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Phase II trial of chemoradiotherapy with S-1 plus cisplatin for unresectable locally advanced head and neck cancer (JCOG0706)

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Key words

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We conducted a phase II study to evaluate the efficacy and safety of chemoradiotherapy concurrent with S-1 plus cisplatin in patients with unresectable locally advanced squamous cell carcinoma of the head and neck. Chemotherapy consisted of S-1 twice daily on days 1–14 at 60 mg/m^2/day and cisplatin at 20 mg/m^2/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. For patients achieving an objective response after chemoradiotherapy, two additional cycles of chemotherapy were administered. Of the 45 enrolled patients, the percentage of clinical complete remission, the primary endpoint, was 64.4% (8 complete response, 21 good partial response) on central review. After a median follow-up of 3.52 years, 3-year local progression-free survival was 62.2%, with 3-year progression-free survival of 60.0%, 3-year overall survival of 64.4%, and 3-year time to treatment failure of 48.9%. Grade 3 or 4 toxicity included pharyngeal mucositis (46.7%), oral mucositis (44.4%), dysphagia (46.7%), anorexia (42.2%), radiation dermatitis (26.7%), neutropenia (26.7%), and febrile neutropenia (4.4%). No treatment-related deaths were observed. This combination showed promising efficacy with acceptable toxicities.

Head and neck cancers (HNC) 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 present with locally advanced disease (stage III/IV).

Concurrent chemoradiotherapy is standard of care for unresectable locally advanced SCCHN.[2] However, half of these cases will recur, indicating a clear need for further therapeutic intervention. Although multiple clinical trials and the MACH-NC meta-analysis indicated a survival benefit from platinum-based CRT,[3] an optimal CRT regimen has yet to be established.

The oral fluoropyrimidine S-1 consists of tegafur, gimeracil (CDHP), and potassium oxonate.[4] As monotherapy, S-1 led to a response rate of 34.1% in patients with progressive or recurrent SCCHN.[5] A previous study showed that S-1 had a greater effect on radiosensitivity in human non-small-cell lung cancer xenografts in mice than UFT, which is also an oral fluoropyrimidine derivative but does not contain CDHP.[6,7] Radiosensitivity was enhanced by CDHP 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.

Our previous phase I study of concurrent CRT with S-1 plus CDDP in patients with unresectable locally advanced SCCHN showed that S-1 at 60 mg/m^2/day for 14 days was well tolerated with concurrent CRT with CDDP and activity was also highly promising.[8]

Here, we conducted a phase II study to evaluate the efficacy and safety of concurrent CRT with S-1 plus CDDP for patients with unresectable locally advanced SCCHN.

Patients and Methods

Patients. For inclusion in the study, patients had to fulfill all of the following criteria: histologically proven squamous cell carcinoma; primary lesion located at oropharynx, hypopharynx or larynx; unresectable locally advanced HNC that fulfills at least one of the following conditions: (i) primary lesion or cervical lymph node metastasis invasion to carotid artery, cranial base, or cervical vertebrae; (ii) cervical lymph node metastasis of N2c or N3 (UICC/TNM, 6th edition); or (iii) T4 primary lesion located at oropharynx; no fistula due to primary lesion or cervical lymph node metastasis; no distant metastasis; age between 20 and 75 years; ECOG PS of 0 or 1; no prior radical surgery for HNC; no prior treatment for any other malignancies with chemotherapy, radiation therapy, or endocrine therapy; sufficient organ function; normal electrocardiogram; and written informed consent.

Patients were excluded for any of the following conditions: active bacterial or fungal infection; simultaneous or metachronous (within 5 years) double cancers except carcinoma *in situ* or intramucosal tumor; women during pregnancy or breastfeeding; active gastrointestinal bleeding; pleural effusion, pericardial effusion or massive ascites; history of severe heart disease, heart failure, myocardial infarction within 6 months or angina pectoris attack within 6 months; cerebrovascular disease within 6 months; serious medical problem including poorly controlled diabetes mellitus, chronic pancreatitis, and poorly controlled hypertension; hepatitis B surface antigen positive; impossibility of refraining from smoking and drinking during treatment; administration of continuous systemic steroids; and requiring anticoagulant agent.

Treatment. The protocol treatment consisted of concurrent CRT, adjuvant chemotherapy, and salvage surgery if applicable (Fig. 1). First, patients received concurrent CRT with S-1 plus CDDP. Chemotherapy consisted of S-1 twice daily at a dose of 60 mg/m^2/day on days 1–14, and a 2-h infusion of CDDP at 20 mg/m^2/day on days 8–11, repeated twice with a 5-week interval. The rationale for the divided doses of CDDP is described in our previous phase I study.[8] Prophylactic use of granulocyte-colony stimulating factor was not permitted. Radiation therapy was carried out once daily with 70 Gy/35 fractions over 7 weeks using high-energy photons of 4–10 MV X-rays and 3-D radiotherapy planning, starting on day 1. Intensity-modulated radiotherapy was unavailable during this study. The GTV included the volumes of both the primary tumor and metastatic cervical lymph nodes with a short axis of 1 cm or larger. The CTV1 included GTV and bilateral regional cervical lymph node area with a 1–2 cm margin, and CTV2 included GTV with a 0.5–2 cm margin. The PTVs for CTV1 and CTV2 (PTV1 and PTV2) were defined as CTV plus 0.5–1-cm margins around CTV to compensate for set-up variations and internal organ motion. A total of 40 Gy was delivered toward PTV1, and then an additional 30 Gy was boosted to PTV2.

For patients with an objective response including CR, good PR, and PR at the first evaluation after completion of CRT, two additional cycles of adjuvant chemotherapy with S-1 plus CDDP at the same dose level during CRT were repeated with a 4-week interval starting 4 weeks after the completion of CRT. When a patient achieved CR or good PR after completion of adjuvant chemotherapy, additional treatment was not permitted unless recurrence was observed. When a patient had persistent disease or recurrence after completion of adjuvant chemotherapy, salvage surgery was considered.

Treatment evaluation and dose modification. Baseline evaluation consisted of history, physical examination, upper gastrointestinal endoscopy, radiographic imaging, routine laboratory studies, and electrocardiogram. Safety assessments were repeated weekly during the protocol treatment. Toxicities were evaluated according to the Common Toxicity Criteria for Adverse Events version 3.0.

Doses of chemotherapy were modified in cases of severe hematological or non-hematological toxicities. As patients received two chemotherapeutic agents, dose adjustment was

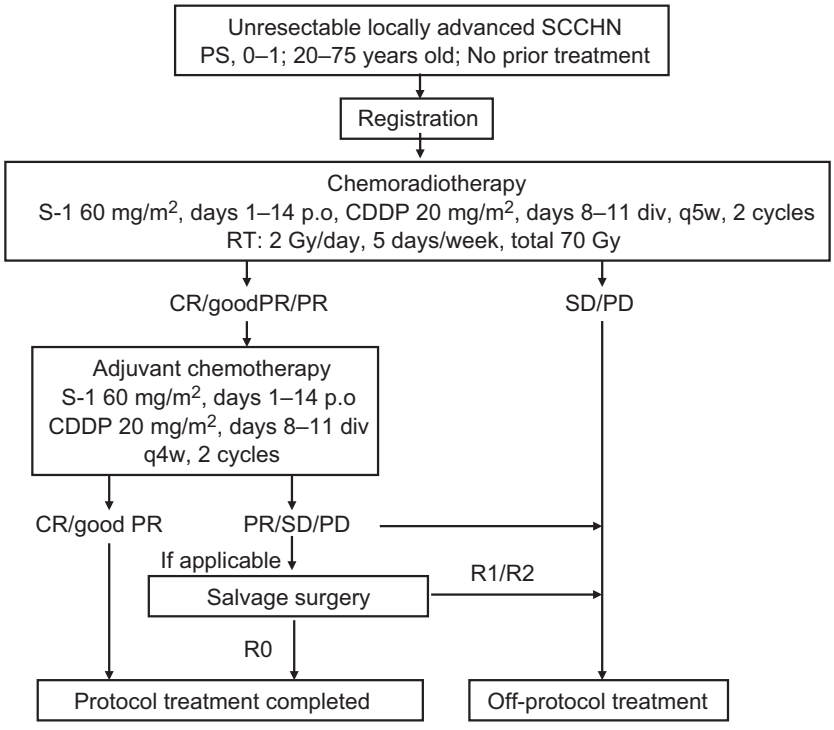

Fig. 1. Schema of a phase II study to evaluate the efficacy and safety of chemoradiotherapy concurrent with S-1 plus cisplatin (CDDP) in patients with unresectable locally advanced squamous cell carcinoma of the head and neck (SCCHN). CR, complete response; PD, progressive disease; PR, partial response; PS, performance status; RT, radiotherapy; SD stable disease, stable disease.

carried out for each individual agent according to the type of observed toxicities. If an observed toxicity was assumed to be related with both agents, the doses of both agents were reduced. If multiple toxicities occurred during a treatment cycle, the toxicity with the highest grade was used as the parameter for dose adjustment.

Grade 4 hematological toxicities or grade 3 infection required a dose reduction of two drugs. Grade 3 diarrhea, mucositis, or skin reaction required a reduction in S-1 dose. Grade 2 neurotoxicity required a reduction in CDDP dose. Grade 3 neurotoxicity required the discontinuation of CDDP. Creatinine clearance was calculated at the beginning of each cycle according to the Cockcroft–Gault formula. Creatinine clearance values ≥60 mL/min required no dose modification, 50–59 mL/min required a reduction in both S-1 and CDDP by one dose level, 40–49 mL/min required a reduction of both S-1 and CDDP by two dose levels, and those <40 mL/min required the cessation of both S-1 and CDDP. The protocol treatment was terminated if more than two dose reductions were required or if there was a treatment delay of >14 days due to toxicity.

All enrolled patients were followed up for at least 3 years. Efficacy and safety were evaluated at least every 3 months during the first year, at least every 4 months during the second year, and then every 6 months thereafter. Data on the use and method of nutritional support were reported at 2, 6, 12, and 24 months after registration.

Study design and statistical analysis. This trial was designed as a multicenter, prospective, single-arm phase II study to evaluate the efficacy and safety of CRT with S-1 plus CDDP. The study protocol was approved by the Japan Clinical Oncology Group Protocol Review Committee and the institutional review board of each participating institution. This trial was registered at the UMIN Clinical Trials Registry as UMIN000001272 (http://www.umin.ac.jp/ctr/index.htm).

In this phase II trial, the planned sample size was 45 patients, which was calculated by Southwest Oncology Group's two-stage attained design[9] based on an expected clinical complete remission rate of 60% and a threshold of 40%, with an interim one-sided alpha of 0.02 for futility, final alpha of 0.105, and a power of 0.9. If at least 10 clinical complete remissions occurred after the first 25 patients enrolled, another 20 patients were to be accrued. If the clinical complete remission rate was as high as 23 patients out of the total 45 patients, the subsequent phase III trial was expected to be designed to confirm the superiority of CRT with S-1 plus CDDP compared to CRT with CDDP alone.

The primary endpoint was the clinical complete remission rate, which was the proportion of CR and good PR in all eligible patients.

Good PR is characterized as a secondary change unique to post CRT that is regarded as remaining scar but not residual tumor. Good PR in this study was defined as lesions ≤10 mm in size or not enhanced on contrasted computed tomography scan.

The secondary endpoints were local PFS, PFS, OS, TTF, proportion of patients achieving nutritional support-free survival, and adverse events. Local PFS was defined as the time from enrolment to local disease progression or death from any cause. Progression-free survival was defined as the time from enrolment to any disease progression or death from any cause. Overall survival was defined as days from enrolment to death from any cause. Time to treatment failure was defined as the time from enrolment to any disease progression, off-protocol treatment, or death from any cause. Proportion of nutritional support-free survival denoted the percentage of surviving patients not requiring any nutritional support at the time of treatment start and then 2, 6, 12, and 24 months after registration. Confidence intervals of the percentage of clinical complete remission were estimated by the Clopper–Pearson method. Survival curves were estimated by the Kaplan–Meier method, and compared by the two-sided log–rank test. Analyses were carried out using SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

Patients and disease characteristics. From July 2008 to July 2010, 45 eligible subjects were accrued from 12 sites, consisting of 43 males and 2 females with median age 63 years and ECOG PS 0/1 (36/9). There were no ineligible patients and all patients were included in the primary analysis of efficacy and adverse events. Their characteristics are listed in Table 1. The most common primary site was oropharynx (58%, 26/45). Stage distribution is listed in Table 2. All but one patient had either primary site with T3 or T4 or neck lymph node with N2b or worse. Before starting CRT, 8 patients required feeding tubes including percutaneous endoscopic gastrostomy feeding tube (n = 7) and nasal tube (n = 1). Thirty-five patients underwent prophylactic percutaneous endoscopic gastrostomy feeding tube placement.

Treatment. A patient flow diagram is shown in Figure 2. Forty-two patients completed two cycles of chemotherapy concurrently with RT. Three discontinued two cycles of chemotherapy due to grade 4 cardiac troponin T increased, grade 3 hemorrhage – lung or grade 2 creatinine increased. Only 2 of 42 patients who completed two cycles of chemotherapy did not start adjuvant chemotherapy due to patient refusal or lung metastasis. Six patients discontinued two cycles of adjuvant chemotherapy due to patient refusal (n = 1) or adverse events (n = 5). In total, 34 patients completed two cycles of adjuvant chemotherapy. After completion of two cycles of adjuvant chemotherapy, five patients who did not achieve CR or good PR received R0 salvage surgery, and two patients received

Table 1. Characteristics of patients with unresectable locally advanced head and neck cancer who participated in a phase II trial of chemoradiotherapy with S-1 plus cisplatin (n = 45)

Characteristic		No. of patients
Age, years	Median	63
	Range	45–75
Sex	Female	2
	Male	43
PS	0	36
	1	9
Primary site	Oropharynx	26
	Hypopharynx	15
	Larynx	4
Histology	SCC W/D	10
	SCC M/D	17
	SCC P/D	10
	SCC unknown	8

M/D, moderately differentiated; P/D, poorly differentiated; PS, performance status; SCC, squamous cell carcinoma; W/D, well differentiated.

Table 2. Stage distribution of patients with unresectable locally advanced head and neck cancer who participated in a phase II trial of chemoradiotherapy with S-1 plus cisplatin (*n* = 45)

	T1	T2	T3	T4a	T4b	Total
N0	0	0	0	2	0	2
N1	0	0	0	0	0	0
N2a	0	1	0	1	1	3
N2b	0	3	2	2	3	10
N2c	0	4	5	10	5	24
N3	1	3	0	2	0	6
Total	1	11	7	17	9	45

off-protocol salvage surgery. Thus, a total of 7 patients received salvage surgery.

Toxicity. Overall toxicities during CRT and adjuvant chemotherapy are listed in Tables 3 and 4, respectively. The most common grade 3 or 4 toxicities included pharyngeal mucositis (46.7%), oral mucositis (44.4%), dysphagia (46.7%), anorexia (42.2%), radiation dermatitis (26.7%), neutropenia (26.7%), and febrile neutropenia (4.4%). During adjuvant chemotherapy, the most common grade 3 or 4 toxicities included neutropenia (17.5%), dysphagia (17.5%), pharyngeal mucositis (7.5%), and anemia (12.5%). On day 16 after the first cycle of chemotherapy, one patient developed grade 4 cardiac troponin T increase due to heart ischemia. One patient with a previously inserted stent graft for aneurysm of thoracic aorta developed grade 3 hemorrhage – lung after one cycle of chemotherapy. One patient developed grade 4 pharyngeal edema related with radiation toxicity during fourth cycle of adjuvant chemotherapy. No treatment-related deaths were observed. All seven patients received salvage surgery successfully without severe complication during surgery. After completion of surgery, one developed grade 3 partial necrosis of skin flap. No other grade 3 or worse complication was observed.

Treatment outcomes. Efficacy data are listed in Table 5. All patients enrolled in this study were assessable for response. The percentage of clinical complete remission was 75.6% (95% confidence interval, 60.5–87.1) with 8 CR and 26 good PR on the investigator read and 64.4% (one-sided $P < 0.0001$; 95% confidence interval, 48.8–78.1) with 8 CR and 21 good PR on central review, which rejected the null hypothesis that the percentage of clinical complete remission was 40% or less. A total of 18 patients had disease progression including primary site ($n = 9$), cervical lymph node ($n = 5$), distant metastasis ($n = 11$), and clinical progression ($n = 5$), which included an intrabronchial lesion, pharyngeal swelling with dysphagia, right cervical lymph node swelling, residual tumor at the site of salvage surgery, and multiple relapses at the lingual root, left neck and right supraclavicular fossa. Two patients who received salvage surgery achieved grade 3 pathological response (Table 6). After a median follow-up of 3.52 years for all enrolled patients, 3-year local PFS was 62.2%, with 3-year PFS of 60.0%, 3-year OS of 64.4%, and 3-year TTF of 48.9% (Fig. 3). The proportion of nutritional support-free survival before treatment, and 2 and 6 months after enrolment was 82.2%, 35.6%, and 68.9%, respectively. The number of patients who needed a feeding tube 12 and 24 months after enrolment were 5 and 3, respectively.

Survival analyses according to age (<65 years *vs.* ≥65 years), PS, sex, primary site, T stage (T1–2 *vs.* T3–4), and N stage (N0–2b *vs.* N2c–3) indicated that patients with PS 1 had significantly worse OS (HR, 2.76; $P = 0.032$) and TTF (HR, 3.18; $P = 0.0078$), and had a worse trend in both local PFS (HR, 2.11; $P = 0.12$) and PFS (HR, 2.27; $P = 0.084$) compared with patients with PS 0. No other parameter showed a statistically significant difference in clinical outcomes.

Discussion

Results of this phase II study showed that S-1 in combination with CRT resulted in encouraging activity, with a clinical complete remission rate of 64.4% in patients with unresectable locally advanced SCCHN. Toxicities were manageable and were tolerated by most patients. Despite all patients having unresectable disease, this combination showed promising efficacy with 3-year OS of 64.4%.

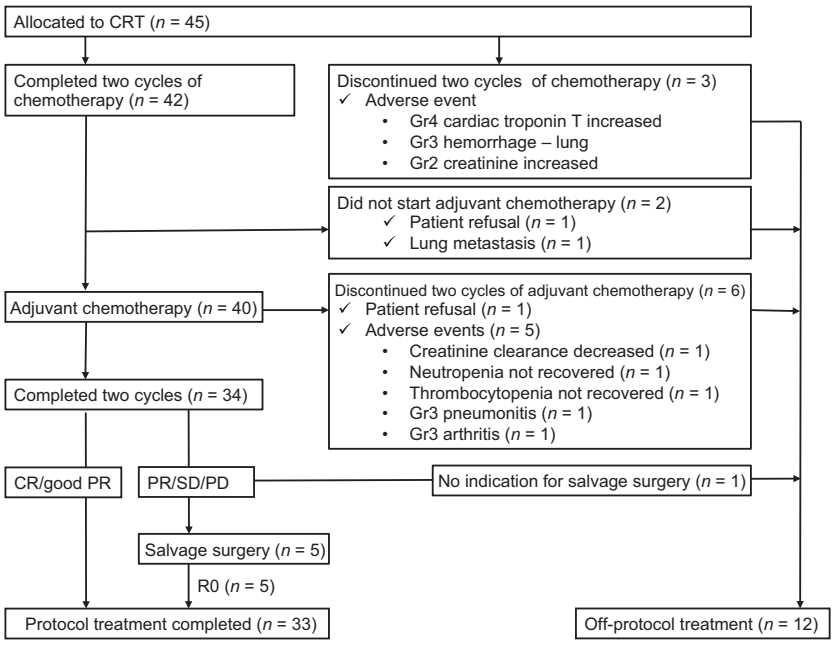

Fig. 2. Patient flow diagram of a phase II study to evaluate the efficacy and safety of chemoradiotherapy concurrent with S-1 plus cisplatin in patients with unresectable locally advanced squamous cell carcinoma of the head and neck. CR, complete response; CRT, concurrent chemoradiotherapy; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3. Overall toxicities in patients with unresectable locally advanced head and neck cancer who participated in a phase II trial of chemoradiotherapy with S-1 plus cisplatin (n = 45)

	No. of patients				
	Grade 1	Grade 2	Grade 3	Grade 4	Grades 3–4, %
Leukopenia	8	17	14	1	33.3
Neutropenia	12	10	10	2	26.7
Febrile neutropenia	–	–	2	0	4.4
Anemia	9	18	4	1	11.1
Thrombocytopenia	9	4	3	1	8.9
Anorexia	11	7	19	0	42.2
Mucositis – pharynx	4	15	21	0	46.7
Mucositis – oral cavity	3	15	20	0	44.4
Dysphagia	5	11	21	0	46.7
Radiation dermatitis	9	22	12	0	26.7
Xerostomia	19	15	7	–	15.6
Salivary gland change	11	20	5	0	11.1
Diarrhea	11	4	0	0	0.0
Larynx edema	9	1	0	0	0.0
Dyspnea	0	1	0	0	0.0

Graded according to Common Toxicity Criteria for Adverse Events version 3.0.

Table 4. Overall toxicities during adjuvant chemotherapy treatment in patients with unresectable locally advanced head and neck cancer (n = 40)

	No. of patients				
	Grade 1	Grade 2	Grade 3	Grade 4	Grades 3–4, %
Leukopenia	9	19	10	0	25.0
Neutropenia	8	19	7	0	17.5
Febrile neutropenia	–	–	0	0	0.0
Anemia	10	17	4	1	12.5
Thrombocytopenia	10	1	3	0	7.5
Anorexia	9	6	3	0	7.5
Mucositis – pharynx	12	7	3	0	7.5
Mucositis – oral cavity	9	7	3	0	7.5
Dysphagia	7	12	7	0	17.5
Radiation dermatitis	10	1	0	0	0.0
Xerostomia	22	13	0	–	0.0
Salivary gland change	15	16	1	0	2.5
Diarrhea	4	1	0	0	0.0
Larynx edema	8	1	1	1	5.0
Dyspnea	1	0	2	0	5.0

Graded according to Common Toxicity Criteria for Adverse Events version 3.0.

Table 5. Efficacy data in a phase II trial of chemoradiotherapy with S-1 plus cisplatin in patients with unresectable locally advanced head and neck cancer (n = 45)

Assessment	No. of patients						
	CR	Good PR	PR	SD	PD	%CR	95% CI
Investigator	8	26	5	0	6	75.6	60.5–87.1
Central	8	21	9	1	6	64.4	48.8–78.1†

†79%CI, 54.1–73.9. CI, confidence interval; CR, complete response; % CR, proportion of CR + good PR; PD, progressive disease; PD, progressive disease; PR, partial response; SD, stable disease.

In this trial, the primary endpoint was the percentage of clinical complete remission, which was the proportion of CR and good PR in all eligible patients. The revised Response Evaluation Criteria in Solid Tumors guidelines (version 1.1), published in 2009, recommended that FDG-PET might be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.[10] At the time that we planned this trial, however, this revised version had not been published. Furthermore, the usefulness of FDG-PET has not been validated in the treatment of HNC after completion of CRT. Based on this rationale, we have defined good PR as scar lesion. Although PFS would have been a more appropriate primary endpoint in the treatment of locally advanced HNC, complete remission is useful as a means of avoiding unnecessary therapy for treatment decision-making after the completion of CRT. Patients who achieved CR or good PR had significantly better survival than patients who did not, indicating that this endpoint

Table 6. Salvage surgery in patients with unresectable locally advanced head and neck cancer who participated in a phase II trial of chemoradiotherapy with S-1 plus cisplatin (*n* = 7)

	No. of patients
Reason for salvage surgery	
PR/SD/PD	5
Recurrence	2
Surgery	
Primary site	3
Neck dissection	6
Curability	
R0	6
R1	1
Pathological grade†	
Grade 0	1
Grade 1b	1
Grade 2	1
Grade 3	2
Other‡	2

†Pathological response was evaluated according to the General Rules for Clinical Studies on Head and Neck Cancer (5th edition), where the responses were classified into five grades based on the proportion of the tumor area affected by degeneration or necrosis: 0, no evidence of treatment effect; 1a, viable tumor cells occupy more than two-thirds of the primary tumorous area; 1b, viable tumor cells remain in more than one-third but less than two-thirds of the primary tumorous area; 2, viable tumor cells remain in less than one-third of the primary tumorous area; 3, no viable tumor cells remain. ‡Two patients received off-protocol salvage surgery after recurrence, so pathological grade could not be evaluated. PD, progressive disease; PR, partial response; SD, stable disease.

would be a good surrogate of OS, although this study included only a small number of patients. Further large studies are needed to validate this endpoint as a surrogate of OS.

S-1 contains CDHP, which inhibits dihydropyrimidine dehydrogenase. As 50% of CDHP is excreted in the urine, renal dysfunction may directly affect the inhibitory effect on dihydropyrimidine dehydrogenase and lead to increased 5-FU concentrations.[11] In a previous phase I study,[8] all four patients whose CCr was decreased to <60 mL/min after the first cycle of chemotherapy developed febrile neutropenia lasting more than 4 days. Based on these results, it was considered that dose modification according to CCr could have reduced or prevented these toxicities. Therefore, the current study has adopted dose modification according to CCr in treatment with S-1 as well as recent studies of S-1.[12] The incidence of febrile neutropenia was 25% (3/12) in the previous phase I study and 4.4% (2/45) in this phase II study, indicating that dose modification of S-1 according to CCr would successfully contribute to the lower incidence of this toxicity.

Recently, multiple clinical studies have indicated that the prognosis for patients with HPV-associated oropharyngeal cancer is significantly better than that with HPV-negative cancer of a comparable stage.[13–17] In this study, although 58% of enrolled patients had oropharyngeal cancer, we have not carried out an HPV analysis and, furthermore, not collected information of smoking history. Although a retrospective study revealed that approximately 30% of patients with oropharyngeal cancer were HPV-positive in Japan,[18] there were no significant differences in OS according to the primary site in this phase II study. This indicates that a higher population of oro-

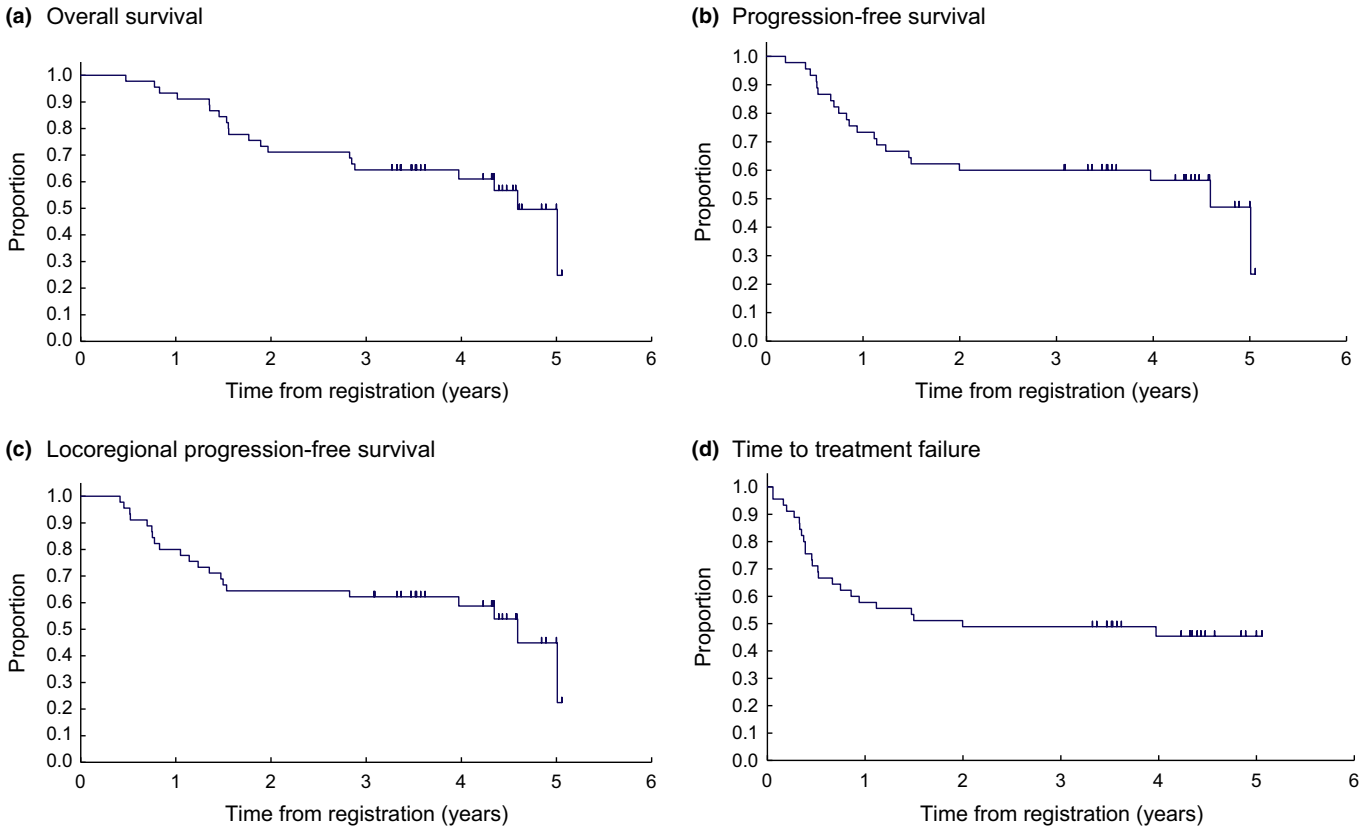

Fig. 3. Clinical outcomes in a phase II study to evaluate the efficacy and safety of chemoradiotherapy concurrent with S-1 plus cisplatin in patients with unresectable locally advanced squamous cell carcinoma of the head and neck. (a) Overall survival. (b) Progression-free survival. (c) Locoregional progression-free survival. (d) Time to treatment failure.

pharyngeal cancer would not be associated with better prognosis.

Although a meta-analysis showed no survival advantage by adding adjuvant chemotherapy,[3] there have been no randomized trials of definitive therapy with or without adjuvant chemotherapy after CRT in the treatment of locally advanced SCCHN and several studies indicated that adjuvant chemotherapy could decrease distant failure.[19,20] In this study, 75.6% (34 patients) of enrolled patients completed two cycles of adjuvant chemotherapy, indicating that this treatment schedule would be feasible in this population. Although 43 (96%) of enrolled patients had N2 or N3, 24.4% (11 patients) developed distant metastasis, which was better than previous reports of clinical trials for unresectable locally advanced SCCHN.

A previous study 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 to be higher in white than Japanese patients in a comparable dose range of S-1[21] This is mostly attributed to different polymorphisms in the *CYP2A6* gene between Asians and whites.[22,23] Therefore, the dose of S-1 in the present study is likely unsuitable for Western patients, and further study to determine the recommended dose of S-1 concurrent with CRT for these patients would be required.

Most HNC patents receiving CRT develop dysphagia, and difficulty in swallowing capsules containing S-1 may be problematic. Nutritional support by feeding tube replacement in these patients is indispensable. Our previous pharmacokinetic findings showed that administration of S-1 as a suspension through a feeding tube was interchangeable with oral administration of whole capsules.[17] S-1 can therefore be given to all HNC patients regardless of their difficulty in swallowing capsules.

Although not permitted in the current study, newer RT technologies, including intensity modulated RT and image-guided RT, can improve the sparing of normal tissues, and thus increase the daily tumor dose without an increase in normal tissue toxicity. This will, in turn, lead to improvement in both the patients' quality of life and in locoregional control for patients with locally advanced HNC.

In conclusion, this combination showed promising efficacy with acceptable toxicities.

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Disclosure Statement

The authors have no conflict of interest.

Abbreviations

CCr	creatinine clearance
CDDP	cisplatin
CDHP	5-chloro-2,4-dihydropyrimidine
CR	complete response
CRT	concurrent chemoradiotherapy
CTV	clinical target volume
ECOG	Eastern Cooperative Oncology Group
5-FU	5-fluorouracil
FDG	18-fluoro-deoxyglucose
GTV	gross tumor volume
HNC	head and neck cancer
HPV	human papillomavirus
HR	hazard ratio
OS	overall survival
PFS	progression-free survival
PR	partial response
PS	performance status
PTV	planning target volume
RT	radiotherapy
SCCHN	squamous cell carcinoma of the head and neck
TTF	time to treatment failure
UFT	ftorafur with uracil
SD	stable disease
PD	progressive disease

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