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Early glottic cancer treatment with concurrent chemoradiotherapy with once-daily orally administered S-1

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ABSTRACT

Glottic carcinoma is the most common laryngeal cancer. The outcomes for T1 bulky Glottic carcinoma and T2N0 Glottic carcinoma after radiation therapy alone are unsatisfactory. This study was conducted to evaluate the efficacy and safety of unique concurrent chemoradiotherapy regimen using S-1 for early glottic cancer. Concurrent chemoradiotherapy consisted of 60 Gy in 30 fractions with once-daily, orally administered S-1 exclusively within three to six hours prior to each irradiation. Twenty-one consecutive patients treated with this regimen were retrospectively reviewed. Initial complete remission was achieved in all patients without any subsequent local and/or regional recurrences to the last follow-up. The 4-year local control, overall survival, and disease-free survival rates were all 100%. No significant toxicities were observed, except for three cases with Grade 3 acute dermatitis.This regimen is highly effective and well-tolerated, and these results encourage further research to long-term efficacy and functional preservation.

Keywords: early glottic carcinoma, radiation therapy, concurrent chemoradiotherapy

Abbreviations:
GC: glottic carcinoma
RT: radiation therapy
CCRT: concurrent chemoradiotherapy
LC: local control

INTRODUCTION

Glottic carcinoma (GC) is the most common laryngeal cancer. Because of symptomatic hoarseness, it is usually detected early. The recommended treatment for early GC with the intention to preserve the larynx is radiation therapy (RT), transoral laser therapy, or a partial laryngectomy.[1,2] For patients with unfavourable or deeply invasive T2N0 GC, concurrent chemoradiotherapy (CCRT) with cisplatin is recommended.[2] For T1N0 GC, the local control (LC) rate with RT alone has been reported to range from 82% to 93%.[3,4] However, the outcomes for T1 bulky GC

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and T2N0 GC after RT alone are unsatisfactory; the LC rate has been reported to range from 74% to 76% and from 65% to 80%, respectively.[5,6,7]

Various CCRT regimens with several antineoplastic agents have been adopted to improve the LC rate for T2N0 GC; however, the optimal regimen is still undetermined. S-1 is an orally administered antineoplastic agent that was found to be effective against a variety of solid tumours including head and neck cancer. Additionally, it has been reported that S-1 acts not only as an antitumor medication but also as a radiosensitizer.[8,9,10,11,12] Therefore, we conducted a phase I study of patients with head and neck cancer at the Nagoya University Hospital from February 2004 to June 2007. The results of the study concluded that 55.3mg/m^2/day was the recommended dose for phase II study which we have previously reported with 14 patients.[13,14] With the successful outcome of phase II study, our institution has treated favourable T2N0 or T1 bulky N0GC with this regimen until 2016.

The purpose of the present study was to review the clinical outcomes of favourable T2N0 GC and T1 bulky N0 GC and to evaluate the feasibility, efficacy, and potential toxicity of our protocol.

MATERIALS AND METHODS

This study was approved by the institutional review board and the ethics committee of the Nagoya University Hospital, after which clinical records of each patient were collected retrospectively.

Patient Population

The clinical records of 21 consecutive patients who received definitive CCRT for favourable T2N0 or T1 bulky N0 glottic squamous cell carcinomas between January 2007 and December 2016 were reviewed. All tumours were staged according to the 2002 Union for International Cancer Control staging classification system.[15] Favourable T2 was defined as a superficial tumour on radiographic imaging with normal cord mobility. T1 bulky was defined as a tumour involving an entire true vocal cord and/or a horseshoe-shaped tumour involving the anterior commissure plus more than one third of both true vocal cords.6 Twenty (95%) were male and one (5%) was female. The median patient age was 66 years (58–75 years), and the median study follow-up time was 4years (2.0–9.0 years). Patient characteristics are described in Table 1. The tumours of 3 patients (14%) were classified as favourable T2N0 and those of 18 patients (86%) as favourable T1 bulky N0. According to the Eastern Cooperative Oncology Group criteria, the performance status was 0 for 13 patients (62%) and 1 for 8 patients (38%).

Concurrent Chemoradiotherapy

Our CCRT protocol has been described in a previous report.[14] To summarize briefly, oral S-1 and RT were initiated on the same day. S-1 was taken only once a day after breakfast, and RT was delivered 3–6 hours afterwards. The dose of S-1 was 55.3 mg/m^2/day, which was determined by our phase I study.[13] RT consisted of 2.0 Greys (Gy)/fraction/day, 5 days/week, for a total of 30 fractions. On the days when RT was not performed, S-1 was also not administered. RT was initiated after appropriate immobilization with a thermoplastic mask and 3D CT-based techniques. All patients underwent RT with a 4-MV photon beam using parallel opposed lateral fields. Pairs of wedge filters were used for better dose homogeneity.

Table 1 Ptatients' characteristics

Characteristics	Number of patients n = 21 (%)
Age at diagnosis (years)	
Median (range)	66 (58–75)
Sex	
Male	20 (95)
Female	1 (5)
ECOG performance status	
0	13 (62)
1	8 (38)
Smoker	
Current	12 (57)
Former	7 (33)
Never	2 (10)
History of habitual drinking	
Yes	14 (67)
No	7 (33)
T classification	
T1 bulky	3 (14)
T2 favorable	18 (86)
Anterior commisure invasion	
Yes	6 (29)
No	15 (71)

ECOG: Eastern Cooperative Oncology Group

Evaluation Of Response And Toxicity

The outcomes of this study were: clinical response after primary CCRT, the LC rate, overall and disease-free survival rate, and CCRT protocol completion rate and toxicity. A clinical complete response was recognized according to the combined results from fiberscope, computed tomography, and/or magnetic resonance imaging, which were performed 1 to 2 months after the end of CCRT. A clinical complete response was defined as the complete disappearance of all measurable lesions as observed with a fiberscope, without any evidence of progression or lymph node metastases on computed tomography or magnetic resonance imaging. The completion rate was determined as the proportion of patients who completed both chemotherapy and RT according to the protocol. Adverse events were classified according to the Common Terminology Criteria for Adverse Events version 3.0.

Statistical analysis

Four-year LC, overall survival, and disease-free survival rates were calculated using the Kaplan-Meier method.

RESULTS

Completion Rate

CCRT was delayed or discontinued in 3 patients, reducing the CCRT protocol completion rate to 86% (18/21 patients). One patient with T2N0 GC showed a grade 1 serum creatinine increase on day 38 after treatment initiation. RT was continued up to 60 Gy without interruption, but S-1 administration was discontinued that day and was never restarted. Another patient with T2N0 GC had a grade 1 fever on day 29. Since the cause of the fever could not be determined, both S-1 administration and RT were delayed. After the fever resolved, only RT was restarted on day 34 and continued to 70 Gy. The third patient who had T1 bulky N0 GC was taking warfarin regularly, and subcutaneous bleeding was detected on day 32. Considering that S-1 may have amplified the anticoagulant effect of warfarin, S-1 administration was discontinued on day 32. RT, however, was continued up to 60 Gy without interruption.

Response and Survival

For all 21 patients, clinical complete response was achieved, and all were alive without any evidence of local recurrence or metastases at the last follow up. Thus, the 4-year LC, overall, and disease-free survival rates were 100%.

Toxicity

The toxicities are summarized in Table 2. Grade 3 acute dermatitis in the radiation field was observed in 3 patients. However, all were healed by topical steroid and no other grade 3 or higher toxicities were observed.

Table 2 Toxicities (CTCAE version 3.0)

	Grade (% of patients) (n = 21)			
	1	2	3	Grade 4 or 5
Acute				
Hematologic				
Leukopenia	0	0	0	0
Neutropenia	0	0	0	0
Anemia	7 (33)	0	0	0
ALT	2 (9.5)	0	0	0
AST	2 (9.5)	0	0	0
Total bilirubin	2 (9.5)	1 (4.8)	0	0
Creatinine	2 (9.5)	0	0	0
Non-hematologic				
Dermatitis	10 (48)	8 (38)	3 (14)	0
Mucositis	7 (33)	14 (67)	0	0
Nausea	1 (4.8)	0	0	0
Diarrhea	2 (9.5)	0	0	0
Fever	1 (4.8)	0	0	0
Late				
Non-hematologic				
Hypothyroidism	1 (4.8)	1 (4.8)	0	0

CTCAE: Common Terminology Criteria for Adverse Events
AST: Aspartate aminotransferase
ALT: Alanine aminotransferase

DISCUSSION

Our group previously reported efficacy and safety of concurrent chemoradiotherapy unique regimen using S-1.[14] S-1 is one of the antineoplastic agents used for some CCRT regimens, is a combination of tegafur (a prodrug of 5-fluorouracil (5-FU)), gimeracil (an inhibitor of dihydropy - rimidine dehydro genase), and oteracil potassium (a suppressor of gastrointestinal toxicities).[16] The original S-1 dose was twice-daily for 28 days, followed by 14 days of rest. However, the optimal dosing and administration schedule for combining S-1 with RT has not been determined. The radiosensitizing effects of 5-FU are affected by the concentration and duration of 5-FU during RT.[17,18] A comparison of once- and twice-daily administrations of S-1, which result in the same total dosage, have demonstrated higher blood concentrations of 5-FU with once-daily administrations.[19] The CCRT protocol for favourable T2N0 or T1 bulky N0 GC in our institution was designed based on the hypothesis that a higher sensitization effect can be obtained by administering RT while keeping the S-1 blood concentration high. In the present study, we revaluated our regimen including newly treated 7 patients with longer follow-up period.

In the present study, the initial response rate was 100%, and the 4-year LC, overall, and disease-free survival rates were also 100%. Several reports on S-1-based CCRT regimens for early GC are shown in Table 3. Of these, our regimen adopted lowest RT dose and lowest total S-1 dosage. However, the effectiveness was still comparable to that of recent studies and superior to that of RT alone. This may be because there was no period when administration of S-1 was paused during treatment. However, it is necessary to consider the outcomes carefully because the sample size in the present study was small and because recent studies with S-1 regimens might include impaired cases of T2 GC, whereas ours did not. In our institution, CCRT with high-dose cisplatin and 5-FU is administered to patients with unfavourable T2 GC because of the poor outcomes found in our experiments with CCRT and low-dose cisplatin /5FU for T2N0 GC, which suggested that for those cases, S-1 was ineffective.[23,24] In contrast, we included T1 bulky cases because the low 5-year LC rate reported was equivalent to that of T2 cases.

Table 3 Clinical studies of CCRT with S-1 for early glottic cancer

Authors	N	Radiation	S-1 dosage per day	S-1 schedule	total S-1 dosage (mg/m^2)	Therapeutic effect (%)			Toxicities (≧Grade 3) (%)	
						RR	3-year LC	3-year OS	Dermatitis	Mucositis
Nonoshita et al[20] 2010	23	70 Gy /35 fr	65 mg/m^2 twice a day	4 wks On /2 wks Off /1 wk On	2275	100	95.4	100	0	56.5
Nakayama et al[21] 2010	22	60 Gy /30 fr	80 mg/m^2 twice a day	3 wks On /1 wk Off /2 wks On	2800	100	94.7	85.4	N/A	22.7
Ikeda et al[22] 2008	12	60–70 Gy /30–35 fr	55.3 mg/m^2 twice a day	2 wks On /2 wks Off /1 wk On	1936	100	N/A	N/A	16.7	16.7
Present study	21	60 Gy /30 fr	55.3 mg/m^2 once a day		1659	100	100 (4 year)	100 (4 year)	14	0

CCRT: Concurrent chemoradiotherapy
RR: Response rate
LC: Local control rate
OS: Overall survival rate
N/A: not available
Wk: week

With regard to adverse events, the rate of grade 3 dermatitis is slightly higher (14%, 3 out of 21 patients) in the present study than our previous report (7.7%, 1 /14 patients). Although, JCOG0701, led by Kodaira et al, documented that standard fractionated RT (66–70 Gy in 2.0 Gy/fraction over 7 weeks) without chemotherapy resulted in 4.0% (7/177) developing grade 3 mucositis and 10.2% (18/177) developing grade 3 dermatitis.[25] The Grade 3 dermatitis in present study population still can be comparable with that of recent studies with S-1 regimens and RT alone. Recent studies with S-1 regimens shown in Table 3 have also reported 16.7–56.5% of cases developed grade 3 or higher mucositis. However, no mucositis grade 3 or higher was seen in the present study. This may be because the total dose of S-1 was lower than that in other studies.

Since S-1 is an oral agent, patients can receive outpatient RT and follow an S-1 regimen. There is little question that oral chemotherapy has many potential benefits regarding patients' quality of life. Liu et al reported that patients prefer oral to intravenous chemotherapy providing that efficacy is not compromised.[26] However, adherence to S-1 is a concern. The adherence rate to antineoplastic agents can be low, and nonadherence may have a negative impact on the treatment of the malignancy. In their review, Greer et al documented that the rate of adherence to antineoplastic agents ranged from 46% to 100% and that self-reported adherence rates tended to be higher than those calculated based on pharmacy data or electronic medication event monitoring systems.[27] The S-1 administration protocol adopted in the present study was simpler than the original in 2 respects. First, patients took S-1 only once a day on weekdays. Second, there was no period of time during the treatment when administration of S-1 was paused. In addition, medical workers could confirm that patients took the S-1 by asking the patients or examining empty capsules before RT. This simple and monitorable protocol may assist patients in taking S-1 as prescribed.

CONCLUSION

Although the limitations of this retrospective study include the small sample size and relatively short follow-up period, CCRT with once-daily administration of S-1 for early GC is feasible, well tolerated, and effective.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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