6 months)

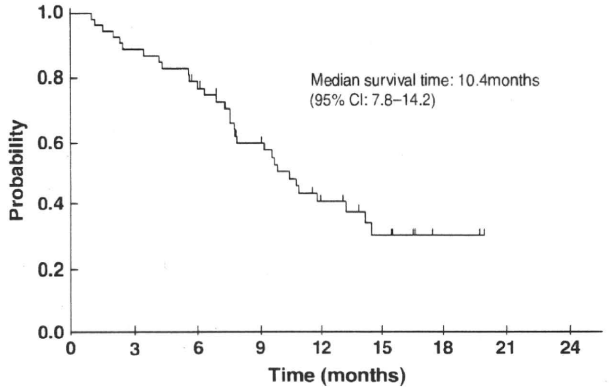

Fig. 2 Overall survival curve for patients with esophageal cancer treated with weekly paclitaxel and who had received prior platinum therapy. The median follow-up time of patients for overall survival was 9.1 months, with a median overall survival of 10.4 months (95% CI: 7.8, 14.2 months)

Response and survival

Response to therapy is shown in Table 2. Response rate is typically used as a primary endpoint in the phase II study of single agents in advanced esophageal cancer [21]; in this study, the overall response rate was 44.2% (23/52; 95% CI: 30.5, 58.7%) among patients evaluable for response. Among all treated patients, the response rate was 43.4% (23/53; 95% CI: 29.8, 57.7%), corroborating the result in the 52 response-evaluable patients. CR occurred in 4 patients and PR in 19. Responses were seen in 20 of 41 patients (48.8%) with recurrent disease and in 3 of 11 patients (27.3%) with advanced disease. Among the 29 patients without response, 14 showed stable disease (SD) on therapy, including 4 patients with advanced disease. Twenty-two of 51 (43.1%) patients with squamous cell carcinoma had responses. Median duration of overall response was 4.8 months (95% CI; 3.2, 7.1) for the 23 patients with CR or PR (95% CI: 3.2, 7.1 months). One patient had disease progression after 5.5 months in CR. Three patients were censored without disease progression, in which CR duration was ≥6.9 months. The median follow-up time for overall survival and time to progression was 9.1 months and 3.9 months, respectively. The median time to progression was 3.9 months (95% CI: 2.8, 4.6 months) (Fig. 1). Median overall survival was 10.4 months (95% CI: 7.8, 14.2 months) (Fig. 2).

Toxicity

Toxicity in the 53 assessable patients is shown in Table 3. Grade 3 or 4 non-hematologic toxicity was infrequent. The most common Grade 3 or 4 non-hematologic toxicities were anorexia (9.4%), fatigue (9.4%), constipation (7.5%),

Table 3 Toxicity, $n = 53$

	n (%)	
	All grades	≥Grade 3
Hematologic adverse events		
Leukopenia	43 (81.1)	24 (45.3)
Neutropenia	42 (79.2)	28 (52.8)
Anemia	4 (7.5)	2 (3.8)
Thrombocytopenia	6 (11.3)	1 (1.9)
Non-hematologic adverse events		
Nausea	23 (43.4)	1 (1.9)
Constipation	15 (28.3)	4 (7.5)
Diarrhea	15 (28.3)	1 (1.9)
Stomatitis	13 (24.5)	0 (0)
Vomiting	13 (24.5)	0 (0)
Anorexia	26 (49.1)	5 (9.4)
Fatigue	38 (71.7)	5 (9.4)
Pyrexia	18 (34)	0 (0)
Edema	9 (17.0)	1 (1.9)
Hypersensitivity	2 (3.8)	1 (1.9)
Myalgia	16 (30.2)	0 (0)
Arthralgia	15 (28.3)	0 (0)
Neuropathy: sensory	43 (81.1)	3 (5.7)
Neuropathy: motor	8 (15.1)	0 (0)
Pneumonia	6 (11.3)	4 (7.5)
Febrile neutropenia	2 (3.8)	2 (3.8)
Infection	2 (3.8)	1 (1.9)
Interstitial lung disease	3 (5.7)	2 (3.8)
Alopecia	44 (83.0)	0 (0)
Rash	15 (28.3)	1 (1.9)
Nail disorder	5 (9.4)	0 (0)

pneumonia (7.5%), and sensory neuropathy (5.7%). Sensory neuropathy of any grade was observed in 81.1% of patients. Other common non-hematologic toxicities of any grade were alopecia (83.0%), fatigue (71.7%), anorexia (49.1%), nausea (43.4%), pyrexia (34.0%), myalgia (30.2%), constipation (28.3%), diarrhea (28.3%), arthralgia (28.3%), rash (28.3%), stomatitis (24.5%), and vomiting (24.5%). One patient experienced a Grade 4 hypersensitivity reaction (anaphylactic shock) and recovered with appropriate measures and treatment discontinuation.

The most common forms of Grade 3 or 4 hematologic toxicities were neutropenia (52.8%) and leukopenia (45.3%). Grade 3 or 4 thrombocytopenia was rare, occurring in only 1 patient (1.9%). Neutropenia and leukopenia of any grade occurred in 81.1% and 79.2% of patients, respectively. Out of a total of 146 cycles delivered, leukopenia of any grade occurred in 81.5% (119) of cycles and neutropenia occurred in 80.8% (118) of cycles. Median nadirs of leukocyte count and neutrophil count were 2,000/μL (range: 800–2,980/μL) and 957/μL (range: 101–1,463/μL), respectively. In most cases, leukocyte and neutrophil counts returned to normal (decreases of Grade 1 or lower) and median time to recovery was 14 days for leukocytes and 8.5 days for neutrophils.

There were a total of 15 serious adverse events related to paclitaxel in 12 patients: pneumonia (4), interstitial lung disease (3), febrile neutropenia (2), ileus (1), hypersensitivity (1), herpes zoster (1), tuberculosis (1), anorexia (1), and respiratory failure (1). One patient had 4 serious laboratory adverse events related to paclitaxel: anemia, neutropenia, leukopenia, and thrombocytopenia. There were no treatment-related deaths.

Adverse events resulted in discontinuation of therapy in 18 (34.0%) patients, the most common events being myelosuppression ($n = 3$) and sensory neuropathy ($n = 3$). Dose reductions for toxicity occurred in 23 patients (43.4%). The most common reason for a dose reduction for toxicity was sensory neuropathy (10 [18.9%]). Adverse events leading to skipped or delayed dosing occurred in 126 courses (19.6%) and 21 courses (22.6%), respectively. The most common reason for skipped or delayed doses was neutropenia (28 [52.8%]).

Discussion

Results of this study demonstrate that weekly paclitaxel 100 mg/m^2 administered by 1-h infusion (median dose intensity 78.5 mg/m^2/week) shows substantial anti-tumor activity in patients with advanced or recurrent esophageal cancer. In this study, the overall response rate was 44.2% and included four complete responders. The median duration of response was 4.8 months (95% CI: 3.2, 7.1 months) in 23 responding patients, and their median treatment time of 5.9 months was therefore long.

Patients had either progressed on platinum-based therapy or they had discontinued treatment for reasons of toxicity. The rate of response observed in the current trial is considerably higher than the 13% response rate observed by Ilson et al. [21] in a previous study of weekly paclitaxel for a similar patient population (advanced or recurrent esophageal cancer). Moreover, the latter study enrolled patients with or without prior chemotherapy, and only 1 partial response (1/21, 5%) was observed among patients previously treated. The higher response rate observed in our study and the activity against esophageal cancer refractory to prior chemotherapy may be due to the higher dose of paclitaxel administered (100 mg/m^2/week versus 80 mg/m^2/week) in the current study. Most patients in the current study had squamous cell carcinoma, whereas two-third of the patients in Ilson study had adenocarcinoma.

There is currently no standard systemic therapy for advanced or recurrent esophageal cancer, and therefore response rates are of interest in a palliative setting. As expected, the response rate in the current study was higher among patients with recurrent (48.8%) than among those with advanced disease (27.3%). Although a small number of patients with metastatic disease were included in this study, the rate of response compares favorably to rates achieved with other single agents used in populations with advanced esophageal carcinoma, e.g., docetaxel and vinorelbine [25, 26].

In the current trial, partial response or stable disease was seen in 7/11 patients with metastatic disease. Among all patients who did not respond, 48.3% (14/29) showed stabilization of disease on therapy. Median overall survival for all patients was 10.4 months. Other studies have reported median survival times of between 7 and 13 months for patients with recurrent or advanced esophageal carcinoma treated with paclitaxel alone or in combination with chemotherapy [13, 15, 21, 27]. In this study, the response rates for recurrent/advanced patients with a TFI >6 months and with a TFI ≦6 months were 61.5% (8/13) and 38.5% (15/39), respectively. However, there was no significant relationship between TFI and response rate as has been seen in other studies [28].

Paclitaxel was fairly well tolerated in this study. The most common types of Grade 3–4 hematologic toxicity were neutropenia and leukopenia, which were relatively common. However, only 2 patients (3.8%) developed febrile neutropenia. While the majority of patients (81.1%) experienced sensory neuropathy of Grade 1 or higher, only 5.7% of patients experienced Grade 3–4 sensory neuropathy. Dose reductions for toxicity were required for 23 (43.4%) patients, most commonly for sensory neuropathy, leukopenia, and neutropenia. The median time from nadir

to recovery was 14 days for leukopenia and 8.5 days for neutropenia. There were no treatment-related deaths. All treatment-related serious adverse events were previously known adverse effects of paclitaxel.

In summary, our results show that paclitaxel administered weekly at a dose of 100 mg/m^2 has high activity and manageable toxicity in patients with advanced or recurrent esophageal cancer. While esophageal cancer is relatively sensitive to chemotherapy, relapse is common and responses are typically short-lived, underscoring the need for second-line chemotherapy. Our study suggests that paclitaxel at the dose administered is a promising option for patients who have been previously treated with platinum-based chemotherapy and warrants further investigation in a phase III study.

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●症 例●

腹膜転移を伴う高度進行・再発胃癌におけるS-1＋Paclitaxel併用療法のFeasibility試験（OGSG0401）

木村 豊[*1,2] 町田 浩久[*1,3] 藤谷 和正[*1,4] 山本 守敏[*1,5] 富永 和作[*1,3]
矢野 浩司[*1,2] 下川 敏雄[*1,6] 瀧内比呂也[*1,7] 辻仲 利政[*1,4] 古河 洋[*1,8]

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Combination of S-1 and Paclitaxel for Advanced/Recurrent Gastric Cancer Patients with Peritoneal Metastasis, Feasibility Study (OGSG0401): Yutaka Kimura[*1,2], Hirohisa Machida[*1,3], Kazumasa Fujitani[*1,4], Moritoshi Yamamoto[*1,5], Kazunari Tominaga[*1,3], Hiroshi Yano[*1,2], Toshio Shimokawa[*1,6], Hiroya Takiuchi[*1,7], Toshimasa Tsujinaka[*1,4] and Hiroshi Furukawa[*1,8] ([*1]*Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG)*, [*2]*Dept. of Surgery, NTT West Osaka Hospital*, [*3]*Dept. of Gastroenterology, Osaka City University Graduate School of Medicine*, [*4]*Dept. of Surgical Oncology, National Osaka Medical Center*, [*5]*Dept. of Internal Medicine, NTT West Osaka Hospital*, [*6]*Graduate School of Medicine and Engineering, University of Yamanashi*, [*7]*Cancer Chemotherapy Center, Osaka Medical College*, [*8]*Dept. of Surgery, Sakai-Municipal Hospital*)

Summary

Background: The standard therapy for gastric cancer with peritoneal metastasis has remained unclear. Purpose: This prospective feasibility study was aimed to investigate the efficacy and safety of S-1 plus paclitaxel for advanced/recurrent gastric cancer patients with peritoneal metastasis able to take oral feeding. Patients and methods: Seven patients were enrolled in this study. Paclitaxel 50 mg/m^2 was administered on days 1 and 8. S-1 was administered orally at 40 mg/m^2 bid for 14 consecutive days, followed by a 1-week rest. Overall survival, the response rate and safety were examined for efficacy and tolerability. Results: The median survival time was 310 days. The response rate in five patients was 80.0%. Grade 3 toxicity was observed in two patients. Combination chemotherapy of weekly paclitaxel and S-1 demonstrated efficacy and tolerable toxicity. This regimen will be one of the initial treatment options for unresectable or metastatic gastric cancer with peritoneal metastasis. **Key words**: Peritoneal metastasis from gastric cancer, S-1, Paclitaxel (*Received Mar. 19, 2009/Accepted Jun. 18, 2009*)

要旨 臓器転移を有する症例と比べて，予後が不良である腹膜転移を有する進行胃癌に対する標準治療は明らかでない。経口摂取が可能な腹膜転移を伴う高度進行・再発胃癌患者を対象にS-1＋paclitaxel（PTX）併用療法の有効性および安全性を検討することを目的としてfeasibility試験を行った。対象と方法: 対象は経口摂取が可能な腹膜転移を伴う高度進行・再発胃癌患者7例。投与方法は，S-1 80 mg/m^{2}を2週投与1週休薬とし，PTX 50 mg/m^{2}をday 1，8に投与し，3週を1コースとした。全生存期間（OS），無増悪生存期間（PFS），腫瘍縮小効果（RECIST評価，腹水評価），経口摂取可能期間，安全性（有害事象発現率とその重症度）を評価項目として，本療法の有用性と認容性を検討した。結果: 登録症例の年齢の中央値は64歳（50～75歳），男性5例，女性2例，投与コースの中央値は7コース（5～20コース）であった。OSは310日，PFSは152日，測定可能病変を有する5例でのRECIST評価による抗腫瘍効果はCR 1例，PR 3例，SD 1例，腹水は著効2例，有効3例，無効3例，経口摂取期間の中央値は161日であった。grade 3の有害事象を2例に認めた。結語: S-1＋PTX併用療法は，安全に施行可能で腹水に対して有効であり，経口摂取が可能な腹膜転移を伴う進行・再発胃癌に対するレジメンの候補の一つになり得ると思われた。

[*1] 大阪消化管がん化学療法研究会（OGSG）
[*2] NTT西日本大阪病院・外科
[*3] 大阪市立大学・消化器内科
[*4] 国立病院機構大阪医療センター・外科
[*5] NTT西日本大阪病院・内科
[*6] 山梨大学大学院・医学工学総合研究部
[*7] 大阪医科大学化学療法センター
[*8] 市立堺病院・外科

連絡先: 〒543-8922 大阪市天王寺区烏ヶ辻2-6-40 NTT西日本大阪病院・外科
木村 豊

はじめに

胃癌の腹膜播種は再発形式のなかでも最も多く，その治療は困難を極め予後不良である[1]。このような腹膜転移を有する進行胃癌に対して，これまで5-FU単剤やMTX＋5-FU療法による治療が行われてきたが，いまだに標準治療は確立されていない[2,3]。

5-FUのプロドラッグであるS-1は，進行・再発胃癌に対して後期臨床第Ⅱ相試験で奏効率44.6%と高い奏効率を示し[4]，第Ⅲ相臨床試験（JCOG9912）において5-FUに対して非劣性が示された[5]。S-1は内服薬ではあるが，5-FUが腹水中へ良好に移行することが報告され，実地臨床において腹膜転移症例に対する有効性が報告されている[6,7]。また，第Ⅲ相臨床試験（SPIRITS）の結果，S-1＋CDDP併用療法は腹膜転移症例が含まれる測定可能病変のない対象にも有用であると報告された[1]。

微小管蛋白重合の促進によって細胞分裂を阻害するpaclitaxel（PTX）は，静脈内投与でも腹水への移行が良好なことからweekly PTX療法として腹膜転移胃癌症例に汎用され，腹水が消失したとの報告も散見される[8]。

そこでわれわれは，腹膜転移を伴う高度進行・再発胃癌に対してS-1およびPTX両薬剤を用い，高度進行・再発胃癌を対象にS-1＋PTX併用療法の有効性および安全性を検討することを目的としてfeasibility試験を行った。

Table 1 Patients characteristic and treatment course

Patients characteristic	(n=7)
Sex: male/female	5/2
Age (median)	64 (50-75)
Performance status (ECOG): 0/1	6/1
Histology: tub/por/sig	0/4/3
Metastatic site: N/H/P (ascites)	3/1/7 (7)
Disease status: primary/recurrent	7/0
Pretreatment: Yes/No	0/7
Treatment course (median)	7 (5-20)

Ⅰ．対象・方法

腹膜転移または癌性腹水を有する高度進行・再発胃癌症例を対象とし，症例の選択基準は，① 組織学的に胃癌であることが確認されている。② 腹膜転移または癌性腹水を有する高度進行・再発胃癌症例（腹膜転移以外の臓器転移の有無は問わない）：(1) 画像診断（注腸/小腸造影またはCT検査）で腹膜転移または癌性腹水が認められた切除不能胃癌（臨床所見で腹膜転移・癌性腹水を認めないcP0の単開腹術または腹腔鏡検査症例を除く），(2) 組織診，細胞診または画像診断で腹膜転移または癌性腹水が認められた再発胃癌（吻合術，その他の姑息的手術に終わった症例を含む）。③ 測定可能病変の有無は問わない。④ 経口摂取が可能。⑤ 前治療として化学療法や放射線療法の既往がない（ただし，S-1およびPTX以外の抗癌剤による術前化学療法または術後補助化学療法後の再発症例で前治療終了後3週間以上経過している場合は適格）。⑥ 年齢が20歳以上，75歳以下。⑦ 文書にて同意が得られている。⑧ 投与開始日より9週間以上の生存が期待される。⑨ 活動性と臓器機能が保たれている：(1) performance status (PS)（ECOG分類）0～2，(2) 十分な骨髄，肝，腎機能を有するとした。なお，② の画像による腹膜転移・癌性腹水の診断基準は，注腸/小腸造影で明らかな癌性腸管狭窄または腸管壁の変形所見を有すること，またはCTで明らかな腹膜腫瘤または腹水の存在が確認できることとした。

投与スケジュールは，S-1 80 mg/m^{2}を2週投与1週休薬とし，PTX 50 mg/m^{2}をday 1，8に投与し，3週を1コースとした。評価項目を全生存期間（OS），無増悪生存期間（PFS），腫瘍縮小効果（RECIST評価，胃癌取扱い規約第13版による癌性腹水に対する効果判定），経口摂取可能期間，安全性（有害事象発現率とその重症度）とした。2004年4月から登録を開始し，2007年12月で終了した。

Table 2 Registered patients

No.	Age/sex	PS	Histology	Course	Metastatic site*	RECIST	Evaluation of ascites	Outcome (comment)
1	75/M	1	por	7	N/P	PR	Effect	Death
2	69/M	0	sig	6	P	—	Effect	Death
3	64/M	0	sig	5	N/P	PR	Good effect	Death
4	50/M	0	por	8	P	SD	No effect	Death
5	59/F	0	sig	20	H/P	CR	Good effect	Alive (gastrectomy)
6	53/F	0	por	6	P	—	No effect	Death
7	67/M	0	por	7	N/P	PR	Effect	Death

*N: Lymph node, P: Peritoneum, H: Liver

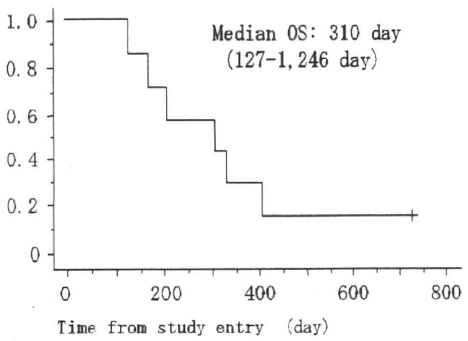

Fig. 1 Overall survival (OS)

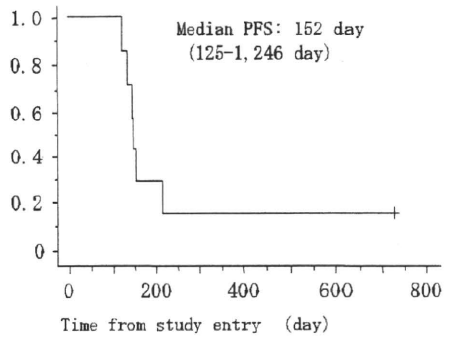

Fig. 2 Progression-free survival (PFS)

Table 3 Adverse events

Toxicity (n=7)	Grade 1	Grade 2	Grade 3	≧Grade 3 (%)
Hematologic				
Leukopenia	1	4	1	1 (14.3)
Neutropenia	1	2	1	1 (14.3)
Anemia	4	1	0	0
Thrombopenia	0	0	0	0
Nonhematologic				
Anorexia	2	3	0	0
Nausea/vomiting	1	2	0	0
Diarrhea	1	1	0	0
Fatigue	1	0	0	0
Hepatic dysfunction	1	1	1	1 (14.3)
Acomia	3	1	0	0
Peripheral neuropathy	1	0	0	0
Dysgeusia	0	1	0	0

Ⅱ. 結　果

登録された症例は7例で，年齢(中央値)は64歳(50～75歳)，男性5例，女性2例。投与コースの中央値は7コース(5～20コース)であった(Table 1)。登録症例の一覧をTable 2に示す。OSは310日(127～1,246日)(Fig. 1)，PFSは152日(125～1,246日)(Fig. 2)であった。測定可能病変を有するのは5例で，RECIST評価による抗腫瘍効果はCR 1例，PR 3例，SD 1例で，腹水は著効2例，有効3例，無効3例であった。経口摂取期間の中央値は161日(97～1,246日)であった。grade 3の有害事象は白血球・好中球減少1例，肝機能障害1例であった(Table 3)。

本療法に奏効した1例を提示する。症例は56歳，女性。胃体部の3型進行胃癌(T3 N1 H1 P1 M0 cStage Ⅳ，組織型:印環状細胞癌)(Fig. 3, 4, 5)に対して，本療法を重篤な有害事象なく20コース施行した。本治療に奏効(腹水:著効，肝転移巣:CR)したため(Fig. 3, 4, 5)，治療開始1年4か月後に胃全摘，脾摘，胆摘，D2リンパ節郭清を行った。総合所見は，T2 N0 H0 P0 CY0 M0 fStage IB，組織学的効果はGrade 2で，術後2年9か月経過して無再発生存中である。

Ⅲ. 考　察

手術不能・再発胃癌の初回治療例に対する第Ⅲ相臨床試験の結果，わが国においてはS-1+CDDP併用療法が標準治療となったが[8]，S-1+PTXの併用療法の有効性についても諸家により報告されている[9-11]。大阪消化器がん化学療法研究会(OGSG)では，切除不能・再発胃癌に対するS-1+PTX併用療法の第Ⅰ/Ⅱ相試験を行い，grade 3以上の有害事象の発生割合も低く，奏効率は48.3%，生存期間は13.9か月，腹膜転移を来しやすい未分化型においても55.6%と高い奏効率を示すことを報告してきた[9]。ついては，同レジメンの腹膜転移を伴う進行・再発胃癌に対する有用性，安全性を検討する目的でfeasibility試験を行った。

測定可能病変を有しない腹膜転移症例も対象となるS-1 vs S-1+CDDP (SPIRITS)，S-1 vs S-1+CPT-11 (GC0301/TOP-002)，S-1 vs S-1+docetaxel (JACCRO GC03)の三つの第Ⅲ相試験が本臨床試験期間に並行し

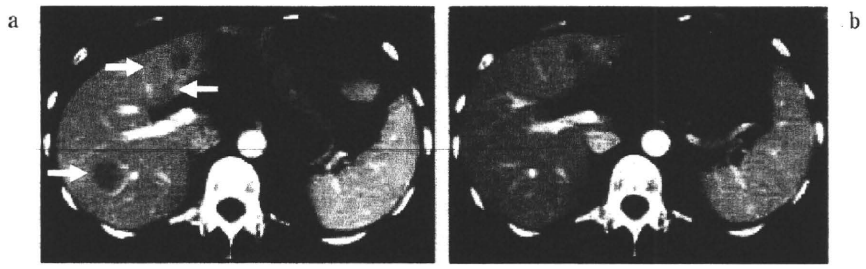

Fig. 3
a: Contrast-enhanced abdominal CT showed liver masses (arrows) on admission.
b: Abdominal CT at the end of 10 courses revealed the disappearance of liver masses.

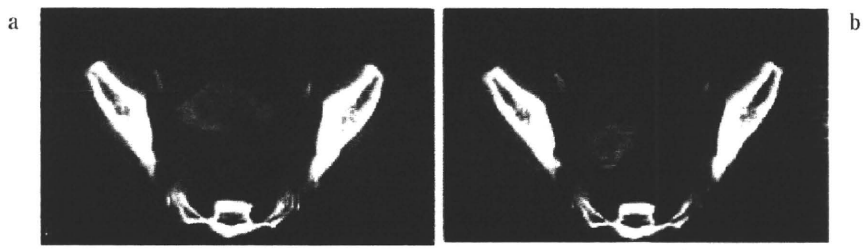

Fig. 4
At pelvic CT, ascites on admission (a) disappeared at the end of 10 courses (b).

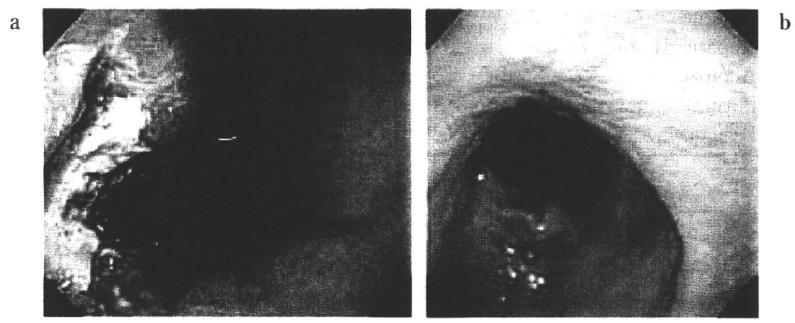

Fig. 5
a: Endoscopic examination revealed Type 3 tumor.
b: The tumor reduced at the end of 10 courses.

て実施され対象が重なっていたため，わずか7例の症例登録ではあった。しかし，S-1+PTX併用療法は重篤な有害事象も少なく安全に施行でき，全生存期間は310日，腹水減少（消失）率は71（29）%と良好な結果であったことから，経口摂取が可能な腹膜転移を伴う高度進行・再発胃癌に対する有望なレジメンの一つになり得ると考えられた。

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