

Clinical Study Protocol

Study Protocol for Assessing the Efficacy of Compression Therapy Using Stockings and Sleeves to Prevent Docetaxel-Induced Peripheral Neuropathy in Breast Cancer Patients

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Taxanes are key drugs for patients with breast cancer. A major adverse effect associated with the administration of the taxane docetaxel is chemotherapy-induced peripheral neuropathy (CIPN). We are conducting a single-center, single-arm, open-label historical control trial to evaluate the ability of compression therapy using stockings or sleeves to prevent CIPN due to docetaxel treatment. The primary endpoint is the incidence of all-grade CIPN according to patients' records until 3 weeks after the fourth docetaxel administration. This study's results will clarify whether compression therapy using stockings or sleeves can prevent CIPN in breast cancer patients.

Key words: breast cancer, docetaxel, neuropathy, compression

Chemotherapy-induced peripheral neuropathy (CIPN) has been problematic among patients with cancer who undergo chemotherapy. The overall incidence of CIPN is estimated to be approx. 40% in patients treated with multiple agents [1, 2]. With regard to the treatment of existing CIPN, the best available data support a moderate recommendation for treatment with duloxetine [1]. Because there are no established preventive measures for CIPN due to the dearth of high-quality, consistent evidence, some patients experience severe CIPN, resulting in a reduction in their quality of life and the cessation or dose reduction of chemotherapy [3, 4]. CIPN can last for a long period, causing discomfort, numbness, or tingling in the hands or feet, weakness or difficulty feeling small objects, foot pain, trouble walking, and trouble working [5].

Taxanes are key drugs for patients with breast cancer

in both adjuvant/neoadjuvant and metastatic disease settings. The taxane docetaxel is used for adjuvant purposes in patients with breast cancer, as it improves the recurrence-free survival and overall survival of this patient population [2, 4, 6]. Docetaxel promotes the stabilization of microtubules and causes G2M cell-cycle arrest. However, CIPN is a major adverse effect associated with the administration of docetaxel, with an any-grade frequency reported to range from 25.5% to 64.4% [2, 7] and grade 2-4 frequency at 35% [3].

In patients with breast cancer, compression therapy using stockings and sleeves, combined with medication using select prophylactic drugs such as the traditional Kampo medicine goshajinkigan (with the so-called "3S" approach) was reported to prevent or relieve CIPN that is due to another taxane, nanoparticle albumin-bound paclitaxel (nab-PTX) [8]. Notably, a meta-analysis indicated that goshajinkigan itself did not prevent CIPN

in patients undergoing neurotoxic chemotherapy [9]. Tsuyuki *et al.* [10]. showed that compression therapy using surgical gloves prevented the incidence and decreased the severity of CIPN in patients' hands due to nab-PTX treatment. While the two above-mentioned measures (medication and compression) seemed to have some degree of preventative effect on CIPN, the proposal underlying the mechanisms differed (*i.e.* increased arteriole flow with minimal flow through capillaries [8] and decreased microvascular flow [10], resulting in a decrease in the nab-PTX exposure to the peripheral nerve).

We have speculated that compression therapy alone (using stockings and sleeves) could be effective in preventing or decreasing the severity of CIPN (in the feet and hands, respectively). Docetaxel and paclitaxel are two taxanes that have been particularly well investigated, especially in adjuvant/neoadjuvant settings [11-13]. At our institute, we have used docetaxel most frequently in both adjuvant and neoadjuvant settings and for the treatment of metastatic disease.

The present study will assess the safety and efficacy of compression therapy using stockings and sleeves for preventing CIPN induced by docetaxel in patients with breast cancer.

Endpoints

Primary endpoint. The primary endpoint is the incidence of all-grade CIPN according to patients' records until 3 weeks after the fourth docetaxel administration.

Secondary endpoints. The secondary endpoints are the (1) the incidence of CIPN by grade, (2) the incidence of all-grade CIPN according to the patients' records at 3 weeks after each docetaxel administration, (3) the completion rate of the compression therapy, (4) the incidence of adverse events due to the compression therapy, (5) the completion rate of chemotherapy, and (6) the relative dose intensity of the chemotherapy.

Eligibility Criteria

Eligible patients are women with histologically confirmed invasive breast cancer who are 20-79 years of age scheduled to receive docetaxel at a dose of 75 mg/m² intravenously every 3 weeks for 4 cycles as first-line chemotherapy for recurrent/metastatic disease or as

neoadjuvant/adjuvant therapy. Patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer will receive anti-HER2 agents before docetaxel in each cycle (trastuzumab; initial dose 8 mg/kg, loading dose 6 mg/kg). In patients with distant metastasis or a high risk of recurrence who are receiving adjuvant/neoadjuvant therapy, pertuzumab (initial dose 840 mg/kg, loading dose 420 mg/kg) will also be administered after the trastuzumab administration.

Patients with peripheral neuropathy at baseline or receiving prior chemotherapy for any type of cancer will be excluded. Patients with four cycles of epirubicin treatment with cyclophosphamide with or without 5-fluorouracil given sequentially before docetaxel for adjuvant or neoadjuvant purposes will be allowed to participate.

Treatment Methods

Study design. This is a single-center, single-arm, open-label historical control trial to evaluate the effect of compression therapy on preventing CIPN caused by docetaxel. This study has been approved by the Clinical Research Review Board of Nagasaki University (CRB7180001) and has been registered in the Japan Registry of Clinical Trials (jRCT, registration no. jRCTs072180038). The protocol was designed and will be managed in accordance with the Declaration of Helsinki (1964) and the Clinical Trial Act (2018).

Recruitment, setting, and informed consent. The study design is illustrated in Fig. 1 As part of our routine clinical work, we evaluate adverse events—including CIPN—in each cycle of chemotherapy. For this study's control group (without compression), we collected data from 52 consecutive patients who met the above-described criteria between 2012 and 2016. Patients in the intervention group were recruited from Nagasaki University from June 2017. Women were recruited when they received the explanation of their chemotherapy regimen. All candidates were screened again to determine whether they were eligible for the study and were provided a participant information sheet and asked to provide their written consent. Participants were informed that they had the right to withdraw from the study at any time without having to give a reason.

Treatment and assessment schedule. The patients will wear stockings (Okamoto Corp., Osaka, Japan)

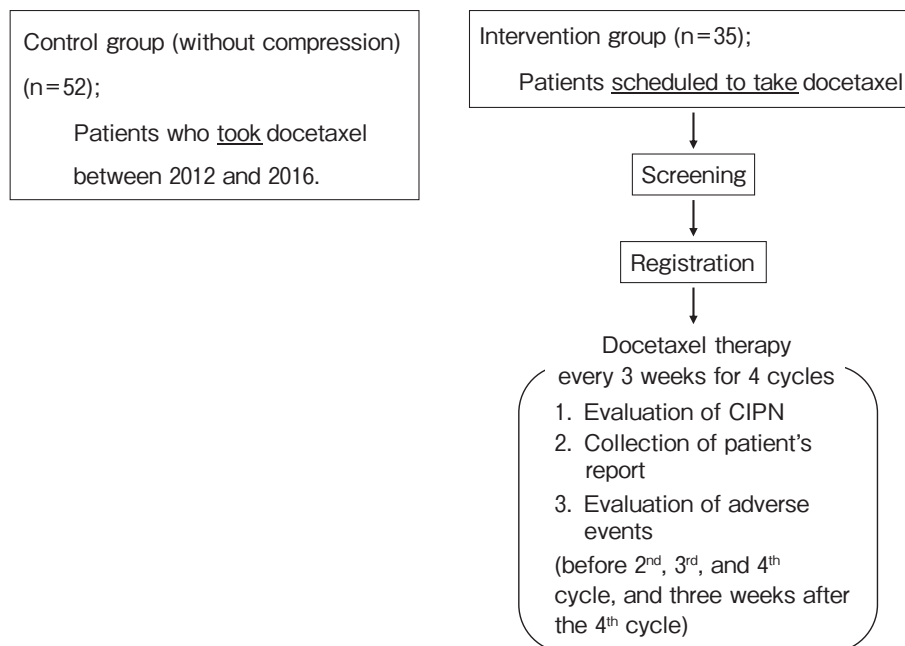


Fig. 1 Study design. CIPN: chemotherapy-induced peripheral neuropathy.

and sleeves (Okamoto Corp.) for 24 h from the beginning of docetaxel therapy [8]. There are four sizes of stockings or sleeves, and the optimal size will be determined based on the circumference of the patient's ankle and calf and her wrist and upper arm to obtain 15-20 mmHg of pressure.

CIPN will be assessed by the treating surgeons or nurses using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 at pretreatment, before each treatment cycle, and at 3 weeks after the fourth docetaxel administration (Fig. 1). All patients in this study received standard care for CIPN. The patients will record their adherence to wearing stockings and sleeves and any relevant adverse events immediately before receiving cycles 2 to 4 and at 3 weeks after cycle 4 of docetaxel (Fig. 1, 2).

Safety monitoring. When a patient develops a severe adverse event in this study, the investigator will report it to the principal investigator, who will then inform all other investigators of the event and additionally report it to The Clinical Research Review Board in Nagasaki University.

Data management. Data will be collected in case-report form and given a study code; de-identified data will be used for the analyses. All hardcopies will be de-identified using the study code and stored securely in

the hospital setting. All data will be discarded 5 years after the completion of the study.

Statistical Considerations

The results of a previous study indicated that compression therapy using stockings and sleeves and medication therapy using select prophylactic drugs, including goshajinkigan (the '3S' approach), reduced CIPN induced by nab-PTX from 100% to 65% of the patients [8]. Based on the retrospective data of 52 patients who were treated with docetaxel at our hospital between 2012 and 2016, the incidence of CIPN is 63% (the control group). While we expect that compression therapy alone can reduce the rate of CIPN induced by docetaxel to a degree similar to that achieved by the 3S approach, the incidence of CIPN was $\leq 41\%$ (63% multiplied by 0.65) in the intervention group. With a beta level of 0.2 and an alpha level of 0.05 (one-sided), we calculated that the trial would need to include 32 patients in the intervention group. Therefore, considering a 10% potential withdrawal rate, we plan to enroll 35 patients.

Analyses of the primary and secondary outcomes will be based on an intention-to-treat analysis. The patients' clinicopathologic features will be compared between the intervention and control groups.

ID	
Name	
Date of the last docetaxel administration	/ /
Number of cycles of docetaxel	1 2 3 4
Were you able to wear the sleeves as instructed?	Yes No
If "No", please describe your 1. reasons, and 2. details (How long you could wear them, etc.)	1. 2.
Were you able to wear the stockings as instructed?	Yes No
If "No", please describe your 1. reasons, and 2. details (How long you could wear them, etc.)	1. 2.
Adverse events relevant to wearing sleeves and stockings	
Rubefaction	Yes No
Itching	Yes No
others	Yes No

Fig. 2 Patient records.

Associations between variables will be assessed using Fisher's exact test, and all analyses will be one-sided at a significance level of 0.05. All statistical analyses will be conducted with EZR (Saitama Medical Center, Jichi Medical University, Japan).

Discussion

In a 2014 study, compression therapy using stockings and sleeves plus medication therapy using select prophylactic drugs, including goshajinkigan—the so-called '3S' approach—was reported to prevent or relieve CIPN induced by the taxane nab-PTX [8]. Goshajinkigan is a Japanese traditional drug composed of 10 medical herbs [14]. It has been shown to relieve diabetic neuropathy [15]. The suggested mechanisms by which goshajinkigan exerts a neuroprotective effect include the activation of κ -opioid receptors [16] and the promotion of nitric oxide production to improve the blood supply to the nerves [17], caused mainly by the aconite root in goshajinkigan. However, because goshajinkigan itself was not shown to prevent CIPN in a meta-analysis [9], we speculate that the effect of the 3S approach for preventing CIPN could be achieved by compression only.

As noted above, there are no established prophylactic strategies against CIPN, and some patients suffer from severe symptoms, resulting in the reduction or cessation or change of drugs. Moreover, once CIPN

occurs it can be difficult to treat, and patients may suffer from the symptoms for a long time (even after the taxane treatment is discontinued), resulting in a decrease in the patient's quality of life [18] and difficulty working [5]. If compression therapy as a prophylactic intervention can prevent CIPN effectively and safely, patients can take drugs at the desired relative dose intensity and still maintain a good quality of life.

The sleeves and stockings to be used in the present study are categorized as "general medical devices" and can promote the return of lymph flow and venous flow. They are readily available to the public, and there have been no reports of severe side effects. We expect that these compression devices will prevent CIPN in both the hands and feet. If our study reveals that compression therapy is safe and effective for preventing CIPN due to docetaxel, we will proceed to a phase III randomized study. Similar investigations should be performed in patients receiving other chemotherapy for other types of cancer.

Trial status. The trial is currently in the recruitment phase. Recruitment commenced in June 2017 and is expected to be completed by November 30, 2020. Data collection will be completed by March 31, 2021.

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