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Title: Comparison of acute toxicities associated with cetuximab-based bioradiotherapy and platinum-based chemoradiotherapy for head and neck squamous cell carcinomas: a single-institution retrospective study in Japan.

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Running title: Acute toxicities of cetuximab-based BRT and platinum-based CRT

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ABSTRACT

Conclusion. Grade ≥ 3 mucositis/stomatitis and inability to feed orally were problematic for patients undergoing cetuximab-based bioradiotherapy (BRT) as well as platinum-based chemoradiotherapy (CRT). Severe mucositis/stomatitis and radiation dermatitis should be addressed carefully in patients undergoing cetuximab-based BRT as well.

Objectives. The efficacy of cetuximab-based BRT in locally advanced head and neck squamous cell carcinomas has been established. However, the safety of cetuximab-based BRT in comparison with platinum-based CRT is currently under investigation.

Method. We retrospectively analyzed 14 patients undergoing cetuximab-based BRT and 29 patients undergoing platinum-based CRT to compare the incidence of acute toxicities. In BRT group, an initial cetuximab loading dose of 400 mg/m² was delivered one week before the start of radiotherapy. Seven weekly infusions of 250 mg/m² of cetuximab followed during the definitive radiotherapy. In CRT group, cisplatin was administered at a dose of 40mg/m² weekly during the definitive radiotherapy.

Results. The BRT group had a higher incidence of Grade ≥ 3 radiation dermatitis than did the CRT group (36% vs 3%, respectively, $p < 0.01$). The incidence rate of Grade ≥ 3 mucositis/stomatitis was 64.3 % and 41.4% in the BRT and CRT group, respectively ($p = 0.1484$), while the incidence rate of the inability to feed orally was 38.5% and 55.2%, respectively ($p = 0.2053$).

INTRODUCTION

Platinum-based chemoradiotherapy (CRT) has been the standard treatment for patients with locally advanced head and neck squamous cell carcinomas (HNSCC) with the aim of preserving function or improving survival. However, this intensive chemoradiotherapy is associated with significant acute and late toxicity [1-4]. In our institution, weekly cisplatin regimen ($40\text{mg}/\text{m}^2$) has been used for chemoradiotherapy since 2006 [5,6]. The feasibility of this regimen has been examined by Japan Clinical Oncology Group (JCOG-1008) in comparison with the tri-weekly cisplatin regimen ($100\text{mg}/\text{m}^2$), which has been regarded as the world standard for intensive chemoradiotherapy [7].

A trial by Bonner et al. demonstrated the efficacy of cetuximab in association with high-dose radiation therapy in locally advanced HNSCC [8,9]. They reported that the incidence of acute toxicities commonly associated with radiotherapy of the head and neck, including mucositis, xerostomia and dysphagia, did not differ significantly between a cetuximab-based BRT arm and a radiotherapy alone arm. However, the safety of cetuximab-based BRT in comparison with platinum-based CRT is currently under investigation. In Japan, cetuximab has been available for patients with HNSCC since December 2012. Yokota et al. first reported a high incidence (85.7%) of Grade ≥ 3 mucositis/stomatitis in Japanese patients undergoing cetuximab-based BRT and emphasized the need of prophylactic percutaneous endoscopic gastrostomy [10]. We analyzed the incidence of acute toxicities in order to compare the level of safety of cetuximab-based BRT and platinum-based CRT.

MATERIAL AND METHODS

Patients. A total of 43 patients with locally advanced HNSCC were treated by

platinum-based CRT or cetuximab-based BRT at our institution between April 2013 and November 2014.

Approval for this study was obtained from the Institutional Review Board at Hokkaido University. Completion of the survey was regarded as implied consent for participation.

Patient eligibility and treatment selection. An Eastern Cooperative Oncology Group performance status of 0-1 was required in addition to the following criteria: a white cell count of at least 4,000/mm³, a platelet count of at least 100,000/mm³, a hemoglobin concentration of at least 9.5 g/dL, serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase levels of less than twice the upper limit of the normal range, a total bilirubin concentration of <2.0 mg/dL, a serum creatinine concentration of <1.5g/dL, a blood urea nitrogen concentration of <25 mg/dL, and a creatinine clearance of >60 mL/min.

In general, cisplatin-based CRT was recommended for patients aged 75 years or younger. However, cetuximab-based BRT was considered for patients who were intolerant to cisplatin chemotherapy due to problem with organ function, such as renal disease, liver disease, and cardiovascular disease.

Bioradiotherapy and chemoradiotherapy. The irradiation plan was 40 Gy in 20 fractions of 2 Gy over four weeks for the primary site and all nodal areas, immediately followed by a boost of 30 Gy in 15 fractions to the primary cancer and metastatic nodal area over an additional three weeks (total dose, 70 Gy).

In cetuximab-based BRT group, an initial cetuximab loading dose of 400 mg/m² was delivered over 120 min, one week before the start of radiotherapy. Seven weekly infusions of 250 mg/m² of cetuximab followed during radiotherapy. Doxycycline 100mg/day was administered orally for all patients to prevent acneiform rash.

In platinum-based CRT group, cisplatin was administered at a dose of 40mg/m² on weeks 1, 2, 3, 5, 6, and 7 of the radiotherapy. Patients received

prophylactic hydration and 5HT₃ antagonists plus dexamethasone and/or neurokinin-1 receptor antagonist for anti-emetic prophylaxis.

Dentists provided weekly oral care for all patients, and all patients were educated on skin care by pharmacists and nurses.

Evaluation and statistics. Toxicities were graded using the Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0. Pre-treatment nutrition status was evaluated according to the method used in previous reports. Nutritional factors included three constitutional indices, serum albumin and Onodera's prognostic nutrition index, calculated as $10 \times \text{serum albumin (g/dl)} + 0.005 \times \text{total lymphocyte count (per mm}^3\text{)}$ [11-13]. Differences in TN classification, gender, ~~and~~ primary sites, and the probability of acute toxicities were evaluated by chi-squared test. Differences in age and nutrition index were calculated using an unpaired t-test. The incidence rates of acute complications in the BRT and CRT groups were compared by chi-squared test. Fisher's test was applied for values <4 . In addition, the Kaplan-Meier method was used for the incidence rate curves of Grade ≥ 3 mucositis/stomatitis and the inability to feed orally.

The time of interest was the period from the start of radiotherapy to Grade ≥ 3 mucositis/stomatitis or the inability to feed orally. Patients requiring complete parenteral nutrition or tube feeding due to the primary tumor at the start of treatment were excluded from the calculation of the incidence rate of inability to feed orally. A log-rank test was used to compare the incidence rate curves.

The durations of both Grade ≥ 3 mucositis/stomatitis and the inability to feed orally were calculated. However, patients who did not recover due to primary disease or treatment-related death were excluded for the calculation of duration.

RESULTS

Patient demographics. Fourteen patients underwent cetuximab-based BRT. In this

group, thirteen patients were hospitalized during treatment, and the remaining patient who started BRT in an out-patient setting was hospitalized after seven courses of cetuximab administration due to severe mucositis. This group also consisted of eight patients who preferred BRT to CRT or radiation alone, two patients who had renal disease, one patient who had liver cirrhosis, and three patients who had cardiovascular disease.

Twenty-nine patients underwent platinum based CRT in a hospital setting.

Patient demographics for each group are shown in Table 1. The cetuximab-based BRT group consisted of older patients than did the platinum-based CRT group. The mean nutrition indices of the BRT group and the CRT group were 45.9 and 52.4, respectively ($p < 0.01$).

Treatment compliance and clinical outcomes. In cetuximab-based BRT group, the median irradiation dose was 70 Gy (range, 60 to 70 Gy). Cetuximab was weekly administered a median of 8 times (range, 5 to 8 times). Two patients stopped cetuximab administration after five and six courses because of poor compliance. One patient stopped cetuximab administration after five courses because of severe sepsis and interstitial pneumonia. Intensive treatment (e.g., ventilator support and catecholamine support) was required for 60 days, after which the patient recovered and achieved a complete response of his locoregional disease.

In platinum-based CRT group, the median irradiation dose was 70 Gy (range, 52 to 70 Gy). Cisplatin was weekly administered a median of five times (range, 1 to 6 times). One patient of CRT group developed severe sepsis resulting from aspiration pneumonia following severe mucositis, and stopped radiotherapy after a dose of 52 Gy. Unfortunately, he died of uncontrolled pneumonia and sepsis.

In BRT group, 9 patients (64%) remain alive without any evidence of disease. One patient has died of recurrent primary disease, and two patients have died of lung metastases. The remaining two patients are alive with recurrent primary diseases.

In CRT group, 23 patients (79%) are alive without any evidence of disease.

Two patients have died of recurrent primary disease, one patient has died of severe acute toxicities, and one patient has died of other disease. The remaining two patients are alive with lung metastases.

Acute toxicities. Grade ≥ 3 acute toxicities in each group are shown in Table 3. There were significant difference in the incidence of Grade ≥ 3 leukopenia between BRT and CRT group (0% vs 52%, $p < 0.01$), and the BRT group had a significantly higher incidence of Grade ≥ 3 radiation dermatitis than did the CRT group (43% vs 3%, $p < 0.01$).

Incidence rate curves of Grade ≥ 3 mucositis/stomatitis and inability to feed orally. The incidence rate of Grade ≥ 3 mucositis/stomatitis in the BRT and CRT group was 64.3 % and 41.4%, respectively ($p = 0.1484$, Figure 1). The median numbers of days to the onset of Grade ≥ 3 mucositis/stomatitis in the BRT and CRT groups were 38 and 38.5 from the start of radiotherapy, respectively. The median duration of Grade ≥ 3 mucositis/stomatitis in the BRT group was 21 days, which was equal to that in the CRT group.

One patient in the BRT group required complete tube feeding due to his primary tumor at the start of treatment. This case was excluded for the calculation of the incidence rate of inability to feed orally. The incidence rate of the inability to feed orally in the BRT and CRT group was 38.5% and 55.2%, respectively ($p = 0.2053$, Figure 2). The median numbers of days to the onset of inability to feed orally in the BRT and CRT groups were 35 and 23.5 from the start of radiotherapy, respectively. No significant differences were observed in the incidence rates of either Grade ≥ 3 mucositis/stomatitis or the inability to feed orally. The median durations of inability to feed orally in the

BRT and CRT groups were 46 and 40 days, respectively.

DISCUSSION

The cetuximab-based BRT was expected to be safer than the more intensive chemoradiotherapy based on the results of Bonner's trial [8,9]. Although patient's demographics showed marked tendency for cetuximab-based BRT to be applied for older patients who did not tolerate platinum-based CRT in our current study, patients undergoing BRT completed with a median of 70 Gy and cetuximab administration a median of 7 times. However, it was found that there were no significant differences in the incidence of either Grade \geq 3 mucositis/stomatitis or inability to feed orally between the groups. It is, therefore, possible that cetuximab-based BRT is not significantly safer than intensive chemoradiotherapy.

The incidence rate of Grade \geq 3 mucositis/stomatitis for cetuximab-based BRT was reported to range from 21% to 57% in previous papers from US and Europe [8,9,14-16]. However, this rate increased to 64.3%-85.7% in previous papers from China and Japan and in this current study [10,17,18]. It is speculated that Asians experience severe mucositis/stomatitis at a higher frequency than Westerners when treated with cetuximab-based BRT.

We compared the incidence rates of acute toxicities between BRT group and CRT group in this current study. It is likely that Grade \geq 3 mucositis/stomatitis was associated with cetuximab-based BRT with an increased frequency comparing platinum-based CRT, though there was no significant difference statistically. Yokota et al. reported that Grade \geq 3 mucositis/stomatitis was associated with BRT with a high frequency (85.7%). And he found that characteristic white-coated mucosal lesion covering a wide area of pharynx. In our study, same lesion was observed in 7 cases

(78%) of all 9 cases with Grade \geq 3 mucositis/stomatitis in the BRT group. In addition, cetuximab-based BRT increased significantly the incidence of Grade \geq 3 radiation dermatitis comparing platinum-based CRT. From those results, it was considered that severe mucositis/stomatitis and radiation dermatitis should be addressed carefully for patients undergoing cetuximab-based BRT. Therefore, it was considered to be difficult to use cetuximab-based BRT for patients who cannot manage self oral care and self skin care carefully or those with poor performance status.

Sepsis is one of the more common fatal toxicities experienced by patients treated with BRT or CRT. In our current study, sepsis was observed in 21% of patients in the BRT group. All three patients with sepsis had Grade \geq 3 mucositis/stomatitis in our study. Therefore, it was speculated that there is a significant correlation between sepsis and mucositis. Moreover, we experienced one patient with severe sepsis who needed intensive treatment consisting of ventilation support and catecholamine support. Therefore, sepsis should be carefully addressed during cetuximab-based BRT.

There were some limitations to this study. The clearest limitation is the strong selection bias between the two treatment arms. Inequalities of age and nutrition status between the BRT and CRT groups could also have affected the potential for acute toxicities. Moreover, the retrospective nature and small number of patients were also shortcomings. A multi-institutional prospective study should be planned to allow a less biased comparison of the acute toxicities.

Although the cetuximab-based BRT group consisted of older patients and those with poorer nutrition, the cetuximab-based BRT was more likely to decrease the incidence of the inability to feed orally. It is, therefore, possible that cetuximab-BRT offers an advantage in terms of oral feeding.

CONCLUSION

The incidence of radiation dermatitis was higher in the patients treated with cetuximab-based BRT than in those treated with platinum-based CRT. In addition, cetuximab-based BRT was more likely to decrease the incidence of inability to feed orally, but increase the incidence of Grade \geq 3 mucositis/stomatitis in comparison with platinum-based CRT. Cetuximab-based BRT is not always easier to apply than platinum-based CRT. In particular, severe mucositis/stomatitis and radiation dermatitis should be addressed carefully for patients undergoing cetuximab-based BRT.

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FIGURE LEGENDS

Table 1. Patient demographics

Table 2. The incidence rates of Grade \geq 3 acute toxicities (CTCAE Version 3)

Figure 1. Incidence rate of Grade \geq 3 mucositis/stomatitis

Figure 2. Incidence rate of the inability to feed orally

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Figure 1.

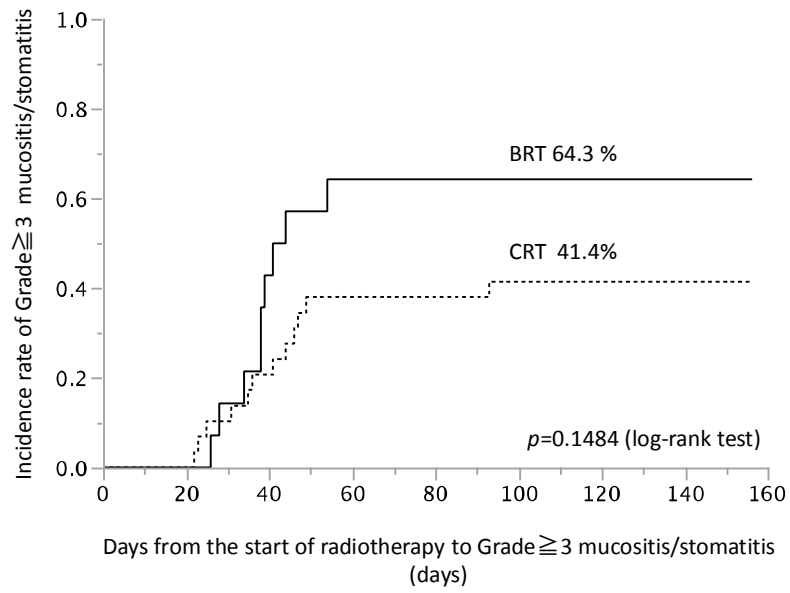


Figure 2.

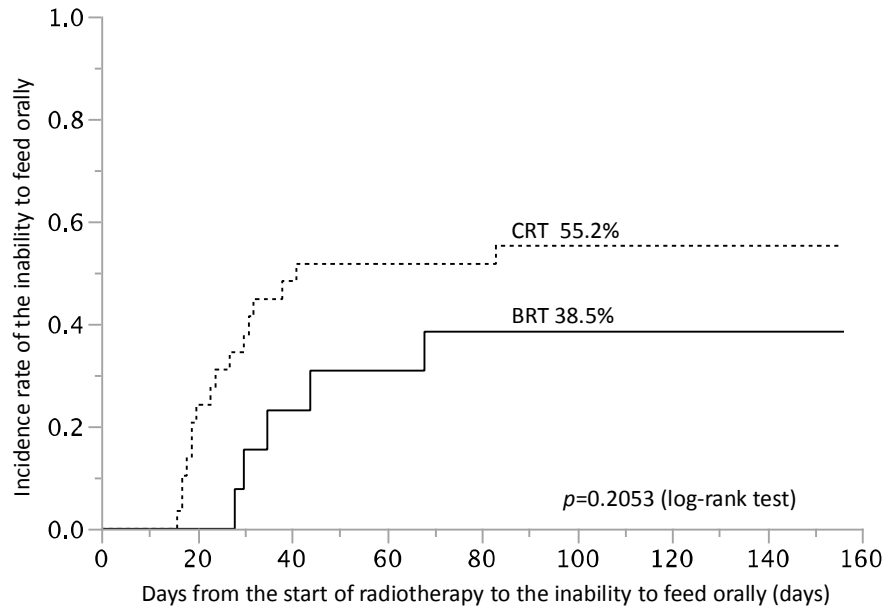


Table 1. Patient demographics

		BRT	CRT	p value
No. of patients		14	29	
Median age (range)		75 (58-81)	61 (41-75)	<0.01
Gender	Male	13	27	0.976
	Female	1	2	
Primary site	Hypopharynx	6	14	0.739
	Others	8	15	
T classification	1-2	8	13	0.449
	3-4	6	16	
N classification	0-1	8	8	0.06
	2-3	6	21	
Prognostic nutritional index mean (range)		45.9 (37.8-54.9)	52.4 (45.9-67.1)	<0.01

BRT: Cetuximab-based bioradiotherapy, CRT: Platinum-based chemoradiotherapy

Table 2. The incidence rates of Grade \geq 3 acute toxicities (CTCAE Version 3)

	BRT (n=14)	CRT (n=29)	p value
Leukopenia	-	52% (15/29)	<0.01
Neutropenia	-	41% (12/29)	<0.01
Febrile neutropenia	-	21% (6/29)	0.154
Anemia	7% (1/14)	10% (3/29)	1
Thrombocytopenia	-	7% (2/29)	1
Mucositis/stomatitis	64% (9/14)	41% (12/29)	0.279
Radiation dermatitis	43% (6/14)	3% (1/29)	<0.01
Skin reaction	7% (1/14)	-	0.326
Renal dysfunction	-	-	-
Pneumonia	7% (1/14)	7% (2*/29)	1
Sepsis	21% (3/14)	7% (2*/29)	0.309

BRT: Cetuximab-based bioradiotherapy, CRT: Platinum-based chemoradiotherapy

* Of these, one patient died of uncontrolled pneumonia and severe sepsis (Grade 5).