Efficacy and Toxicity of Concurrent Chemoradiotherapy with Nedaplatin and S-1 for Head and Neck Cancer

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Objective: We investigated the efficacy and toxicity of concurrent chemoradiotherapy with nedaplatin and S-1 for head and neck cancer, as an alternative to cisplatin and 5-fluorouracil.

Methods: A total of 31 patients were enrolled in this study. S-1 was administered orally twice a day for 14 days followed by a 2-week rest. Nedaplatin was intravenously administered on day 4. If possible, two courses of chemotherapy were performed. The radiotherapy was started concurrently with the administration of S-1.

Results: The overall complete response rate was 81%. The 2-year overall survival rate was 96%. The 2-year relapse-free survival rate was 94%. The main adverse events were hematological toxicity, mucositis and dermatitis.

Conclusions: Our findings suggest that this therapeutic regimen has either an equal or lower toxicity than the conventional cisplatin and 5-fluorouracil, and that it has equal efficacy with regard to the clinical response and short-term outcome. Moreover, it is possible to successfully perform this treatment in an outpatient setting.

Key words: head and neck cancer – concurrent chemoradiotherapy – nedaplatin – S-1

INTRODUCTION

Chemoradiotherapy has been frequently used in patients with head and neck cancer (HNC) because the preservation of organ function is important to maintain the quality of life, and HNC tumors are often unresectable. Concurrent chemoradiotherapy (radiotherapy plus concurrent chemotherapy) for HNC is superior to induction chemotherapy followed by radiotherapy or radiotherapy alone (1,2), and is commonly performed in many institutions.

Radiotherapy with cisplatin (CDDP) and 5-fluorouracil (5-FU) is one of the most popular regimens of chemoradiotherapy for HNC. However, this regimen is limited in its efficacy. Furthermore, CDDP is strongly nephrotoxic, and requires extensive hydration with saline. In addition, 5-FU requires continuous intravenous infusion for 120 h. This treatment presents a major burden for patients. In addition, adverse events such as nephrotoxicity, gastrointestinal symptoms and pancytopenia often occur. Other regimens that have better antitumor effects and lower toxicity are needed.

Nedaplatin (CDGP) is a platinum derivative that was developed as a less nephrotoxic agent (compared with CDDP), which does not require the same level of hydration as the older drug (3). Moreover, it was reported that CDGP is at least as effective as CDDP for HNC (4–6), and CDGP is efficacious and can be feasibly combined with 5-FU (7). S-1 is a novel oral antitumor agent, which consists of tegafur (FT), 5-chloro-2,4-dehydroxypyrimidine (CDHP) and potassium oxonate (Oxo). FT is a prodrug of 5-FU, CDHP enhances the serum 5-FU concentration and Oxo reduces adverse reactions in the digestive tract (8). In short, this drug was designed to enhance the efficacy of 5-FU by maintaining therapeutic plasma 5-FU concentrations for a long duration of time, and to reduce the gastrointestinal toxicity of FT (9,10).

We performed concurrent chemoradiotherapy with CDGP plus S-1 for HNC, because we hoped that this regimen might have greater antitumor effects and lower toxicity than CDDP and 5-FU. We herein report the safety and efficacy of concurrent chemoradiotherapy with CDGP and S-1 for HNC patients.

PATIENTS AND METHODS

Patients

Between September 2006 and May 2009, 31 patients with primary HNC at Ogaki Municipal Hospital, who had not
undergone any previous treatment, were enrolled in this study. The following eligibility criteria were used: histologically or cytologically confirmed head and neck squamous cell carcinoma; pathological stage II or higher (without distant metastasis) disease according to the TNM classification of the sixth UICC (11); Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1; age 20 years or older and no active concomitant malignancy.

Before receiving any treatment, all patients gave a complete history, and had a clinical ear, nose and throat examination, a complete blood cell count, serum chemistries (hepatic and renal function tests and electrolytes), electrocardiogram, chest X-ray, computed tomography (CT) or magnetic resonance imaging (MRI) of the head and neck and a gallium scan or positron emission tomography-CT scan.

TREATMENT OF PATIENTS

We referred to a clinical phase I trial of concurrent chemoradiotherapy combining S-1 plus CDGP and the other articles written about this regimen (12–14), and decided the dose and schedule of S-1 and CDGP based on these studies. S-1 was administered orally twice a day at the following dose on the basis of body surface area: 80 mg/mm² (maximum 120 mg/body), for 14 days followed by a 2-week rest. CDGP was administered intravenously at 90–100 mg/m² over a 2 h period on day 4. Immediately before treatment, all patients received antiemetic therapy with a steroid and a 5-HT₃ antagonist, followed by a dopamine antagonist. For hydration, 500 ml of normal saline was administered over a 1.5 h period. This schedule was repeated twice every 4 weeks.

After the first course of chemotherapy, if unacceptable toxicities that included Grade 1 or higher thrombocytopenia or Grade 2 or higher mucositis occurred, or a patient refused to continue, the second course of chemotherapy was not performed, or only S-1 was administered. When both types of toxicity occurred, the second course was not performed. When only thrombocytopenia or mucositis occurred, only S-1 was administered.

The radiotherapy was started concurrently with the administration of S-1, and was administered at 2 Gy per day 5 days per week. At the primary site, the total dose was as follows: larynx (70 Gy), and oropharynx and hypopharynx (60 Gy). In the cervical lymph nodes, the dose was 36–50 Gy. In cervical lymph node metastases of an unknown primary cancer, the dose was 60 Gy. The cervical lymph nodes were not irradiated in patients with T2N0 glottic carcinoma.

EVALUATION OF ANTITUMOR EFFECTS AND ADVERSE EVENTS

All clinical data were obtained retrospectively from the medical records.

To identify the antitumor effects of the combination treatment regimen, the clinical response and preliminary clinical outcomes were evaluated. The clinical response was assessed for each patient within 2 months after the end of treatment, based on the results of physical examination, laryngoscopy and CT or MRI, using the Response Evaluation Criteria in Solid Tumors (RECIST). The overall survival rate and relapse-free survival were calculated by the Kaplan–Meier method (15).

Adverse events were assessed during the treatment and for 4 weeks after treatment using the 2003 Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0).

RESULTS

PATIENT CHARACTERISTICS

A total of 31 patients were enrolled in the study. Table 1 lists the patient characteristics. Their median age was 66 years (range: 49–76 years). Eighteen patients had an ECOG PS of 0, and 13 had a PS of 1. The median length of follow-up was 22 months (range: 11–54 months). The primary sites were as follows: larynx (17 patients), oropharynx (10 patients), hypopharynx (3 patients) and unknown primary (1 patient). According to the Union International Contre le Cancer criteria, there were 14 patients with stage II disease, 5 with stage III disease, 8 with stage IVA disease and 3 patients with stage IVB disease (Table 2). The Tumor and Lymph Nodal classification is shown in Table 3. None of the patients had a T status of T4. Seventeen patients had lymph node metastases.

DELIVERY OF THE TREATMENTS

Radiotherapy was completed in all patients. Because one patient became severely depressed and temporarily refused treatment, he required an interruption of radiotherapy. A total of 30 patients (97%) received radiotherapy without interruption.

CDGP and S-1 were administered to all patients for at least one course, and 15 patients (48%) received two

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<tr>
<th>Table 1. Patient characteristics</th>
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<tr>
<td>Total</td>
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<td>Gender</td>
</tr>
<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<td>Age (years)</td>
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complete courses. Ten patients (32%) took only S-1 during the second course of chemotherapy. Six patients (19%) received only one course of chemotherapy, and two patients delayed receiving the second course.

**EFFICACY OF THE COMBINATION TREATMENT**

The clinical response of the patients is shown in Table 4. According to the primary site, 30 patients (97%) had a complete response (CR) and 1 patient (3%) had a partial response (PR). Of the 17 patients who initially presented with lymph node metastases, 13 (76%) had a CR and 4 (24%) had a PR. An overall CR was achieved in 26 patients (84%). The patients with a PR in the lymph node metastases were staged as N2 or N3. All of these patients later underwent neck dissections and there were no complications, but none of them were found to have a residual tumor in the neck by histopathological examination. Only one patient with a PR in the primary site had a tumor in the larynx and refused any further treatment. After completing all therapy including surgical resection, 30 patients (97%) were considered disease free.

A relapse was detected in two patients, at the cervical lymph nodes in one patient and as a distant metastasis in the other. The patient who developed cervical node metastases underwent neck dissection and there was no complication. Only one patient died, and this was a patient who developed distant metastases at 12 months after enrollment. The 2-year overall survival rate was 96%. The 2-year relapse-free survival rate was 94%.

**ADVERSE EVENTS**

The acute adverse events are summarized in Table 5. All 31 patients were assessable for adverse events. Grade 3 or 4 adverse events included leukopenia, anemia, thrombocytopenia, nausea, vomiting, mucositis and dermatitis. Treatment-related death did not occur in any of the patients in our study. None of the patients declined further radiotherapy owing to adverse events. The main adverse events were hematological toxicity, mucositis and dermatitis associated with radiation. Grade 3 mucositis was identified in six patients (19.4%), and Grade 3 dermatitis in eight patients (25.8%). Grade 3 or 4 leukopenia was identified in six patients (19.4%).

**DISCUSSION**

Many studies have demonstrated that concurrent chemoradiotherapy with CDDP and 5-FU is effective for HNC (2,16,17). However, toxicites associated with CDDP and/or 5-FU are frequently observed. Therefore, several agents that can be used to replace CDDP or 5-FU have been developed. Several studies suggest that CDGP has more pronounced activity against solid tumors, with less nephrotoxicity and gastrointestinal toxicity than CDDP (18–22). Similarly, S-1 may potentiate the antitumor activity of 5-FU and decrease the toxicities generally associated with 5-FU treatment (23).

With regard to adverse events, concurrent chemoradiotherapy with CDGP and S-1 was as safe as CDDP and 5-FU. Grade 3 or 4 adverse events included leukopenia, anemia, thrombocytopenia, nausea, vomiting, mucositis and dermatitis. Treatment-related death did not occur in any of the patients in our study. None of the patients declined further radiotherapy owing to adverse events. The main adverse events were hematological toxicity, mucositis and dermatitis associated with radiation. Grade 3 mucositis was identified in six patients (19.4%), and Grade 3 dermatitis in eight patients (25.8%). Grade 3 or 4 leukopenia was identified in six patients (19.4%).
Table 5. Adverse events (n = 31)

<table>
<thead>
<tr>
<th>Grade (CTCAE ver.3.0)</th>
<th>Percentage of 3 and 4</th>
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<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>9</td>
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<tr>
<td>Anemia</td>
<td>18</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
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<td>AST</td>
<td>5</td>
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<td>ALT</td>
<td>6</td>
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<td>Bilirubin</td>
<td>3</td>
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<tr>
<td>Creatinine</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
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<tr>
<td>Abdominal pain</td>
<td>3</td>
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<tr>
<td>Diarrhea</td>
<td>2</td>
</tr>
<tr>
<td>Mucositis</td>
<td>10</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>11</td>
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</table>

CTCAE, Common Terminology Criteria for Adverse Events; AST, aspartate transaminase; ALT, alanine transaminase.

delayed or declined further chemotherapy or radiotherapy because of the dermatitis. The incidence of severe (Grade 3 or 4) nephrotoxicity and gastrointestinal toxicity was lower in this study than in studies of chemoradiotherapy with CDDP and 5-FU (nephrotoxicity: 0–1.7%; nausea or vomiting: 5–18.3%). We used only 500 ml of normal saline for intravenous hydration of patients, but none of the patients developed severe nephrotoxicity in this study. Because the patients do not require high doses of intravenous hydration or continuous intravenous infusion over a long time during chemoradiotherapy with CDGP and S-1, it may be easier for patients with complications to receive the treatment, and it may be possible to administer this regimen on an outpatient basis. In fact, we treated five of our patients in the outpatient clinic.

The clinical response and short-term outcome seem to be at least comparable with, if not better than, those of CDDP and 5-FU (24–29). The response and CR rates in this study were 100 and 84%, respectively. The CR rate of the primary site was 97%. These highly positive results may have been obtained because all of the patients were T1–T3, and no patients with T4 disease was included in this study. If patients with T4 disease had been included in this study, it is likely that the CR rate of the primary site would be lower. The CR rate of lymph node metastases was 76%, and the rate in N1 and N2 was 87%. These results suggest that most patients with HNC would experience a CR or PR, and patients with T1–T3 or N1-N2 are more likely to have a CR. The 2-year overall survival and relapse-free rates were 96 and 94%, respectively.

In this study, the median follow-up duration of 22 months was too short to evaluate the long-term outcome. To evaluate the antitumor effects of concurrent chemoradiotherapy with CDGP and S-1, we must treat more patients, particularly more advanced-stage patients, and continue to follow them long term in the future.

Only half of our present patient population received two full courses of the combination regimen. We were afraid that the radiotherapy would need to be temporarily interrupted due to hemorrhagic complications and severe oral mucositis, and decided that the second course of chemotherapy should not be performed or that only S-1 should be administered to the patients showing signs of toxicity. This may be one of the major reasons why none of the patients required an interruption of radiotherapy due to adverse events. The clinical response and short-term outcome of this study are satisfactory, in spite of the fact that only half of the patients received all of the planned courses of the chemotherapy. On the other hand, it is reported that split-course radiotherapy permits many patients to receive two courses of chemotherapy with CDGP and S-1 (13). Under such a regimen, radiotherapy is administered over 3 weeks (5 days per a week) and then is interrupted for a week. Although conventional radiotherapy is generally more effective than split-course radiotherapy, hereafter, we must consider which strategy will provide greater antitumor efficacy.

In conclusion, our results indicate that concurrent chemoradiotherapy with CDGP and S-1 has either an equal or lower toxicity, and equal or better clinical response and short-term outcome, in comparison with CDDP and 5-FU. Because the treatment is much more patient-friendly, and can be administered in the outpatient setting, it will likely be easier to tolerate for patients with complications. To evaluate the long-term outcomes and potential late complications, we must continue to follow these patients long term.

Conflict of interest statement
None declared.

References
Chemoradiotherapy with CDGP and TS-1 for HNC


