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ORIGINAL ARTICLE

Weekly paclitaxel in patients with recurrent or metastatic head and neck cancer

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Abstract
Purpose To evaluate the efficacy and safety of weekly paclitaxel in patients with recurrent or metastatic head and neck cancer (HNC) by combined analysis of early and late phase II trials.
Methods Eligibility criteria included histologically proven HNC with recurrent or metastatic disease, measurable disease, PS 0-2, and one or no prior chemotherapy regimens. Treatment consisted of a 1-h infusion of paclitaxel at a dose of 100 mg/m^2 weekly for 6 weeks of a 7-week cycle. A total of 74 patients were enrolled: 37 between February and November 2004 in an early phase II trial and 37 between October 2005 and July 2006 in a late phase II trial.
Results The median number of treatment cycles was two, and median dose intensity was 84.2 mg/m^2/week. The most common grade 3–4 adverse events were leukopenia (37.5%), neutropenia (30.6%), anemia (12.5%), constipation (8.3%), peripheral neuropathy (5.6%), anorexia (5.6%), and pneumonitis (5.6%). Overall response rate was 29.0% according to RECIST. The median duration of response, median time to progression, and median survival time were 7.4, 3.4, and 14.3 months, respectively.
Conclusions This study demonstrates that weekly paclitaxel has promising activity with acceptable toxicity in the treatment of recurrent or metastatic HNC.

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Keywords Paclitaxel · Head and neck cancer · Phase II study · Weekly infusion

Introduction

Head and necks cancers (HNCs) are the sixth most common cancers worldwide, and approximately 500,000 new cases are projected annually [22]. An estimated 60% of these patients present with locally advanced disease (stage III/IV) [32]. Although the treatment of these locally advanced HNC has progressed, half will recur. While some of these are suitable for salvage treatment, including surgery or chemoradiotherapy, most are scheduled to receive palliative chemotherapy only.

Platinum-based combination chemotherapy is widely used as first-line treatment for recurrent/metastatic HNC. However, while several randomized trials have suggested that combination chemotherapy yields superior response rates, it is also associated with increased toxicity and no significant survival advantage over single agent chemotherapy [1, 4, 5, 15, 31, 35]. A recent randomized trial of platinum-based chemotherapy with or without cetuximab demonstrated significant survival benefit in the arm receiving cetuximab [30]. However, cetuximab was not given to patients in the control arm at the time of progression and it therefore remains unanswered whether the addition of cetuximab to first-line chemotherapy provides a survival benefit over sequential use of platinum-based chemotherapy followed by cetuximab at the time of progression. In other words, standard therapy in first-line treatment for recurrent/metastatic HNC has not yet been established. Furthermore, treatment options for patients who are refractory to platinum-based chemotherapy are limited. Optimal treatment options for these patients are therefore desirable.

Paclitaxel is a novel diterpenoid isolated from the bark of the Pacific yew, *Taxus brevifolia* [34]. Paclitaxel has high-affinity binding to microtubules, promotes microtubule assembly, and stabilizes tubulin polymers against depolymerization affecting cells in the G2/M-phase [24, 26].

Previous studies of high-dose tri-weekly paclitaxel (200–250 mg/m^2) in patients with advanced or recurrent/metastatic HNC demonstrated treatment activity, with an overall response of 35–40%, but that this regimen was associated with severe neuropathy and myelosuppression [6, 27]. Since the survival of patients with recurrent or metastatic HNC is limited, additional consideration should be given to their quality of life.

Previous studies of weekly paclitaxel at a reduced single dose for other cancers demonstrated comparable efficacy to a high-dose tri-weekly regimen with milder toxicities, including neuropathy and myelosuppression [28].

At the time the present trials were planned, only one prospective phase II study of weekly paclitaxel in the treatment of recurrent or metastatic HNC had appeared. Results showed acceptable toxicities but the poor response rate of 9.3% (4/43) [3]. Thus, no data were available to support the practical use of weekly paclitaxel in the treatment of recurrent or metastatic HNC, albeit that weekly paclitaxel has been widely used in the treatment of HNC patients who are refractory to a platinum-based chemotherapy.

Here, therefore, we conducted two multicenter, phase II trials, an early and late phase II trial of weekly paclitaxel in patients with recurrent or metastatic HNC, to evaluate efficacy and safety in the two trials and to confirm data on safety and efficacy between them.

Patients and methods

The subjects of the present study were patients enrolled in two multicenter trials, an early and a late phase II trial of weekly paclitaxel in the treatment of recurrent or metastatic HNC. To allow the safety and efficacy of these trials to be compared, they were conducted under the same design. Each trial was conducted at 19 institutions in Japan.

Eligibility criteria included histologically or cytologically proven HNC with recurrent or metastatic disease; age 20 years or older but less than 75; a measurable lesion; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; adequate organ function, as defined by an absolute neutrophil count (ANC) >2,000/μL, platelet count >100,000/μL, hemoglobin >9.0 g/dL, AST <100 IU/L, ALT <100 IU/L, total bilirubin <1.5 mg/dL, and serum creatinine <1.5 mg/dL; and life expectancy >2 months from the beginning of treatment. Patients were excluded if they had received two or more prior regimens of chemotherapy for recurrent/metastatic HNC. The study protocol was reviewed and approved by the ethics committee of each of the participating institutions before patient enrollment began. Informed consent was obtained from all patients.

Treatment

On the basis of the results of a phase I trial of weekly paclitaxel in solid tumors [20], patients in both the early and late phase trials received a 1-h iv infusion of paclitaxel at a dose of 100 mg/m^2 weekly over a 7-week cycle on days 1, 8, 15, 22, 29, and 36, followed by 2 weeks of rest until unacceptable toxicity, patient refusal, or disease progression were observed. Patients received premedication with 8 mg dexamethasone (iv), 50 mg ranitidine (iv),

and 50 mg diphenhydramine hydrochloride (po) 30–60 min prior to paclitaxel infusion.

Dose modification of paclitaxel by 20 mg/m^2 was allowed if a patient experienced any of the following adverse events: (1) febrile neutropenia, (2) grade 3 or 4 thrombocytopenia, (3) grade 3 or 4 non-hematological toxicity, (4) grade 2 or higher peripheral neuropathy or myalgia/arthralgia, or (5) any toxicity that caused a dose to be skipped or required a dose reduction at the discretion of the physician. Dose reduction to less than 60 mg/m^2 was not allowed.

Study endpoints

The primary endpoints in each trial were safety and response rate as assessed by WHO criteria, which could be compared to historical data. Secondary endpoints were duration of response, response rate based on the response evaluation criteria in solid tumors (RECIST), median time to progression (TTP), and median survival time (MST). The response rates and adverse events were evaluated by an independent safety and efficacy assessment committee. Responses were assessed by CT and/or MRI scans every 4 weeks. Adverse events were evaluated every week according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 2.0. A subject's TTP was defined as the time from the date of the enrollment in the present study to the first documentation of disease progression, subsequent therapy, or death. The duration of response was defined as the time from the date of the first confirmation of response to the first documentation of disease progression.

Statistical design

To confirm safety and efficacy, applications for approval of anti-neoplastic drugs in Japan typically require two studies conducted under the identical design, an early and a late phase II trial. If the early trial does not demonstrate promising activity, the late trial is withheld. In each of the present studies, the expected response rate was considered to be 25% and the threshold response rate was set at 10%. Thirty-six patients were needed to evaluate efficacy in each study in order to reject the hypothesis that the true efficacy rate was below the threshold response rate, giving $\alpha = 0.025$ (one-sided) and $\beta = 0.3$. A survival curve was estimated using the Kaplan–Meier method [16]. In the present trials, safety and efficacy analyses were conducted on an intention-to-treat (ITT) population, defined as all patients enrolled in the study who received at least one dose of paclitaxel. All statistical analyses were carried out using SAS Version 8.2.

Results

Patient characteristics

A total of 74 patients were enrolled, 37 between February and November 2004 in the early phase II trial and 37 between October 2005 and July 2006 in the late phase II trial. The two trials had one patient each who did not receive any administration of paclitaxel due to PS 3 or ANC <2,000/μL. Patient characteristics are shown in Table 1. Of note, a total of 25 (34.7%) patients had advanced cancer, 47 (65.3%) had recurrent cancer, and 62 (86.1%) had a prior history of chemotherapy, including platinum-based chemotherapy (76.4%). Of these, 23 (31%) had received prior platinum-based chemotherapy for recurrent/metastatic disease. No relevant differences in patient characteristics were observed between individuals in the early and late phase trial groups.

Treatment administration

For both the early and late phase trials, the combined median number of treatment cycles was 2.0 (range 1–10) and the median number of doses was 12 (range 1–50). The combined median interval between cycles was 14.0 days (range 13–28 days), and the median dose intensity was 84.2 mg/m^2/week (range 43.0–107.7 mg/m^2/week).

Safety

The safety evaluation was conducted in 72 patients who received at least one dose of paclitaxel. Adverse events are shown in Table 2. The most common grade 3–4 non-hematological adverse events were constipation (8.3%), peripheral neuropathy (5.6%), anorexia (5.6%), and pneumonitis (5.6%), while grade 3–4 hematological adverse events were leukopenia (37.5%), neutropenia (30.6%), and anemia (12.5%). No deaths related to paclitaxel treatment were seen during the study period. The incidence of greater than grade 2 peripheral neuropathy was 25.0% (18/72).

The percentage of patients requiring dose reductions was 34.7% (25/72). Although 16.7% (12/72) of patients required cessation of therapy, only 5.6% (4/72) was unable to complete the protocol of at least one cycle of paclitaxel. The most common reason for cessation was peripheral neuropathy, seen in 6.9% (5/72) of patients. The median time to onset of peripheral neuropathy was 34 days (range 1–141), and the median dose of onset was 500 mg/m^2 (range 100–1600 mg/m^2). In those patients who experienced peripheral neuropathy, 14.5% (8/55) recovered, 7.3% (4/55) remitted, and 78.2% (43/55) failed to recover by the end of the protocol.

Table 1 Patient characteristics

Characteristics	Number of subjects (%)		
	Total, $n = 72$	Early phase II study, $n = 36$	Late phase II study, $n = 36$
Sex			
Male	56 (77.8)	30 (83.3)	26 (72.2)
Female	16 (22.2)	6 (16.7)	10 (27.8)
Age			
Median age (range)	61 (41–74)	60.5 (44–74)	62.5 (41–74)
P.S. (ECOG)			
0	48 (66.7)	22 (61.1)	26 (72.2)
1	22 (30.6)	13 (36.1)	9 (25.0)
2	2 (2.8)	1 (2.8)	1 (2.8)
Disease status			
Advanced	25 (34.7)	10 (27.8)	15 (41.7)
Recurrent	47 (65.3)	26 (72.2)	21 (58.3)
Histopathological diagnosis			
Squamous cell carcinoma	61 (84.7)	32 (88.9)	29 (80.6)
Adenoid cystic carcinoma	4 (5.6)	1 (2.8)	3 (8.3)
Others	7 (9.7)	3 (8.3)	4 (11.1)
Primary lesion			
Oral cavity	8 (11.1)	8 (22.2)	0
Paranasal cavity	8 (11.1)	3 (8.3)	5 (13.9)
Nasopharynx	8 (11.1)	4 (11.1)	4 (11.1)
Oropharynx	12 (16.7)	6 (16.7)	6 (16.7)
Hypopharynx	18 (25.0)	7 (19.4)	11 (30.6)
Larynx	6 (8.3)	3 (8.3)	3 (8.3)
Salivary gland	7 (9.7)	1 (2.8)	6 (16.7)
Others	5 (6.9)	4 (11.1)	1 (2.8)
Prior treatment			
Chemotherapy*	62 (86.1)	32 (88.9)	30 (83.3)
Cisplatin-based chemotherapy	55 (76.4)	29 (80.6)	26 (72.2)
Others	7 (9.7)	3 (8.3)	4 (11.1)
Surgery	36 (50.0)	20 (55.6)	16 (44.4)
Radiotherapy	60 (83.3)	30 (83.3)	30 (83.3)

PS performance status, *ECOG* Eastern Cooperative Oncology Group

* Including adjuvant chemotherapy, neoadjuvant chemotherapy, and chemoradiotherapy

Efficacy

Thirty-six patients in each study were assessed for efficacy (Table 3). Overall response rates (RRs) in the early and late trial were 33.3% (95% CI: 18.6, 51.0%) and 36.1% (95% CI: 20.8, 53.8%), respectively. In combined analysis of two trials, RR according to WHO and RECIST criteria were 34.7% (95% CI: 23.9, 46.9%) and 29.0% (95% CI: 18.7, 41.2%), respectively. RR according to the WHO criteria in the 55 patients who received prior platinum-based chemotherapy was 32.7% and 30.4% in the 23 patients who received prior platinum-based chemotherapy for recurrent/metastatic disease (Table 4). RR in the 60 patients who received prior radiotherapy, including adjuvant therapy, neoadjuvant therapy, and chemoradiotherapy, was 30.0 and 58.3% in the 12 patients who did not receive prior radiotherapy.

The median duration of response was 8.5 months (95% CI: 5.4, 11.5 months) in the early trial, 6.9 months (95% CI: 3.2, 7.9 months) in the late trial, and 7.4 months (95% CI: 5.4, 9.4 months) in total.

The median follow-up period in all patients was 13.8 months (range: 1.6-33.8 months). Median TTP and MST were 3.4 months (95% CI: 3.0, 4.6 months; Fig. 1) and 14.3 months (95% CI: 11.0, 19.4 months; Fig. 2), respectively. In the 64 patients excluding those with nasopharyngeal cancer, median TTP and MST were 3.2 months (95% CI: 2.9, 4.3 months) and 13.0 months

Table 2 Adverse events

	Total ($n = 72$)				Early phase II study ($n = 36$)				Late phase II study ($n = 36$)			
	≥Grade 1		≥Grade 3		≥Grade 1		≥Grade 3		≥Grade 1		≥Grade 3	
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Nausea	22	30.6	2	2.8	9	25.0	1	2.8	13	36.1	1	2.8
Anorexia	19	26.4	4	5.6	10	27.8	1	2.8	9	25	3	8.3
Constipation	22	30.6	6	8.3	10	27.8	5	13.9	12	33.3	1	2.8
Fatigue	47	65.3	2	2.8	25	69.4	1	2.8	22	61.1	1	2.8
Peripheral neuropathy	55	76.4	4	5.6	27	75.0	1	2.8	28	77.8	3	8.3
Pneumonitis	8	11.1	4	5.6	5	13.9	3	8.3	3	8.3	1	2.8
Alopecia	68	94.4			34	94.4			34	94.4		
Rash	28	38.9			15	41.7			13	36.1		
ALT	25	34.7			17	47.2			8	22.2		
Leukopenia	65	90.3	27	37.5	32	88.9	13	36.1	33	91.7	14	38.9
Neutropenia	60	83.3	22	30.6	29	80.6	13	36.1	31	86.1	9	25.0
Anemia	59	81.9	9	12.5	29	80.6	3	8.3	30	83.3	6	16.7
Thrombocytopenia	7	9.7			6	16.7			1	2.8		

ALT alanine aminotransferase

Table 3 Response according to WHO and RECIST criteria

Criteria	Study	Number of patients						RR (%)	95% CI
		Assessable patients	CR	PR	NC/SD	PD	NE		
WHO	Total	72	5	20	23	18	6	34.7	23.9, 46.9
	Early	36	2	10	9	11	4	33.3	18.6, 51.0
	Late	36	3	10	14	7	2	36.1	20.8, 53.8
RECIST	Total	69	4	16	33	9	7	29.0	18.7, 41.2
	Early	35	2	7	15	7	4	25.7	12.5, 43.3
	Late	34	2	9	18	2	3	32.4	17.4, 50.5

CR complete response, *PR* partial response, *NC* no change, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *RR* response rate, *CI* confidence interval, *WHO* World Health Organization, *RECIST* response evaluation criteria in solid tumors

(95% CI: 9.9, 16.9 months), respectively. As 11 patients (15.3%) had non-squamous cell carcinomas histology, which included 4 with adenoid cystic carcinoma and 7 with either mucoepidermoid tumor, adenocarcinoma, poorly differentiated carcinoma, acinar cell carcinoma, carcinoma, large cell carcinoma, or undifferentiated carcinoma, MST was also determined excluding these patients. MST was 13.4 months in the 61 patients with squamous cell carcinomas and 11.7 months in the 45 patients with squamous cell carcinomas of the oral cavity, paranasal cavity, oropharynx, hypopharynx, and larynx cancer. In the 23 patients who had received prior platinum-based chemotherapy for recurrent/metastatic disease, median TTP and MST were 3.2 months (95% CI: 2.5, 6.7 months) and 11.4 months (95% CI: 7.4, 19.4 months), respectively.

Discussion

Here, we conducted early and late phase II trials of weekly paclitaxel in patients with recurrent or metastatic HNC. Results demonstrated comparable safety and efficacy between the two trials. Further, the combined RR of the two trials was comparable to those previously reported in studies of tri-weekly paclitaxel in patients with advanced or recurrent HNC [6, 27]. All adverse events that occurred in the two trials were manageable, and no treatment-related deaths were observed. Although most patients had received prior chemotherapy, MST was 14.3 months, which was superior to that of previous studies in first-line patients with recurrent or metastatic HNC.

Of interest, MST in the 64 patients excluding those with nasopharyngeal cancer and in the 23 who had received

Table 4 Response rates according to patient characteristics (WHO)

Characteristic	Number of patients					RR (%)
	CR	PR	NC	PD	NE	
Sex						
Male	3	16	19	14	4	33.9
Female	2	4	4	4	2	37.5
Age (Years)						
<65	4	12	12	16	6	32.0
≥65	1	8	11	2		40.9
Histopathological diagnosis						
Squamous cell carcinoma	3	16	21	16	5	31.1
Adenoid cystic carcinoma		1	1	2		25.0
Others	2	3	1		1	71.4
Primary lesion						
Oral cavity		4	1	2	1	50.0
Nasal cavity				1		0
Paranasal cavity	1	2	4	1		37.5
Maxillary sinus				1		0
Nasopharynx	1	3	3		1	50.0
Oropharynx	1	4	3	4		41.7
Hypopharynx	1	4	8	3	2	27.8
Larynx		1	2	2	1	16.7
Salivary gland	1	2	1	2	1	42.9
Tympanum			1			0
External auditory canal				2		0
Prior radiotherapy						
None		7	1	3	1	58.3
Radiotherapy*	5	13	22	15	5	30.0
Prior chemotherapy						
None	1	3	3	2	1	40.0
Cisplatin-based chemotherapy	4	14	17	16	4	32.7
Others		3	3		1	42.9

CR complete response, *PR* partial response, *NC* no change, *PD* progressive disease, *NE* not evaluable, *RR* response rate, *WHO* World Health Organization

* Including adjuvant therapy, neoadjuvant therapy, and chemoradiotherapy

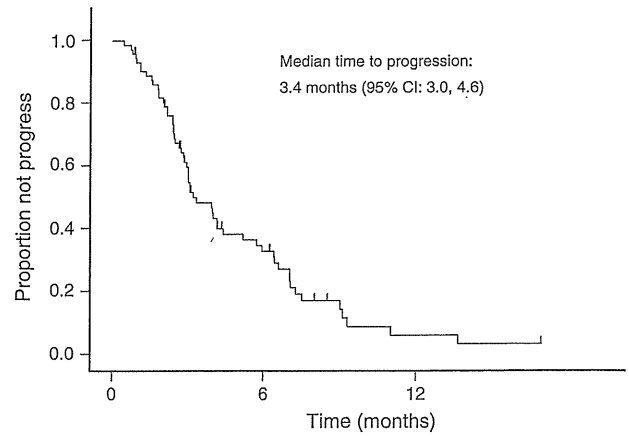

Fig. 1 Combined time to progression from the early and late phase II studies. The median time to progression was 3.4 months (95% CI: 3.0, 4.6 months)

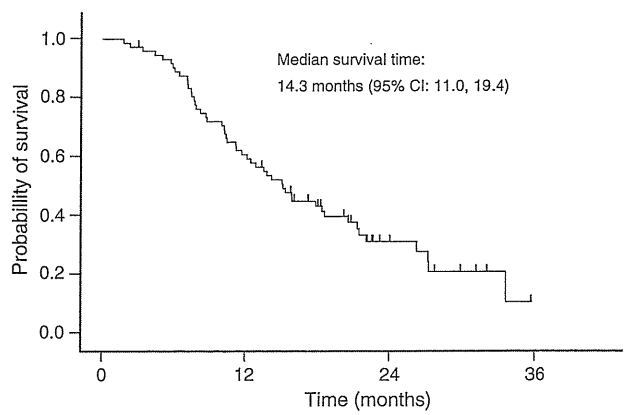

Fig. 2 Combined overall survival from the early and late phase II studies. The median follow-up time of patients for overall survival was 13.8 months, with a median overall survival time of 14.3 months (95% CI: 11.0, 19.4 months)

prior platinum-based chemotherapy for recurrent/metastatic disease was 13.0 and 11.4 months, respectively. Allowing for the fact that this was a nonrandomized trial with a relatively small number of patients, these results are nevertheless better than those in the previous studies, particularly in showing that weekly paclitaxel was active in the treatment of HNC whether patients had received prior platinum-based chemotherapy or not.

Recently, the addition of cetuximab to platinum-based chemotherapy was shown to significantly prolong overall survival without exacerbating chemotherapy-associated toxicity or quality of life in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN) [10]. Furthermore, the addition of cetuximab to paclitaxel was also shown to exert promising activity in a first-line setting of a phase II trial, which had an RR of 71% and a complete response rate of 20%. Weekly paclitaxel might therefore be a good alternative to platinum-based chemotherapy for first-line patients with recurrent or metastatic SCCHN.

Treatment options for patients with recurrent or metastatic HNC who are refractory to platinum-based chemotherapy are limited. Several second-line chemotherapy regimens with cytotoxic agents, including methotrexate, vinorelbine, bleomycin, docetaxel, and S-1, have been investigated in the treatment of patients with recurrent or metastatic HNC after previous platinum-based chemotherapy [7, 11–14, 36]. Response rates and MST in these studies were 10–46.2% and less than 5 months, respectively, and it has accordingly not been possible to draw definitive conclusions on their clinical benefit.

Recently, a single institutional prospective study of weekly paclitaxel (80 mg/m^2, weekly, 6 consecutive weeks) in SCCHN patients in whom platinum-based chemotherapy failed demonstrated a response rate of 43.3% and MST of 8.5 months [9]. Although this rate is superior to that of the present study, the study was conducted at a single institution and had no independent safety and efficacy assessment committee, while our study was a multicenter trial with independent safety and efficacy assessment committees. Further, our present study demonstrated a better duration of response and survival, which might be associated with the higher dose of paclitaxel in the present study.

A combined analysis of second-line use of cetuximab with or without platinum-based chemotherapy for patients with recurrent/metastatic SCCHN in whom platinum-based chemotherapy failed concluded that cetuximab would be effective as monotherapy and could be considered a therapeutic option [29]. However, the response rate, median TTP and MST of cetuximab alone in these patients were 13%, 2.3, and 5.9 months, respectively, indicating the need for further optimization of treatment options.

Although the number of patients who had previously received platinum-based chemotherapy for recurrent/metastatic disease in the present study was small, weekly paclitaxel showed a superior response rate and survival to that of previously reported agents and may therefore also be promising in second-line treatment following cisplatin-based regimens. Recently, weekly taxane-based chemotherapy was shown to exhibit promising activity as an induction chemotherapy in the primary therapy setting [17, 25, 33], suggesting that this dose-dense strategy may be particularly applicable to sequential treatment programs for HNC.

Long-term administration of weekly paclitaxel increases the incidence and severity of peripheral neuropathy, which often reduces quality of life. In our present patients who experienced peripheral neuropathy, 14.5% recovered and 7.3% remitted, while 78.2% failed to recover by the end of the protocol. Such sustained peripheral neuropathy may be limiting for patients receiving longer-term palliative therapy. Several studies have investigated anti-neuropathy drugs, including amifostine, gabapentin, and vitamin E, but all failed to demonstrate any benefit for these patients [2, 8, 18, 19, 21, 23]. The development of effective anti-neuropathy drugs is desirable.

Several limitations of the present study warrant mention. First, subjects included eight patients with nasopharyngeal cancer, which is considered to carry a better prognosis than other HNCs. Second, subjects included chemo-naive patients and patients who had not been confirmed to be refractory to platinum-based chemotherapy. Third, the present trials were nonrandomized, and differences in patient populations due to selection bias may have influenced outcomes and toxicity rates and thereby limit comparisons between studies. Fourth, the study included a range of histological subtypes. In other words, the subjects represented a markedly heterogeneous population.

In summary, this study demonstrated that weekly paclitaxel has promising activity with acceptable toxicity in the treatment of recurrent or metastatic HNC. Paclitaxel may be a good treatment option for recurrent or metastatic HNC.

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Phase I trial of combination chemotherapy with docetaxel, cisplatin and S-1 (TPS) in patients with locally advanced or recurrent/metastatic head and neck cancer

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Background: We investigated the maximum tolerated dose (MTD) of combination therapy with docetaxel, cisplatin, and S-1 (TPS) in patients with locally advanced or recurrent/metastatic head and neck cancer (HNC).

Patients and methods: Treatment consisted of docetaxel (Taxotere) at doses of 50, 60, and 70 mg/m^2; cisplatin at 70 mg·m^2/day on day 1; and S-1 twice daily on days 1–14 at doses of 40, 60, and 80 mg·m^2/day, repeated every 3 or 4 weeks.

Results: Forty patients were enrolled. MTD was not reached until level 4. Subjects at expanded dose were limited to patients with locally advanced disease. Two dose-limiting toxic effects (DLTs) were observed at dose level 5 (TPS: 70/70/80 mg·m^2/day, every 3 weeks), namely one grade 3 infection and one grade 3 hyperbilirubinemia, establishing this as the MTD. Of 12 patients treated at dose level 6 (TPS: 70/70/60 mg·m^2/day, every 3 weeks), 2 DLTs were seen. Six achieved a complete response and 22 a partial response, giving a response rate of 70%.

Conclusions: TPS was well tolerated. The recommended phase II dose as induction chemotherapy for locally advanced HNC was determined as 70/70/60 mg·m^2/day every 3 weeks. Antitumor activity was highly promising and warrants further investigation.

Key words: cisplatin, docetaxel, head and neck cancer, S-1

introduction

Head and neck cancers (HNCs) are the sixth most common cancer in the world, and ~500 000 new cases are projected annually [1]. An estimated 60% of these patients will present with locally advanced disease (stage III/IV).

Platinum-based chemotherapy is widely used for recurrent/metastatic HNC. The combination of docetaxel, cisplatin, and 5-fluorouracil (5-FU) (TPF) has been considered the standard regimen for induction chemotherapy for locally advanced squamous cell carcinoma of the head and neck (SCCHN) [2, 3]. Nevertheless, this combination is stressful to patients, and the continuous infusion of 5-FU in this combination reduces quality of life, owing not only to toxicity but also to inconvenience and catheter-related complications. Other options with improved safety profiles and greater convenience are thus highly desirable.

In response to this need, one growing trend has been the substitution of conventional 5-FU with the oral prodrug of 5-FU. S-1 is a novel oral fluoropyrimidine derivative, which consists of tegafur, gimeracil (5-chloro-2, 4-dihydrogenase; CDHP), and potassium oxonate (Oxo) at a molar ration of 1 : 0.4 : 1 [4]. Tegafur is a prodrug of 5-FU. CDHP augments the activity of 5-FU by inhibiting dihydropyrimidine dehydrogenase. Oxo reduces gastrointestinal (GI) toxicity by inhibiting orotate phosphoribosyl transferase and 5-FU phosphorylation in intestinal mucosa [5].

S-1 has shown activity against HNC, producing a response rate of 34% [6]. A combination of cisplatin and S-1 shows promising efficacy (response rate: 67.6%) with acceptable toxicity for locally advanced HNC [7]. Furthermore, a combination of docetaxel and S-1 has demonstrated promising efficacy with acceptable toxicity for many cancers [8–11].

Based on these promising results, we speculated that replacing 5-FU with S-1 in combination with docetaxel and cisplatin would be a reasonable alternative to continuous

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infusion of 5-FU. To our knowledge, however, combination therapy with docetaxel, cisplatin, and S-1 (TPS) in the treatment of HNC has not been investigated.

Here, we conducted a phase I study of a combination therapy with TPS in patients with locally advanced or recurrent/metastatic HNC.

patients and methods

eligibility criteria

All patients had a histologically or cytologically confirmed diagnosis of HNC with recurrent/metastatic or unresectable locally advanced disease. Eligibility also required an Eastern Cooperative Oncology Group performance status of zero or one, age 20–75 years, and adequate organ function. Written informed consent was required from all patients before the start of study therapy.

Patients were excluded for any of the following conditions: history of prior chemotherapy; concurrent active malignancy except excised intramucosal gastric or esophageal cancer, which could be removed by endoscopic mucosal resection; pharyngeal fistula; active bleeding from the GI tract; active infection; serious medical problem that might interfere with the achievement of study objectives; pregnancy or lactation; or expected survival of <3 months.

The study was approved by the Institutional Review Board at the National Cancer Center.

study design

The study was conducted as an open-label, single arm, phase I, single-institution dose-escalation study aimed at testing the safety of combination therapy with TPS in patients with locally advanced or recurrent/metastatic HNC. A total of six dose combinations were planned (Table 1).

Toxic effects were evaluated according to National Cancer Institute—Common Toxicity Criteria for Adverse Events version 2.0. A minimum of three assessable patients was treated at each dose level. If one of the three patients at a given dose level experienced a dose-limiting toxicity (DLT), three additional patients were accrued at the same dose level. The maximum tolerated dose (MTD) was defined as the dose at which two or more patients of six experienced a DLT. After the MTD was determined, three more patients were treated at the next lower dose level. If no or only one of the six patients experienced a DLT, an additional six patients were accrued at the same dose level to determine the recommended dose (RD). No intra-patient dose escalation was allowed.

DLT was defined as any of the following adverse events occurring within 30 days after completion of the first cycle of TPS: (i) febrile neutropenia lasting >4 days; (ii) grade 4 thrombocytopenia (<10 000/mm^3); (iii) grade 4 vomiting; (iv) grade 3 or 4 nonhematological toxic effects except grade 3 anorexia, nausea, vomiting, stomatitis, esophagitis, and infection due to stomatitis; (v) cessation of treatment due to an adverse event; or (vi) treatment-related death.

treatment

Chemotherapy consisted of a 1-h infusion of docetaxel at escalating doses of 50, 60, and 70 mg/m^2; a 2-h infusion of cisplatin at 70 mg·m^2/day on day 1; and S-1 twice daily on days 1–14 at escalating doses of 40, 60, and 80 mg·m^2/day. This regimen was repeated every 3 or 4 weeks. Prophylactic use of granulocyte colony-stimulating factor was not allowed but ciprofloxacin was administered on days 5 through 15.

The dose escalation schema is depicted in Table 1. At dose levels 1–4, treatment was repeated every 4 weeks, with a maximum of six cycles allowed until unacceptable toxicity, patient refusal or disease progression was observed. At dose levels 5 and 6, the subject had to have locally advanced HNC and to have received TPS every 3 weeks with a maximum of three cycles allowed. Patients with locally advanced HNC who recorded a response after completion of three cycles of TPS were able to receive definitive treatment, including concurrent chemoradiotherapy.

treatment evaluation and dose modifications

Baseline evaluation consisted of history, physical examination, radiographic imaging, routine laboratory studies, and electrocardiogram. Safety assessments were repeated weekly after the start of chemotherapy.

Doses were modified in case of severe hematological or nonhematological toxic effects. Since patients received three chemotherapeutic agents, dose adjustment was carried out for each individual agent based on its estimated causal relationship to the toxicity; if multiple agents were felt to be causing the toxicity, dose reduction was carried for multiple agents according to the RD reduction schedule below. If multiple toxic effects occurred during a treatment cycle, the toxicity with the highest grade was used as the parameter for dose adjustment.

Grade 4 hematological toxic effects or grade 3 infection required a dose reduction of all three drugs. Grade 3 diarrhea, mucositis, or skin reaction required a reduction in S-1 dose. Grade 2 neurotoxicity required a reduction in cisplatin dose. Grade 3 neurotoxicity required the discontinuation of cisplatin. Creatinine clearance (CCr) was calculated at the beginning of each cycle according to the Cockcroft–Gault formula. CCr values >60 ml/min required no dose modification; those from 50 to <60 ml/min required a reduction in both S-1 and cisplatin by one dose level; those from 40 to <50 ml/min required a reduction of both S-1 and cisplatin by two dose levels; and those <40 ml/min required the cessation of both S-1 and cisplatin. Patients were removed from treatment if more than two dose reductions were required or if there was a treatment delay of >21 days due to toxicity.

Tumors responses were evaluated according to RECIST.

Table 1. Dose escalation schema and DLTs

Dose level	Docetaxel (mg/m^2)	Cisplatin (mg/m^2)	S-1 (mg·m^2/day)	Cycle (weeks)	Subject	DLT frequency	DLT
1	50	70	40	4	R/M and LA	0/4	
2	60	70	40	4	R/M and LA	0/3	
3	60	70	60	4	R/M and LA	0/3	
4	60	70	80	4	R/M and LA	1/12	Grade 3 infection
5	70	70	80	3	LA	2/6	Grade 3 infection, grade 3 hyperbilirubinemia
6	70	70	60	3	LA	2/12	Grade 3 diarrhea, grade 3 ALT/AST↑

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; LA, locally advanced disease; R/M, recurrent/metastatic disease.

end points and statistical methods

The primary end point in this study was the MTD and RD of this regimen. Secondary end points included the safety and tolerability of this combination and relative dose intensity and efficacy, including response rate, progression-free survival (PFS), and overall survival (OS).

Relative dose intensity was calculated as the ratio of the actual to planned dose intensity in milligrams per square meter per week. The survival curve was estimated using the Kaplan–Meier method. Safety and efficacy analyses were both conducted on an intention-to-treat (ITT) population, defined as all patients enrolled in the study who received at least one dose of chemotherapy. A subject's PFS was defined as the time from the date of the first administration of chemotherapy to the first documentation of disease progression, subsequent therapy, or death. OS was determined from the date of the first administration of chemotherapy to the date of death or the last confirmation of survival. Statistical data were obtained using the SPSS software package (SPSS 11.0 Inc., Chicago, IL).

results

patient and disease characteristics

From November 2004 to September 2008, a total of 40 patients were enrolled, consisting of 33 males and 7 females with a median age of 50 years (range 22–74 years). Patient characteristics in the ITT population are listed in Table 2.

Table 2. Patient characteristics

Characteristic	No. of patients ($n = 40$)
Age, years	
Median	50
Range	22–74
Sex	
Male	33
Female	7
Eastern Cooperative Oncology Group performance score	
0	35
1	5
Site of primary tumor	
Hypopharynx	9
Oral cavity	1
Oropharynx	10
Salivary gland	3
Nasopharynx	13
Nasal cavity	3
Histology	
Squamous cell carcinoma	23
Adenoid cystic carcinoma	3
Undifferentiated carcinoma	9
Others	5
Disease status	
Recurrent/metastatic disease	11
Locally advanced disease	29
Prior treatment	
None	31
Surgery alone	4
Surgery with adjuvant radiotherapy	1
Radiotherapy alone	4

Twenty-nine cases were locally advanced cancer and 11 were recurrent/metastatic cancer.

treatment administration

A total of 116 cycles was administered (median = 3, range 1–6) over six dose levels. Twenty cycles required dose reduction, while six required a delay of >7 days due to toxicity. Six patients discontinued treatment due to disease progression and two due to treatment-related toxicity, while two other patients refused further treatment due to fatigue. Three of 11 patients with recurrent/metastatic disease completed six cycles of TPS as a palliative chemotherapy, whereas 27 of 29 patients with locally advanced disease completed three cycles of TPS as induction chemotherapy. Twenty-four patients received subsequent chemoradiotherapy concurrently with cisplatin (cisplatin 20 mg/m^2, i.v., days 1–4, days 22–25, days 43–46) after completion of TPS. One patient received chemoradiotherapy with 5-FU plus cisplatin (5-FU 400 mg/m^2, i.v., days 1–5, days 29–33, cisplatin 20 mg/m^2, i.v., days 1–4, days 29–32). Four patients received proton beam therapy concurrently with cisplatin at the same schedule as chemoradiotherapy. One patient for whom no response was documented after two cycles of TPS received palliative chemoradiotherapy. Median total dose of photon therapy and proton beam therapy was 70 Gy (range 66–70) and 70 Gy (range 65–70), respectively.

dose escalation and DLT

DLTs are listed in Table 1. No DLTs were observed until dose level 3. At dose level 4, one patient experienced grade 3 infection, leading cohort expansion, but no further DLTs were observed at this dose level. Although MTD was not reached by this level, further escalation was not initially planned. An additional six patients were accrued at this level to determine the RD. Since MTD was not reached by dose level 4 and the dose intensities of docetaxel and cisplatin at this level (docetaxel 15 mg·m^2/week, cisplatin 17.5 mg·m^2/week) were markedly lower than that of previous studies of induction TPF for locally advanced HNC (docetaxel 25 mg·m^2/week, cisplatin 25 mg·m^2/week), we amended the protocol to include a dose escalation of docetaxel and shortening of treatment cycle and limited the subjects to patients with locally advanced disease. In other words, MTD was evaluated at dose level 5 or 6 to determine the RD of TPS as induction chemotherapy for locally advanced HNC.

At dose level 5, two DLTs were observed, namely one grade 3 infection and one grade 3 hyperbilirubinemia, establishing this as the MTD. The relative dose intensity at this dose level was 0.67 (range 0.40–0.85). In the 12 patients at dose level 6, two DLTs were observed, namely one grade 3 elevation of alanine aminotransferase/aspartate aminotransferase and one grade 3 diarrhea. The relative dose intensity at this dose level was 0.92 (range 0.41–1.0). Based on the results, the RD of this combination was determined as docetaxel 70 mg/m^2, cisplatin 70 mg/m^2, and S-1 60 mg/m^2 for 14 days, every 3 weeks.

toxicity

Overall toxic effects during TPS administration are listed in Table 3. Grade 3 or 4 hematological toxic effects are listed by

dose level in Table 4. At dose level 5, all patients experienced grade 4 neutropenia. Grade 2 or 3 nonhematological toxic effects are listed by dose level in Table 5. No grade 4 nonhematological toxic effects were observed during any course.

Major common grade 3 or 4 toxic effects in patients with locally advanced disease during chemoradiotherapy or proton beam therapy were mucositis (48%), dysphagia (34%), leucopenia (28%), anemia (17%), dermatitis (17%), and neutropenia (14%). Toxicity was as expected and manageable.

Table 3. Overall toxicity during TPS administration ($n = 40$)

Toxicity	No. of patients				%
	Grade				Grade
	1	2	3	4	3–4
Hematological toxicity					
Leucopenia	6	20	12	0	30
Neutropenia	6	9	12	12	60
Febrile neutropenia	0	0	5	0	13
Anemia	22	14	3	0	8
Thrombocytopenia	15	2	0	0	0
Nonhematological toxicity					
Nausea	16	14	1	0	3
Vomiting	12	3	0	0	0
Anorexia	15	14	6	0	15
Fatigue	13	7	0	0	0
Mucositis	5	3	1	0	3
Diarrhea	6	3	1	0	3
Elevated bilirubin	5	12	1	0	3
Elevated AST	14	3	1	0	3
Elevated ALT	10	6	1	0	3
Elevated creatinine	6	1	1	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

treatment outcomes

Efficacy data are listed in Table 6. All patients enrolled in this study were assessable for response to TPS. There were 6 complete and 22 partial responses, giving an overall response rate of 70% [95% confidence interval (CI) 59.1–80.8], broken down as 4 complete and 18 partial responses in the 29 patients with locally advanced disease, and 2 complete and 4 partial responses in the 11 with recurrent/metastatic disease. One of these latter two complete responders, who had residual disease after completion of radiotherapy for poorly differentiated squamous cell carcinoma of the nasopharynx, achieved a complete response after receiving three cycles of TPS without further treatment and remains alive without evidence of recurrence as of ~5 years later. Another patient, who had previous radiotherapy for undifferentiated carcinoma of the nasopharynx and multiple mediastinal lymph node metastases 4 months after receiving lobectomy for lung metastasis, achieved a complete response after completion of six cycles of TPS followed by S-1 alone for 2 years and is alive without evidence of disease progression as of >4 years after treatment. Although no objective response was observed in patients with adenoid cystic carcinoma, eight of nine patients with undifferentiated carcinoma achieved an objective response.

Of the 29 patients with locally advanced disease, 23 (79%; 95% CI, 64% to 93%) experienced complete remission after completion of definitive chemoradiotherapy or proton beam

Table 4. Grade 3 or 4 hematological toxicity during TPS administration by dose level

Toxicity	Grade 3 or 4 hematological toxicity											
	No. of patients											
	Dose level 1 ($n = 4$)		Dose level 2 ($n = 3$)		Dose level 3 ($n = 3$)		Dose level 4 ($n = 12$)		Dose level 5 ($n = 6$)		Dose level 6 ($n = 12$)	
	Grade		Grade		Grade		Grade		Grade		Grade	
	3	4	3	4	3	4	3	4	3	4	3	4
Leucopenia	1	0	0	0	0	0	3	0	5	0	1	0
Neutropenia	0	1	0	0	0	0	5	0	0	6	5	4
Febrile neutropenia	0	0	0	0	0	0	0	0	1	0	4	0
Anemia	0	0	0	0	0	0	0	0	0	0	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0	0	0	0	0

Table 5. Grade 2 or 3 nonhematological toxicity during TPS administration by dose level

Toxicity	Grade 2 or 3 nonhematological toxicity											
	No. of patients											
	Dose level 1 ($n = 4$)		Dose level 2 ($n = 3$)		Dose level 3 ($n = 3$)		Dose level 4 ($n = 12$)		Dose level 5 ($n = 6$)		Dose level 6 ($n = 12$)	
	Grade		Grade		Grade		Grade		Grade		Grade	
	2	3	2	3	2	3	2	3	2	3	2	3
Anorexia	0	0	2	0	0	1	6	2	3	0	3	3
Nausea	1	0	0	0	1	0	5	1	2	0	4	0
Mucositis	0	0	0	0	2	0	1	1	0	0	0	0
Diarrhea	0	0	0	0	0	0	1	0	2	0	0	1
Infection	0	2	0	0	0	0	0	1	0	1	0	3

Table 6. Efficacy ($n = 40$)

Subject	No. of patients					%	
	CR	PR	SD	PD	NE	RR	95% CI
All ($n = 40$)	6	22	10	1	1	70	59.1–80.8
Disease status							
LA ($n = 29$)	4	18	6	1	0	76	62.2–89.8
R/M ($n = 11$)	2	4	4	0	1	55	38.7–71.2
Histology							
SCC ($n = 23$)	3	15	4	1	0	78	56.3–92.5
ACC ($n = 3$)	0	0	3	0	0	0	0–70.8
Undiff ($n = 9$)	2	6	1	0	0	89	51.8–99.7
Others ($n = 5$)	1	1	2	0	1	40	5.3–85.3

ACC, adenoid cystic carcinoma; CI, confidence interval; CR, complete response; LA, locally advanced disease; NE, not evaluated; PD, progressive disease; PR, partial response; RR, response rate; R/M, recurrent/metastatic disease; SCC, squamous cell carcinoma; SD, stable disease; Undiff, undifferentiated carcinoma.

therapy. Three patients achieved a partial response and the remaining three patients showed progressive disease, including bone metastasis ($n = 2$). With a median follow-up time of 19 months (range 6–52 months), locoregional recurrence and distant metastasis were observed in nine and four patients, respectively. A total of six patients died due to disease progression. Although the patient population was heterogeneous, the estimated 1-year PFS and OS in all patients were 64% and 85%, respectively. The estimated 1-year PFS in patients with recurrent/metastatic and locally advanced disease were 33% and 74%, respectively.

discussion

The past 5–10 years has seen an increasing trend for the substitution of conventional 5-FU with oral prodrugs of 5-FU, including S-1 and capecitabine, in chemotherapy regimens. Two randomized trials for advanced gastric cancer evaluated the safety and efficacy of S-1 compared with that of 5-FU: in one trial, S-1 showed statistically significant noninferiority to 5-FU ($P < 0.001$) [12], while in another trial [13], S-1 plus cisplatin was statistically noninferior to 5-FU plus cisplatin and had a significantly superior safety profile. These randomized trials have identified S-1 as a valuable substitute for bolus or infusional 5-FU in the treatment of gastric cancer.

Three trials of TPS in the treatment of advanced gastric cancer have been reported [14–16]. Given recognition in Japan that S-1 is a key drug in the treatment of gastric cancer, S-1 dose was fixed (S-1 80 mg·m^2/day on days 1–14) in all three trials, whereas dose intensities of docetaxel and cisplatin were markedly lower (docetaxel 10 or 20 mg·m^2/week, cisplatin 17.5 or 20 mg·m^2/week) than those of the standard TPF regimen (docetaxel 25 mg·m^2/week, cisplatin 25 mg·m^2/week) for SCCHN [2, 3]. Given the outcomes of the TAX 323 and TAX324 studies [2, 3], which demonstrated that, in addition to cisplatin, docetaxel is a key drug in the treatment of SCCHN, these TPS regimens would therefore not be appropriate substitutes for TPF in the treatment of SCCHN.

In contrast to the situation for gastric cancer, no randomized trial has compared S-1 with 5-FU for HNC and no previous studies have investigated TPS in the treatment of HNC. The present study is thus the first trial of TPS in the treatment of HNC. Results showed that the incidence of hematological toxic effects was comparable to that in TAX 323 and TAX324, whereas no grade 4 nonhematological toxic effects or treatment-related deaths were seen. At dose level 5 (docetaxel 70 mg/m^2, cisplatin 70 mg/m^2, and S-1 80 mg/m^2, every 3 weeks), two DLTs were observed, establishing this as the MTD. All patients at this level experienced grade 4 neutropenia and the relative dose intensity was 0.67, suggesting that this dose would not be feasible. At dose level 6 (docetaxel 70 mg/m^2, cisplatin 70 mg/m^2, and S-1 60 mg/m^2, every 3 weeks), 2 of 12 patients developed DLTs and the relative dose intensity at this dose level was 0.92, suggesting the feasibility of this dose as the RD of a phase II trial.

The rate of treatment-related death with the most widely accepted standard TPF regimen is 2.3% [2]. This is of concern, given that the goal of treatment for patients with locally advanced SCCHN is cure. Although the docetaxel and cisplatin doses at dose level 6 (docetaxel 70 mg/m^2, cisplatin 70 mg/m^2, and S-1 60 mg/m^2, every 3 weeks) were slightly lower than those with standard TPF, the incidence of febrile neutropenia (33%) was higher than that with standard TPF (5.2%), suggesting that further dose escalation may increase the risk of the treatment-related death. Hence, no further dose escalation was undertaken.

Many patients with locally advanced HNC experience dysphagia due to the primary tumor, and difficulty in swallowing capsules containing S-1 may be problematic. Nutritional support via feeding tube replacement in these patients is indispensable. Our previous pharmacokinetic findings showed that administration of S-1 as a suspension via a feeding tube was interchangeable with oral administration of whole capsules [17]. S-1 can therefore be administered to all HNC patients regardless of difficulty in swallowing capsules.

Although efficacy was not a primary end point of this study, antitumor activity (overall response rate 70%) was highly promising. Moreover, both patients with recurrent/metastatic nasopharyngeal cancer achieved a complete response after treatment, and remain alive and without recurrence at >4 years post-treatment. Although the number of patients was small and nasopharyngeal cancer is more sensitive to chemotherapy than other primary sites of HNC, antitumor activity was noteworthy. Furthermore, toxic effects during definitive therapy were relatively mild compared with those in previous studies of concurrent chemoradiotherapy for locally advanced SCCHN, suggesting that three cycles of TPS would not compromise the delivery of subsequent chemoradiotherapy.

During dose levels 1–4, this study included patients with recurrent/metastatic disease. If TPS had shown feasible and promising efficacy in these patients, this would have been encouraged further investigation to establish a new standard of care in the treatment of recurrent/metastatic SCCHN. Of 11 patients with recurrent/metastatic disease, however, 2 refused further treatment due to fatigue, even though they had achieved a clinical response and experienced no severe toxic effects, and almost all had limited treatment options if they had proved refractory to this combination. We therefore excluded patients with recurrent/metastatic disease from receiving dose levels 5

and 6. Recently, the addition of cetuximab to platinum-based chemotherapy was shown to significantly prolong OS without exacerbating chemotherapy-associated toxicity or quality of life in patients with recurrent/metastatic SCCHN [18]. The addition of molecular-targeted drugs such as cetuximab to platinum-based chemotherapy would therefore be more feasible and appropriate than that of docetaxel to platinum-based chemotherapy in the treatment of recurrent/metastatic SCCHN.

Concern has been expressed over the considerable ethnic differences in the tolerated doses of S-1. These relate to the varying efficiency rates of conversion of tegafur to 5-FU by CYP2A6 of the CYP450 enzyme system, now identified as the principal enzyme responsible for this conversion process [19–22]. A phase I study of S-1 plus cisplatin in Western patients with advanced gastric carcinoma showed that the S-1 dose tolerated by Western patients is lower than that by Japanese patients but that the area under the curve of 5-FU appears higher in white than Japanese patients in a comparable dose range of S-1 [23]. This is mostly attributed to different polymorphisms in the *CYP2A6* gene among Asians and whites. The RD of the present study is likely unsuitable for Western patients, and further study to determine the RD of TPS for these patients is required. Moreover, further study of the present TPS should be done in Asian patients to clarify whether TPS is superior to TPF.

In conclusion, we found that treatment with TPS was well tolerated and feasible in patients with locally advanced HNC. This regimen demonstrated sufficient activity to warrant phase II testing and may be an optimal substitute for TPF in the treatment of locally advanced SCCHN. A randomized trial comparing TPS with TPF in patients with locally advanced SCCHN is warranted.

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disclosure

None of the authors declare conflicts of interest.

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Phase I trial of chemoradiotherapy with the combination of S-1 plus cisplatin for patients with unresectable locally advanced squamous cell carcinoma of the head and neck

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The aim of the present study was to determine the maximum tolerated dose (MTD) of S-1 in combination with chemoradiotherapy (CRT) in patients with unresectable locally advanced squamous cell carcinoma of the head and neck, and evaluate the difference in pharmacokinetics of S-1 when administered as a suspension via a feeding tube or orally as a capsule. Chemotherapy consisted of administration of S-1 twice daily on days 1–14 at escalating doses of 40, 60 and 80 mg/m^2 per day, and cisplatin at 20 mg/m^2 per day on days 8–11, repeated twice at a 5-week interval. Single daily radiation of 70 Gy in 35 fractions was given concurrently starting on day 1. Two additional cycles of chemotherapy were planned after the completion of CRT. Before starting CRT, each patient received S-1 via two different administration methods. Twenty-two patients were enrolled. The MTD was reached with S-1 at 80 mg/m^2 per day, with two of six patients experiencing febrile neutropenia lasting more than 4 days. All four patients whose creatinine clearance was decreased to <60 mL/min after the first cycle of chemotherapy developed febrile neutropenia lasting more than 4 days. Pharmacokinetic analysis revealed that the 5-fluorouracil area under the curve did not significantly differ by the administration route. S-1 at 60 mg/m^2 per day for 14 days was well tolerated with concurrent CRT. Administration of S-1 as a suspension or by whole capsule can be considered therapeutically interchangeable. Although these data are preliminary, activity was highly promising, and this approach warrants further investigation. (*Cancer Sci*, doi: 10.1111/j.1349-7006.2010.01799.x, 2010)

Head and necks cancers are the sixth most common cancer in the world, and approximately 500 000 new cases are projected annually.(1) An estimated 60% of these patients will present with locally advanced disease (stage III/IV).

In the last 20 years, the integration of concurrent chemoradiotherapy (CRT) has advanced the treatment of locoregionally advanced squamous cell carcinoma of the head and neck (SCCHN), improving locoregional control and overall survival (OS) compared with radiotherapy (RT) alone while allowing organ preservation. However, half of these cases will recur, indicating a clear need for further therapeutic intervention. Moreover, although ample data provide a high level of evidence for the benefit of platinum-based CRT for unresectable locally advanced SCCHN,(2) an optimal CRT regimen is yet to be defined.

S-1 is a novel oral fluoropyrimidine derivative that consists of tegafur, 5-chloro-2, 4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) at a molar ratio of 1:0.4:1. Tegafur is a prodrug of 5-fluorouracil (5-FU).(3) CDHP augments the activity of 5-FU by inhibiting dihydropyrimidine dehydrogenase (DPD). Oxo reduces gastrointestinal (GI) toxicity by inhibiting orotate phosphoribosyl transferase and 5-FU phosphorylation in intestinal mucosa.

S-1 has been shown to be active against head and neck cancer, producing a response rate of 34%.(4) The combination of cisplatin (CDDP) and S-1 shows promising activity (response rate 67.6%) with acceptable toxicity for locally advanced head and neck cancer.(5) The combination of S-1 and fractionated radiotherapy is more effective against human oral cancer xenografts than either modality alone.(6)

A previous study demonstrated that the combination of S-1 and fractionated radiotherapy was more effective against human oral cancer xenografts than either treatment alone,(6) while another demonstrated that S-1 had a greater effect on radiosensitivity in human non-small-cell lung cancer xenografts in mice than uracil/tegafur (UFT), which also is an oral fluoropyrimidine derivative but does not contain CDHP.(7,8) CDHP enhanced radiosensitivity in human lung cancer cells in a dose escalation-dependent manner, suggesting that S-1 might be a more powerful enhancer of radiosensitivity in cancer than 5-FU or UFT.

Against this, however, no study has reported the feasibility and safety of S-1 in combination with CRT in patients with locally advanced SCCHN. We therefore conducted a single institutional, phase I, dose-escalation study of S-1 in combination with CRT in patients with unresectable locally advanced SCCHN.

Because CRT not only improves locoregional control but also exacerbates toxicities such as mucositis and dysphagia, patients may have difficulty in swallowing capsules. S-1 should therefore be administered as a suspension via a feeding tube. To date, however, no adequate bioavailability data for S-1 when administered as a suspension via a feeding tube has been available. For this reason, we also evaluated the difference in pharmacokinetics of S-1 when administered as a suspension via a feeding tube or orally by capsule.

Patients and Methods

Eligibility. Eligibility for the present study required a histologically or cytologically confirmed diagnosis of SCCHN with unresectable locally advanced disease, including postoperative local recurrence. Careful evaluation for unresectability was required from a multidisciplinary conference, which included head and neck surgeons, radiation oncologists and medical

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oncologists. Criteria for unresectability were carefully defined as follows: (i) technical unresectability, considered to mean tumors fixed to the carotid artery, mastoid, base of the skull or cervical spine; and (ii) physician determination of low surgical curability based on neck lymph node metastases such as N2c-3. Medical unsuitability for resection was not sufficient for patient eligibility; eligibility also required an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, age 20–75 years and adequate organ function. Written informed consent was required from all patients before the start of any therapy.

Patients were excluded if they had any of the following conditions: previous chemotherapy or radiotherapy; concurrent active malignancy except excised intramucosal gastric or esophageal cancer that could be removed by endoscopic mucosal resection; pharyngeal fistula; active bleeding from the GI tract; active infection; serious medical problem that might interfere with the achievement of study objectives; pregnancy or lactation; or expected survival <3 months.

Treatment. Baseline evaluation included patient history, physical examination, panendoscopy, dental evaluation, head and neck magnetic resonance imaging (MRI), computed tomography (CT) scan of the chest and abdomen, routine laboratory studies and electrocardiography (EKG). The treatment schedule is shown in Fig. 1.

Radiotherapy was done with 70 Gy/35 fractions over 7 weeks using six mega volt (MV) X-ray and 3-D radiotherapy techniques, and was started on day 1. Intensity-modulated radiotherapy was unavailable during this study. Gross tumor volume (GTV) was determined based on endoscopic or radiographic findings. Clinical target volume (CTV) was defined by adding 0.5 to 1 cm to the GTV. Planning target volume (PTV) was determined by adding appropriate margins to the CTV with consideration for physiological organ motion and daily set-up error. All patients underwent prophylactic nodal irradiations encompassing bilateral upper, middle and lower jugular, accessory and retropharyngeal lymph nodes up to 40–46 Gy. An additional 24–30 Gy was added to the PTV. Maximum dose to the spinal cord was restricted to 46 Gy, and posterior neck node was boosted using a 9–12 MeV electron beam as indicated. The radiotherapy dose was prescribed to the midplane along the beam axis, and dose deviation within the PTV was restricted to ±5% of the prescribed dose.

Chemotherapy consisted of administration of S-1 twice daily on days 1–14 at escalating doses of 40, 60 and 80 mg/m^2 per day, and 2-h infusion of CDDP at 20 mg/m^2 per day on days 8–11, repeated twice with a 5-week interval. Hydration consisted of 1 L of normal saline solution over 2 h prior to CDDP, as well as mannitol 12.5 gm by i.v. bolus infusion and 2 L of normal saline solution over 4 h following CDDP administration. Two additional cycles of S-1 and CDDP at the same dose level of CRT, repeated with a 4-week interval, were planned 4 weeks after the completion of CRT. Neutrocytes had to have recovered to at least 2000 cells/mm^3 and grade 1 creatinine or >50 mL/min of creatinine clearance was required by the time of the next cycle.

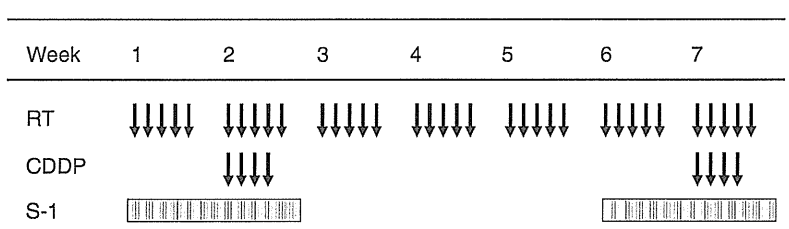
All patients underwent emplacement of a percutaneous endoscopic gastrostomy (PEG) feeding tube prior to the initiation of treatment. Prophylactic use of granulocyte-colony stimulating factor was not permitted. Additional treatment was not permitted unless persistent disease or disease progression was observed. When a patient had persistent or recurrent disease at the completion of CRT, surgical salvage was considered.

Toxicity. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 2.0. Any of the following adverse events observed within 30 days after the completion of CRT was deemed a dose-limiting toxicity (DLT): (i) febrile neutropenia lasting more than 4 days; (ii) grade 4 thrombocytopenia; (iii) grade 3 or 4 non-hematological toxicities except grade 3 anorexia, nausea, vomiting, stomatitis, esophagitis, infection due to stomatitis, dysphagia and skin toxicity; (iv) cessation of treatment due to an adverse event; or (v) treatment-related death. The maximum-tolerated dose (MTD) was defined as the dose at which more than two of six patients experienced a DLT. The recommended safe dose for further study was assessed at the dose level immediately below the MTD.

A minimum of three assessable patients was treated at each dose level. If one of the three patients at a given dose experienced a DLT, three more patients were accrued at the same dose level. If more than two of six patients at a given dose experienced a DLT, three more patients were treated at the next lower dose level. If less than one of six patients experienced a DLT, an additional six patients were accrued at the same dose level to determine the recommended dose.

Sample collection. Before the initiation of CRT, patients who gave consent underwent pharmacokinetic investigation. A single dose of S-1 as a capsule formulation was administrated orally 4 days before the start of CRT (day -4), while the same dose was given through a feeding tube as a suspension 2 days before the start of CRT (day -2). Suspensions were prepared by simple dissolution of a S-1 capsule in hot water. Peripheral blood samples were drawn before and at 0.5, 1, 2, 4, 6, 8, 10 and 24 h after each administration. Heparinized blood was centrifuged at 3000 rpm for 15 min at 4°C, and plasma was stored at −80°C.

Pharmacokinetic analysis. Tegafur, 5-FU, CDHP and Oxo were analyzed according to the method of Matsushima *et al.*[9] Pharmacokinetic parameters of Tegafur, 5-FU, CDHP and Oxo were estimated according to a standard noncompartmental method. Maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}) were taken from the observed data. The area under the plasma-concentration time curve (AUC) for time 0 to infinity was estimated by summing AUC from 0 to time t (AUC_{0-t}) and C_{tlast}/k, where C_{tlast} was the concentration at the last measured point. The apparent rate constant of elimination (k) was estimated by linear regression on the logarithm of the plasma



RT: 2 Gy/Fr x 33 or 35 Fr (total 70 Gy)
CDDP: 20 mg/m²/day, iv, days 8–11, days 43–46
S-1: 40, 60, 80 mg/m²/day, twice daily po, days 1–14, days 36–49

Fig. 1. Treatment schedule. Two additional cycles of S-1 and cisplatin (CDDP) at the same dose level of the chemoradiotherapy (CRT), repeated at a 4-week interval, were planned 4 weeks after the completion of the CRT. RT, radiotherapy.

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concentrations versus time, and AUC_{0-t} was estimated using the log trapezoidal method.

Criteria for response. Tumor responses were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) by panendoscopy, MRI of the head and neck and CT scan of the chest and abdomen.

End-points and statistical methods. The primary end-point in the present study was the MTD and DLT of S-1 in combination with a fixed dose of CDDP and RT. Safety and feasibility of this treatment were evaluated in patients with unresectable locally advanced SCCHN. Secondary end-points included complete response rate, progression-free survival (PFS), locoregional PFS, overall survival (OS) and pharmacokinetics of S-1 when administered as a suspension via the feeding tube.

The survival curve was estimated using the Kaplan–Meier method. Safety and efficacy analyses were both conducted on an intention-to-treat (ITT) population, defined as all patients enrolled in the study who received at least one dose of RT. A subject's PFS was defined as the time from the date of the first administration of CRT to the first documentation of disease progression, subsequent therapy or death. The OS was determined from the date of the first administration of CRT to the date of death or the last confirmed date of survival. Locoregional PFS was defined as the time from the date of the first administration of CRT to the first documentation of locoregional disease progression. Statistical data were obtained using the SPSS software package (SPSS 11.0 Inc., Chicago, IL, USA).

This study was conducted at the National Cancer Center Hospital East. The protocol was approved by the Institutional Review Board at the National Cancer Center.

Results

Patient and disease characteristics. Twenty-two patients were enrolled between February 2003 and January 2005. One patient did not receive CRT because it made the performance status worse due to disease progression, leaving 21 patients in the ITT population. Patient characteristics in the ITT population are listed in Table 1. The most common site of the primary lesion was the hypopharynx (59%). One patient had unresectable local recurrence after total larnyngectomy for hypopharyngeal cancer and the other 20 had never received any prior treatment for head and neck cancer.

Treatment administration. A total of 69 cycles of chemotherapy was administered. The number of cycles was two in seven patients, three in three patients, four in 10 patients and six in one patient. The reasons for the administration of less than four cycles were toxicities ($n = 2$), physician decision due to concern about tolerance ($n = 2$) and patient refusal due to achievement of complete remission ($n = 6$). One patient received six cycles due to persistent disease that could not be removed by salvage surgery.

Three patients were treated at the dose level of S-1 40 mg/m^2 without DLT. Of the first three patients who received S-1 at the 60 mg/m^2 dose level, one patient blacked out after straining at stool due to constipation on day 16 and developed grade 3 ischemic colitis, but reported recovery within 1 week under conservative treatment including hydration. Because he finished taking S-1 on day 14 and did not develop any GI toxicity including mucositis or diarrhea before suffering from this colitis, the safety committee decided that this colitis was not likely related to the study treatment. Two other patients had no DLT and dose escalation subsequently proceeded. Of the first three patients treated at a dose level of S-1 80 mg/m^2, one developed febrile neutropenia lasting more than 4 days, leading to the accrual of an additional three patients at this level. Thus, six patients were treated at the dose level of S-1 80 mg/m^2, of whom two developed febrile neutropenia lasting more than 4 days. The MTD was therefore set at 80 mg/m^2 per day of S-1.

Table 1. Patients' characteristics

Characteristic	No. patients ($n = 21$)
Age (years)	
Median	62
Range	45–73
Sex	
Male	19
Female	2
ECOG performance score	
0	15
1	6
Site of primary tumor	
Hypopharynx	13
Pharynx	1
Oropharynx	5
Nasopharynx	2
AJCC stage	
IV	20
Local relapse	1
T stage	
T1	4
T2	5
T3	3
T4	8
Local relapse	1
N stage	
N0	3
N2a	1
N2b	2
N2c	6
N3	8

AJCC, American Joint Committee on Cancer.

Three additional patients were treated at the dose level of S-1 60 mg/m^2, one of whom experienced grade 3 diarrhea with grade 3 infection. To determine the recommended dose of S-1, six additional patients (total of 12 patients) were treated at the dose level of S-1 60 mg/m^2, three of whom developed febrile neutropenia lasting for more than 4 days. One of them experienced febrile neutropenia lasting for 2 weeks despite using granulocyte colony-stimulating factor supports and the diagnosis of myelodysplastic syndrome was made by bone marrow study. One week after the completion of CRT, another of these three patients who experienced febrile neutropenia developed grade 3 diarrhea, which occurred 1 day after the development of febrile neutropenia. Because the administration of S-1 had finished 1 week previously, this diarrhea was not related to S-1 but to the neutropenia or antibiotic drugs, and was not regarded as a DLT.

During CRT, eight patients (38%) received administration of S-1 via a feeding tube, and a total of 14% of the planned doses of S-1 were administered via a feeding tube during CRT. The number of patients who received S-1 via a feeding tube at each dose level was one of three at 40 mg/m^2, four of 12 at 60 mg/m^2 and three of six at 80 mg/m^2.

All patients were treated with conventional 3-D RT and received planned doses of CDDP. One patient received a total of 68 Gy while the other 20 received 70 Gy. Four patients required the splitting of RT due to adverse events, including colitis in one patient, grade 3 dermatitis and infection in one patient and neutropenia in two patients. Of the two patients who developed neutropenia, one was treated at the dose level of S-1 80 mg/m^2, while the second was treated at 60 mg/m^2.

Toxicity. Overall toxicities during treatment are listed in Table 2. Grade 3 or 4 toxicities by the S-1 dose level are listed in Table 3. The incidence of grade 3 or 4 neutropenia and febrile neutropenia increased with increasing dose, with half of those

treated at 80 mg/m^2 experiencing febrile neutropenia. All four patients whose creatinine clearance was decreased to <60 mL/min after the first cycle of chemotherapy developed febrile neutropenia lasting more than 4 days. Of these, two each were treated at S-1 dose levels of 60 and 80 mg/m^2.

The incidence of grade 3 or 4 mucositis and dysphagia increased with increasing dose and occurred in all patients treated at 80 mg/m^2, indicating that S-1 at 80 mg/m^2 was intolerable in this treatment. One patient who achieved a complete response after completion of CRT experienced pharyngeal stricture as an adverse event, declined surgical treatment and is still alive without any evidence of recurrence. Fifteen patients (71%) received nutritional support via a feeding tube, with a median feeding tube duration of 199 days and 1-year feeding tube dependence of 14%.

Pharmacokinetic analysis of S-1. Pharmacokinetic data on administration of S-1 as oral capsules (day -4) and suspensions via a feeding tube (day -2) were available for 16 patients (Table 4). Tmax values for tegafur, 5-FU, CDHP and Oxo were significantly lower with the suspension than oral capsules, while Cmax values for tegafur, CDHP and Oxo were significantly higher. However, the Cmax for 5-FU and AUC of all parameters did not significantly differ by administration route. Moreover, although no clear relationship was seen between any parameter and adverse events, a weak correlation was seen between the AUC of tegafur and the rate of neutropenia ($P = 0.106$).

Treatment outcomes. Of the 21 patients treated with CRT, 18 experienced a complete response. Two additional patients who had been diagnosed with residual neck lymph node metastasis underwent salvage neck dissection, and pathology revealed no residual tumor. With a median follow up of 49 months (range,

Table 2. Overall toxicity (n = 21)

Toxicity	No. patients (Grade)				% of patients	
	1	2	3	4	Grade 1–2	Grade 3–4
Hematological toxicity						
Leucopenia	8	4	3	5	57	38
Neutropenia	5	2	3	5	33	38
Febrile neutropenia	–	–	6	0	–	29
Anemia	10	6	3	2	76	24
Thrombocytopenia	10	2	2	1	57	14
Non-hematological toxicity						
Nausea	4	4	5	0	38	24
Vomiting	8	2	0	0	48	0
Anorexia	4	3	1	0	33	5
Fatigue	5	6	1	0	52	5
Mucositis	4	1	14	1	24	71
Dysphagia	3	1	15	0	19	71
Dermatitis	3	12	3	0	71	14
Diarrhea	1	2	2	0	14	10
Elevated bilirubin	2	1	0	0	14	0
Elevated AST	2	4	0	0	29	0
Elevated ALT	3	4	0	0	33	0
Elevated creatinine	2	1	0	0	14	0
Xerostomia	7	12	0	0	90	0
Salivary change	3	9	0	0	57	0

ALT, alanine transaminase; AST, aspartate transaminase.

Table 3. Grade 3 or 4 toxicity by S-1 dose level

	Grade 3 or 4 toxicity					
	S-1 dose level: 40 mg/m^2 per day (n = 3)		S-1 dose level: 60 mg/m^2 per day (n = 12)		S-1 dose level: 80 mg/m^2 per day (n = 6)	
	No. patients	%	No. patients	%	No. patients	%
Hematological toxicity						
Leucopenia	1	33	5	42	2	33
Neutropenia	1	33	4	33	3	50
Febrile neutropenia	0	0	3	25	3	50
Anemia	0	0	4	33	1	17
Thrombocytopenia	0	0	2	17	1	17
Non-hematological toxicity						
Anorexia	0	0	3	25	2	33
Mucositis	1	33	7	58	6	100
Dysphagia	1	33	8	67	6	100
Dermatitis	0	17	2	17	1	17
Diarrhea	0	1	2	17	0	0

Table 4. Phamacokinetics of S-1 by the administration route (n = 15)

	Administration route			
	Oral (n = 15)	Feeding tube (n = 15)	Ratio	P-value
Tegafur				
T_{max} (min)				
Median	126.0	65.0	0.50	0.0012
Range	30–483	28–246	0.13–1.03	
C_{max} (ng/mL)				
Median	1571.0	1841.1	1.11	0.0009
Range	729–2373	804–2658	0.95–1.49	
AUC (μg × min/mL)				
Median	1416.6	1421.8	0.99	0.64
Range	573.2–3888.1	408.1–4306.5	0.71–1.16	
5-FU				
T_{max} (min)				
Median	239.0	121	0.78	0.013
Range	60–483	59–246	0.26–2.00	
C_{max} (ng/mL)				
Median	120.1	107.4	1.00	0.56
Range	26.5–188.6	29.4–176.5	0.73–1.47	
AUC (μg × min/mL)				
Median	33.6	29.4	0.94	0.63
Range	12.5–54.2	16.8–48.7	0.64–1.34	
CDHP				
T_{max} (min)				
Median	120.0	62	0.50	0.0009
Range	60–483	30–246	0.12–1.03	
C_{max} (ng/mL)				
Median	183.8	205.2	1.22	0.04
Range	72.0–358.8	101.5–584.6	0.71–1.78	
AUC (μg × min/mL)				
Median	66.0	65.7	1.03	0.15
Range	28.6–83.3	37.9–115.0	0.83–1.42	
Oxo				
T_{max} (min)				
Median	120.0	118.0	0.51	0.0005
Range	90–243	58–122	0.26–1.01	
C_{max} (ng/mL)				
Median	26.2	35.0	1.51	0.041
Range	3.8–60.1	11.5–212.4	0.48–3.58	
AUC (μg × min/mL)				
Median	7.5	9.2	1.39	0.21
Range	1.9–18.7	3.1–57.9	0.68–4.71	

5-FU, 5-fluorouracil; CDHP, 5-chloro-2,4-dihydroxypyridine; Oxo, potassium oxonate.

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44–62 months), local recurrence only, distant metastasis and both local recurrence and distant metastasis were observed in four, four and one patient, respectively. A total of nine patients died, five from local recurrence, three from disease progression of distant metastases and one from progression of residual neck lymph node. Estimated rates of 3-year locoregional PFS, PFS and OS were 75%, 48% and 62% respectively.

Discussion

In this phase I study of S-1 in combination with CRT in patients with unresectable locally advanced SCCHN, MTD of S-1 was 80 mg/m^2 per day. S-1 at 60 mg/m^2 per day for 14 days with concurrent CRT was well tolerated, and provided promising activity in these patients. Administration of S-1 as a suspension via a feeding tube or by oral capsule can be considered therapeutically interchangeable.

S-1 contains CDHP, which inhibits DPD. As 50% of CDHP is excreted in the urine, renal dysfunction might directly affect the inhibitory effect on DPD and lead to increased 5-FU concentrations.[10] Although the current standard dosing regimen for cisplatin is a single intravenous infusion of 100 mg/m^2, this regimen has a higher incidence of renal toxicities than lower doses. We therefore selected divided doses of the CDDP to reduce renal toxicity.

The incidence and severity of both hematological and non-hematological toxicities increased in accordance with the increasing dose. At a dose level of S-1 80 mg/m^2, half experienced febrile neutropenia lasting more than 4 days and all developed grade 3 or 4 mucositis, indicating that the dose of S-1 80 mg/m^2 was intolerable. The MTD was therefore set at 80 mg/m^2 per day of S-1. Two patients treated with S-1 at 60 mg/m^2 experienced grade 3 diarrhea. One of these patients did not receive anti-diarrhea drugs until the development of grade 3 diarrhea and infection, which was regarded as a DLT. The second experienced grade 3 diarrhea following grade 3 febrile neutropenia. Because the administration of S-1 had finished 1 week previously, this diarrhea was not related to S-1 but to the neutropenia or antibiotic drugs, and was not regarded as a DLT. However, this patient experienced grade 3 febrile neutropenia for more than 4 days, which was regarded as a DLT. Three patients experienced grade 3 febrile neutropenia for more than 4 days at S-1 60 mg/m^2. In other words, four of 12 patients receiving S-1 at 60 mg/m^2 experienced a DLT. Another experienced febrile neutropenia lasting 2 weeks despite the use of granulocyte colony-stimulating factor and was subsequently diagnosed with myelodysplastic syndrome on bone marrow study, indicating that this patient was inappropriate for evaluation of the recommended dose of S-1 in combination with CRT.

In the present study, all four patients whose creatinine clearance was decreased to <60 mL/min after the first cycle of chemotherapy developed febrile neutropenia lasting more than 4 days, and two of these were treated at a dose level of S-1 60 mg/m^2. The higher incidence of febrile neutropenia in the present study is therefore likely related to decreased creatinine clearance. Grade 1 creatinine or creatinine clearance of more than 50 mL/min had to have occurred by the time of the next cycle, while dose modification according to creatinine clearance was not performed. Dose modification according to creatinine clearance could have reduced or prevented these toxicities. Based on these results, we are convinced of the need for dose modification according to creatinine clearance in the treatment with S-1. In this regard, recent studies of S-1 have indeed used dose modification according to creatinine clearance.[11,12]

Although a slightly higher incidence of DLT was observed at this level, suggesting that it was not suitable for consideration as the recommended dose (RD), these toxicities might have been reduced by dose modification according to creatinine clearance and appropriate anti-diarrhea medication. Furthermore, this dose level was well tolerated in the other eight patients, with acceptable toxicity. We therefore established S-1 at 60 mg/m^2 per day as the RD. The clinically appropriate dose of S-1 in combination with CRT can only be determined in phase II trials.

Previous studies demonstrated a significant correlation between 5-FU plasma concentration, in particular 5-FU AUC, and therapeutic activity and toxicity.[13–17] Moreover, two phase I studies of S-1 showed a significant correlation between diarrhea grade and 5-FU AUC,[17,18] one of which additionally demonstrated a significant correlation between diarrhea grade and 5-FU Cmax.[18]

In the present study, pharmacokinetic analysis revealed that the Tmax of all parameters, including tegafur, 5-FU, CDHP and Oxo, were significantly lower on administration as a suspension, whereas the Cmax of tegafur, CDHP and Oxo were significantly higher than with oral capsules, indicating that the absorption of S-1 is higher in suspension. However, the Cmax for 5-FU and AUC of all parameters did not significantly differ by the administration route, indicating that the two routes can be considered therapeutically interchangeable.

In the present study, 18 of 21 patients achieved a complete response, while an additional two patients who had been pathologically diagnosed revealed no residual tumor on salvage neck dissection, with 3 years OS of 61.9%. Considering the small number of patients, these findings indicate that this regimen may provide promising activity in patients with unresectable locally advanced SCCHN.

Severe mucositis in locally advanced SCCHN patients receiving CRT frequently leads to dysphasia and weight loss. These patients may require adequate nutritional support to avoid treatment interruption, which can adversely impact the treatment outcome. However, although the relative benefits of prophylactic versus therapeutic PEG feeding tube placement are controversial, we are convinced that prophylactic PEG feeding tube replacement is indispensable to the completion of these high-intensity treatments. Although all PEG feeding tube replacements in this study were performed by pull techniques, few severe complications and no tumor seeding were observed. Furthermore, despite the high incidence of toxicities, all but one patient completed the CRT, indicating the likely usefulness of a prophylactic PEG feeding tube.

Feeding tube placement prior to CRT due to pre-existing dysphagia and advanced T stage are associated with prolonged feeding tube dependence.[19] In the present study, 71% of patients received nutritional support via a feeding tube, with a median feeding tube duration of 199 days and a 1-year feeding tube dependence of 14%. Additionally, one patient who achieved a complete remission subsequently experienced pharyngeal stricture after the completion of CRT, indicating that all patients should receive evaluation by a speech-language pathologist throughout the course of CRT, swallowing exercises, even though a feeding tube is in place, and rapid rehabilitation.

Concern has been expressed over the considerable ethnic differences in the tolerated doses of S-1. These relate to the varying efficiency rates of conversion of tegafur to 5-FU by CYP2A6 of the CYP450 enzyme system, now identified as the principal enzyme responsible for this conversion process.[20–23] A phase I study of S-1 plus CDDP in Western patients with advanced gastric carcinoma showed that the S-1 dose tolerated by Western patients is lower than that by Japanese patients, but that the AUC of FU appears higher in white rather than Japanese patients in a comparable dose range of S-1.[24] This is mostly attributed to different polymorphisms in the *CYP2A6* gene among Asians and whites. The RD of the present study is likely to be unsuitable for Western patients, and further study

to determine the RD of this combination for these patients is required.

In conclusion, S-1 at 60 mg/m^2 per day for 14 days was well tolerated with concurrent CRT with CDDP. Furthermore, no difference was seen in the pharmacokinetics of S-1 between administration as a suspension and orally as a whole capsule, indicating that these can be considered therapeutically interchangeable. Although these data are preliminary, activity was highly promising, and this approach warrants further investigation. A multicenter phase II study of this approach by the Japan Clinical Oncology Group (JCOG) is ongoing.[11]

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Disclosure Statement

The authors have no conflict of interest.

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