Cancer Chemother Pharmacol (2011) 67:1265–1272
DOI 10.1007/s00280-010-1422-x

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

Received: 31 March 2010 / Accepted: 29 July 2010 / Published online: 12 August 2010

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

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

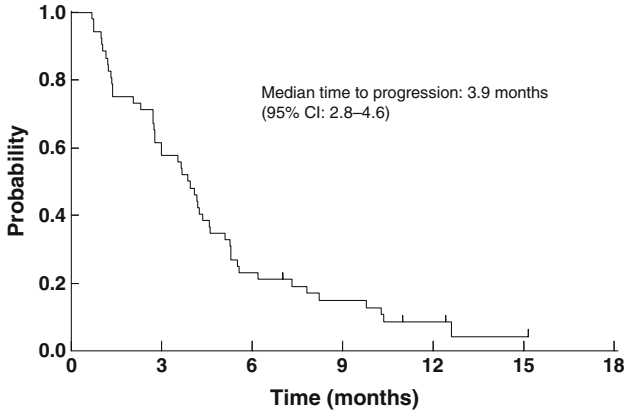

Fig. 1 Time to progression curve for patients with esophageal cancer treated with weekly paclitaxel and who had received prior platinum therapy. The median follow-up time of patients was 3.9 months, with a median time to progression of 3.9 months (95% CI: 2.8, 4.6 months)

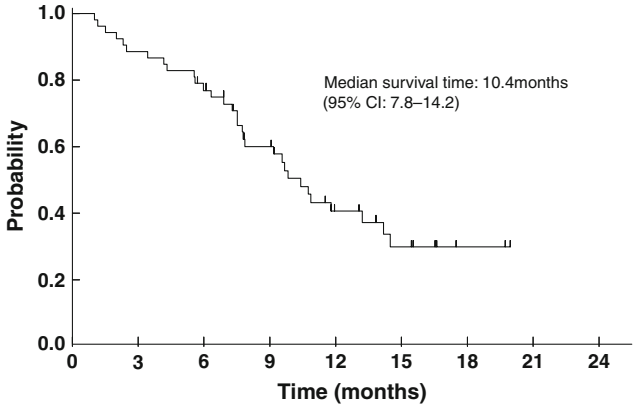

Fig. 2 Overall survival curve for patients with esophageal cancer treated with weekly paclitaxel and who had received prior platinum therapy. The median follow-up time of patients for overall survival was 9.1 months, with a median overall survival of 10.4 months (95% CI: 7.8, 14.2 months)

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.

Acknowledgments The Paclitaxel Esophageal Cancer Study Group comprises the following institutions: National Cancer Center Hospital, Tokyo; National Cancer Center Hospital East, Chiba; Shizuoka Cancer Center, Shizuoka; Aichi Cancer Center Central Hospital, Aichi; Osaka Medical College, Osaka; Tochigi Cancer Center, Tochigi; Kinki University School of Medicine, Osaka; The Cancer Institute Hospital of JFCR, Tokyo; Kitasato University East Hospital, Kanagawa; Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; Saitama Cancer Center, Saitama; and Graduate School of Medicine, Osaka University, Osaka, Japan. This study was supported by a grant from Bristol-Myers K.K.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ (2007) Cancer statistics, 2007. CA Cancer J Clin 57:43–66
2. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55:74–108
3. Blot WJ, McLaughlin JK (1999) The changing epidemiology of esophageal cancer. Semin Oncol 26:2–8
4. Devesa SS, Blot WJ, Fraumeni JF Jr (1998) Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 83:2049–2053
5. Vizcaino AP, Moreno V, Lambert R, Parkin DM (2002) Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973–1995. Int J Cancer 99: 860–868
6. Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y (1994) Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg 220:364–372
7. Baba M, Aikou T, Yoshinaka H, Natsugoe S, Fukumoto T, Shimazu H, Akazawa K (1994) Long-term results of subtotal esophagectomy with three-field lymphadenectomy for carcinoma of the thoracic esophagus. Ann Surg 219:310–316
8. Fujita H, Kakegawa T, Yamana H, Shima I, Toh Y, Tomita Y, Fujii T, Yamasaki K, Higaki K, Noake T (1995) Mortality and morbidity rates, postoperative course, quality of life, and prognosis after extended radical lymphadenectomy for esophageal cancer. Comparison of three-field lymphadenectomy with two-field lymphadenectomy. Ann Surg 222:654–662
9. Mera K, Otsu A (2003) Practice of chemotherapy in esophageal cancer. Clin Gastroenterol 6:291–297
10. Iizuka T, Kakegawa T, Ide H, Ando N, Watanabe H, Tanaka O, Takagi I, Isono K, Ishida K, Arimori M (1992) Phase II evaluation of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus: a Japanese Esophageal Oncology Group Trial. Jpn J Clin Oncol 22:172–176
11. Ajani JA, Ilson DH, Daugherty K, Pazdur R, Lynch PM, Kelsen DP (1994) Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J Natl Cancer Inst 86:1086–1091
12. Gong Y, Ren L, Zhou L, Zhu J, Huang M, Zhou X, Wang J, Lu Y, Hou M, Wei Y (2009) Phase II evaluation of nedaplatin and paclitaxel in patients with metastatic esophageal carcinomas. Cancer Chemother Pharmacol 64:327–333
13. El Rayes BF, Shields A, Zalupski M, Heilbrun LK, Jain V, Terry D, Ferris A, Philip PA (2004) A phase II study of carboplatin and paclitaxel in esophageal cancer. Ann Oncol 15:960–965
14. Ilson DH, Ajani J, Bhalla K, Forastiere A, Huang Y, Patel P, Martin L, Donegan J, Pazdur R, Reed C, Kelsen DP (1998) Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the esophagus. J Clin Oncol 16:1826–1834
15. Lin CC, Hsu CH, Cheng JC, Wang HP, Lee JM, Yeh KH, Yang CH, Lin JT, Cheng AL, Lee YC (2007) Concurrent chemo radiotherapy with twice weekly paclitaxel and cisplatin followed by esophagectomy for locally advanced esophageal cancer. Ann Oncol 18:93–98
16. Abu-Rustum NR, Aghajanian C, Barakat RR, Fennelly D, Shapiro F, Spriggs D (1997) Salvage weekly paclitaxel in recurrent ovarian cancer. Semin Oncol 24:S15
17. Fennelly D, Aghajanian C, Shapiro F, O'Flaherty C, McKenzie M, O'Connor C, Tong W, Norton L, Spriggs D (1997) Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. J Clin Oncol 15:187–192
18. Horiguchi J, Rai Y, Tamura K, Taki T, Hisamatsu K, Ito Y, Seriu T, Tajima T (2009) Phase II study of weekly paclitaxel for advanced or metastatic breast cancer in Japan. Anticancer Res 29:625–630
19. DeVore RF III, Jagasia M, Johnson DH (1997) Paclitaxel by either 1 h or 24 h infusion in combination with carboplatin in advanced non-small cell lung cancer: preliminary results comparing sequential phase II trials. Semin Oncol 24:S12
20. Maier-Lenz H, Hauns B, Haering B, Koetting J, Mross K, Unger C, Bauknecht T, du BA, Meerpohl HG, Hollaender N, Diergarten K (1997) Phase I study of paclitaxel administered as a 1 h infusion: toxicity and pharmacokinetics. Semin Oncol 24:S19
21. Ilson DH, Wadleigh RG, Leichman LP, Kelsen DP (2007) Paclitaxel given by a weekly 1 h infusion in advanced esophageal cancer. Ann Oncol 18:898–902
22. Nokihara H, Tamura T, Matsumoto Y (2002) Weekly paclitaxel in solid tumor, a phase I trial. Jpn J Lung Cancer 42. Abstract E-13
23. Seidman A, Hudis C, Albanell J, Tong W, Tepler I, Currie V, Moynahan M, Theodoulou M, Gollub M, Baselga J, Norton L (1998) Dose-dense therapy with weekly 1 h paclitaxel infusions in the treatment of metastatic breast cancer. J Clin Oncol 16:3353–3361
24. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, national cancer institute of the United States, national cancer institute of Canada. J Natl Cancer Inst 92:205–216
25. Conroy T, Etienne PL, Adenis A, Wagener DJ, Paillot B, Francois E, Bedenne L, Jacob JH, Seitz JF, Bleiberg H, Van Pottelsberghe C, Van Glabbeke M, Delgado FM, Merle S, Wils J (1996) Phase II trial of vinorelbine in metastatic squamous cell esophageal carcinoma. European organization for research and treatment of cancer gastrointestinal treat cancer cooperative group. J Clin Oncol 14:164–170

26. Muro K, Hamaguchi T, Ohtsu A, Boku N, Chin K, Hyodo I, Fujita H, Takiyama W, Ohtsu T (2004) A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. Ann Oncol 15:955–959
27. Cho SH, Chung IJ, Song SY, Yang DH, Byun JR, Kim YK, Lee JJ, Na KJ, Kim HJ (2005) Bi-weekly chemotherapy of paclitaxel and cisplatin in patients with metastatic or recurrent esophageal cancer. J Korean Med Sci 20:618–623
28. Takashima A, Shiraro K, Hirashima Y, Takahari D, Okita N, Akatsuka S, Eguchi Nakajima T, Matsubara J, Yasui H, Asakawa T, Kato K, Hamguchi T, Muro K, Yamada Y, Shimada Y (2008) Chemosensitivity of patients with recurrent esophageal cancer receiving perioperative chemotherapy. Dis Esophagus 21:607–611