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)