

The Impact of Peripheral Cooling on Chemotherapy-Induced Peripheral Neuropathy: An Integrative Review

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a prevalent, potentially long-lasting side effect of select chemotherapies. It contributes to suboptimal chemotherapy dosing, and its symptoms negatively impact patients' quality of life. To date, interventions to effectively prevent this toxicity have not been established, and interventions to treat CIPN have produced only modest results. The purpose of this integrative review is to examine the impact of regional cooling applied to distal extremities on the severity of CIPN. A literature review was performed using SCOPUS and PubMed databases. The search was not restricted by date but was restricted to English language. Forty-two articles were identified in the search, and six were included in the review after applying inclusion and exclusion criteria. Results related to protective effects from peripheral cooling against CIPN were variable. Four out of six studies demonstrated benefit of peripheral cooling in reducing the severity of CIPN. There was evidence to suggest that applying a relatively greater degree of cooling compared with a lesser degree may confer benefit in reducing the severity of CIPN. Both direct application of cooling and use of compression to achieve fingertip cooling showed potential benefit.

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and potentially physically and emotionally distressing side effect of select chemotherapeutic agents including platinum-based drugs and taxanes (Bakitas, 2007; Shah et al., 2018). Estimates of CIPN incidence and prevalence vary, ranging from 29% to 68%, depending on time point of assessment, neurotoxic drug administered, and other factors (Pereira et al., 2016; Seretny et al., 2014; Shah et al., 2018). The mechanism of nerve injury is thought to differ among neurotoxic drugs, although the shared, predominant type of injury is sensory and may be associated with significant pain,

burning, numbness, and deficits in proprioception (Miltenburg & Boogerd, 2014; Shah et al., 2018). Symptoms typically occur in the hands and feet in a “stocking and glove” distribution pattern (Bhatnagar et al., 2014).

Chemotherapy-induced peripheral neuropathy may be associated with decreased quality of life, reduced functional abilities, and may prevent patients from returning to work (Miltenburg & Boogerd, 2014; Mols, Beijers, Vreugdenhil, & van de Poll-Franse, 2014; Tofthagen, 2010; Zanville et al., 2016). Functional limitations of CIPN relate to hand pain, hand numbness affecting fine motor skills, and foot pain and numbness, which may cause difficulty walking (Bhatnagar et al., 2014; Zanville et al., 2016). Symptoms and severity of CIPN are also associated with an increased risk of falls (Tofthagen, Overcash, & Kip, 2012). Symptoms of CIPN contribute to feelings of depression and loss of purpose when patients lose the ability to engage in activities they enjoy (Tofthagen, 2010). The duration of CIPN symptoms ranges from months to years following treatment and may be permanent (Miltenburg & Boogerd, 2014).

Chemotherapy-induced peripheral neuropathy may result in reduced, suboptimal chemotherapy dosing, discontinuation of the causative agent, or delays in treatment that may decrease the efficacy of treatment (Bhatnagar et al., 2014; Speck et al., 2013). Dose reductions or limitations including delays due to CIPN are estimated to occur in 10% to 24.5% of breast cancer patients receiving taxane therapy (Bhatnagar et al., 2014; Speck et al., 2013). Bhatnagar and colleagues reported that CIPN-related dose reductions are more common in African American patients and patients with diabetes (Bhatnagar et al., 2014).

To date, there have been no proven interventions to prevent CIPN, and options to treat CIPN are limited, with qualified or moderate levels of recommendation (Cavaletti & Marmiroli, 2010; Hershman, Lacchetti, & Loprinzi, 2014). Recent studies have explored the benefits of applying cooling, or cryotherapy, to distal extremities to prevent CIPN. It is theorized that the application of cooling protects against side effects of chemotherapy by reducing drug distribution at the cooled area through vasoconstriction, thus decreasing cellular uptake, and by decreasing biochemical activity

in target tissues (Bandla et al., 2016; Sundar et al., 2016; Trüeb, 2009). This relatively new strategy offers a potentially promising option for the prevention of CIPN. However, a consolidated review of findings from studies on this topic has not yet been published. The goal of this integrative review is to examine current evidence regarding the impact of peripheral cooling on the severity of CIPN.

METHODS

A literature review was performed using SCOPUS and PubMed databases. The search was not restricted by date but was restricted to the English language. Databases were searched using a combination of keywords and MeSH terms, including cooling, cryotherapy, hypothermia, cancer, oncology, and neuropathy. Bibliographies were also searched for relevant articles. A total of 42 articles were produced in the searches, four of which were duplicates. Six articles were included in the review after applying inclusion and exclusion criteria. Inclusion criteria were use of peripheral cooling concurrent with peripherally neurotoxic chemotherapy, measurement of peripheral neuropathy as an outcome, randomized control trials, nonrandomized control trials, self-controlled trials, historically controlled trials, and publication in a peer-reviewed journal. Articles were excluded if they were case studies, abstracts only, or editorials (see Figure 1 describing the flow of the literature search).

RESULTS

Sample Characteristics

Subjects in five out of six studies were undergoing treatment for breast cancer (Eckhoff, Knoop, Jensen, Ejlertsen, & Ewertz, 2013; Griffiths, Kwon, Beaumont, & Paice, 2018; Hanai et al., 2018; Sundar et al., 2016; Tsuyuki et al., 2016). Subjects in one study were undergoing treatment for gynecologic cancer (Sato et al., 2016). Patients in five of the studies ranged in age from 23 to 84 years (Eckhoff et al., 2013; Griffiths et al., 2018; Sato et al., 2016; Sundar et al., 2016; Tsuyuki et al., 2016). Only the mean age of 56 was provided for the sixth study (Hanai et al., 2018). Inclusion and exclusion criteria varied as related to staging criteria, features of disease, treatment history, and comorbidities. Peripherally neurotoxic agents received by these patients included paclitaxel, albumin-bound

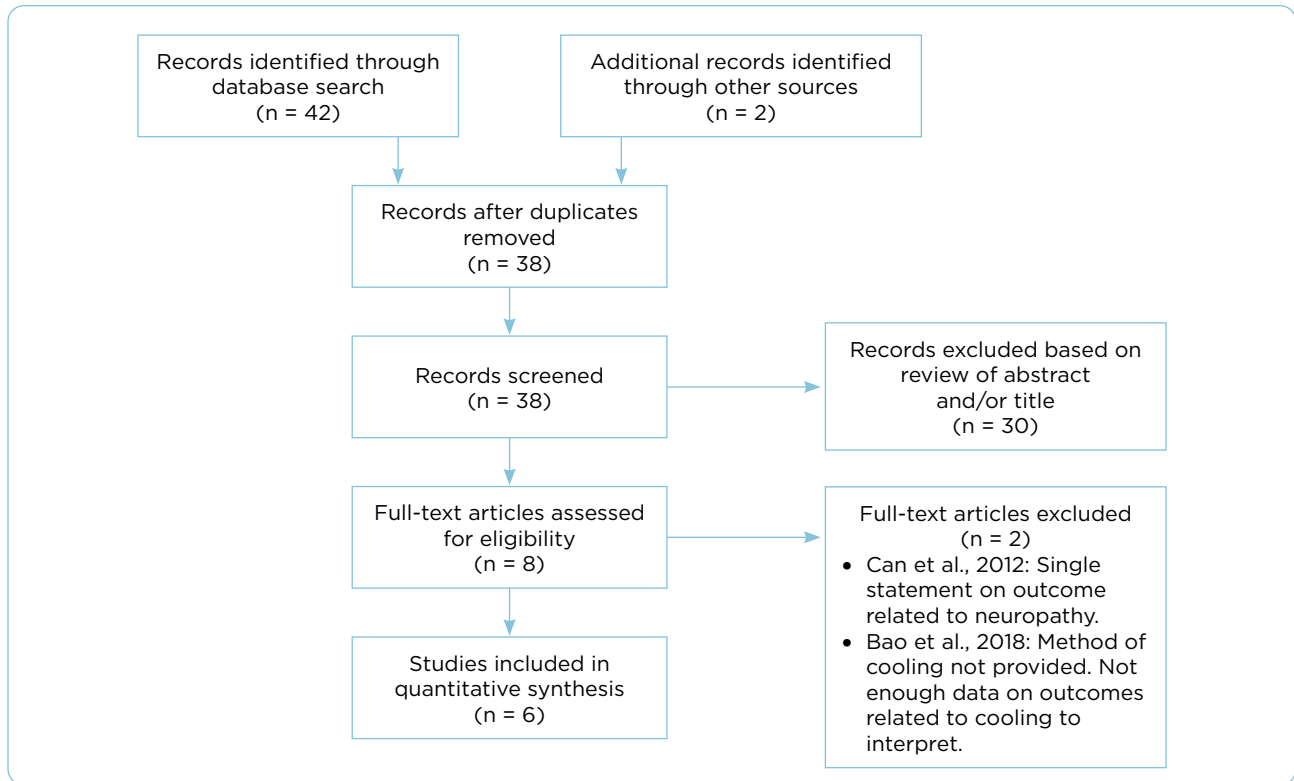


Figure 1. Flow diagram of literature search. Adapted from Moher, Liberati, Tetzlaff, & Altman (2009).

paclitaxel, docetaxel, and platinum-based drugs, and were administered alone, in combination with other agents on this list, or with other nonperipherally neurotoxic chemotherapy agents (see summary of the included studies in Table 1).

Impact of Regional Cooling on Severity of CIPN

The results will be discussed by categories of degree of cooling and method of cooling (see Table 2 for a summary of results categorized by the degree of cooling and method of cooling). Degree of cooling refers to the temperature change applied or achieved in each study, where a greater degree of cooling describes “colder” temperatures applied or achieved and a lesser degree of cooling describes “less cold” temperatures applied or achieved. The method of cooling refers to whether direct application of a cooling device or the use of compression was used in the study to achieve a decrease in temperature at the intervention site.

Degree of Cooling

For the purpose of this review, studies were categorized as providing a relatively greater degree

of cooling or a relatively lesser degree of cooling. This categorization of studies as providing a relatively greater or lesser degree of cooling was determined based on a wide gap that existed between applied or achieved cooling temperatures within the studies. A relatively greater degree of cooling is defined in this review to be between -20°C and -30°C of applied cooling temperature and was used in four studies (Eckhoff et al., 2013; Griffiths et al. 2018; Hanai et al., 2018; H. Ishiguro, personal communication, November 21, 2018; Sato et al., 2016). A relatively lesser degree of cooling was used in two studies and is defined here as either an applied cooling temperature of $\geq 22^{\circ}\text{C}$, used in one of the lesser degree of cooling studies, or achieving a $\leq 2.2^{\circ}\text{C}$ decrease in skin temperature, used in the second lesser degree of cooling study reviewed here (Sundar et al., 2016; Tsuyuki et al., 2016; see Table 1 for degree of cooling applied or achieved).

Greater Degree of Cooling

Three out of four studies that applied a relatively greater degree of cooling as defined in this review demonstrated statistically significant benefits in

Table 1. Overview of Results from Studies on Regional Cooling and Chemotherapy-Induced Peripheral Neuropathy

Initial author (year)	Study objectives	Study design and sample size	Duration of cooling	Method and degree of cooling	Outcome measures and time points	Results regarding CIPN severity	Study limitations
Eckhoff (2013)	Comparison of dose reduction resulting from CIPN in two chemotherapy regimens	Randomized, prospective phase III trial N = 1,725 686 subjects used cooling intervention	90 min (15 min prior to and after treatment, 60 min during treatment)	Frozen socks and gloves Gloves/socks stored at -20°F, changed at 45 min	National Cancer Institute's Common Toxicity Criteria, version 2.0, translated into Danish, including sensory neuropathy symptoms Responses recorded at baseline and on day 20 after each cycle for cycles 1-6	Odds ratio of ≥ grade 2 peripheral neuropathy reduced if patients wore frozen socks and gloves during treatment following chemotherapy 1 (odds ratio: 0.56; 95% CI = 0.38-0.81, <i>p</i> < .002) Similar benefit after subsequent chemo cycles (odds ratio: 0.59; 95% CI = 0.46-0.76, <i>p</i> < .0001), although analysis of impact of preexisting peripheral neuropathy not performed in statistics for late peripheral neuropathy group	Study was not designed to evaluate impact of cooling on neuropathy. Use of frozen socks and gloves was elective; not randomized.
Griffiths (2018)	Assess efficacy of cryotherapy in the prevention of paclitaxel-induced peripheral neuropathy	Randomized control study Randomization to dominant vs. non-dominant side N = 29	3 hours 30 min, including 15 min prior to and post treatment	Elasto-Gel glove/sock to one side cooled to -25°C to -30°C, changed every 45-50 min	Neuropathic Pain Symptom Inventory and Brief Pain Inventory; quantitative sensory testing including monofilament test, vibratory test with tuning fork, manual dexterity testing, and Neurophen test for pinprick sensitivity Measurements at baseline, 2 weeks post treatment completion, and at first, fifth, ninth, and final weekly paclitaxel treatments	No significant difference in Neuropathic Pain Symptom Inventory scores for symptoms in hands (<i>p</i> > .15) or feet (<i>p</i> > .30); no significant difference in quantitative sensory testing results (<i>p</i> > .15); and pain severity using the Brief Pain Inventory was increased for all measures across time	Small sample size with high dropout rate (29 down to 7) in part due to discomfort with intervention
Hanai (2018)	Evaluate efficacy of cryotherapy to prevent CIPN	Prospective self-controlled trial N = 36	90 min (15 min prior to and after treatment, 60 min during treatment)	Elasto-Gel gloves and socks on dominant side, changed at 45 min	Monofilament test, thermosensory testing, vibratory test with tuning fork, Patient Neurotoxicity Questionnaire, grooved pegboard test (Lafayette Instrument Company) for manipulative dexterity, conduction velocity and action potential amplitude of median nerve using Neuropack X1, and current perception thresholds on hands and feet using Neurometer CPT	Occurrence of Patient Neurotoxicity Questionnaire grades D or E peripheral neuropathy reduced with intervention (hand: 2.8% vs. 41.7%, <i>p</i> < .001; foot: 2.8 vs. 36.1%, <i>p</i> < .001) Decreased impairment on intervention side: hand tactile sensitivity (27.8% vs. 80.6%, <i>p</i> < .001), foot tactile sensitivity (25.0% vs 63.9%, <i>p</i> < .001), hand warm sense (8.8% vs. 32.4%, <i>p</i> = .02), foot warm sense (33.4% vs. 57.6%, <i>p</i> = .04), and manipulative dexterity (<i>p</i> = .005)	Small sample size

Note. CIPN = chemotherapy-induced peripheral neuropathy; CTCAE = Common Terminology Criteria for Adverse Events.

Table 1. Overview of Results from Studies on Regional Cooling and Chemotherapy-Induced Peripheral Neuropathy (cont.)

Initial author (year)	Study objectives	Study design and sample size	Duration of cooling	Method and degree of cooling	Outcome measures and time points	Results regarding CIPN severity	Study limitations
Hanai (2018; cont.)				Cooled to -25°C to -30°C (H. Ishiguro, personal communication, November 21, 2018)	Symptoms assessed at baseline and before every cycle of paclitaxel administration during outpatient care	No statistically significant preservation of hand or foot cold sense; vibration perception, electrophysiological measurements	
Sato (2016)	Investigate efficacy of peripheral cooling in preventing paclitaxel-induced peripheral neuropathy	Historical controlled cohort N = 40, controls = 142	3 hours	Elasto-Gel gloves/socks Cooled to -30°C and changed hourly	Evaluation by physician or pharmacist using CTCAE version 4.0 Evaluation before the start of each cycle and 3 weeks after the last chemotherapy in the regional cooling group. Retrospective data from historical cohort provided data from comparable time points	Reduced incidence of ≥ grade 2 peripheral neuropathy in the intervention group (5.0%-9.1%) vs. the control group (22.5%-35.8%); $p < .05$ at the fourth cycle and $p < .01$ after the fifth cycle	Historical control cohort study design weakens the strength of study findings
Sundar (2016)	Determine whether limb hypothermia is protective against paclitaxel-induced peripheral neuropathy and assess safety and tolerability	Prospective, internally controlled pilot trial Intervention randomized to one side at lower leg and foot N = 20	1 hour prior to infusion, 30 min post infusion, no longer than 4 hours total	Continuous flow hypothermia to one lower leg and foot, 22°C coolant temperature	Motor and sensory nerve conduction studies Assessed at baseline, and after 1, 3, and 6 months	Correlation between motor nerve amplitude preservation at 6 months and degree of skin cooling achieved, which demonstrated statistical significance ($p < .0005$) Improved preservation of sensory nerve action potential amplitude in the sural nerve. Did not achieve statistical significance ($p = .16$) Difference in sensory nerve velocity did not demonstrate statistical significance (.09 < $p < .89$) Compound motor action potential amplitudes of motor nerves more preserved at 3 months post treatment. Did not achieve statistical significance. Extensor digitorum brevis compound motor action potential amplitudes more preserved on intervention side below fibula head ($p = .07$) and above fibula head ($p = .10$).	Small sample size Although clinical exams for neuropathy and total neuropathy scores were performed, comparisons between intervention and control side not included in evaluation

Note. CIPN = chemotherapy-induced peripheral neuropathy; CTCAE = Common Terminology Criteria for Adverse Events.


 Table continued on following page

Table 1. Overview of Results from Studies on Regional Cooling and Chemotherapy-Induced Peripheral Neuropathy (cont.)

Initial author (year)	Study objectives	Study design and sample size	Duration of cooling	Method and degree of cooling	Outcome measures and time points	Results regarding CIPN severity	Study limitations
Tsuyuki (2016)	Evaluate efficacy of compression with surgical gloves to prevent nanoparticle albumin-bound paclitaxel-associated peripheral neuropathy	Prospective self-controlled clinical trial N = 42	90 min (30 min prior to and post infusion, 30 min during infusion)	Compression with two surgical gloves sized one-size too small worn on the dominant hand Gloves decreased temperature of fingertips by 1.6–2.2°C	CTCAE version 4.0 and Patient Neurotoxicity Questionnaire Baseline, before each treatment cycle, and 1 week after nab-paclitaxel was administered	CTCAE results: Decrease in the incidence of ≥ grade 2 peripheral neuropathy in the intervention side ($p < .0001$). The occurrence of ≥ grade 2 sensory neurotoxicity decreased from 76.1% to 21.4%, and that of motor neurotoxicity decreased from 57.1% to 26.2% Patient Neurotoxicity Questionnaire results: significantly lower grades of peripheral neuropathy in the intervention side ($p < .0001$)	Not randomized No objective measurements Small sample size

Note. CIPN = chemotherapy-induced peripheral neuropathy; CTCAE = Common Terminology Criteria for Adverse Events.

Table 2. Impact of Degree and Method of Cooling on Chemotherapy-Induced Peripheral Neuropathy Severity

	Eckhoff (2013)	Griffiths (2018)	Hanai (2018)	Sato (2016)	Sundar (2016)	Tsuyuki (2016)
Degree of cooling						
Colder	++	--	++	++		
Less cold					+/-	++
Method of cooling						
Direct cold	++	--	++	++	+/-	
Compression						++

Note. ++ = statistically significant improvement in CIPN severity; -- = no statistically significant improvement; +/- = mixed results regarding statistically significant improvement; colder = between -20°C and -30°C applied cooling temperature; less cold = $\geq 22^\circ\text{C}$ applied cooling temperature or $\leq 2.2^\circ\text{C}$ drop in skin temperature.

reducing the severity of peripheral neuropathy (Eckhoff et al., 2013; Hanai et al., 2018; Sato et al., 2016). Eckhoff and colleagues (2013) conducted a randomized, prospective, phase III trial of 1,725 Danish breast cancer patients to evaluate CIPN in patients receiving two docetaxel-based chemotherapy regimens. Patients received either three cycles of epirubicin and cyclophosphamide followed by three cycles of docetaxel or six cycles of docetaxel and cyclophosphamide. Subjects were offered the option of using cooled socks and gloves worn on hands and feet during infusions to prevent potential nail toxicity (Eckhoff et al., 2013). Outcomes were measured using the National Cancer Institute's Common Toxicity Criteria translated into Danish, with responses recorded at baseline and on day 20 after each cycle for cycles one through six (Eckhoff et al., 2013). Although not among the primary aims of the study, researchers reported finding incidentally a reduced odds ratio (OR) of \geq grade 2 peripheral neuropathy in patients who wore frozen socks and gloves during treatment following chemotherapy cycle one (OR: 0.56; 95% confidence interval [CI] = 0.38–0.81, $p < .002$). A similar benefit was reported after subsequent chemotherapy cycles (OR: 0.59; 95% CI = 0.46–0.76, $p < .0001$), although analysis of the impact of preexisting peripheral neuropathy was not calculated in the late peripheral neuropathy group (Eckhoff et al., 2013).

The study by Hanai and colleagues (2018) examined the use of a relatively greater degree of cooling using cooled socks and gloves worn on the dominant hand and foot in a prospective, self-controlled trial of 36 breast cancer patients receiving weekly paclitaxel for at least twelve cycles. Out-

comes were measured using a monofilament test, thermosensory testing, vibratory sense testing, the Patient Neuropathy Questionnaire (PNQ), electrophysiological evaluation, and objective evaluation of dexterity (Hanai et al., 2018). Symptoms were assessed at baseline and before every cycle of paclitaxel administration during outpatient care. Results related to CIPN severity included reduced occurrence of grades D or E peripheral neuropathy according to the PNQ on the intervention side (hand: 2.8% vs. 41.7%, $p < .001$; foot: 2.8 vs. 36.1%, $p < .001$). In addition to results related to CIPN severity, this study also reported beneficial results of the intervention related to CIPN incidence, including decreased impairments in hand tactile sensitivity (27.8% vs. 80.6%, $p < .001$), foot tactile sensitivity (25.0% vs. 63.9%, $p < .001$), hand warm sense (8.8% vs. 32.4%, $p = .02$), foot warm sense (33.4% vs. 57.6%, $p = .04$), and manipulative dexterity ($p = .005$). There was no statistically significant reduction in the incidence of impairments in hand or foot cold sense, vibration perception, or electrophysiological measurements (Hanai et al., 2018).

Sato and colleagues (2016) conducted a historically controlled cohort study of 40 subjects compared with 142 historical controls undergoing treatment for gynecologic cancers. Subjects received every-3-week paclitaxel and platinum therapy with carboplatin or cisplatin. Researchers applied a relatively greater degree of cooling through the use of cooled socks and gloves and measured outcomes using the Common Terminology Criteria for Adverse Events (CTCAE) administered by a physician or pharmacist (Sato et al., 2016). Symptoms were recorded before the start of each cycle and 3 weeks after the last che-

motherapy in the regional cooling group. Peripheral neuropathy symptom data from the historical control group were available at comparable time points. The authors reported a significantly lower incidence of \geq grade 2 peripheral neuropathy in the intervention group (5.0%–9.1%) vs. the control group (22.5%–35.8%), with $p < .05$, at the fourth cycle and $p < .01$ after the fifth cycle.

One study in the greater degree of cooling category did not demonstrate a protective effect against CIPN (Griffiths et al., 2018). This self-controlled study included 29 breast cancer patients receiving anthracycline plus paclitaxel. Subjects were provided cooled socks and gloves randomized to be worn on the dominant vs. nondominant hand and foot. Outcomes were measured using the Neuropathic Pain Symptom Inventory (NPSI), the Brief Pain Inventory (BPI), and Quantitative Sensory Testing (QST) and were recorded at baseline, 2 weeks post treatment completion, and at first, fifth, ninth, and final weekly paclitaxel treatments (Griffiths et al., 2018). Researchers demonstrated no significant difference in NPSI scores for symptoms in hands ($p > .15$) or feet ($p > .30$), no significant difference in QST results ($p > .15$), and reported that pain severity using the BPI was increased for all measures across time (Griffiths et al., 2018).

Lesser Degree of Cooling

One of the two studies that applied a relatively lesser amount of cooling as defined in this review achieved statistically significant benefits in the severity of peripheral neuropathy (Tsuyuki et al., 2016). This prospective, self-controlled study included 42 breast cancer patients who received compression therapy with two surgical gloves sized one size too small worn on the dominant hand, which resulted in a decrease in fingertip temperature on the intervention side. Subjects received nab-paclitaxel every 3 weeks for four cycles. Outcomes were measured using the CTCAE and the PNQ and were recorded at baseline, before each treatment cycle, and 1 week after nab-paclitaxel was administered. CTCAE results demonstrated a decrease in the incidence of \geq grade 2 peripheral neuropathy on the intervention side ($p < .0001$). The occurrence of \geq grade 2 sensory neurotoxicity decreased from 76.1% to

21.4%, and that of motor neurotoxicity decreased from 57.1% to 26.2%. Patient Neuropathy Questionnaire results demonstrated significantly lower grades of peripheral neuropathy on the intervention side ($p < .0001$).

The study by Sundar and colleagues (2016) also involved a lesser degree of cooling and reported mixed results in terms of protective benefit, with the majority of their findings not achieving statistically significant benefit. The researchers examined the impact of continuous flow hypothermia applied to the lower leg and foot, randomized to one side, in an internally controlled prospective pilot trial of 20 breast cancer patients receiving weekly paclitaxel for twelve cycles. Cooling was achieved using a thermoregulator device to supply water cooled to 22°C to a limb-cooling wrap applied at the lower leg and foot. Outcomes were measured with motor and sensory nerve conduction studies and were assessed at baseline and after 1, 3, and 6 months (Sundar et al., 2016). The researchers observed a correlation between motor nerve amplitude preservation at 6 months and degree of skin cooling achieved, which demonstrated statistical significance ($p < .0005$). Researchers also reported improved preservation of sensory nerve action potential amplitude in the sural nerve on the intervention side; however, this relationship did not achieve statistical significance ($p = .16$). Difference in sensory nerve velocity between the limbs also did not demonstrate statistical significance ($0.09 < p < 0.89$). The compound motor action potential (cMAP) amplitudes of motor nerves were more preserved on the intervention side at 3 months post-treatment evaluation; however, these results also did not achieve statistical significance (extensor digitorum brevis cMAP amplitudes more preserved on intervention side below fibula head [$p = .07$] and above fibula head [$p = .10$]).

Method of Cooling

Results of studies in this review were also categorized by the method of cooling they employed, either using direct-cooling or compression. Five out of the six included studies provided direct application of cooling, using either precooled gloves and socks or a limb-cooling wrap with continuously flowing cooled water supplied to the wrap (Eckhoff et al., 2013; Griffiths et al., 2018; Hanai et

al., 2018; Sato et al., 2016; Sundar et al., 2016). A single study used compression with tightly fitting surgical gloves, which achieved fingertip cooling (Tsuyuki et al., 2016). Of note, the use of compression, while not a direct method of cooling, was considered in this review to be an indirect method of cooling given the resulting decrease in fingertip temperature documented within the study. Details of the method applied in each study are described in Table 1.

Direct Cooling

Three out of five studies that used direct cooling demonstrated statistically significant benefit in the severity of peripheral neuropathy (Eckhoff et al., 2013; Hanai et al., 2018; Sato et al., 2016). One direct cooling study reported mixed results in terms of protective benefits with mostly nonsignificant findings related to benefit (Sundar et al., 2016). The final direct cooling study demonstrated no protective benefit in the prevention of peripheral neuropathy (Griffiths et al., 2018). Detailed descriptions and results of these studies are outlined above in the section titled “degree of cooling” in Table 1.

Compression

The one study in this review that achieved fingertip cooling by compression with surgical gloves demonstrated statistically significant benefits in the severity of peripheral neuropathy on the intervention side (Tsuyuki et al., 2016). A detailed description of this study and its results are outlined in the section titled “degree of cooling” in Table 1.

DISCUSSION

Impact of Degree of Cooling on Severity of CIPN

By evaluating the findings of the studies reviewed here within categories of “colder” and “less cold,” the evidence presented in these studies suggests that applying a relatively greater degree of regional cooling compared with a lesser degree may confer benefit in reducing the severity of CIPN. It should be noted that the majority of studies reviewed (four out of six) used relatively greater degrees of cooling, which limits comparison and moderates the strength of this finding. Three out of the four studies within the relatively greater

degree of cooling category demonstrated a protective benefit against CIPN (Eckhoff et al., 2013; Hanai et al., 2018; Sato et al., 2016). The fourth study in the “colder” category demonstrated no protective benefit, although it experienced a substantial dropout rate of over 75%, which left only seven subjects in the final analysis (Griffiths et al., 2018). The significant dropout rate and small final number of subjects in the Griffiths and colleagues study precluded adequate power, by their own analysis, to evaluate the effectiveness of the cooling intervention (2018). Their results should be considered accordingly. Another factor that may have contributed to the different results reported in the Griffiths study compared to other studies in the “colder” category is the difference in outcome measurement tools. Of the studies reviewed here, only the Griffiths study used the BPI, NPSI, and QST tools to measure outcomes; however, the battery of quantitative tests performed in the Hanai and colleagues (2018) study appears similar to the QST.

The two studies in the “less cold” category were essentially split in their findings which, when compared to the findings in the “colder” studies, could suggest less protection against CIPN associated with a lesser amount of cooling; however, additional data from future studies is needed to confirm this conclusion. Within the “less cold” category, the Sundar et al. (2016) study showed limited statistically significant benefit in nerve conduction study outcomes with the administration of continuous flow hypothermia; however, this study is limited due to its small sample size and therefore has limited power. The Tsuyuki and colleagues (2016) study reported more compelling benefit from the use of compression with surgical gloves, which also achieved a relatively lesser degree of cooling. Congruent with the hypothesis that less cold may confer less benefit, the singular finding of benefit that achieved statistical significance in the study by Sundar and colleagues (2016) was the correlation between the amount of skin cooling achieved and motor nerve amplitude preservation at 6 months ($p < .0005$), where greater degrees of skin cooling provided greater benefit. The potentially increased protective effects of “colder” peripheral cooling temperatures suggested in studies reviewed here are consistent

with the increased protective effects associated with lower temperatures of cold caps in the prevention of chemotherapy-induced alopecia (Komen, Smorenburg, van den Hurk, & Nortier, 2013).

Impact of Method of Cooling on Severity of CIPN

Three out of five studies that used direct application of cooling demonstrated statistically significant benefits in reducing the severity of CIPN (Eckhoff et al., 2013; Hanai et al., 2018; Sato et al., 2016). The Sundar and colleagues (2016) study applied direct cooling, although they did not demonstrate a similarly robust benefit, which may be explained by the lesser degree of cooling used in the study or the small sample size and limited power of the study. The Griffiths and colleagues (2018) study also applied direct cooling and did not demonstrate statistically significant benefits, although findings were limited by the significant dropout rate (Griffiths et al., 2018). Additionally, the difference in the findings by Griffiths and colleagues (2018) compared with findings in the studies by Eckhoff and colleagues (2013), Hanai and colleagues (2018), and Sato and colleagues (2016) may be attributable to the different outcome measurement tools used in the Griffiths and colleagues study.

The single study in this review that achieved fingertip cooling by compression with surgical gloves demonstrated statistically significant benefits with the intervention (Tsuyuki et al., 2016). It should be noted that it is uncertain to what degree the observed benefit in this study is attributed to a decrease in circulation at target tissues compared with a resulting decrease in temperature. Additional studies are needed to further assess the validity of the findings in the Tsuyuki study and to discern benefit from compression compared with direct cooling. Fingertip cooling by compression offers a promising area for further study given its low cost, ease of application, and seemingly good tolerability.

Given the limiting factors described here, including variable applied cooling temperature, significant patient dropout in the Griffiths and colleagues study, and having only one study that used compression to achieve cooling, it is difficult to draw conclusions about the effectiveness of direct

cooling compared with compression. However, the results do suggest that both methods are potentially of benefit and should be further explored.

Limitations of the Review

The limitations of this review include the small number of available studies on the topic, the small sample size in five of the six studies, variations in cooling methods, and inconsistent design of controls. Variations in patient characteristics, drug regimens used, and outcome measures are also significant limitations. No two studies used the same profile of measurement tool(s), although the CT-CAE was used in two studies as was the PNQ (Hanai et al., 2018; Sato et al., 2016; Tsuyuki et al., 2016). However, other differences in methods among those studies preclude a stronger comparison of their outcomes. Also of note, only two studies collected both objective and subjective measurements of peripheral neuropathy symptoms, and the combination of measurement tools used in these studies was variable (Griffiths et al., 2018; Hanai et al., 2018). The difference in drug regimens used within the studies is of particular concern since the mechanism of nerve injury is theorized to differ between peripherally neurotoxic chemotherapies (Shah et al., 2018). This is further confounded by the fact that the mechanism of potential benefit of cooling in preventing CIPN is not completely understood (Bandla et al., 2016). The studies reviewed here also differed in their drug dosing, drug combinations, administration schedules, and infusion durations. Due to these variations, the impact of regional cooling controlling for drug regimens could not be undertaken here. An additional limitation is this review's use of "colder" compared with "less cold" categories in interpreting findings. While a practical approach to discerning the impact of different cooling methods, it creates a limitation as there are not sufficient data available currently within the literature to populate a continuum of colder to less cold categories and the associated findings.

Limitations Regarding Duration of Cooling

All studies reviewed applied cooling throughout the neurotoxic agent infusion. The infusion time varied among the studies. All but one of the studies also mentioned applying cooling for some period of time before and after the infusion, rang-

ing from 15 to 60 minutes (Eckhoff et al., 2013; Griffiths et al., 2018; Hanai et al., 2018; Sundar et al., 2016; Tsuyuki et al., 2016). The total cooling time ranged from 1.5 to 4 hours. Differences in the duration of cooling, including differences in pre- and post-infusion cooling, may have influenced results in these studies; however, this potential influence was not evaluated here due to confounding variables outlined above in this section.

Dropout Due to Intervention Intolerance

Of the studies reviewed here, only the Griffiths and colleagues (2018) study described intolerance of the cooling intervention as a significant factor or limitation. In this study, which began with 29 subjects and ended with seven, 10 out of 22 patients who dropped out did so due to the inability to tolerate the cold socks and gloves. Notably, subjects in the study by Griffiths and colleagues (2018) were required to wear the cooled stockings and gloves for the longest period of time of the four studies in the “colder” category in this review (30 minutes longer than the study by Sato and colleagues [2016] and 2 hours longer than the studies by Eckhoff and colleagues [2013] and Hanai and colleagues [2018]). The study by Sato and colleagues (2016) described one patient out of 63 who elected to discontinue regional cooling due to cold-related discomfort. The study by Hanai and colleagues (2018) mentioned that no patients dropped out due to cold intolerance.

Tolerability and Safety Compared With Other Studies

The true level of tolerability of peripheral cooling has not been determined, and the range of tolerability reported in the studies reviewed here is in keeping with the range of tolerability reported in other studies that used cooling to prevent dermatologic toxicities. A 2016 safety and tolerability pilot study of 15 subjects receiving continuous flow hypothermia to distal extremities reported tolerability with coolant temperatures as low as 22°C (Bandla et al., 2016). Four out of six studies included in this review applied cooling far colder than the tolerable limit recommended in the Bandla study (Eckhoff et al., 2013; Griffiths et al., 2018; Hanai et al., 2018; Sato et al., 2016), with only one of the studies, by Griffiths and colleagues (2018), reporting significant cold

intolerance. Two studies conducted by Scotte and colleagues evaluated the impact of frozen socks and gloves on docetaxel-induced nail toxicities using cooling temperatures of -25°C to -30°C (Scotte et al., 2005; Scotte et al., 2008). These studies reported cold intolerance in 11% of subjects (Scotte et al., 2005) and 2% of subjects (Scotte et al., 2008). None of the six studies included in this integrative review reported serious adverse events associated with the cooling intervention. Of note, the 2018 systematic review that examined the use of cooling to prevent chemotherapy-induced dermatologic toxicities reported a single case of frostbite within the eight studies reviewed that used frozen socks or gloves (Marks et al., 2018).

An additional consideration regarding safety is that according to some experts, warm compresses should be used to manage potential or actual extravasation near the injection site of select chemotherapies (de Lemos & Walisser, 2005; Pérez Fidalgo et al., 2012). This consideration is discussed further in the next section on implications for practice and further study.

IMPLICATIONS FOR PRACTICE AND FURTHER STUDY

Implications for practice based on this review include providing patients with current data on the risk and benefit profile of peripheral cooling to protect against CIPN. Patients are entitled to understand available options that may reduce their risk of adverse events with peripherally neurotoxic chemotherapy agents. Patients may be counseled that there are limited data on using regional cooling to reduce the severity of CIPN. Advanced practitioners may advise patients that to date, more studies have examined the benefits of applying greater degrees of cooling using cooled socks and gloves than other methods that apply less cooling, and that perhaps as a result, there is more evidence to suggest that applying a relatively greater degree of cooling using the same method may provide more benefit compared with less cooling. It should be emphasized that using a greater degree of cooling poses a small but serious risk of frostbite and may be associated with intervention-related discomfort. Patients may also be advised that a single, small study suggests protective benefits against CIPN through the use of com-

pression with surgical gloves and that patients in this study did not experience significant intolerance or adverse events (Tsuyuki et al., 2016).

At this time, there is insufficient evidence for or against the use of peripheral cooling to prevent CIPN. Larger, randomized controlled trials are needed to better understand the impact of peripheral cooling on CIPN. Future studies should evaluate the impact of different amounts and methods of cooling, including compression and direct cooling in isolation and combined. They should control for the potentially different impact cooling may have on CIPN in the setting of different chemotherapy drug regimens. Future studies should also consider recommendations from some experts to apply warm compresses to manage extravasation near infusion sites with select chemotherapies and evaluate whether recommendations should be made regarding placement of infusion sites away from areas of cooling (de Lemos & Walisser, 2005; Pérez Fidalgo et al., 2012). The results of several trials currently underway involving compression and cooling therapy as they impact peripheral neuropathy and nail toxicity should be evaluated for implications and study design considerations. Finally, as considered in the use of scalp cooling to prevent chemotherapy-induced alopecia, future studies should consider whether peripheral cooling would increase the risk of metastases at cooled tissue sites (Christodoulou, Tsakalos, Galani, & Skarlos, 2006).

CONCLUSIONS

Evidence of protective effects of peripheral cooling against CIPN is variable. Applying a relatively greater degree of regional cooling compared with a lesser amount may confer benefit in reducing the severity of CIPN. Both direct application of cooling and use of compression to achieve fingertip cooling show potential benefit in reducing CIPN severity. ●

Disclosure

The authors have no conflicts of interest to disclose.

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