HN1_3.3

Patient handbook

Phase II Multicenter Randomized Controlled Study on Preventing Oral Mucositis during Chemotherapy for Breast Cancer with A Steroid Gargle

Created: November 29, 2017, ver. 1.1
April 23, 2018, ver. 1.2
April 3, 2019, ver. 1.3

Department of Breast and Endocrine Surgery, 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 withdrawl 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

Breast cancer is the most common cancer in women, with a lifetime cumulative incidence risk of 1 in 12. About 40% of patients are reported to undergo chemotherapy for initial breast cancer.

4. Purpose of the study

1. Why is this study being conducted?

Oral mucositis (stomatitis) is one of the most common (20-60%) side effects of chemotherapy for breast cancer. Stomatitis can cause symptoms such as pain, ulcers, and bleeding. These can prevent patients from eating and worsen their nutritional status, which may necessitate treatment being suspended. Therefore, this condition not only damages quality of life, but can also interfere with treatment. Yet while oral care is said to be an effective method for preventing stomatitis, standard prevention methods have not been established. Stomatitis is said to be caused by the development and exacerbation of excessive inflammation. It is often treated with a steroid ointment after it occurs.

2. Purpose of the study

The purpose of this study is to examine whether a gargle containing a steroid can prevent stomatitis during breast cancer chemotherapy (EC or TC).

5. Content of the study

(1) Eligible patients are people who:

(1) have been diagnosed with invasive breast cancer by needle biopsy or tissue biopsy

(2) are scheduled to undergo Ec90/EC100/TC therapy

(3) have not previously undergone breast cancer chemotherapy

(4) do not have oral mucositis prior to treatment

(5) do not have improperly fitting dentures

(6) have performance status (PS) 0-1 (Examples: People who can carry on with life without restrictions the same as before onset, or people who can perform light housework and office work but not strenuous activities.)

(7) are at least 20 years old but not over 80 years old when they provide consent

(8) exhibit laboratory test values at the time of registration that meet the following conditions:

① Leukocyte count ≥ 4000/mm^3 and ≤ 12,000/mm^3 or neutrophil count ≥ 2000/mm^3
② Hemoglobin ≥ 9.0 g/dL
③ Platelet count ≥ 100,000/mm^3
④ AST and ALT ≤ 2.5 x the institution's upper limit of normal (ULN)
⑤ Total bilirubin or direct bilirubin ≤ ULN
⑥ Serum creatinine ≤ 1.5 x ULN

(9) signed the consent form

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 subjects of this study—patients undergoing chemotherapy for breast cancer—will be divided into 2 groups.

Group A (39 people)	Use a steroid gargle 4 times per day.
Group B (39 people)	Do nothing in particular to prevent stomatitis.

Each subject 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 with appropriate treatment if they experience stomatitis. There are no restrictions on what treatments can be provided for stomatitis. The subjects will also keep a simple diary about their side effects.

(3) Medication used (group A only)

For this study, patients will use a steroid gargle 4 times per day for 2 minutes each time.
Dexamethasone elixir: 10 ml after breakfast, lunch, and dinner, and before bed

The commercially available version of the drug in this study is used to treat intractable stomatitis but has not been shown to be the effective for preventing stomatitis.

(4) Schedule

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

	0-4 weeks before	Day of 1st administr	Day of 2nd administr	Day of 3rd administr	Day of 4th administr	3-4 weeks after the end

	administration	ation	ation	ation	ation	of administration
Examinations by Department of Breast and Endocrine Surgery	Exam 1	Exam 2	Exam 3	Exam 4	Exam 5	Exam 6
Examinations by Perioperative Oral Management Center	Exam 1		Exam 2	Exam 3	Exam 4	Exam 5
Consent obtained	○	-	-	-	-	-
Gargle with test drug	-	○	○	○	○	-
Subjective symptoms of oral mucositis (diary), other findings	○	○	○	○	○	○
Subjective symptoms of other adverse events, objective findings	-	○	○	○	○	○
Taste and saliva tests	-	△	-	-	△	△
Measurement of salivary bacterial count	-	△	-	-	△	△
Sample collection (saliva)	-	△	-	-	△	△

○: Must be performed, △: Performed if necessary

(5) Survey items, observation items, examination items

・Patient characteristics: gender, birthdate, height, weight, complications, medical history, current disease history, pretreatment

・Concomitant drugs, therapies

・Subjective symptoms, objective findings, and grade assessments for oral mucositis, taste disturbances

・Saliva amount

・Number of bacteria, inflammatory cytokines in saliva

・Side effect diary (attached)

(6) Duration of participation

The duration of your participation in this study is from the day you start chemotherapy to the day the fourth cycle begins. This is expected to be about 3 months, but it may change depending on your condition.

(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

This study will be conducted from the day it is approved by the Nagasaki University Hospital administrator to September 30, 2020. (Recruitment period: day approved by Nagasaki University Hospital administrator to December 31, 2019)

(2) Number of participants

Seventy-eight patients from Nagasaki University Hospital, Nagasaki Medical Center, and Nagasaki Genbaku Hospital are expected to participate in this study.

Of these, 28 patients are expected to participate from Nagasaki University Hospital.

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

(1) Expected benefits

Subjects who participate in this study may have a lower incidence of oral mucositis from using dexamethasone elixir. 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

The items described below in "(3) Expected side effects and complications" could occur.

(3) Expected side effects and complications

Although this drug contains a steroid, it is used as a gargle and thus will probably have little effect on the body overall. An analysis of oral candidiasis and other infections caused by local steroid application at our hospital did not show any relationship between application of steroid ointments in the mouth and the occurrence of oral candidiasis. With this gargle as well, there seems

to be little risk of developing infections such as oral candidiasis.

There is a possibility you could experience other unknown side effects.

Members of group B will receive regular medical care. Therefore, we believe their participation in the study will not lead to any additional side effects or complications.

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.

Whatever your needs, please contact the researcher in charge.

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 Transplantation and Gastroenterological 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

As the gargle used in this study will be paid for with a "Project Mirai" grant from Relay for Life Japan (RFLJ) 2017, you will not incur any costs in addition to your usual treatment expenses.
Also, you will not be provided with an honorarium for 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. 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 the Department of Transplantation and Gastrointestinal Surgery, not to the patients.

19. Study implementation system

≪Principal investigator≫
Name: Susumu Eguchi
Affiliation: Department of Transplantation and Gastroenterological Surgery, Nagasaki University Hospital

≪Partner research institutes≫
Department of Surgery, Nagasaki Medical Center
Name: Shigeto Maeda
Department of Thoracic, Breast, and Endocrine Surgery, Nagasaki Genbaku Hospital

Name: Hideki Taniguchi

≪Principal investigator at Nagasaki University Hospital≫
Name: Satoshi Eguchi (Professor)
Department: Nagasaki University Hospital, Department of Transplantation and Gastroenterological Surgery

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: Satoshi Eguchi
Address: Sakamoto 1-7-1, Nagasaki, Nagasaki Prefecture
Tel: 095-819-7316

To be kept by the hospital, (copy) for patients
ver. 1.3

Consent form

Study title: Phase II multicenter randomized controlled study on preventing oral mucositis during chemotherapy for breast cancer with a steroid gargle

Items to be explained

1. About clinical studies
2. Participating in a clinical study
3. Your disease
4. Purpose of the study
5. Content of the study
6. Other Treatments
7. Planned study duration and number of participants
8. Expected benefits and drawbacks
9. 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)