Abstract. Background: Concurrent chemoradiotherapy (CCRT) improves survival and organ preservation in patients with head and neck squamous cell carcinoma (HNSCC), compared with radiotherapy. However, such regimens are not always feasible because of substantial toxicities. Therefore, we evaluated the feasibility of S-1, administered on alternate days, and concurrent radiotherapy among elderly patients with HNSCC. Patients and Methods: Nineteen eligible patients were treated with CCRT. S-1 was administered at a dose of 80 mg/day on alternate days with the intention to reduce the toxicity. Results: With a median follow-up period of 19.2 months, the two-year overall survival rates were 62.5% for patients with stage III disease and 50.0% for those with stage IV. The Complete Response (CR) rates were 100% for stage II and 66.7% for stage III/IV disease. Grade 3 mucositis occurred in three patients. Grade 3 or 4 hematological toxicities were not observed. Conclusion: CCRT with S-1 administered on alternate days was effective and well-tolerated among elderly patients with HNSCC.

Most head and neck cancer cases are diagnosed while the patients are in their fifth or sixth decade of life (1). However, as a result of increasing life expectancy, a rise in the incidence of head and neck squamous cell carcinoma (HNSCC) among elderly populations is expected. Between 2005 and 2010, the average life expectancy in Japan was 82.7 years, the highest in the world (2). Thus, the problem of how to treat elderly patients with HNSCC must be resolved.

Platinum-based concurrent chemoradiotherapy (CCRT) regimens have improved overall survival, disease-free survival, and locoregional control of the disease and have reduced distant metastasis, when examined in randomized trials where they were compared with radiotherapy alone (3). Cisplatin and 5-fluorouracil combined with taxane as an induction chemotherapy regimen and followed by CCRT has reportedly prolonged the survival of advanced HNSCC patients (4). However, such heavy regimens are not always suitable for elderly patients or patients with comorbidities because of the substantial toxicities that are often involved. Thus, selecting a treatment modality can be difficult if a patient cannot undergo treatment with an anticancer agent and concurrent radiotherapy because of advanced age, comorbidity, or poor general status in unresectable cases. Thus, the use of S-1 as a radiosensitizer in less toxic regimens must be considered.

S-1 is an oral anticancer drug that consists of a mixture of 1 M tegafur, 0.4 M 5-chloro-2,4-dehydroxypyrimidine (CDHP), and 1 M potassium oxonate: tegafur is a prodrug of fluorouracil, CDHP is a potent reversible inhibitor of fluorouracil degradation, and potassium oxonate reduces the gastrointestinal toxicity induced by fluorouracil (5, 6). In a pharmacokinetic study of S-1, the plasma fluorouracil concentrations were shown to be almost equivalent to those obtained with the continuous venous infusion of fluorouracil (9). In addition to the high response rates, the incidences of adverse effects were shown to be low. In late phase II clinical trials of S-1 alone in a total of 449 patients, the incidences of greater than grade 3 adverse reactions were less than 10%, with the exception of neutropenia (11.1%) (10). The radiosensitizing effect of S-1 for head and neck cancer has been reported by several investigators (11, 12) and has been applied clinically (13-15). These reports led us to use S-1 concurrently with radiotherapy in elderly cases.

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When performing chemoradiation with S-1, the schedule often consists of two weeks of S-1 administration followed by one week of rest. It is reported that the administration of S-1 on alternate days can reduce the incidence of adverse effects without compromising the therapeutic effects of S-1 (16, 17). Thus, we administered S-1 on alternate days and performed CCRT in elderly patients with HNSCC.

The purpose of this study was to present our experience at the Kyorin University Hospital and its related institutions, in using CCRT and S-1 administered on alternate days for the treatment of elderly HNSCC patients and to compare our findings with previous literature on feasibility, toxicity and tumor response.

Patients and Methods

Eligibility criteria. Patients enrolled in this study were required to fulfill the following criteria: (i) histologically-proven HNSCC (except thyroid cancer) and measurable or evaluable lesions; (ii) a performance status of 0 to 3 on the Eastern Cooperative Oncology Group (ECOG) scale; (iii) a life expectancy of at least 3 months; (iv) an age of 75 years or older; (v) cases who could not undergo surgical excision or cases who could not undergo an ordinary chemotherapy regimen because of a poor general status; and (vi) the provision of written informed consent. The Ethics Committee of our institute approved the study.

Treatment schedule. In the consecutive-day regimen, the recommended dose of S-1 is 80 mg/day, according to a phase I study of concurrent radiotherapy with S-1 (18, 19). Because it is reported that S-1 administered on alternate days is less toxic than consecutive-day treatment, dosage of S-1 on alternate days was to be given as 80 mg/day on an outpatient basis. If a patient developed toxicities, the patient’s daily dose was reduced, or S-1 administration was discontinued.

All the patients underwent external beam radiotherapy. Three-dimensional conformal radiotherapy was delivered through a linear accelerator with a 4-MV X-ray. Conventional fractionation was used with a daily dose of 1.8-2.0 Gy, 5 times per week. The initial radiation fields generally encompassed the primary tumor, bilateral neck regions, and the supraclavicular fossae. Two lateral fields with or without a single anterior field were used. After a dose of 40-45 Gy had been administered, the primary lesion and the lymphadenopathy were boosted-with to a total dose of 66-70 Gy in a reduced field.

Evaluation of toxicity. A complete blood cell count and measurements of liver and renal function were assessed at least every week during the treatment. Non-hematological toxicities were also verified at least every week by patient interview and physical examination. The toxicity was evaluated according to the National Cancer Institute common toxicity criteria (NCI-CTC), version 3.0 (20).

Evaluation of tumor response. The response-to-treatment was assessed based on the sum of the diameters as measured directly with callipers or using radiological images, according to the Response Evaluation Criteria In Solid Tumors (RECIST) (21). A complete response (CR) was defined as the disappearance of all target lesions for at least four weeks. A partial response (PR) was defined as a decrease in the sum of the diameters of the target lesions by at least 30%, using the baseline sum of the diameters for at least four weeks as a reference. Progressive disease (PD) was defined as an increase in the sum of the diameters of the target lesions by at least 20%, using the smallest sum as a reference, or the appearance of new lesions. Stable disease (SD) was defined as neither a sufficient shrinkage to qualify as a PR nor a sufficient increase to qualify as a PD, using the smallest sum of the diameters during the study as a reference. The response rate was defined as the sum of the CR and PR rates.

Results

Patient characteristics. Between 2008 and 2012, 19 elderly patients with newly-diagnosed head and neck cancer and without distant metastases were started on CCRT with S-1 administered on alternate days at the Kyorin University Hospital or the Musashimurayama Hospital.

The patients’ characteristics are shown in Table I. Fourteen (73.7%) of the patients were men, and the median age was 84 years (range=75-98 years). According to the National Institute on Aging and the National Institutes of Health subcategories (22), age is defined as follows: ‘young old’ (65-74 years), ‘older old’ (75-85 years), and ‘oldest old’ (>85 years). Twelve patients were older old, and seven were oldest old. The primary sites were the larynx in six patients, the hypopharynx in seven patients, the oropharynx in five patients, and the oral cavity in one patient. Four patients had a T2 primary lesion, and fifteen patients had a T3-4 primary lesion. Twelve (63.2%) patients had node-positive disease. The stage distribution according to the International Union Against Cancer 2002 classification (23) was as follows: four patients had stage II, nine patients had stage III, and six patients had stage IV disease. All the patients have had some episodes of systemic disease, and high-risk patients were included in this study.

Adverse events. The adverse events observed during treatment are listed in Table II. Grade 3 mucositis was observed in three patients. No other grade 3 or 4 toxicities were observed, and no deaths from toxicities occurred during or after CCRT. The acute adverse events are also summarized in Table II. Sixteen patients received the full treatment as planned, nineteen patients received full-dose radiotherapy, and sixteen patients received full-dose chemotherapy. One patient (case 8) was given 50 mg/day S-1 as a chemotherapy dose from day 1 because of an extremely advanced age and poor performance status, and S-1 administration was terminated in two patients because of a febrile illness of uncertain cause in case 11 and mucositis in case 17. S-1 administration was not stopped during the treatment schedule because of toxicity induced by CCRT except for one case, and all the cases except for case 17 were treated on an outpatient basis during and after CCRT.

Therapeutic results. Fourteen out of the nineteen patients showed a CR, and four and one of the nineteen patients a PR
and an SD, respectively. The CR rate of the patients to the treatment regimen examined in this study was 100% for stage II patients and 66.7% for stage III/IV patients. The results are shown in Table III. Out of the ten CR cases with stage III/IV tumors, one had a recurrence (10.0%). This case had a lymph node recurrence at 3 months after CCRT but was unable to undergo salvage surgery and died from the disease. The median follow-up period was 19.2 months (range 3-44 months). The two-year overall survival rates for patients with stage II, III, and IV disease were 75.0%, 62.5%, and 50.0%, respectively (Figure 1).

Case 7 developed lymph node metastasis in her neck one year after CCRT and underwent a total neck lymph node dissection. This patient is alive without disease at present. Five patients with PR died as a result of cancer progression because they could not undergo salvage surgery for advanced diseases or had a poor general status. Only one patient (case 3) died from an unrelated cause.

Discussion

Recently, concurrent chemoradiotherapy has been shown to be highly effective for increasing survival and organ preservation in patients with locally advanced head and neck cancer (3, 24-28). Although CCRT reportedly improves survival by 6.5% over locoregional treatment alone, with the greatest benefit seen in platinum-based regimens (25), severe toxicities are unfortunately common; thus, these regimens are not applicable to all patients. Reduced organ function, comorbidities, and
different cell cycles. The cell cycle of normal cells is only 0.5 days, whereas that of tumor cells is 5 to 7 days. Shirasaka et al. hypothesized that when fluorouracil is given on alternate days, the tumor cells would be exposed to fluorouracil at regular intervals, resulting in sufficient antitumor effectiveness, but because of their shorter cell cycle, normal cells would only be exposed to fluorouracil every other day, thereby reducing toxicity (35-37). As mentioned earlier, S-1 is an oral fluorouracil antitumor drug composed of a mixture of three pharmacological agents. The antitumor effects of S-1 or regimens that contain S-1 have been previously demonstrated for a variety of solid tumors, including gastric (38-40), colorectal (41), biliary tract (42), and head and neck cancer (8, 43). Alternate-day treatment with S-1 was also associated with milder adverse events without compromising therapeutic effectiveness in clinical or pre-clinical studies (17, 44, 45). With regard to CCRT with S-1, Tsuji et al. reported that the recommended dose of S-1 for consecutive day regimens was 80 mg/day (40 mg, twice daily) for cases with glottic cancer (18). The use of an alternate-day S-1 regimen with concurrent radiotherapy has not been previously reported. However, based on the theory of Shirasaka et al. and some research that has verified their hypothesis, we assumed that the same volume of S-1 could be administered more effectively without increasing the incidence of adverse events; thus, we administered 80 mg/day of S-1 on alternate days in addition to performing concurrent radiotherapy.

The CR rate of CCRT in the present study for stage III or stage IV was 66.7%. The two-year overall survival rates of patients with stage III and stage IV disease were 62.5% and 50%, respectively. The only grade 3 toxicity was mucositis, and no other grade 3 or higher hematological toxicities were observed. The reported two-year overall survival rates in studies using a platinum-based regimen with concurrent radiotherapy against head and neck cancer in elderly patients were 75% for stage III and 29% for stage IV. In the same report, grade 3 mucositis, neutropenia, leukocytopenia, and Alanine transaminase and Aspartate aminotransferase elevations were observed in 20% of the cases (14). Boscolo-Rizzo et al. reported that grade 3 or greater severe acute toxicities in studies using a platinum-based regimen with CCRT, following induction chemotherapy in elderly patients with HNSCC (median age=71 years; range=66-77 years) were observed in 65.9% of the patients and that treatment was discontinued in 15.9% (46). For the alternate-day S-1 regimen, the therapeutic results were comparable to previously reported results and the adverse events were more tolerable. Our population only comprised ‘older old’ and ‘oldest old’ (36.8%) patients. In previous reports of elderly patients with head and neck cancer, the populations were mainly composed of ‘young old’ or ‘older old’ patients. Therefore, our study provides results for patients of considerably advanced ages.

Figure 1. Overall survival curve according to disease stage. Survival curves were calculated using the Kaplan-Meier method. The two-year overall survival rate in Stage II, Stage III, and Stage IV patients were 75.0%, 62.5% and 50.0%, respectively.
The main weakness of this study was the limited number of enrolled patients and the relatively short observation period. Thus, this treatment option should not be adopted without first obtaining further data. Significantly, the toxicity of this treatment appears to be tolerable for the majority of patients. In conclusion, the present regimen of concurrent chemoradiotherapy with S-1 administered on alternate days is feasible and well-tolerated among elderly patients with head and neck cancer, suggesting that this regimen may be beneficial. Further studies are warranted to confirm the benefits of this regimen and to determine a more appropriate dose.

References


