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Prophylactic bundle for radiation-induced oral mucositis in oral or oropharyngeal cancer patients

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Abstract

Objective: In order to prevent and treat radiation-induced adverse events, especially oral mucositis, in patients with oral or oropharyngeal cancer receiving radiotherapy or chemoradiotherapy, a prophylactic bundle, i.e., a set of oral care management procedures, is conducted and assessed. *Subjects and methods:* The subjects were 30 patients with squamous cell carcinoma of the oral cavity or oropharynx who underwent radiotherapy. The patients received the prophylactic bundle to prevent radiation-induced oral mucositis during radiotherapy. *Results:* Severe oral mucositis, grade 3, was observed in 5 of 30 patients (17%). The occurrence of oral mucositis was lower than in previous reports. The prophylactic bundle included the use of spacers, administration of pilocarpine hydrochloride, appropriate oral care, and use of steroid ointment during radiotherapy. *Conclusions:* This preliminary study suggests that the prophylactic bundle, when performed in oral or oropharyngeal cancer patients, decreases severe radiation-induced oral mucositis. Further evaluation is needed in multi-centre, prospective, randomized trials.

Keywords: oral mucositis; radiotherapy; head and neck cancer; prophylactic bundle

Introduction

Current treatments for head and neck cancer are surgery, radiotherapy (RT), chemotherapy (CT), and combinations thereof [1]. Exposure of the oral cavity and salivary glands to high-dose RT can have dramatic effects on the patient's oral health. Common acute toxic effects associated with RT include mucositis [2], dry mouth (xerostomia) [3], oral candidiasis [4], loss of taste, dysphagia, and hoarseness caused by laryngeal edema [5, 6]. In particular, oral mucositis causes severe pain and affects the dietary intake, oral infections, mouth care, and quality of life of the patient [2].

Oral mucositis occurs in most patients who undergo RT and chemoradiotherapy (CRT) for head and neck cancers [7]. The mechanisms of radiation-induced oral mucositis are believed to be similar to those of CT-induced mucositis [2]. The generation of reactive oxygen species (free radicals) with RT or CT plays a role in the initiation of mucosal injury. Free radical activation leads to the upregulation of pro-inflammatory cytokines; cytokines such as tumor necrosis factor-alpha (TNF-α), produced mainly by macrophages, injure mucosal cells and activate molecular pathways that amplify mucosal injury. In a systematic review, the mean incidence of oral mucositis in patients with head and neck cancer receiving RT or CRT was 80%, with 34–57% of the patients experiencing severe oral mucositis [5].

Supportive care during RT or CRT includes oral care, narcotic analgesics, intravenous hydration, and enteral nutrition, as necessary [1]. However, no method for preventing or treating oral mucositis has met with large-scale approval or use. Indeed, no intervention has yet been able to prevent or successfully treat oral mucositis. It would seem to be necessary to combine various interventions that act at different phases of mucositis [8]. In this study, we developed a prophylactic bundle of treatments to prevent radiation-induced oral mucositis

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in patients with oral or oropharyngeal cancer receiving RT, and examined its efficacy in preventing severe oral mucositis.

Materials and methods

Patient eligibility

The subjects consisted of 30 patients, 50 to 84 years old, with squamous cell carcinoma of the oral cavity or oropharynx, who underwent RT or CRT at Nagasaki University Hospital between October 2011 and February 2013. Patients scheduled to undergo RT to the oral or oropharyngeal region were referred immediately to the Oral Management Center of Nagasaki University Hospital to receive oral management before and during RT. All patients gave written informed consent. The study was approved by the ethics committee of Nagasaki University Hospital. Age, gender, primary site, TN stage, RT dose, use of CT, nutrition, and use of opioid analgesics during RT were examined from patient medical records.

Oral care management procedures

We refer to these procedures as the prophylactic bundle used to prevent radiation-induced oral mucositis.
1) Extraction of any infected tooth before RT: Before beginning RT, each patient underwent extraction of any infected tooth to prevent osteoradionecrosis of the jaws, according to the criterion of Yamagata et al. [9] (Table 1). 2) Use of spacers: During RT, the patient's entire dentition was covered by spacers to prevent scatter radiation, especially coming from any metallic restoration(s) and enamel surfaces exposed to the oral mucosa, except in edentulous jaws (Figure 1). The thickness of the spacers was typically 3 mm; however, for metal restorations in molars, the thickness of the spacers was 5 mm. 3) Administration of pilocarpine hydrochloride: Pilocarpine is a parasympathomimetic agent that functions primarily as a muscarinic agonist and causes pharmacological stimulation of exocrine glands in humans, resulting in salivation [10]. Pilocarpine was administered at a dose of 5 mg three times daily beginning the first day of RT until at least the end of RT. If the side effects such as sweating or nausea occurred, patients were administered a dose of 2.5 mg four times daily. Pilocarpine was contraindicated in patients with obstructive pulmonary disease, severe ischemic heart disease, stricture of the gastrointestinal tract or the bladder neck, Parkinson's disease, and iritis. Twelve patients were given pilocarpine in this study. 4) Oral care: Patients received professional oral care by a dental hygienist at least weekly until the end of RT. The oral care method included removal of dental plaque via professional mechanical tooth-cleaning methods and gentle removal of mucosal debris with a water-drenched sponge, to keep the oral cavity as clean as possible. 5) Oral rinsing and saliva substitute: Oral rinsing with azulene, 2% viscous lidocaine, or lidocaine mixed with an equal volume of azulene was performed at least four times daily. Azulene mouthwash is approved for the treatment of oral mucositis. In addition, patients used a commercial saliva substitute, REFRE-CARE H (Otsuka Pharmaceutical, Tokyo, Japan) containing the antibacterial agent hinokitiol. 6) Steroid ointment: When oral mucositis appeared, 0.1% steroid ointment (dexamethasone) softens with olive oil was applied to the oral mucosa four times per day, after meals and before bedtime. The olive oil was used to soften the steroid ointment. 7) Topical fluoride gels: When the salivary gland is radiated, salivary secretion is reduced and the risk of dental caries increased. Topical fluoride gels were used to help prevent dental caries before the onset of oral mucositis. Patients were education about the risk of dental caries, osteoradionecrosis, and the need for self-care with fluoride toothpastes after RT.

Table 1 Criteria for tooth extraction before radiotherapy [9]

Apical periodontitis
symptomatic
asymptomatic
periapical radiolucency of the maximal diameter greater than 5mm (If there is sufficient time for treatment, teeth are treated with root canal filling.)
Marginal periodontitis
symptomatic (gingival swelling, pain, purulent discharge)
asymptomatic
severe mobility
a probing depth greater than 8mm
Partially erupted third mollar
pericoronitis or purulent drainage

Figure 1 Spacer to prevent scatter radiation coming from metallic restorations and enamel exposed to the oral mucosa. The spacers were 3 or 5 mm thick.

Evaluation of oral mucositis

Oral mucositis was recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, ver. 4.0). The criteria for oral mucositis were as follows: Grade 1: asymptomatic or mild symptoms and intervention not indicated; Grade 2: moderate pain, but not interfering with oral intake or modified diet; Grade 3: severe pain and interfering with

oral intake; Grade 4: life-threatening consequences and urgent intervention indicated; Grade 5: death

Statistical analyses

The collected data were analyzed using Ekuseru-Toukei 2010 for Windows (Social Survey Research Information, Tokyo, Japan). Chi-square test was used to compare the prevalence of grades of oral mucositis according to two variables: chemotherapy and the use of opioid analgesics; a p-value of <0.05 was considered significant.

Results

Patient characteristics

Of the 30 patients, 29 were referred to the Oral Management Center before RT, and 1 was referred for oral care after developing oral mucositis during RT. The background factors of the patients are summarized in Table 2. The primary tumor was in the oral cavity in 20 cases and in the oropharynx in 10 cases. Most patients had stage 2 or 4 tumors (80%) and stage 0–2 nodes (100%). Concomitant CT was performed in 21 patients. The CT regimen was a combination of cisplatin and 5-fluorouracil (5FU) in ten patients, cisplatin alone in eight, tegafur-gimeracil-oteracil (S-1) in two, and cetuximab in one patient. The daily RT dose was 1.8 or 2.0 Gy.

Table 2 Patient characteristics

		n (%)
Sex	male	23 (77)
	female	7 (23)
TN stage	T1	3 (10)
	T2	11 (37)
	T3	3 (10)
	T4	13 (43)
	N0	8 (27)
	N1	3 (10)
	N2	19 (63)
	N3	0 (0)
Therapy	postoperative chemoradiotherapy	12 (40)
	postoperative radiotherapy	8 (27)
	chemoradiotherapy	9 (30)
	radiotherapy alone	1 (3)
Daily dose	1.8	18 (60)
	2	12 (40)
	mean+S.D.	**range**
Total dose (Gy)	60.6+5.5	38-66
Age	63.6+9.5	50-84

Clinical outcomes

The RT was completed in 28 patients, while it was discontinued because of a psychiatric disorder (total 38 Gy) in one and ended with the death of another patient from renal dysfunction (total 48 Gy). No patient had to discontinue RT due to severe oral mucositis (Table 3). Severe oral mucositis of grade 3 was observed in 5 of 30 patients (17%). No oral mucositis of grades 4–5 were observed. Severity of oral mucositis tended to be enhanced with CT (Table 4). One of the five patients with grade 3 oral mucositis received oral ingestion and tube feeding because of severe oral pain, and two patients consumed soft food or liquid diets. Eleven of the patients (37%) were treated with opioid analgesics because of pain from oral mucositis or cancer. The higher grade of oral mucositis was observed in patients using opioid analgesics, but the difference was not significant ($p=0.071$).

Table 3 Completion of radiotherapy in the patients

	n (%)
Completion of radiotherapy	
completed on schedule	26 (87)
discontinuation	2[a] (7)
stopping due to adverse events	1[b] (3)
death	1[c] (3)

[a] because of surgery and nausea by chemotherapy
[b] because of psychiatric disorder
[c] because of renal dysfunction

Table 4 Severity of oral mucositis according to each treatment during radiotherapy

	Oral mucositis			P value[d]
	Grade 1	Grade 2	Grade 3	
Chemotherapy				
presence	4	12	5	0.273
absence	2	7	0	
Type of nutrition				
tube feeding[a]	0	2	1	—
oral ingestion	5	13[b]	3[c]	
oral ingestion & tube feeding	1	4	1	
Use of opioid analgesic				
presence	1	6	4	0.071
absence	5	13	1	
n (%)	6 (20%)	19 (63%)	5 (17%)	

[a] since before radiotherapy.
[b] One patient discontinued oral ingestion because of anastomotic leakage in the neck.
[c] One patient discontinued oral ingestion because of prevention of aspiration pneumonia.
[d] Chi-square test was conducted.

Discussion

Thirty patients with oral or oropharyngeal cancer received oral care during RT with or without CT. The occurrence of severe oral mucositis of grade 3 in patients receiving the oral management procedures was 17%. In a 2003 systematic review, the mean incidence of severe

oral mucositis in patients with head and neck cancer receiving RT with or without CT was 34–57%. This review assessed the distribution of the five mucositis scales used in the trials, and NCI-CTC was used in 10% of 33 trials [5]. Another study demonstrated that the prevalence of severe oral mucositis was 57% in 135 head and neck cancer patients receiving RT with or without CT and oral mucositis was recorded according to the EORTC/RTOG criteria [3]. This suggests that our prophylactic bundle of treatments to prevent radiation-induced oral mucositis in RT reduced severe oral mucositis, as compared to previous studies. No interventional study of oral care during RT has been able to successfully prevent or treat oral mucositis in head and neck cancer patients. The Mucositis Study Group of MASCC/ISOO reviewed clinical practice guidelines for the care of patients with oral mucositis and recommended oral assessment prior to the initiation of cytotoxic therapy to treat oral/dental infection and traumatic surfaces, maintenance of good oral hygiene, reducing oral irritants, and frequent oral rinsing and effective pain management when pain due to mucositis occurred [11]. According to a systematic review [12], cryotherapy (ice chips) and keratinocyte growth factor (palifermin) [13, 14] helped prevent mucositis, and sucralfate effectively reduced the severity of mucositis while seven other interventions showed weaker evidence of benefit, including *Aloe vera*, amifostine, intravenous glutamine, granulocyte-colony stimulating factor (G-CSF), honey, laser treatment, and antibiotic lozenges containing polymyxin/tobramycin/amphotericin (PTA). However, cryotherapy is not useful for preventing oral mucositis in patients undergoing RT; regarding palifermin, there is no definitive evidence for its safety or efficacy profile [15]; and sucralfate is not recommended in the practice guidelines mentioned above (MASCC 2008). Therefore, to date, no single method that can prevent or treat oral mucositis effectively during RT has been reported. We believe that it is necessary to combine various interventions that act on the different phases of mucositis [8].

Here, we outlined the oral management used to reduce or prevent adverse events in oral or oropharyngeal cancer patients receiving RT with or without CT (Table 5). The protocol has three important steps that should be performed before, during, and after RT. First, a pre-RT oral examination and treatment are needed to remove any infected dental/oral foci before beginning RT [16] to prevent osteoradionecrosis, which is a very serious complication [17] involving the irreversible, progressive devitalization of irradiated bone, and is characterized by necrotic soft tissue and bone that fails to heal spontaneously [4]. Second, during RT, the oral cavity should be kept as clean and moist as possible to decrease symptoms of oral mucositis, oral candidiasis [18], and herpes simplex virus-1 infection. RT induces xerostomia, and saliva substitutes and cholinergic stimulants (pilocarpine) are helpful [10, 19]. The oral cavity should be monitored and should receive professional oral care at least once per week until the end of RT. Steroid ointment therapy is especially important to prevent severe oral mucositis. We used a mixture of dexamethasone ointment and olive oil immediately after oral mucositis appeared. We think that this is one of the most important treatments in our prophylactic bundle. Third, after the completion of RT, radiation-induced xerostomia is near universal in long-term survivors, and is moderate-to-severe in about 60% of patients [20], and those patients have the highest rate of decayed/missing/filled teeth. Therefore, patients should use fluoride products and should continue to be followed to keep the teeth and gums healthy [1, 21, 22]. We think that this oral management is applicable to patients receiving RT for head and neck cancers in addition to oral or oropharyngeal cancer.

Table 5 Oral management procedures

Pre-radiotherapy	
	extraction of infected teeth
	preparation of spacers
During radiotherapy	
	administer of pilocarpine hydrochloride
	weekly professional oral care
	oral rinsing and saliva substitute
	use of olive oil-based steroid ointment
After radiotherapy	
	topical application of fluoride
	recall at dental office

Our study has two limitations. First, the sample size was small. Because head and neck cancer makes up 6% of all cancers [23] and Nagasaki University Hospital had approximately 30 patients with oral or oropharyngeal cancer receiving RT in 18 months. However, RT leads to severe oral mucositis and other adverse events. Therefore, we need to indicate that oral management can prevent adverse events as soon as possible. Second, we did not have a control group. Although, we tried to compare these results with a past group of oral or oropharyngeal cancer patients who did not receive specific oral care during RT in our hospital, the clinical impression of oral mucositis was not described using the same criteria in patient medical records. Therefore, we compared the effects in this study with previous studies in other hospitals.

Conclusion

This preliminary study indicated that the incidence of severe oral mucositis was lower than previous systematic review and suggested that our prophylactic bundle of treatments to counteract radiation-induced oral mucositis in patients with oral or oropharyngeal cancer was effective. Further study, in a multi-centre, prospective, randomized clinical trial, is needed to confirm the efficacy of these treatments.

Conflict of interest

All the authors declare that they have no conflict of interest.

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