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Original article

Randomized controlled trial of cryotherapy to prevent paclitaxel-induced peripheral neuropathy (RU221511I); an ACCRU trial

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ABSTRACT

Purpose: This pilot trial aimed to assess if cooling hands and feet with crushed ice during receipt of paclitaxel helps prevent peripheral neuropathy.
Methods: This prospective, randomized trial compared cryotherapy to standard care in patients initiating paclitaxel weekly x 12. For those on cryotherapy, hands and feet were cooled starting 15 min prior to and ending 15 min after each paclitaxel dose. EORTC QLQ-CIPN20 was completed at baseline, weekly x12, then monthly x6. Area under the curve (AUC) was calculated for subscale scores, adjusting for baseline, and compared between arms (Wilcoxon rank-sum test). Cross-study comparisons used data from 2 prior similarly-conducted neuropathy trials.
Results: Forty-six patients were accrued. Three withdrew and one was ineligible. Of the remaining 42 (21 cryotherapy, 21 control), 39 (19 cryotherapy, 20 control) were analyzable for AUC. Cryotherapy was well tolerated, but the AUC of the CIPN20 sensory scores over 12 weeks of paclitaxel was not found to differ between the study arms (mean difference 3.45, 95% CI -3.13 to 10.02, $p = 0.26$). However, the control arm of the current trial experienced less neuropathy than did the placebo arms of two previous similar trials. When our cryotherapy arm was compared to the combined control arms from all three trials, the cryotherapy arm had less neuropathy (Wilcoxon Rank-Sum $p = 0.01$).
Conclusion: While there was no difference in CIPN20 scores identified between the 2 study arms in the current phase II trial, further investigation is needed given that the control arm experienced less neuropathy than was expected.

1. Introduction

Peripheral neuropathy is one of the primary dose-limiting toxicities of many chemotherapeutic agents, including taxanes [1]. Paclitaxel, one of the most commonly used neurotoxic drugs, is often administered at 80 mg/m^2 weekly for twelve weeks as part of neoadjuvant or adjuvant treatment for breast cancer. The symptoms of chemotherapy-induced peripheral neuropathy (CIPN) due to paclitaxel usually begin during treatment, worsen with greater cumulative doses, and improve or completely resolve after paclitaxel therapy finishes. However, in some patients, these symptoms persist indefinitely, substantially impairing quality of life and potentially impacting the choice of subsequent treatments. CIPN symptoms are usually sensory, often including numbness and tingling, and are sometimes compounded by shooting/burning pain [2]. Older age, diabetes, and African American race seem to increase risk [3]. In a small study, Hershman and colleagues showed that more than half of women who received adjuvant taxane therapy for breast cancer had numbness and/or discomfort in their hands and/or feet between 6 months and 2 years after completion of

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chemotherapy [4].

The paclitaxel acute pain syndrome (PAPS), usually manifesting as pain in the back, hips, shoulders, thighs, legs, and/or feet beginning 1–2 days after paclitaxel infusion and lasting 4–5 days, has also been recognized as a type of chemotherapy-induced neuropathy [5–7]. The ability/willingness of a patient to complete (and/or a provider to administer) the recommended full course of taxane therapy can be impeded by the development of PAPS and/or the numbness/tingling and pain associated with CIPN.

ASCO guidelines, published in 2014, reviewed the results of 42 randomized trials that assessed interventions to prevent CIPN and concluded that none of the tested methods had been proven to be effective [1]. Newer reports since then have still failed to identify an effective preventative approach [8–11], with the exception of a recent report regarding the use of ganglioside-monosialic acid (GM-1) [12], which will require confirmation.

Cryotherapy (cryo) during chemotherapy has been proven to reduce alopecia [13,14], mucositis [15,16], and onycholysis, [17–21]; additionally, there are data suggesting that cryotherapy may prevent ocular toxicity from 5-fluorouracil [22]. In addition, case reports and retrospective series have suggested that there may be less CIPN if hands and feet are cooled before, during, and after the administration of each taxane dose; this technique has also been used to try to prevent taxane-induced onycholysis [17,23,24]. One such study was a Danish retrospective evaluation of docetaxel-associated neuropathy, in which 597 of 1725 patients who received docetaxel as part of treatment for early stage breast cancer had self-reported grade 2–4 neuropathy during treatment, but the odds of CIPN was reduced in those who had chosen to wear frozen gloves and socks during treatment (OR 0.56; 95% CI 0.38–0.81) [25]. In addition, a recent small trial in Japan also identified less neuropathy in hands and feet on which frozen socks and gloves were worn during weekly paclitaxel therapy [26]. The mechanism through which cryotherapy may protect against toxicity is postulated to be vasoconstriction, resulting in reduced delivery of neurotoxic chemotherapy to the target tissue.

The current trial was designed to obtain additional pilot data regarding the potential for cryotherapy to prevent paclitaxel-associated neuropathy to inform a more definitive phase III cooperative-group clinical trial.

2. Methods

Patients participating in this clinical trial needed to be scheduled to receive paclitaxel at a dose of 80 mg/m2 I.V. for breast cancer (in the adjuvant or neo-adjuvant setting), every week for a planned course of 12 weeks, without any other concurrent cytotoxic chemotherapy (but with Her2-directed therapy allowed concurrently). Eligible patients must have had a life expectancy of 6 months and an ECOG performance status of 0–1. They could not have had a prior history of diabetic neuropathy or any other peripheral neuropathy. They could not have been diagnosed with fibromyalgia. They could not a have received prior neurotoxic chemotherapy and were excluded if they had a history of Raynaud's disease or cryoglobulinemia.

When patients enrolled on this clinical trial, they were randomized to receive standard care versus topical cryotherapy, the latter starting fifteen minutes prior to initiation of each paclitaxel dose and finishing 15 min following the completion of each dose; cryotherapy was performed using bags of crushed ice on the hands and feet. During cryotherapy, patients wore cotton gloves over their hands, which were each inserted into the pocket of a quart-sized plastic bag 2/3 full of ice, and if no IV was in the hand, another quart-sized bag, 2/3 full of ice, was placed on top of each hand. Additionally, patients wore light cotton socks on their feet, which were then placed on top of and beneath similar bags of ice (1/2 full gallon-sized bags below each foot and on top of each foot). Patients in the cryotherapy arm were allowed to remove hands and feet from contact with ice if needed for comfort; ice was replenished if it melted. Non-opioid (e.g., acetaminophen 500 mg every six hours as needed) and opioid (e.g., oxycodone 5 mg every one to two hours as needed) pain medications were allowed at clinician's discretion during the twelve week course of paclitaxel therapy (particularly for treating the paclitaxel acute pain syndrome symptoms). Use of integrative medicine techniques (e.g., acupuncture) was also allowed if desired.

Prior to the initiation of paclitaxel (at baseline), patients were asked to complete a Pre-Paclitaxel Questionnaire including two yes/no questions about: 1) chronic aches and pain; and 2) regular use of pain medications (with the request to list those taken regularly), along with a 0 (not at all) to 10 (as bad as it can be) linear analogue scale regarding how distressing such aches and pains were over the prior week. After initiation of paclitaxel, patients were then asked to complete a daily Post-Paclitaxel Questionnaire including 0 (none) to 10 (as bad as can be) linear analogue scales reporting on the least, worst, and average severity of new aches/pains since the last dose of paclitaxel over the prior 24 h, for 6 days. This was done to gather daily data regarding the incidence and severity of any paclitaxel acute pain symptoms (previously often referred to as paclitaxel-induced arthralgias/myalgias). An Acute Pain Syndrome Symptom Summary Questionnaire was administered prior to each subsequent dose of paclitaxel as another assessment of the acute pain associated with the prior dose of paclitaxel. Also, CTCAE neuropathy grading occurred at baseline and prior to each dose of paclitaxel. Additionally, nurse phone calls occurred on day 2 of cycle 1 and then about every 30 days for the 6 months following the completion of paclitaxel (to ask patients how they were doing and to remind them to complete study questionnaires). For the patients who received cryotherapy, on each day of paclitaxel administration, following treatment, the nurse was asked to complete a Cryotherapy Toleration Form, choosing “very well,” “moderately well,” “moderately poorly,” or “very poorly,” to categorize the patient's tolerance of the cryotherapy that day; elaborative comments were also solicited from the nurse.

The primary endpoint of the study was the score on the sensory scale of the EORTC QLQ CIPN-20. The EORTC QLQ CIPN-20 was administered on paper to patients at baseline and before each dose of paclitaxel, as well as every 30 days for six months after completion of the 12 weeks of paclitaxel. A desired sample size of 46 (23 per arm) was decided based on logistics and finances, producing 80% power to detect an improvement of 0.85 standard deviations in the area under the CIPN-20 sensory score curve in the cryotherapy arm compared to the control arm. Differences between cryotherapy and control arms were compared in an exploratory fashion to assess if patients in the cryotherapy arm appeared to have less severe neuropathic symptoms. The EORTC QLQ CIPN-20 subscale scores were summarized and plotted by treatment arm. The area under the curve (AUC) was calculated for weeks 1–12 using the trapezoidal rule after adjusting for baseline score and compared between arms using the Wilcoxon rank-sum test. The AUC was calculated for baseline –month 6 of follow-up using the trapezoidal rule, adjusting for baseline score, and compared between arms using the Wilcoxon rank-sum test. All other secondary endpoints were summarized by arm and compared between arms using the Wilcoxon rank-sum test for continuous variables and the Fisher's exact test for categorical variables.

This study received institutional review board approval.

3. Results

Fig. 1, a CONSORT diagram, depicts enrollment details.

Baseline characteristics, including pre-paclitaxel patient-reported neuropathy scores, are displayed in Table 1. All participants were white, and none reported that they were Hispanic (though two, one in each arm, were uncertain of their ethnicities). Approximately half of the patients on both arms received doxorubicin-cyclophosphamide (AC) prior to starting paclitaxel. Two received trastuzumab (one in each arm), and one received pertuzumab (in the cryotherapy arm). There were no statistically significant differences in any of the baseline factors between the two study arms.

The study's primary endpoint, the AUC of the CIPN20 sensory scores over the 12 weeks of paclitaxel treatment, adjusted for baseline scores, did not substantially differ between the arms (Fig. 2), with a mean difference of 3.45 (95% confidence interval = (−3.13, 10.02); p-value = 0.26). The results with regards to individual CIPN20 items related to tingling, numbness, and shooting/burning pain are illustrated in Fig. 3. There were no apparent differences between the study arms related to reasons for early cessation of study-related treatment, PAPS symptoms (Fig. 4), or the use of non-opioid or opioid pain medications, for treating PAPS symptoms. Although paclitaxel doses were not rigorously collected, there were five patients for whom paclitaxel dose reductions were recorded in the comment section of the case report forms: two in the control arm (one noted to be due to neuropathy, one noted to be due to leukopenia) and three in the cryotherapy arm (one noted to be due to paresthesias, with no reason provided for the other two).

The AUC of the CIPN20 sensory scores, adjusted for baseline score, also did not differ over months 1–6 of follow-up, and only one symptom was significantly less in the cryotherapy arm (problems standing/walking because of difficulty feeling the ground, p = 0.02). In addition, there were no significant differences between the cryotherapy vs. control arms in clinician-reported neuropathy; only one patient in the cryotherapy arm had CTCAE documentation of extremity pain (grade 2), one in the control arm had CTCAE documentation of peripheral motor neuropathy (grade 2), and one in the control arm had CTCAE documentation of peripheral sensory neuropathy (grade 2). Furthermore, the proportion of patients who used non-prescription or opioid pain medications did not differ significantly between the arms at any time point. During the first week of paclitaxel, 6 patients in the cryotherapy arm and 9 patients in the control arm used a non-prescription pain medication, while only 2 in the control arm used an opioid (p = 0.51).

Table 1
Baseline characteristics.

	Cryotherapy (N = 21)	Control (N = 21)
Age		
Median (IQR)	53 (45–56)	55 (49–66)
Age Group		
≤50 years	8 (38%)	9 (43%)
>50 years	13 (62%)	12 (57%)
Gender		
Female	20 (95%)	21 (100%)
Male	1 (5%)	0 (0%)
Performance Score		
0	18 (86%)	18 (85.7%)
1	3 (14%)	3 (14.3%)
Diabetes		
Yes	0 (0%)	1 (5%)
No	21 (100%)	20 (95%)
Tumor Status		
Resected with no residual	10 (48%)	16 (76%)
Unresected	10 (48%)	5 (24%)
Recurrent	1 (5%)	0 (0%)
Prior AC Therapy		
Yes	10 (48%)	11 (52%)
No	11 (52%)	10 (48%)
Baseline CIPN20:		
Autonomic Score		
Mean (SD)	96 (7)	96 (10)
Motor Score		
Mean (SD)	96 (8)	97 (5)
Sensory Score		
Mean (SD)	97 (6)	97 (6)

AC = doxorubicin and cyclophosphamide.

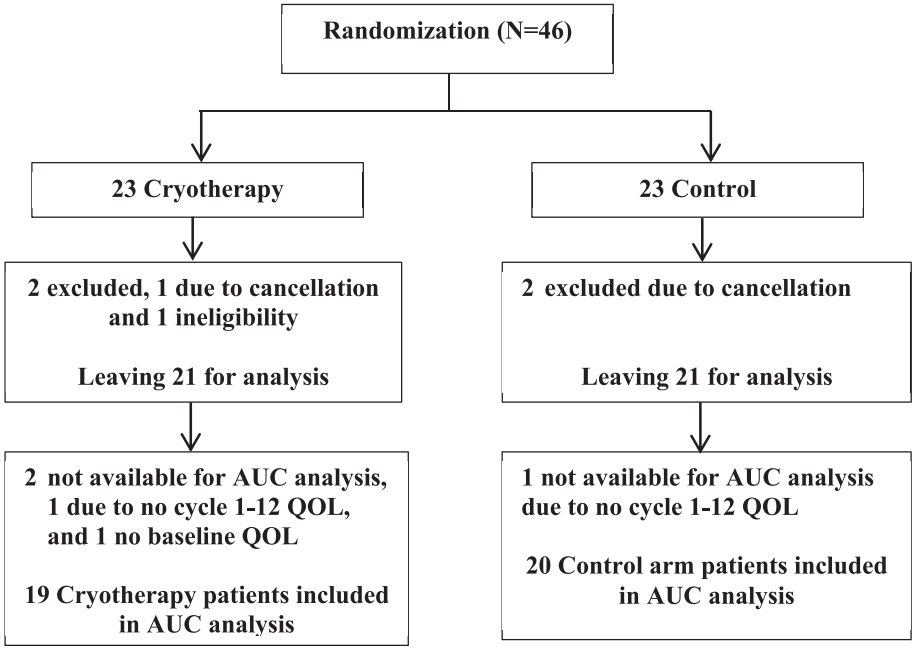


Fig. 1. CONSORT diagram.

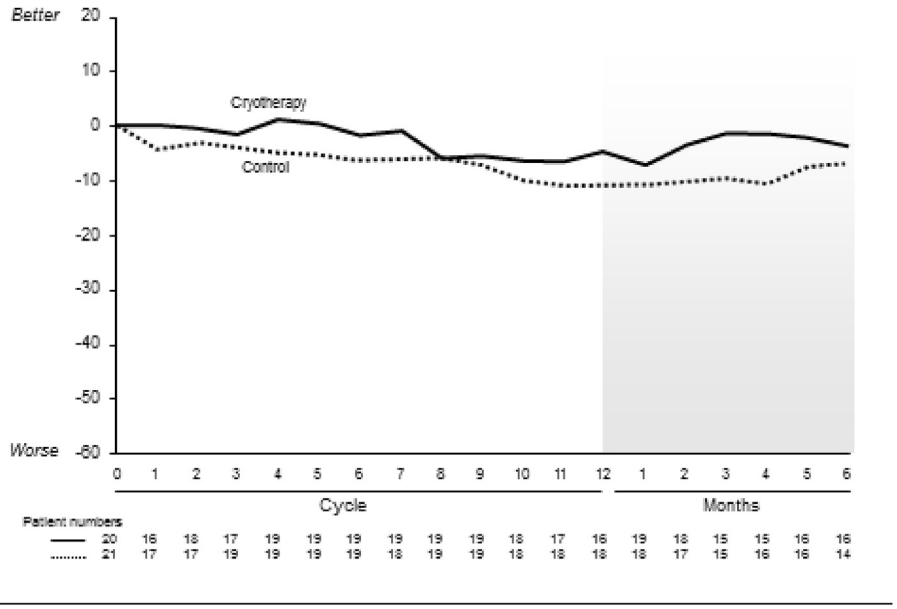


Fig. 2. CIPN during 12 weeks of treatment and 6 months of follow-up represented as the mean change from baseline in EORTC QLQ-CIPN20 sensory scores. Higher scores represent fewer symptoms.

The tolerability of cryotherapy treatments varied among patients, with only a minority of patients experiencing substantial side effects. Three of 21 patients on the cryotherapy arm (14.3%) had cryotherapy altered due to side effects for at least one cycle (one for cycles 1 and 2 – refused trying cryotherapy due to an allergic reaction to pertuzumab; one for cycle 11; and one for cycles 1, 3, and 5–10 (during which the patient took breaks from cryotherapy, resuming when side effects improved or resolved). After the first treatment, 12 (57%) were rated by the nurses to have tolerated the cryotherapy very well, 7 (33%) moderately well, and 2 (10%) had missing data. After the second treatment, when data were available for all 21 cryotherapy-treated patients, 13 (62%) were reported by the nurses to have tolerated it very well, 6 (29%) moderately well, 1 (5%) moderately poorly, and 1 (5%) very poorly. After the 12th treatment, 13 (62%) were reported by the nurses to have tolerated cryotherapy very well, 3 (14%) moderately well, and 5 (24%) had no available data. There were no episodes of frostbite, but there was some discomfort related to numbness/tingling and redness/irritation of the skin.

Our group had conducted two previous trials, using a similar approach, to investigate minocycline and pregabalin as drugs that might be able to help prevent paclitaxel-induced CIPN. Understanding the risks of cross-study comparisons, the CIPN20 Sensory Score results from the three trials are illustrated in Fig. 5. These demonstrate that the control arm of the current trial experienced much less neuropathy than did the placebo arms of the other 2 trials. When the cryotherapy arm of the current trial was compared to the combined control arms from the three trials, during the 12 week treatment period and for 6 months following completion of treatment, a Wilcoxon Rank Sum p value is 0.01, supporting that there was less neuropathy seen in our cryotherapy arm than in the combined control arms (Fig. 5B). Cross-study findings regarding pain, numbness and tingling of upper and lower extremities show similar findings, supporting that patients on the cryotherapy arm of the current trial fared better.

4. Discussion

Reports available at the time this current trial was developed, as reviewed in the Introduction section, suggested that cryotherapy might protect hands and feet from taxane-induced neurotoxicity. Other recent reports also suggest that topical cryotherapy can decrease paclitaxel-associated neuropathy.[25, 26, 28] One of these included 40 patients with gynecologic cancer receiving paclitaxel 150–175 mg/m2; compared to 142 historical controls, cool mitts and slippers seemed to reduce the incidence of CTCAE grade 2 + CIPN in the fourth to sixth cycles, but there was no evidence of differences in rates of prescription of pain medication or reductions in chemotherapy dose between the cooled group and the controls [27]. The authors of this retrospective trial noted the pilot nature of their results.

More recently, Hanai et al. reported results of a trial involving 40 breast cancer patients treated with weekly paclitaxel, similar to the current study [26]. On the dominant hand side, frozen gloves and socks were used for a time period akin to what was used in the current report. Thirty-six patients who received the full cumulative dose of 960mg/m2 were analyzed, excluding four patients who did not get to this dose level. Objective and subjective neuropathy were clinically and statistically significantly less in the hand that received the cryotherapy than in the other hand. The authors concluded that cryotherapy was useful for preventing subjective symptoms of CIPN and objective neurologic dysfunction. However, that manuscript may be critiqued for its small number of patients and for using the dominant side for the treatment, as repetitive muscular use of one side may actually decrease neuropathy (supported by trials that suggest that exercise may decrease CIPN) [28]. Additionally, the fact that some patients dropped out and were not analyzed raises some concern.

In another study, a phase I proof-of-concept, randomized, internal-control trial involving patients with early stage breast cancers who received weekly paclitaxel, patients received hypothermia of one leg for up to 12 cycles. They were evaluated, at baseline, and at 1, 3 and 6 months from the start, with nerve conduction studies and the Total Neuropathy Score instrument. The authors concluded, in a meeting abstract, that cryotherapy decreased neuropathy [29].

Interestingly, a recent phase II (n = 42) Japanese study, currently published only as a meeting abstract, evaluated wearing two

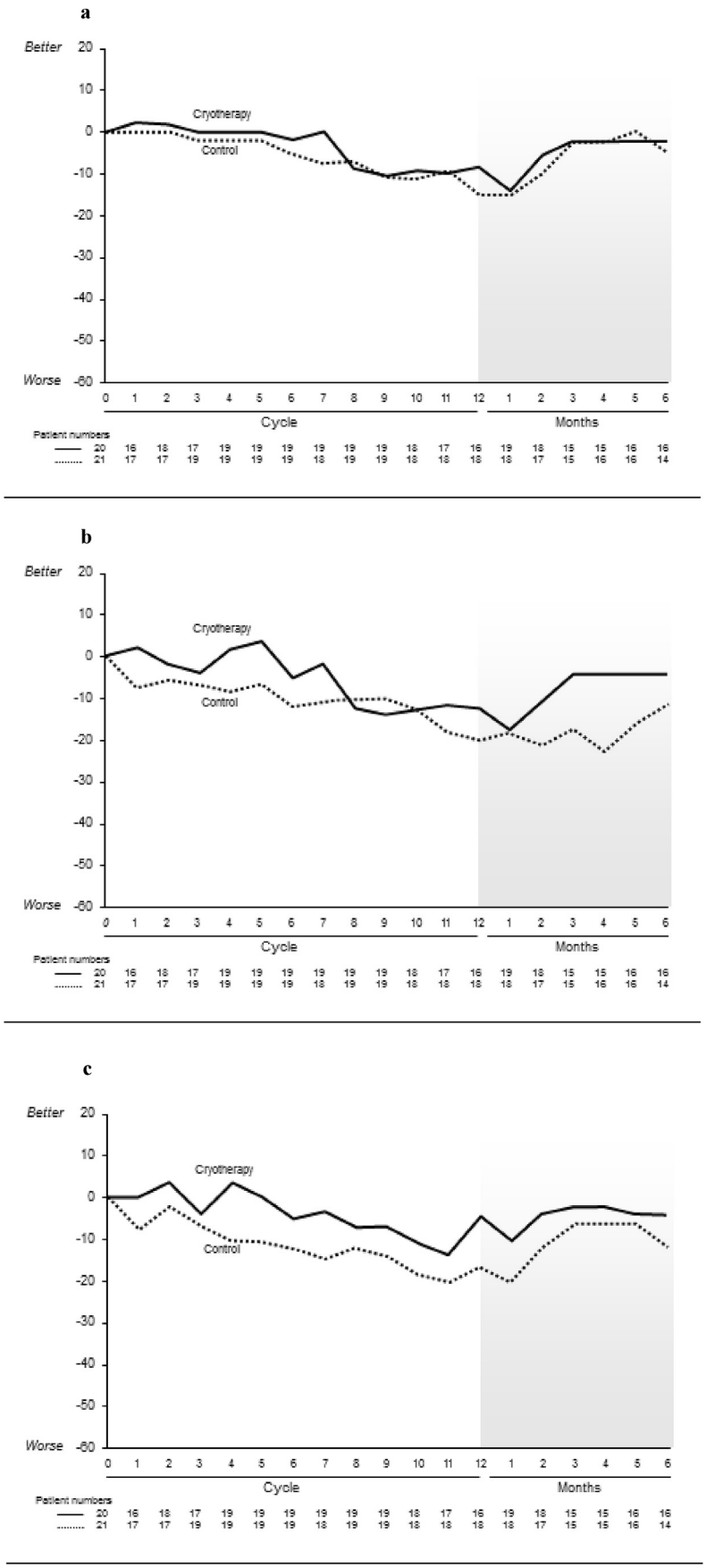
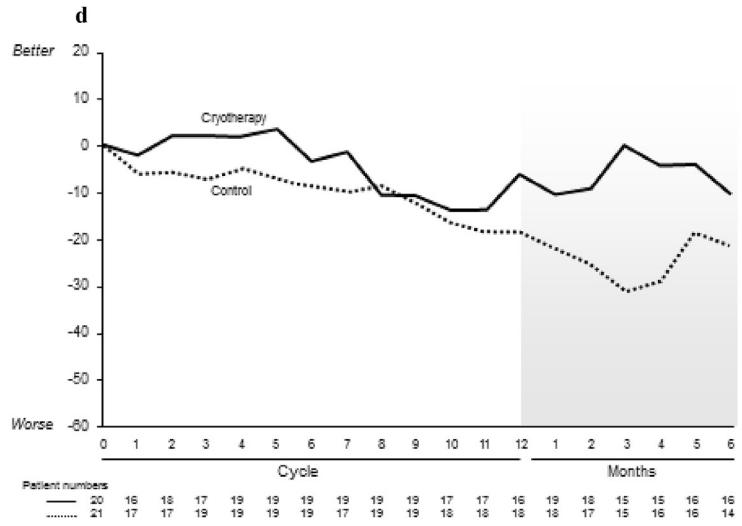
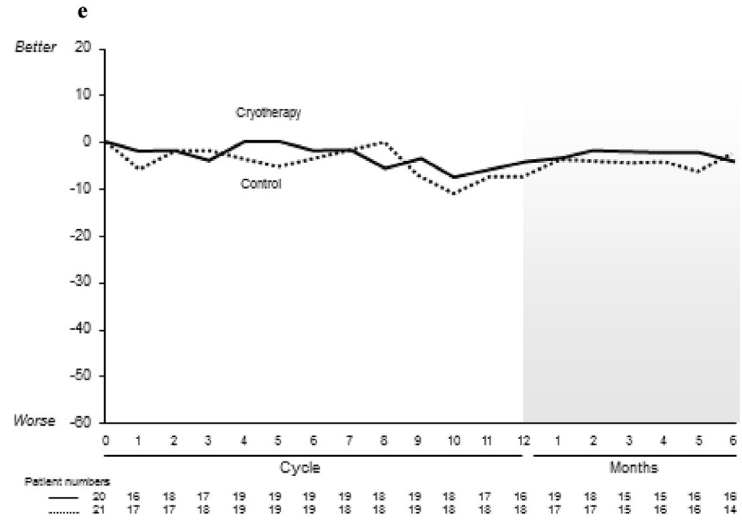


Fig. 3. Mean change from baseline in EORTC QLQ-CIPN20 selected individual item scores during treatment and over 6-month follow-up for tingling fingers/hands (a), tingling toes/feet (b), numbness fingers/hands (c), numbness of toes/feet (d), shooting burning pain of fingers/hands (e), and shooting burning pain of toes/feet (f). Higher scores represent fewer symptoms.





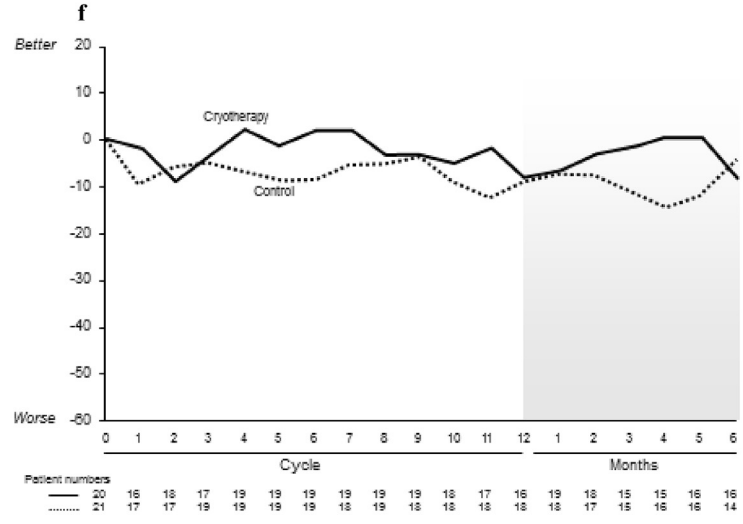


Fig. 3. (*continued*).

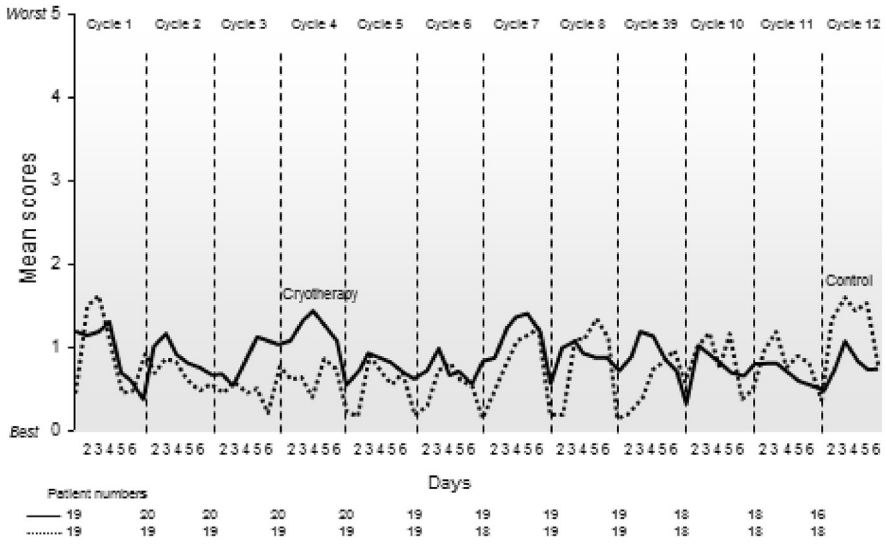


Fig. 4. Mean worst pain daily scores over 6 days following paclitaxel doses for each cycle. Higher scores represent more pain.

surgical gloves that were one size too small, on the dominant hand for 90 min (30 before, 30 during, 30 after) to reduce the blood flow to that hand during each of four nab-paclitaxel infusions (260 mg/m2); this led to less neuropathy (measured by CTCAE and by the Patient Neurotoxicity Questionnaire) in that hand, compared to the other (ungloved) hand [30]. The temperature of the fingertips on the hand wearing the two gloves was found to be decreased by 1.6–2.2 °C, compared to before chemotherapy; rates of CTCAE grade 2 or higher sensory neuropathy (21% vs. 76%) and motor neuropathy (26% vs. 57%) were both reported to be dramatically different between the gloved and ungloved hands, respectively. In addition, a recent report at the 2018 ASCO meeting identified that combining cryotherapy with compression allowed patients to tolerate lower temperatures and appeared promising, based on nerve conduction studies [31].

Given these other data supporting that decreasing blood flow by cryotherapy or glove restriction can decrease paclitaxel-induced neuropathy, it is somewhat surprising that the current trial did not demonstrate less neuropathy in the cryotherapy arm. Reasons for this may include the method that we used to provide cryotherapy (a practical, inexpensive technique). Of note, however, we used a similar practical approach to conduct the first published trials that demonstrated the ability of cryotherapy to decrease 5FU-associated oral mucositis [19,20]. These trials (and those that followed) eventually led to oral cryotherapy being recommended in international guidelines for the use of daily bolus dose 5-fluorouracil [18]. The similarity between the outcomes of our two study arms might be due entirely to chance, given the small number of patients evaluated in this pilot trial, and the fact that our control arm fared remarkably well. This contention is supported by the cross-study comparison illustrated in Fig. 5. Had the neuropathy in our control arm replicated that seen in the placebo arms of the minocycline and pregabalin studies, our results would have been encouraging enough, even without supporting data from other trials, to proceed forward with a larger phase III trial. Additionally, had we conducted the current trial without a control arm, arguing to compare it to previous phase II trial results, we would have considered our data to be encouraging, supporting the conduct of a subsequent phase III, more-definitive, trial.

Despite making the multiple comparisons between arms above, it is worth noting that the current trial was not designed as a phase III definitive trial. Rather, it was designed as a pilot trial to assess whether or not cryotherapy appears promising as a means of decreasing paclitaxel associated neuropathy, to facilitate the conduct of a subsequent, more definitive, randomized, controlled, phase III clinical trial. It was limited by its small sample size and ethnically homogeneous patient population. The fact that all of our participants were white may have contributed to the fact that both arms experienced little neuropathy (because African American patients have been previously shown to develop more CIPN).

Of note, there have been some previous reports of frostbite associated with cryotherapy given in an attempt to prevent paclitaxel-associated neuropathy. Thus, caution is advised. More sophisticated means of providing this treatment will hopefully demonstrate improved efficacy and not result in substantial toxicity. To conclude, the converging evidence from this and other studies supports ongoing work in this area.

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Conflicts of interest

CLL reports grant funding from Breast Cancer Research Foundation during the conduct of this study and a consultant/advisory role with PledPharma, Metys, Disarm Therapeutics, and Asahi – all regarding efforts to reduce chemotherapy-induced neuropathy. MEL reports personal fees and non-financial support, outside the submitted work and Consulting for MERCK SHARP & DOHME CORPORATION, GALDERMA, JANSSEN RESEARCH & DEVELOPMENT, LLC, ABBVIE, INC., HELSINN HEALTHCARE SA, NOVOCURE INC, BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG, F. HOFFMANN-LA ROCHE AG, ALLERGAN INC., AMGEN INC., E.R. SQUIBB & SONS, L.L.C., NOVARTIS PHARMACEUTICALS CORPORATION, EMD SERONO, INC., ASTRAZENECA PHARMACEUTICALS LP,

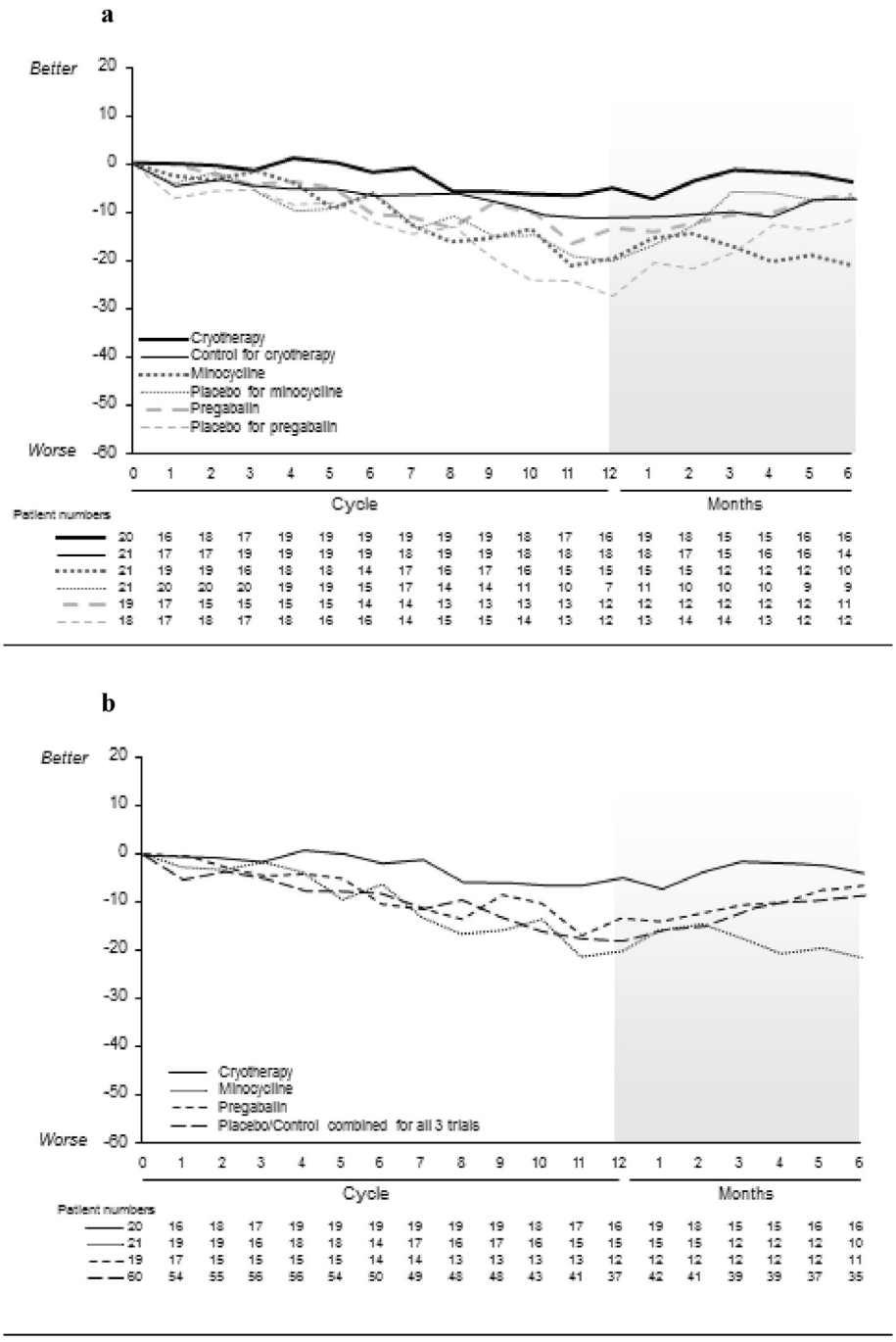

Fig. 5. CIPN during 12 weeks of treatment represented as the mean change in EORTC QLQ-CIPN20 sensory scores for patients participating in the current trial and in two prior trials that had evaluated minocycline and pregabalin, using virtually identical protocol methodologies. Higher scores represent fewer symptoms. Fig. 5A illustrates data with the individual control arms for the 3 trials shown separately, while 5B combines the control arms into one line.

GENENTECH, INC, LEO PHARMA INC, SEATTLE GENETICS, DEBIOPHARM, LINDI, BAYER, MANNER SAS, MENLO THER, CELLDEX, ABBVIE, LUTRIS, PIERRE FABRE, LEGACY HEALTHCARE, ROCHE, AMRYT PHARMA, JOHNSON & JOHNSON, PAXMAN COOLERS, ADJUCARE, DIGNITANA, BIOTECHSPERT, PAREXEL, and ADGERO. All other authors declare that they have no conflict of interest.

Ethical statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee ad with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

Informed Consent Statement: Informed consent was obtained from all individual participants included in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at

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