Multi-institutional phase II trial of S-1 in patients with oral squamous cell carcinoma

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The aim of this study was to investigate the efficacy and safety of an oral fluoropyrimidine anticancer agent, S-1, in patients with oral squamous cell carcinoma. Patients with pathologically confirmed squamous cell carcinoma and at least one measurable lesion were enrolled. Oral administration of S-1 (40 mg/m^2 twice daily) for 28 days was followed by a 14-day rest period. A total of 41 consecutive eligible patients were enrolled in the study between October 2002 and August 2004. The sites of the primary tumor were the gingiva (n=18), the tongue (n=12), the palate (n=5), the oral floor (n=4), the buccal mucosa (n=1), and the labial mucosa (n=1). A median of two cycles of treatment (range, 1–5) was administered. A complete response was achieved in nine patients and a partial response in eight patients, for an overall response rate of 41.5% (95% confidence interval, 26.4–56.5%). The 3-year survival rate was 76.4% (95% confidence interval, 62.8–90.0%). Although grade 3 anemia and anorexia occurred in two patients each (4.9%), and grade 3 neutropenia, thrombocytopenia, nausea, vomiting, stomatitis, and diarrhea in one patient each (2.4%), no grade 4 toxicities were observed. S-1 exhibits definite antitumor activity in patients with oral squamous cell carcinoma and is well tolerated. ***Anti-Cancer Drugs*** **19:85–90**

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Introduction

In 2002, there were globally 274 000 patients with cancer of the oral cavity and almost two thirds of them were men. In developed countries, cancer of the oral cavity is the 11th most common cancer in male patients and the 13th most common cancer in female patients; in developing countries, it is the sixth most common cancer in male patients and 10th most common in female patients [1]. Oral squamous cell carcinoma (OSCC) accounts for the majority of oral cancers. It is a significant public health problem everywhere, because oral function is very important for breathing, eating, and conversation. Despite recent advances in surgery, radiotherapy, chemotherapy, and immunotherapy, the survival rate of advanced-stage OSCC in Japan is below 50% [2,3]. As 5-fluorouracil (5-FU), cisplatin, and docetaxel (TXT) are now available for the treatment of OSCC patients in Japan, combined therapy has been tried to increase their therapeutic effect. Combined therapy, however, has been reported to cause severe gastrointestinal side effects or myelosuppression. Systemic chemotherapy is not often suitable for elderly patients or patients with complications, and extended operations might also be inappropriate for such patients. The development of new effective chemotherapeutic agents to improve the outcome of patients with OSCC is thus to be hoped for.

In the last few years, a new oral fluoropyrimidine anticancer agent, S-1, has been developed by Taiho Pharmaceutical Co. Ltd (Tokyo, Japan). The design of S-1 was based on the theory of biochemical modulation of 5-FU. In phase II studies, S-1, among the many oral anticancer agents tested so far, has yielded the highest response rate against unresectable advanced carcinomas [4]. S-1 is a novel, orally administered combination of tegafur, 5-chloro-2,4-dihydroxypyridine, and oteracil potassium in a 1 : 0.4 : 1 molar-concentration ratio [5]. 5-Chloro-2,4-dihydroxypyridine is a competitive inhibitor of dihydropyrimidine dehydrogenase, which is involved in the degradation of 5-FU, and acts to maintain efficacious concentrations of 5-FU in plasma and tumor tissue [6]. Oteracil potassium is a competitive inhibitor of orotate phosphoribosyltransferase and inhibits the phosphorylation of 5-FU in the gastrointestinal tract, thereby reducing the serious gastrointestinal toxicity associated with 5-FU [7].

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In a phase II trial against advanced and recurrent head and neck cancer (59 eligible patients), S-1 yielded a high response rate of 28.8% with acceptable toxicities [8]; it also yielded a higher response rate in gastric [9,10], colorectal [11], and breast cancers [12]. The main adverse events were hematological toxicity, including anemia, leukopenia, and neutropenia; gastrointestinal toxicity, including anorexia, diarrhea, and nausea; and skin toxicity [4]. The response rates for advanced gastric cancer [9], colorectal cancer [11], breast cancer [12], non-small cell lung cancer [13], and head and neck cancer [8,14] in the late phase II studies conducted in Japan have been 44–49, 35, 42, 22, and 29–46%, respectively. Efficacy of S-1 against gastrointestinal cancer has also been reported in European patients, with response rates for advanced gastric cancer [15] and colorectal cancer [16] of 32 and 24%, respectively. Few previous reports, however, have described the efficacy and safety of S-1 in the treatment of head and neck cancer, including OSCC [17].

In a phase I study in Japanese patients, S-1 was administered orally for 28 days. The maximum allowed dose of S-1 was 150 mg once daily or 75 mg twice daily, and leukopenia was the dose-limiting toxicity. As the pharmacokinetic profile of S-1 revealed that twice-daily administration maintained therapeutic 5-FU levels without increasing the maximum 5-FU concentration in the blood [18,19], oral administration of S-1 at a dose of 75 mg twice daily for 28 consecutive days, followed by a 14-day rest period, was recommended. Three phase II studies of twice-daily S-1, administered as a single agent for the treatment of metastatic gastric malignancy, have yielded response rates of approximately 50%, with minimal toxicity [9,10,20].

On the basis of these results, we have conducted a phase II study of S-1 in the treatment of the patients with OSCC and tried to evaluate the efficacy and safety of S-1 in patients with OSCC.

Patients and methods

Eligibility

Patients were required to meet the following eligibility criteria: histologically confirmed OSCC; at least one measurable lesion; no prior antitumor treatment; no residual lesion 4 weeks after the prior anticancer therapy (i.e. after resection, radiotherapy, and/or chemotherapy); Eastern Cooperative Oncology Group performance status of 0–2; age 20–80 years; adequate organ function, defined as a leukocyte count of 3500–12 000 mm^3, neutrophil count of more than 2000 mm^3, platelet count of more than 100 000 mm^3, hemoglobin level of more than 9.0 g/dl, aspartate aminotransferase and alanine aminotransferase levels within 2.0 times the upper limit of normal (ULN), a serum total bilirubin level within 2.0 times the ULN, and serum creatinine level within the ULN; and an estimated life expectancy of at least 3 months. The exclusion criteria were as follows: active concomitant malignancy, inability to take oral medication, severe complications, watery diarrhea, interstitial pneumonia, lung fibrosis, heart disease, renal disease, liver disease, insulin-dependent severe diabetes, marked pleural effusion or ascites, pregnancy or lactation, reproductive activity (if a man), and a decision by the primary doctor to exclude the patient. On enrollment in the study, the eligibility of the patient was confirmed via facsimile by the central administration office (Tokushima). All patients gave written informed consent prior to enrollment in the study, and the protocol was approved by the institutional ethics committee of each participating institution.

Treatment plan and dose modifications

S-1 was administered orally at a dose of 40 mg/m^2 twice daily, once each after breakfast and dinner. The following three initial doses based on body surface area (BSA) were established: BSA $< 1.25\ m^2$, 80 mg/day; $1.25\ m^2 \leq$ BSA $< 1.50\ m^2$, 100 mg/day; and BSA $\geq 1.50\ m^2$, 120 mg/day. S-1 at the respective dose was administered to each patient for 28 consecutive days, and was followed by a 14-day rest period. Courses of this treatment were repeated until any of these outcomes occurred: disappearance of the tumor, loss of therapeutic effect, occurrence of disease progression, unacceptable toxicity, or patient refusal to continue. When hematologic or nonhematologic toxicity of grade 3 or greater occurred, administration was temporarily interrupted until the toxicity subsided to grade 1 or less [National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0]. If the daily dose of S-1 was considered intolerable, the re-treatment dose was reduced by 20 mg/day (minimum dose, 60 mg/day). If a rest period of more than 28 days was required because of toxicity, the patient was withdrawn from the study. Patients were not allowed to receive concomitant radiation therapy or chemotherapy during the study. Patients maintained a daily journal in which they recorded the doses of S-1 that they were given and any signs or symptoms that they experienced.

Baseline evaluation and follow-up evaluation

The baseline evaluation before treatment consisted of a medical history; physical examination; performance status assessment; complete blood count of serum, urea, and electrolyte; liver function tests; coagulation studies; and measurement of serum tumor marker (squamous cell carcinoma antigen and carcinoembryonic antigen) levels. To accurately define the extent of the disease and the target lesions, chest radiography and abdominal computed tomography (CT) were performed within the 2 weeks preceding the chemotherapy. A CT scan was performed to detect metastatic disease and local invasion. Patients were reevaluated after every cycle (i.e. every 6 weeks), and then every 2 months after the completion of

the experimental therapy. Blood cell counts were performed weekly during treatment, and serum chemistry was performed before every new cycle. The NCI-CTC scale (version 2.0) was used to evaluate treatment-related side effects.

Evaluation of response and toxicity

The response was assessed according to the Japan Society for Cancer Therapy criteria [21], which are similar to the World Health Organization criteria. Briefly, a complete response (CR) means the disappearance of all lesions and no occurrence of any new lesions for a minimum of 4 weeks. A partial response (PR) is defined as a reduction of 50% or more in the aggregate of the product (in each lesion) of the two longest perpendicular diameters: this reduction should be sustained for a minimum of 4 weeks. Stable disease (SD) was defined as a reduction of less than 50 or an increase of less than 25% in the aggregate measure (computed as above) for a minimum of 4 weeks. Progressive disease (PD) was defined as an increase of 25% or more in this aggregate measure, the appearance of any new lesion, or a deterioration in clinical status consistent with disease progression. Response was assessed by making direct measurements. Adverse events were evaluated according to NCI-CTC version 2.0. Objective responses and adverse events were confirmed by an external review committee.

Statistical analysis

A minimum of 36 patients needed to be enrolled in the study, to be able to reject the null hypothesis that the lower limit of the 95% confidence interval (CI) of the expected response rate (35%) would be $< 15\%$, under conditions of an α error of 0.05 (one side) and a β error of 0.1. The overall survival time of the eligible patients was defined as the time between the start of the treatment and death from any cause, and the overall survival was estimated by the Kaplan–Meier method. Compliance was calculated for all treatment courses as the ratio of the total dose actually taken to the total dose scheduled.

Results

Patients

Between October 2002 and August 2004, a total of 41 patients were enrolled in this study, and all patients were concluded to be eligible. The patients' characteristics are summarized in Table 1. Before starting this study, three patients had been treated by surgical resection, five patients by surgical resection with neoadjuvant therapy, four patients by chemotherapy (including 5-FU-containing regimens, cisplatin, or taxanes), and five patients by chemoradiotherapy. They had all, however, presented with measurable lesions at the time of enrollment into this study. In addition, 10 patients had cervical lymph node metastasis at the time of enrollment into the study.

Treatment

Overall, the 41 patients received a total of 91 cycles of chemotherapy, and the median number was two cycles (range, 1–5). The dose of S-1 was reduced in 18 patients either because of grade 3 adverse events (10 patients: neutropenia in one, anemia in two, thrombocytopenia in one, nausea in one, vomiting in one, anorexia in two, stomatitis in one, and diarrhea in one) or because the attending physician judged that it was necessary in eight patients. The primary doctor reduced the dose of S-1 when the BSA of the patient was reduced owing to the grade 2 events of nausea, anorexia, or stomatitis. Except

Table 1 Patient characteristics ($n=41$)

Characteristics	No. of patients
Sex	
Male	22
Female	19
Median age; years (range)	69 (38–80)
ECOG PS	
0	39
1	2
Primary tumor site	
Gingiva	14
Tongue	12
Palate	4
Oral floor	4
Sinus	4
Others	3
Stage[a]	
I	10
II	9
III	8
VI	14
Previous treatment	
Surgery	8
None	33

[a]Stage groupings were classified according to the 1997 International Union Against Cancer criteria.
ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2 Response

Site of lesions	CR	PR	SD	PD	NE	Response rate (%)
Overall	9	8	17	1	6	41.5
Gingiva	4	3	5	1	1	50.0
Tongue	3	2	6	0	1	41.7
Palate	2	0	1	0	1	50.0
Oral floor	0	0	3	0	1	0
Sinus	0	2	2	0	0	50.0
Others	0	1	0	0	2	33.3

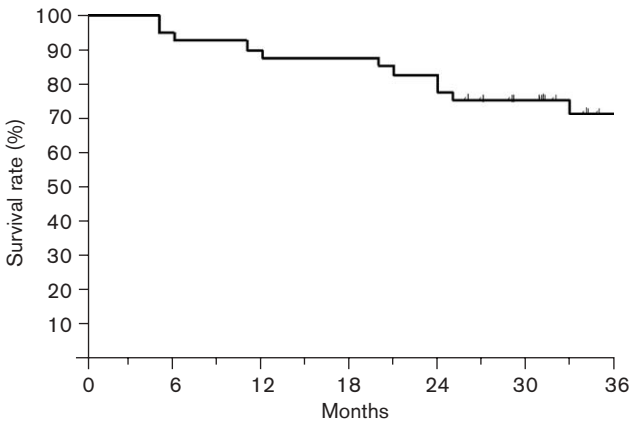
CR, Complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
Response rate = CR + PR.

for two patients in whom treatment was abandoned because of toxicities (grade 3 stomatitis and diarrhea), all patients were treated as inpatients during the first cycle. The overall compliance rate was 95.3%.

Response and survival

A CR was achieved in nine of the 41 patients and a PR in eight patients, yielding an overall response rate of 41.5% (95% CI, 26.4–56.5%) (Table 2). Seventeen patients showed SD, one showed PD, and six could not be evaluated. At the time of the analysis, nine of the 41 patients had died because of disease progression. The median time to progression was 27.0 months (range, 2.0–52.0 months), and the median follow-up period was 46.5 months. As shown in Fig. 1, the median survival time was 34.0 months (range, 5.0–52.0 months), and the 3-year survival rate was 76.4% (95% CI, 62.8–90.0%).

Fig. 1



Overall survival time.

Toxicity

All 41 patients were assessed for the toxicities that are listed in Table 3. Treatment was generally well tolerated throughout the study. Although hematologic and gastrointestinal toxicities were common, most were mild and transient. No patient discontinued treatment because of hematologic or gastrointestinal toxicities. Severe grade 3 events were observed in eight patients (19.5%): anemia and anorexia in two patients (4.9%), and neutropenia, thrombocytopenia, nausea, vomiting, stomatitis, and diarrhea in one patient each (2.4%). No grade 4 toxicities were observed. No signs of cumulative toxicity were noted.

Discussion

This study was conducted to evaluate the objective response rate and toxicity in OSCC patients treated with an oral regimen of S-1 in a multi-institutional study. A response rate of 41.5%, which was equal to or greater than the response rates in previous reports [8,14], was achieved. S-1 has the same marked therapeutic efficacy in OSCC patients as in gastric cancer patients [9].

The first cycle was administered as inpatient therapy, as we started this study at the early part of commercial availability of S-1 and as the investigator wanted to closely observe the adverse effects and safety issues. Subsequently, the patients in this study could be shifted for therapy as outpatients. The most common adverse events in this study were myelosuppression, stomatitis, and gastrointestinal toxicity. We were able to detect them

Table 3 Treatment-related adverse events ($n=41$): worst grade reported during treatment period

	Grade[a]					
Toxicity	1	2	3	4	Grade 1–4 (%)	Grade 3–4 (%)
Hematologic						
Leukopenia	12	9	0	0	51.2	0
Neutropenia	5	11	1	0	41.5	2.4
Anemia	15	8	2	0	61.0	4.9
Thrombocytopenia	12	0	1	0	31.7	2.4
Nonhematologic						
Nausea	1	1	1	0	7.3	2.4
Vomiting	1	1	1	0	7.3	2.4
Anorexia	7	5	2	0	34.1	4.9
Stomatitis	7	8	1	0	39.0	2.4
Diarrhea	4	1	1	0	14.6	2.4
Total bilirubin	10	3	0	0	31.7	0
ALT	5	0	0	0	12.2	0
AST	5	0	0	0	12.2	0
Fatigue	8	1	0	0	22.0	0
Fever	2	0	0	0	2.4	0
Rash	2	2	0	0	9.8	0
Pigmentation changes	3	0	0	0	7.3	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]National Cancer Institute Common Toxicity Criteria, version 2.0.

easily within one cycle, as they occurred soon after the start of S-1. We were therefore able to start outpatient S-1 chemotherapy with the second cycle, and to observe the high response rate of 41.5% as expected.

It was recently reported that the schedule of a 2-week administration followed by a 1-week rest seems more feasible than the oral 4-week administration followed by a 2-week rest, of S-1 as adjuvant chemotherapy for locoregionally advanced squamous cell carcinoma of the head and neck [17]. Many institutions have gradually selected the schedule of a 2-week administration followed by a 1-week rest instead of the schedule of a 4-week administration followed by a 2-week rest, for various cancer treatments. We followed a similar schedule of S-1, to reduce the prolonged period of toxicity. The dose was reduced in 18 (43.9%) of the 41 patients in this study, which was a high rate. The primary doctor checked the inpatients' conditions in detail during the first cycle, and was able to reduce the S-1 dose before grade 3 anorexia or stomatitis occurred. This might have led to an increase in the quality of life of the patients. Also, the S-1 regimen was administered successfully and compliance was good. Except for the two patients in whom treatment was abandoned because of toxicities (grade 3 stomatitis and diarrhea), all patients were ultimately treated as outpatients. The overall compliance rate was 95.3%, and good compliance is known to increase the likelihood of a favorable therapeutic response. We can treat outpatients by chemotherapy with S-1 in some cases; although, during the initial course of this study, the OSCC patients had been treated as inpatients. These observations suggest that the appropriate dose of S-1 might be less than 80 mg/m^2/day, although the dose of 80 mg/m^2/day seems to be generally used to treat patients with various cancers.

We have established the appropriate dose of S-1 in combination with radiotherapy and have attempted to identify its safety and clinical efficacy in a multi-institutional phase II study (ongoing). This combined therapy is a useful form of concurrent chemoradiotherapy that can improve the response rate and quality of living of patients with advanced OSCC, including stage IV. Actually, this therapy has been found to have a dramatic therapeutic effect in patients with stage IV disease [22].

A combination of cisplatin or TXT with S-1 has recently been tried, in the treatment of various cancers. Combination therapy with S-1 and cisplatin has already been used for gastric cancer, and an excellent response rate of 76% has been reported in a phase II study [23]. Combination therapy with S-1 and TXT has also been used to treat gastric cancer, and an excellent response rate of 56.3% and mild adverse effects have been reported in a phase II study [24]. Combined therapy with S-1 and low-dose cisplatin has been reported to be suitable as neoadjuvant chemotherapy for OSCC. Although the combined therapy regimen exerted high antitumor activity in that phase II study (CR 36.4%, and PR 25.0%), grade 4 adverse effects were observed [25]. Clinical trials are essential to determine which of these chemotherapeutic agents is most suitable for use in combination with S-1.

The results of this study showed that S-1 single-agent chemotherapy cured some cases of stage III OSCC, and that a good therapeutic effect was achieved in some patients. Use of S-1 must be expected in neoadjuvant as well as in adjuvant chemotherapy. Moreover, S-1 is the choice for patients who refuse extended surgery or intensive chemotherapy or radiotherapy. S-1 could be useful for elderly patients and patients with complications.

In conclusion, the results of this study indicate that S-1 is a safe and active agent in the treatment of patients with OSCC, and that S-1 is a promising agent with the potential to become a valuable oral treatment option for patients with OSCC.

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