Initial experience of radiotherapy plus cetuximab for Japanese head and neck cancer patients

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ABSTRACT

In Japan, cetuximab with concurrent bioradiotherapy (BRT) for squamous cell carcinoma of head and neck (SCCHN) was approved in December 2012. We herein report our initial experience of BRT, with special emphasis on acute toxicities of this combination therapy. Thirty-one non-metastatic SCCHN patients who underwent BRT using cetuximab between July 2013 and June 2014 were retrospectively evaluated. All patients received cetuximab with a loading dose of 400 mg/m² one week before the start of radiotherapy, followed by 250 mg/m² per week during radiotherapy. The median cycle of cetuximab was seven cycles and the median dose of radiotherapy was 70 Gy. Twenty-five patients (80.6%) accomplished planned radiotherapy and six cycles or more cetuximab administration. Six patients (19.4%) discontinued cetuximab. Grade 3 dermatitis, mucositis and infusion reaction occurred in 19.4%, 48.3% and 3.2%, respectively. One patient experienced Grade 3 gastrointestinal bleeding caused by diverticular hemorrhage during BRT. Grade 3 drug-induced pneumonitis occurred in two patients. The response rate was 74%, including 55% with a complete response. BRT using cetuximab for Japanese patients with SCCHN was feasible as an alternative for cisplatin-based concurrent chemoradiation, although longer follow-up is necessary to evaluate late toxicities.

KEYWORDS: head and neck cancer, cetuximab, radiotherapy, acute toxicity, initial experience

INTRODUCTION

The number of patients with squamous cell carcinoma of the head and neck (SCCHN) has increased in Japan, and >16 000 patients suffered from oral/pharyngeal or laryngeal cancer, accounting for 2.3% of all cancer cases in 2006 [1, 2]. Cisplatin-based concurrent chemoradiotherapy is one of the standard treatments for locoregionally advanced SCCHN [3, 4]. However, in clinical practice, patients in poor medical condition sometimes fail to receive the full dose of chemotherapy during definitive radiotherapy for SCCHN, in which the treatment volume includes a large amount of oral/pharyngeal mucosa. Cetuximab, epidermal growth factor receptor (EGFR)-targeting monoclonal antibody, has been demonstrated to have antitumor activity for SCCHN expressing EGFR [5]. Because targeted therapy agents such as cetuximab are directed selectively at a specific target, a combination of these agents and radiotherapy is considered to be better tolerated than conventional chemotherapy. Bonner et al. reported that bioradiotherapy (BRT) had a significant survival advantage over radiotherapy alone for the treatment of SCCHN [6, 7]. In addition, there was no significant difference in acute radiation dermatitis between the groups with and without cetuximab in that study. In
Japan, based on these results, cetuximab for SCCHN was approved by the Ministry of Health, Labour and Welfare in December 2012. We herein report our initial experience of treating SCCHN with definitive radiation therapy and concurrent cetuximab, with special emphasis on acute toxicities for this combination therapy.

MATERIALS AND METHODS

Patients

Between July 2013 and June 2014, 31 non-metastatic SCCHN patients underwent BRT with cetuximab in our hospital. Patient characteristics are shown in Table 1. The median age was 72 years (range, 52–83 years). The primary tumor site was the hypopharynx in 14, oropharynx in 12, larynx in four, and maxillary sinus in one. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0 in 17, 1 in 12, and 2 in two. Reasons for not receiving standard cisplatin-based concurrent chemoradiation were patient’s age ≥75 years in 10, cardiovascular disease in four, cerebral vascular disease in two, diabetes mellitus in two, hepatitis in one, schizophrenia in one, poor medical status due to history of preceding other cancer treatment in four, and attending physician’s discretion in seven. All patients had a histologically confirmed diagnosis of SCCHN. The stage of the tumor was determined on the basis of physical examination, pharyngo–laryngoscopy, and radiographic methods such as computed tomography (CT) or magnetic resonance imaging (MRI), and PET/CT if available. According to the UICC stage system (7th edn 2009), one was Stage I, two were Stage II, four were Stage III, and the remaining 24 (77.4%) were Stage IV. This retrospective study was approved by the Institutional Review Board of our hospital and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all patients.

Radiotherapy planning and techniques

All patients were consecutively treated with same high-energy linear accelerator (Clinac iX, Varian). CT-based 3D treatment planning was performed for all. Targets and organs at risk were contoured on the planning CT. The gross tumor volume (GTV) included the gross extent of the primary disease and involved lymph node metastases, taking clinical and radiological findings into account; the clinical target volume (CTV) was defined by adding 10–15 mm margin to the GTV. In addition, the nodal CTV was set by considering the lymph node level (depending on the primary tumor and involved

Table 1. Patient and tumor characteristics

| Median age, years (range) | 72 (52–83) |
|---------------------------|------------|
| Gender                    |            |
| Male                      | 29         |
| Female                    | 2          |
| ECOG PS                   |            |
| 0                         | 17         |
| 1                         | 12         |
| 2                         | 2          |
| Comorbidities*            |            |
| The elderly patients (≥75 y/o) | 10         |
| Cardiovascular disease    | 4          |
| Cerebral vascular disease | 2          |
| Diabetes Mellitus         | 2          |
| Hepatitis                 | 1          |
| Schizophrenia             | 1          |
| Poor medical status       | 4          |
| Discretion of physician   | 7          |
| Primary tumor site        |            |
| Hypopharynx               | 14         |
| Oropharynx                | 12         |
| Larynx                    | 4          |
| Maxillary sinus           | 1          |
| T-stage                   |            |
| T1                        | 3          |
| T2                        | 9          |
| T3                        | 8          |
| T4a                       | 10         |
| T4b                       | 1          |
| N-stage                   |            |
| N0                        | 10         |
| N2b                       | 13         |
| N2c                       | 7          |
| N3                        | 1          |
| UICC stage                |            |
| I                         | 1          |

Continued
nodal sites). The planning target volume (PTV) was defined by an additional circumferential 5–10 mm margin to accommodate the daily patient set-up uncertainty. Tumor and critical structure delineation were performed on co-registered diagnostic MRI images if necessary. Patients received once-daily radiotherapy that consisted of 2.0 Gy per fraction, five fractions per week, to the prescribed total dose of 70 Gy in 7 weeks. Three-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiation therapy (IMRT) was performed. When the target volume did not contain a large volume of major salivary gland or oral–pharyngeal mucosa, 3DCRT was selected (n = 26), otherwise IMRT was applied (n = 5) as an initial treatment. In the case of IMRT, the PTV was modified by subtracting 3–5 mm from the skin surface. After administration of 40–50 Gy, target volumes were shrunk to cover the primary tumor and gross nodal disease with generous margins. In 11 cases initially treated with 3DCRT to the dose of 40–46 Gy, the radiotherapy technique was changed to IMRT for the remaining treatment course because it seemed difficult to deliver adequate dose to the target while safely sparing the spinal cord from exceeding this dose level.

**Schedule of cetuximab**

All patients were treated according to the Bonner Protocol [6, 7]. An intravenous loading dose of cetuximab (400 mg/m²) was administered in the week before beginning radiotherapy, followed by 250 mg/m² per week during radiotherapy. Cetuximab was discontinued for Grade 3 or worse hypersensitivity. Premedication included intravenous chlorpheniramine and dexamethasone. Patients received oral prophylaxis of acne with clarithromycin (400 mg/day). Oral magnesium supplements were titrated up to three tablets of magnesium oxide (250 mg per tablet) given three times daily.

**Toxicity and response assessment**

Patients were examined every week by both radiation oncologists and head and neck surgeons. Adverse events were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (CTCAEv4). Patients who developed greater than Grade 2 dermatitis were intensively managed by our skin care team. Responses to BRT were assessed by physical examination, endoscopy, and CT and/or MRI, and classified according to the Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1.

**Statistical analysis**

In this study, the effects of patient factors or radiotherapy parameters on the development of Grade 3 dermatitis/mucositis were examined. All statistical analyses were done with StatMate V (ATMS Co. Ltd, Tokyo, Japan). Fisher’s exact test was used to compare categorical variables, such as age, sex, and primary tumor subsites.

**RESULTS**

The median follow-up time was 12 months (2–18 months). Table 2 shows the number of cetuximab cycles and doses of radiotherapy. The median cycle of cetuximab was 7 cycles and the median dose of radiotherapy was 70 Gy. Six patients (19.4%) discontinued cetuximab administration. Only four patients received less than six cycles of cetuximab. One patient who developed infective endocarditis at 36 Gy received only four cycles of cetuximab and was not able to complete the planned BRT thereafter. Of three patients who received five cycles of cetuximab, drug-induced pneumonitis and hypersensitivity reaction developed in each one. Another patient who received five cycles of cetuximab due to severe dermatitis accomplished radiotherapy. To four patients who received six cycles of cetuximab, two changed their treatment strategy at BRT of 56 Gy and 66 Gy, respectively. In total, 25 (80.6%) patients accomplished the planned 70 Gy of radiotherapy and six cycles or more of cetuximab administration.

Treatment-related acute toxicity profiles are shown in Table 3. There was no Grade 4 or worse acute adverse event. Grade 3 dermatitis, mucositis and infusion reaction occurred in 6 patients (19.4%), 15 patients (48.4%) and one patient (3.2%), respectively. Typical cases of Grade 3 dermatitis/mucositis are shown in Figs 1 and 2. Confluent painful mucositis with moderate edema dominated the pharyngeal wall, epiglottis, pharyngo–epiglottic fold, and tongue base.

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### Table 2. Cycles of cetuximab administration and dose of radiotherapy

| Cetuximab cycles | Grade 2 (%) | Grade 3 (%) |
|------------------|-------------|-------------|
| 4                | 1           |             |
| 5                | 3           |             |
| 6                | 4           |             |
| 7                | 13          |             |
| 8                | 7           |             |
| 9                | 2           |             |
| 10               | 1           |             |
| Dose of radiotherapy |          |             |
| <60 Gy           | 3           |             |
| 60–69 Gy         | 2           |             |
| 70 Gy            | 26*         |             |

*including one patient who discontinued cetuximab administration due to severe dermatitis.

### Table 3. Treatment-related acute toxicity

| Event                          | Grade 2 (%) | Grade 3 (%) |
|--------------------------------|-------------|-------------|
| Dermatitis                     | 19 (61.3)   | 6 (19.4)    |
| Mucositis                      | 15 (48.4)   | 15 (48.4)   |
| Xerostomia                     | 10 (32.3)   | 0 (0)       |
| Acne-like skin rashes          | 7 (22.6)    | 2 (6.5)     |
| Infusion reaction              | 0 (0)       | 1 (3.2)     |
| Hypomagnesemia                 | 1 (3.2)     | 2 (6.5)     |
| Drug-induced lung injury       | 0 (0)       | 2 (6.5)     |
| GI bleeding                    | 0 (0)       | 1 (3.2)     |
of the patient. One month after BRT, thick yellowish mucositis remained in the pharyngeal wall, epiglottis, and pharyngo–epiglottic fold, with increased edema of the epiglottis. Confluent moist desquamation with a whitish-yellow surface (which indicated superficial infection) developed in both sides of the neck down to the supraclavicular area, corresponding to the radiotherapy field. It took almost one month after completion of BRT for recovery from the skin/mucosa reaction. A Grade 2 and 3 acne-like skin rash occurred in seven and two patients, respectively, and the locations of the rash were the face, the irradiated neck, the chest wall and the back. Grade 3 drug-induced pneumonitis occurred in two patients with a smoking history; one patient experienced this during the fifth week of BRT and the other experienced two weeks after completion of the radiotherapy treatment (Fig. 3). For both patients, the management of pneumonitis required steroid pulse therapy. The latter patient also experienced Grade 3 gastrointestinal (GI) bleeding caused by diverticular hemorrhage during BRT. That patient required endoscopic hemostasis and blood infusion for anemia. Grade 3 hypomagnesemia occurred in two patients, despite initial attempts to prevent hypomagnesemia using oral magnesium intake.

A total of 18 patients required active nutritional support: nasogastric tube feeding in 15 patients and intravenous hyperalimentation in 3. The median time for beginning tube feeding was 3.5 weeks after the start of BRT. Fifteen patients with Grade 3 mucositis required hospitalization during BRT. In total, 29 patients were admitted to hospital due to dysphagia or mucositis. The median time for developing mucositis after the start of radiotherapy was 19 days, and the median time required for healing of mucositis after completion of BRT was 31 days.

The effects of radiotherapy technique or patient factor on the development of Grade 3 dermatitis or mucositis were evaluated. Five of 26 patients treated initially with 3DCRT developed Grade 3 dermatitis, whereas one patient treated with IMRT experienced Grade 3 dermatitis. Grade 3 mucositis was observed in 14 patients and one patient, respectively, of those treated with 3DCRT and IMRT. However, there was no statistically significant difference between the two groups concerning the development of Grade 3 skin/mucosal toxicities, probably due to the small number of patients in the IMRT group. Among the 11 patients who initially underwent 3DCRT and changed to IMRT for the later treatment course, one and eight patients developed Grade 3 dermatitis and mucositis, respectively. There was also no significant difference in age, sex or primary tumor subsite between patients with or without Grade 3 skin/mucosal toxicities.

Fig. 1. (A) Hypopharyngeal tumor with pool of saliva and normal mucosa before the start of bioradiotherapy. (B) Decrease in the tumor bulk and development of Grade 3 mucositis during bioradiotherapy. (C) Confluent mucositis one month after the end of bioradiotherapy.

Fig. 2. (A) Grade 3 dermatitis with contact bleeding occurred at one week after bioradiotherapy. (B) Resolution of dermatitis at 4 weeks after bioradiotherapy.
Complete response was obtained in 17 patients (54.8%) and partial response in six (19.4%), resulting in a response rate of 74.2%. During the follow-up period, seven patients relapsed in the radiotherapy field. At the time of data analysis, two patients had developed multiple lung metastases and died of respiratory failure.

**DISCUSSION**

The results of the present study show that Grade 3 radiation dermatitis and mucositis occurred in ~20% and ~52% of SCCHN patients treated with BRT. Although some investigators had reported much higher Grade 3/4 dermatitis in patients receiving BRT [8–11], the incidence rates in the present study are quite similar to those originally reported by Bonner et al. [6]. Most patients could complete BRT, and only six patients received less than six cycles of cetuximab. Thus, concerning the compliance of cetuximab and radiotherapy, our findings suggest that BRT for Japanese patients with SCCHN is, in general, a tolerable and acceptable treatment, as reported in a previous Phase II study conducted in Japan [12]. The adverse event profile in this study was mostly in line with that expected with the concomitant administration of cetuximab and radiotherapy. The overall incidence of Grade 3 or 4 adverse events in this study was similar to that seen in the cetuximab plus radiotherapy arm of the Bonner trial. In two patients, however, unexpected Grade 3 toxicities of GI bleeding or interstitial pneumonitis were observed. Murakami et al. reported that 4 patients out of 15 who received BRT experienced GI bleeding, which had not previously been reported by foreign investigators. They reported that most patients with GI bleeding also experienced severe dermatitis and mucositis, requiring total parenteral nutrition, suggesting that these patients might have had susceptibility for cetuximab not only in their gastrointestinal tract, but also in their skin epithelia and pharyngeal mucosa [11]. In the present study, one patient experienced diverticular hemorrhage, requiring endoscopic hemostasis and blood transfusion for anemia during BRT. Although it is still unknown whether or not GI bleeding is due to racial characteristics of Asian patients, physicians in Japan should pay special attention to the occurrence of GI bleeding during BRT.

Pneumonitis requiring steroid pulse therapy is another concern. Drug-induced lung injury (DLI) requiring steroid pulse therapy occurred in two patients with a history of smoking in this study. Severe DLI occurring during treatment sometimes induces respiratory failure, and can be fatal. Satoh et al. indicated that older age and prior interstitial lung disease were the primary factors associated with the onset of DLI [13]. They recommended that in the case of suspected or confirmed DLI, the cetuximab-based chemotherapy should be discontinued immediately, and comprehensive management, including consultation with a pulmonologist and steroid pulse therapy, should be implemented as soon as possible. Because a considerable number of patients receiving Gefitinib for non-small cell lung cancer succumbed to death due to interstitial pneumonitis in Japan compared with the rest of the world, this type of adverse event should closely monitored when using EGRF inhibitor for cancer treatment in Japan [13, 14, 15].

Management of adverse events required rigorous patient care in this study. Although the overall incidence of Grade 3 adverse events was similar to that reported by others [6, 7, 16–19], most patients required unexpected hospitalization and nutritional support. Yokota et al. evaluated the mucosal findings in 14 Japanese patients who received BRT [20]. Twelve patients (86%) developed Grade ≥3 mucositis, and most of them needed nutritional intervention. Yokota et al. recommended prophylactic percutaneous endoscopic gastrostomy in patients planning to receive BRT for SCCHN. Sakashita et al. reported a high incidence (64%) of Grade ≥3 mucositis/stomatitis in patients receiving BRT [21]. They concluded that Grade ≥3 mucositis/stomatitis and the inability to feed orally were problematic for patients undergoing BRT. Our results were very similar to the results in these reports. Most patients in the current study also required active nutritional support. It was considered that relatively poor patient background, compared with that of those patients who underwent standard cisplatin-based chemoradiotherapy, was responsible for the deterioration of general condition during BRT. We examined the effect of radiotherapy technique and patient factors on the development of dermatitis or mucositis. However, there was no significant association between development of Grade 3 dermatitis/mucositis and patient...
age, sex, the primary tumor subsites or radiation technique. It was reported that a higher radiation dose to the skin was significantly correlated with the development of Grade 3 dermatitis in the cetuximab cohort [9, 22]. Most our patients received the prescribed total dose of radiotherapy, and it was difficult for us to discern the effect of skin dose on the development of Grade 3 dermatitis.

Concerning the management of dermatitis and mucositis, no definitive consensus has yet been established [23]. Bernier et al. devised the grading of and therapy for dermatitis due to cetuximab [24, 25]. They indicated that the glucocorticosteroid creams or ointments could be helpful for treating xerosis, by reducing water loss from the skin. However, there is no consensus regarding the efficacy of glucocorticosteroid in the management of radiation dermatitis induced by cetuximab. Some authors suggest that topical glucocorticoids may potentiate the cutaneous toxicity of EGRF inhibitors [26]. Gutiérrez et al. on the other hand, described in their systematic review that the use of corticosteroids is not contra-indicated in the presence of radiation dermatitis if the overall treatment time of any corticosteroid-containing treatment is limited to 1–2 weeks [27]. In contrast, we have practiced long-term use of steroid cream, because of its versatility and because the steroid contributes to the reduction of inflammation. The topical treatment for wet desquamation was a mixture of dimethyl isopropylazulene and gentamicin sulfate covered with silicon gauzes. Dry desquamation and acne-like skin rashes were treated with topical corticosteroid. In addition, it was considered important to keep the skin clean, moist and anti-inflammatory. To maintain these conditions, it seems that continuous use of the steroid is necessary at this time. In the future, it is expected that more effective topical medicine than steroid cream will be available in clinical practice.

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The limitations of this retrospective study include selection bias and intervention bias. The number of patients was too small to perform meaningful statistical analyses. However, this study showed that BRT was generally tolerable for SCCHN patients in Japan.

CONCLUSION

Concurrent radiotherapy with cetuximab was generally well tolerated. BRT was acceptable for the patients with SCCHN who were either older or had comorbidities. The response rate was 74.2%. Despite Grade 3 dermatitis or mucositis being experienced in considerable numbers of patients, most could have received the planned dose of radiotherapy. However, severe adverse events such as interstitial pneumonia and GI bleeding, neither of which was reported in the Japanese Phase II study, have been experienced. Although it was considered that the employment of cetuximab for Japanese patients with SCCHN was feasible as an alternative for cisplatin-based concurrent chemoradiation, physicians in Japan must be very cautious about using BRT.

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