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Efficacy of Hand Cooling and Compression in Preventing Taxane-Induced Neuropathy
The POLAR Randomized Clinical Trial

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IMPORTANCE Chemotherapy-induced peripheral neuropathy (CIPN) is a common, dose-limiting adverse effect of taxane-based chemotherapies. Currently, there is no established strategy for prevention or treatment.

OBJECTIVE To compare the effectiveness of 1-sided hand cooling and compression for preventing CIPN in patients with primary breast cancer receiving taxane-based chemotherapy.

DESIGN, SETTING, AND PARTICIPANTS The POLAR randomized clinical trial was conducted at the National Center for Tumor Diseases Heidelberg between November 2019 and January 2022. Female patients with breast cancer who received weekly nab-paclitaxel–based or paclitaxel-based neoadjuvant or adjuvant chemotherapy were enrolled. Patients with prior chemotherapy, preexisting neuropathy, or neuropathy-related comorbidities were excluded.

INTERVENTIONS Patients were randomized 1:1 to cooling or compression of the dominant hand. No intervention was performed on the other hand. Cooling was performed with a frozen glove and compression was applied by 2 surgical gloves (1 size smaller than the tight-fitting size) 30 minutes before, after, and during taxane administration.

MAIN OUTCOMES AND MEASURES The primary end point was the efficacy to prevent grade 2 or higher sensory CIPN evaluated by Common Terminology Criteria for Adverse Events, version 5.0. Further CIPN assessment included the clinical version of the Total Neuropathy Score and QLQ CIPN20. CIPN rates were compared between intervention groups. Nail toxic effects, quality of life, CIPN-associated dose reductions, treatment discontinuations, and risk factors were evaluated. Follow-up examinations were performed 1 week, 1 month, and 6 to 8 months after the last taxane dose.

RESULTS A total of 122 female patients with primary breast cancer (mean [SD] age, 50 [12] years) were randomized to either cooling or compression of the dominant hand. Twenty-one individuals withdrew from the study, so 101 patients were included in the final analysis (n = 52 and n = 49 for cooling and compression, respectively). Both interventions significantly reduced the incidence of grade 2 or higher CIPN (cooling: 15 participants experiencing high-grade CIPN in the cooling arm [29%] vs 26 in the control arm [50%]; *P* = .002; effect size, 21.15% [95% CI, 5.98%-35.55%]; compression: 12 participants experiencing CIPN in the intervention arm [24%] vs 19 in the control arm [38%]; *P* = .008; effect size, 14.29% [95% CI, 2.02%-27.24%]). CIPN was the main reason for treatment discontinuations in 16 of 24 participants (67%). The predominant risk factors were the cumulative taxane dosage and the neurotoxic agent. Participants experiencing grade 2 or higher CIPN showed a reduced global health status during and 6 to 8 months after taxane therapy.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, cooling and compression were highly effective and significantly reduced the risk of high-grade CIPN.

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Visual Abstract

Supplemental content

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Breast cancer is the most common cancer worldwide. Over the past decades, the number of long-term survivors has increased due to the rising prevalence and medical progress, leading to rising incidence and falling mortality rates. With a mortality to incidence ratio of 15%, many patients survive breast cancer.[1-3]

Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting adverse effect of cytotoxic drugs, including taxanes, platinum therapies, vinca alkaloids, and eribulin which occurs in 58% to 78% of patients, and up to 30% live with long-term disability.[4]

Currently, there is no established strategy for CIPN prevention or treatment.[5,6] Therefore, CIPN often results in dose reductions, treatment delays, or discontinuations.

During the past decades, the preventive effect of topical cryotherapy has been studied for a broad spectrum of cytotoxic adverse effects, such as mucositis; alopecia; and cutaneous, ocular, and nail toxic effects.[7-11] Multiple trials have evaluated the effectiveness of preventing CIPN with various study designs, different underlying neurotoxic agents, and different methods of cryotherapy.[12-16]

The effectiveness of compression has been less studied and only 3 trials have evaluated the preventive effect of compression, with conflicting results.[17-19] Due to limited and conflicting efficacy data, neither cryotherapy nor compression therapy is currently recommended in routine clinical practice.[5,6] In this trial, we investigated and compared the effectiveness of 1-sided hand cooling or compression for the prevention of CIPN.

Key Points

Question Can hand cooling and compression prevent chemotherapy-induced peripheral neuropathy (CIPN) in patients undergoing taxane-based chemotherapy for primary breast cancer?

Findings In this randomized clinical trial of 122 female patients with primary breast cancer, hand cooling and compression significantly reduced the incidence of grade 2 or higher CIPN.

Meaning Both hand cooling and compression are highly effective in preventing sensory CIPN during taxane-based chemotherapy.

Methods

Patients and Treatment Details

In this prospective, randomized, self-controlled, single-center trial, patients undergoing weekly taxane-based chemotherapy for primary breast cancer between November 2019 and January 2022 at the National Center for Tumor Diseases Heidelberg were eligible for participation. Patients with prior chemotherapy, preexisting neuropathy, or neuropathy-related comorbidities (eg, diabetes), as well as patients taking drugs that could mask CIPN-associated symptoms (eg, serotonin-norepinephrine reuptake inhibitors), were excluded. Chemotherapy regimens followed our standard institutional protocols, including weekly solvent-based paclitaxel (starting dose, 80-90 mg/m^2, weekly or on days 1 and 8 of a 22-day cycle) or nab-paclitaxel (starting dose, 125 mg/m^2, weekly). Chemotherapy was administered via ports. During the recruitment period, the study information was made publicly available online via the National Center for Tumor Diseases Heidelberg study cockpit. Unfortunately, it only became apparent after recruitment was completed that the registration on our institutional homepage did not fully meet the required 24-item trial registration dataset standards. See Supplement 1 for the trial protocol. This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee Heidelberg. All participants provided written informed consent. We adhered to the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. Details on sample size calculation are provided in the eAppendix in Supplement 2.

Interventions

Participants were randomized 1:1 to cooling or compression of the dominant hand. No intervention was performed on the other hand, which served as an intraindividual control, or the feet. Cooling was performed using frozen gloves (Elasto-Gel [Akromed]) that were stored at −20 °C for more than 3 hours before use. Gloves were changed every 30 minutes. Participants in the compression group wore 2 latex-free surgical gloves that were 1 size smaller than the tight-fitting size on their dominant hand (eFigure 1 in Supplement 2). Interventions were performed 30 minutes before, 30 minutes after, and during taxane administration.

Clinical Assessment

The schedule of the CIPN assessment is shown in eFigure 2 in Supplement 2. CIPN was scored weekly using the Common Terminology Criteria for Adverse Events (CTCAE) criteria, version 5.0 (sensory and motor neuropathy score), and the patient self-report questionnaire European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) for patients with CIPN (CIPN20), German version, which contains 20 items. Each item was scored on a Likert scale ranging from 1 (not at all) to 4 (very much). Scores were transformed into a 0-to-100 scale, with higher scores indicating more severe complaints.[20] The clinical version of the Total Neuropathy Score (TNSc) was performed before, after half of the planned taxane therapy, and after taxane therapy, and within the follow-up visits.[21-23] Nail toxic effects were assessed by CTCAE criteria and documented by photography. Dose reductions, dose delays, treatment discontinuations, and potential risk factors (cumulative taxane dosage, body mass index [calculated as weight in kilograms divided by height in meters squared], smoking, alcohol intake, hemoglobin A_{1c} [HbA_{1c}] levels) were documented. Participants were categorized as moderate (≤5 drinks/wk or ≤12 g/d) and high alcohol intake (>5 drinks/wk or >12 g/d) and classified as nonsmokers (never smoked regularly) or smokers (history of regular smoking). Quality of life was assessed using the validated EORTC QLQ for patients with cancer (C30).[24] Follow-up examinations were performed 1 week, 1 month, and 6 to 8 months after the last taxane dose. Documentation was performed using the CANKADO online system.[25]

Table 1. Patient Characteristics and Treatment Details Stratified by Intervention

Variable	No. (%)		
	Compression (n = 61)	Cooling (n = 61)	Total (N = 122)
Age, mean (SD), y	50 (13)	49 (11)	50 (12)
Dominant hand			
Right side	59 (97)	54 (89)	113 (93)
Left side	2 (3)	7 (11)	9 (7)
BMI, mean (SD)[a]	24 (4.4)	27 (6.6)	26 (5.7)
ER status			
Positive	32 (52)	30 (49)	62 (51)
Negative	29 (48)	31 (51)	60 (49)
PgR status			
Positive	27 (44)	23 (38)	50 (41)
Negative	34 (56)	38 (62)	72 (59)
ERBB2 status			
Positive	5 (8)	3 (5)	8 (7)
Negative			
Chemotherapy			
Adjuvant	18 (30)	15 (25)	33 (27)
Neoadjuvant	43 (70)	46 (75)	89 (73)
Taxane			
Nab-paclitaxel	35 (57)	37 (61)	72 (59)
Sb-paclitaxel	21 (34)	23 (38)	44 (36)
Switch	5 (8)	1 (2)	6 (5)
No. of taxane administrations			
4-6	2 (4)	2 (4)	4 (4)
7-9	4 (9)	16 (31)	20 (20)
10-12	41 (87)	34 (65)	75 (76)
NE	14	8	22
Cumulative taxane dose, mean (SD), mg			
Nab-paclitaxel	1278 (279)	1193 (250)	1231 (264)
Paclitaxel	914 (127)	861 (173)	887 (152)
Other agents			
Carboplatin	17 (28)	20 (33)	37 (30)
Epirubicin/cyclophosphamide	51 (84)	55 (90)	106 (87)
Trastuzumab ± pertuzumab	5 (8)	3 (5)	8 (7)
Immune checkpoint inhibitor	2 (3)	6 (10)	8 (7)
Discontinuation of chemotherapy			
Any reason	10 (19)	14 (29)	24 (24)
Due to CIPN	7 (13)	9 (18)	16 (16)
Missing data, No.[b]	9	12	21
Dose reduction			
Any reason	20 (38)	20 (41)	40 (40)
Due to CIPN	8 (15)	9 (18)	17 (17)
Missing data, No.[b]	9	12	21
Dose delay			
Any reason	26 (50)	30 (61)	56 (55)
Due to CIPN	3 (6)	2 (4)	5 (5)
Missing data, No.[b]	9	12	21

Abbreviations: BMI, body mass index; CIPN, chemotherapy-induced peripheral neuropathy; ER, estrogen receptor; NE, not evaluated; PgR, progesterone receptor; Sb, solvent based.

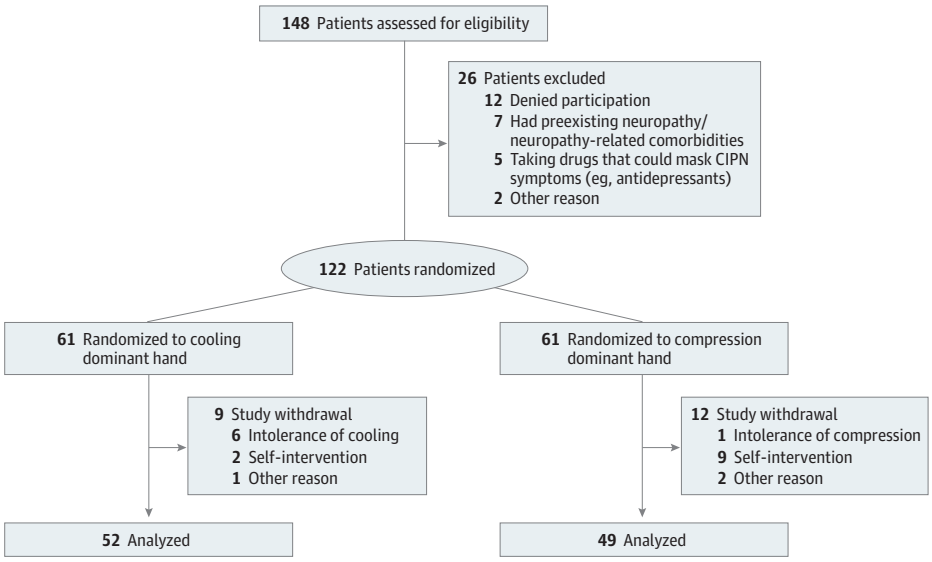
[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Missing information was due to study withdrawal (n = 21).

Statistical Analysis

The primary objective was to evaluate the efficacy of cooling and compression in preventing grade 2 or higher sensory (high-grade) CIPN during chemotherapy, as determined by CTCAE, version 5.0, using the McNemar test with effect sizes and approximate 95% CIs. Therefore, the occurrence of high-grade CIPN (yes/no) in the interventional vs the noninterventional hand was used as the primary end point. Only if the null hypothesis of the primary end point (no reduction of both rates) was rejected, it was further tested if there was a difference

Figure 1. Study Flow Diagram



A total of 122 patients were included in this randomized clinical trial. Participants were randomized 1:1 into cooling or compression of the dominant hand. There were 21 study individuals who withdrew from the study, and 101 participants were included in the efficacy analysis. CIPN indicates chemotherapy-induced peripheral neuropathy.

between the reduction for high-grade CIPN between cooling and compression by comparing the rates of 2 or higher CIPN in the intervention arm vs the control arm (hierarchical test procedure, χ^2 test). Effect estimates and ratios of empirical distributions were reported with associated 95% CIs, and other measures were reported as absolute and relative frequencies. Effect sizes denote the absolute (nonstandardized) difference between the respective subgroups. All statistical tests were 2-sided, and $P < .05$ was considered statistically significant. To assess risk factors and quality-of-life influences, participants were grouped into those who developed high-grade CIPN on any extremity at any time and those who did not. We analyzed risk factors for persistent CIPN by comparing participants with transient CIPN (grade 2 or higher, resolving to grade 1 or 0 within 1 month after therapy) to those with persistent grade 2 or higher CIPN 1 month after therapy.

Results

Patient Characteristics

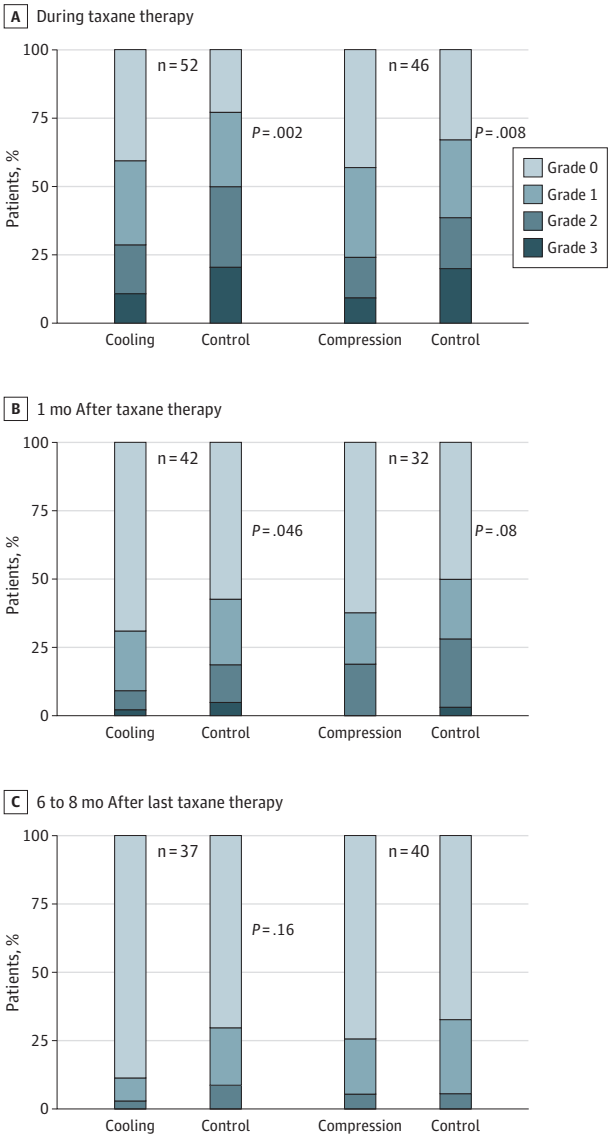
A total of 122 female patients with primary breast cancer were randomized to either cooling or compression of the dominant hand (mean [SD] age, 50 [12] years). Patient and tumor characteristics are summarized in **Table 1**. Treatment details were well balanced. Nine participants in the cooling group and 12 in the compression group withdrew from the study (**Figure 1**). The main reason for study withdrawal in the cooling group was intolerance to cooling in 6 participants. In the compression group, only 1 patient did not tolerate the intervention. Two participants in the cooling and 9 participants in the compression group discontinued to perform both-sided self-interventions. A total of 101 participants were included in the efficacy analysis. CIPN was the main reason for treatment discontinuations in 16 of 24 participants (67%) and dose reductions in 17 of 40 participants (43%) (Table 1).

Efficacy Data

Cooling almost halved the risk of developing high-grade CIPN (relative risk reduction, 42%), with only 15 participants (29%) experiencing high-grade CIPN in the cooling arm vs 26 participants (50%) in the control arm (**Figure 2**; $P = .002$; effect size, 21.15% [95% CI, 5.98%-35.55%]). In the compression group, 12 participants (24%) experiencing CIPN in the intervention arm vs 19 participants (38%) in the control arm ($P = .008$; effect size, 14.29% [95% CI, 2.02%-27.24%]; relative risk reduction, 37%). No significant differences were found between the interventional groups (effect size, −5.47% [95% CI, −34.29% to 23.36%]). Forty-six participants (46%) experienced high-grade CIPN within the legs. No difference in CIPN incidence was observed between both legs. Sensitivity analysis that accounts for missing data also revealed a significant effect of the interventions when assuming that all individuals who withdrew from the study had the same CIPN grade on both hands (ie, no effect; cooling vs control: effect size, 18.03% [95% CI, 5.08%-30.71%]; compression vs control: effect size, 11.48% [95% CI, 1.63%-22.22%]) or when taking into account the last CIPN grade that was observed before withdrawal (ie, last observed; cooling vs control: effect size, 21.31% [95% CI, 7.56%-34.37%]; compression vs control: effect size, 16.39% [95% CI, 4.87%-28.09%]). The only scenario where no significance was reached was when assuming that all individuals who withdrew from the study had high-grade CIPN on the interventional hand but not on the control hand (ie, worst case; cooling vs control: effect size, 3.28% [95% CI, −13.47% to 19.86%]; compression vs control: effect size, −8.20% [95% CI, −23.59% to 7.52%]; eTable 3 in Supplement 2).

Differences between the control and interventional hand were consistently observed when evaluating the EORTC QLQ-CIPN20 for sensory symptoms (cooling vs control: effect size, 4.90% [95% CI, 2.70%-7.11%]; compression vs control: effect size, 3.20% [95% CI, 0.09%-6.31%]) and motor symptoms (cooling vs control: effect size, 2.98% [95% CI, 0.99%-

Figure 2. Efficacy of Hand Cooling and Compression Evaluated via Common Terminology Criteria for Adverse Events (CTCAE) Criteria



Incidence of chemotherapy-induced peripheral neuropathy (CIPN) evaluated via CTCAE, version 5, criteria on the interventional and noninterventional hand was measured at different time points. A, Values measured after administration of half of the planned taxane dose (cooling vs compression: 58% vs 63%; P = .71). B, Values measured 1 month after taxane therapy (cooling vs compression: 50% vs 67%; *P* = .08). C, Values measured 6 to 8 months after the last taxane therapy (cooling vs compression: 33% vs 100%; *P* = .14). Differences were evaluated using the McNemar test.

4.97%]; compression vs control: effect size, 2.02% [95% CI, −0.25% to 4.29%]). The TNSc revealed differences between the control and interventional hand only in the compression group (effect size, 0.39% [95% CI, 0.12%-0.66%]), while no difference was seen in the cooling group (effect size, 0.10% [95% CI, −0.08% to 0.28%]). No differences in the EORTC QLQ-CIPN20 subscales and the TNSc were observed between both legs (**Table 2**).

One month after the last taxane application, differences between the intervention and control hand were observed (Figure 2). In the cooling group, high-grade CIPN was 50% lower in the interventional hand than in the control hand (4 vs 8 participants; *P* = .046; effect size, 9.52% [95% CI, −2.16% to 22.62%]). In the compression group, high-grade CIPN was 33% lower in the interventional arm (6 vs 9 participants; *P* = .08; effect size, 9.38% [95% CI, −4.91% to 25.02%]).

After 6 to 8 months, only very few participants showed persistent high-grade CIPN. In the cooling group, 3 participants had high-grade CIPN in the control hand and 1 patient in the interventional hand. In the compression group, only 2 participants showed persistent high-grade CIPN in both hands. Numbers were too small to draw valid statistical conclusions concerning the long-term efficacy (Figure 2).

Incidence of nail toxic effects is shown in eTable 1 in Supplement 2. Cooling and compression reduced the incidence of grade 2 or higher nail toxic effects on the interventional hand compared to the control hand (cooling: 6 vs 15; effect size, 17.64% [95% CI, 4.50%-30.87%; compression: 15 vs 19; effect size, 8.16% [95% CI, −1.85% to 19.60%]).

Exploratory Analysis of Risk Factors for CIPN

To identify risk factors for CIPN, participants were stratified by CIPN (high-grade vs grade 1 or 0 CIPN; eTable 2 in Supplement 2). High-grade CIPN was more common with nab-paclitaxel than solvent-based paclitaxel and the cumulative nab-paclitaxel dosage correlated with the incidence of high-grade CIPN. Overall, participants treated with nab-paclitaxel received higher taxane doses than those treated with paclitaxel (mean [SD], 1231 [264] mg vs 887 [152] mg, respectively). Participants who received carboplatin simultaneously had a lower CIPN risk. Participants treated with carboplatin and nab-paclitaxel (n = 17) received lower concomitant cumulative dosages than participants without platin (n = 39) (985 mg vs 1338 mg, respectively). Age, body mass index (BMI), HbA_{1c} levels, alcohol intake, smoking, or pathologic complete response rates were not associated with the incidence of high-grade CIPN.

Eighteen participants showed transient and 15 participants persistent high-grade CIPN 1 month after the last taxane application. No differences were observed in potential risk factors between both groups (eTable 2 in Supplement 2).

Quality-of-Life Outcomes

EORTC QLQ-C30 scores were evaluated by comparing participants with and without high-grade CIPN at any time point in at least 1 extremity during therapy (eFigure 3 in Supplement 2). Participants who later developed high-grade CIPN showed higher rates of fatigue (effect size, 12.68 [95% CI, 4.99-20.38]), reduced physical functioning (effect size, −2.37 [95% CI, −7.91 to 3.17]), more constipation (effect size, 7.95 [95% CI, −0.81 to 16.72]) and insomnia (effect size, 11.09 [95% CI, 2.34-19.83]) before taxane application. After half of the planned taxane cycles, participants with high-grade CIPN showed a worse global health status (effect size, −11.47 [95% CI, −18.96 to −3.97]), which continued to be reduced 1 week (effect size, −3.85 [95% CI, −11.89 to 4.19]), 1 month (effect size, −21.87 [95%

Table 2. Efficacy of Hand Cooling and Compression Measured by Quality-of-Life Questionnaire and Total Neuropathy Score

Outcome	Control hand, mean (SD)	Intervention hand, mean (SD)	Difference in means (95% CI)[a]	Right foot, mean (SD)	Left foot, mean (SD)	Difference in means (95% CI)[a]
Cooling group (n = 52)						
EORTC QLQ-CIPN20 sensory symptoms	15.41 (12.75)	10.51 (11.37)	4.9 (2.70 to 7.11)	17.94 (18.13)	16.33 (17.14)	1.61 (−1.90 to 5.11)
EORTC QLQ-CIPN20 motor symptoms	8.18 (14.50)	5.2 (10.77)	2.98 (0.99 to 4.97)	6.22 (12.95)	5.84 (12.80)	0.38 (−0.16 to 0.90)
TNSc	0.8 (1.83)	0.7 (1.75)	0.1 (−0.1 to 0.3)	1.02 (2.37)	1.04 (2.42)	´−0.02 (−0.11 to 0.07)
Compression group (n = 49)						
EORTC QLQ-CIPN20 sensory symptoms	15.08 (19.02)	11.88 (16.08)	3.2 (0.09 to 6.31)	17.53 (20.04)	18.34 (22.70)	´−0.81 (−3.02 to 1.60)
EORTC QLQ-CIPN20 motor symptoms	9.16 (18.40)	7.14 (16.92)	2.02 (−0.25 to 4.29)	10.59 (18.66)	10.82 (21.76)	´−0.23 (−2.81 to 2.36)
TNSc	1.2 (2.09)	0.82 (1.62)	0.38 (0.12 to 0.66)	1.65 (2.79)	1.55 (2.68)	0.1 (−0.04 to 0.25)

Abbreviations: EORTC QLQ-CIPN20, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Chemotherapy-Induced Peripheral Neuropathy; TNSc, Total Neuropathy Score.

[a] The 95% CIs for the difference in means were derived from the *t* distribution.

CI, −34.68 to −9.05]) and 6 months (effect size, −13.02 [95% CI, −22.98 to −3.06]) after the last taxane application. Additionally, participants with high-grade CIPN showed reduced physical functioning during (effect size, −7.13 [95% CI, −12.69 to −1.58]) and 1 week after therapy (effect size, −11.39 [95% CI, −18.86 to −3.93]), reduced social functioning during (effect size, −11.43 [95% CI, −21.51 to −1.36]), 1 month (effect size, −9.24 [95% CI, −19.86 to 1.39]) and 6 months after therapy (effect size, −9.32 [95% CI, −20.18 to 1.55]), and reduced role functioning during (effect size, −7.15 [95% CI, −16.01 to 1.72]), 1 week (effect size, −14.36 [95% CI, −26.01 to −2.71]) and 6 months after therapy (effect size, −8.76 [95% CI, −18.04 to 0.52]). Participants with high-grade CIPN experienced more pain (effect size, 10.76 [95% CI, 1.18-20.34]) and fatigue (effect size, 9.19 [95% CI, −0.61 to 18.98]) during therapy. Furthermore, emotional functioning was reduced 6 months after therapy (effect size, −6.17 [95% CI, −13.66 to 1.31]), and patients with high-grade CIPN experienced more nausea and vomiting at this time (effect size, 3.95 [95% CI, −0.76 to 8.66]).

Discussion

In this randomized clinical trial, high-grade CIPN was observed in up to 50% of participants, and nearly 1 in 5 women discontinued chemotherapy due to CIPN.[4,20] Cooling and compression were highly effective and almost halved the risk of high-grade CIPN. Participants treated with nab-paclitaxel showed a higher risk, likely due to higher cumulative taxane dosages or different solvents (Cremophor EL vs solvent free). Current data indicate a higher risk in patients who are older, African American, diabetic, or have prior subclinical polyneuropathy.[26-28] There is controversial data regarding smoking and alcohol intake.[29,30] We observed no differences in age, BMI, HbA_{1c} levels, alcohol intake, or smoking between participants developing high-grade CIPN and those who did not. Interestingly, there is evidence that age affects duration more than severity.[31] A more pronounced numerical difference in age and HbA_{1c} levels was observed when evaluating risk factors for persistent CIPN; however, numbers were small, and differences were not statistically significant.

Few participants experienced persistent high-grade CIPN after 6 to 8 months. Currently, no risk factors reliably predict transient vs persistent CIPN. Investigating these factors and the distinct pathophysiological characteristics is crucial in developing effective prevention strategies for patients with long-term symptoms.

Participants with high-grade CIPN showed a worse global health status during therapy that continued to be reduced 6 to 8 months after the last taxane application despite only 6.5% still showing high-grade CIPN at this time point. This suggests that the long-term disability due to CIPN is underestimated by CTCAE criteria.

One of the main problems when comparing results from clinical trials is the lack of uniformity in CIPN assessment.[32,33] We decided to assess CIPN using CTCAE criteria, the TNSc as well as EORTC QLQ-CIPN20 because good interobserver and intraobserver reliability has been described for the TNSc and CTCAE subscales, and test-retest values were high for the EORTC QLQ-CIPN20.[32]

As the clinical assessment of CIPN is inevitably linked to patients' subjective perceptions, we opted for a unilateral, self-controlled approach. We cannot definitively rule out that this influenced the observed results. In clinical practice, peripheral neuropathy is mostly equal bilaterally. However, there might be a bias because our intervention was not blinded to participants or health professionals, the self-controlled design can reduce the effects of unknown potential confounders. This could be a decisive advantage, especially because possible clinical and genetic risk factors, are still poorly understood. The differing CIPN rates between the control arms (50% vs 38%), further support this approach.

Twenty-one participants (17%) withdrew from the study, mainly because they wanted to perform self-intervention on both hands. We performed a sensitivity analysis to account for missing data. The only scenario where no significance was reached was when assuming that all individuals who withdrew from the study had high-grade CIPN on the interventional hand only. As this effect was only observed temporar-

ily in 1 patient in our trial, we assume that this scenario can be ruled out.

Limitations

This study has several limitations. Patients with preexisting neuropathy, neuropathy-related comorbidities, and patients taking antidepressant drugs were excluded from this trial, which limits generalizability. Furthermore, we cannot definitively rule out that our unilateral, self-controlled approach influenced the observed results. In clinical practice, peripheral neuropathy is mostly equal bilaterally. However, there might be a bias because our intervention was not blinded to participants or health professionals.

The POLAR trial was unintentionally registered late on ClinicalTrials.gov. Late registration occurred without any intention to bias the reporting, and study design, inclusion criteria, exclusion criteria, end points, and sample size adhered strictly to the trial protocol (Supplement 1), which was approved beforehand by the Ethics Committee Heidelberg.

Conclusions

POLAR is the first randomized clinical trial, to our knowledge, comparing the efficacy of cooling and compression for CIPN prevention. Both methods nearly halved the risk of high-grade sensory CIPN. Compression, being accessible, cost-effective, and well tolerated, could have an important role in clinical practice. These findings may enhance the tolerability of taxane therapies beyond gynecological oncology.

ARTICLE INFORMATION

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Author Contributions: Dr Michel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Michel and Schwarz: equal contribution.
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