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

（日本人の頭頸部癌患者に対するセツキシマブ併用放射線治療の初期経験）

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Abstract

In Japan, cetuximab with concurrent radiotherapy (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 7 cycles and median dose of radiotherapy was 70 Gy. Twenty-five (80.6%) patients accomplished planned radiotherapy and 6 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 gastro-intestinal bleeding caused by diverticular hemorrhage during BRT. Grade3 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 was necessary to evaluate late toxicities.

Keyword: Head and neck cancer; Cetuximab; Radiotherapy; Acute toxicity; Initial experience

INTRODUCTION

Numbers of patients with squamous cell carcinoma of the head and neck cancer (SCCHN) has been increased in Japan, and more than 20,000 patients suffered from oral/pharyngeal or laryngeal cancer, accounting for 2.7% of all cancer cases [1,2]. Cisplatin based concurrent chemoradiotherapy is one of the standard treatment for locoregionally advanced SCCHN [3,4]. However, in the clinical practice, patients with poor medical condition sometimes fail to receive full dose of chemotherapy during definitive radiotherapy for SCCHN, where treatment volume includes wide range of oral/pharyngeal mucosa. Cetuximab, epidermal growth factor receptor (EGFR)-targeting monoclonal antibody, has shown the antitumor activity for SCCHN expressing EGFR [5]. Because targeted therapy agents such as cetuximab are directed selectively at specific target, combination of these agents and radiotherapy is considered to be more tolerated than conventional chemotherapy. Bonner et al. reported that bioradiatherapy (BRT) had 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 with and without cetuximab groups in that study. Based on these results, in Japan, 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 of this combination therapy.

MATERIALS AND METHODS

Patients

Between July 2013 and June 2014, 31 non-metastatic SCCHN patients underwent BRT using cetuximab in our hospital. Patient characteristics were shown in Table 1. The median age was 72 years (range; 52 – 83 years). The primary tumor site was 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 higher than or equal to 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 ed. 2009), one was stage I, two were stage II, four were stage III, and 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). The CT-based three-dimensional 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 10-15mm margin to the GTV. In addition, nodal CTV was set by considering lymph node level depending on the primary tumor and involved nodal sites. The planning target volume (PTV) was defined with additional circumferential 5-10 mm margin to accommodate the daily patient set-up uncertainty. Tumor and critical structure delineation were performed on co-registrated 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. The three-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiation therapy (IMRT) was performed. When target volume did not contain large volume of major salivary grand or oral-pharyngeal mucosa, 3DCRT was selected

(n=26), otherwise IMRT was applied (n=5), as an initial treatment. In case of IMRT, PTV was modified by subtracting 3 to 5 mm from the skin surface. After administration of 40 to 50 Gy, target volumes were shrunken to cover the primary tumor and gross nodal disease with generous margins. In 11 cases initially treated with 3DCRT to the dose of 40 to 46 Gy, radiotherapy technique was changed to IMRT for the remaining treatment course because it seemed difficult to deliver adequate dose to the target with safely sparing the spinal cord above 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 a 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 (400mg/day). Oral magnesium supplements were titrated up to 3 tablets of magnesium oxide (250 mg per tablet) given 3 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 of 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, 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 median dose of radiotherapy was 70 Gy. Six patients (19.4%) discontinued cetuximab administration. Only

four patients received less than 6 cycles of cetuximab. One patient who developed infective endocarditis at 36 Gy received only 4 cycles of cetuximab and was not able to complete planned BRT thereafter. Of three patients who received 5 cycles of cetuximab, drug-induced pneumonitis and hypersensitivity reaction developed each in one. Another one patient who received 5 cycles of cetuximab due to severe dermatitis accomplished radiotherapy. Of four patients who received 6 cycles of cetuximab, two changed their treatment strategy at BRT of 56Gy and 66Gy, respectively. In total, 25 (80.6%) patients had accomplished planned 70 Gy of radiotherapy and 6 cycles or more 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 grade3 dermatitis/mucositis are shown in Fig1, 2. Confluent painful mucositis with moderate edema dominated the pharyngeal wall, epiglottis, pahryngo-epiglottic fold, and tongue base of the patient. One month after BRT, still thick yellowish mucositis remains in the pharyngeal wall, epiglottis, and pahryngo-epiglottic fold with increased edema of the epiglottis. Confluent moist desquamation with white-yellowish surface which indicated superficial infection developed in both side of neck down to supraclavicular area corresponding to radiotherapy field. It took almost one month after completion of

BRT to recover skin/mucosa reaction. Grade 2 and 3 acne-like skin rash occurred in seven and two patients, respectively, and the locations of rash were the face, irradiated neck, the chest wall and the back. Grade3 drug-induced pneumonitis occurred in two patients with a smoking history, one patient experienced at the fifth weeks during BRT and the other experienced two weeks after the completion of the radiation therapy (Fig. 3). For both patients, management of pneumonitis required steroid pulse therapy. The latter patient also experienced grade 3 gastro-intestinal (GI) bleeding caused by diverticular hemorrhage during BRT. That patient required endoscopic hemostasis and blood infusion for anemia. Grade3 hypomagnesemia occurred in 2 patients, despite initial attempts for preventing hypomagnesemia using oral magnesium intake.

Eighteen patients required active nutritional support, nasogastric tube feeding in 15 patients and intravenous hyperlimentation in three. The median time of beginning tube feeding was 3.5 weeks after the start of BRT. Fifteen patients with grade 3 mucositis required hospitalization during BRT. In total, twenty-nine patients admitted to hospital due to dysphagia or mucositis. The median time of developing mucositis after the start of radiotherapy was 19 days, and the median time required for healing of mucositis after completion of BRT was 31days.

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. Grade3 mucositis was observed in 14 patients and one patient, respectively for 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 IMRT group. Among 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 and primary tumor subsite between patients with and without grade 3 skin/mucosal toxicities.

Complete response was obtained in 17 and partial response in six, resulting the response rate of 74.2%. During the follow-up period, seven patients relapsed in radiotherapy field. At the time of data analysis, two patients developed multiple lung metastases and died of respiratory failure.

DISCUSSSION

Results of the present study show that grades 3 radiation dermatitis and mucositis occurs in approximately 20% and 52% of HNSCC patients treated with BRT. Although some investigators had reported much higher G3/4 dermatitis in patients receiving BRT [8–11], the incidence rates in the present study are quite similar as compared with those originally reported by Bonner et al. [6]. Most patients could complete BRT and only six patients received less than 6 cycles of cetuximab. Thus,

concerning the compliance of cetuximab and radiotherapy, our findings suggest that BRT for Japanese patients with SCCHN is, in general, tolerable and acceptable treatment. 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 event in this study was similar to that seen in the cetuximab plus radiotherapy arm of the Bonner trial. In three patients, however, unexpected grade 3 toxicities of GI bleeding or interstitial pneumonitis were observed. Murakami et al. reported four patients out of 15 who received BRT experienced GI bleeding which was not yet reported from 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 skin epithelium and pharyngeal mucosa [11]. In the present study, one experienced diverticular hemorrhage requiring endoscopic hemostasis and blood transfusion for anemia during BRT. Although it is still unknown whether GI bleeding was due to racial characteristics of Asian patients or not, physicians in Japan should pay special attention to occurrence of GI bleeding during BRT. Pneumonitis requiring steroid pulse therapy is another concern. Drug-induced lung injury (DLI) requiring steroid pulse therapy was 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. [12] They recommended that in case of suspected or confirmed DLI, the cetuximab-based chemotherapy should be discontinued immediately, and adequate approaches including consultation with a pulmonologist and steroid pulse therapy, should be implemented as soon as possible. Because not a small numbers of patients receiving Gefitinib for non-small cell lung cancer succumbed to death due to interstitial pneumonitis in Japan as compared to in the rest of the world, this type of adverse event should closely monitored when using EGRF inhibitor for cancer treatment in Japan [12,13,14].

Management of adverse events required rigorous patients care in this study. Although the overall incidence of grade 3 adverse events was similar to those reported by others [6,7,15–18], most patients required unexpected hospitalization and nutritional support. It was considered that relatively poor patient's background, as compared with those who underwent standard cisplatin-based chemoradiation, was responsible for deterioration of general condition during BRT. We examined the effect of radiotherapy technique or patient factor on the development of dermatitis or mucositis. However, there was no significant association between development of grade 3 dermatitis/mucositis and patient's age, sex, the primary tumor subsites and radiation technique. It was reported that higher radiation dose to the skin was significantly correlated with the development of grade 3 dermatitis in

the cetuximab cohort [9,19]. Most our patients have received prescribed total dose of radiotherapy, and it was difficult for us to access the effect of skin dose on the development of grade 3 dermatitis.

Concerning the treatment for dermatitis and mucositis, no definitive consensus is still established. [20] Bernier et al. devised the grading and a therapeutic method of dermatitis by cetuximab [21,22]. They indicated that the glucocorticosteroid creams or ointments could be helpful to treat xerosis, which reduce 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 [23]. 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 corticosteroids-containing treatment is limited to 1-2 weeks. [24] In contrast, we have used steroid cream for a long term, because the versatility of steroid was wide and the steroid contributed to the improvement of inflammation. Topical treatment for wet desquamation was the mixture of Dimethyl isopropylazulene and Gentamicin sulfate covered with the silicon gauzes. Dry desquamation and acne-like skin rashes were treated with topical corticosteroid. In addition, it is important to keep the skin clean, moist and anti-inflammatory. To keep these conditions, it seems that the continuous use of the steroid is necessary at this time. In the future, it is expected that more effective topical medicine

than steroid cream can be available in the clinical practice. As for acne-like rash, patients were treated with oral antibiotics, and no patients experienced skin infection in this study.

The limitations of this retrospective study include selection bias and intervention bias. Number of patient 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 had either older age or comorbidities. Response rate was 74.2%. Despite grade3 dermatitis or mucositis experienced in considerable numbers of patients, most could have received planned dose of radiotherapy. It was considered that the employment of cetuximb for Japanese patients with SCCHN was feasible as an alternative for cisplatin-based concurrent chemoradiation, although longer follow-up was necessary to evaluate late toxicities.

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A B C

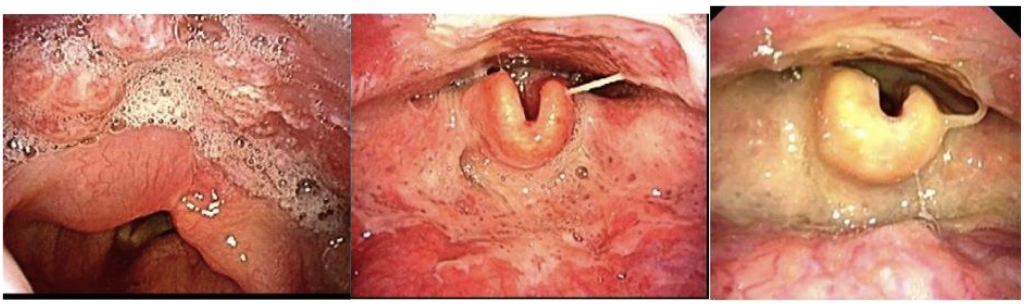

Fig. 1

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.

A B

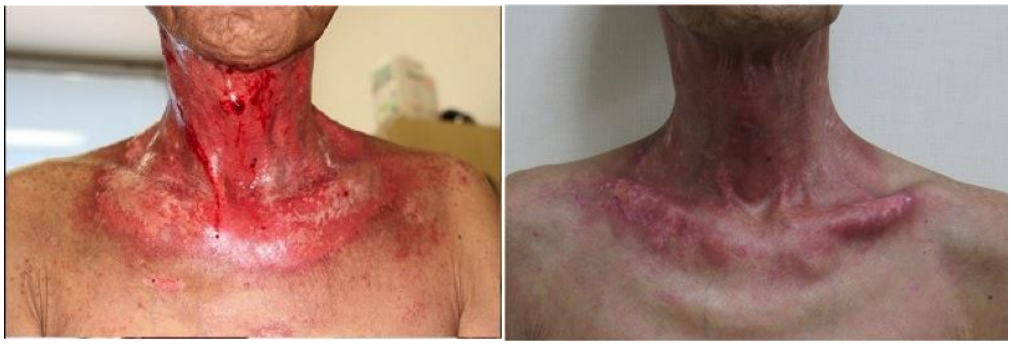

Fig. 2

A) Grade3 dermatitis with contact bleeding occurred at one week after bioradiotherapy.

B) Resolution of dermatitis at 4 weeks after bioradiotherapy.

A B

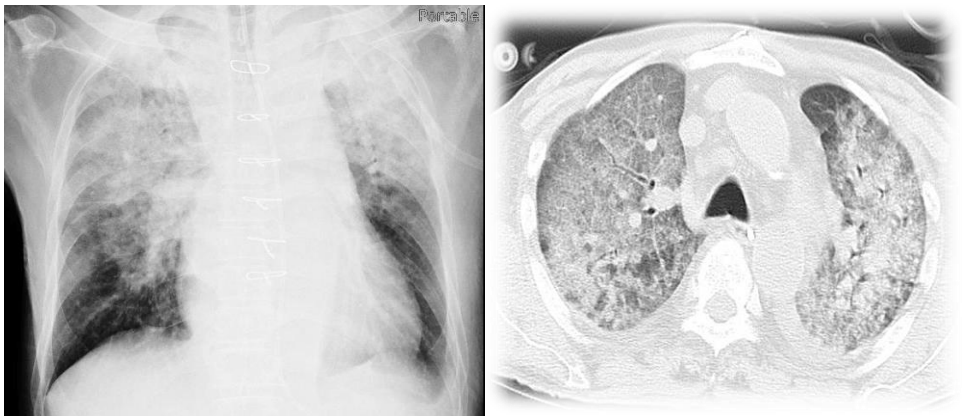

Fig. 3

Drug-induced lung injury (DLI) developed at 2 weeks after the end of bioradiotherapy in patient with oropharynx cancer. He also had diverticular hemorrhage at the second week of bioradiotherapy.

A) Bilateral interstitial infiltration and consolidation can be seen on chest X-ray image.

B) Chest computed tomography scan shows widespread ground-glass opacity with peribroncho-vascular thickness which was predominant in bilateral upper lung.

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
II	2
III	4
IVA	23
IVB	1

*: reason not receiving standard cisplatin-based chemoradiation

Table 2. Cycles of cetuximab administration and dose of radiotherapy

Cetuximab cycles	
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

	Grade 2 (%)	Grade 3 (%)
Dermatitis	19 (61.3)	6 (19.4)
Mucositis	15 (48.4)	15 (48.4)
Xerostomia	10 (32.3)	0 (0)
Acune-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)

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