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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)

Sakiko Soutome ,[1] Mitsunobu Otsuru,[2] Maho Murata,[2] Yumiko Kawashita,[1] Masako Yoshimatsu,[3] Madoka Funahara,[4] Yoshiko Yamamura,[5] Takumi Hasegawa,[6] Shin-ichi Yamada,[7] Yuka Kojima,[8] Hirokazu Nakahara,[9] Yasuyuki Shibuya,[10] Masahiro Umeda,[2] Toshiyuki Saito[1]

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For numbered affiliations see end of article.

Correspondence to
Dr Sakiko Soutome;
sakiko@nagasaki-u.ac.jp

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.

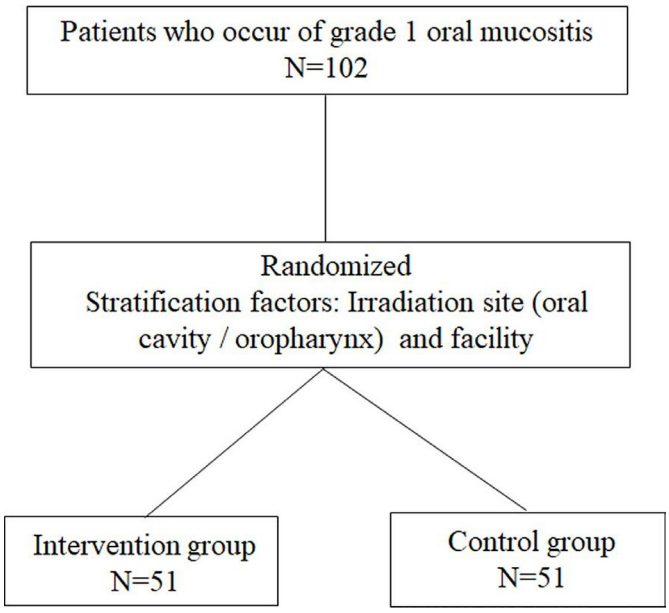

Figure 1 Flow chart of participants.

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.

Author affiliations
[1]Department of Oral Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[2]Department of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[3]Oral Management Center, Nagasaki University Hospital, Nagasaki, Japan
[4]Kyushu Dental University, School of Oral Health, Fukuoka, Japan
[5]Department of Oral Surgery, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, UK
[6]Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine, Kobe, Japan
[7]Department of Dentistry and Oral Surgery, Shinshu University School of Medicine, Matsumoto, Japan

[8]Department of Dentistry and Oral Surgery, Kansai Medical University, Osaka, Japan
[9]Department of Oral and Maxillofacial Surgery, Graduate School of Medicine, Osaka City University, Osaka, Japan
[10]Department of Oral and Maxillofacial Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

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Contributors All authors met the criteria of authorship as outlined in the ICMJE and approved this manuscript for submission. Specific contributions were as follows; Conception or design of the work: SS, MO and MU; Acquisition: YKa, MY, MM, YY, TH, S-iY, HN, YS and YKo, Analysis: TS and MF; Interpretation of data for the work: SS, MO and MU; Drafting the work: SS, MO and MU; Revising it critically for important intellectual content: YKa, MY, MM, YY, TH, S-iY, HN, YS, YKo, TS, and MF; Final approval of the version to be published; all authors; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

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Competing interests None declared.

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ORCID iD
Sakiko Soutome http://orcid.org/0000-0002-4646-587X

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Patient handbook

Multicenter interventional study of preventive effects of betamethasone valerate ointment for radiation-induced severe oral mucositis in patients with oral or oropharyngeal cancer: protocol for a randomized controlled phase II trial (Bet-ROM study)

Created: April 15, 2020, ver. 1.0
April 26, 2021, ver. 2.0

Oral Care center, Nagasaki University Hospital

Introduction

This handbook provides an explanation of the clinical study "Phase II multicenter randomized controlled study on preventing oral mucositis during chemotherapy for breast cancer with a steroid gargle" being conducted by the Department of Breast and Endocrine Surgery at Nagasaki University Hospital.

1. About clinical studies

Our current methods of diagnosing and treating diseases were achieved through a long process of progress and development. Further medical progress and development are important so patients can continue to receive even safer and more effective treatments. A great deal of research is necessary for this kind of progress and development in diagnosis and therapy, and some of it needs to be carried out on healthy people and patients. This kind of research is called clinical studies. Clinical studies can only be carried out with the understanding and cooperation of patients.

Nagasaki University Hospital actively engages in clinical studies to fulfill our mission as a university hospital to contribute to the development of medical care. Patients' human rights and safety are of utmost importance when conducting these studies. Nagasaki University Hospital created the Nagasaki University Clinical Research Screening Committee to rigorously examine each potential clinical study. The present study is being conducted with the approval of the Certified Clinical Research Screening Committee and the administrator of Nagasaki University Hospital.

This study is not what is called a "clinical trial," which is conducted by pharmaceutical companies and others to examine the safety and efficacy of new drugs to obtain approval from the Ministry of Health, Labour and Welfare.

2. Participation is of your own free will and accord

After you have listened to an explanation of this study and understood it thoroughly, you may decide freely whether or not you want to participate.

If you would like to participate, please sign the Consent Form and give it to the researcher in charge. Even if you agree to participate in the study, you can end your participation at any time. If you decide not to participate in the study, you will incur no disadvantage with regard to future treatment.

● Withdrawal of consent

Even if you agree to participate in this study, you can stop at any time. If you wish to do so, please submit a signed letter withdrawing your consent to the researcher in charge, or you can convey this withdrawal verbally.

Even if you withdraw midway through the study, you will not experience any disadvantage in terms of future treatment.
If you stop participating in the study, all your specimens, information, and other data obtained through this study will be discarded.

3. Disease covered by this study

Radiation-induced severe oral mucositis in patients with oral or oropharyngeal cancer

4. Purpose of the study

1. Why is this study being conducted?

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. Oral mucositis not only decreases the patient's quality of life, but can also lead to RT interruption and affect life prognosis.

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. However, currently, there is no established method to prevent or treat RT-induced oral mucositis.

We previously conducted a multicenter, randomized clinical trial to investigate the impact of topical dexamethasone administration on the prevention of severe oral mucositis. We reported that patients in the intervention group showed a significantly lower incidence of grade 3 oral mucositis when they received RT alone. However, in those undergoing CRT, the efficacy of dexamethasone ointment was not demonstrated1. This may be the fact that dexamethasone oral ointment 1 mg /g is considered to classified in medium class steroid ointment and its strength is low. However, strong-class steroid ointments such as Rinderon-V® 0.12% ointment are not applied for the oral mucositis and are not currently used for the prevention or treatment of radiation-induced oral mucositis. As described above, it is not clarified the method to suppress onset of oral mucositis during CRT or BRT, only symptomatic treatments such as gargling with local anesthetics and systemic administration of opioids are available in head and neck cancer.

2. Purpose of the study

The present study will examine whether the reducing the incidence or delaying the onset of radiation-related oral mucositis in Grades 2 and 3 by application of betamethasone (Rinderon V®) in a randomized, multi-center, open-label, phase II study in patients with head and neck cancer undergoing concomitant radiotherapy with cisplatin or cetuximab whose oral cavity is contained in the irradiation field.

5. Content of the study

(1) Eligible patients are people who:

Patients will be included in the study when they satisfy all the following criteria:

a) Patients with cancer of the oral cavity or oropharynx treated with concomitant intensity-modulated radiation therapy with cisplatin or cetuximab

b) Conventionally fractionated RT with 50 Gy or more

c) Patients in the age range of 20 to 90 years

In addition, the physician in charge will check your treatment history, current medical condition, medication, and other aspects to make an overall assessment as to whether you can participate in the study.

(2) Study methods

The patients of this study - patients undergoing radiotherapy for head and neck cancer - will be divided into 2 groups.

Group A (51 people)	Use Rinderon-V® ointment 5 times a day
Group B (51 people)	Not use Rinderon-V® ointment

Each patient has a 50% probability of being assigned to either group.

Neither you nor the researcher in charge will choose the group you are assigned to.

All patients will be provided oral hygiene instruction according to the oral hygiene status by a dental hygienist, and professional oral cleaning. Professional oral cleaning means that under the direction of a dentist, a dental hygienist perform oral hygiene instruction and cleaning of the tooth surface, tongue, and oral mucosa by oral hygiene tools for patients.

(3) Medication used (group A only)

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 (upon waking up, after each meal, and before going to bed).

(4) Schedule

The study will be carried out according to the schedule below.

	Registration*1	Allocation*1	After allocation	End	Cancel
	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	
Assessment of eligibility criteria	●				
Obtain consent	●				
Registration	●				
Patient Characteristics*2	●				
Oral examinations*3		●	●	●	●
Allocation		●			
Start of RinderonV® administration4		●			
Adverse events			●	●	●
Treatment related factors*5				●	●

*1 The registration date and allocation date may be the same day.

*2 Age, sex, smoking habit, drinking habit, use of denture, primary tumor site, surgery before RT, scheduled RT dose, hemoglobin, albumin, and creatinine before RT.

*3 Oral mucositis (CTCAE v3.0 and v5.0), oral candidiasis.

*4 These would be evaluated only in the bethametasone group.

*5 Total RT dose, RT method, irradiation area, concurrent therapy, number of teeth, spacer, mouth wash containing local anesthetics, opioids, pilocarpine hydrochloride, minimum value of white blood cell count and lymphocyte count during RT.

(6) Duration of participation

The duration of your participation in this study is the day of development of grade 3 oral mucositis or completion of RT from the day you agree.

(7) Treatment after the study ends

After completion of the study, appropriate treatment will be provided based on your pathology and condition. If you have any questions, please feel free to contact the researcher in charge at any time.

6. Other treatments

Even if you do not participate in the study, the researcher in charge will still provide you with the best treatment for your condition.

7. Planned study duration and number of participants

(1) Study duration

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

(2) Number of participants

One hundred two patients 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 are expected to participate in this study.

8. Expected benefits and drawbacks (side effects, complications)

(1) Expected benefits

Subjects who assigned to Rinderon group can expect the reduction or delay oral mucositis. All subjects will receive detailed examinations and explanations. This study could also contribute to the development of new treatments and medications for your disease.

(2) Expected drawbacks

It is considered that participating in this research will not cause any direct disadvantage to participate.

(3) Expected side effects and complications

There is a possibility you could experience other unknown side effects.
During the study, the subjects will be carefully observed for any side effects or other unwanted symptoms. Any unwanted symptoms will be treated appropriately. If you feel any different from usual, please inform the researcher in charge immediately.

9. Guidelines to follow

Please observe the following while taking part in this study.

Follow the instructions of the researcher in charge during the study.

If you have any unusual symptoms, please inform the researcher in charge immediately.

10. Termination of the study

Your participation in the study may be terminated in the following cases.

Please note that the study may have to be terminated against your will. Even if the study is terminated, the researcher in charge will provide you with the best possible treatment.

- If you want to stop participating in the study
- If it is determined you do not meet the conditions for participating in the study.
- If you cannot come to the hospital on the predetermined days or are otherwise unable to participate in the study.
- If the entire study is terminated due to factors such as safety issues, the effects are found to be insufficient, or there are too few participants to carry out the study.
- If the researcher in charge decides to halt your participation due to the state of your illness or your course of treatment.
- If the researcher in charge decides the study should be terminated for any other reason.

11. Information about the study

You will be promptly notified if during the study we obtain any new information that may affect your safety or willingness to participate. You will then be free to decide whether you want to continue participating in the study.

In addition, please inform us if you would like to know anything about the study protocol or other information regarding this study. This excludes other patients' personal information or matters that would interfere with the study overall. If you wish, we will inform you of the study's results.

12. Submission of test results

Of the tests performed for this study, those that are directly related to your medical care will be explained to you by the researcher in charge, in the same way as is done in regular medical care. You will not be informed about other test results that are not directly related to your medical care, though these can be explained to you if you wish. Please contact the researcher in charge.

13. Protection of personal information

To protect personal information, an identification number will be assigned to each patient, and this number will be used when handling samples and data. Information that could be used to identify individual subjects will not be used. A correspondence table will be created that links you to your identification number. This correspondence table will be kept inside the hospital and will not be taken outside.

In addition, people involved in the study (including outside parties) may directly examine your medical records to check that the study is being conducted properly. However, this will be done confidentially based on the Personal Information Protection Law. There is no need to worry about leaks of information related to your privacy (address, name, phone number, etc.). In addition, reports and other materials will not contain information that could be used to identify you.

Your personal information will not be disclosed even when the results of the study are presented at conferences or published in medical journals.

14. Handling of samples and data obtained for this study

(1) Handling of samples and data

Your personal data will be handled with great care and be strictly managed to prevent external leaks. Your samples or data will not be submitted to outsiders for analysis or any other reason.

(2) Sample, data storage

Samples and data obtained for this study will be stored at Nagasaki University Hospital Department of Oral Surgery for at least 5 years after completion of the study, but if possible will be stored for longer.

When samples and data are discarded, we will be careful to prevent leaks of personal information.

15.Responding to and compensation for health damage

If health damage occurs because of this study, the patient's health insurance will be used to provide treatment as is done under normal insurance care. These costs will be borne by the patient and no financial compensation will be provided, such as for loss of income or hospital beds that are not fully covered by insurance. In the unlikely event that health damage occurs, appropriate medical treatment will be provided within the scope of insurance care.

16. Financial burdens

You will have to pay for the cost of this research period using your health insurance as you would normally receive medical treatment. There is no burden on the patient. The cost of this study is the same as the cost of receiving the same treatment without participating in the study.

17. Conflicts of interest and funding sources

Conflicts of interest refer to situations in which third parties could be concerned that a study has not been conducted fairly and appropriately. This includes falsifying data and giving preferential treatment to specific companies due to economic interests with the outside parties.

The principal investigator and researchers in charge of the study have been screened by Nagasaki University Hospital's Conflict of Interest Screening Committee, which confirmed they do not have stakes in any company or organization that could harm the reliability of the study.

18. Monitoring

In this study, monitoring will be carried out by a monitor appointed by the principal investigator according to a pre-made monitoring procedure manual to ensure that the study is conducted properly.

19. Intellectual property rights

The results of this study may generate patent rights or other forms of intellectual property. If this happens, the intellectual property rights will belong to Nagasaki University Hospital, not to the patients.

20. Study implementation system

≪Principal investigator≫

Name: Sakiko Soutome

Affiliation: Oral care Center, Nagasaki University Hospital

Address: Sakamoto 1-7-1, Nagasaki, Nagasaki Prefecture

Tel: 095-819-7663

≪Partner research institutes≫

Name: Yuka Kojima

Affiliation: Kansai Medical University Hospital

Name: Shin-ichi Yamada

Affiliation: Shinshu University Hospital

Name: Yasuyuki shibuya
Affiliation: Nagoya City University Hospital

Name: Hirokazu Nakahara
Affiliation: Osaka City University Hospital

Name: Yoshiko Yamamura
Affiliation: Tokushima University Hospital

Name: Takumi Hasegawa
Affiliation: Kobe University Hospital

20. Inquiries, contact information

If you have any questions or concerns about the study, please do not hesitate to contact the ≪researcher in charge≫.

Principal investigator
Name: Sakiko Soutome
Address: Sakamoto 1-7-1, Nagasaki, Nagasaki Prefecture
Tel: 095-819-7663

To be kept by the hospital, (copy) for patients
ver. 2.0

Consent form

Multicenter interventional study of preventive effects of betamethasone valerate ointment for radiation-induced severe oral mucositis in patients with oral or oropharyngeal cancer: protocol for a randomized controlled phase II trial (Bet-ROM study)

Items to be explained

1. About clinical studies
Participating in a clinical study
3. Your disease
Purpose of the study
Content of the study
Other Treatments
Planned study duration and number of participants
Expected benefits and drawbacks
Guidelines to follow
10. Termination of the study
11. Information about the study
12. Submission of test results
13. Protection of personal information
14. Handling of samples and data obtained for the study
15. Responding to and compensation for health damage
16. Financial burdens
17. Conflicts of interest and funding sources
18. Intellectual property rights
19. Implementation system
20. Inquiries, contact information
21. Consultation office for opinions and complaints

[Signature of researcher] I explained the study to the patient.

Date of explanation:

Name of explainer:_____(signature)

[Patient's signature]

I have received an explanation of and understand the above items, and agree to participate in this study of my own free will and accord. I will receive a copy of the patient handbook and this consent form.

Consent Date:

Patient's name:_____(signature)