Multifractionated paclitaxel and cisplatin combined with 5-fluorouracil and leucovorin in patients with metastatic or recurrent esophageal squamous cell carcinoma

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This study assessed the clinical activity and safety of twice-weekly paclitaxel and cisplatin combined with 5-fluorouracil and leucovorin (TP-HDFL) in patients with recurrent or metastatic esophageal squamous cell carcinoma. The regimen, composed of paclitaxel 35 mg/m^2 1-h intravenous infusion on days 1, 4, 8 and 11; cisplatin 20 mg/m^2 2-h intravenous infusion on days 2, 5, 9 and 12; and 5-flourouracil 2000 mg/m^2 and leucovorin 300 mg/m^2 24-h intravenous infusion on days 5 and 12; repeated every 21 days. Forty-one patients (median age 51), 15 with de-novo metastatic disease and 26 with recurrent disease, were enrolled. Grades 3–4 neutropenia, leukopenia and diarrhea occurred in 37.8, 29.4 and 14.2% of cycles, respectively. One patient died of invasive fungal infection. Three complete responses, 13 partial response and 13 stable diseases were observed. The intent-to-treat response rate was 39.0% (95% confidence interval: 24–54). The median progression-free and overall survival were 6.3 and 8.9 months (range 1–50+), respectively. Twice-weekly TP-HDFL has the activity and toxicity profile similar to the previously reported same three-drug combination for advanced esophageal cancer. *Anti-Cancer Drugs* 18:703–708 © 2007 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2007, **18**:703–708

Keywords: antineoplastic combined chemotherapy protocol, carcinoma, esophageal neoplasms, squamous cell, paclitaxel

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Presented at the 41st Annual Meeting of the American Society of Clinical Oncology, Orlando, FL, May 13–17, 2005.

Received 29 October 2006 **Revised form accepted** 18 December 2006

Introduction

Palliative chemotherapy is the primary treatment option for recurrent or metastatic esophageal cancer. The combination of cisplatin and 5-fluorouracil (5-FU) is the most commonly used regimen for patients with advanced esophageal cancer. Reported response rates vary between 30 and 40% [1]. Single-agent paclitaxel had significant antitumor activity for advanced esophageal cancer [2]. When paclitaxel (175 mg/m^2 over 3 h) was added to cisplatin and 5-FU combination for advanced esophageal cancer, the combination produced a response rate of 48% with significant toxicity. Grade 3 or 4 neutropenia and diarrhea occurred in 57 and 24% of patients, respectively. Forty-eight percent of patients required one or more hospitalizations for treatment-related toxicity [3]. The optimal dose and schedule of each component in this combination chemotherapy remain to be established.

Paclitaxel is highly dose- and schedule-dependent. Hematologic toxicity is related to the exposure duration of the bone marrow stem cells to the threshold level of paclitaxel (50 nmol/l). Hematologic toxicity might be avoided if paclitaxel is administered weekly or twice weekly, i.e. multifractionated, based on lower doses. The weekly paclitaxel schedule is well tolerated and usually without cumulative myelosuppression [4]. Preliminary results of a direct comparison for advanced breast cancer showed superiority of paclitaxel 80 mg/m^2 1-h infusion weekly compared with paclitaxel 175 mg/m^2 3-h infusion every 3 weeks in terms of response rate and time to progression [5]. Moreover, the twice-weekly paclitaxel schedule had been combined with cisplatin and etoposide or vinorelbine in treating advanced gastric cancer and nonsmall-cell lung cancer [6–8].

5-FU is also highly dose- and schedule-dependent. Infusional 5-FU had a superior response rate and toxicity profile compared with bolus 5-FU. The activity of 5-FU can be enhanced by biochemical modulation with leucovorin. A phase III trial for advanced colorectal cancer showed superiority of high-dose 5-FU (2600 mg/m^2) given as a weekly 24-h infusion with leucovorin (HDFL) compared with bolus 5-FU and leucovorin in terms of response rate and time to progression-free survival [9].

Preclinical studies suggested that synergism between paclitaxel and cisplatin or 5-FU was sequence-dependent. The cytotoxic effect was better when the tumor cells were exposed to paclitaxel first, followed by cisplatin or 5-FU 24 h later [10,11]. We postulated that

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multifractionated administration of paclitaxel followed 24 h later by cisplatin and 5-FU might provide the best drug interaction and improve the efficacy of the chemotherapy combining these drugs. A phase II trial was conducted to test whether twice-weekly paclitaxel and cisplatin combined with 5-FU and leucovorin (twice-weekly TP–HDFL) is an effective and safe regimen for advanced esophageal cancer.

Patients and methods

The protocol was reviewed and approved by the Ethics Committee of National Taiwan University Hospital. All patients provided written informed consent before entering the trial. Patients were enroled from February 2001 to February 2005 and were followed up until 15 December 2005.

Patients

Eligible patients had histologically confirmed squamous cell carcinoma of the esophagus that was either de-novo metastatic or recurrent from previous definitive local treatment. The patients were required to have at least one bidimensionally measurable lesion defined by computed tomography scan. An esophageal lesion, which had been previously treated by radiotherapy or concurrent chemoradiotherapy, was not used as the sole measurable lesion. Patients had not received systemic chemotherapy for recurrent or metastatic diseases before. Other eligibility criteria included a Karnofsky performance scale of 60% or higher, adequate bone marrow reserve (defined as leukocyte count $\geq 4000/\mu l$ and platelet count $\geq 100\,000/\mu l$), and adequate liver (aspartate transaminase and alanine transaminase ≤ 3.5 times the upper limits of reference values, and total bilirubin ≤ 2.0 mg/dl) and kidney (serum creatinine ≤ 1.5 mg/dl) functions.

Treatment

A Port-A Cath (Gish Biomedical, Inc., Rancho Santa Margarita, California, USA) was implanted in all patients to facilitate chemotherapy administration and nutritional support. The chemotherapy regimen consisted of paclitaxel 35 mg/m^2 1-h intravenous infusion on days 1, 4, 8 and 11; cisplatin 20 mg/m^2 2-h intravenous infusion on days 2, 5, 9 and 12; 5-FU 2000 mg/m^2 and leucovorin 300 mg/m^2 24-h intravenous infusion, started after the end of cisplatin infusion on days 5 and 12 (Fig. 1). The treatment cycles were repeated every 3 weeks when the patient's leukocyte count was $\geq 3000/\mu l$, platelet count was $\geq 75\,000/\mu l$ and nonhematologic toxicities recovered to $\leq$ grade 1 according to the National Cancer Institute's Common Toxicity Criteria.

Fig. 1

Drug	Dose	Day				
		1	2	3	4	5
Paclitaxel	35 mg/m^2 i.v. 1h	↓			↓	
Cisplatin	20 mg/m^2 i.v. 2 h		↓			↓
5-Fluorouracil	2000 mg/m^2					↓
Leucovorin	300 mg/m^2 i.v. 24 h					
		8	9	10	11	12
Paclitaxel	35 mg/m^2 i.v. 1h	↓			↓	
Cisplatin	20 mg/m^2 i.v. 2 h		↓			↓
5-Fluorouracil	2000 mg/m^2					↓
Leucovorin	300 mg/m^2 i.v. 24 h					
Repeated every 21 days						

Regimen.

Premedication for the first dose of paclitaxel included dexamethasone 20 mg, diphenhydramine 30 mg and ranitidine 50 mg intravenous bolus 1 h before treatment. If the patient did not experience any hypersensitivity to paclitaxel, the premedication was modified to dexamethasone 8 mg plus diphenhydramine and ranitidine for the second dose, and simplified to diphenhydramine and ranitidine alone in the remaining doses. Appropriate antiemetics and hydration for cisplatin were used.

Dose modification

On day 8 of each course, a full dose of chemotherapy was given provided the patient had a leukocyte count $\geq 2000/\mu l$ and platelet count $\geq 50\,000/\mu l$. When patients had active infection, febrile neutropenia, or grade 3 or 4 mucositis or diarrhea, the treatment was stopped until these problems were resolved. Dose modification for the subsequent courses was made based on the encountered hematologic and nonhematologic toxicities. If there was a $\geq$ grade 3 leukopenia or neutropenia, or a delay of scheduled protocol because of inadequate recovery of hemogram for more than 10 days, the next dose of cisplatin was reduced to 15 mg/m^2. If similar toxicity could not be prevented by cisplatin dose modification, the next dose of 5-FU was reduced to 1500 mg/m^2. If there was a $\geq$ grade 3 mucositis or diarrhea, the next dose of 5-FU was reduced to 1500 mg/m^2 and was further reduced to 1000 mg/m^2 in the next dose if similar toxicity could not be prevented by one dose modification. Cisplatin was withheld if the serum creatinine was ≥ 2.0 mg/dl. Cisplatin was resumed when serum creatinine level returned to ≤ 1.5 mg/dl. If there was a $\geq$ grade 3 sensory neuropathy, the next dose of cisplatin was reduced to 15 mg/m^2.

Toxicity evaluation

Toxicities were evaluated and recorded according to the National Cancer Institute's Common Toxicity Criteria, version 2.0, for adverse event reporting. During the treatment, all patients had a hemogram and blood chemistry checked every week and every cycle, respectively.

Response evaluation

Clinical responses were evaluated according to the World Health Organization criteria [12]. The response had to last for at least 4 weeks to qualify as a response. Responses were evaluated every two cycles by computed tomography scan. Patients whose tumor had a complete response (CR) underwent two additional courses of treatment as consolidation. Patients whose tumor had a partial response (PR) or showed a stable disease (SD) continued treatment until disease progression or intolerable toxicity occurred.

Statistical analysis

The primary objective of this study was to determine the response rate of recurrent or metastatic esophageal cancer to the twice-weekly TP–HDFL regimen. On the basis of findings of our previous study [13], this study was designed to include 40 patients to provide an 80% power to detect a lower 95% confidence limit higher than the hypothetical null response rate of 30%, provided that the true response rate was $\geq 45\%$.

Follow-up duration was calculated from the entry date to the end of the study on 15 December 2005. Progression-free survival was defined as the duration between the entry date and the date of documented disease progression, death owing to other causes (censored) or last follow-up (censored). Overall survival was defined as the duration between the entry date and the date of patient death or last follow-up (censored). Both the progression-free survival and overall survival were calculated using the Kaplan–Meier method. The relationship between survival and clinical parameters was analyzed using the log-rank test. The differences in objective responses in terms of clinical parameters were evaluated using χ^2 or Fisher's exact test.

Results

Patient characteristics

Between February 2001 and February 2005, 41 patients (40 men and one woman) were enroled in the study. The pretreatment characteristics of these patients are listed in Table 1. Only one woman included in this study reflects the epidemiology of esophageal cancer in Taiwan (Taiwan Cancer Registry Annual Report 2001, available at http://crs.cph.ntu.edu.tw/crs_c/annual.html, last accessed on 12 December 2006). All 41 patients had squamous cell carcinoma of the esophagus. Fifteen patients had de-novo metastatic disease. The other 26 had recurrent disease from previous definitive local treatments. Among them, five patients had been treated with esophagectomy alone, seven patients with definitive chemoradiotherapy alone and 14 patients with preoperative chemoradiotherapy. As for concurrent chemoradiotherapy, 17 patients received daily cisplatin 6 mg/m^2 intravenously days 1–5 and continuous infusion of 5-FU 225 mg/m^2/day on days 1–7 [14], and four patients received twice-weekly paclitaxel 35 mg/m^2 1-h intravenously on days 1 and 4, and cisplatin 15 mg/m^2 intravenously on days 2 and 5 [15]. All 41 patients were evaluable for response and toxicity.

Treatment

A total of 190 courses of twice-weekly TP–HDFL were administered (median 5, range 1–9). An average of 94% (range 63–100), 89% (range 50–100) and 84% (range 50–100) of the planned paclitaxel, cisplatin and 5-FU doses, respectively, were given. Three patients received less than two courses of twice-weekly TP–HDFL because of personal reasons.

Toxicity

The toxicities are summarized in Table 2. Grade 3 or 4 leukopenia and neutropenia occurred in 29.4 and 36.8% of treatment cycles, respectively. Grade 3 or 4 thrombocytopenia occurred in 5.8% of treatment cycles. Treatment-related mortality occurred in one patient, who died of invasive fungal infection. The most common grade 3 or 4 nonhematologic toxicity was diarrhea, which occurred in 14.2% of treatment cycles. Other nonhematologic toxicities were generally mild.

Response and survival

Objective response occurred in 16 patients, including three CRs. The response rate in the intent-to-treat analysis was 39.0% (95% confidence interval: 24–54) with 7% CR rate. SD occurred in 15 patients (37%). There were no significant differences in objective response rates in terms of age (<60 vs. ≥ 60), sex, Karnofsky performance status (>60 vs. 60), liver metastasis, number of metastatic sites (0 vs. 1 vs. >1), extent of disease (limitedly disseminated defined as lymph node metastasis confined to either celiac or supraclavicular region vs. extensively disseminated), hemoglobin (normal vs. elevated), alkaline phosphatase and lactate dehydrogenase. Of the 17 patients who received prior concurrent chemoradiotherapy with cisplatin and 5-FU, three achieved PR. Of the four patients who received prior concurrent chemoradiotherapy with paclitaxel and cisplatin, one achieved CR and two had PR. The response rate of patients with de-novo metastasis (50%) was higher than that of patients with recurrence from definitively treated local disease (29%), albeit not statistically significantly ($P = 0.14$).

Table 1 Patient characteristics ($n=41$)

	No. of patients	Percentage
Total no.	41	100
Age	51 (range 38–73)	
Sex (M:F)	40:1	
Karnofsky performance status		
90–100	12	29
70–80	27	66
60	2	5
Disease status		
De-novo metastatic	15	61
Recurrent	26	39
Prior therapy		
Esophagectomy	5	12
Chemoradiotherapy	7	17
Chemoradiotherapy → esophagectomy	14	34
Disease extent		
Extensive disseminated[a]		
Lung	14	34
Liver	7	17
Lung and liver	6	15
Lung, liver, and bone	4	10
Limited disseminated[b]		
Lymph node	10	24

[a]Distant metastasis or lymph node metastasis in both celiac and supraclavicular regions.
[b]Lymph node metastasis confined to either celiac or supraclavicular regions.

The median duration of follow-up was 37.4 months (range: 10–59 months). As of 15 December 2005, two patients were still alive with disease 10 and 50 months after enrollment, respectively. One patient who initially presented with de-novo lung metastasis had SD after six cycles of the protocol treatment and was still progression-free 10 months after enrollment. The other patient, who developed a metastatic neck mass with invasion to part of the lower cervical spine 46 months after receiving segmental resection of a lower-third esophageal cancer, had SD after three cycles of the protocol treatment. Subsequently, the patient received local irradiation and was still progression-free 50 months after enrollment. The median overall and progression-free survival was 8.9 (range 1–50+) and 6.3 months, respectively. The actuarial 1-year survival rate was 29% (Fig. 2). There were no significant differences in median overall or progression-free survival in terms of age, sex, Karnofsky performance status, liver metastasis, number of metastatic sites, extent of disease, hemoglobin, alkaline phosphatase and lactate dehydrogenase.

Table 2 Toxicity ($n=190$)

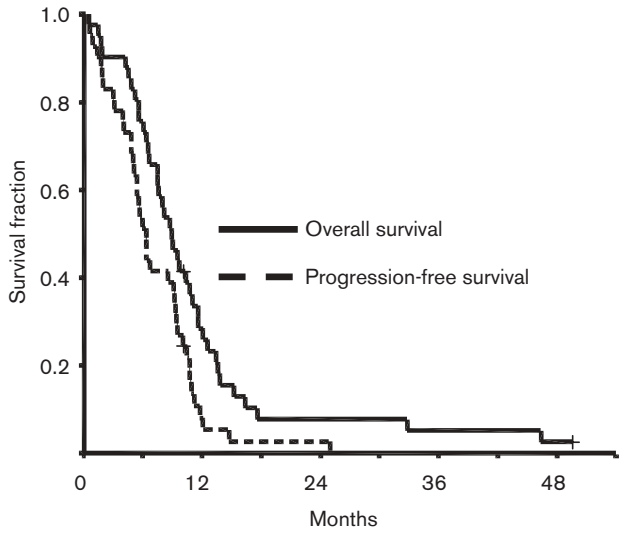
	Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	*n*	%	*n*	%	*n*	%
Hematologic								
Leukopenia	35	18.4	59	31.1	43	22.6	13	6.8
Neutropenia	24	12.6	31	16.3	47	24.7	23	12.1
Anemia	21	11.1	113	59.5	44	23.2	1	0.5
Thrombocytopenia	32	16.8	28	14.7	9	4.7	2	1.1
Nonhematologic								
Infection	5	2.6	25	13.2	4	2.1	5	2.6
Alopecia	16	8.4	131	68.9	1	0.5	–	–
Mucositis	33	17.4	29	15.3	9	4.7	2	1.1
Nausea	64	33.7	18	9.5	3	1.6	–	–
Vomiting	41	21.6	17	9.0	2	1.1	2	1.1
Diarrhea	37	19.5	55	28.9	13	6.8	14	7.4
Hepatic toxicity	40	21.1	6	3.2	4	2.1	2	1.1
Renal toxicity	39	20.5	16	8.4	1	0.5	0	
Neurotoxicity	44	23.2	6	3.2	2	1.1	0	

Discussion

Paclitaxel, cisplatin and 5-FU are individually active agents in advanced esophageal squamous cell carcinoma. This three-drug regimen utilizing the unique multifractionated dosing scheme has demonstrated activity in this tumor. Hematologic toxicity was common, but manageable.

The twice-weekly TP–HDFL regimen was active for recurrent or metastatic esophageal cancer with an objective response rate of 39% and a CR rate of 7%. As shown in Table 3, the activity surpassed that reported for the three-drug combination regimens using cisplatin and 5-FU, combined with etoposide or methotrexate (response rate 28–34%, CR rate 0–4%) [13,16]. The activity, however, appeared to be similar to that of the same three-drug regimen including cisplatin and 5-FU, combined with paclitaxel administered at 175 mg/m^2 over 3 h, repeated every 3 weeks (response rate 48%, CR rate 11%) [3]. Furthermore, the activity of the current regimen was within the range of the activity of two-drug regimen using paclitaxel and cisplatin (response rate 37–43%, CR rate 0–15%) [17–19].

Fig. 2



Overall and progression-free survival.

Inferences on the basis of a direct comparison of results among different studies can be misleading and should be made with caution. Patient characteristics, which are prognostically significant, are usually not comparable among different studies. For example, the histological type of adenocarcinoma is an independent good prognostic factor in esophageal cancer patients treated with esophagectomy [20]. Furthermore, patients with prior exposure to chemotherapy are less likely to respond to systemic chemotherapy than chemonaive patients [21,22]. In the current study, all 41 patients had squamous cell carcinoma on histology. Half of the enroled patients had recurrent disease and had been previously exposed to chemotherapeutic agents. Thus, compared with the previous reports listed in Table 3, our study probably enrolled a group of patients with a less favorable prognosis.

The hematologic toxicity of the twice-weekly TP–HDFL regimen was common, but manageable. The addition of multifractioned paclitaxel to cisplatin and 5-FU was originally designed to reduce hematologic toxicity and, therefore, facilitate compliance. Indeed, 84–94% of the planned doses of chemotherapy were administered in this study. Our study, however, failed to demonstrate less hematologic toxicity than another study using the same three-drug (paclitaxel, cisplatin, and 5-FU) regimen with different doses and schedules [3]. The incidence of grade 3 or 4 neutropenia and thrombocytopenia in this study was the same as that in the study by Ilson *et al.* [3]. The nonhematologic toxicity profile is different in these two studies, with similar grade 3 or 4 mucositis, more grade 3 or 4 diarrhea and fewer grade 3 or 4 sensory peripheral neuropathy using the multifractionated

Table 3 Cisplatin/5-FU-based three-drug combinations in advanced esophageal cancer

References	Regimen	Histology	*n* (SCC + AC)	Response rate (%)	Complete response (%)	Median survival (months)
Polee *et al.* [16]	Cisplatin 5-FU Etoposide	SCC	69 (69 + 0)[a]	34	4	9.5
Hsu *et al.* [13]	Cisplatin 5-FU Methotrexate	SCC + AC	26 (25 + 1)	28	0	5
Ilson *et al.* [3]	Cisplatin 5-FU Paclitaxel	SCC + AC	61 (31 + 30)	48	11	10
This study	Cisplatin 5-FU Paclitaxel	SCC	41 (41 + 0)	39	7	8.9

AC, adenocarcinoma; 5-FU, 5-fluorouracil; SCC, squamous cell carcinoma.
[a]Total case number (case number of SCC + case number of AC).

schedule. Few of our patients were admitted to the hospital because of treatment-related toxicity. Given the different nonhematologic toxicity profile, our multi-fractionated regimen could be considered in patients with underlying predisposing factors (e.g. alcoholism, diabetes mellitus) to neuropathy.

Our results indicate that the twice-weekly TP–HDFL regimen has activity similar to the previously reported standard-dose three-drug combination, has more diarrhea, but less peripheral neuropathy, and does not warrant further investigation for recurrent or metastatic squamous cell carcinoma.

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