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Preventive effects of betamethasone valerate ointment for radiation-induced severe oral mucositis in patients with oral or oropharyngeal cancer: protocol for a multicentre, phase II, randomised controlled trial (Bet-ROM study)

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ABSTRACT

Introduction This is a randomised, multi-centre, open-label, phase II study to evaluate the efficacy of betamethasone valerate ointment on radiation-induced oral mucositis in patients with head and neck cancer undergoing concomitant radiotherapy with cisplatin or cetuximab.

Methods and analysis The trial will take place at seven hospitals in Japan. Patients will be randomised (1:1) into betamethasone and control groups after the occurrence of grade 1 oral mucositis. In the betamethasone group, patients will use betamethasone valerate ointment five times a day, in addition to usual oral hygiene guidance. The primary endpoint is the incidence and onset time of grade 3 oral mucositis. The secondary endpoints are the incidence and onset time of grade 2 oral mucositis, incidence and onset time of oral candidiasis, completion of radiation therapy and adverse events. Target accrual is 102 patients with a two-sided type I error rate of 5% and 80% power to detect an 80% risk reduction in the incidence of grade 3 oral mucositis.

Ethics and dissemination This study was approved by the Clinical Research Review Board of Nagasaki University (No. CRB20-009). All participants will be required to provide written informed consent. Findings will be disseminated through scientific and professional conferences and peer-reviewed journal publication. The datasets generated during the study will be available from the corresponding author on reasonable request.

Trial registration number jRCTs071200013.

Strengths and limitations of this study

- This study will be the first randomised controlled trial to evaluate the prevention of severe oral mucositis using a strong-class steroid ointment.
- This study will have clinical implications for head and neck cancer patients undergoing radiotherapy.
- Data centres and registration systems, independent of researchers, will be used in the study.
- This study has the limitation of being an open-label trial.

INTRODUCTION

Radiation therapy (RT) for oral or oropharyngeal cancers often results in severe oral mucositis. Grade 2 oral mucositis, which requires a change in diet due to oral pain, occurs in more than 90% of patients. Grade 3 oral mucositis, which makes oral feeding difficult, occurs in 14% of patients receiving RT alone, while it occurs in 35% of those receiving combination therapy of RT and chemotherapy or biotherapy such as with cisplatin or cetuximab.[1] Oral mucositis not only decreases the patient's quality of life, but can also lead to RT interruption and affect life prognosis. Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) Clinical Practice Guidelines recommends that benzydamine mouthwash be used to prevent oral mucositis in patients with head and neck cancer receiving moderate dose RT without concomitant chemotherapy,[2] but benzydamine mouthwash cannot be used in Japan and there is little evidence that it is effective for RT combined with cisplatin or cetuximab.

Dermatitis at the irradiated site is inevitable during RT. Therapy for RT-induced dermatitis involves keeping the skin clean and moist and applying medium-class steroid ointments

such as hydrocortisone butyrate ointment 0.1% for grade 1 dermatitis and strong-class steroid ointments such as betamethasone valerate ointment 0.12% for grade 2 or 3 dermatitis.[3 4] However, currently, there is no established method to prevent or treat RT-induced oral mucositis.

The current model of mucositis pathogenesis comprises five stages[5 6]; the fourth stage is the mucosal ulceration phase. Microbiological studies have shown that the number of oral mucosal bacteria increases dramatically during this phase. These organisms contribute to the severity of mucositis by producing cell wall products that penetrate into the submucosa and stimulate macrophages to secrete inflammatory cytokines and other mediators of tissue injury. Thus, it is important to prevent the increase in oral bacteria and suppress the overproduction of inflammatory cytokines to prevent the aggravation of oral mucositis. In addition to controlling oral bacteria by oral care, it is necessary to suppress inflammatory cytokine overproduction by steroids.

We previously conducted a multicentre, randomised clinical trial to investigate the impact of topical administration of dexamethasone ointment 0.1% on the prevention of RT-induced severe oral mucositis. We reported that patients in the intervention group had a significantly lower incidence of grade 3 oral mucositis when they received RT alone. However, in patients undergoing combination therapy with RT and anticancer drugs, dexamethasone ointment was not effective.[7] This may be because dexamethasone oral ointment is a medium-class steroid ointment, and its strength is similar to that of hydrocortisone butyrate ointment for dermatitis. Moreover, although the use of medium-class steroid ointments such as dexamethasone or triamcinolone acetonide ointment is permitted for oral mucositis under the Public Health Insurance System in Japan, betamethasone ointment is only permitted for dermatitis and cannot be used for oral mucositis. Therefore, only oral administration of pain relievers, including opioids and gargling with local anaesthetics, is available for RT-induced oral mucositis in Japan.

Oral candidiasis often occurs during RT for head and neck cancer. Researchers have speculated that the use of steroid ointment during RT increases the risk of developing oral candidiasis, although evidence suggests otherwise. In a retrospective study of 300 patients with head and neck cancer undergoing RT, Kawashita *et al* found that low leucocyte count and oral mucositis of grade 2 or higher were independent risk factors for developing oral candidiasis, but the use of a topical steroid ointment was not a risk factor.[8] Similarly, another multicentre study of 326 patients with oral or oropharyngeal cancer undergoing RT found that low leucocyte count and oral mucositis were significantly associated with a higher incidence of oral candidiasis, while the application of steroid ointment did not promote oral candidiasis.[9]

Therefore, we performed a pilot trial to examine whether it is possible to prevent severe oral mucositis by applying betamethasone valerate ointment, a strong-class steroid ointment, in patients with oral and oropharyngeal cancer undergoing chemoradiation therapy (CRT) or bioradiation therapy (BRT). The preliminary results of this study (unpublished data) suggested that this drug is effective in preventing severe oral mucositis during CRT or BRT; therefore, this larger-scale, randomised phase II study was planned.

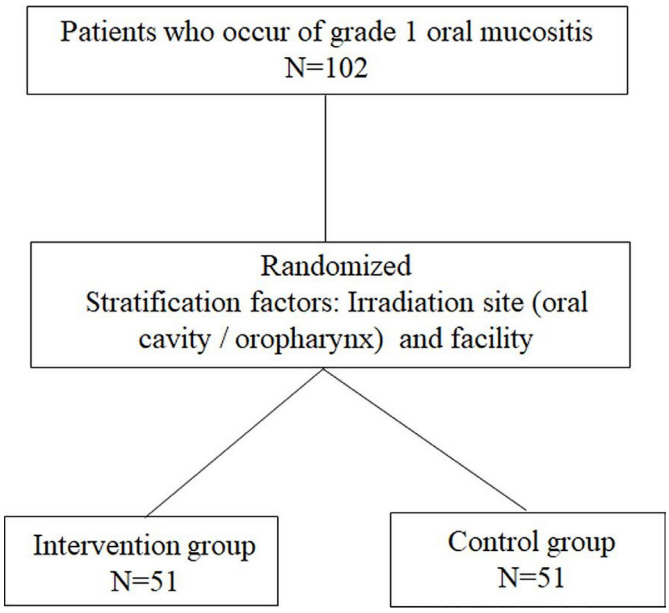

Figure 1 Flow chart of participants.

METHODS AND ANALYSIS

Summary

This study is being performed to investigate the efficacy of 0.12% betamethasone valerate ointment for the prevention of severe oral mucositis during concomitant RT with cisplatin or cetuximab. This study is of high clinical significance as it has the potential to reduce severe oral mucositis in patients with head and neck cancer. Hence, this study follows a superior study design. The participant flow chart is shown in figure 1.

Purpose

This study will examine whether the application of betamethasone valerate ointment can reduce the incidence or delay the onset of RT-induced grade 2–3 oral mucositis in a randomised controlled trial in patients with head and neck cancer undergoing concomitant RT with cisplatin or cetuximab.

Endpoints

Primary endpoint

- Incidence and time from start of RT to onset of grade 3 oral mucositis.

Secondary endpoint

- Incidence and time from start of RT to onset of grade 2 oral mucositis.

- Incidence and time from start of RT to onset of oral candidiasis.
- Completion rate for RT.
- Adverse events due to ointment application.

Eligibility criteria

Inclusion criteria

Patients will be included in the study when they satisfy all the following criteria: (1) Patients with cancer of the oral cavity or oropharynx treated with concomitant intensity-modulated RT with cisplatin or cetuximab; (2) Conventionally fractionated RT with 50 Gy or more and (3) Patients in the age range of 20–90 years

Exclusion criteria

Patients will be excluded from the study when any of the following criteria apply: (1) Patients with problem in judgement or cognitive function; (2) Patients who are allergic to the drugs used; (3) Women who are or may be pregnant; (4) Oral cavity not included in the field of RT and (5) When the researcher determines that the participant is not suitable for this study.

Patient assignment and data management

Patients will be recruited from Nagasaki University Hospital, Kobe University Hospital, Kansai Medical University Hospital, Shinshu University Hospital, Nagoya City University Hospital, Osaka City University Hospital, and Tokushima University Hospital from 11 May 2020 to 30 June 2023.

The Clinical Research Center of Kyushu Dental University will allocate the patients randomly after the occurrence of grade 1 oral mucositis to the betamethasone or control group in a 1:1 ratio using a stratified allocation method that minimises the effects of the allocation adjustment factors. The allocation algorithm will be determined by the person responsible for the biostatistical analysis: RT site (oral/oropharyngeal) and facility (facility name). Data management will be performed by Kyushu Dental University (MF).

Treatment and assessment schedule

1. Betamethasone group: After starting RT, patients will be provided oral hygiene instructions by a dental hygienist according to their oral hygiene status. The dental hygienist will also perform a professional oral cleaning, under the supervision of a dentist, by following oral hygiene instructions to clean the tooth surface, tongue and oral mucosa using oral hygiene tools. At the point of grade 1 oral mucositis onset, the patients will apply betamethasone valerate ointment (Rinderon V ointment 0.12%) five times a day (on waking up, after each meal, and before going to bed). If applying the ointment becomes difficult due to pain, it will be adjusted with olive oil to obtain an appropriate viscosity. If oral candidiasis develops, the application of betamethasone valerate ointment will be discontinued.
2. Control group: After starting RT, patients will receive oral hygiene instructions and professional oral cleaning as in the betamethasone group but will not be administered betamethasone valerate.

Patients in both groups will be followed up until grade 3 oral mucositis development or completion of RT. Other routine oral management, consisting of change in diet, administration of analgesics or opioids, use of spacers to minimise radiation backscatter in patients with metallic dental restorations, administration of pilocarpine hydrochloride and topical application of fluoride, will be given to both groups at the discretion of the radiologist or dentist. Oral candidiasis will be diagnosed by an oncologist or dentist based on clinical symptoms, regardless of the results of the Candida culture test.

The data collection schedule is shown in table 1.

Statistical analysis

Main analysis and assessment criteria

The difference in the incidence of grade 3 oral mucositis between the betamethasone and control groups will be analysed using Fisher's exact test. The null hypothesis 'no difference in the incidence of grade 3 oral mucositis between the betamethasone and control groups' will be tested.

Secondary analysis

1. Summarise each evaluation item.
2. The period from the start of RT to the onset of grades 2 and 3 oral mucositis will be calculated using the Kaplan-Meier method, and the difference between the betamethasone and control groups will be tested using the log rank test.
3. The difference in the incidence of grade 2 oral mucositis between the betamethasone and the control groups will be analysed by Fisher's exact test.
4. The difference in the incidence of oral candidiasis between the betamethasone and the control groups will be analysed by Fisher's exact test.
5. The period from the start of RT to the onset of oral candidiasis will be calculated using the Kaplan-Meier method, and the difference between the betamethasone and control groups will be tested using the log rank test.
6. The risk factor for grade 3 oral mucositis will be analysed by logistic regression and Cox proportional hazard model.

Sample size calculation

In a previously published retrospective study of 326 patients undergoing RT for oral and oropharyngeal cancer and a randomised controlled trial of 124 patients, grade 3 oral mucositis occurred in approximately 40% of patients with concomitant RT with cisplatin or cetuximab.[6 8] In our preliminary study of patients with head and neck cancer undergoing concomitant RT with cisplatin or cetuximab who were administered betamethasone valerate ointment after the development of grade 2 oral mucositis, the incidence of grade 3 oral mucositis was 11.1%. Based on these results, the incidence of grade

Table 1 Data collection schedule

	Registration*	Allocation*	After allocation	End	
	RT start ±7 days	Onset of grade 1 mucositis and no onset of candidiasis	At least once a week	Onset of grade 3 mucositis or RT end	Cancel
Assessment of eligibility criteria	●				
Obtain consent	●				
Registration	●				
Patient Characteristics†	●				
Oral examinations‡		●	●	●	●
Allocation		●			
Start of RinderonV administration§		●			
Adverse events			●	●	●
Treatment-related factors¶				●	●

*The registration date and allocation date may be the same day.
†Age, sex, smoking habit, drinking habit, use of denture, primary tumour site, surgery before RT, scheduled RT dose, haemoglobin, albumin and creatinine before RT.
‡Oral mucositis (CTCAE V.3.0 and V.5.0), oral candidiasis.
§These would be evaluated only in the betamethasone group.
¶Total RT dose, RT method, irradiation area, concurrent therapy, number of teeth, spacer, mouth wash containing local anaesthetics, opioids, pilocarpine hydrochloride, minimum value of white cell count and lymphocyte count during RT.
RT, radiation therapy.

3 oral mucositis was assumed to be 15% in the betamethasone group and 40% in the control group. Assuming that the α error is 0.2 and the power is 0.80, the required number of cases is 92. With an assumed drop-out of 10%, the target number of cases is 102 patients.

Study period

The study period of this trial will be from the day it is released by the Japan Registry of Clinical Trials (jRCT) to 30 June 2024; the participant entry period will be from the day it is released by jRCT to 30 June 2023.

Patient and public involvement

This study will be carried out without patient or public involvement. Neither the patient nor the public is involved in the development of the research question, study design or implementation of this trial. Patients will not be invited to develop patient-relevant outcomes, interpret the results or participate in the writing or editing of the final manuscript for readability or accuracy. Because the interventions in our study are routine procedures during clinical work, the burden of the intervention will be assessed by the patients themselves.

ETHICS AND DISSEMINATION

This study was approved by the Clinical Research Review Board of Nagasaki University (No. CRB20-009) and registered at the jRCT on 11 May 2020 (jRCTs 071200013). Details are available at the following address: https://jrct.niph.go.jp/re/reports/detail/15078. All participants will be required to provide written informed consent. A copy of the consent form is included in online supplemental material.

Any protocol changes that impact the study conduct and/or participant risk–benefit profile, including changes in objectives, design, sample size, participant characteristics, staff changes or significant administrative aspects, will require approval from the relevant Institutional Review Board. Minor protocol corrections and/or clarifications that do not affect study conduct or the participant risk/benefit profile are viewed as administrative changes and will be documented internally.

The study investigators will have full access to and ownership of all data. Deidentified data will be made available to other interested investigators for additional analyses, on reasonable request, following reports of primary outcomes and with appropriate data use agreement. The findings of this study will be disseminated through scientific and professional conferences and a peer-reviewed journal.

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