

Neoadjuvant Chemotherapy with S-1 for Patients with Oral Squamous Cell Carcinoma

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Abstract

S-1, an oral anticancer drug, is comprised of tegafur (a prodrug of 5-fluorouracil) and two biochemical modulators that have effect-enhancing and adverse reaction-reducing activities. Neoadjuvant chemotherapy (NAC) using S-1 has not been reported. Between April 2003 and March 2008, 103 patients with previously untreated oral squamous cell carcinoma (OSCC) received some courses of S-1 NAC (S-1 80 mg/m²/day as the NAC until 1 week preoperatively). Tumor size and histopathologic effect were evaluated before and after treatment. Among 103 cases, 10 cases had complete responses and 53 cases had partial responses (overall response rate [RR], 61.2%). Twenty-two (21.4%) patients had adverse events. Most patients had mild toxicities in the bone marrow and digestive tract (grade 1, 19 cases). Only three patients (2.9%) had grade 2 neutropenia or grade 4 thrombocytopenia. We examined the relationship between the RR and the clinicopathologic behaviors. The RR of the pN2 cases (33.3%) was significantly lower than that of the pN0 cases (69.4%). The RR was not correlated with tumor size, differentiation type, distant metastasis, and the period of administration. The data indicates that S-1 caused only mild toxicity and had highly effective antitumor activity. Furthermore, the RR of S-1 NAC might predict regional lymph node metastasis.

Keywords: S-1; 5-Fluorouracil; Neoadjuvant chemotherapy

Introduction

Oral squamous cell carcinomas (OSCCs), the most common cancer of the head and neck, accounts for over 300,000 new cancer cases worldwide annually (Lippman et al., 2005). If detected at an early stage, survival from oral cancer exceeds 90% at 5 year, whereas the survival with a diagnosis of late-stage disease is only 30%. The most important prognosticator of survival in OSCC is the presence of regional lymph node metastasis (Spira and strong, 1971). Therefore, the surgery, including neck dissection, has been the mainstay of treatment for primary OSCCs.

S-1 is an oral anticancer drug comprised of tegafur (FT), a prodrug of 5-fluorouracil (5-FU), 5-chloro-2, 4-dihydropyridine (CDHP), and potassium oxonate (Oxo). CDHP reversibly inhibits degradation of 5-FU by dihydropyrimidine dehydrogenase, resulting in prolonged high serum concentrations of 5-FU, thereby enhancing the antitumor activity of FT. Oxo is selectively distributed to the gastrointestinal tract, where high concentrations inhibit orotate phosphoribosyltransferase, which phosphorylates 5-FU to an active metabolite in humans. Inhibition of this enzyme reduces gastrointestinal toxicity. (Shirasaka et al., 1996a; Shirasaka et al., 1996b; Schoffski et al., 2004)

S-1 has been used for adjuvant chemotherapy after primary treatment of head and neck cancer (Tsukuda et al., 2005). However, neoadjuvant chemotherapy (NAC) with S-1 monochemotherapy has not been reported. The aim of NAC is to improve the treatment results by achieving downstaging of the tumor before treatments, surgery and radiotherapy. Other groups have reported that advanced gastric cancer was tried to use S-1 NAC (Kochi et al., 2004; Yano et al., 2002). However, no convincing evidence has been obtained regarding the contribution of NAC to improved survival prognosis (Yano et al., 2002). In the present study, we retrospectively examined 103 patients with primary OSCC to evaluate the effect of NAC with S-1 monochemotherapy on clinical behavior.

Materials and Methods

Patients

One hundred and three patients previously diagnosed with OSCC at the Division of Oral-Maxillofacial Surgery, Chiba University Hospital (Chiba, Japan) were enrolled in this study from April 2003 to March 2008. The protocol was approved by the Institutional Review Board of Chiba University. All patients provided written informed consent before study entry. All patients received NAC with S-1 before surgical resection of the primary tumor with simultaneous neck dissection.

Treatment schedules

To suppress tumor growth during the preoperative period, the patients underwent NAC with S-1 on an outpatient basis. S-1 (80 mg/m²/day) was administered orally after breakfast and dinner. One course of medication comprised 2 weeks of administration and 1 week of withdrawal. The course was repeated until 1 week before surgery.

Evaluation of treatment effects

The extent of the disease was evaluated by measuring the tumor

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size and histopathologic findings of biopsy specimens after NAC. Histopathologic diagnosis of each neoplastic tissue was performed according to the World Health Organization criteria by the Department of Pathology, Chiba University Hospital. Clinicopathologic staging was determined by the TNM classification of the International Union against Cancer. The treatment response was evaluated using the Response Evaluation Criteria in Solid Tumors criteria. Briefly, a complete response (CR) was defined as the complete disappearance of clinically detectable tumor and negative biopsy results for the primary site; a partial response (PR) as a decrease of 50% or more of the sum of the products of the largest perpendicular dimensions of all measurable lesions; no change (NC) as a decrease of less than 50% in total tumor size; and progressive disease (PD) as progression of the tumor size after treatment. The toxicity of this NAC was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

Statistical analysis

The statistical significance of the ECT2 expression levels was evaluated using Fisher's exact test. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

The exclusion criteria were shown in Table 1. There were 41 women and 62 men (mean age, 64.6 years; range, 29-91 years). The primary tumor sites were the tongue (51 cases), lower gingiva (25 cases), buccal mucosa (12 cases), upper gingiva (9 cases), and mouth floor (6 cases) (Table 2).

Periods of administration of S-1

The periods of administration were 7 to 13 days in 28 cases,

3 or more Performance Status*
Hemoglobin < 8.0 g/dl
White blood count < 3,000/mm ³
Platelet count < 100,000/mm ³
Total bilirubin > 3 mg/dl
GOT or GPT >150 IU/L
Serums creatinine > 1.5 mg/dl
Patients with COPD
Patients with coagulopathy

*ECOG score (Oken et al., 1982).
GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; COPD, chronic obstructive pulmonary disease.

Table 1: Exclusion criteria.

	No.	%
Gender		
Female	41	39.8
Male	62	60.2
Age		
20-29	1	1.0
30-39	6	5.8
40-49	7	6.8
50-59	20	19.4
60-69	26	25.2
70-79	28	27.2
80-89	14	13.6
90-99	1	1.0
Primary tumor site		
Tongue	51	49.5
Lower gingiva	25	24.3
Buccal mucosa	12	11.7
Upper gingiva	9	8.7
Mouth floor	6	5.8
Total	103	

Table 2: Distribution of gender, age, and primary tumor site.

Days	CR+PR	NC+PD	Total	RR (%)
7-13	17	11	28	60.7
14-20	35	23	58	60.3
21-35	11	6	17	64.7
Total	63	40	103	61.2

Table 3: Correlation between treatment effects and administration period.

Events	Grade*			
	1	2	3	4
Nausea	6	-	-	-
Neutropenia	3	2	-	-
Rash	3	-	-	-
Diarrhea	2	-	-	-
Itching	2	-	-	-
Headache	2	-	-	-
Trichorrhea	1	-	-	-
Thrombocytopenia	-	-	-	1

*Grading according to the CTCAE v3.0

Table 4: Adverse events.

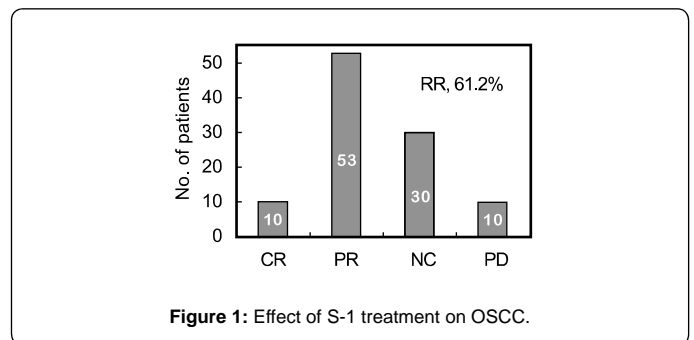


Figure 1: Effect of S-1 treatment on OSCC.

14 to 20 days in 58 cases, and 21 to 35 days in 17 cases (average administration period, 14.7 days). The response rates (RRs) of 7 to 13 days, 14 to 20 days, and 21 to 35 days were 60.7%, 60.3%, and 64.7%, respectively. The RRs did not differ significantly among the periods of administration (Table 3).

Toxicity

Adverse events associated with NAC developed in 22 cases (21.4%). The primary toxic effects were bone marrow depression and gastrointestinal toxicity. Among them, 19 grade 1 events were observed. Only three cases had grade 2 neutropenia (2 cases, 1.9%) and grade 4 thrombocytopenia (1 case, 1.0%) (Table 4). No treatment-related deaths occurred.

Response to NAC

The treatment effects are listed in Figure 1. The rates of antitumor effects were a CR in 10 cases (9.7%), a PR in 53 cases (51.5%), NC in 30 cases (29.1%), and PD in 10 cases (9.7%). Of the 103 patients evaluated for a tumor response, 63 patients (61.2%) achieved a CR/PR. The relationship between the RR for S-1 and clinical behaviors was shown in Table 5. Interestingly, the RR of the pN2 cases (33.3%) was significantly lower than those of the pN0 (69.4%) and pN1 cases (50.0%) ($p < 0.05$, Fisher's exact test). No significant differences were found among the other parameters (tumor size, histopathologic types of tumor, and distant metastasis).

Discussion

The purpose of NAC is to improve the treatment results by achieving tumor downstaging by controlling tumor cell activity in the proliferative layer and reducing tumor volume (Athanasiadis et al.,

	CR+PR	NC+PD	Total	RR (%)
Tumor size				
T1+T2	30	19	49	61.2
T3+T4	33	21	54	61.1
Lymph node metastasis				
pN0	50	22	72	69.4*
pN1	8	8	16	50.0
pN2	5	10	15	33.3*
Histopathologic tumor types				
Well	40	24	64	62.5
Moderately	20	14	34	58.8
Poorly	3	2	5	60.0
Distant metastasis				
Negative	60	35	95	63.2
Positive	3	5	8	37.5
Total	63	40	103	61.2

*p < 0.05, Fisher's exact test

T1, Tumor 2 cm or less in greatest dimension; T2, Tumor more than 2 cm but not more than 4 cm in greatest dimension; T3, Tumor more than 4 cm; T4, Tumor invades surrounding organs.

pN0, Pathologically no regional lymph node metastasis; pN1, Pathologically metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension; pN2, Pathologically metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.

Table 5: Correlation between treatment effects and clinical behavior.

1997). The most important treatment goal was to prevent local tumor progression and regional lymph node metastasis preoperatively. The essential conditions for NAC are low-grade toxicity and high antitumor activity. In the present study, we used S-1, which can be administered on an outpatient basis, for NAC while patients awaited surgery for OSCC.

The standard regimen of S-1 is a 4-week period of administration followed by a 2-week drug-free period. A comparative study of the 4- and the 2-week regimens showed that the incidence of adverse events was lower in the 2-week regimen group (77%) than in the 4-week regimen group (93%) (Kimura et al., 2003). Therefore, in the current study, we adopted the 2-week regimen, i.e., 2-week administration followed by a 1-week drug-free period, and withdrew administration of S-1 until 1 week preoperatively. Among the 103 cases, the administration period ranged from 7 to 35 days (mean, 14.7 days). The RRs of three periods of administration (short, intermediate, and long term) were 60.7%, 60.3%, and 64.7%, respectively, suggesting that the periods of administrations were not correlated with the RR of S-1. These data suggested that we should administer S-1 NAC despite a short time until surgery.

In the current study and previous reports (Sakata et al., 1998; Sugimachi et al., 1999; Koizumi et al., 2000; Kawai et al., 2003), the incidence of grade 2 or higher adverse events was extremely low (2.9%) (Table 4). Because Oxo in S-1 inhibits severe gastrointestinal toxicity (Takechi et al., 1997), the toxicity rate of S-1 was lower than that of other antitumor drugs, such as 5-FU and CDDP (Shirasaka et al., 2009; Meta-Analysis Group in Cancer, 1998; Higby et al., 1973; Hayes et al., 1977; Blachley et al., 1981). Therefore, we used S-1 as the NAC for outpatient administration.

CDHP in S-1 inhibits dihydropyrimidine dehydrogenase, resulting in a prolonged high serum concentration of 5-FU (Shirasaka et al., 1996a; Shirasaka et al., 1996b; Schoffski et al., 2004; Fukushima et al., 2005). Two recent phase II studies of S-1 in Japanese patients with head and neck cancer reported high RRs of 46.2% (Inuyama et al., 1998) and 28.8% (Inuyama et al., 2001), respectively. Our S-1 NAC study also found a high RR (61.2%). Our RR data was clearly higher than that in other studies, such as Inuyama et al. (2001) and Kimura et al. (2003) They adopted advanced or recurrent cancer cases for S-1

adjuvant chemotherapy studies. Since we adopted operable patients for S-1 NAC study, the RR might be greater than other studies. We then examined the correlation between the RR and clinicopathologic status. Among the clinical variables analyzed, the RR was unrelated to tumor size, differentiation types, and distant metastasis. Interestingly, we found that our regimen was related closely to regional lymph node metastasis. These data suggested that the group with a low RR was comprised of patients with the potential for a high rate of lymph node metastasis.

S-1 monochemotherapy of NAC was a useful and convenient method for outpatients, because it has high effective antitumor activity and low toxicity. Our results indicated that the RR of S-1 treatment in pN2 cases was lower than that in pN0 cases. The appropriate treatment has to be determined for patients at high risk of regional lymph node metastasis. Further studies on administration of S-1 NAC to outpatients and confirmation of safety and efficacy may result in increased use. Furthermore, the RR of S-1 NAC might be an indicator of regional lymph node metastasis.

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