Phase II Study of Concurrent Chemoradiotherapy with S-1 in Patients with Stage II (T2N0M0) Squamous Cell Carcinoma of the Pharynx or Larynx

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Received July 9, 2014; accepted September 9, 2014

Objective: The goals of treatment for head and neck cancer are cure and organ-function preservation. For organ preservation, primary treatment via radiotherapy alone is thought to be insufficient for Stage II squamous cell carcinoma of the larynx, oropharynx or hypopharynx. The objective of the present study was to investigate the efficacy and safety of concurrent chemoradiotherapy with S-1 for patients with Stage II squamous cell carcinoma of the pharynx or larynx for primary organ preservation.

Methods: Previously untreated patients with Stage II squamous cell carcinoma of the larynx, oropharynx or hypopharynx received three courses of S-1 (40 or 50 mg twice a day; 2 weeks of administration followed by 1 week of rest every 3 weeks) during conventional radiotherapy (a single daily fraction of 1.8 Gy) to a total dose of 70.2 Gy. The primary endpoint was the local control rate at 3 years.

Results: From August 2009 to October 2012, 37 patients were evaluated for the study. The overall response rate was 100%. The 3-year local control rate was 89.0% (95% confidence interval, 78.9–99.2%), and the 3-year overall survival rate was 97.2% (95% confidence interval, 91.8–100%). Mucositis and dermatitis in the radiation field were the most common acute adverse events observed. The rates of Grade 3 mucositis and dermatitis were 27 and 35%, respectively. No patients experienced Grade 4 acute adverse events. The treatment completion rate was 89.2%.

Conclusion: Concurrent chemoradiotherapy with S-1 was safe and effective in improving local control for Stage II squamous cell carcinoma of the pharynx or larynx.

Key words: chemoradiotherapy – S-1 – laryngeal cancer – oropharyngeal cancer – hypopharyngeal cancer
INTRODUCTION

Radiotherapy (RT) is the most widely used primary treatment for early-stage squamous cell carcinoma (SCC) of the head and neck. The goals of treatment for head and neck cancer are cure and organ-function preservation.

The disease-specific survival rates after RT alone as primary treatment for SCC of the larynx, oropharynx or hypopharynx were 86–100% for Stage I (T1N0M0) tumors, and 79–100% for Stage II (T2N0M0) tumors (1–7). Regarding the survival rate, RT alone is thought to be adequate for Stage I–II tumors of these primary sites.

The local control rates (LCRs) after RT alone for SCC of the larynx or oropharynx were 77–100% (2–6,8) for Stage I tumors. However, for Stage II tumors, the LCRs after RT alone for SCC of the larynx, oropharynx or hypopharynx were 62–80% (2–4,6–8). For local control and organ preservation, primary treatment via RT alone is thought to be insufficient for Stage II SCC of these primary sites.

Transoral surgery, open partial laryngectomy or pharyngectomy are considered alternative primary treatments and salvage surgery for early-stage SCC of the larynx (3,5), oropharynx (9,10) or hypopharynx (11,12). The transoral approach for laryngeal cancer has been reported to result in poor voice quality, because voice quality after transoral excision for glottic lesions is closely associated with the extent of the resection (3), particularly in patients with T2 tumors. Hemilaryngectomy has also been reported to result in poor voice quality (13). The use of transoral surgery for T2 tumors in oropharyngeal cancer is limited by tumor size, subsite or deep invasion to the tongue base or constrictor muscles (9,10).

In patients with hypopharyngeal cancer who received transoral laser surgery with or without post-operative RT, the voice quality (13). The use of transoral surgery for T2 tumors also performed.

Therefore, with the aim of improving the LCR with primary RT and minimizing the need for salvage surgery, concurrent chemoradiotherapy (CCRT) with S-1 in patients with Stage II SCC of the larynx, oropharynx or hypopharynx was used. S-1 is an oral fluoropyrimidine developed to improve the tumor-selective cytotoxicity of 5-fluorouracil (5-FU) and reduce gastrointestinal toxicity through the addition of two modulators, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) (14).

The results of a Phase II clinical trial of CCRT (RT with S-1) designed to evaluate its efficacy and tolerability in patients with Stage II (T2N0M0) SCC of the larynx, oropharynx or hypopharynx are reported.

PATIENTS AND METHODS

PATIENT ELIGIBILITY CRITERIA

Patients from four institutions were enrolled into the study. Eligible patients had to have a previously untreated, measurable and histologically proven SCC of the larynx, oropharynx or hypopharynx. Additional criteria were: Stage II cancer without synchronous multiple cancer, according to the 2002 staging system of the Union Internationale Contre le Cancer (UICC) sixth edition; performance status 0–1, according to the criteria proposed by the Eastern Cooperative Oncology Group (ECOG); age between 20 and 80 years; sufficient bone marrow function (neutrophil count ≥2000 cell/mm³, hemoglobin ≥10 g/dl, and platelet counts ≥100 000 mm³); no abnormalities of the liver, heart or lungs; creatinine clearance ≥60 ml/min; and a life expectancy of at least 3 months. Computed tomography (CT), magnetic resonance imaging and neck ultrasonography were performed in all patients to evaluate tumor extent and the presence of nodal metastases. To check for distant metastases, positron emission tomography or a combination of chest CT, abdominal ultrasonography and bone scintigraphy was performed. To evaluate synchronous multiple cancers, gastrointestinal fibersoncopy was also performed.

The study protocol was approved by the appropriate institutional review boards. All patients provided their written, informed consent. This study was registered with the University Hospital Medical Information Network Clinical trials registry (UMIN-CTR), identification number UMIN000002168.

TREATMENT SCHEDULE AND STUDY DESIGN

Enrolled patients received three courses of S-1 according to a schedule of 2 weeks of administration followed by 1 week of rest during RT. The daily dose of S-1 was 50 mg twice a day for patients with a body surface area (BSA) ≥1.5 m², or 40 mg twice a day for those with a BSA <1.5 m². The minimum dose of S-1 administered was 80 mg/day (40 mg twice a day).

RT was delivered in conventional fractions of 1.8 Gy to a total dose of 70.2 Gy, 5 days per week, using 4–6 MV X-rays. The radiation fields were set up as follows: the primary tumor alone for the glottic larynx; the primary tumor, and prophylactically, the bilateral cervical lymph node area (levels Ib–III) for the supraglottic larynx; the primary tumor, and prophylactically, the bilateral cervical lymph node area (levels Ib–IV) for the subglottic larynx; and the primary tumor, and prophylactically, the bilateral cervical lymph node area (levels Ib–IV and retropharyngeal lymph node area) for the oropharynx and hypopharynx. Lateral opposed fields were used for the glottic and supraglottic larynx. For the subglottic larynx, oropharynx and hypopharynx, radiation fields were lateral opposed fields to the upper neck and anterior field to the lower neck. The cervical lymph node area received prophylactic doses of 39.6–45 Gy.

STATISTICAL CONSIDERATIONS

The primary end point was the LCR at 3 years. The secondary endpoints were progression-free survival (PFS), relapse-free survival (RFS), overall survival (OS), acute adverse events (AAEs), treatment completion rate and response rate. LCR
and survival rates were estimated using the Kaplan–Meier method. Local control was defined as the absence of any residual or relapsed disease at the primary site, the absence of salvage surgery for the primary site and no death. PFS was defined as no progressive disease and no death, and RFS was defined as the absence of any relapse disease and no death. AAEs were assessed during the treatment and for 4 weeks after treatment using the 2009 Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Treatment completion criteria included the following: interruption of radiotherapy of < 1 week; 66 Gy or more total dose of RT; or 28 days or more total period of S-1 administration. The tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (15).

The sample size rationale and decision rules were based on a one-stage Fleming design with a 5% type I error (one-sided) and 80% power. For an expected 85% LCR at 3 years and a null hypothesis of 65%, 29 eligible patients were needed in this study. In anticipation of excluded cases due to ineligibility or other problems that would prevent participation, it was determined that 35 patients would need to be identified to obtain 29 eligible patients.

RESULTS

PATIENT CHARACTERISTICS

From August 2009 to October 2012, 39 patients were enrolled and 37 were evaluated for the study; two patients were excluded because of ineligibility from synchronous double cancers. Patient characteristics are summarized in Table 1. Most patients (97%) were males. The primary tumor sites were mainly (70%) the larynx. With respect to the subsite of the larynx, 25 of 26 cases were glottic type and one was subglottic type. The median follow-up for all patients treated with CCRT was 43 (range, 18–56) months.

TREATMENT RESPONSE, LOCAL CONTROL AND SURVIVAL RATES

A complete response was observed in all patients at 4 weeks after CCRT; therefore the overall response rate was 100%. Three patients with SCC of the larynx underwent total laryngectomy for recurrent primary tumor. Only one patient died from retropharyngeal lymph node recurrence of SCC of the hypopharynx. The others were alive without remnant or relapsed disease. The 3-year LCR (primary endpoint) was 89.0% (95% confidence interval (CI), 78.9–99.2%) (Fig. 1). The 3-year OS rate was 97.2% (95% CI, 91.8–100%) (Fig. 2). Both the PFS and RFS rates at 3 years were 89.1% (95% CI, 79.0–99.2%).

AAEs and Treatment Completion Rate

AAEs for all patients are listed in Table 2. Mucositis and dermatitis in the radiation field were the most common AAEs observed. There were no patients experiencing Grade 4 AAEs. In three patients, chemotherapy was stopped after < 28 days of S-1 administration due to AAEs: febrile neutropenia, neutropenia or liver dysfunction. RT was interrupted for 7 days due to febrile neutropenia in one patient, but all patients completed the total radiation dose of 66–70.2 Gy (median 70 Gy). The treatment completion rate was 89.2% (33 of 37 patients).

Tube feeding was performed temporarily in six patients; five patients required nasogastric alimentation for difficulty of oral intake due to Grade 3 mucositis (larynx and hypopharynx one patient each and oropharynx, three patients), and one patient had a gastrostomy tube inserted to relieve passage obstruction due to hypopharyngeal tumor. This patient regained the ability for oral intake after the treatment and the gastrostoma was closed. No patients required a tracheostomy.

Table 1. Patient characteristics (n = 37)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients, n (%)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>68</td>
</tr>
<tr>
<td>Range</td>
<td>49–79</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (97)</td>
</tr>
<tr>
<td>Female</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>26 (70)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>6 (16)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Histopathological differentiation</td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>12 (33)</td>
</tr>
<tr>
<td>Moderately</td>
<td>19 (51)</td>
</tr>
<tr>
<td>Poorly</td>
<td>6 (16)</td>
</tr>
</tbody>
</table>

Figure 1. Local control rate (LCR). Kaplan–Meier estimate of local control in Stage II squamous cell carcinoma of the larynx, oropharynx or hypopharynx. The 3-year LCR is 89.0% (95% confidence interval, 78.9 to 99.2%).
DISCUSSION

In SCC of the head and neck (SCCHN), chemotherapy consists mainly of three drugs: platinum analog, 5-FU and/or taxanes. In a meta-analysis of chemotherapy in head and neck cancer (MACH-NC), the effects of a platinum analog were significantly higher than other agents when used as single-agent chemotherapy (16). In another meta-analysis, 5-FU as a single drug and cisplatin as a single drug or in combination with 5-FU showed the greatest benefit (17). However, when these agents are used at high doses, severe toxicity ensues from the nephrotoxicity and hemotoxicity of cisplatin or the mucositis and cardiotoxicity that occur with 5-FU. We designed a regimen based on divided low-dose administration of 5-FU alone to reduce toxicity. We chose S-1, which has pharmacokinetic properties resembling those of a 5-FU continuous intravenous infusion (18,19) and the advantage of being orally administrated, because the radiosensitizing efficacy of 5-FU depends strongly on exposure time to tumor cells (20,21). S-1 showed its own antitumor activity in patients with advanced or recurrent SCCHN in a Phase II trial, with an overall response rate of 28.8% (22). There have been several Phase I studies of CCRT with S-1 for SCC of the head and neck (23–27). The dose and schedule of S-1 administration in CCRT were different in each report, because they were not standardized. Therefore, we previously performed a pilot study involving 12 patients with Stage II SCC of the glottic larynx with the same dose and schedule as in the present study (28).

In the previous articles (2–4,6–8), 5-year LCRs were reported to be 62–80.4% for Stage II SCC of the larynx, oropharynx or hypopharynx treated with RT alone. In a retrospective analysis, it was reported that CCRT improved the LCR or the larynx-preservation rate significantly as compared with RT alone for patients with Stage II SCC of the larynx and hypopharynx (29–31). To improve the LCR with primary RT and to minimize the need for salvage surgery, clinicians have performed CCRT for Stage II SCC of the glottic larynx, and retrospective reports have found it to be effective (32–36). Although there has been a prospective examination of CCRT for Stage II SCC of the glottic larynx as a Phase II study, the sample size was not calculated to evaluate the LCR (25). Therefore, the present Phase II study of CCRT with S-1 was performed in patients with Stage II SCC of the pharynx or larynx with LCR as the primary endpoint. In retrospective analyses of CCRT, the 3-year LCRs were 87.7–95.4% for Stage II laryngeal cancer (32,35,36), and the 5-year LCR was 79.3% for Stage I–II hypopharyngeal cancer (31). In the present study, S-1 chemotherapy was given concurrently with conventional RT for Stage II SCC of the larynx, oropharynx or hypopharynx, and a good result was obtained, with an OS rate of 97.2% (95% CI, 91.8–100%) and an LCR of 89.0% (95% CI, 78.9–99.2%) at 3 years.

The human papilloma virus (HPV) status of SCC of the oropharynx was not investigated in the present study. It has been considered that HPV-positive tumors have a tendency to metastasize early to lymph nodes, and the HPV-positive rate was found to be very low in Stage II SCC of the oropharynx (37). Although the minority of cases had primary cancer in the oropharynx in the present study, the detection of HPV status of SCC of the oropharynx is needed in a large-scale future study. The indication for CCRT needs to be discussed for HPV-positive patients with Stage II SCC of the oropharynx because of its high radiation-sensitivity (38).

In the study using RT alone as primary treatment, serious complications were observed in <5% of patients (39,40). In the present study, one patient (2.7%) experienced Grade 3 neutropenia and infection as severe AAEs and stopped chemotherapy and interrupted RT. These AAEs improved after chemotherapy discontinuation and administration of recombinant human granulocyte colony-stimulating factor and

Figure 2. Overall survival (OS) rate. Kaplan–Meier estimate of OS in Stage II SCC of the larynx, oropharynx or hypopharynx. The 3-year OS rate is 97.2% (95% confidence interval, 91.8–100%).

Table 2. Treatment-related acute adverse events (n = 37)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6</td>
</tr>
<tr>
<td>Anemia</td>
<td>30</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>24</td>
</tr>
<tr>
<td>ALT/AST</td>
<td>6</td>
</tr>
<tr>
<td>Creatinine</td>
<td>2</td>
</tr>
<tr>
<td><strong>Non-hematologic</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>5</td>
</tr>
<tr>
<td>Mucositis</td>
<td>2</td>
</tr>
<tr>
<td>Cardia</td>
<td>0</td>
</tr>
<tr>
<td>Skin (radiation field)</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
</tr>
</tbody>
</table>
antibiotics. Since this was a clinical study, all patients were hospitalized. With greater experience with this treatment, it is expected that outpatient-based treatment would be possible. However, in the present study, nasogastric tube feeding was required in five patients (13.5%), included one patient with severe AEs. In these patients, an inpatient setting may be needed in the middle of the treatment course.

In conclusion, the present data showed that a primary organ preservation treatment approach using CCRT with three courses of S-1 is feasible and tolerable for selected patients with Stage II SCC of the pharynx or larynx. Based on the high OS and LCR shown in the present study, a large, randomized comparison of CCRT with S-1 versus RT alone in patients with Stage II SCC of the larynx, oropharynx or hypopharynx should be conducted. In the present study, there were no criteria to choose the modality of treatment for Stage II, such as tumor bulkiness or vocal cord mobility impairment for the larynx. In fact, many patients with Stage II SCC of the larynx, oropharynx or hypopharynx for whom organ-function preservation surgery with the transoral approach would be inappropriate will be registered, and a subgroup analysis to explore the modality for Stage II will be performed in a large-scale future study of CCRT with S-1.

**Conflict of interest statement**

None declared.

**References**


