Breast Cancer Research and Treatment
https://doi.org/10.1007/s10549-021-06477-0

CLINICAL TRIAL

Preventing taxane-related peripheral neuropathy, pain and nail toxicity: a prospective self-controlled trial comparing hilotherapy with frozen gloves in early breast cancer

Annemarie Coolbrandt[1,2] · K. Vancoille[1] · E. Dejaeger[1] · H. Peeters[1] · A. Laenen[3] · P. Neven[4] · K. Punie[4] · H. Wildiers[4]

Received: 28 September 2021 / Accepted: 2 December 2021

Abstract

Purpose The prevention of taxane-related toxicities at the extremities is highly important for patients' treatment and quality-of-life. Several studies endorse hand/foot-cooling using frozen gloves as a prophylactic intervention. Unlike frozen gloves, hilotherapy produces cooling at a constant temperature. Comparative data with frozen gloves are unavailable.

Methods This prospective self-controlled study explores the efficacy of hilotherapy at the right hand and foot compared to frozen gloves at the left in patients with early breast cancer treated with weekly paclitaxel 80 mg/m^2 or three-weekly docetaxel 75 mg/m^2. Patient-reported outcomes were collected at baseline, 6, 12, 18 and 24 weeks after the start of treatment. Primary and secondary endpoints were the incidence of any-grade and ≥ grade 2 side-effects (peripheral neuropathy, pain and nail toxicities), and perceived comfort of both interventions.

Results Sixty-two patients participated. The incidence of any-grade side-effects was similar on both sides, 85.5% with hilotherapy and 90.3% with frozen gloves ($p = 1.000$). The incidence of ≥ grade 2 side-effects at the extremities was significantly lower with hilotherapy: 43.6% compared to 61.3% with frozen gloves ($p = 0.013$). Perceived comfort was significantly better for hilotherapy than for frozen gloves ($p < 0.0001$).

Conclusions Compared to frozen gloves, continuous cooling of hands and feet using hilotherapy produces better prevention of ≥ grade 2 patient-reported side-effects at the extremities (peripheral neuropathy, pain and nail toxicities). Perceived comfort was significantly better for hilotherapy. From a clinical and patient perspective, hilotherapy is a better alternative for preventing clinically significant taxane-related side-effects.

Keywords Taxane · Cryotherapy · Frozen gloves · Hilotherapy · Peripheral neuropathy · Nail toxicity · Prevention · Supportive care

Background

The taxane compounds paclitaxel and docetaxel play an important role in the treatment of breast cancer [1]. However, their use is associated with side-effects threatening quality-of-life of patients during and long after treatment. One of the typical taxane-related side-effects is nail toxicity, occurring in up to 40% of patients treated with taxanes [2–5]. Some of these nail toxicities, such as paronychia and onycholysis, can drastically affect daily functioning and quality-of-life [2, 4, 6, 7]. More than one decade ago, a self-controlled study showed that cryotherapy positively influenced the prevalence of nail toxicities, with a substantial statistically significant reduction in the overall incidence of fingernail toxicities as well as onycholysis [8, 9]. This study

✉ Annemarie Coolbrandt
annemarie.coolbrandt@uzleuven.be

1 Department of Oncology Nursing, University Hospitals Leuven, Herestraat 49, Leuven, Belgium

2 Department of Public Health and Primary Care, Academic Centre for Nursing and Midwifery, KU Leuven, Leuven, Belgium

3 Interuniversity Centre for Biostatistics and Statistical Bioinformatics, KU Leuven, Leuven, Belgium

4 Multidisciplinary Breast Centre, University Hospitals Leuven, Leuven, Belgium

leveraged the introduction of frozen gloves as a standard-of-care supportive treatment in patients receiving docetaxel in our hospital and many others. A systematic review concluded that the use of frozen gloves was endorsed by 4 (67%) of 6 studies to prevent nail toxicity and by 3 (60%) of 5 studies to prevent cutaneous hand changes [10]. Another systematic review confirmed that the intervention provides effective prophylactic management for taxane-induced nail toxicity [11]. Finally, the ESMO Clinical Practice Guidelines on the prevention and management of dermatological toxicities stated that frozen gloves (− 10 to − 30 °C for a total duration of 90 min) and to a lesser extent frozen socks should be systematically advised in patients treated with taxanes [II, A] [12].

Another taxane-related and dose-limiting side-effect affecting the extremities is chemotherapy-induced peripheral neuropathy (CIPN). CIPN occurs in up to 42% patients treated with paclitaxel [13] and the incidence of severe (≥ grade 2) neuropathy is 27% in patients receiving weekly paclitaxel [14]. Treatments with docetaxel are associated with severe neuropathy (≥ grade 2) in 16 to 23% of the patients [14, 15]. CIPN affects not only physical well-being and functioning but also social and emotional well-being and quality-of-life in general [16]. Moreover, CIPN usually has a prolonged course and frequently persists for many years [15]. The ASCO Guideline update on CIPN reviewed and described 5 trials studying the role of cryotherapy in decreasing taxane-induced neuropathy [17]. The authors argued that, although proof of benefit has not yet been established, available data support that cryotherapy may, in part, prevent CIPN symptoms and appears to be reasonably safe. The ASCO Guideline concluded that no recommendations can be made on the use cryotherapy for the prevention of CIPN outside the context of a clinical trial [17]. The ESMO-EONS-EANO Clinical Practice Guideline noted the heterogeneity of available study results, but concluded that the prevention of CIPN with cryotherapy can be considered [II, C] [18]. Encouraged by the risk of developing long-term, irreversible taxane-induced CIPN and by those studies confirming the effective prophylactic management of cryotherapy such as the one of Hanai and colleagues [19], hand/foot-cooling with frozen gloves and socks became standard-of-care for preventing paclitaxel-induced neuropathy in several institutions including our hospital.

The application of frozen gloves isn't without challenges. First, cryotherapy has been demonstrated to be uncomfortable for patients. Several comparative studies faced substantial drop-out rates, sometimes higher than 50%, as a result of patient discomfort and intolerance of the frozen gloves [20–22]. Secondly, the temperature of frozen gloves can rapidly increase. This requires personnel attention to change frozen gloves during chemotherapy administration. Finally, frozen gloves have become unavailable on the Belgian market, urging for alternative ways to apply cryotherapy. A new way of cooling, i.e., hilotherapy, was presented by Hilotherm GmbH. Hilotherapy devices provide continuous flow therapy to achieve constant cooling of hands and feet. Hilotherapy is expected to perform better than frozen gloves based on the assumption that vasoconstriction is better maintained under constant cooling. A retrospective single-arm study of hilotherapy in patients with breast, gynecological, and pancreatic cancer showed that none of the included patients developed NCI CTCAE grade > 2 peripheral neuropathy [23]. Yet, comparative data with frozen gloves are not available.

This study addresses the question whether hilotherapy performs better in preventing taxane-related side-effects at the extremities (i.e., peripheral neuropathy, pain and nail toxicities) compared to frozen gloves in patients with early breast cancer.

Methods

Design

A prospective self-controlled trial (ClinicalTrials.gov Identifier: NCT04659980) was designed to compare the incidence of taxane-related side-effects in any-grade between frozen gloves and hilotherapy. The full methodology is described in the eMethods of the Supplement.

Setting

The study took place between June 2019 and November 2020 at the oncology daycare center of the University Hospitals Leuven, Belgium.

Selection of patients

The study included adult (≥ 18 years) patients with breast cancer treated with weekly paclitaxel 80 mg/m^2 (12 cycles) or three-weekly docetaxel 75 mg/m^2 (4 or 6 cycles) in an adjuvant or neo-adjuvant setting. Patients were excluded from this study: 1\ if they presented with peripheral neuropathy or pain in the extremities at baseline, regardless of whether this was related to a prior chemotherapy treatment or another condition, 2\ if they had Raynaud's phenomenon, cold intolerance or any condition to the nails or peripheral blood vessels that could pose a risk to the compliance with the study interventions, 3\ if their understanding of the Dutch language was insufficient for self-reporting the side-effects under investigation. Patients were excluded from the analysis if they received less than two thirds of planned treatment cycles, for other reasons than the side-effects investigated in this study.

A sample size of 61 patients was determined on the basis of a McNemar test with 80% power and a level of statistical significance of 5%. The estimation was performed to detect a difference of 25% in the incidence of the primary outcome (i.e., any-grade) between both groups (50% in the control group and 25% in the intervention group), based on available data [3, 19]. Given the lack of information, it was based on the conservative assumption of a low correlation ($r = 0.1$) between paired (left–right) measurements.

Interventions

We compared two devices for cooling of hands and feet. The intervention set-up is illustrated in eFigure 1 of the Supplement. We used Peters Surgical frozen gloves at the left hand and foot. They were refrigerated for at least 3 h at − 18 to − 20 °C. Based on previous studies, each patient wore the frozen gloves for 90 min: 15 min before the infusion, during the 1-h docetaxel or paclitaxel infusion, and until 15 min post-infusion. Pre- and post-cooling times of 15' in the cryotherapy-protocol of this study was based on previous studies [8, 9, 19], although little evidence is available to support this protocol. Frozen gloves were changed after 45 min. Thin inner gloves were worn to prevent frostbite.

We used Hilotherm ChemoCare at the right hand and foot, offering continuous cooling at a constant temperature of 10–12° [23, 24]. Based on the manufacturer's instructions, hilotherapy cuffs were applied as from 30 min prior to the administration of the taxane and until 30 min post-infusion, thus for a total duration of 120 min. As for the frozen gloves, patients wore inner gloves on their right side as well.

Both intervention fidelity and patients' use of (firming) nail polish, gel nails, manicure and pedicure were reported as part of the study.

Study procedure

We recruited a consecutive sample of patients starting weekly paclitaxel 80 mg/m^2 or three-weekly docetaxel 75 mg/m^2 on Monday, Tuesday or Friday (based on the availability of the study nurses). The study nurses informed eligible patients orally. Additionally, patients were offered written study information to consider study participation. All patients agreeing to participate in the study, signed informed consent.

Data collection

Data were collected before the start of treatment (T0/baseline), after 6 weeks (T1), 12 weeks (T2), 18 weeks (T3) and 24 weeks or 6 months (T4). The last two time points (T3 and T4) were set to account for side-effects developing or deteriorating after the end of treatment. We primarily used patient-reported data to evaluate incidence and severity of side-effects under study: peripheral neuropathy, pain at fingers/hands or toes/feet, and nail toxicities. We used the Patient-Reported Outcomes version of the Common Toxicity Criteria for Adverse Events (NCI—PRO-CTCAE™ v1.0) [25]. Additionally, patients indicated if these side-effects were more severe at the left side, the right side or if they were equally severe or absent.

The primary outcome in this study was a binary composite endpoint, namely patient-reported incidence of (at least) one of (any-grade) side-effects at the level of the extremities (peripheral neuropathy, pain at fingers/hands and toes/feet and/or nail toxicities). The outcome took value 1 if at least one of these side-effects was observed at (at least) one time point, and 0 otherwise. Likewise, we studied the patient-reported incidence of ≥ grade 2 (≥ G2) side-effects (i.e., G2/moderate, G3/severe or G3/very severe) with the outcome taking value 1 if at least one side effect was graded G2 or higher at (at least) one time point. We used composite outcome measures (i.e., an endpoint that consists of 2 or more distinct endpoints) to equally account for all side-effects targeted by hand/foot-cooling and to avoid competing side-effects in outcome measurement. In order to understand which components or side-effects were most responsible for any effect of the intervention, we also studied patient-reported incidence and severity of the individual side-effects and present data of all composite components alone. We focused at ≥ G2 toxicities as these can be considered as clinically significant side-effects [26]. While in clinical trials severe toxicity is traditionally defined as grade 3–4, lower-grade toxicity has shown relevance in clinical decision-making [27]. Incidence of grade 3 and 4 toxicities (G3/4) wasn't considered as a formal endpoint in this study and is therefore presented numerically only.

At time points associated with chemotherapy administration, patients were asked to self-report the comfort of both interventions using a 5-point Likert scale (0 = very uncomfortable, 4 = very comfortable). Patients were asked to rate three items: contact with the glove, tolerance of the cold temperature and impact on mobility. Also, at these time points nail toxicities (paronychia, nail discoloration, nail ridging and nail loss) were observed by the study nurse using the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE v4.0).

Statistical analysis

The difference between cross-sectional paired binary observations (e.g., the primary study endpoint: patient-reported incidence of (at least) one of the side-effects at the level of the extremities) was analyzed using the McNemar test.

The difference between cross-sectional paired continuous or ordinal observations (e.g., worst grade of patient-reported

neuropathy or pain) was analyzed using the Wilcoxon signed rank test.

One-sample test for location was performed on patients' judgement regarding which side was better. The Signed rank test was used for aggregated continuous outcomes, or the Sign test for a three-levelordinal outcome.

Linear mixed models were used to analyze longitudinal data on comfort. Random intercepts for patient and side were modelled to account for clustering at patient level and side level. The main effect of side is estimated averaged over time points; and presented as the mean difference with 95% confidence interval.

A Cox proportional hazards model was used to analyze time-to-event outcomes. The robust sandwich estimate of Lin and Wei (1989) was used to account for clustering. Results are presented as hazard ratios with 95% confidence intervals. Results are illustrated by Kaplan–Meier curves.

Regarding perceived comfort of both interventions, all three items (contact, cold, mobility) were compared separately and using a sum score.

All tests were performed at a 2-sided 5% significance level. Analyses have been performed using SAS software (version 9.4 of the SAS System for Windows).

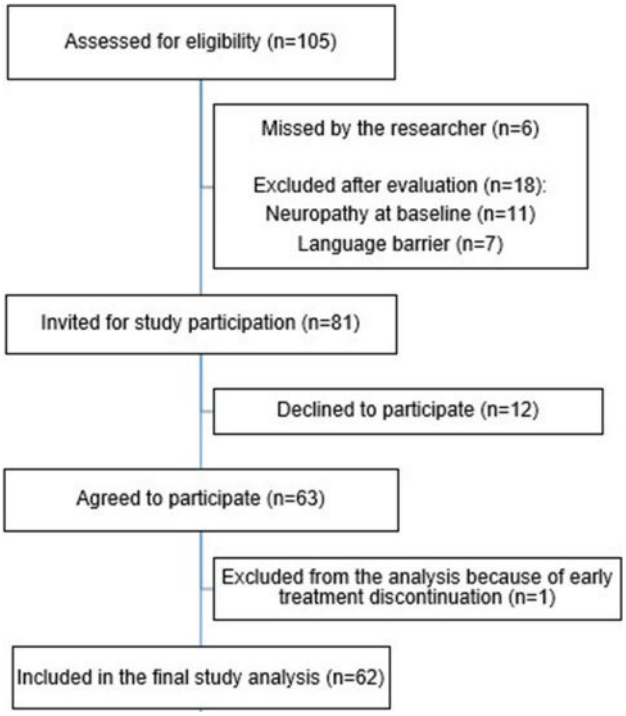

Fig. 1 Consort diagram

Results

Patient flow is illustrated in Fig. 1. A total of 105 patients were found potentially eligible for this study. Six patients couldn't be informed by the investigators. Eighteen patients turned out to be ineligible after evaluation, because they presented with neuropathy at baseline ($n=11$) or because they weren't able to understand the patient-reported questionnaires ($n=7$). Of the remaining 81 patients, 63 chose to participate (response rate of 77.7%). Finally, one patient was excluded from the study during treatment, as she stopped chemotherapy treatment early due to poor general tolerance of chemotherapy ($n=1$).

Patient characteristics are described in Table 1. All 62 participants were women with a mean age of 53.1 years. The large majority of participants was right-handed. Two thirds (67.7%) received paclitaxel-based treatment and one third (32.3%) treatment with docetaxel. Twelve participants (19.4%) stopped treatment early because of peripheral neuropathy ($n=4$), hematological toxicity ($n=3$), infection risk during COVID19-pandemic ($n=2$), poor general tolerance of chemotherapy ($n=3$). Eight patients (12.9%) had dose reductions for reasons of peripheral neuropathy ($n=5$), hematological toxicity ($n=2$) and persistent sinusitis with fever ($n=1$). Almost two thirds (64.5%) used firming nail polish to prevent nail toxicities.

Figure 2 illustrates the results on patient-reported incidence of any-grade and ≥ G2 side-effects at the extremities with hilotherapy versus frozen gloves. Numerical results are shown in Table 2. Patient-reported incidence of side-effects was similar with hilotherapy as with frozen gloves (85.5% versus 90.3%, $p=1.00$) (see Fig. 2 and Table 2). However, the incidence of ≥ G2 side-effects was significantly lower with hilotherapy compared to frozen gloves, with 43.6% of patients presenting with ≥ G2 side-effects at the hilotherapy side, compared to 61.3% on the side with frozen gloves ($p=0.013$). G3/4 side-effects occurred in 22.6% with hilotherapy compared to 27.4% with frozen gloves.

Looking at the individual patient-reported side-effects (see Fig. 2, Table 2, eFigure 2 and 3), the incidence of neuropathy was comparable on both sides. There was numerically less ≥ G2 neuropathy with hilotherapy compared to frozen gloves (40.3% compared to 50.0%), but this didn't reach the predetermined level of statistical significance ($p=0.109$). Worst grade of patient-reported neuropathy was significantly lower with hilotherapy ($p=0.048$). G3/4 neuropathy occurred in 11.3% with hilotherapy compared to 17.7% with frozen gloves. A trend to significance was noted for the incidence of patient-reported pain at hands/fingers and feet/toes ($p=0.070$). Both the incidence of ≥ G2 pain and the worst grade of patient-reported pain were significantly lower with hilotherapy ($p=0.039$ and $p=0.0009$). The incidence of G3/4 pain was 11.3% with hilotherapy compared to 14.5% with frozen gloves. Regarding patient-reported nail toxicities, their incidence was significantly lower with hilotherapy ($p=0.039$) but the incidence of severe nail toxicities was

Table 1 Patient characteristics

	Total sample ($n=62$)
Age, mean (SD)	53.1 (11.3)
Gender, *n*(%)	
Male	0 (0%)
Female	62 (100%)
Dominant hand, *n*(%)	
Left	8 (12.9)
Right	54 (87.1)
Previous chemotherapy use[a], *n*(%)	
Yes	3 (4.8%)
No	59 (95.2%)
Taxane, *n*(%)	
Paclitaxel	42 (67.7%)
Docetaxel	20 (32.3%)
Chemotherapy regimen, *n*(%)	
EC—Paclitaxel	22 (35.5%)
EC—Paclitaxel-Carboplatin	6 (9.7%)
Paclitaxel	14 (22.6%)
Docetaxel-Cyclophosphamide	18 (29.0%)
Docetaxel-Carboplatin	2 (3.2%)
Cumulative dose, mean(SD)	
Paclitaxel	1590,6 (246.1)
Docetaxel	760.4 (137.3)
Discontinuation of taxane treatment, *n*(%)	
Yes	12 (19.4%)
No	50 (80.6%)
Taxane dose reduction, *n*(%)	
Yes	8 (12.9%)
No	54 (87.1%)
Use of other nail-protective strategies, *n*(%)	
Plain nail polish	12 (19.4%)
Firming nail polish	40 (64.5%)
Gel nails	3 (4.8%)
Manicure	6 (9.7%)
Pedicure	10 (16.1%)

[a]Not including anthracyclines used in the current (neo-)adjuvant regimen

similar ($p=1.000$). Nurse-reported nail toxicities were not significantly different. Patient-reported outcomes for docetaxel and paclitaxel separately are reported in eTable 1 of the Supplement.

In the time-to-event analyses, all hazard ratios (Table 3) were in favor of hilotherapy, with clinically relevant and statistically significant hazard ratios of 0.750 ($p=0.014$) for ≥ G2 neuropathy, 0.785 ($p=0.018$) for any-grade pain at the extremities, 0.609 ($p=0.019$) for ≥ G2 pain, and 0.766 ($p=0.015$) for nail toxicities. These hazard ratios imply risk reductions of 21 to 39%, in favor of hilotherapy. Percentages of symptom-free patients per time point (eTable 2 in the Supplement) and Kaplan–Meier curves (eFigure 4 in the Supplement) show that with hilotherapy, hands and feet longer remained symptom-free.

Patients' left–right comparisons per side-effect (eTable 3 in the Supplement) confirmed earlier results with significantly more patients reporting worse symptoms at the left (frozen gloves) than at the right (hilotherapy).

Finally, perceived comfort (Table 4) was consistently and significantly better for hilotherapy than for frozen gloves, globally as well as on all three aspects we explored: contact with the cuff/glove, cold and patient mobility.

Regarding the fidelity to the intervention, we noted fidelity issues on the left side (frozen gloves) in 15 of the patients (24.2%). It concerned patients intentionally pulling out the glove for a little while, in all cases because of difficulty bearing the cold or having cold-related pain in the extremities. There were no intentional fidelity issues on the right side (hilotherapy).

Discussion

Given the impact of CIPN and nail toxicities as well as the chronical course and lack of pharmacological interventions to reverse CIPN, prophylaxis of these side-effects is essential for treatment completion and quality-of-life of patients with early breast cancer. So far, the majority of available studies exploring cooling of hands and feet have applied cryotherapy using frozen gloves and socks. Our study is, to the best of our knowledge, the first to investigate the efficacy of hilotherapy in preventing neuropathy, pain and nail toxicity at the extremities using a prospective and comparative design. Our results show that patient-reported all-grade side-effects at the extremities where high and not significantly different between both sides. Nevertheless, the application of hilotherapy resulted in a statistically significant and clinically relevant reduction in ≥ G2 side-effects at the extremities as a composite endpoint (43,6% at the hilotherapy side versus 61,3% at the side of the frozen gloves). Additionally, for the individual toxicities, several significant improvements and trends for hilotherapy compared to frozen gloves were observed with regard to incidence, severity and time-of-onset of patient-reported side-effects. Based on this comparative analysis, hilotherapy seems to be superior to frozen gloves in the prevention of clinically significant taxane-related side-effects at the extremities. On top of its efficacy, our study showed that perceived comfort was significantly better for hilotherapy than for frozen gloves.

Pre- and post-cooling times of 15 min in the cryotherapy-protocol of this study was based on previous studies[8, 9, 19], although little evidence is available to support this protocol. Likewise, and with lack of evidence, 30 min pre- and post-infusion cooling times were applied

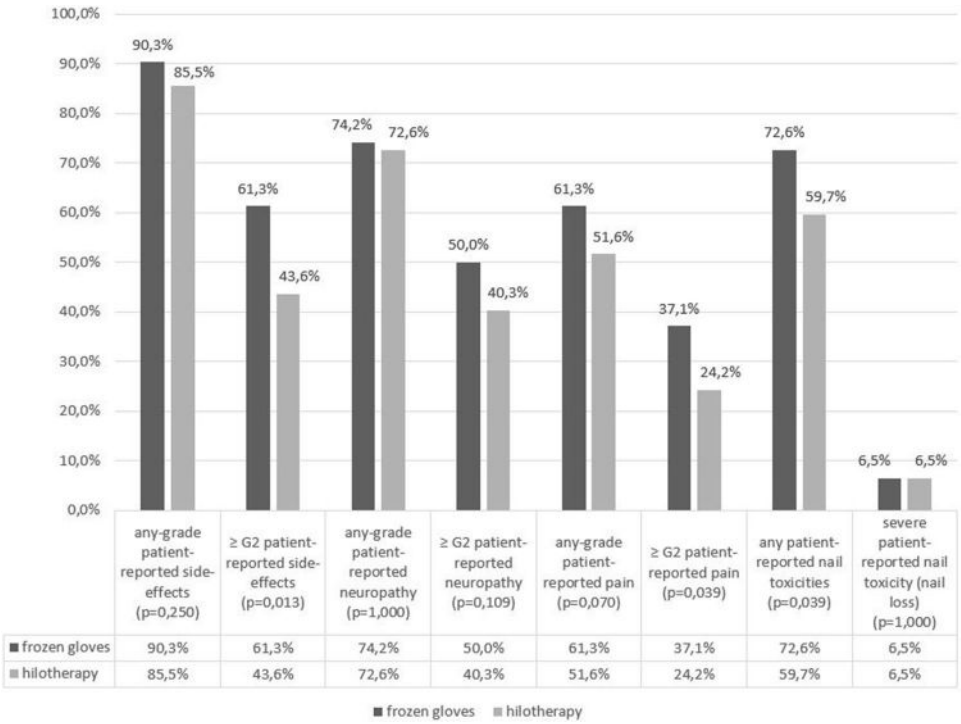

Fig. 2 Incidence of any-grade and ≥ G2 side-effects at the extremities

Table 2 Patient-reported and nurse-reported outcomes with frozen gloves versus hilotherapy: numerical results

	Left (frozen gloves)	Right (hilotherapy)	*p*-value
Incidence of (any-grade) patient-reported side-effects at the extremities, *n*(%)	56 (90.3%)	53 (85.5%)	0.250
Incidence of ≥ G2* patient-reported side-effects at the extremities, *n*(%)	38 (61.3%)	27 (43.6%)	**0.013**
Incidence of (any-grade) patient-reported neuropathy, *n*(%)	46 (74.2%)	45 (72.6%)	1.000
Incidence of ≥ G2 patient-reported neuropathy, *n*(%)	31 (50.0%)	25 (40.3%)	0.109
Worst grade of patient-reported neuropathy, mean(SD)	1.45 (1.12)	1.26 (1.02)	**0.048**
Incidence of (any-grade) patient-reported pain at hands/fingers and feet/toes, *n*(%)	38 (61.3%)	32 (51.6%)	0.070
Incidence of ≥ G2 patient-reported pain at hands/fingers and feet/toes, *n*(%)	23 (37.1%)	15 (24.2%)	**0.039**
Worst grade of patient-reported pain, mean (SD)	1.15 (1.13)	0.87 (1.03)	**0.009**
Incidence of patient-reported nail toxicities, *n*(%)	45 (72.6%)	37 (59.7%)	**0.039**
Incidence of severe patient-reported nail toxicities (i.e., nail loss), *n*(%)	4 (6.5%)	4 (6.5%)	1.000
Incidence of nurse-reported paronychia, mean (SD)	5 (8.1%)	1 (1.6%)	0.125
Incidence of nurse-reported discoloration, mean (SD)	26 (41.9%)	23 (37.1)	0.615
Incidence of nurse-reported nail ridging, mean (SD)	8 (12.9%)	6 (9.7%)	0.438
Incidence of nurse-reported nail loss, *n*(%)	3 (4.8%)	1 (1.6%)	0.500

All bold values represent statistically significant results ($p < 0..05$)

* ≥ G2 neuropathy, ≥ G2 pain and/or the presence of nail loss

Table 3 Results of the time-to-event analyses

	Hazard ratio (95% CI)	*p*-value
Any-grade patient-reported neuropathy	0.891 (0.748;1.062)	0.198
≥ G2 patient-reported neuropathy	0.750 (0.569;0.988)	**0.041**
Any-grade patient-reported pain at hands/fingers and feet/toes	0.785 (0.643;0.960)	**0.018**
≥ G2 patient-reported pain at hands/fingers and feet/toes	0.609 (0.403;0.921)	**0.019**
Patient-reported nail toxicities	0.766 (0.618;0.950)	**0.015**
Severe patient-reported nail toxicities (i.e., nail loss)	0.965 (0.286;3.262)	0.954

All bold values represent statistically significant results ($p < 0..05$)

Table 4 Patient-reported comfort of frozen gloves versus hilotherapy

	Left (frozen gloves)	Right (hilotherapy)	*p*-value
Contact with the glove/cuff[a], mean (95%CI)	1.492 (1.217;1.768)	2.693 (2.418;2.969)	**< 0.0001**
Tolerance of the cold temperature[a], mean(SD)	1.206 (0.949;1.463)	2.868 (2.610;3.125)	**< 0.0001**
Impact on mobility[a], mean(SD)	1.544 (1.283;1.806)	1.862 (1.601;2.124)	**< 0.0001**
Total comfort score[b], mean(SD)	4.207 (3.524;4.891)	7.380 (6.696;8.063)	**< 0.0001**

All bold values represent statistically significant results ($p < 0..05$)

[a]Assessed on a 5-point Likert scale, with maximum score of 4 (0 = very uncomfortable, 4 = very comfortable)

[b]Sum score of all comfort items, with maximum score of 12

with hilotherapy based on the manufacturer's instructions. Given the higher temperature of hilotherapy cuffs compared to frozen gloves, it is likely that longer pre-cooling is necessary to establish vasoconstriction at the start of taxane administration. However, it cannot be ruled out that the better results for hilotherapy in our study are partially explained by the extra 15 min of pre- and post-cooling. As in the studies of both Beijers and Can [20, 28], freezer temperature was − 18 °C to − 20 °C in our study, while other studies stored frozen gloves at − 25 °C to − 30 °C [8, 9, 22]. Degree of cooling might impact the degree of skin temperature reduction and consequently vasoconstriction-induced toxicity prevention. However, a small self-controlled study comparing degree of freezing concluded that frozen gloves stored at − 10 to − 20 °C and worn for 1 h without replacement are almost as effective in preventing nail toxicity as gloves frozen at -25 to − 30 °C and worn for 90 min, with replacement halfway [29]. Moreover, degree of cooling might impact tolerability as well.

While it is known that scalp cooling achieves the best results when the scalp temperature decreases below 18 °C [30], little is known about the temperature needed to maintain sufficient vasoconstriction for preventing side-effects at the extremities. Constant cooling is supposed to better maintain vasoconstriction than frozen gloves and it might also avoid cold-induced vasodilatation as a counter reaction to temporarily cooling and decreased blood flow in fingers and toes, as described by Youssef et al.[31] In this study, we did not assess skin temperature on hands and feet and/or vasoconstriction. Future research is needed to gain more insight in the finger/ toe response during cooling with hilotherapy and with frozen gloves. Such research would also help to inform cooling protocols, including pre- and post-cooling time and cooling temperature. Notably, recent studies have examined cryocompression combining continuous flow limb cooling with pressure to achieve better cooling. Cryocompression demonstrated significantly greater skin temperature reductions compared to continuous flow cooling, with similar tolerability [32, 33]. Further study is needed to understand if lower skin temperature improves efficacy in the prevention of neurotoxicity.

While most studies on prevention of peripheral neuropathy and/or nail toxicities are self-controlled [8, 9, 19, 22, 34], self-controlled studies, as the one reported here, are prone to detection bias, especially when blinding is impossible. Unblinded patients in our study might have had higher expectations of hilotherapy as the novel intervention compared to frozen gloves. In this study, nurses observed nail toxicities in addition to patient-reported nail toxicities but no objective assessment or clinician-reported grading was used to evaluate neuropathy and pain. However, patient-reported outcomes have been pushed forward for symptom-monitoring, especially for more subjective symptoms [35–37]. Finally, we used a single-item patient-reported screening tool only to assess severity of peripheral neuropathy and pain and we didn't make use of any more comprehensive measure. Since short-form PRO screening may still lead to underestimation of CIPN, association of more extensive CIPN evaluations is recommended in future studies [26].

We applied hilotherapy at the right (mostly the dominant side) and frozen gloves at the left. Other studies have used the non-dominant hand and foot acted as the control [8, 9, 19]. Ruddy and colleagues recommended against using the dominant side for the treatment, as exercise and muscular use of the dominant side may decrease neuropathy [38]. Others have argued that right hand dominance could be a confounding variable when consistently using the left hand as the intervention side and the right side as case–control [22]. However, this argument is less relevant for the feet, and we did not observe relevant differences between hands and feet.

Finally, the self-reported incidence of any of these side-effects, i.e., the primary endpoint, was much higher (85.5 and 90.3% at the hilotherapy and the frozen gloves sides, respectively) than estimated in the sample size calculation, which impacted the power to observe a significant difference in the primary endpoint, but also once more stresses the importance of these side-effects and preventive strategies. Given the consistent benefit across secondary endpoints and in particular the relevant reduction in incidence

of ≥ G2 toxicity, the overall preventive effect of hilotherapy for taxane-induced side-effects at the extremities was found to be superior to frozen gloves in this study. As our self-controlled design didn't allow comparing the incidence of dose reduction and treatment discontinuation, future research is recommended to understand whether hilotherapy can reduce neuropathy-related dose-limiting events and increase the proportion of patients completing the planned dose of treatment.

Conclusion

This study shows that continuous cooling of hands and feet at a constant temperature using hilotherapy devices produces superior efficacy in the prevention of ≥ G2 taxane-induced toxicities at the extremities when compared to frozen gloves. The perceived comfort also was significantly better for hilotherapy than for frozen gloves. From a clinical and patient perspective, hilotherapy seems a better alternative for preventing clinically significant side-effects.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-021-06477-0.

Funding This work was supported by the Estée Lauder University Fund. We thank Hilotherm and High Tech Laser for providing hilotherapy devices for the duration of the study.

Data availability Data are available upon request to the authors (https://doi.org/10.5281/zenodo.4478972).

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of UZ/KULeuven.

Consent to participate Informed consent was obtained from all individual participants included in this study.

Consent for publication Informed consent was obtained from all individual participants included in this study.

References

1. Swain SM, Tang G, Geyer CE Jr, Rastogi P, Atkins JN, Donnellan PP, Fehrenbacher L, Azar CA, Robidoux A, Polikoff JA et al (2013) Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. J Clin Oncol 31(26):3197–3204
2. Gilbar P, Hain A, Peereboom VM (2009) Nail toxicity induced by cancer chemotherapy. J Oncol Pharm Pract 15(3):143–155
3. Marrs J, Newton S (2004) Chemotherapy-induced nail changes: an unsightly nuisance. Clin J Oncol Nurs 8(5):527–528
4. Minisini AM, Tosti A, Sobrero AF, Mansutti M, Piraccini BM, Sacco C, Puglisi F (2003) Taxane-induced nail changes: incidence, clinical presentation and outcome. Ann Oncol 14(2):333–337
5. Piraccini BM, Iorizzo M, Antonucci A, Tosti A (2004) Drug-induced nail abnormalities. Expert Opin Drug Saf 3(1):57–65
6. Baker J, Ajani J, Scotte F, Winther D, Martin M, Aapro MS, von Minckwitz G (2009) Docetaxel-related side effects and their management. Eur J Oncol Nurs 13(1):49–59
7. Belyayeva E, Gregoriou S, Chalikias J, Kontochristopoulos G, Koumantaki E, Makris M, Koti I, Katoulis A, Katsambas A, Rigopoulos D (2013) The impact of nail disorders on quality of life. Eur J Dermatol 23(3):366–371
8. Scotte F, Banu E, Medioni J, Levy E, Ebenezer C, Marsan S, Banu A, Tourani JM, Andrieu JM, Oudard S (2008) Matched case-control phase 2 study to evaluate the use of a frozen sock to prevent docetaxel-induced onycholysis and cutaneous toxicity of the foot. Cancer 112(7):1625–1631
9. Scotte F, Tourani JM, Banu E, Peyromaure M, Levy E, Marsan S, Magherini E, Fabre-Guillevin E, Andrieu JM, Oudard S (2005) Multicenter study of a frozen glove to prevent docetaxel-induced onycholysis and cutaneous toxicity of the hand. J Clin Oncol 23(19):4424–4429
10. Marks DH, Qureshi A, Friedman A (2018) Evaluation of prevention interventions for taxane-induced dermatologic adverse events: a systematic review. JAMA Dermatol 154(12):1465–1472
11. Huang KL, Lin KY, Huang TW, Loh EW, Hua YM, Su HC, Tam KW (2019) Prophylactic management for taxane-induced nail toxicity: A systematic review and meta-analysis. Eur J Cancer Care (Engl) 28(5):e13118
12. Lacouture ME, Sibaud V, Gerber PA, van den Hurk C, Fernandez-Penas P, Santini D, Jahn F, Jordan K, clinicalguidelines@esmo.org EGCEa: Prevention and management of dermatological toxicities related to anticancer agents: ESMO Clinical Practice Guidelines(). *Ann Oncol* 2021, **32**(2):157–170.
13. Ghoreishi Z, Keshavarz S, Asghari Jafarabadi M, Fathifar Z, Goodman KA, Esfahani A (2018) Risk factors for paclitaxel-induced peripheral neuropathy in patients with breast cancer. BMC Cancer 18(1):958
14. Sparano JA, Wang M, Martino S, Jones V, Perez EA, Saphner T, Wolff AC, Sledge GW Jr, Wood WC, Davidson NE (2008) Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 358(16):1663–1671
15. Eckhoff L, Knoop AS, Jensen MB, Ejlertsen B, Ewertz M (2013) Risk of docetaxel-induced peripheral neuropathy among 1,725 Danish patients with early stage breast cancer. Breast Cancer Res Treat 142(1):109–118
16. Matsuoka H, Nakamura K, Matsubara Y, Ida N, Saijo M, Ogawa C, Masuyama H (2018) The influence of chemotherapy-induced peripheral neuropathy on quality of life of gynecologic cancer survivors. Int J Gynecol Cancer 28(7):1394–1402
17. Loprinzi CL, Lacchetti C, Bleeker J, Cavaletti G, Chauhan C, Hertz DL, Kelley MR, Lavino A, Lustberg MB, Paice JA et al (2020) Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update. J Clin Oncol 38(28):3325–3348
18. Jordan B, Margulies A, Cardoso F, Cavaletti G, Haugnes HS, Jahn P, Le Rhun E, Preusser M, Scotte F, Taphoorn MJB et al (2020) Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO-EONS-EANO Clinical Practice Guidelines for diagnosis, prevention, treatment and follow-up. Ann Oncol 31(10):1306–1319

19. Hanai A, Ishiguro H, Sozu T, Tsuda M, Yano I, Nakagawa T, Imai S, Hamabe Y, Toi M, Arai H et al (2018) Effects of cryotherapy on objective and subjective symptoms of paclitaxel-induced neuropathy: prospective self-controlled trial. J Natl Cancer Inst 110(2):141–148
20. Beijers AJM, Bonhof CS, Mols F, Ophorst J, de Vos-Geelen J, Jacobs EMG, van de Poll-Franse LV, Vreugdenhil G (2020) Multicenter randomized controlled trial to evaluate the efficacy and tolerability of frozen gloves for the prevention of chemotherapy-induced peripheral neuropathy. Ann Oncol 31(1):131–136
21. Griffiths C, Kwon N, Beaumont JL, Paice JA (2018) Cold therapy to prevent paclitaxel-induced peripheral neuropathy. Support Care Cancer 26(10):3461–3469
22. McCarthy AL, Shaban RZ, Gillespie K, Vick J (2014) Cryotherapy for docetaxel-induced hand and nail toxicity: randomised control trial. Support Care Cancer 22(5):1375–1383
23. Oneda E, Meriggi F, Zanotti L, Zaina E, Bighe S, Andreis F, Rueda S, Zaniboni A (2020) Innovative approach for the prevention of chemotherapy-induced peripheral neuropathy in cancer patients: a pilot study with the hilotherm device, the poliambulanza hospital experience. Integr Cancer Ther 19:1534735420943287
24. Hilotherm GmbH H: 10–12° Hilotherapy for the prevention of polyneuropathy (CIPN) and hand-foot syndrome (HFS). In.: Hilotherm GmbH; 2020. https://www.hilotherm.com/wp-content/uploads/2020/08/HT_ChemoCare_Broschuere_EN_NEU2020_web.pdf.
25. Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC, Mendoza TR, Hay J, Atkinson TM, Abernethy AP *et al* (2014) Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst. 106(9):244
26. McCrary JM, Goldstein D, Trinh T, Timmins HC, Li T, Friedlander M, Bosco A, Harrison M, Maier N, O'Neill S et al (2019) Optimizing clinical screening for chemotherapy-induced peripheral neuropathy. J Pain Symptom Manage 58(6):1023–1032
27. Kalsi T, Babic-Illman G, Fields P, Hughes S, Maisey N, Ross P, Wang Y, Harari D (2014) The impact of low-grade toxicity in older people with cancer undergoing chemotherapy. Br J Cancer 111(12):2224–2228
28. Can G, Aydiner A, Cavdar I (2012) Taxane-induced nail changes: Predictors and efficacy of the use of frozen gloves and socks in the prevention of nail toxicity. Eur J Oncol Nurs 16(3):270–275
29. Ishiguro H, Takashima S, Yoshimura K, Yano I, Yamamoto T, Niimi M, Yamashiro H, Ueno T, Takeuchi M, Sugie T et al (2011) Degree of freezing does not affect efficacy of frozen gloves for prevention of docetaxel-induced nail toxicity in breast cancer patients. Support Care Cancer 20(9):2017–2024
30. Komen MMC, Smorenburg CH, Nortier JWR, van der Ploeg T, van den Hurk CJG, van der Hoeven JJM (2016) Results of scalp cooling during anthracycline containing chemotherapy depend on scalp skin temperature. Breast 30:105–110
31. Youssef A, D'Haene M, Vleugels J, De Bruyne G, Aerts JM (2019) Localised model-based active controlling of blood flow during chemotherapy to prevent nail toxicity and onycholysis. Journal of Medical and Biological Engineering 39(1):139–150
32. Bandla A, Sundar R, Liao LD (2016) Sze Hui Tan S, Lee SC, Thakor NV, Wilder-Smith EP: Hypothermia for preventing chemotherapy-induced neuropathy - a pilot study on safety and tolerability in healthy controls. Acta Oncol 55(4):430–436
33. Bandla A, Tan S, Kumarakulasinghe NB, Huang Y, Ang S, Magarajah G, Hairom Z, Lim JSJ, Wong A, Chan G et al (2020) Safety and tolerability of cryocompression as a method of enhanced limb hypothermia to reduce taxane-induced peripheral neuropathy. Support Care Cancer 28(8):3691–3699
34. Kanbayashi Y, Sakaguchi K, Ishikawa T, Ouchi Y, Nakatsukasa K, Tabuchi Y, Kanehisa F, Hiramatsu M, Takagi R, Yokota I et al (2020) Comparison of the efficacy of cryotherapy and compression therapy for preventing nanoparticle albumin-bound paclitaxel-induced peripheral neuropathy: A prospective self-controlled trial. Breast 49:219–224
35. Atkinson TM, Ryan SJ, Bennett AV, Stover AM, Saracino RM, Rogak LJ, Jewell ST, Matsoukas K, Li Y, Basch E (2016) The association between clinician-based common terminology criteria for adverse events (CTCAE) and patient-reported outcomes (PRO): a systematic review. Support Care Cancer 24(8):3669–3676
36. Basch E, Barbera L, Kerrigan CL, Velikova G (2018) Implementation of patient-reported outcomes in routine medical care. Am Soc Clin Oncol Educ Book 38:122–134
37. Basch E, Iasonos A, McDonough T, Barz A, Culkin A, Kris MG, Scher HI, Schrag D (2006) Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study. Lancet Oncol 7(11):903–909
38. Ruddy KJ, Le-Rademacher J, Lacouture ME, Wilkinson M, Onitilo AA, Vander Woude AC, Grosse-Perdekamp MT, Dockter T, Tan AD, Beutler A et al (2019) Randomized controlled trial of cryotherapy to prevent paclitaxel-induced peripheral neuropathy (RU221511I); an ACCRU trial. Breast 48:89–97
39. Coolbrandt A, Vancoille K, Dejaeger E, Peeters H, Laenen A, Neven P, Punie K, Wildiers H (2021) Preventing taxane-related peripheral neuropathy, pain and nail toxicity: A prospective self-controlled trial comparing hilotherapy with frozen gloves in early breast cancer. Zenodo. https://doi.org/10.5281/zenodo.4478973