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

This observational study was performed as an ancillary analysis of a randomized trial investigating the preventive effect of cryotherapy on weekly paclitaxel-induced CIPN in breast cancer patients (UMIN000034966). Eligible cases 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 after completion of weekly paclitaxel therapy.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is an important adverse event which is associated with deterioration of quality of life and survivorship [1, 2]. In breast cancer, the agents with high incidence of CIPN are microtubule inhibitors such as taxane. Taxane-related CIPN is dose-dependent and cumulative and typically shows symmetric stocking and glove distribution. Although taxane-related CIPN is gradually improved over time after completion of chemotherapy, substantial proportion of cases suffered from persistent sensory and motor neuropathy in limbs. 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[3]. 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 therapy[3].

Because there is limited evidence of treatment to alleviate symptomatic CIPN, preventive approaches are important in the treatment of CIPN. Recent studies showed the possibility of a preventive effect of cryotherapy or compression therapy on taxane-related CIPN in breast cancer patients[4-6]. A mechanism underlying the preventive effect of cryotherapy and compression therapy is considered that these therapy during paclitaxel infusion reduces paclitaxel perfusion in limbs, which results in a prevention of peripheral neuropathy[2, 4]. In a phase II multicenter study of compression therapy, 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, 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 at a cumulative paclitaxel dose of 960mg/m^2. We also showed a preventive effect of cryotherapy on weekly paclitaxel-related CIPN in a randomized clinical trial (UMIN000034966), in which 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) [6]. Although these studies showed the preventive effect of cryotherapy or compression therapy on CIPN during paclitaxel therapy, the incidence of persistent CIPN years after completion of paclitaxel therapy have not been evaluated.

Considering the impact of persistent CIPN on survivorship, we planned an observational study as an ancillary analysis of the previous randomized trial to clarify the preventive effect of cryotherapy on taxane-related persistent CIPN. In this study, we show a preventive effect of cryotherapy on persistent CIPN at more than one year after completion of weekly paclitaxel.

Methods

Study design and participants

This observational study was performed as an ancillary analysis of a randomized trial investigating the preventive effect of cryotherapy on weekly paclitaxel-induced CIPN in breast cancer patients (UMIN000034966). Detailed information and results of the randomized trial are described in a previous report [6]. Because the randomized study was completed with an assessment of CIPN at the end of weekly paclitaxel therapy, we planned an observational study as an ancillary analysis of the previous trial to clarify the preventive effect of cryotherapy on persistent CIPN after completion of weekly paclitaxel therapy. Of the 44 cases in the previous randomized trial, cases that could provide a response to a questionnaire for CIPN at more than one year after completion of paclitaxel therapy were eligible in this study. Cases were called back and asked for repeat questionnaire for CIPN. In total, 38 cases provided 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 observational 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[7]. 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)[8].

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 multivariate 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 therapy 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 therapy, 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 therapy. 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. 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

Multivariate logistic regression analysis was used to evaluate the association between clinicopathological factors, including age, cryotherapy, height, weight, adjuvant endocrine therapy, adjuvant radiation therapy and length of interval, and the incidence of persistent CIPN (Supplemental Table 1). Age 60 years or older had a significantly increased risk of significant decrease in the FACT-NTX score (odds ratio = 29.7, 95%CI = 2.3-391.6, p < 0.01). Cryotherapy was marginally associated with significant decrease in the FACT-NTX score (odds ratio = 5.0 95%CI = 0.6-42.9, p = 0.15). The other clinicopathological factors were not associated with significant decrease in the FACT-NTX score.

Discussion

In this observational study as an ancillary analysis of a previous 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. Age 60 years or older was a significant predictive factor for persistent CIPN in multivariate logistic regression analysis.

With the widespread administration of systemic adjuvant therapy for breast cancer, a substantial proportion of patients has an excellent prognosis[9, 10]. In HER2 positive breast cancer, the introduction of adjuvant trastuzumab with taxane-based chemotherapy resulted in significant improvement of long-term prognosis[11-13]. 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[14]. Thus, persistent CIPN has become an important issue for the growing number of breast cancer survivors who received adjuvant taxane-based therapy.

In our study, persistent CIPN determined with significant decrease of FACT-NTx score was observed in approximately quarter of all cases (26.3%) with median of 2.3 years after completion of weekly paclitaxel. In addition, more than one-third (36.8%) of cases in control group showed persistent CIPN. Common symptom of persistent CIPN was sensory neuropathy, with the finding more than cases showed hand and foot numbness in control group. Our finding of the incidence of persistent CIPN is compatible with previous reports[3, 15, 16]. In a randomized trial of acetyl-L-carnitine (SWOG S0715), 34.4% on the placebo arm reported a significant decrease of FACT-NTx score from baseline at 104 weeks from randomization[16]. In an observational study of early-stage breast cancer patients who received adjuvant paclitaxel therapy also showed that severe symptoms of numbness or discomfort for the hands and the

feet in a quarter of cases [3]. Although our study is cross-sectional analysis with various duration since completion of paclitaxel therapy, the duration seems a small impact on the incidence of CIPN. A multivariate logistic regression analysis in our study showed that interval from end of paclitaxel therapy was not associated with persistent CIPN. In SWOG S0715 also showed persistent low NTX scores at weeks 12, 24, 36, 52, and 104[16]. In the prospective observational study, the mean scores on the FACT NTx score low 12 months after treatment[3]. These findings show that taxane-related CIPN can persist over years and persistent CIPN is an important clinical issue to be resolved in breast cancer patients.

As risk factors of CIPN, age and is reported to be associated with an incidence of CIPN and persistent CIPN. In regard to incidence of CIPN, a cohort study including 333 participants treated with paclitaxel or oxaliplatin showed that an older age was associated with worse CIPN in multivariate analysis[17]. A cohort study of the Southwest Oncology Group database also showed that the incidence of grade2-4 taxane-induced CIPN increases by 4% for each year of age[18]. In regard to persistent CIPN, a retrospective analysis of 219 breast cancer cases showed that age 60 years or younger showed a significant less duration of taxane-related CIPN (HR 0.55, P=0.027)[15]. SWOG S0715 trial also showed age 60 years or older had an risk factor for occurrence of CIPN at year 1 (HR 1.74, p=0.02) and year 2 (HR 1.67, p=0.04)[16]. In our study, age 60 years or older was shown as a significantly increased risk of persistent CIPN. The incidence of persistent CIPN was 8.7% and 53.3% in the age < 60 and age 60 or older, respectively. These findings indicate that pronounced precaution should be taken to prevention and treatment of CIPN when older patients are treated with weekly paclitaxel.

Although no effective treatment of persistent CIPN has not been reported, preventive approach of CIPN could be associated with decrease of persistent CIPN. At first, occurrence of CIPN is significant risk factor of persistent CIPN. A retrospective study showed that duration of CIPN was significantly longer in cases with Grade2/3 peripheral neuropathy compared with Grade1 peripheral neuropathy (HR 0.55, p=0.015) [15]. In our study, no case without CIPN during paclitaxel therapy showed persistent CIPN, whereas half of cases (50%) that experienced CIPN during weekly paclitaxel therapy showed persistent CIPN. These findings suggest that prevention of CIPN during taxane-based therapy leas to a prevention of persistent CIPN. As shown in previous clinical trials, cryotherapy or compression therapy may be associated with decrease in incidence of CIPN in breast cancer patients[4-6, 9-11]. A randomized trial or ancillary analysis of previous randomized trials are warranted to confirm the preventive effect of cryotherapy or compression therapy on persistent CIPN.

Our study has several limitations. First, the nature of unplanned ancillary analysis results in 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. Finally, although the degree of persistent CIPN seems to be fixed over time, further serial assessments of CIPN on individual case might strengthen the findings of our study[1].

In conclusion, we showed that cryotherapy resulted in a numerical decrease in the incidence of persistent CIPN at more than one year after completion of treatment in breast cancer patients treated with weekly paclitaxel. A prospective randomized trial with a long-term period is warranted to confirm the preventive effect of cryotherapy on persistent CIPN.

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	

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.

factors		cryotherapy (n = 19)	Control (n = 19)	p value*
	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.				

Table 2
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

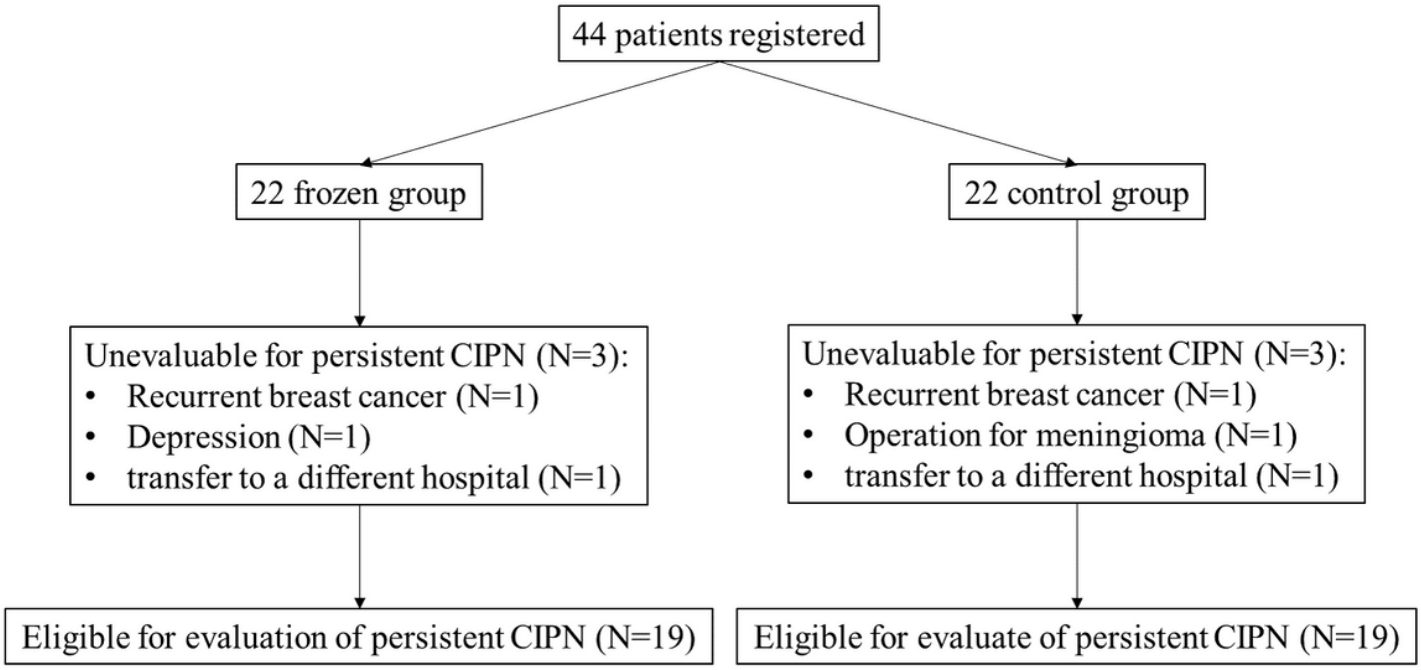

Figure 1

Consort diagram for this survey

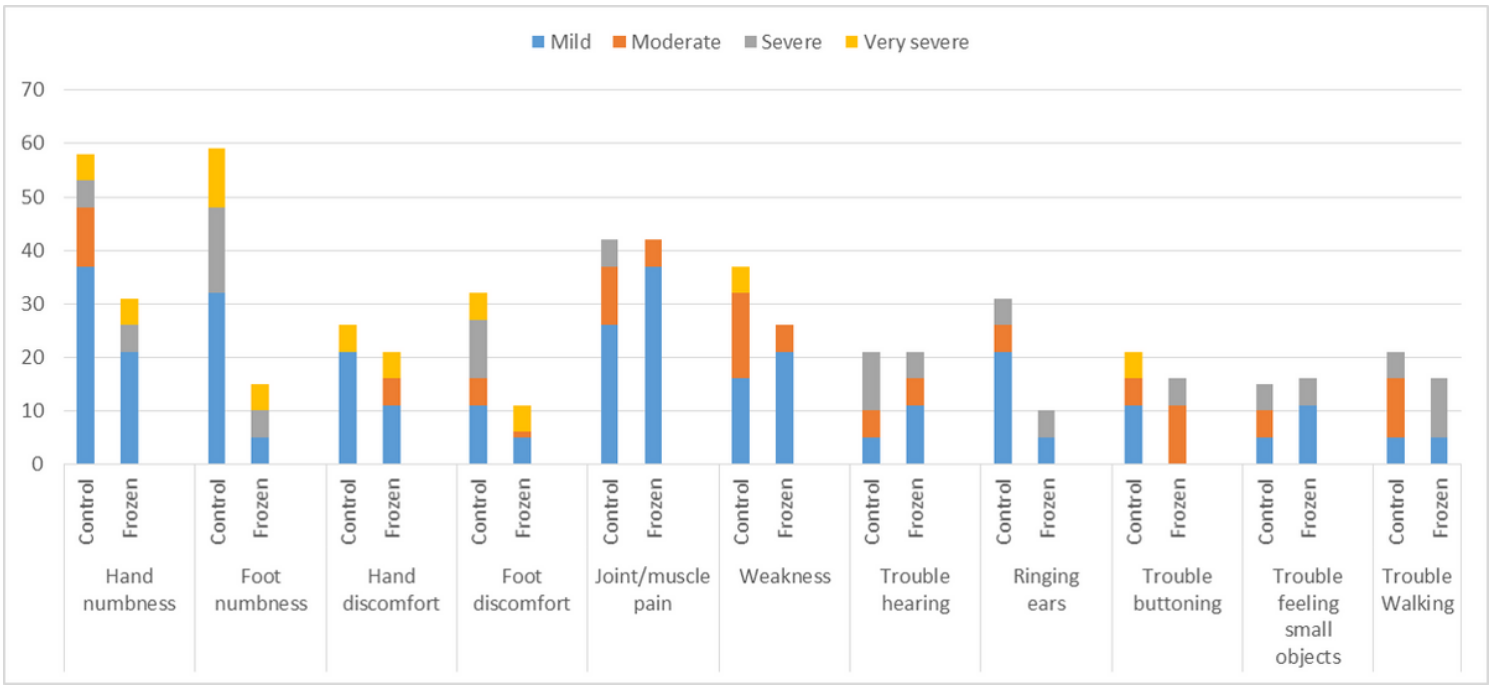

Figure 2

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

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalTable1.docx