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Critical Evaluation of a Prospective Study of Concurrent Chemoradiotherapy with S-1 for Early Glottic Carcinoma

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Abstract. *Aim: To improve the outcomes of radiotherapy alone for T2 glottic carcinoma (GC), we initiated a prospective study of concurrent chemoradiotherapy with S-1 for patients with early GC, primarily T2 cases. We report the efficacy and safety of this protocol. Patients and Methods: Eligible patients had T1b or T2 glottic squamous cell carcinomas. Patients received S-1 (55.3 mg/m^2/day, once daily) and radiotherapy (2 Gy/day, five days/week, to a total of 30 fractions). Results: Thirteen patients were eligible. Complete responses were observed in all 13 patients (100%). At a median follow-up duration of 53 months (range=23-68 months), the 3-year local control and overall survival rates were both 100%. Grade 3 dermatitis occurred in only one patient. Conclusion: This chemoradiotherapy protocol is well -tolerated and effective in patients with early glottic carcinoma. Furthermore, due to its once-daily administration, this protocol is considered to be easier than usual chemoradiotherapy, and makes outpatient-treatment possible.*

Glottic carcinoma (GC) is the most common laryngeal cancer. It is usually detected early due to the symptomatic occurrence of hoarseness (1). The recommended treatment strategies for early GC with intent of larynx preservation are mainly radiotherapy (RT), transoral laser therapy and partial laryngectomy (1, 2).

For T1 GC, the local control (LC) rate for RT alone has been reported to range from 82%-93%. However, the outcomes of RT-alone for T2 GC are unsatisfactory; the LC rate has been reported to range from 65%-80% (3-5). To improve the LC rate for T2N0 GC, clinicians have begun to perform hyperfractionated RT (6, 7) and chemoradiotherapy (CRT).

Several different regimens and administration methods are used for CRT. Oral anti-tumor agents include tegafur-uracil (UFT) (8, 9) and S-1 (12-22), while intravenously-infused agents include carboplatin (CBDCA) (9) and cisplatin (CDDP) (10, 11); however, the optimal drug for CRT remains to be determined.

The anti-tumor effect of S-1 (12) has been demonstrated in a variety of solid tumors; not only in adenocarcinomas, including advanced gastric, colorectal and pancreas cancer (13-16), but also in squamous cell carcinoma, including head and neck cancer (17-22). An original S-1 dosage is twice-daily administration for 28 days, followed by 14 days of rest. However, the optimal dosing and administration schedule for combing S-1 with RT remains to be determined.

In our phase I/II study protocol for head and neck cancer, we administered S-1 once-daily, 3-6 h prior to RT and tried to achieve not only systemic therapy, but also as the radiosensitizer. The results of our phase I study (23) showed that the recommended dose (RD) was 55.3 mg/m^2/day (80 mg/day, if body surface area was 1.5 m^2) and dose-limited toxicity was mucositis; a Grade 3 acute adverse event that occurred to the patients who received whole-neck irradiation. Thus, in the present study, we selected the patient with early GC, which requires only small-field irradiation. We initiated a prospective study of concurrent CRT (CCRT) with S-1 for patients with early GC, primarily T2 cases, using the dose established in the phase I study to evaluate the efficacy and safety of the protocol.

Patients and Methods

Eligibility criteria. Patients with histologically- or cytologically-confirmed glottic squamous carcinoma and measurable disease, at a mainly T2 GC without evidence of distant metastases, were eligible for this study. We excluded T2 cases with impaired vocal cord mobility (T2 impaired). Even a T1b stage tumor was considered eligible if it was bulky.

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Key Words: Head and neck cancer, S-1, early glottic cancer, concurrent chemoradiotherapy, phase I/II study, prospective study, recommend dose, radiosentitizer.

Table I. *Patients' characteristics*.

Characteristics	Number of patients, n=13 (%)
Age at diagnosis (years)	
Median (range)	67 (59-75)
Sex	
Male	12 (92.3)
Female	1 (7.7)
Smoker	
Current	11 (84.6)
Former	1 (7.7)
Never	1 (7.7)
ECOG performance status	
0	10 (76.9)
1	3 (23.1)
T classification	
T1b	1 (7.7)
T2	12 (92.3)

ECOG, Eastern Cooperative Oncology Group.

Table II. *Clinical course of the 13 patients*.

Case	Age/ sex	T-stage	S-1 (days)	RT (Gy)	Admission	Response
1	62/M	1b (involve anterior commissure)	30	60	○	CR
2	59/M	2 (supraglottic)	27	60	○	CR
3	64/M	2 (supraglottic)	30	60	○	CR
4	60/F	2 (supraglottic)	30	60	○	CR
5	64/M	2 (supraglottic)	30	60	○	CR
6	70/M	2 (supraglottic)	30	60	○	CR
7	67/M	2 (transglottic)	30	60	○	CR
8	62/M	2 (subglottic)	20	70	-	CR
9	69/M	2 (supraglottic)	30	60	○	CR
10	75/M	2 (subglottic)	30	60	○	CR
11	72/M	2 (subglottic)	30	60	○	CR
12	72/M	2 (supraglottic)	30	60	-	CR
13	67/M	2 (transglottic)	30	60	○	CR

S-1, total duration of administration; RT, radiotherapy (total radiation dose (Gy)); ○, admitted to hospital; CR, complete response; supraglottic/ subglottic, extention to the supraglottis/subglottis; transglottic, vertical crossing of the glottis, as in the spread of carcinoma from the supraglottic to the subglottic area.

TNM staging was evaluated by endoscope, computed tomography (CT) scan, magnetic resonance imaging (MRI) according to the 2002 staging classification system of the Union International Contre Le Cancer (UICC) (24). Additional eligibility criteria included age 20-75 years, no prior chemotherapy or history of radiotherapy to the planned irradiation area, Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, projected life expectancy of at least 3 months and adequate bone marrow, liver, and kidney functions.

The present study was approved by the Investigational Review Board of our hospital (No. 158034) and written informed consent was obtained from all participants prior to enrollment.

Treatment schedule. The treatment schedule has been described previously in our phase I study (23). S-1 was given in an oral tablet form as formulated by Taiho Pharmaceutical Co. (Tokyo, Japan). S-1 was taken orally once daily after breakfast and RT with 2 Gy/ day, five days/ week, to a total of 30 fractions (total dose of 60 Gy), was delivered. Oral S-1 and radiotherapy were started on the same day and RT was performed between 3 and 6 hours after oral administration of S-1. S-1 was not administered on Saturdays or Sundays, when RT was not performed. The dose of S-1 was 55.3 mg/m^2/ day, which was determined to be the RD in our phase I study (23).

Radiotherapy. Conventional RT was performed with 4-MV photons at 2 Gy/ fraction/ day. The total dose delivered was 60Gy/ 30 fractions over a 6-week period. RT was planned for all patients after appropriate immobilization, with a thermoplastic mask and 3D CT-based techniques. Two parallel-opposed lateral fields were used with a pair of wedge filters. The field size was 6×6 cm at the start of therapy and was reduced to 5×5 cm after administration of 40 Gy according to reduction of the size of tumor.

Evaluation of response and toxicity. At 1 to 2 months after the end of CCRT, the clinical response was assessed for each patient according to the combined findings of fiberscope, CT scanning or MRI. A clinical complete response (cCR) was defined as a complete disappearance of all measurable lesions by fiberscope, without any evidence of progression or lymph node metastases by CT or MRI.

Patients were monitored for toxicity throughout the treatment. Complete blood counts and blood chemistry measurements were conducted weekly; urinalysis was performed twice a week until CCRT. Adverse events were classified according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0.

Statistical analysis. The primary endpoint was response rate; secondary endpoints were completion rate, progression-free survival (PFS), local control (LC), overall survival (OS) and toxicity. The completion rate was determined as the proportion of patients who completed the treatment. LC was defined as the time until an event of local disease progression or a residual tumor. OS was defined as the time from date of registration to date of death and PFS as the time from registration to documented progression or death from any cause, whichever occurred first. The rates of PFS, LC and OS analyses were all estimated using the Kaplan-Meier method. The statistical data was obtained using an SPSS software package (SPSS 11.0 Inc. Chicago, IL, USA).

Results

Patients' characteristics (Table I). A total of 13 patients who were enrolled in the trial at the Nagoya University Hospital between January 1, 2007 and December 31, 2012 were eligible. The median patient age was 67 years (range=59-75 years); 12 patients (92.3%) were male and 1 patient (7.7%)

was female. Most patients were current smokers. The primary symptom in all patients was hoarseness. One patient (7.7%) had a T1b tumor that involved the anterior commissure (bulky) and 12 patients had T2 tumors (92.3%); in 7 cases, the tumor extended to the supraglottis; in 3 cases, the tumor extended to the subglottis; and in 2 cases, the tumors were transglottic.

Response and survival (Table II). Out of all 13 patients, 11 patients (84.6%) initiated CCRT in the hospital since this was a clinical study and 9 patients left the hospital before completion of therapy; the other 2 patients received outpatient care throughout the treatment course. The overall treatment time of all patients was 43 days (range=38-59 days).

The completion rate was 84.6% (11/13 patients). In two patients, CCRT was interrupted. One patient (case 2) showed a Grade 1 serum creatinine increase. His physician decided to stop the S-1 38 days after the start of therapy, but RT was continued to 60 Gy. Another patient (case 8) had Grade 1 fever. His physician decided to stop the S-1 and RT 29 days after the start of therapy because the origin of his fever could not be determined. After a 6-day treatment interruption, his fever declined and only RT was restarted to 70 Gy on the assumption that the therapy would be changed to RT alone at an early time point. At this point (December 11, 2014), the overall response rate was 100% (13/13) with all patients showing cCR. For the current analysis, the median follow-up time was 53 months (range=23-68 months). All patients who successfully achieved treatment completion remain alive without evidence of local recurrence or metastasis; thus, the 3-year PFS rates, the 3-year LC rates and 3-year OS rates are 100%.

Toxicity (Table III). The only severe acute toxicity was Grade 3 dermatitis in one patient (7.7%). In this patient, skin erosion emerged in the radiation field after 56 Gy had been administered. The skin erosion resolved following treatment with pasting medicine. With respect to late toxicity, no severe events (up to Grade 3) have been observed to date.

Table III. *Toxicities (NCI-CTC version2.0)*.

	Grade (% of patients) (n=13)				
	1	2	3	4	Grade 3 (%)
Acute					
Hematologic					
Leukopenia	0	0	0	0	0
Neutropenia	0	0	0	0	0
Anemia	1 (7.7)	0	0	0	0
Thrombocytopenia	0	0	0	0	0
GOT	1 (7.7)	1 (7.7)	0	0	0
GPT	4 (30.8)	1 (7.7)	0	0	0
Total bilirubin	0	2 (15.4)	0	0	0
Creatinine	2 (15.4)	0	0	0	0
Non-hematologic					
Mucositis	5 (38.5)	8 (61.5)	0	0	0
Nausea	0	0	0	0	0
Diarrhea	1 (7.7)	0	0	0	0
Dermatitis	6 (46.2)	6 (46.2)	1 (7.7)	0	7.7
Anorexia	1 (7.7)	0	0	0	0
Fever	1 (7.7)	0	0	0	0
Late					
Hypothyroidism	1 (7.7)	1 (7.7)	0	0	0

NCI-CTC, National Cancer Institute-Common Toxicity Criteria; GOT, glutamate oxaloacetate transaminase; GPT, glutamic pyruvic transaminase.

Discussion

RT is the most widely used definitive treatment for early GC with the intent to preserve the larynx (1, 2). However, the LC rate of T1b bulky and T2 GC for RT alone still leaves much to be desired (3-5, 25, 26). S-1 (12), a novel oral antitumor agent, is a combination of tegafur (a prodrug of 5-fluorouracil (5-FU)), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase) and oteracil potassium (a suppressor of gastrointestinal toxicities). The radiosensitizing effects of 5-FU are influenced by the concentration and duration of 5-FU during RT (27, 28). According to the comparison between once- and twice-daily administration of S-1, when the daily dose is the same, the blood concentration of 5-FU is higher with once-daily administration (29). We designed the present protocol on the hypotheses that we could obtain a higher sensitization effect by administering RT during the period of high S-1 blood concentration. There exist a number of mechanisms by which 5-FU could increase radiation sensitivity at the cellular level; one of them is through killing of S-phase cells, which are relatively radioresistant (27). Furthermore, the radiosensitizing effect of S-1 in a tablet form, *in vivo* and *in vitro*, has been reported by several investigators. Harada *et al*. reported that S-1 increases the *in vivo* radioresponse of tumor xenografts derived from oral cancer cells; furthermore, the authors reported that S-1 *in vitro* exerts an enhancing effect on radiation of these cells by suppressing the activation of Akt / PKB, an important survival signal (30, 31). Zeng *et al*. reported that S-1 enhances radiosensitivity by suppressing radiation-induced hypoxia-inducible factor-1 (HIF-1) activation and inducing endothelial cell apoptosis (32). Moreover, gimeracil may enhance the antitumor effect of irradiation through partial suppression of homologous recombination-mediated DNA repair in human cancer xenograft models *in vivo* (33, 34). These basic researches prove validity of our protocol.

Table IV. *Clinical studies of chemoraditation with S-1 for early glottic cancer.*

Authors (reference)	N	Radiation	S-1 (/day)	S-1 administration	Total dose of S-1 (mg/m^2)	Therapeutic effect (%)			Toxicity (≥Grade 3) (%)	
						RR	3-year LC	3-year OS	Dermatitis	Mucositis
Nonoshita *et al*. (19)2010	23	70 Gy/35 fr	65 mg/m^2 twice a day	4 weeks on-> 2 weeks off ->1 week on	2275	100	95.4	100	0	56.5
Nakayama *et al*. (20)2010	22	60 Gy/30 fr	80 mg/m^2 twice a day	3 weeks on-> 1 week off->2 weeks on	2800	100	94.7	85.4	-	22.7
Ikeda *et al*. (21)2008	12	60-70 Gy/ 30-35 fr	55.3 mg/m^2 twice a day	2 weeks on->2 week off (two cycles)->1 week on	1936	100	-	-	16.7	16.7
Tsuji *et al*. (22)2006	9	60 Gy/30 fr	55.3 mg/m^2 once a day	2 weeks on-> 2 week off->2 weeks on	1659	88.9	-	-	0	0
Present study	13	60 Gy/30 fr	55.3 mg/m^2 once a day	Concomitantly with irradiation	1659	100	100	100	7.7	0

RT, Radiotherapy; RR, response rate; LC, local control rate; OS, overall survival rate.

Clinicians have reported several S-1-based CCRT regimens for early GC (Table IV). In those studies, S-1 was administered for 2-4 weeks followed by 1-2 weeks, like an original S-1 dosage. On the other hand, in our protocol, S-1 was administered orally on the day of irradiation during RT. To our knowledge, no clinical trial with this protocol for early GC has been reported.

In the present study, acute toxicities, such as Grade 3 mucositis or dermatitis, had a less occurrence rate than in a recent study of CCRT for GC. The difference is likely related to a lower total dose of S-1 used in the current study. However, it is unclear whether a twice-daily administration could increase the adverse event because few data are available to compare. Trotti *et al*. (6) reported that in RT-alone, total 70 Gy in 35 fractions, Grade 3 mucositis and dermatitis were seen in 4.2% and 5.0%, respectively. The result of this study and the present study show the comparable safety of our protocol with RT-alone. Although the sample size was small in the present study, the effectiveness compared favorably with that of the current study and superior to that of RT alone. However, we should compare the outcome carefully because T2 GC in the current study might include impaired cases, which we excluded. We excluded T2 impaired cases because the poor outcome of our experiments of CCRT with low-dose CDDP/5FU (11, 26) for T2N0 GC indicated the inefficacy of S-1 for those cases. In contrast, we included T1 bulky cases because the 5-year LC rate reported (25, 26) was as poor as that of T2 cases. As a practical treatment, in our Institution, we have administered CCRT with high-dose CDDP (and 5-FU) for T2 impaired cases. The good outcome in the present study might be caused by an appropriate selection of patients and show the eligible patients for our protocol and the need for the individualized therapy of early GC.

The other objective of this protocol was to establish outpatient care. Because this is a once-daily after breakfast therapy, we can confirm whether patients have taken S-1 on the days of irradiation and maintain good compliance. Moreover, our method shortens the treatment period to about 6 weeks from 7 weeks in the conventional RT for early GC, which lightens the burdens of both the medical facilities and patients and makes outpatient treatment possible.

For the future, in order to show the superiority of our methods, a phase II study at multiple Institutions and randomized trials of RT-alone *versus* CCRT with S-1 are required.

Conclusion

CCRT using S-1 for early GC achieved good LC and showed safety. In addition, the present findings indicate that CCRT with our protocol is easier than the usual methods, thus making outpatient treatment possible.

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