ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL RESEARCH

A randomized controlled trial of hand/foot-cooling by hilotherapy to prevent oxaliplatin-related peripheral neuropathy in patients with malignancies of the digestive system

A. Coolbrandt[1,2*], H. Tobback[1,3], R. Govaerts[1,3], L. Vandezande[1], M. Vinckx[1], A. Laenen[4], H. Wildiers[5,6], C. Verslype[3,6], J. Dekervel[3,6], F. Van Herpe[3,6] & E. Van Cutsem[3,6]

[1]Department of Oncology Nursing, University Hospitals Leuven, Leuven; [2]Department of Public Health and Primary Care, Academic Centre for Nursing and Midwifery, KU Leuven, Leuven; [3]Department of Digestive Oncology, University Hospitals Leuven, Leuven; [4]Interuniversity Centre for Biostatistics and Statistical Bioinformatics, KU Leuven, Leuven; [5]Department of General Medical Oncology, University Hospitals Leuven, Leuven; [6]Department of Oncology, KU Leuven, Leuven, Belgium

Available online xxx

Background: Both acute and chronic symptoms of oxaliplatin-induced peripheral neuropathy (OIPN) affect patients' treatment dose and duration as well as quality-of-life. Hand/foot-cooling has been shown to reduce taxane-induced peripheral neuropathy but there is unclear evidence in the setting of oxaliplatin.

Patients and methods: In a monocentric, open-label phase II trial, patients with malignancies of the digestive system receiving oxaliplatin-based chemotherapy were randomly assigned to receive either continuous cooling of hands and feet using hilotherapy at 11°C during oxaliplatin infusion compared with usual care (no cooling). The primary endpoint was grade $\geq$2 neuropathy-free rate in 12 weeks after initiation of chemotherapy. Secondary endpoints included OIPN-related treatment alterations, acute OIPN symptoms and perceived comfort of the intervention.

Results: The intention-to-treat population included 39 patients in the hilotherapy group and 38 in the control group. The grade $\geq$2 neuropathy-free rate at 12 weeks was 100% in the experimental group versus 80.5% in the control group ($P = 0.006$). This effect was persistent at 24 weeks (66.0% versus 49.2%, respectively) ($P = 0.039$). Next, treatment alterations-free rate at week 12 was 93.5% in the hilotherapy group compared with 83.3% in the control group ($P = 0.131$). Patients in the hilotherapy group experienced significantly less acute OIPN symptoms of numbness or tingling [odds ratio (OR) 0.05, 95% confidence interval (CI) 0.02-0.11, $P < 0.0001$], pain (OR 0.06, 95% CI 0.02-0.15, $P < 0.0001$) and/or cold sensitivity (OR 0.02, 95% CI 0.01-0.05, $P < 0.0001$) in fingers or toes as well as less pharyngeal cold sensitivity (OR 0.14, 95% CI 0.05-0.42, $P = 0.0005$). The majority of patients in the hilotherapy group rated the intervention as neutral, rather comfortable or very comfortable.

Conclusions: In this first study on hand/foot-cooling in oxaliplatin alone, hilotherapy significantly reduced the incidence of grade $\geq$2 OIPN at 12 and 24 weeks. Hilotherapy also reduced acute OIPN symptoms and was generally well tolerated.

Key words: oxaliplatin, cooling, hilotherapy, peripheral neuropathy, supportive care

INTRODUCTION

Oxaliplatin is associated with peripheral neuropathy that can be acute and transient as well as chronic and persisting. In its acute form, oxaliplatin-induced peripheral neuropathy (OIPN) is typically provoked by exposure to cold and is characterized by paresthesia and/or dysesthesia in hands and feet and/or in the mouth/throat.[1] Acute OIPN can sometimes be associated with motor effects such as muscle cramping. The chronic form of OIPN is characterized by sensory changes similar to cisplatin-induced peripheral neuropathy, with tingling and/or numbness in the extremities. OIPN severity typically increases with cumulative dose. Symptoms are sometimes reversible, but may also persist long after treatment.[1] An observational study in CAPOX- and FOLFOX-treated patients showed 94% neurotoxicity during or within 2 months after stopping treatment and 69% long-term neurotoxicity years after treatment cessation.[2] OIPN not only negatively affects quality-of-life, physical and role functioning but also treatment course, leading to dose modifications or treatment

*Correspondence to: Dr Annemarie Coolbrandt, Department of Oncology Nursing, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium. Tel: +32(0)16/341314

E-mail: annemarie.coolbrandt@uzleuven.be (A. Coolbrandt).

discontinuation.[2-6] Given the lack of evidence on drug or non-drug prophylaxis or treatment, education on avoiding cold touch and oxaliplatin dose modification remain the only strategies for managing OIPN today.[1,7]

In the past few decades, cooling interventions have gained importance as prophylactic strategies for chemotherapy-induced nail toxicity and alopecia.[8-12] A self-controlled trial in 40 patients showed that cryotherapy is also able to reduce peripheral neuropathy in patients treated with paclitaxel.[13] Given the advice on avoiding cold touch, there are limited data on cooling in the context of oxaliplatin.

Whereas continuous cooling has become the standard of care for scalp cooling, cooling of hands and feet is often applied using frozen gloves that are uncomfortable to patients and require personnel attention to change gloves as their temperature rapidly rises.[14-16] Only recently, Hilotherapy® was presented by Hilotherm GmbH, Argenbühl-Eisenharz/Allgäu, Germany for continuous hand/foot-cooling at a constant temperature. We found that, compared with frozen gloves, continuous cooling of hands and feet using hilotherapy (11°C) produced better prevention of grade ≥2 patient-reported side-effects at the extremities (peripheral neuropathy, pain and nail toxicities) in patients with breast cancer treated with taxane-containing regimens. Noteworthy, perceived comfort was significantly better for hilotherapy.[17] Therefore, hilotherapy seems more suitable for further study on cooling interventions in the context of OIPN.

The aim of this randomized controlled trial (RCT) is to evaluate to what extent hand/foot-cooling using hilotherapy compared with standard care without cooling is effective in preventing grade ≥2 peripheral neuropathy. On top of that, this study explores to what extent hand/foot-cooling can avoid treatment alterations and can prevent acute OIPN. Given the novelty of hilotherapy in this setting, the study explores patient comfort and compliance as well.

MATERIALS AND METHODS

Study design

We conducted an RCT (ClinicalTrials.gov Identifier: NCT04913376) with a parallel design, stratification based on risk of peripheral neuropathy and 1 : 1 allocation in patients with a malignancy of the digestive system treated with oxaliplatin.

Setting and participants

We recruited a consecutive sample of patients starting oxaliplatin treatment at the University Hospitals Leuven, Belgium. The study included adult patients (≥18 years) with a malignancy of the digestive system, regardless of tumor type and setting (adjuvant or palliative), starting any oxaliplatin-based treatment (oxaliplatin 85 mg/m^2 every 2 weeks or 130 mg/m^2 every 3 weeks), whether or not in combination with another cytostatic agent (5-fluorouracil, irinotecan, capecitabine) but not in combination with docetaxel. In the latter combination, hand/foot-cooling is already standard of care to prevent docetaxel-related nail toxicity. Patients with high risk for OIPN based on previous (neurotoxic) chemotherapy or diabetes mellitus were eligible provided they had grade 0 or 1 peripheral neuropathy at the time of inclusion. Given the patient-reported outcomes used in this study, cognitive capability and sufficient understanding of the Dutch language were additional inclusion criteria in this study. Patients with clinically significant cold allergy, Raynaud's phenomenon, or nail or peripheral vascular disease were excluded from this study, as well as patients with grade ≥2 peripheral neuropathy at treatment initiation. All patients signed informed consent to participate in this study.

Procedures

Patients received oral and written information before or at the day of treatment start. After informed consent and before randomization, patients completed a screening questionnaire, including a baseline peripheral neuropathy measurement used to stratify participants into a group with no increased risk (grade 0 at baseline) and a group with increased risk of grade ≥2 OIPN (grade 1 at baseline). Next, each participant was randomly assigned to the intervention or control group in a 1 : 1 ratio. Randomization was stratified based on baseline risk of grade ≥2 peripheral neuropathy and applied via Research Electronic Data Capture (REDCap).[18,19]

Hand/foot-cooling was provided using hilotherapy with Hilotherm® ChemoCare devices using an electrically driven closed cooling system to produce continuous cooling at a constant temperature. We applied a fixed temperature of 11°C and used Hilotherm® hand- and foot-cuffs of the first-generation model. Hilotherapy cuffs were worn from 30 min before administration, during the 2-h oxaliplatin administration and until 30 min after the end of administration. Participants in the intervention arm were able to continue hilotherapy for the entire duration of their oxaliplatin-based treatment. The control group received standard care (no cooling).

Endpoints

Primary endpoint was grade ≥2 neuropathy-free rate (G2NF) in 12 weeks after initiation of chemotherapy. Secondary endpoints included:

- For chronic neuropathy as experienced at treatment visits:
  - o grade ≥2 neuropathy-free rate (G2NF) in 24 weeks
  - o any-grade neuropathy-free rate in 12 weeks
  - o grade ≥2 OIPN interference with usual or daily activities-free rate
- For acute (and transient) OIPN symptoms as experienced in the first few days after oxaliplatin administration:

  - o severity of numbness or tingling in fingers or toes, pain in fingers or toes, cold sensitivity and pharyngeal cold sensitivity
  - o duration of acute OIPN symptoms (in numbers of days)
- Treatment alterations-free rate in 12 weeks (i.e. proportion of patients without OIPN-related oxaliplatin dose modification and/or stop)
- Perceived comfort of the intervention

Clinical data were extracted from the electronic patient record. Patients self-reported the severity of OIPN via Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) on a 5-point Likert scale (G0/none, G1/mild, G2/moderate, G3/severe, G4/very severe).[20] PRO-CTCAE™ was also used to evaluate OIPN interference with daily activities (G1/not at all, G2/a little bit, G3/somewhat, G4/quite a bit, G5/very much) and the severity of acute OIPN as experienced in the first few days after oxaliplatin administration (i.e. numbness or tingling in fingers or toes, pain in fingers or toes, cold sensitivity, pharyngeal cold sensitivity). Duration of acute OIPN was evaluated as the number of days OIPN symptoms lasted. Next to the short-form PRO-CTCAE™, patients completed the European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20-item scale (EORTC QLQ-CIPN20) every 6 weeks (T0-T4).[21]

Additionally, participants in the hilotherapy group reported the perceived comfort with regard to contact with the hilotherapy cuff, the tolerance of the temperature and the restrictions on mobility on a 5-point Likert scale (1/very burdensome to 5/very comfortable). Patients also assessed to what extent hand/foot-cooling influenced any existing peripheral neuropathy. Finally, compliance with the intervention was monitored by the study nurses with each application of hand/foot-cooling and any patient report of (perceived) suboptimal cooling of hands and feet was registered.

Data were collected before the start of treatment (T0/baseline) and every 6 weeks until 24 weeks regardless of treatment status (T1/6 weeks, T2/12 weeks, T3/18 weeks, T4/24 weeks). Except for EORTC QLQ-CIPN20, data were also collected at every other 2- or 3-weekly oxaliplatin administration up to 12 weeks (Q1-Q4). All study data were collected and managed using REDCap electronic data capture tools.

Statistical analyses

A sample size calculation for a one-sided log-rank test, assuming 80% power, 5% significance level, 5% drop-out rate at 12 weeks and a 12-week incidence of grade $\geq$2 neuropathy of 70% in the control group and 40% in the experimental group determined a sample size of 66 patients. We assumed an incidence of 70% grade $\geq$2 peripheral neuropathy in the control group based on the study by Soveri et al.[2] (2019) and aimed for a reduction in incidence to 40% in the hilotherapy group based on previous comparative studies on cryotherapy.

An intent-to-treat analysis was carried out for this study. The primary outcome in this study was conceptualized as a time-to-event outcome, where the event takes the value 1 if OIPN was rated grade 2 or higher, or 0 otherwise, and the time component being the number of weeks between chemotherapy initiation and the first occurrence of the event. Patients without event were censored at 12 weeks or at their last follow-up in case of drop-out. The groups were compared using a stratified log-rank test. A Cox model was applied to estimate the hazard ratio with 95% confidence interval. In a similar fashion, time-to-event analyses were carried out for grade $\geq$2 neuropathy-free rate in 24 weeks, treatment alterations-free rate in 12 weeks, $\geq$ grade 2 OIPN interference-free rate in 12 weeks and any-grade neuropathy-free rate in 12 weeks after treatment initiation. Given the small number of patients with increased risk for neuropathy, a planned subgroup analysis of increased risk and no increased risk patients was not carried out.

Longitudinal analyses were applied for severity and duration of acute OIPN, OIPN severity and interference with daily activities and OIPN according to EORTC-QLQ CIPN20. Since there were no differences at baseline for any of these endpoints, they were not corrected for in the longitudinal analyses. Linear mixed models were used for continuous outcomes, reporting results as mean differences, or proportional odds models for ordinal outcomes, reporting results as odds ratios (ORs). Random effects were included to account for the longitudinal data structure. The fixed effects model included treatment, time and a time by treatment interaction.

The indicators for the comfort of the cooling intervention (patient-reported comfort and compliance) were descriptively analyzed.

A one-sided significance test was carried out for the primary outcome, two-sided tests were carried out for all other outcomes. All tests were evaluated at a 5% significance level. Analyses have been carried out using SAS software (version 9.4 of the SAS System for Windows, SAS Institute, Cary, NC).

Ethical considerations

This study was performed in line with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of UZ/KULeuven. All patients received oral and written information to decide on study participation and signed informed consent.

RESULTS

Patient characteristics

Patient flow is illustrated in Figure 1. Between May 2021 and January 2022, 139 patients were screened for this study, 77 of whom enrolled in the study and were randomized into the experimental group (n = 39) and the control group (n = 38).

Patient characteristics are described in Table 1. Participants had a mean age of 62.8 years. Most of them were male (n = 41, 61.2%) and treated for colorectal cancer (n = 43,

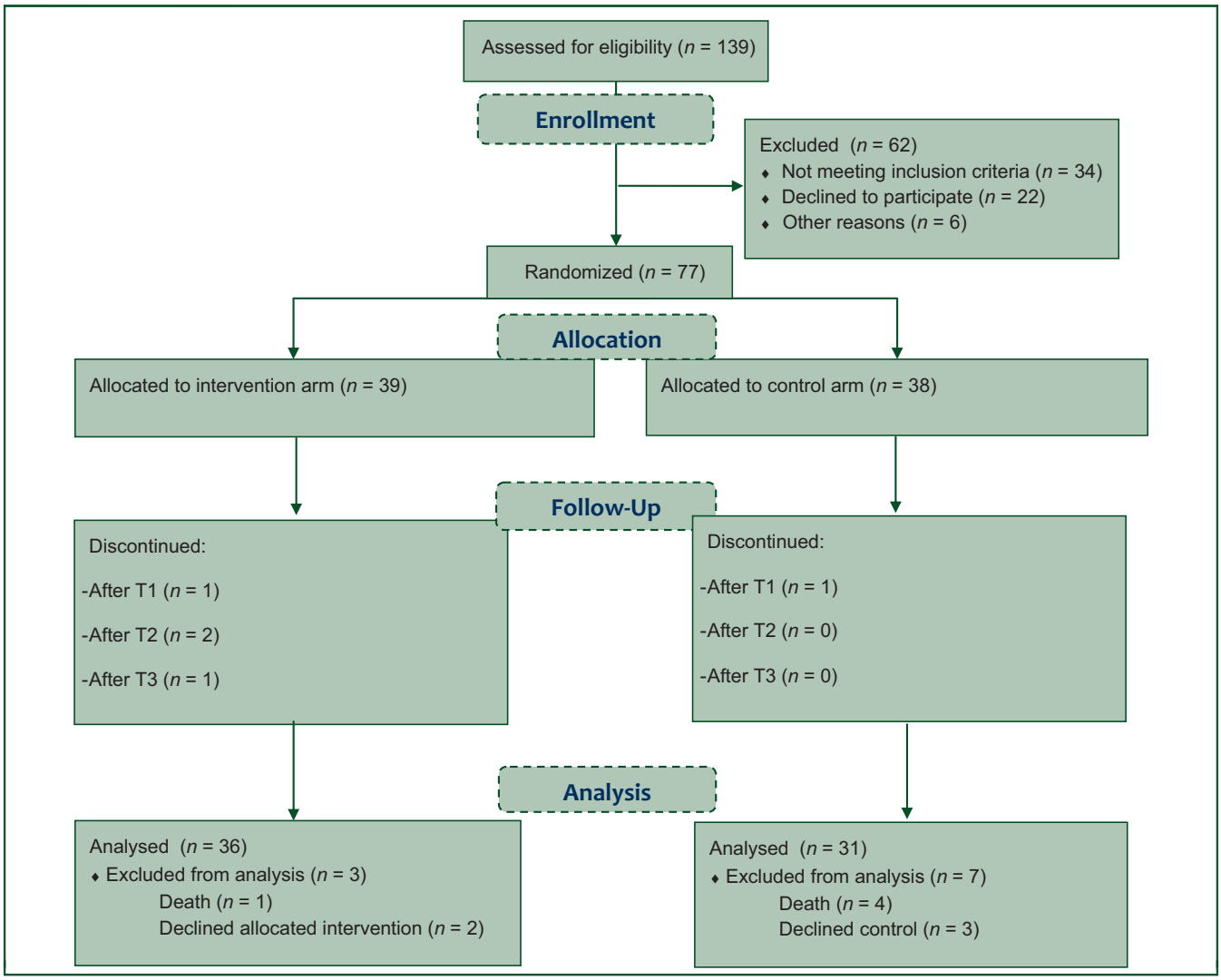

Figure 1. CONSORT diagram illustrating the participant flow in the study.

64.2%). Treatment intent was curative (adjuvant, neoadjuvant) in 37 participants (41.6%) and palliative in 33 (49.3%). Only six patients (9.0%) were treated with oxaliplatin 130 mg/m^2, five of whom participated in the control group. A minority had diabetes ($n = 16$, 23.9%) or had been treated with chemotherapy before ($n = 17$, 25.4%). Seven participants (10.5%) had grade 1 neuropathy and/or pain at baseline and were stratified into the group with increased risk of grade $\geq$2 peripheral neuropathy. There were no statistically significant differences between both groups on any of the demographical or clinical characteristics or on any of the baseline measures. A (non-significant) imbalance was noted regarding the oxaliplatin dosage in the two groups, however, with five patients in the control group receiving the 130 mg/m^2 dose, compared with only one patient in the experimental group ($P = 0.095$).

Chronic neuropathy

Table 2 presents the time-to-event analyses on grade $\geq$2 OIPN. In the period of 12 weeks after the start of treatment, hand/foot-cooling demonstrated a statistically significant prophylactic effect with 100.0% of patients in the experimental group being free of grade $\geq$2 OIPN at 12 weeks against 80.5% (95% CI 61.7% to 90.7%) event-free patients in the control group ($P = 0.006$) (see Figure 2 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101205). In the period of 24 weeks after the start of treatment, the G2NF rate was significantly higher in the experimental group (at 24 weeks: 66.0%, 95% CI 45.6% to 80.3%) than in the control group (49.2%, 95% CI 30.2% to 65.7%) ($P = 0.039$) (see Figure 2). Regarding any-grade OIPN in 12 weeks, more patients were event-free in the experimental group (at 12 weeks 66.3%, 95% CI 48.3% to 79.3%) compared with the control group (45.2%, 95% CI 27.4% to 61.4%), but this was not statistically significant ($P = 0.151$) (see Figure 3A). Patients in the experimental group reported less grade $\geq$2 interference with usual or daily activities compared with the control group in both 12-week and 24-week periods after treatment initiation (see Figure 3B and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101205), but this was not

Table 1. Patient characteristics

	Total sample, *n* (%) *N* = 77	Experimental group, *n* (%) *n* = 39	Control group, *n* (%) *n* = 38	*P*
Demographic and clinical characteristics				
Age (years), mean (SD)	63.3 (10.8)	65.03 (11.0)	61.6 (10.5)	0.116
Sex				0.355
Female	30 (39.0)	13 (33.3)	17 (44.7)	
Male	47 (61.0)	26 (66.7)	21 (55.3)	
Diagnosis				0.606
Esophageal carcinoma	14 (18.2)	6 (15.4)	8 (21.1)	
Pancreatic carcinoma	12 (15.6)	8 (20.5)	4 (10.5)	
Primary hepatobiliary tumor	3 (3.9)	1 (2.6)	2 (5.3)	
Colorectal cancer	48 (62.3)	24 (61.5)	24 (63.2)	
Metastatic disease				0.818
No	32 (41.6)	17 (43.6)	15 (39.5)	
Yes	45 (58.4)	22 (56.4)	23 (60.5)	
Treatment setting				0.908
Adjuvant	23 (29.9)	11 (28.2)	12 (31.6)	
Neoadjuvant	14 (18.2)	8 (20.5)	6 (15.8)	
Palliative	40 (52.0)	20 (51.3)	20 (52.6)	
Protocol				0.325
Modified FOLFOX	62 (80.5)	32 (82.1)	30 (79.0)	
FOLFIRINOX	9 (11.7)	6 (15.4)	3 (7.9)	
CAPOX	6 (7.8)	1 (2.6)	5 (13.2)	
Dose of oxaliplatin at start				0.095
85 mg/m^2	68 (91.9)	38 (97.4)	30 (85.7)	
130 mg/m^2	6 (8.1)	1 (2.6)	5 (14.3)	
Number of oxaliplatin treatment cycles, mean (SD)	8.0 (3.7)	8.6 (3.4)	7.3 (3.9)	0.155
Cumulative oxaliplatin dose in mg/m^2, mean (SD)	948.4 (232.9)	965.3 (81.9)	931.1 (322.3)	0.451
Presence of neurotoxicity risk factors				
Diabetes	18 (23.4)	9 (23.1)	9 (23.7)	1.000
Chemotherapy in history	21 (27.3)	12 (30.8)	9 (23.7)	0.610
Neurotoxic chemotherapy in history	11 (14.3)	7 (17.9)	4 (10.5)	0.653
Medication affecting neuropathic pain	1 (1.3)	1 (2.6)	0 (0.0)	1.000
Baseline neuropathy at hands and/or feet	6 (7.8)	4 (10.3)	2 (5.3)	0.675
Baseline pain at hands and/or feet	4 (5.2)	1 (2.6)	3 (7.9)	0.358
Baseline risk for ≥G2 neuropathy				0.711
No increased risk of ≥G2 peripheral neuropathy[a]	69 (89.6)	34 (87.2)	35 (92.1)	
Increased risk of ≥G2 peripheral neuropathy[b]	8 (10.4)	5 (12.8)	3 (7.9)	
Baseline EORTC-CIPN20 score, mean (SD)	3.2 (4.5)	3.6 (5.5)	2.8 (3.3)	0.916

EORTC-CIPN20, European Organisation of Research and Treatment of Cancer-Chemotherapy-Induced Peripheral Neuropathy 20-item scale; SD, standard deviation.
[a]Baseline grade 0 for both peripheral neuropathy and pain.
[b]Grade 1 for peripheral neuropathy and/or pain.

statistically significant ($P = 0.130$ and $P = 0.065$, respectively). The mean difference of patient-reported severity of OIPN on the EORTC QLQ-CIPN20 questionnaire at 24 weeks was −0.57 (95% CI −2.99 to 1.86, $P = 0.645$).

Longitudinal analyses for OIPN severity and interference at 12 and 24 weeks are shown in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101205. Significant time by group interactions were noted. Except for patient-reported OIPN severity at 24 weeks, all ORs were <1, but this was only statistically significant for OIPN interference with daily activities at 12 weeks (OR = 0.17, 95% CI 0.05-0.53, $P = 0.002$). Since the OR of 1.52 (95% CI 0.61-3.81, $P = 0.371$) for OIPN severity at 24 weeks indicated a potential negative effect of the cooling intervention, we carried out sensitivity analyses to further explore this result (see Supplementary Table S2,

Table 2. Longitudinal analyses for acute OIPN as experienced in the first few days after oxaliplatin administration for patients receiving oxaliplatin, treated with or without hilotherapy

	Odds ratio (95% CI)	*P* value
Patient-reported numbness or tingling in fingers or toes	0.05 (0.02-0.11)	<0.0001
Patient-reported pain in fingers and toes	0.06 (0.02-0.15)	<0.0001
Patient-reported cold sensitivity of hands or feet	0.02 (0.01-0.05)	<0.0001
Patient-reported pharyngeal cold sensitivity	0.14 (0.05-0.42)	0.0005
	Mean difference (95% CI)	***P* value**
Patient-reported duration of acute neuropathy in number of days	−3.12 (−4.77 to −1.46)	0.0002

OIPN, oxaliplatin-induced peripheral neuropathy.

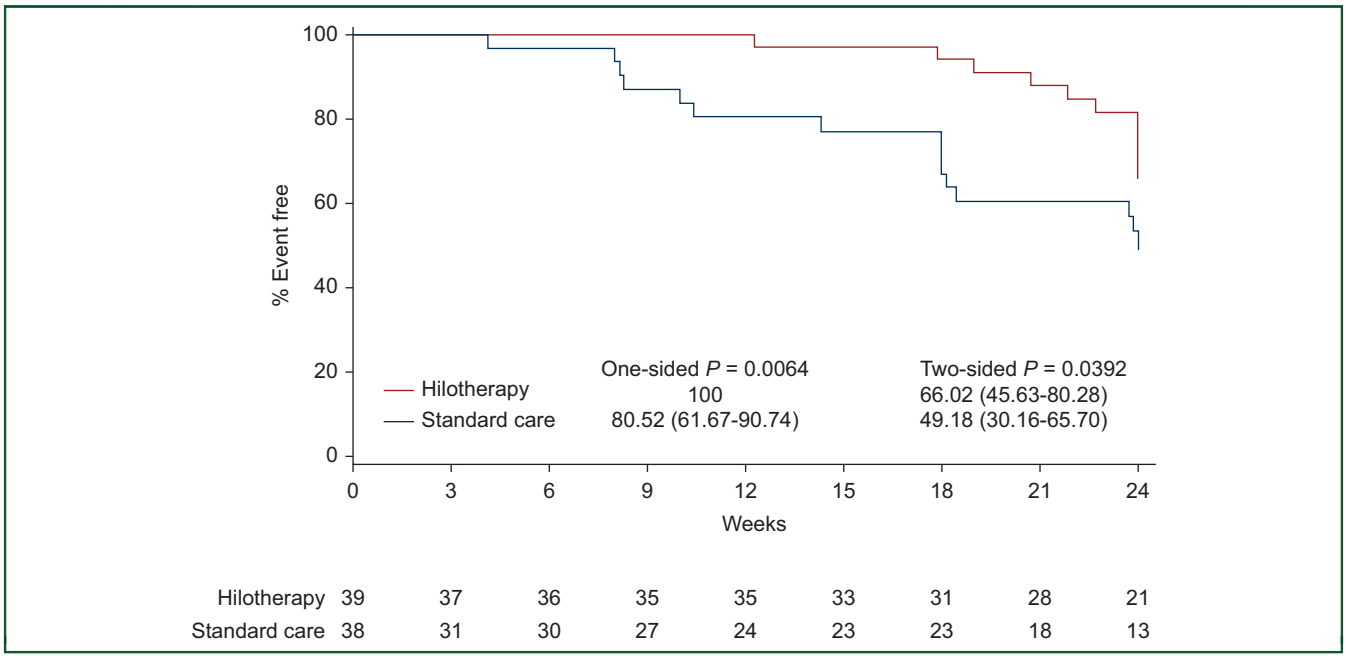

Figure 2. **Kaplan–Meier curve for grade ≥2 peripheral neuropathy at 12 weeks (primary endpoint) and at 24 weeks, for patients receiving oxaliplatin, treated with or without hilotherapy.**

available at https://doi.org/10.1016/j.esmoop.2023.101205). Interestingly, when considering the intervention as a time-varying variable, all ORs were <1, including the OR for OIPN severity at 24 weeks.

Acute (and transient) OIPN symptoms

Table 2 shows the results of the longitudinal analyses for acute OIPN. Regarding the severity of acute OIPN symptoms, ORs were lower than 0.10 for acute numbness or tingling in fingers or toes, pain in fingers and toes and cold sensitivity of hands and feet ($P < 0.0001$). Regarding pharyngeal cold sensitivity, the OR was 0.14 (95% CI 0.05-0.42, $P = 0.0005$). Patient-reported duration of acute OIPN was significantly lower in the experimental group, with a negative mean difference of −3.12 days (95% CI −4.77 to −1.46 days, $P = 0.0002$).

OIPN-related treatment alterations

When considering OIPN-related treatment alterations, a time-to-event analysis showed that 93.5% (95% CI 76.3% to 98.4%) of patients in the experimental group did not have any OIPN-related treatment alteration at 12 weeks, against 83.4% (95% CI 66.6% to 92.2%) in the control group ($P = 0.131$) (see Figure 3C and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101205). At 12 weeks, OIPN-related dose modification was decided in 5.1% of patients in the experimental group compared with 18.4% in the control group ($P = 0.087$) (see Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101205). At 24 weeks, 12.8% of the patients in the experimental group had had OIPN-related dose reduction compared with 29.0% of patients in the control group ($P = 0.098$). Also, 23.1% of patients in the experimental group had stopped oxaliplatin because of OIPN compared with 13.2% in the control group ($P = 0.377$) (see Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101205).

Treatment comfort and compliance

Figure 4 reports on the comfort of hilotherapy as perceived by the experimental group. Contact with the cuffs, tolerance of the cold and limitation of mobility were perceived 'neutral' at 52.8%, 54.9% and 47.7% of all hilotherapy sessions in the study respectively. Contact with the cuffs and tolerance of the cold was perceived burdensome at ∼10% of all sessions. Overall, limitation of mobility was perceived worst as this was scored as burdensome at >25% of all sessions. Only one patient reported that OIPN symptoms were more severe during cooling at one time point, whereas the majority did not observe any change in OIPN symptoms during the cooling intervention (see Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2023.101205).

Regarding the fidelity to the intervention, four patients stopped the cooling intervention prematurely (see Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2023.101205). Two patients stopped cooling at the feet but continued the cooling intervention at the hands. On a total of 296 hilotherapy sessions in this study, perceived suboptimal cooling of the hands was reported to the study nurses 26 times (0.09%) by 20 patients compared with 7 reports (0.02%) by 4 patients of suboptimal cooling of the feet.

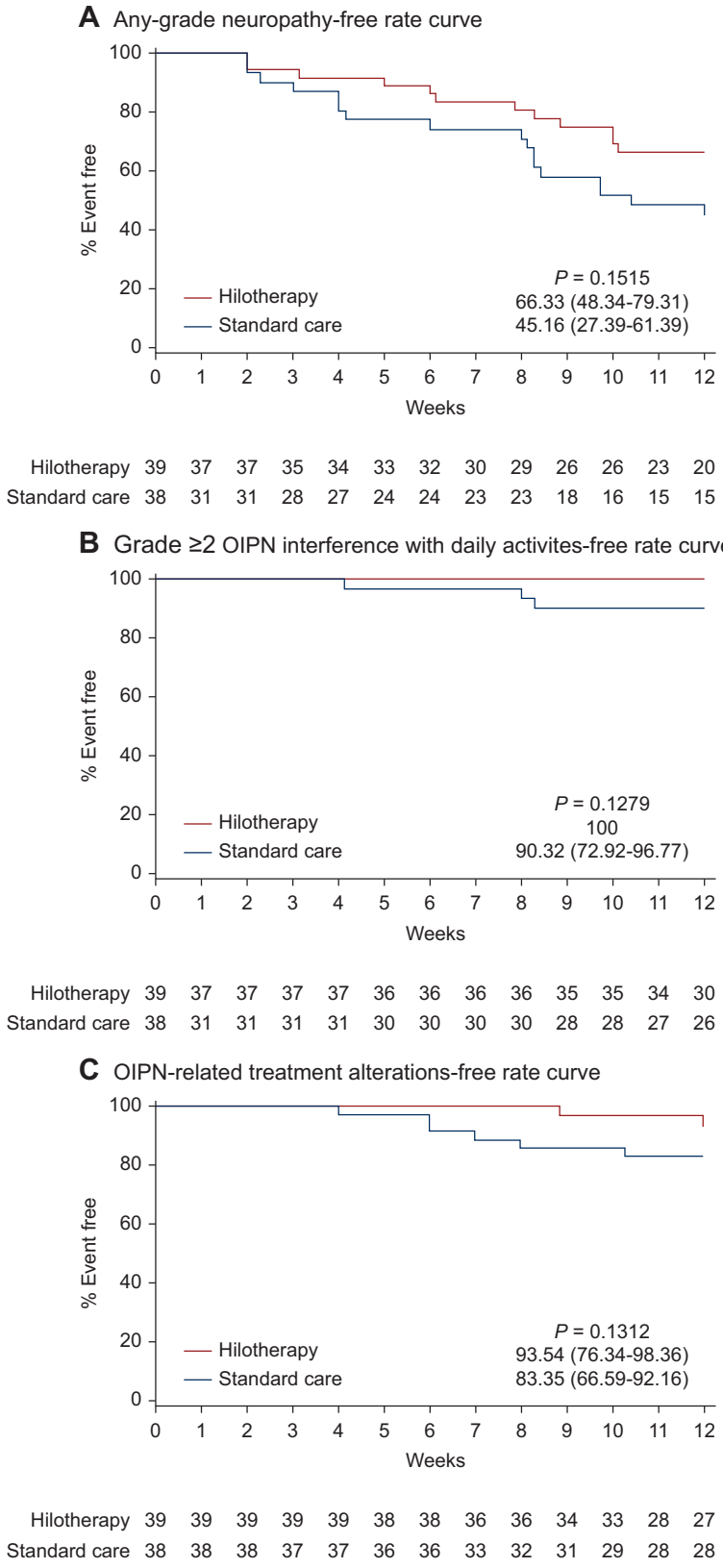

Figure 3. Kaplan–Meier curve for OIPN-related treatment alterations, grade ≥2 OIPN interference with daily activities and any-grade neuropathy at 12 weeks, for patients receiving oxaliplatin, treated with or without hilotherapy.
OIPN, oxaliplatin-induced peripheral neuropathy.

DISCUSSION

OIPN can have a devastating impact on a patient's functioning and quality-of-life during and long after treatment. Next, OIPN often results in dose modification or treatment discontinuation. So far, pharmacological and non-pharmacological interventions for preventing or treating OIPN are lacking. In this RCT, hand/foot-cooling demonstrated a statistically significant prophylactic effect with 100.0% G2NF in the experimental group at 12 weeks after the start of treatment against 80.5% in the control group ($P = 0.006$). At 24 weeks, G2NF was still significantly higher in the experimental group (66.0%) than in the control group (49.2%) ($P = 0.039$). Noteworthy based on the EORTC QLQ-CIPN20, hilotherapy failed to produce a significant reduction of peripheral neuropathy at 24 weeks. We did not carry out subscale analyses to explore effects on sensory, motor and autonomic symptoms.

Although several studies have explored cryotherapy for the prevention of taxane-induced peripheral neuropathy, there are limited data on cooling in the context of oxaliplatin. In a randomized study studying the effect of oral cryotherapy on oxaliplatin-induced oral thermal hyperalgesia, the oral cryotherapy group had a significantly smaller exacerbation of symptoms associated with cold exposure and significantly less difficulty consuming cold drinks and food.[22] In an RCT studying frozen gloves in a sample of patients with mixed treatments (docetaxel, paclitaxel and oxaliplatin), cryotherapy failed to produce a significant reduction of peripheral neuropathy. The study, however, faced a large dropout rate due to intolerance of the intervention.[14] Moreover, whereas patients on oxaliplatin treatment made up the majority in this study (61.6%, 118/190), the study did not present a subgroup analysis. In this study, CIPN was assessed with the EORTC QLQ-CIPN20 alone. Cooling during the administration of oxaliplatin seems counterintuitive as acute OIPN symptoms are often cold-induced and patients are therefore instructed on avoiding cold touch and cold drinks.[1]

The cooling intervention in this study achieved a strong and statistically significant reduction in severity and duration of acute neuropathy, both peripheral ($P < 0.0001$) and pharyngeal ($P = 0.0005$). Interestingly, a study applying oral cryotherapy for the prevention of oxaliplatin-induced oral thermal hyperalgesia had observed a significant reduction in peripheral neuropathy as well. The authors hypothesized that oral cooling might lower the core temperature and result in secondary peripheral vasoconstriction, or that the correlation between oral and peripheral neuropathy resulted from a lowered nociceptive threshold due to hypersensitivity.[22] The same mechanisms could explain the vice versa effect of peripheral cooling on pharyngeal cold sensitivity. As acute neuropathy has been recognized as a risk factor for developing chronic or persistent neuropathy in patients with colorectal cancer,[23-29] the cooling intervention's positive effect on acute neuropathy symptoms may, to a certain extent, explain the prophylactic effect on chronic neurotoxicity.

OIPN prevention may be relevant for avoiding treatment alterations and improving treatment completion. In a retrospective analysis of 350 patients receiving oxaliplatin on the NCCTG N08CB trial, only 39% completed treatment without alteration, 20% had a dose reduction or delay due to neuropathy and 10% discontinued early due to neuropathy.[30] Thus, OIPN-related treatment alterations are highly prevalent. Our study showed that 93.5% of patients in the experimental group did not have any OIPN-related treatment alteration at 12 weeks, against 83.4% in the control group, although this was not statistically significant ($P = 0.131$). Future study in larger samples is recommended to further explore the prophylactic effect of hand/foot-cooling on treatment alterations. As grade $\geq$2 neuropathy is associated with decreased physical and role functioning,[2] preventing $\geq$ grade 2 neuropathy is also of relevance for improving patients' daily functioning. In this study, patients in the experimental group reported less OIPN interference with daily activities but not to the level of statistical significance.

Hand/foot-cooling for preventing chemotherapy-induced nail toxicity or peripheral neuropathy is typically applied using frozen gloves and socks.[11-14,16] The discomfort of frozen gloves is well known, however, with up to 34% of the patients quitting the intervention in the study by Beijers et al.[14] Also, frozen gloves produce unstable cooling and need to be changed regularly during treatment administration. This may particularly be impractical during a 3-h cooling intervention for oxaliplatin. As a self-controlled trial in taxane treatments for breast cancer showed that hilotherapy produced better prevention of grade $\geq$2 patient-reported side-effects at the extremities and was more comfortable than frozen gloves,[17] we used hilotherapy in this study, adding to the little available evidence on 'machine cooling' of hands and feet. Whereas continuous cooling is assumed to produce a more stable vasoconstriction, its effect on skin temperature and/or vasoconstriction was not studied in this RCT. Future research about the finger/toe response during a continuous cooling intervention may be useful to optimize the intervention. Meanwhile, other devices for delivering continuous hand/foot-cooling during chemotherapy are being developed.[7]

This first study on continuous cooling in patients treated with oxaliplatin shows that the 3-h cooling intervention was overall acceptable to patients. Limitation of mobility scored worst and was thus perceived as the most burdensome aspect of the intervention. When implementing hand/foot-cooling in daily practice, tolerability is expected to require attention in some patients.

We carried out an RCT to study hand/foot-cooling in oxaliplatin. As blinding is not easily achievable in this type of intervention, both participants and study personnel were unblinded. Given the subjective and patient-reported primary endpoint, a lack of blinding increases the risk of bias. Patient-reported outcomes have, however, been pushed forward for symptom monitoring, especially for more subjective symptoms.[31-33] Only one objective outcome was included in our study, namely OIPN-related treatment

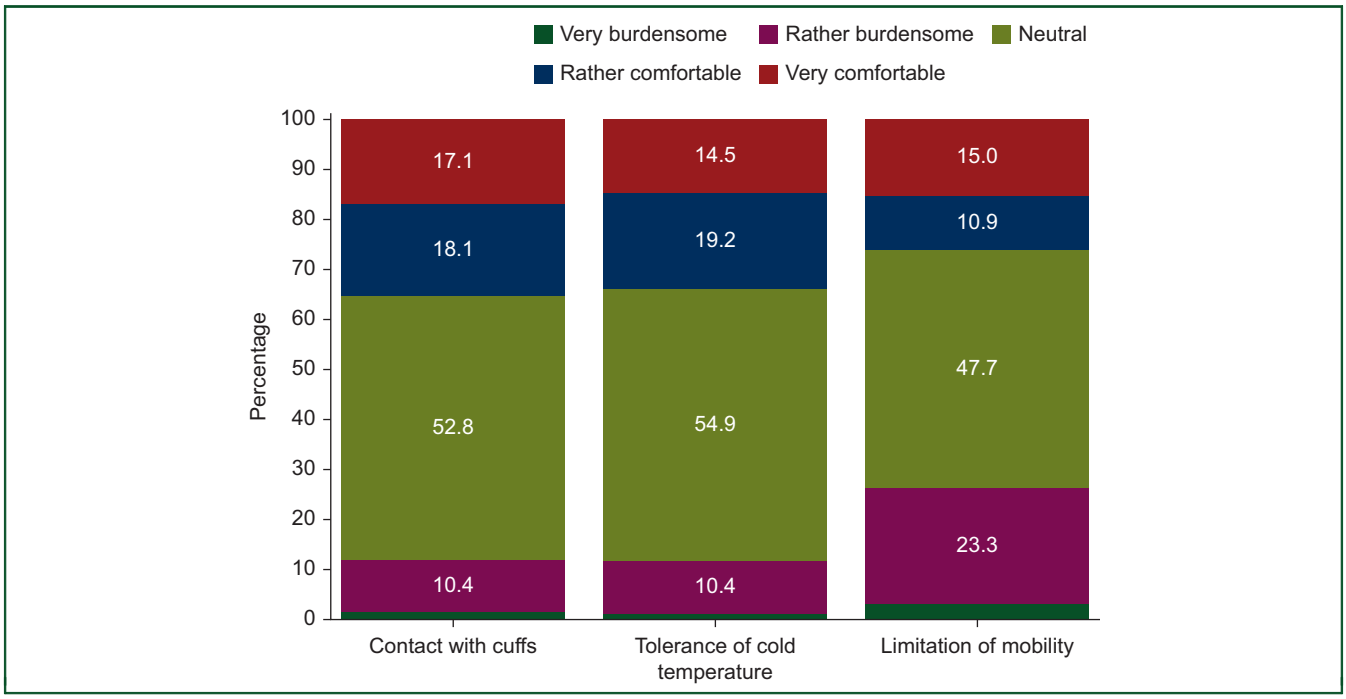

Figure 4. **Tolerability ratings for hilotherapy sessions across all time points.**

alterations. This outcome confirmed, although less strongly and not to a level of significance, the superiority of the cooling intervention compared with the standard of care. This endpoint was considered a secondary endpoint in this study and could be further explored in a study with a larger sample size.

In this first study on cooling during oxaliplatin administration, our sample was heterogeneous with regards to stage of disease and treatment setting and study follow-up was limited to 6 months after the start of treatment. Further study in a larger, more homogeneous sample and with long-term follow-up is therefore recommended. The (non-significant) imbalance of 130 mg/m^2 dosage between the two groups (i.e. five patients on CAPOX treatment in the control group against one in the experimental group) is unlikely to have biased the results of this study, as higher representation of CAPOX treatments in the control group would be expected to favor OIPN in the control group.[6,34] Stratification based on treatment and oxaliplatin dosage would avoid this imbalance in future studies. Whereas randomization was stratified based on the risk of neurotoxicity, very few participants ($n = 8$, 10.4%) had grade 1 neuropathy and/or pain at baseline and were stratified into the group with increased risk of grade $\geq$2 peripheral neuropathy. Thus, the effect of cooling in patients with increased risk should be explored in future studies.

Conclusion

This first RCT on continuous hand/foot-cooling at a constant temperature (11°C) during oxaliplatin treatment demonstrated a statistically significant prophylactic effect on grade $\geq$2 OIPN at both 12 and 24 weeks and on the severity and duration of acute OIPN symptoms. Finally, the cooling intervention was acceptable for the majority of patients. Thus, hand/foot-cooling presents itself as a promising way to reduce the devastating impact of OIPN.

ACKNOWLEDGEMENTS

We thank Hilotherm GmbH and BeMedico for providing hilotherapy devices for the duration of the study.

FUNDING

This work was supported by the Estée Lauder University Fund (KU Leuven, no grant number).

DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

Data are available upon request to the authors (https://doi.org/10.5281/zenodo.7495771).

REFERENCES

1. Sereno M, Gutierrez-Gutierrez G, Gomez-Raposo C, et al. Oxaliplatin induced-neuropathy in digestive tumors. *Crit Rev Oncol Hematol*. 2014;89:166-178.
2. Soveri LM, Lamminmaki A, Hanninen UA, Karhunen M, Bono P, Osterlund P. Long-term neuropathy and quality of life in colorectal cancer patients treated with oxaliplatin containing adjuvant chemotherapy. *Acta Oncol*. 2019;58:398-406.
3. Kidwell KM, Yothers G, Ganz PA, et al. Long-term neurotoxicity effects of oxaliplatin added to fluorouracil and leucovorin as adjuvant therapy for colon cancer: results from National Surgical Adjuvant Breast and Bowel Project trials C-07 and LTS-01. *Cancer*. 2012;118:5614-5622.
4. Mols F, Beijers T, Lemmens V, van den Hurk CJ, Vreugdenhil G, van de Poll-Franse LV. Chemotherapy-induced neuropathy and its association

with quality of life among 2- to 11-year colorectal cancer survivors: results from the population-based PROFILES registry. *J Clin Oncol*. 2013;31:2699-2707.
5. Pachman DR, Qin R, Seisler DK, et al. Clinical course of oxaliplatin-induced neuropathy: results from the randomized phase III trial N08CB (Alliance). *J Clin Oncol*. 2015;33:3416-3422.
6. Yoshino T, Yamanaka T, Oki E, et al. Efficacy and long-term peripheral sensory neuropathy of 3 vs 6 months of oxaliplatin-based adjuvant chemotherapy for colon cancer: the ACHIEVE phase 3 randomized clinical trial. *JAMA Oncol*. 2019;5:1574-1581.
7. Binder J, Unver E, Clayton J, et al. A limb hypothermia wearable for chemotherapy-induced peripheral neuropathy: a mixed-methods approach in medical product development. *Front Digit Health*. 2020;2:573234.
8. Lacouture ME, Sibaud V, Gerber PA, et al. Prevention and management of dermatological toxicities related to anticancer agents: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2021;32:157-170.
9. Nangia J, Wang T, Osborne C, et al. Effect of a scalp cooling device on alopecia in women undergoing chemotherapy for breast cancer: the SCALP randomized clinical trial. *JAMA*. 2017;317:596-605.
10. Rugo HS, Klein P, Melin SA, et al. Association between use of a scalp cooling device and alopecia after chemotherapy for breast cancer. *JAMA*. 2017;317:606-614.
11. Scotte F, Banu E, Medioni J, et al. 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*. 2008;112:1625-1631.
12. Scotte F, Tourani JM, Banu E, et al. Multicenter study of a frozen glove to prevent docetaxel-induced onycholysis and cutaneous toxicity of the hand. *J Clin Oncol*. 2005;23:4424-4429.
13. Hanai A, Ishiguro H, Sozu T, et al. Effects of cryotherapy on objective and subjective symptoms of paclitaxel-induced neuropathy: prospective self-controlled trial. *J Natl Cancer Inst*. 2018;110:141-148.
14. Beijers AJM, Bonhof CS, Mols F, et al. Multicenter randomized controlled trial to evaluate the efficacy and tolerability of frozen gloves for the prevention of chemotherapy-induced peripheral neuropathy. *Ann Oncol*. 2020;31:131-136.
15. Griffiths C, Kwon N, Beaumont JL, Paice JA. Cold therapy to prevent paclitaxel-induced peripheral neuropathy. *Support Care Cancer*. 2018;26:3461-3469.
16. McCarthy AL, Shaban RZ, Gillespie K, Vick J. Cryotherapy for docetaxel-induced hand and nail toxicity: randomised control trial. *Support Care Cancer*. 2014;22:1375-1383.
17. Coolbrandt A, Vancoille K, Dejaeger E, et al. Preventing taxane-related peripheral neuropathy, pain and nail toxicity: a prospective self-controlled trial comparing hilotherapy with frozen gloves in early breast cancer. *Breast Cancer Res Treat*. 2022;192:293-301.
18. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208.
19. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377-381.
20. Basch E, Reeve BB, Mitchell SA, et al. 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*. 2014;106:dju244.
21. Postma TJ, Aaronson NK, Heimans JJ, et al. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. *Eur J Cancer*. 2005;41:1135-1139.
22. Bauman B, Mick R, Martinez E, et al. Efficacy of oral cryotherapy during oxaliplatin infusion in preventing oral thermal hyperalgesia: a randomized trial. *J Natl Compr Canc Netw*. 2019;17:358-364.
23. Alejandro LM, Behrendt CE, Chen K, Openshaw H, Shibata S. Predicting acute and persistent neuropathy associated with oxaliplatin. *Am J Clin Oncol*. 2013;36:331-337.
24. Argyriou AA, Cavaletti G, Briani C, et al. Clinical pattern and associations of oxaliplatin acute neurotoxicity: a prospective study in 170 patients with colorectal cancer. *Cancer*. 2013;119:438-444.
25. Argyriou AA, Polychronopoulos P, Iconomou G, Chroni E, Kalofonos HP. A review on oxaliplatin-induced peripheral nerve damage. *Cancer Treat Rev*. 2008;34:368-377.
26. Attal N, Bouhassira D, Gautron M, et al. Thermal hyperalgesia as a marker of oxaliplatin neurotoxicity: a prospective quantified sensory assessment study. *Pain*. 2009;144:245-252.
27. Gebremedhn EG, Shortland PJ, Mahns DA. The incidence of acute oxaliplatin-induced neuropathy and its impact on treatment in the first cycle: a systematic review. *BMC Cancer*. 2018;18:410.
28. Park SB, Goldstein D, Lin CS, Krishnan AV, Friedlander ML, Kiernan MC. Acute abnormalities of sensory nerve function associated with oxaliplatin-induced neurotoxicity. *J Clin Oncol*. 2009;27:1243-1249.
29. Velasco R, Bruna J, Briani C, et al. Early predictors of oxaliplatin-induced cumulative neuropathy in colorectal cancer patients. *J Neurol Neurosurg Psychiatry*. 2014;85:392-398.
30. Hertz DL, Dockter TJ, Satele DV, Loprinzi CL, Le-Rademacher J. Neuropathy severity at the time of oxaliplatin treatment alteration in patients with colon cancer (Alliance A151912). *Support Care Cancer*. 2021;29:7855-7863.
31. Atkinson TM, Ryan SJ, Bennett AV, et al. The association between clinician-based common terminology criteria for adverse events (CTCAE) and patient-reported outcomes (PRO): a systematic review. *Support Care Cancer*. 2016;24:3669-3676.
32. Basch E, Barbera L, Kerrigan CL, Velikova G. Implementation of patient-reported outcomes in routine medical care. *Am Soc Clin Oncol Educ Book*. 2018;38:122-134.
33. Basch E, Iasonos A, McDonough T, et al. Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study. *Lancet Oncol*. 2006;7:903-909.
34. Mamo A, Easaw J, Ibnshamsah F, et al. Retrospective analysis of the effect of CAPOX and mFOLFOX6 dose intensity on survival in colorectal patients in the adjuvant setting. *Curr Oncol*. 2016;23:171-177.