Outpatient Oral Chemotherapy with S-1 for Unresectable or Distant Metastatic Head and Neck Cancer

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Abstract. Background: This retrospective study evaluated the efficacy and safety of S-1 chemotherapy for unresectable or distant metastatic head and neck cancer. S-1 is an oral anticancer agent containing a combination of 2 modulators and tegafur, which is a pro-drug of 5-fluorouracil. Patients and Methods: S-1 was orally administered to 27 patients with unresectable and/or distant metastatic head and neck cancer at a dose based on the patient’s body surface area in an outpatient setting. Results: The response rate was 11.1% (three out of the 27 cases: one case of a complete response and two cases of a partial response). The cumulative survival rate of patients with squamous cell carcinoma (n=18) was 7/18 (38.9%) and 4/18 (22.2%) at 12 and 24 months, respectively, with a median survival time of eight months. Most adverse events were mild (up to grade 2). Conclusion: S-1 therapy is a useful, effective anticancer treatment for unresectable or distant metastatic head and neck cancer, with relatively mild side-effects, and can be administered while maintaining the quality of life of the patient.

S-1 is an oral anticancer agent. It consists of tegafur, gimeracil (5-chloro-2, 4-dihydrogenase) and potassium oxonate at a molar ratio of 1:0.4:1. Tegafur is a pro-drug of 5-fluorouracil (5-FU). Gimeracil causes prolonged retention of 5-FU in the blood and enhances the pharmacological actions of 5-FU by competitively inhibiting its degradation.

Potassium oxonate is localized in the mucosa of the gastrointestinal tract following oral administration and alleviates gastrointestinal toxicities induced by 5-FU. S-1 has been widely used in the treatment of gastric, colorectal, head and neck, non-small cell lung, breast, pancreatic and biliary tract cancer. S-1 monotherapy in patients with advanced head and neck squamous cell carcinoma (HNSCC) achieves a good response rate (46.2% in an early phase II study and 28.3% in a late phase II study) with mild adverse events (1, 2). In addition, it has been suggested that monotherapy is preferable to combination therapy (3, 4). Because unresectable or distant metastatic head and neck cancer is usually incurable, the goal of treatment is to achieve prolonged survival while maintaining the quality of life for the patient. Therefore, this retrospective study focused on the possibility of long-term administration of S-1 in an outpatient setting and administered S-1 chemotherapy for unresectable or distant metastatic head and neck cancer with the aim of achieving prolonged survival without interrupting daily life (5). We, herein, report the efficacy and safety of S-1 monochemotherapy for unresectable or distant metastatic head and neck cancer in an outpatient setting.

Patients and Methods

The participants in this study included 27 patients with unresectable or distant metastatic head and neck cancer to whom S-1 was administered during the period from July 2006 to October 2011. In this study, unresectable cases were defined as those involving the cervical vertebrae, brachial plexus, deep neck muscles or carotid artery. All patients received treatments before S-1 administration. The clinical characteristics of the patients are shown in Table 1. All patients were initially administered S-1 orally at a dose based on the patient’s body surface area (BSA) as follows: BSA <1.25 m²: 80 mg/d; 1.25 m² BSA<1.5 m²: 100 mg/d; and BSA≥1.5 m²: 120 mg/d. S-1 was administered for either 14 or 28 consecutive days followed by a 7- or 14-day rest period, respectively. In some cases, the dose was adjusted between 80 mg/day and 120 mg/day depending on renal function, bone marrow function, or side-effects. The chemotherapy was administered in an outpatient setting for all patients and was continued until the patient refused to continue the therapy due to the
development of uncomfortable side-effects. The survival period was calculated from the initiation of S-1 administration to death or November 1, 2012, using the Kaplan-Meier method. The time-to-progression (TTP) was defined as the period from the initiation of S-1 therapy to the first day that progression was noted. Patients with squamous cell carcinoma (SCC) were divided into two groups: Group A, which consisted of patients (n=9) who continued S-1 administration after tumor progression was noted; and group B, which consisted of patients (n=6) who discontinued S-1 therapy for any reason before tumor progression was noted. We eliminated two patients in whom the first day of tumor progression was not apparent and one patient who exhibited a complete response. We compared the two groups using the Kaplan-Meier method.

Results

The S-1 administration period, excluding periods of rest, ranged from 2 to 310 weeks (mean: 54.2 weeks). The total dose of S-1 ranged from 1,400 mg to 938,000 mg (mean: 18,876 mg). Out of the 27 patients, five, including four with tumors and one without tumor, survived until November 1, 2012; the survival duration of these five patients following the initiation of S-1 administration ranged from 22 to 71 months. The response rate was 11.1% [three out of the 27 patients: one case of a complete response (CR) and two cases of a partial response (PR)]. The cumulative survival rate for patients overall (n=27) was 51.9% and 29.6% at 12 and 24 months, respectively, with a median survival time (MST) of 14 months. The cumulative survival rate of patients with SCC (n=18) was 38.9% and 22.2% at 12 and 24 months, respectively, with an MST of eight months. Four patients with SCC (22.2%) survived more than 24 months (Figure 1). Six patients (22.2%), including two with SCC (11.1%), exhibited a TTP of more than 12 months. The two patients with SCC (11.1%) demonstrated a TTP of more than 24 months.

We compared the survival time from the initiation of S-1 administration to death and found a significant difference between groups A and B (p=0.034) (Figure 2). The MSTs from the initiation of S-1 in groups A and B were 18.0 and 7.5 months, respectively. In addition, we compared the survival time from the onset of tumor progression and found a significant difference between the two groups (p=0.027) (Figure 2). The MSTs from the onset of tumor progression in groups A and B were 8.0 and 3.5 months, respectively.

Most adverse events were mild, i.e. up to grade 2 according to the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0®) (Table II) (6). Only one patient developed grade 3 fatigue; however, the patient recovered quickly following withdrawal of the medication.

Representative cases. The first case involved a 57-year-old male who complained of left otorrhea. The erosion was located throughout the entire circumference of the external canal. The cytological analysis revealed malignant cells, and left lateral temporal bone resection was performed. A pathological examination identified SCC of the left external
ear canal. Eight years later, cervical lymph node metastasis developed involving the deep neck muscles and carotid artery. We diagnosed this case as an unresectable case. The patient received concurrent chemoradiotherapy (consisting of 66 Gy of cisplatin and radiotherapy); however, an evaluation revealed stable disease. S-1 was then administered in an outpatient setting. The patient achieved a PR after three cycles and a CR after 30 cycles (Figure 3). At an early stage, he experienced an adverse event of grade 1 anorexia; however, he recovered quickly with continuation of the therapy. He was found to be free of relapse at the 6-year follow-up.

The second case involved a 63-year-old male who complained of left cervical adenopathy. The mass was hard, mobile and located in the left neck. A fine-needle aspiration biopsy of the cervical lymph node revealed malignant cells, and left neck dissection was performed. The histopathological diagnosis was SCC with an occult primary lesion. Two years later, multiple lung metastases were found on computed tomography (CT). Tegafur-uracil (UFT), an oral anticancer agent consisting of a combination of tegafur and uracil, was then administered in an outpatient setting. However, eight months later, we switched the medication to S-1 due to metastasis growth (Figure 4). The patient survived for 33 months after the initiation of S-1 administration with metastasis growth. Despite the presence of multiple lung metastases, he was able to be treated in an outpatient setting with long-term drug administration and survived for a long period with a good quality of life.

Discussion

The ultimate goal of chemotherapy for unresectable and distant metastatic head and neck cancer is to prolong the survival of patients with a good quality of life, as the disease is usually incurable. Although the administration of intensive chemotherapy generally requires hospitalization, S-1 chemotherapy can be administered in an outpatient setting, with relatively mild adverse events. In this study, most of the patients (26 out of the 27 cases, 96.3%) experienced adverse events of less than grade 2, primarily including anorexia and anemia. Consequently, all patients were able to be treated in an outpatient setting with comparatively long-term drug

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Table II. Incidence (%) of adverse events (CTCAE v4.0®).

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>3 (11.1)</td>
<td>2 (7.4)</td>
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<tr>
<td>Anemia</td>
<td>4 (14.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Hyperpigmentation</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ocular surface disease</td>
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<td>1 (3.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
<td>1 (3.7)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 2. Kaplan-Meier curves of the survival times in group A (S-1 continued after tumor progression) and B (discontinued S-1 before tumor progression) from the initiation of S-1 (A) and from the onset of tumor progression (B).
administration. The patients were able to undergo anticancer chemotherapy with a good quality of life.

MSTs of 5.0-8.7 months and response rates (RRs) of 3.9-36% have been reported in phase III trials of therapy for recurrent or metastatic HNSCC (7-12). Among the patients with SCC in our report, the MST of eight months is equivalent to the findings of the phase III trials, despite a RR of only 11.1%. It has not been proven whether a high RR translates into an improved survival rate in patients with recurrent head and neck cancer (3). Furthermore, it has been reported that tumor shrinkage is not essential for survival (13). Therefore, the aim of chemotherapy is to achieve prolonged survival, even without tumor shrinkage, by continuing the administration of chemotherapy for as long as possible (5). In our cases, four patients with SCC (22.2%) survived for more than 24 months. It has been reported that patients with recurrent or metastatic HNSCC have a median survival of 6-9 months, with a one-year survival rate of 40%, and that such patients infrequently survive beyond two years (14). Due to the differences in patients’ backgrounds, such as the Performance Status (PS), treatment history, or clinical status at the time of diagnosis, the present results obviously cannot be compared with those of other studies. However, with regard to unresectable or distant metastatic head and neck cancer, our results are satisfactory.

We focused our attention on the relationship between the time of discontinuation of S-1 and the survival duration. Some patients discontinued the therapy after complaining that S-1 had no effect against tumor progression. However, our results demonstrated that S-1 was effective in prolonging the survival time after tumor progression. This finding suggests that S-1 slows tumor growth, even after tumor progression is found. Many reports of chemotherapy use TTP as an indicator of drug efficacy; however, we focused on the survival time

Figure 3. Contrast-enhanced computer tomographic scan of a 57-year-old male with squamous cell carcinoma of the left external ear canal. A: Before chemoradiotherapy. The tumor involved the left deep muscles and carotid artery. B: One month after chemoradiotherapy (before S-1 administration), stable disease was observed. C: After 30 cycles of S-1 therapy, a complete response was observed.

Figure 4. X-ray images of a 63-year-old male with squamous cell carcinoma of the left cervical lymph node with an occult primary lesion. As time passed, the nodular area of opacity in the middle lung increased. A: Before UFT administration. B: Before S-1 administration, eight months after the initiation of UFT. C: One year after S-1 administration.
from the onset of tumor progression. As shown in the representative cases, some patients survived successfully for long periods with tumor progression by continuing S-1 administration as long as possible. We believe that it is important to continue S-1 administration in order to prolong the survival duration, even after tumor progression is found.

S-1 chemotherapy for unresectable or distant metastatic head and neck cancer is a safe and effective anticancer chemotherapy that can be administered in the outpatient setting with mild adverse events, prolonging survival duration while maintaining the patient’s quality of life.

References


