Cryotherapy for the prevention of weekly paclitaxel-induced peripheral adverse events in breast cancer patients

Hideo Shigematsu1 · Taizo Hirata2 · Mai Nishina1,3 · Daisuke Yasui1 · Shinji Ozaki1,4

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Abstract
Purpose This randomized phase II study was conducted to investigate the efficacy of cryotherapy in preventing peripheral neuropathy and dermatological adverse events in breast cancer patients treated with weekly paclitaxel.
Methods Patients treated with 12 weekly doses of paclitaxel for breast cancer were randomized (1:1) into a cryotherapy or control group. The primary endpoint was the percentage of patients with a marked decrease in the Functional Assessment of Cancer Therapy-Neurotoxicity (FACT-NTX) score. The secondary endpoints were Patient Neurotoxicity Questionnaire (PNQ), Common Terminology Criteria for Adverse Event (CTCAE) for peripheral neuropathy, and FACT-Taxane score.
Results Forty-four patients were randomly assigned to the cryotherapy (n = 22) or control groups (n = 22). The percentage of patients with a marked decrease in FACT-NTX scores was significantly lower in the cryotherapy group than in the control group (41 vs. 73%, p = 0.03). The incidence of CTCAE grade ≥2 sensory (p = 0.001) and motor peripheral neuropathy (p = 0.01), and PNQ grade D or higher for sensory peripheral neuropathy (p = 0.02), and decrease in the FACT-Taxane score (p = 0.02) were also significantly lower in the cryotherapy group than in the control group. There were no serious side effects associated with cryotherapy.
Conclusion Cryotherapy is an effective approach for prevention of peripheral neuropathy and dermatological adverse events in breast cancer patients treated with weekly paclitaxel.

Keywords Breast cancer · Peripheral neuropathy · Dermatological adverse events · Cryotherapy · Weekly paclitaxel

Introduction
In a randomized clinical trial evaluating the adjuvant therapy of breast cancer, weekly paclitaxel showed superiority in relapse-free survival and overall survival compared with tri-weekly paclitaxel [23, 24]. Because weekly paclitaxel regimen results in increased dose intensity and cumulative dosage compared with tri-weekly paclitaxel, the weekly schedule is associated with a high incidence of peripheral neuropathy [5, 6].
There was a reported incidence of 27 and 8% for grades ≥ 2 and 3/4 peripheral neuropathy with weekly paclitaxel [23]. Although paclitaxel-induced peripheral neuropathy tends to improve after treatment, it may persist in 50–80% of patients, and 25% of these demonstrate strong neuropathy [9, 25]. Another peripheral adverse effect of paclitaxel is dermatological adverse events, which includes nail changes and cutaneous toxicities [12–14]. Systemic investigation showed an incidence of 43.7% for all grade nail changes with paclitaxel treatment [2]. Paclitaxel treatment also causes inflammation of the skin which can lead to cutaneous sclerosis [13, 17]. Although these paclitaxel-related peripheral adverse events are not life threatening, they can substantially deteriorate quality of life (QOL) and subsequently lead to reduction of dose intensity or treatment disruptions [16] [21].

Although there are no established medications for preventing taxane-induced peripheral neuropathy and dermatological adverse events [11], some studies reported that suppression of peripheral circulation via cryotherapy or compression therapy may be effective in preventing these peripheral adverse events. In a retrospective study of breast cancer patients treated with taxane, lower incidences of peripheral neuropathy and nail disorder have been reported in patients treated with cryotherapy than in those who were not [18]. In self-controlled trials of weekly paclitaxel treatment for breast cancer patients, suppression of peripheral circulation via cryotherapy has been reported to be effective in the prevention of peripheral neuropathy [8]. Compression therapy using surgical gloves has also been reported to be useful for the prevention of peripheral neuropathy in self-controlled comparative studies of breast cancer patients treated with nab-paclitaxel every 3 weeks [26]. However, these reports are retrospective studies or self-controlled trials, and thus, the efficacy of cryotherapy for preventing these adverse effects should be confirmed in randomized controlled trials.

With these findings, we conducted a randomized phase II study of cryotherapy for the prevention of peripheral neuropathy and dermatological adverse events in breast cancer patients treated with weekly paclitaxel.

Methods

Study design and participants

This randomized phase II controlled trial enrolled breast cancer patients undergoing 12 weekly doses of paclitaxel. The inclusion criteria were a diagnosis of invasive breast cancer, age 20 years or older, scheduled for a regimen of 12 weekly doses of paclitaxel, adequate organ function, an Eastern Cooperative Oncology Group Performance Status (PS) of 0 or 1, and no history of taxane-based chemotherapy within the last 12 months. The exclusion criteria were grade ≥ 2 peripheral neuropathy as assessed according to the Common Terminology Criteria for Adverse Event (CTCAE) [1], current treatment with drugs affecting peripheral neuropathy, and co-morbidity of Raynaud’s syndrome. Eligible patients were randomized (1:1) into the combination therapy group (cryotherapy using frozen gloves/socks) and the control group. Randomization was performed under a permuted block randomization scheme (block size of four), stratified by age (< 65 vs. 65 and older) and presence of grade 1 peripheral neuropathy.

This study adhered to the ethical standards laid down in the Helsinki Declaration and the ethical principles for clinical research. Further, this study was approved by the Ethics Committee of the National Hospital Organization of Kure Medical Center and Chugoku Cancer Center (Approval number 28-70) and is registered in the University Hospital Medical Information Network (UMIN000034966). All patients received a detailed explanation of the study from the primary physician, and written informed consent was obtained prior to enrollment.

Chemotherapy regimen

Twelve weekly doses of paclitaxel therapy comprised infusion of 80 mg/m² paclitaxel on days 1, 8, and 15 in a 21-day cycle for a total of four cycles. Adjuvant anti-human epidermal growth receptor (HER) therapy was used in HER2-positive breast cancer patients. The addition of bevacizumab was allowed in advanced and recurrent breast cancer.

Cryotherapy

For cryotherapy, patients wore frozen (− 20 °C) gloves/socks (Elasto-Gel, mittens, and slippers) on both hands and feet continuously for 15 min before paclitaxel infusion until 15 min after infusion in accordance with previous report regarding cryotherapy (total 90 min) [18]. This treatment was performed throughout the 12 weekly doses of paclitaxel in the experimental group. The use of drugs that may affect peripheral neuropathy (e.g., acetyl-L-carnitine, vitamin E, glutamine, gabapentin, tricyclic antidepressants, and opioids) and compression therapy with surgical gloves was prohibited.

Assessment measures

The primary endpoint was the percentage of patients with a significant decrease in their Functional Assessment of Cancer Therapy-Neurotoxicity (FACT-NTX) score [3]. Briefly, the FACT-NTX is an 11-item tool used for evaluating symptoms and concerns specifically associated with chemotherapy-induced neuropathy. A lower FACT-NTX score means a worsening of peripheral neuropathy. A significant decrease in FACT-NTX score was defined as a decrease exceeding...
10% or 6 points of the standard value before weekly paclitaxel [6, 10]. The secondary endpoints were Patient Neurotoxicity Questionnaire (PNQ) grade D or higher [20], Common Terminology Criteria for Adverse Event (CTCAE) grade ≥ 2 for sensory and motor peripheral neuropathy [1], Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane) score [3], and tolerability of cryotherapy. The total FACT-Taxane score was calculated based on an evaluation of skin and nail toxicity. A decrease in the FACT-Taxane score reflects a worsening of dermatological symptoms including skin and nail changes. These endpoints were evaluated at baseline, completion of 3, 6, 9, and 12 weekly doses of paclitaxel. In cases that discontinued 12 weekly doses paclitaxel, neuropathy was evaluated at the discontinuation of the paclitaxel treatment.

Compliance to cryotherapy was determined as good when frozen gloves/socks were appropriately installed during each paclitaxel treatment (total 90 min). In cases who could not wear frozen gloves/socks for continuous 90 min and/or interrupted cryotherapy by wearing thermal gloves/socks inside the frozen gloves/socks, compliance to cryotherapy was determined as poor compliance. Localized skin symptoms of eczema and frostbite and general symptoms of bodily chills and headache were assessed as safety markers of cryotherapy.

**Statistical analysis**

The primary outcome was the percentage of patients with a significant decrease in FACT-NTX score according to the intention-to-treat principle. We included all patients who underwent at least one dose of weekly paclitaxel in the efficacy analyses. Age (younger than 65 vs. 66 and older) and CTCAE peripheral neuropathy (grade 0 vs. grade 1) were used as stratification factors for randomization.

In a phase II self-controlled trial of compression therapy comparing the protected hand with the non-protected hand in the same patient, the incidence of CTCAE grade 2 or higher peripheral neuropathy was 21% on the affected hand and 76% on the control hand in breast cancer patients who received nab-paclitaxel treatment [26]. We assumed that the protective effect of cryotherapy is as effective as compression therapy. Therefore, the percentage of patients with a significant decrease in their FACT-NTX score was estimated at 30 and 70% for the cryotherapy group and control group, respectively. In order to detect the difference between the two groups with 80% power and a significance level for a one-sided test of 0.05, 40 cases are required. Furthermore, taking into account dropout cases, 44 cases (22 cases per group) were planned as the total sample size in this study.

A chi-square test was used as a significance test to compare the percentage of patients with a significant decrease in their FACT-NTX score between the cryotherapy group and control group. A two-sided \( p \) value < 0.05 was considered significant.

**Findings**

**Patient characteristics**

Between February 2017 and September 2018, 44 patients were randomized into the cryotherapy group (\( n = 22 \)) and control group (\( n = 22 \)) (Table 1). All patients were administered at least one dose of weekly paclitaxel. There were no significant differences in age, body mass index, performance status, history of chemotherapy, therapeutic purpose, and weekly paclitaxel treatment regimen between the two groups. Chemotherapy discontinuation occurred in two patients in the cryotherapy group and in three patients in the control group. The reasons for discontinuation were interstitial pneumonia (one patient in each group), worsening peripheral neuropathy (one patient in control group), rash (one patient in cryotherapy group), and depression (one patients in control group).

**Safety and compliance with cryotherapy**

Of the 22 patients in the cryotherapy group, 15 (68%) showed good compliance, while 7 (32%) showed poor compliance. Among subjects showing poor compliance with cryotherapy, four underwent intermittent cryotherapy and three wore thermal insulation gloves/socks inside the frozen gloves/socks. There were no serious side effects associated with cryotherapy, including localized eczema, frostbite, chills or headaches, were observed.

**Efficacy of cryotherapy**

The percentage of patients who showed a marked decrease in FACT-NTX scores was significantly lower in the cryotherapy group than in the control group: (41 vs. 73%, \( p = 0.03 \)). After completion of 12 weekly doses of paclitaxel or termination of paclitaxel treatment, the average decrease in the FACT-NTX subscale score was 6.1 and 11.2 in the cryotherapy and the control groups, respectively, and the magnitude of decrease in the FACT-NTX subscale score was significantly lower in the cryotherapy group (95% CI, 0.5 to 9.6; \( p = 0.03 \); Fig. 1b). Of the 22 patients in the cryotherapy group in this study, 7 (32%) were determined as poor in compliance to cryotherapy. The incidence of significant peripheral neuropathy by determined using the FACT-NTX tended to be lower in the good compliance group (33%) than in the poor compliance group (57%). The incidence of CTCAE grade ≥ 2 or higher peripheral sensory neuropathy was significantly lower in the cryotherapy group than in the control group (9 vs. 54%; \( p = 0.001 \); Fig. 2a). The incidence of CTCAE grade ≥ 2 motor peripheral neuropathy was significantly lower in the cryotherapy group than in the control group (5 vs. 32%; \( p = 0.01 \); Fig. 2b). The incidence of PNQ Grade D or higher peripheral sensory...
neuropathy was significantly lower in the cryotherapy group (14 vs. 42%; \( p = 0.02 \); Fig. 2c). Meanwhile, there were no significant differences in the incidence of PNQ grade D or higher peripheral motor neuropathy between the cryotherapy and the control groups (14 and 23%; \( p = 0.4 \); Fig. 2d). The average FACT-Taxane score reduced by 2.0 and 4.6 points in the cryotherapy and the control groups, respectively, with the change being lower in the cryotherapy group (95% CI, 0.4 to 4.8; \( p = 0.02 \); Fig. 3).

**Discussion**

In this study, we investigated the efficacy of cryotherapy for preventing peripheral sensory neuropathy and dermatological adverse events associated with weekly paclitaxel in breast cancer patients. No severe cryotherapy-related adverse events were noted, and the incidence of peripheral neuropathy was lower in the cryotherapy group. These findings indicate that cryotherapy is a well-tolerated and effective modality against peripheral sensory neuropathy and dermatological adverse events in patients treated with weekly paclitaxel.

The clinical practice guidelines of American Society of Clinical Oncology do not present an established preventive procedure and management protocol for chemotherapy-induced peripheral neuropathy (CIPN) [11]. The use of tricyclic antidepressants, anticonvulsants, various vitamins, or glutamine preparations has been investigated in randomized clinical trials, but none have been proven effective for prevention or alleviation of CIPN [11]. Only duloxetine, a selective serotonin-norepinephrine reuptake inhibitor, has been reported to be effective in alleviating the symptoms of CIPN, but subgroup analysis of chemotherapy regimens have shown no benefit for paclitaxel therapy-induced peripheral neuropathy [22]. Further, duloxetine yields adverse events such as sleepiness and thirst and is limited by low tolerability. There is also no medication that has been established for preventing or treating dermatological adverse events. While external medication may not be helpful, topical steroids, moisturizer or

### Table 1 Clinicopathological characteristics of the patients

| Characteristics | Control group (n = 22) | Cryotherapy group (n = 22) |
|-----------------|-----------------------|---------------------------|
| Age (years)     |                       |                           |
| <77             | 16 73                 | 17 23                     |
| ≥66             | 6 27                  | 5 27                      |
| Mean body mass index (kg/m² (SD)) | 1.5 (0.1) | 1.5 (0.1) |
| Peripheral neuropathy |                   |                           |
| CTCAE 0         | 20 91                 | 20 91                     |
| CTCAE 1         | 2 9                   | 2 9                       |
| Performance status |                    |                           |
| 0               | 22 100                | 20 91                     |
| 1               | 0 0                   | 2 9                       |
| Prior chemotherapy |                    |                           |
| None            | 5 23                  | 4 18                      |
| Anthracycline   | 16 73                 | 18 82                     |
| Taxane          | 1 5                   | 0 0                       |
| Treatment       |                       |                           |
| Neoadjuvant     | 6 27                  | 4 18                      |
| Adjuvant        | 15 68                 | 17 77                     |
| Palliative      | 1 5                   | 1 5                       |
| Paclitaxel regimen |                    |                           |
| Paclitaxel alone | 9 41                  | 9 41                      |
| Paclitaxel and anti-HER2 therapy | 13 59 | 12 55                   |
| Paclitaxel and bevacizumab | 0 0 | 1 5                     |

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; SD, standard deviation
protective varnish is generally administered as a palliative treatment.

Recently, preliminary reports showed the possibility of cryotherapy or compression therapy on affected hands and feet for the prevention of taxane-induced peripheral neuropathy and dermatologic toxicity [4, 8, 18, 19, 26]. In a self-controlled study evaluating the effect of frozen gloves/socks to prevent weekly paclitaxel-related peripheral neuropathy in patients with breast cancer, there was a significant decrease in the occurrence of both objective and subjective signs of CIPN [8]. The primary end point in this study was incidence of objective CIPN evaluated by tactile sensation as assessed by the Semmes-Weinstein monofilament test at a cumulative paclitaxel dose of 960 mg/m². While the incidence of objective CIPN events was 81 and 64 on control-sided hands and feet, respectively, 28 and 25% were reported to have had objective CIPN events on the intervention sided hands and feet, respectively. Similarly, in a self-controlled study evaluating the effect of compression gloves to prevent CIPN in breast cancer patients treated with triweekly nab-paclitaxel treatment, less frequent peripheral neuropathy as measured by the CTCAE and PNQ was seen in the treated hand compared with the other control hand [26]. However, these results are still preliminary due to the nature of the study design, and confirmation of the effect in a randomized controlled trial or larger studies is warranted to establish cryotherapy as a preventive procedure for taxane-induced peripheral adverse events. With these findings, we conducted a randomized phase II study to confirm the effect of cryotherapy for the prevention of peripheral neuropathy and dermatological adverse events in breast cancer patients treated with weekly paclitaxel.

Consistent with previous studies, we confirmed the effect of cryotherapy for prevention of taxane-induced peripheral neuropathy and dermatological adverse events. The incidence of clinical meaningful peripheral neuropathy was significantly
lower in the cryotherapy group compared with the control group. In this study, peripheral neuropathy was assessed by multiple subjective evaluation methods including FACT-NTX, PNQ, and CTCAE. Among these methods, we determined a change of FACT-NTX score as a primary endpoint because the 11-item neurotoxicity components of the questionnaire were shown to demonstrate excellent consistency and validity with CIPN symptoms and QOL deterioration [3]. Although CTCAE is generally assessed for evaluation and validity with CIPN symptoms and QOL deterioration [15], patient education and encouragement of adherence to cryotherapy may be crucial to maximize the protective effect in terms of taxane-induced peripheral toxicity.

There are several limitations to this study. First, this study is a relatively small-sized phase II trial. Our findings about the effectiveness and safety of cryotherapy need to be confirmed in a large clinical trial with objective assessment of peripheral neuropathy, like electromyography. Second, our study focused on weekly-paclitaxel-based regimens. Other taxane-based regimens, such as docetaxel or nab-paclitaxel, should be evaluated in future studies. Finally, there was a progressive deterioration in FACT-NTX score in association with the cumulative doses of paclitaxel in the cryotherapy group. Therefore, other modalities, such as compression therapy, may be considered in combination with cryotherapy to prevent CIPN in advanced/recurrent breast cancer where long-term drug administration is required.

Conclusion

In conclusion, cryotherapy was effective in preventing peripheral neuropathy and dermatological adverse events associated with weekly paclitaxel regimens in breast cancer treatment. Further studies on cryotherapy are warranted to establish a preventive approach for peripheral neuropathy and dermatological adverse events in breast cancer patients undergoing taxane-based chemotherapy.

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Compliance with ethical standards

Conflict of interest This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the Ethics Committee of the National Hospital Organization of Kure Medical Center and Chugoku Cancer Center (Approval number 28-70) and is registered in the University Hospital Medical Information Network (UMIN000034966). All patients received a detailed explanation of the study from the primary physician, and written informed consent was obtained prior to enrollment.

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