Preventive Effect of Cryotherapy on Persistent Chemotherapy-induced Peripheral Neuropathy After Completion of Weekly Paclitaxel Therapy for Breast Cancer

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Abstract

Background

Chemotherapy-induced peripheral neuropathy (CIPN) is an important adverse event of taxane-based chemotherapy, which can persist in a substantial proportion of patients for years. Cryotherapy therapy is shown to be effective in prevention of CIPN during chemotherapy, but its protective effect on persistent CIPN has not been reported.

Methods

Cases enrolled in a randomized trial investigating the preventive effect of cryotherapy on weekly paclitaxel-induced CIPN in breast cancer patients (UMIN000034966) were evaluated for Functional Assessment of Cancer Therapy-Neurotoxicity (FACT-NTX) score and Patient Neurotoxicity Questionnaire (PNQ) at more than one year after completion of weekly paclitaxel.

Results

Thirty-eight cases were evaluated for persistent CIPN with a median 2.3 (1.3-3.1) years after completion of weekly paclitaxel. The incidence of a significant decrease in FACT-NTX scores was numerically lower in the cryotherapy group compared with the control group (15.8% vs. 36.8%, $p = 0.13$). There was also a lower grade of PNQ sensory ($p = 0.02$) and motor ($p = 0.17$) in the cryotherapy group compared with the control group.

Conclusion

In breast cancer patients treated with weekly paclitaxel, cryotherapy resulted in a numerical decrease in the incidence of persistent CIPN at more than one year after completion of weekly paclitaxel treatment.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is an important adverse event associated with weekly paclitaxel for breast cancer, which interferes with activities of daily living and results in a significant deterioration in quality of life[5, 12]. Recent studies showed the possibility of a preventive effect with the use of cryotherapy or compression therapy on taxane-related CIPN in breast cancer patients[4, 15, 18]. In a phase II multicenter study, compression therapy using surgical gloves similarly prevented nanoparticle albumin-bound paclitaxel-related CIPN in breast cancer patients. There was a lower incidence of CTCAE grade2 or higher of sensory (21.4% vs. 76.1%) and motor (26.2% vs. 57.1%) peripheral neuropathies in treated hands than in control hands. In a prospective self-controlled trial evaluating the effect of frozen gloves and socks on weekly paclitaxel related-CIPN, the incidence of objective and subjective CIPN was significantly lower on the intervention side than on the control side at a cumulative paclitaxel dose of 960mg/m^2 . A decrease in tactile sensation was recognized in 28 and 25% of patients in treated hands and feet, respectively, while 81 and 64% of patients reported having a

decrease in tactile sensation in the control hand. The Patient Neurotoxicity Questionnaire (PNQ) survey showed a lower incidence of severe neuropathy in the treated side (3% for hand, 3% for foot) compared with the control side (42% for hand, 36% for foot). We also showed a preventive effect of cryotherapy on weekly paclitaxel-related CIPN in a randomized clinical trial (UMIN000034966)[15]. In our study, the proportion of patients with clinically significant CIPN was significantly lower in the cryotherapy group than in the control group (41 vs. 73%, $p = 0.03$). Although these studies showed the preventive effect of cryotherapy or compression therapy on CIPN during paclitaxel treatment, these protective effects on CIPN years after completion of paclitaxel treatment have not been evaluated.

To clarify the preventive effect of cryotherapy on taxane-related CIPN after completion of treatment, we surveyed the incidence of CIPN at more than one year after completion of treatment in patients who had been registered in our previous randomized trial.

Methods

Study design and participants

Of the 44 cases in a randomized trial investigating the preventive effect of cryotherapy on weekly paclitaxel-induced CIPN in breast cancer patients (UMIN000034966), cases that could provide a response to a questionnaire for CIPN at more than one year after completion of paclitaxel treatment were evaluated in this study. Detailed information and results of the randomized trial are described in a previous report [15]. Briefly, the main inclusion criterion was a diagnosis of invasive breast cancer scheduled for 12 weekly doses of paclitaxel-based treatment. HER2 targeting therapy was combined with weekly paclitaxel in HER2-positive breast cancer. Eligible cases were randomly (1:1) assigned to the cryotherapy group or control group. As cryotherapy, patients continuously wore frozen (-20°C) gloves/socks (Elasto-Gel, mittens, and slippers) on both hands and feet between 15 min before and after paclitaxel infusion (total 90 min). The primary endpoint was incidence of clinical meaningful CIPN after completion of weekly paclitaxel. In total, 38 cases were given a questionnaire for CIPN between April 2020 and October 2020. Six cases were excluded from this survey due to the following reasons: systemic treatment for recurrent breast cancer (2), transfer to different hospital (2), depression (1), and severe neuropathy after meningioma surgery (1) (Fig. 1). 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 adhered to the Helsinki Declaration and the ethical principles for clinical research. All patients received a detailed explanation of the study from the primary physician and informed consent was obtained prior to enrollment.

Evaluation of CIPN

Eligible cases were evaluated using a questionnaire survey for Functional Assessment of Cancer Therapy-Neurotoxicity (FACT-NTX) score and Patient Neurotoxicity Questionnaire. FACT-NTX consists of 11 items evaluating CIPN-associated symptoms with a 0 to 4 score and a lower FACT-NTX score reflects worse peripheral neuropathy[3]. A 6-point or more decrease in the total FACT-NTX score from baseline is

regarded as clinically significant CIPN. PNQ is a patient-reported questionnaire on sensory and motor neuropathy and how they influence daily activity and quality of life. A PNQ grade ranges from A (no symptoms) to E (severe symptom with significant deterioration of daily activity)[16].

Statistical analysis

Patient characteristics were assessed by groups using a Fisher's exact test of categorical variables and t-test for continuous variables. A Fisher's exact test was used to compare the incidence of a clinically significant decrease of the FACT-NTX score and the distributions of each FACT-NTX item and PNQ grade between the cryotherapy and control groups. Predictive factors for a clinically significant decrease of the FACT-NTX score were evaluated using logistic regression analysis. A two-sided p value < 0.05 was considered significant. Statistical analyses were performed using JMP software version 13.2.1 (SAS Institute Inc., Cary, USA).

Findings

Patient Characteristics

Of 38 cases evaluated for persistent CIPN at more than one year after completion of treatment, 19 cases were from the cryotherapy group and 19 were from the control group. The median time from completion of the weekly paclitaxel treatment to questionnaire for persistent CIPN in this study was 2.3 (1.3-3.1) years. There was no statistical difference in regard to baseline clinicopathological factors, including interval from completion of paclitaxel, PS, age, height, weight, stage, subtype, adjuvant endocrine therapy and radiation therapy between the cryotherapy and control group (Table 1). During weekly paclitaxel treatment, there was significantly lower incidence of a clinically significant decrease in FACT-NTX score (31.6% vs. 73.7%, $p = 0.008$) and a lower grade of PNQ sensory ($p = 0.02$) and motor ($p = 0.04$) in the cryotherapy group compared to the control group.

Effect of cryotherapy on incidence of persistent CIPN

All 38 cases responded to the questionnaire for FACT-NTX and PNQ after completion of weekly paclitaxel treatment. The incidence of a clinically significant decrease in the FACT-NTX score was 15.8% and 36.8% in the cryotherapy and control group, respectively, showing a numerically lower incidence in the cryotherapy group ($p = 0.14$) (Table 2). Figure 1 shows the distribution of scores for each questionnaire item in FACT-NTX. There was tendency for a lower score for Hand numbness, Foot numbness and Foot discomfort in the cryotherapy group compared with the control group. In the questionnaire for PNQ, there was also a lower grade of sensory ($p = 0.02$) and motor ($p = 0.17$) symptoms in the cryotherapy group compared with the control group (Table 2).

Predictive factor for persistent CIPN

Logistic regression analysis was used to evaluate the association between clinicopathological factors and the incidence of significant decrease in the FACT-NTX score. Age 60 years or older had a significantly increased risk of significant decrease in the FACT-NTX score (odds ratio = 26.6, 95%CI = 3.3-574.5, $p = 0.001$). Cryotherapy was marginally associated with significant decrease in the FACT-NTX score (odds ratio = 4.8 95%CI = 0.7-50.1, $p = 0.12$). The other baseline clinicopathological factors including age, cryotherapy height, weight, adjuvant endocrine therapy, adjuvant radiation therapy and length of interval, were not associated with significant decrease in the FACT-NTX score.

Discussion

In this follow-up study of a randomized trial investigating the preventive effect of cryotherapy on weekly paclitaxel-induced CIPN of breast cancer patients, cryotherapy resulted in a numerical decrease in the incidence of persistent CIPN at more than one year after completion of treatment. In this study, logistic regression analysis showed age 60 years or older was a significant predictive factor for persistent CIPN.

CIPN is a common and prolonged adverse event of weekly paclitaxel which has a negative impact on quality of life[5]. With the introduction of target treatment for breast cancer, a substantial proportion of patients have excellent prognosis after adjuvant weekly paclitaxel-containing therapy. For example, adjuvant weekly paclitaxel and trastuzumab therapy resulted in a 7-year OS of 95% and 7-year RFI of 97.5% in HER2-positive and node negative breast cancer[17]. Thus, long-term CIPN has become an important issue for the growing number of breast cancer survivors who received adjuvant weekly paclitaxel. Although the degree of paclitaxel-induced CIPN reduces over time, a substantial proportion of the population continues to suffer from CIPN even years after completion of taxane-based chemotherapy[13]. A cross-sectional study of 50 consecutive early-stage breast cancer patients who were within 6 and 24 months of completing adjuvant paclitaxel therapy showed that 80% of the patients reported numbness or discomfort in the hands or feet and a quarter of the population suffered from severe symptoms[8]. A prospective study of 50 patients also showed that two-thirds of the population reported persistent numbness in the hands or feet, including a quarter with severe symptoms at 12 months after completion of paclitaxel treatment. A randomized study, which evaluated the preventive effect of Acetyl-L-Carnitine on taxane-related CIPN, showed prolonged clinically significant CIPN in more than 30 percent of the population at week 12, 24, 36, 52, 104 after registration[7]. These results show that taxane-related CIPN can persist over a year and persistent CIPN is an important clinical issue to be resolved in breast cancer patients treated with taxane-based chemotherapy. Our study also showed that a substantial proportion of cases have persistent CIPN after completion of weekly paclitaxel. Persistent CIPN was observed in 10 (26.3%) of 38 cases. Among 20 cases with significant CIPN during weekly paclitaxel, 10 (50%) cases showed persistent CIPN. Meanwhile, no persistent CIPN was observed in cases without significant CIPN during weekly paclitaxel. These findings suggest that prevention of CIPN during taxane-based therapy is associated with a reduction in the occurrence of persistent CIPN.

Previous clinical trials showed the possibility of cryotherapy or compression therapy to decrease incidence of CIPN during taxane-based chemotherapy in breast cancer patients[1, 2, 4, 14, 15, 18]. In

addition to these findings, our study also showed the possibility of cryotherapy in prevention of persistent CIPN after completion of weekly paclitaxel. Although there was no significant difference between the cryotherapy and control groups due to the nature of unplanned analysis, less than half of cases in this study experienced persistent CIPN in the cryotherapy group compared with the control group (15.8% vs. 36.8%). PNQ also showed lower grade persistent CIPN in the cryotherapy group. Since the incidence of CIPN during chemotherapy is a risk factor for persistent CIPN, it is logical that prevention of CIPN during chemotherapy leads to the reduction of persistent CIPN.

As with previous study, age is an important factor for the incidence of persistent CIPN. In a randomized trial of Acetyl-L-Carnitine for prevention of taxane-induced CIPN, women aged 60 years or older had an increased risk of CIPN compared with women younger than age 60 years at a 1 and 2 year follow-up[7]. Our study showed that age 60 or more was a significant predictive factor for persistent CIPN. The incidence of persistent CIPN was 8.7% and 53.3% in the age < 60 and age 60 or older, respectively. The precise mechanism is unknown, however, aging is at least a risk factor for CIPN in patients treated with paclitaxel. A cohort study including 333 participants to identify the association of clinical factors with CIPN persistence in patients treated with paclitaxel or oxaliplatin showed that an older age was associated with worse CIPN in multivariate analysis[11]. A cohort study of the Southwest Oncology Group database that evaluated the incidence of CIPN in clinical trials showed that the incidence of grade2-4 taxane-induced CIPN increases by 4% for each year of age[6]. In this study, the incidence of persistent CIPN was 33.3% and 66.7% in the cryotherapy group and control group, respectively, in age 60 or older. In comparison, there was no difference (7.7% vs. 10%) between these groups at an age less than 60. These findings suggest that pronounced precaution should be taken to prevent CIPN when older patients are treated with weekly paclitaxel.

Our study has several limitations. First, this is an unplanned study of cases enrolled in a previous clinical trial and there was a lack of statistical power to detect the difference between cryotherapy and the control group. Second, evaluation of persistent CIPN in this study was based on a subjective patient questionnaire. Objective evaluation, such as the Semmes-Weinstein monofilament test, should be incorporated to improve the robustness of our finding. A prospective randomized trial with a long-term period is warranted to confirm the preventive effect of cryotherapy on persistent CIPN[9, 10].

Declarations

Funding: This study received no funding.

Conflicts of interest/Competing interests: The authors declare that they have no conflict of interest.

Availability of data and material: Data and material are available

Code availability: Not applicable.

Authors' contributions: HS: study concept, design, data analysis, and writing of the manuscript. YK, TI, and DY: study concept and design. All authors reviewed final manuscript.

Ethics 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 adhered to the Helsinki Declaration and the ethical principles for clinical research.

Consent to participate: All patients received a detailed explanation of the study from the primary physician and informed consent was obtained prior to enrollment.

Consent for publication: Informed consent to have de-identified data published was obtained from all individual participants included in the study.

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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 adhered to the Helsinki Declaration and the ethical principles for clinical research. All patients received a detailed explanation of the study from the primary physician and informed consent was obtained prior to enrollment.

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Tables

Table 1. clinicopathological factors

factors		cryotherapy (n=19)	Control (n=19)	p value*
Age, years	60>	13	10	0.3
	60<=	6	9	
Height, mean(SD), cm		156.5(5.9)	154.1(7.1)	0.3
Weight, mean(SD), kg		52.3(7.1)	55.9(9.1)	0.2
Stage	I	4	2	0.7
	II	8	9	
	III	7	8	
Adjuvant endocrine therapy	yes	15	16	1
	no	4	3	
Adjuvant radiation therapy	yes	14	15	1
	no	5	4	
Decrease in FACT-NTX during weekly paclitaxel**	yes	6	14	0.008
	no	13	5	
PNQ sensory grade during weekly paclitaxel	A	2	1	0.02
	B	11	3	
	C	5	8	
	D	1	6	
	E	0	1	
PNQ motor grade during weekly paclitaxel	A	4	0	0.04
	B	11	9	
	C	3	6	
	D	1	2	
	E	0	2	

Abbreviations: SD, standard deviation; FACT-NTX, Functional Assessment of Cancer Therapy-Neurotoxicity; PNQ, Patient Neurotoxicity Questionnaire

*Factors were compared by treatment groups using Fisher's exact test for categorical variables and t tests for continuous variables. Tests were two-sided.

**A 6-point or more decrease in the total of FACT-NTX score from baseline is regarded as clinically significant CIPN.

Table2. Results of FACT-NTX and PNQ after completion of weekly paclitaxel treatment.

factors		Cryotherapy (n=19)	Control (n=19)	P value*
Interval from weekly paclitaxel to questionnaire, years(SD)		2.5(0.5)	2.6(0.5)	0.4
Significant decrease in FACT-NTX**	yes	3	7	0.13
	no	16	12	
PNQ sensory grade	A	11	5	0.02
	B	6	8	
	C	0	5	
	D	2	1	
	E	0	0	
PNQ motor grade	A	14	11	0.17
	B	3	4	
	C	0	3	
	D	2	1	
	E	0	0	

Abbreviations: SD, standard deviation; FACT-NTX, Functional Assessment of Cancer Therapy-Neurotoxicity; PNQ, Patient Neurotoxicity Questionnaire

*Factors were compared by treatment groups using Fisher's exact test. Tests were two sided.

**A 6-point or more decrease in the total of FACT-NTX score from baseline is regarded as clinically significant CIPN.

Figures

Figure 1

Consort diagram for this survey

Figure 2

Distribution of symptom grade for each questionnaire item of FACT-NTX after weekly paclitaxel in cryotherapy and control group.