Concurrent Chemoradiotherapy with S-1 for T2N0 Glottic Squamous Cell Carcinoma

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In this study, we evaluated the feasibility, efficacy and toxicity of concurrent chemoradiotherapy with S-1 (tegafur-gimeracil-oteracil potassium) for T2N0 glottic carcinoma. A total of 23 patients with T2N0 glottic carcinoma received chemoradiotherapy with S-1. Radiotherapy consisted of five daily fractions of 2 Gy per week, to a total median dose of 70 Gy. S-1 was administered 65 mg/m² per day for 4 weeks, beginning on the day therapy was started, followed by 2 weeks off the drug and twice a day until the end of radiotherapy. Initial local control rate of the primary tumor was achieved in all patients. The median follow-up period for all patients was 38 months. The 3-year local control rate was 95.4%. Regarding adverse reactions, grade 3 mucositis upon clinical examination, mucositis upon functional/symptomatic examination, dysphagia, hepatic toxicity and anemia were observed in 13, 2, 2, 1 and 1 patients, respectively. This chemoradiotherapy did not result in grade 4 acute toxicity or severe late toxicity. Chemoradiotherapy with S-1 was feasible, well tolerated and effective. This therapy is suggested as a possible regimen for improving local control of T2N0 glottic carcinoma.

INTRODUCTION

Definitive radiotherapy is indicated as the primary treatment for early glottic carcinoma. Radiotherapy has the advantage of preserving laryngeal structure and function in the majority of patients. The 5-year local control rates with radiotherapy alone range from 81% to 94% for T1N0 glottic carcinoma and from 67% to 80% for T2N0 glottic carcinoma (T2N0GC).1–4) In cases of T2N0GC, local control with RT alone could be improved upon. To improve the local control rate of T2N0GC, clinicians have begun to perform concurrent chemoradiotherapy (CCRT).5–8) Among chemotherapeutic agents, S-1 is an oral antitumor agent that consists of tegafur and may act as a radiosensitizer. Preclinical and clinical studies have demonstrated the radiosensitizer potency of S-1.9–12)

In our institution, CCRT with S-1 has been used for patients with T2N0GC since 2003. In the present study, we reviewed the clinical outcome of CCRT with S-1 for T2N0GC and evaluated the feasibility, efficacy and toxicity of this regimen.

MATERIALS AND METHODS

The records of 29 patients treated consecutively with definitive radiotherapy to T2N0 glottic squamous cell carcinoma as a primary treatment modality for larynx preservation, according to the International Union Against Cancer (UICC, 1997) TNM classification system between February 2003 and July 2008 were reviewed. Six patients were excluded from analysis because they could not receive concurrent chemoradiotherapy with S-1, due to renal failure (n = 4), liver dysfunction (n = 1) or poor performance status (n = 1). All patients were men, and the median age was 64 years (range 52–78 years). Performance status was between 0 and 1, according to Eastern Cooperative Oncology Group criteria. Radiotherapy was delivered five days a week using a once-daily fractionation of 2.0 Gy; the median total radiation dose was 70 Gy (range: 62–70 Gy). Three patients, who discontinued at 62 Gy, 66 Gy and 68 Gy, respectively, refused further radiotherapy. Four patients underwent radio-
therapy with a 6-MV photon beam and 19 patients with a 4-MV photon beam. Parallel-opposed lateral fields were used and a median field size was 36 (ranging from 28 to 42 cm²). Appropriate wedge filters were used to improve dose homogeneity. S-1 was administered 65 mg/m² per day for 4 weeks, beginning on the day therapy was started, followed by 2 weeks off the drug and then twice a day until the end of radiotherapy. A metachronous malignant tumor of another primary organ was observed in 6 patients. Gastric cancer was observed in 2 patients, mesopharyngeal cancer in 1, esophageal cancer in 1, colon cancer in 1 and thyroid cancer in 1. No synchronous malignant tumors were detected. All patients were treated on an inpatient basis. Initial responses were evaluated with transnasal laryngoscopy four weeks after completion of the concurrent chemoradiotherapy.

The estimated overall survival rate and local control rate were calculated using the Kaplan-Meier method. Toxicity was assessed during and after treatment, using the Common Terminology Criteria for Adverse Events, version 3.0.

RESULTS

The follow-up period for all patients was 6–68 months (median: 38 months) and follow-up period was relatively short. The overall treatment time of all patients was 50–102 days (median: 59 days). Twelve patients interrupted radiotherapy, and the most common causes were mucositis pain (42%) and evaluation of the effect of treatment (42%). S-1 was administered to all patients for over 4 weeks. Because of toxicities (grade 3 anemia, grade 3 hepatic toxicity and grade 3 mucositis upon functional/symptomatic examination), S-1 administration was interrupted in 3 patients. Initial local control of the primary tumor was achieved in all patients. One patient experienced local recurrence and underwent total laryngectomy 8 months after completion of CCRT. The estimated curve of local control is shown in Fig. 1. The 3-year overall survival rate, 3-year cause-specific survival rate and 3-year local control rate of all patients were 100%, 100% and 95.4%, respectively. One patient died of thyroid cancer 38 months after treatment; however, local control of this patient’s glottic carcinoma was maintained.

The treatment-related acute toxicities are summarized in Table 1. Regarding non-hematological toxicity, grade 3 mucositis upon clinical examination was observed in 13 patients. Grade 3 mucositis upon functional/symptomatic examination and dysphagia were each observed in 2 patients. Grade 3 hepatic toxicity was observed in 1 patient. Regarding hematological toxicity, grade 3 or greater toxicity was not observed except in one patient with grade 3 anemia. This CCRT did not result in severe treatment-related late toxicity.

DISCUSSION

In most institutions, early glottic carcinoma is treated with conventional radiotherapy as primary treatment for laryngeal preservation. A standard course of radiation for early glottic cancer usually consists of a total of 60–70 Gy administered in single daily fractions over 6 weeks. For early glottic carcinoma, the published dose-response curves for local control appear to be shallow in the dose range between 60 Gy and 70 Gy.13,14) Although Akine et al. documented that local control rates have a tendency to increase as the total radiotherapy dose increases in the range of 57.5 Gy to 72.5 Gy,15)
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treatment with conventional radiotherapy alone for local control of T2N0GC is thought to be improved upon; the 5-year local control rate ranged from 67% to 80%. To improve the local control rate, clinicians have performed CCRT for T2N0GC and CCRT has been reported to be effective. Itoh et al. reported that administration of low-dose cisplatin and 5-fluorouracil resulted in an initial local control rate of 91.0% and ultimate laryngeal preservation by cordectomy in all cases.5) Akimoto et al. documented that administration of cisplatin (CDDP) alone, CDDP plus docetaxel or docetaxel alone resulted in a 5-year disease-free survival rate of 91.8%. Niibe et al. reported that administration of UFT resulted in a 3-year local control rate of 90.1%. 7) Nishimura et al. documented that administration of carboplatin and UFT resulted in a 5-year larynx preservation survival rate of 93.3%. 8) In the present study, the initial local control rate was 100% and the 3-year local control rate 95.4%, which are nearly the same as the rates of previous studies. Beam energy, field size, daily fraction size, prolonged overtreatment time, impaired cord mobility, anterior commissure involvement and low pretreatment hemoglobin level have been reported as important prognostic factors for local control.16,17) There were no poor prognostic factors applied to the recurrent case in our study.

Among chemotherapeutic agents, S-1 is an oral antitumor agent consisting of tegafu, 5-chloro-2, 4-dihydroxypyridine (CDHP) and potassium oxinate in a molar ratio of 1:0:4:1. Tegafu is a prodrug of 5-fluorouracil (5-FU), and CDHP and potassium oxinate prolong a higher concentration of 5-FU in the bloodstream and diminish the toxicity of 5-FU.18) Although CCRT with S-1 is not considered the standard therapy for head and neck cancer, preclinical and clinical studies have demonstrated the radiosensitizing potency of S-1 and, in this study, S-1 was administered as a radiosensitizer. Harada et al. documented that S-1 greatly enhanced radiosensitivity by suppressing the activation of Akt/PKB.9) Zeng et al. reported that S-1 enhanced radiation-induced apoptosis of endothelial cells by suppressing hypoxia-inducible factor-1 (HIF-1) activity, resulting in increased radiosensitivity.10) In clinical data, Niibe et al. documented that administration of S-1 resulted in a 3-year local control rate of 100% in the 24 T2N0GC patients treated with CCRT using S-1.11) Tsukuda et al. reported that in CCRT with S-1 for locally advanced squamous cell carcinoma of the head and neck, pathologically, complete response rates were 93% in stage III and 54% in stage IV tumors.12) The potency of S-1 as a radiosensitizer has also been demonstrated in other solid tumors, with response rates of 24% for pancreatic cancer,13) 74% for esophageal cancer14) and 22% for lung cancer.15)

With regard to adverse reactions to S-1 for head and neck cancer, Harada et al. documented that administration of S-1 for 2 weeks followed by 1 week of rest or 4 weeks followed by 2 weeks resulted in grade 3 toxicity rates for mucositis, liver dysfunction, leukocytopenia, neutropenia and anemia of 15%, 7%, 11%, 11% and 4%, respectively.11) Tsukuda et al. reported that administration of S-1 for 2 weeks followed by 1 week of rest resulted in grade 3 toxicity rates for mucositis, leukocytopenia and neutropenia of 20%, 6% and 12%, respectively.12) Tsuji et al. documented that administration of S-1 for 2 weeks followed by 2 weeks of rest resulted in grade 3 toxicity rates for mucositis, dysphagia and dermatitis of 5%, 5% and 19%, respectively.22) As previously indicated, in the past studies, CCRT for head and neck cancer with S-1 has been reported to be performed with tolerable adverse events. In the present study, with administration of S-1 for 4 weeks followed by 2 weeks of rest, although grade 3 mucositis upon clinical examination was observed in 13 patients (57%), the grade 3 toxicity rate of mucositis upon functional/symptomatic examination and dysphagia were only 8% and 8%, respectively. Grade 3 toxicity rates of anemia and liver dysfunction were 4% and 4%, respectively, and no grade 4 toxicity was observed. Harada et al. documented that a 2-week application followed by a 1-week rest regimen for oral squamous cell carcinoma reduced adverse reactions and enhanced therapeutic effects, compared with a 4-week application followed by a 2-week rest regimen.11) The optimal schedule of CCRT with S-1 for T2N0GC has not yet been established, so it is important to take the balance between treatment effect and toxicity into account. We need to determine the optimal schedule of CCRT with S-1 for T2N0GC.

Although there are several shortcomings of this retrospective study, including the small patient number and a relatively short follow-up period, we find that concurrent chemoradiotherapy with S-1 for T2N0GC is feasible, well tolerated and effective. This therapy is suggested as a possible regimen to improve the local control of T2N0GC.

REFERENCES


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