Table 1. Patient characteristics

	Phase I study		Phase II study
CDDP (mg/m^2)	60	70	70
No. of patients	4	6	28
Gender			
Male	3	4	25
Female	1	2	3
Age (years)			
Median	57.0	65.5	61.5
Range	49–68	49–73	33–73
Performance status			
0	4	5	20
1	0	1	8
Pathology type			
SCC	4	6	28
Primary disease site			
Oral cavity	1	1	9
Nasopharynx	1	1	3
Oropharynx	1	2	3
Hypopharynx	0	1	6
Larynx	0	0	4
Nasal cavity/paranasal sinus	1	1	2
External acoustic meatus	0	0	1
Classification			
Advance disease	0	3	15
Stage IIb	0	1	0
Stage III	0	1	5
Stage IV	0	1	10
TNM:M1 (lung + liver)	0	0	1
Recurrent disease	4	3	13
Locoregional	3	3	8
Regional lymph node	1	2	4
Distance metastasis (bone)	1	1 (1)	3
Prior treatment			
None	0	3	15
Surgery	1	2	10
Radiation (CCRT)	4 (4)	3 (0)	10 (6)
Chemotherapy (adjuvant)	4 (1)	3 (2)	6 (2)
Assessable (target) lesion			
Locoregional	3	6	22
Regional lymph node	1	4	12
Distance metastasis	1	0	4
Lung	1	0	3
Liver	0	0	1
Skin	0	0	1

CDDP, cisplatin; SCC, squamous cell carcinoma; CCRT, concurrent chemoradiotherapy.

and granulocyte colony-stimulating factor was administered to one patient. The number of confirmed treatment-related deaths in this study was one, a patient who died of pneumonia accompanied by sepsis for Grade 3 leukocytopenia.

Response and Survival

A total of 34 patients were evaluated to determine the response rate at the RD (Tables 3 and 4).

The confirmed response rate (C-RR) with >4-week duration was 44.1% (15/34, 95% CI: 27.4–60.8). There were 2 CRs (5.9%), 13 PRs included 3 distant metastasis which was 2 lungs and skin (PR: 38.2%), 15 cases of SD (44.1%) and 3 cases of PD (8.8%). In the subgroup analysis, the C-RRs per classification were advanced HNC 44.4% (8/18, 95% CI: 24.6–66.3) and recurrent HNC 43.8% (7/16, 95% CI: 19.4–68.1).

The median time to progression in the Phase II study (28 patients) was 100 days (range: 70–140). The median time to PR (50% tumor reduction) and the median overall duration of response in 11 responding patients were 25 days (range: 17–56) and 61 days (range: 38–116), respectively.

We additionally considered the best responses, including patients with a duration time of <4 weeks. The best overall response was 67.6% (95% CI: 51.9–83.4). Among the best responses, there were seven cases of CR (20.6%), 16 of PR (47.1%), seven of SD (20.6%) and three of PD (8.8%). In the subgroup analysis, the best overall responses per classification were advanced HNC 72.2% (13/18, 95% CI: 51.5–92.9) and recurrent HNC 62.5% (10/16, 95% CI: 38.8–86.2).

The median survival time (MST) of 34 patients was 16.7 months (95% CI: 11.4–no data), whereas the 1-year survival rates were 60.1% (Fig. 1). In the subgroup analysis, the 1-year survival rate for advanced HNC was 83.0%, and MST for recurrent HNC was 9.8 months (95% CI: 7.5–13.3) and the 1-year survival rate was 34.4% (Fig. 2). The median follow-up time for survival analysis was 13.1 months (range: 1.84–28.4). The detail of the treatment for 18 patients with advanced HNC after this regimen end was as follows: 8 patients received CCRT, 6 received radiotherapy, 2 received surgery and 2 were untreated. In addition, for 16 patients with recurrent cancer, 2 patients received CCRT, 2 received radiotherapy, 1 received surgery, 5 received adjuvant chemotherapy and 6 were untreated.

Discussion

S-1 is a novel oral anticancer agent consisting of FT, CDHP and Oxo at a molar ratio of 1:0.4:1. FT is a prodrug of 5-FU which is gradually converted to 5-FU and rapidly catabolized by dihydropyrimidine dehydrogenase (DPD) in the liver. CDHP inhibits the catabolism of 5-FU released from FT by DPD. CDHP helps maintain efficient blood and tumor concentrations of 5-FU at much the same levels as continuous infusion of 5-FU. Oxo was selected as a modulator that inhibits phosphorylation of 5-FU in the digestive mucosal cells

Table 2. Toxicity incidence

	Phase I study (first course)										Phase II study/Level 2 (all courses)				
Level	Level 1					Level 2									
CDDP (mg/m^2)	60					70					70				
No. of patients (*n*)	4					6					34				
Toxicities/grade	Grade				>Grade 3	Grade				>Grade 3	Grade				>Grade 3
	1	2	3	4		1	2	3	4		1	2	3	4	
Hematologic toxicity															
Anemia	2	1	1	0	25.0	4	0	1	0	16.7	15	9	2	1	8.8
Leukocytopenia	0	2	0	0	0.0	2	2	0	0	0.0	9	9	3	1	11.8
Neutropenia	0	1	1	0	25.0	2	2	0	0	0.0	8	14	2	2	11.8
Thrombocytopenia	2	0	0	0	0.0	6	0	0	0	0.0	27	1	3	1	11.8
Non-hematologic toxicity															
Anorexia	0	2	1	0	25.0	1	2	3	0	50.0	10	8	8	1	26.5
Nausea	0	1	0	0	0.0	3	1	1	0	16.7	14	9	5	0	14.7
Vomiting	0	0	0	0	0.0	2	1	0	0	0.0	8	3	0	0	0.0
Mucositis	0	0	0	0	0.0	1	2	0	0	0.0	7	5	0	0	0.0
Diarrhea	1	0	0	0	0.0	1	0	1	0	16.7	6	3	1	0	2.9
Fatigue	1	0	0	0	0.0	1	2	1	0	16.7	11	6	2	1	8.8
Alopecia	0	0	0	0	0.0	3	0	0	0	0.0	5	0	0	0	0.0
Rash	1	0	0	0	0.0	1	0	0	0	0.0	5	3	0	0	0.0
Hyperpigmentation	1	0	0	0	0.0	1	1	0	0	0.0	8	2	0	0	0.0

Table 3. Objective response rate at the RD

	No. of patients	CR	PR	SD	PD	NE	Response rate (%)	95% CI (%)
Phase I study								
Level 2	6	1	3	1	1	0	66.7	—
Phase II study								
RD	28	1	10	14	2	1	39.3	21.5–59.4
Total	34	2	13	15	3	1	44.1	27.4–60.8

RD, recommended dose; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; CI, confidence interval.

and that inhibits phosphoribosylaton of 5-FU in the GI mucosa. It achieved high efficacy without increasing GI toxicity, based on biochemical modulation of 5-FU (10). S-1 was consequently approved in Japan for gastric cancer under an accelerated approval regulation system in 1999 (13,14) and subsequently for HNC in 2001 (11,12), colorectal cancer in 2003 (15,16), non-small lung cancer (NSCLC) in 2004 (17,18), breast cancer in 2006 (19), and pancreatic cancer (20,21) and biliary tract cancer in 2007 (22), and clinical trials of its use for renal cell cancer, prostate cancer, liver cancer and cervical cancer are currently under way. In other carcinomas, S-1/CDDP was carried out for advanced gastric cancer (AGC) and NSCLC with response rates of 76% (23) and 47% (24), and acceptable toxicities. In addition, a randomized Phase III study for AGC patients as the first-line chemotherapy, the SPIRITS study, was reported and proved the superiority of S-1/CDDP to S-1 monotherapy (25). The response rate for combination therapy versus monotherapy was 54.0% versus 31% ($P = 0.0018$), and the MST was 13.0 versus 11.0 months (median follow-up time 34.6 months; hazard ratio 0.774; $P = 0.0366$).

This study and other studies on combination therapy for HNC with S-1 plus CDDP analogues, S-1 plus carboplatin combination therapy (S-1/carboplatin) (26) and S-1 plus nedaplatin combination therapy (S-1/nedaplatin) (27) have been conducted since 2002, and the results of these studies have been reported. S-1/CDDP (75 mg/m^2) was also performed in Korea as the first-line remission induction therapy for advanced clinical Stage III/ IV cancer, and a high response rate of 89.7% was reported (28).

In this study of S-1/CDDP administration for advanced/recurrent HNC performed this time, the toxicities observed were mild and acceptable in light of the safety of this combination therapy. As concerns efficacy in this study, the C-RR

Table 4. Objective response rate at the RD (subgroup analysis)

Classification	No. of patients	Response	CR	PR	SD	PD	NE	Response rate (%)	95% CI (%)
Advanced	18	Best over all response	5	8	3	1	1	72.2	51.5–92.9
		Confirmed response	1	7	8	1	1	44.4	24.6–66.3
Recurrent	16	Best over all response	2	8	4	2	0	62.5	38.8–86.2
		Confirmed response	1	6	7	2	0	43.8	19.4–68.1
Total	34	Best over all response	7	16	7	3	1	67.6	51.9–83.4
		Confirmed response	2	13	15	3	1	44.1	27.4–60.8

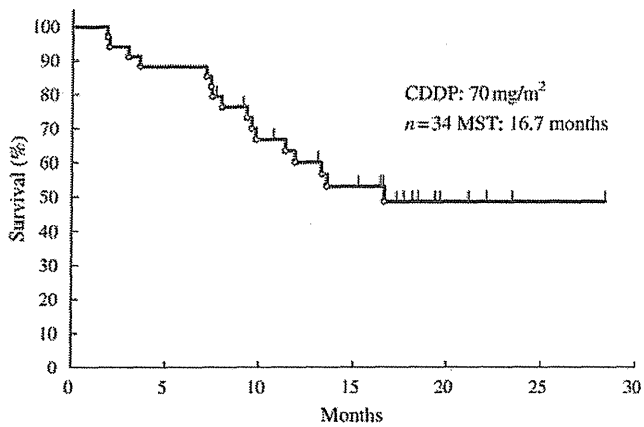

Figure 1. Overall survival.

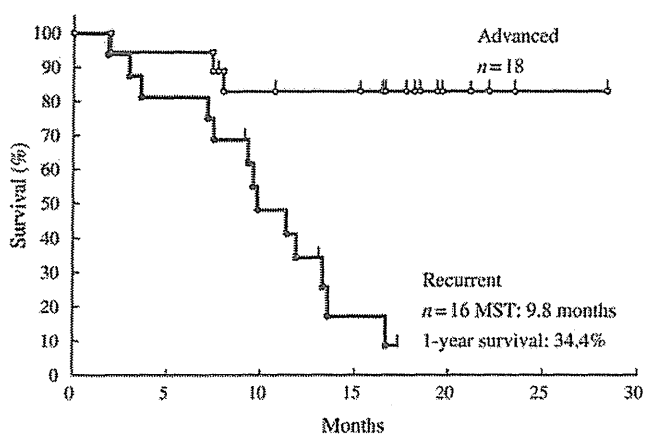

Figure 2. Overall survival of subgroups (advanced and recurrent).

was 44.1% (95% CI: 27.4–60.8), which was lower than the expected response rate of 65% to <35% under these conditions. Evaluation of the C-RR according to advanced HNC accounted for 44.4% and recurrent HNC accounted for 43.8%. The response rate after second-line therapy for recurrent cancer was comparable to the following reported results: 32–48% for 5-FU/CDDP (3,9), 40% for docetaxel/CDDP combination therapy (docetaxel/CDDP) (29) and 41.1% for paclitaxel/CDDP combination therapy (paclitaxel/CDDP) (30) for studies performed overseas, and 40.9% for S-1/carboplatin (26) and 33.3% for S-1/nedaplatin (27) for studies performed in Japan.

The response rate for S-1/CDDP for advanced cancer was lower than the response rates (50–90%) for 5-FU/CDDP (6–8). Suggested reasons for the lower response rate for advanced cancer included the short duration of the average of two administration courses (28) and the involvement of the treatment system for locoregional advanced cancer. The treatment system for locoregional advanced cancer was specified as follows. If chemotherapy is performed as prior treatment, perform two target courses of the therapy and make a decision on the form of treatment to follow according to the therapeutic efficacy at the end of the second course. If the effectiveness evaluation is SD at the end of one course of the preceding chemotherapy, perform radiotherapy or surgery with the addition of postoperative radiotherapy. If PR (50% tumor reduction) is achieved at the end of one course of the preceding chemotherapy, add a second course. If PR continues at the end of second course, perform radiotherapy or surgery with the addition of post-operative radiotherapy; and if CR is achieved, add another course of chemotherapy with radiation irradiation to complete the treatment. As an exception in this study, when a tumor achieved reduction of >50%, we considered the benefit to the patient and allowed the next treatment to be conducted based on the judgment of the doctor. In this study, three of the eight patients with advanced HNC who were evaluated as SD in C-RR showed tumor reduction of >50%, as in the case of five patients administered a second therapy (radiotherapy, chemoradiotherapy) without waiting for the 28-day duration of effect with patient benefit taken into consideration. Considering the action of these results, the best response rate for advanced cancer was 77.2% (95% CI: 51.5–92.9) in this study.

The MST in this study was 16.7 months, and the 1-year survival rate was 60.1%. MST in recurrent cancer was 9.8 months with a 1-year survival rate of 34.4%. These results were comparable to those for cetuximab/CDDP (33), gefitinib/methotrexate (34), docetaxel/CDDP (29), paclitaxel/CDDP (30) and S-1/carboplatin (26). In advanced cancer, the 1-year survival rate was 83.0%, although the observation period was short, and this result was closely similar to that for 5-FU/CDDP (6–8).

As concerns safety, the most common toxicities in this study were hematologic toxicity and GI dysfunction and fatigue, and the hematologic toxicity was mild when compared with the results for conventional 5-FU/CDDP (3,6–9), with an incidence of 11.8%.

The results of this study indicated that S-1/CDDP can be considered to be effective with acceptable toxicities for advanced/recurrent HNC. With respect to recurrent HNC, it was determined that a Phase III comparative study with a CDDP base was necessary, among other things. As concerns locoregional advanced HNC, it is desirable to carry out CCRT. S-1 exhibits radiosensitization action and it is often used in combination with radiation therapy. Tahara et al. (31,32) conducted a Phase I study of CCRT with S-1/CDDP for unresectable advanced HNC and suggested its utility. We plan to conduct a Phase II multicentred trial as a JCOG study.

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Conflict of interest statement

None declared.

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original article

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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

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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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A Pilot Study of Post-operative Radiotherapy with Concurrent Chemotherapy for High-risk Squamous Cell Carcinoma of the Cervical Esophagus

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Objective: After complete resection of carcinomas of the head and neck, including carcinoma of the cervical esophagus, the pattern of first failure is more often locoregional than distant metastasis. We retrospectively evaluated the safety and efficacy of the combination of post-operative radiation and concurrent chemotherapy with low-dose cisplatin for high-risk squamous cell carcinoma of the cervical esophagus.
Methods: From 2005 through 2008, 34 patients with previously untreated squamous cell carcinoma of the cervical esophagus underwent cervical esophagectomy with or without laryngectomy. Of these 34 patients, 11 with disease-positive lymph nodes in the upper mediastinum (M1 lymph/Stage IV) confirmed by pathologic examination were enrolled. Patients received radiotherapy (66 Gy in 33 fractions) and concurrent low-dose cisplatin.
Results: Nine patients completed the planned radiotherapy and two or more courses of chemotherapy. Grade 3 toxicities during chemoradiotherapy were leukopenia (36% of patients), neutropenia (18%) and mucositis (9%). At a median follow-up time of 39.5 months, the overall 1- and 3-year survival rates were 91 and 71%, respectively.
Conclusions: The combination of post-operative radiation and concurrent chemotherapy with low-dose cisplatin is well tolerated and has the potential to improve the rates of locoregional control and overall survival in patients with high-risk advanced squamous cell carcinoma of the esophagus.

Key words: cervical esophageal squamous cell carcinoma – post-operative radiotherapy with concurrent chemotherapy – nodal M1 disease

INTRODUCTION

Locally advanced head and neck cancer is optimally treated with multimodal approach, involving resection followed by radiotherapy and concurrent chemotherapy (1). Carcinoma of the cervical esophagus has a poor prognosis, with reported 3- and 5-year survival rates ranging from 18 to 35.4% and from 12 to 33%, respectively (2). We have previously reported on the prognosis, patterns of first failure and significant clinicopathologic factors affecting survival in cases of squamous cell carcinoma of the cervical esophagus (2). In particular, the 3-year survival rate was 0% in patients with metastasis to mediastinal lymph nodes (M1 lymph/Stage IV). We have maintained that multimodal treatment, such as post-operative radiotherapy with concurrent chemotherapy, is essential for the treatment of cervical esophageal carcinoma (2). On the basis of the results of our previous study, we performed a pilot study and retrospectively assessed the toxic

effects and efficacy of the combination of post-operative radiotherapy and concurrent chemotherapy with low-dose cisplatin in selected patients who had squamous cell carcinoma of the cervical esophagus with metastasis to the upper mediastinal lymph nodes (M1 lymph/Stage IV), a factor indicating an extremely poor prognosis.

PATIENTS AND METHODS

Patients Population and Eligibility

From January 2005 through December 2008, 34 patients with previously untreated carcinoma of the cervical esophagus underwent surgical resection at the National Cancer Center Hospital East. The clinical and pathologic characteristics of the 34 patients are shown in Table 1. Pre-operative and post-operative staging was based on the 1997 International Union Against Cancer TNM classification. Cases with metastasis to the mediastinal lymph nodes were classified as M1-lymph disease.

All patients with metastasis to the upper mediastinal lymph nodes (M1 lymph/Stage IV) defined as complete removal of all macroscopic tumor masses were eligible for the study if they met all of the following criteria: histologically confirmed diagnosis of squamous cell carcinoma; age of 18 years or older and 75 years or younger; performance status of 0 or 1 according to the Eastern Cooperative Oncology Group scale; adequate bone marrow, hepatic and renal function; no previous chemotherapy or radiotherapy; and written informed consent provided before recruitment.

Pre-treatment Evaluation

Pre-treatment evaluations in all patients included physical examination, barium-swallow examination, endoscopy with biopsy, ultrasonography of the neck and computed tomography of the neck and chest.

Study Treatment

The protocol required that radiotherapy be performed as soon as satisfactory healing had occurred after surgery. The protocol also called for radiotherapy to start within 8 weeks after surgery.

The treatment consisted of two or three cycles of cisplatin at a dose of 20 mg/m^2 of body surface area on days 1–4, 22–25 and 43–46, repeated every 3 weeks, with concurrent radiotherapy to a total dose of 66 Gy in 33 fractions over 6 weeks.

Because gross tumors were already resected, gross tumor volume was not defined in the case of adjuvant radiotherapy. Clinical target volume (CTV) was defined as the total volume of the surgical bed of the primary tumor plus volumes and metastatic lymph nodes considered at risk of containing microscopic disease. The CTV was further categorized into two volumes: the CTV boost (CTVb), which included the surgical bed of the primary tumor and metastatic lymph nodes, and the CTV subclinical (CTVs), which included the CTVb plus regional lymph nodes (cervical, supraclavicular and superior mediastinum lymph node areas) (Fig. 1). The upper cervical lymph node area (level II) was excluded from the irradiation field if no lymph node metastasis was found in this area. From four to eight beams were applied from various angles to the CTVs to a total dose of up to 46 Gy. A booster dose of 20 Gy was given to the CTVb using multiple fields to shield the spinal cord for a total dose of 66 Gy.

Table 1. Clinical and pathologic characteristics of 34 patients undergoing surgery for squamous cell carcinoma of the cervical esophagus

Variable	No. of patients
Sex	
Female/male	8/26
Tumor location	
Ce/-Ph/-Ut	18/5/10
Ce-Ph-Ut	1
Clinical T status	
T1/2	5/2
T3/4	15/12
Clinical N status	
N0/1	16/18
Clinical M stage	
M0	25
M1 lymph	9
Clinical stage	
I/II/III/IV	4/8/12/10
Larynx	
Preserved	10
Laryngectomy	24
Pathologic T status	
T1/2	6/2
T3/4	17/9
Pathologic N status	
N0	13
N1	21
Pathologic M status	
M0	20
M1lymph/1 organ	13/1
Pathologic stage	
I/II/III/IV	2/10/8/14
Completeness of resection	
R0/1	30/3
R2	1

Ce, cervical esophagus; Ph, hypopharynx; Ut, upper third of thoracic esophagus.

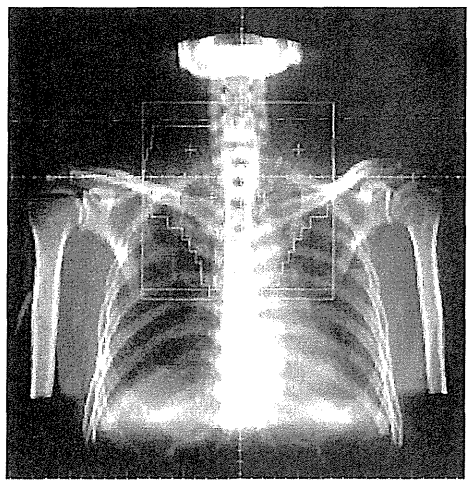

Figure 1. Planning film demonstrating a representative treatment field for post-operative radiation in a patient with metastases to the upper mediastinal lymph nodes.

Toxicity Assessment and Dose Modification

Toxicity assessments, including complete blood cell counts and serum chemistry profiles, were performed weekly during chemoradiotherapy and every 3 weeks during the protocol study. Toxicity assessments for all patients were performed with the National Cancer Institute Common Toxicity Criteria (version 3.0). The dose was reduced by 20% if any toxicity reached Grade 3.

Follow-up

All patients were regularly followed up with routine physical and laboratory examinations at our hospital. Computed tomography of the neck and chest was performed annually to detect possible recurrent disease. The median follow-up period for all patients was 39.5 months (range, 12–64 months).

Statistical Analysis

Survival time was measured from the date of surgery until death or the most recent follow-up examination. Length of survival was determined with the Kaplan–Meier method, and the log-rank test was used for comparisons. All analyses were performed with the SPSS statistical software package (version 17.0.2; SPSS, Inc., Chicago, IL, USA).

RESULTS

Patient Characteristics

Pathologic examination showed lymph node involvement in the upper mediastinum in 13 patients (Table 1). Eleven of 13 patients were enrolled to receive post-operative radiotherapy with concurrent chemotherapy, but 2 of the 13 patients refused post-operative adjuvant treatment. The baseline characteristics of patients enrolled in this protocol are shown in Table 2. The median age was 58 years (age range, 40–70 years), and eight patients were men and three were women. More than 70% of tumors were clinically T3 or T4. Seventy-three percent of tumors had metastasized to lymph nodes before operation. Pathologic characteristics of selected patients with metastases to the upper mediastinal lymph node are listed in Table 3. Seventy-two percent of tumors were T3 or T4, and all patients had regional lymph node involvement. Complete resection (R0) was achieved in 82% of the patients.

Compliance with Treatment

Nine patients (82%) completed post-operative radiotherapy with two or more of concurrent chemotherapy with cisplatin. One patient who had received 66 Gy of radiotherapy stopped chemotherapy after receiving one cycle. Another patient stopped radiotherapy after receiving a radiation dose of 54 Gy. Toxicity was assessed in all 11 patients.

Table 2. Clinical characteristics of selected patients with metastasis to the upper mediastinal lymph nodes

Characteristic	No. of patients (%)
Sex	
Female	3 (27)
Male	8 (73)
Age in years	
Median (range)	58 (40–70)
Tumor location	
Ce	7 (64)
Ce-Ut	3 (27)
Ce-Ph-Ut	1 (9)
Tumor status	
T1	1 (9)
T2	2 (18)
T3	2 (18)
T4	6 (55)
Node status	
N0	3 (27)
N1	8 (73)
Metastatic status	
M0	5 (45)
M1 lymph	6 (55)
Stage	
I	1 (9)
II	0
III	4 (36)
IV	6 (55)

Table 3. Pathologic characteristics and overall survival of selected patients with metastasis to the upper mediastinal lymph nodes

Characteristic	No. of patients (%)	1-year survival (%)	3-year survival (%)	*P* value
Tumor status				
T1/2	3 (27)	100	100	0.517
T3	4 (36)	75	75	
T4	4 (36)	75	50	
Node status				
N0	0			
N1	11 (100)	91	71	
Metastatic status				
M0	0			
M1 lymph	11 (100)	91	71	
Differentiation				
Well	5 (45)	80	60	0.486
Moderate	6 (55)	80	80	
Lymphatic invasion				
Negative	7 (64)	86	69	0.828
Positive	4 (36)	75	75	
Vascular invasion				
Negative	1 (9)	100	100	0.544
Positive	10 (91)	90	68	
Larynx				
Preserved	4 (36)	100	100	0.196
Laryngectomy	7 (64)	86	57	
Residual tumor				
R0	9 (82)	89	64	0.359
R1	2 (18)	100	100	

Survival and Pattern of First Failure

With a median follow-up period of 39.5 months (range, 16–64 months), the median survival time was 33 months. The 1- and 3-year overall survival rates were 90 and 67%, respectively (Fig. 2). Tumors recurred in four patients (36%). The pattern of recurrence was more often distant metastasis (75%) than locoregional spread (0%).

Toxicity

All toxicities are listed in Table 4. The majority of treatment-related toxicities included myelosuppression. Leukopenia, neutropenia and mucositis of Grade 3 or greater occurred in 36, 18 and 9% of the patients, respectively. No patients died during treatment. During and after treatment, no ischemic change or necrosis due to the effects of radiation and concurrent chemotherapy was found in the reconstructed organs.

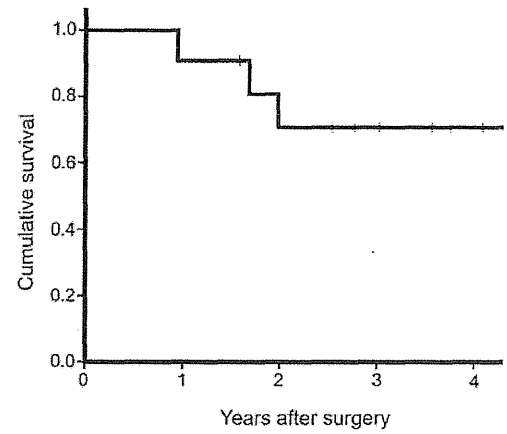

Figure 2. Overall survival curve.

Table 4. Hematologic and non-hematologic adverse events during post-operative radiation and concurrent chemotherapy

Events	G1, no. (%)	G2, no. (%)	G3, no. (%)	G4, no. (%)
Hematologic				
Leukopenia	0	6 (55)	4 (36)	0
Neutropenia	0	5 (45)	2 (18)	0
Anemia	0	2 (18)	0	0
Non-hematologic				
Nausea	7 (64)	0	0	0
Anorexia	7 (64)	1 (9)	0	0
Fatigue	6 (55)	0	0	0
Diarrhea	0	1 (9)	0	0
Esophagitis	1 (9)	0	0	0
Mucositis	2 (18)	0	1 (9)	0
Dysphagia	4 (36)	1 (9)	0	0
Radiation dermatitis	2 (18)	3 (27)	0	0
Renal (creatinine)	3 (27)	7 (64)	0	0

DISCUSSION

Carcinoma of the cervical esophagus extends easily and frequently upward to the hypopharynx or downward to the thoracic esophagus, and most tumors are located at the border of the hypopharynx or the thoracic esophagus. However, carcinoma of the cervical esophagus is a disease distinct from carcinoma of the hypopharynx or thoracic esophagus. Larynx-preserving esophagectomy for carcinoma of the cervical esophagus can be performed safely and can lead to the long-term survival of selected patients (2,3). In the present study, even if patients had metastasis to the upper mediastinal lymph nodes, larynx-preserving cervical esophagectomy could be performed (Table 3). The selection of reconstructive procedure depends on the resected length of the esophagus necessary to ensure adequate distal esophageal margins,

whether gastric pull-up adapts to total esophagectomy and whether free jejunal transfer accommodates the cervical esophagectomy with or without pharyngolaryngectomy.

Kakegawa et al. (4) have reported that the incidence of metastasis to the upper mediastinal lymph nodes (11.4%) is similar to that to the cervical paratracheal lymph nodes (14.3%) and deep cervical lymph nodes (14.3%). In the present study, the incidence of metastasis to the upper mediastinal lymph nodes was 38% (Table 1). The lymphatic drainage of the cervical esophagus is primarily to the paratracheal lymph nodes; therefore, carcinoma of the cervical esophagus spreads easily and frequently upward to the cervical lymph nodes or downward to the upper mediastinal lymph nodes or both. For this reason, we routinely perform dissection of the upper mediastinal lymph nodes as well as that of the bilateral cervical paratracheal and the deep cervical lymph nodes.

The reported 3- and 5-year survival rates for cervical esophageal carcinoma treated with surgical resection range from 18 to 35.4% and from 12 to 42%, respectively (2,5–8). The prognosis of patients with cervical esophageal cancer is worse than that of patients with hypopharyngeal cancer (7,8). Factors previously reported to influence the long-term survival of patients include both carcinoma of the cervical esophagus and carcinoma of the hypopharynx. Therefore, we reported prognostic factors affecting survival in our previous study, including carcinoma of the cervical esophagus (excluding hypopharyngeal cancer). In our previous study, prognostic factors affecting survival after surgical resection were sex, high T factor, lymph node involvement, palpable cervical lymph nodes, vocal cord paralysis, lymphatic invasion and extracapsular invasion (2). In particular, the 3-year survival rate in patients with metastasis to mediastinal lymph nodes (M1 lymph/Stage IV) was 0% (2). Therefore, we believe that carcinoma of the cervical esophagus requires multimodal treatment, such as post-operative radiotherapy with concurrent chemotherapy.

Cooper et al. (9) (Radiation Therapy Oncology Group 9501) and Bernier et al. (1) (European Organization for Research and Treatment of Cancer Trial 22931) have both reported that concurrent post-operative radiotherapy and chemotherapy with cisplatin for locally advanced cancers of the head and neck significantly improves the rates of local and regional control and of disease-free survival compared with post-operative radiotherapy alone. Bernier et al. have also demonstrated an improvement in the overall survival rate. Single-modality treatment after surgical resection cannot guarantee long-term survival; therefore, multimodal therapy, such as post-operative chemotherapy and radiotherapy, is essential for the treatment of cervical esophageal carcinoma. However, we are concerned about the adverse effects of post-operative chemoradiotherapy upon the reconstructed organs, especially free jejunal grafts, and the patient's general condition after the operation. Single- and multi-institutional randomized studies and retrospective studies have shown that the concurrent chemotherapy regimen modified by reducing the platinum dose, increasing its frequency and adding a complementary chemotherapeutic agent remains well tolerated and is more effective than radiotherapy alone (10–12).

On the basis of the results of our previous study and these studies of post-operative adjuvant or definitive radiotherapy with concurrent chemotherapy for locally advanced carcinoma of the head and neck, we performed a pilot study and retrospectively assessed the toxic effects and efficacy of post-operative radiotherapy with concurrent low-dose cisplatin chemotherapy in selected patients with metastasis to the upper mediastinal lymph nodes (M1 lymph/Stage IV), a factor indicating an extremely poor prognosis. Nine patients (82%) completed post-operative radiotherapy and two or more cycles of concurrent chemotherapy with cisplatin. The majority of treatment toxicities included myelosuppression. Leukopenia, neutropenia and mucositis of Grade 3 or greater occurred in 36, 18 and 9% of the patients, respectively. However, during the protocol treatment, no Grade 4 treatment-related toxicity occurred and no patients died. A low dose of cisplatin decreases the likelihood of adverse effects and death related to post-operative treatment with the combination of radiotherapy and concurrent chemotherapy with cisplatin (1). During and after treatment, no reconstructed organs underwent ischemic change or necrosis due to the effects of radiation and concurrent chemotherapy. The combination of post-operative radiation and concurrent chemotherapy with low-dose cisplatin is a well-tolerated treatment with mild-to-moderate adverse effects which causes no damage to reconstructed organs.

With a median follow-up period of 39.5 months (range, 16–64 months), the median survival time was 33 months. The 1- and 3-year overall survival rates were 90 and 67%, respectively (Fig. 2). Tumors recurred in four patients (36%). The pattern of recurrence was more often distant metastasis (75%) than locoregional spread (0%). In our previous study, the 3-year survival rate was 0% in patients with metastasis to mediastinal lymph nodes (M1 lymph/Stage IV), and the pattern of recurrence after operation was more often locoregional spread (82%) than distant metastasis. Triboulet et al. (7) have reported that post-operative radiotherapy for carcinoma of the hypopharynx and cervical esophagus improves survival and achieves a 3-year survival rate of 35%. However, large randomized, controlled studies have demonstrated that the combination of post-operative radiotherapy with concurrent chemotherapy is superior to post-operative radiation alone (1). The combination of post-operative radiation and concurrent chemotherapy with low-dose cisplatin improves the rates of locoregional control and overall survival in patients with locally advanced squamous cell carcinoma of the cervical esophagus. We advocate that the indications for the combination of post-operative radiation with concurrent chemotherapy be expanded to include patients with a high T factor and lymphatic invasion, as this treatment is well tolerated, is associated with mild-to-moderate adverse effects and improves survival rates.

CONCLUSION

The combination of post-operative radiation and concurrent chemotherapy with low-dose cisplatin is well tolerated, is associated with mild-to-moderate adverse effects and has the potential to improve the rates of locoregional control and overall survival in patients with locally advanced squamous cell carcinoma of the esophagus. Therefore, we advocate that the indications for this treatment be expanded to include patients with a high T factor and lymphatic invasion.

Conflict of interest statement

None declared.

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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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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.