Innovative approach for the prevention of chemotherapy-induced peripheral neuropathy (CIPN) in cancer patients: A pilot study with the Hilotherm® device, the Poliambulanza Hospital experience.

Ester Oneda[1]*, Fausto Meriggi[1], Laura Zanotti[2], Elisabetta Zaina[3], Sara Bighè[3], Federica Andreis[4], Sabogal Rueda[4], Alberto Zaniboni[1]

[1] Medical Doctor, Department of Clinical Oncology, Fondazione Poliambulanza, Brescia, Italy

[2] Data Manager, Department of Clinical Oncology, Fondazione Poliambulanza, Brescia, Italy

[3] Nurse, Department of Clinical Oncology, Fondazione Poliambulanza, Brescia, Italy

[4] Psychologist, Department of Clinical Oncology, Fondazione Poliambulanza, Brescia, Italy

*Corresponding Author: Ester Oneda, MD, Department of Clinical Oncology, Fondazione Poliambulanza Bissolati street 57, Brescia, Italy, 25124. Tel: 0303515557 E-mail: dott.ester.oneda@gmail.com

Running title: Hiloterm for prevention of chemotherapy-induced peripheral neuropathy (CIPN) in cancer patients

ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is an adverse event of taxanes, with no effective prevention or treatment available and a highly negative impact on patient quality of life (QoL). The aim of this study is to asses that the constant application of cooled cuffs on the hands and feet prevent and mitigate CIPN.

Methods

Background

Patients with breast, gynecologic and pancreatic cancer who received weekly paclitaxel (PTX), PTX/carboplatin and nab-paclitaxel (nab-PTX)/gemcitabine for any indication at the therapeutic scheduled dosage were included in this prospective study. Hilotherm® Chemo care device forms a closed-loop system with cuffs and tubes through which a coolant flows at a temperature of 10°C (fig. 1). CIPN was monitored using European organization for research and treatment of cancer quality of life questionnaire (EORTC QLQ-C30; edition 3.0), and the tolerability and side effects were scored by using the common terminology criteria for adverse events (CTCAE; T4.03 2017).

Results

To date, we have enrolled 64 patients. Of these, 54 (84%) completed all cooling cycles. Continuous cooling was well tolerated by all patients. No patients had grade > 2 CIPN or had serious or lasting AEs as a result of Hilotherapy. The median time to CIPN onset was 77 days for the entire population.

Conclusion

Hilotherapy have good effectiveness and tolerability, and seems to be able to prevent or reduce the symptoms of CIPN. We are still recruiting patients to obtain more data and to collect data at 3 months after the end of chemotherapy. Prospective studies seem to be warranted.

Keywords: chemotherapy-induced peripheral neuropathy, paclitaxel, neuroprotection, cooling device, Hilotherm®.

INTRODUCTION

Background

Peripheral neuropathy (PN) is a disease or injury that leads to peripheral nerve dysfunction or damage, and it is frequently related to chemotherapy treatment, with a

prevalence from 19% to over 85% [1]. In recent years, cancer treatments have improved survival but also led to many adverse events (AEs) that have worsened the quality of life (QoL) of cancer patients. Chemotherapy drugs aim to arrest cancer progression by eliminating rapidly dividing cancer cells, but their targets and mechanisms of action unfortunately affect normal cells and body structures, causing different side effects, such as anemia, diarrhea, nausea, vomiting, infections, neurological changes, fatigue, hair loss, infertility, pain and PN [2]. Due to these AEs, sometimes it is necessary to stop the treatment or reduce the drugs dosage, which limits the efficacy of cancer treatment. Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most serious side effects and has also become one of the biggest concerns of chemotherapy treatments [3, 4].

Different classes of drugs affect the nervous system in various way, depending on their physical and chemical properties and if they are administered in single or cumulative doses [3]. For example, platinum-based drugs could induce CIPN in 70–100% of patients, taxanes in 11–87% of patients, and thalidomide and its analogues in 20–60% of patients [3]. The intensity, duration and range of the symptoms vary from acute transient thermal sensations, to permanent changes in peripheral nerves accompanied by chronic pain and irreversible nerve damage [4].

CIPN manifests as sensory peripheral neuropathy (SPN) and peripheral motor neuropathy (MPN) [5]. The sensory symptoms generally involve the feet and hands first, presenting as a "glove and stocking" neuropathy with major deficits in the most distal parts of the limbs. The symptoms comprise numbness, tingling, hypoesthesia, altered proprioception, loss of toe and finger dexterity, paresthesias and dysesthesias. Moreover, painful sensations, including spontaneous burning, shooting or electric shock-like pain as well as mechanical or thermal allodynia or hyperalgesia, frequently occur [5-8]. In severe cases, these symptoms can progress to a complete loss of sensory perception. Motor symptoms may present as distal weakness, gait and balance disturbances, and impaired movements. These symptoms strongly interferers with the QoL of patients; for example, these symptoms cause significant problems with everyday activities, such as fastening shirt buttons or opening a bottle, as well as walking or driving [9, 10]. CIPN has implications for health-related QoL [9, 11, 12] and has different and pervasive psychological consequences [13]. In fact,

the presence of chronic pain or distress can significantly increase the risk of depression [14], so the management of CIPN, even with nonpharmacological approaches, improves QoL and promotes mental health for patients [14-19]. In our study we enrolled patients who received taxane-based chemotherapy regimens. The prevalence of CIPN induced by taxanes was approximately 84% after just one or two cycles and up to 97% after completion of therapy [6], 68.1% one month after the end of chemotherapy, 60.0% 3 months after, and 30.0% 6 months after. Taxanes-induced CIPN is predominantly an SPN that is rarely accompanied by motor and autonomic changes [4]. The symptoms may start days after the first dose and are dose dependent but tend to improve after stopping the treatment. Unfortunately, there is substantial interindividual variability in the prevalence, severity, and onset during the chemotherapy course; no specific signs of CIPN suggest a dose reduction, and none of the indications warrant a mitigation of the symptoms when they arise. Moreover, pain and sensory abnormalities may persist for months or even years after the cessation of chemotherapy and can sometimes last for the patient's entire life [7]. Different studies have tried to identify predisposing risk factors of CIPN, such as older age, cooccurrence of neuropathy (e.g., diabetic neuropathy), smoking history, impaired renal function, exposure to other neurotoxic chemotherapeutic agents, paraneoplastic antibodies and cumulative dose of chemotherapeutic agents [20-25]. The only certain risk factor is the dose administered, with increases in risk proportional to the cumulative dose. In studies with patients treated for breast cancer, grade 3 or 4 SPN occurred in 20–35% of patients receiving 250 mg/m^2 of paclitaxel every 3 weeks and in 5–12% of patients using doses < 200 mg/m^2 every 3 weeks [26]. Weekly paclitaxel (PTX) is less myelosuppressive than an every 3-week schedule [27], but in some reports, a weekly schedule is associated with worse neurotoxicity [28, 29]. Nab-paclitaxel (Nab-PTX) is a nanoparticle albumin-bound form of PTX that was originally formulated to enable lower doses and reduce toxicity, but peripheral neuropathy still remains a significant treatment-limiting adverse event. A phase III randomized trial showed a higher rate of grade 3 sensory neuropathy (10% versus 2%) with nab-PTX 260 mg/m^2 every three weeks than with standard paclitaxel 175 mg/m^2 every three weeks [30]. The incidence of SPN may be similar between nab-PTX and docetaxel. In a systematic review of eight studies, the incidence of taxane-acute pain syndrome with nab-PTX use ranged from 13 to 43%

(median 26%), as given in the metastatic disease setting as well as the adjuvant and neoadjuvant settings [31]. The incidence of CIPN with unbound paclitaxel ranged from 0.9 to 86% (median 13%), and that for docetaxel, ranged from 3.6 to 70% (median 10.5%) [30, 31].

To prevent, treat or alleviate CIPN symptoms without limiting the potentially life-saving chemotherapy dosage, a number of drugs have been tested, but none of them are currently used. Antidepressants (such as nortriptyline), duloxetine, gabapentin, and a compounded topical gel containing baclofen, amitriptyline, ketamine, lidocaine, tramadol, tapentadol, buprenorphine and lithium have been tested [32-41]. These agents had a record of efficacy for other common neuropathic pain conditions, but CIPN has a different pathologic origin. The America Society of Clinical Oncology (ASCO) does not recommend any agent for the prevention of CIPN [32]. A number of nonpharmacologic interventions, such as acupuncture, limb hypothermia, surgical glove compression and electrocutaneous nerve stimulation, have also been investigated. However, the paucity of randomized controlled trial evidence prohibited the inclusion of those studies in this systematic review. Moreover, the studies were often conducted in diabetic populations, with no specific focus on CIPN [32].

Objectives

Considering the enormity of this problem, we tested a constant application of cooling cuffs on the hands and feet to reduce the amount of drugs in the capillaries of the extremities, and to prevent or mitigate CIPN in cancer patients treated with taxane regimens.

PATIENTS AND METHODS

Study design

This was a single-center retrospective single-arm study that included patients with breast, gynaecological and pancreatic cancer. The enrolled patients wore cuffs and tubes on their hands and feet with a coolant temperature of 10°C, that worked via the Hilotherm®

Chemo care device (Hilotherm GmbH, Argenbühl-Eisenharz). The aim of the study was to assess the efficacy and safety of Hilotherapy for the prevention of CIPN and its impact on long-term residual CIPN. The primary endpoint was the overall incidence of grade 2 or higher PTX/nab-PTX-induced SPN in patients who used Hilotherapy, as evaluated by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The incidence of PTX/nab-PTX-induced PN in published literature was used as the control group. The secondary endpoints included the incidence of withdrawal from Hilotherapy due to cold intolerance, and the impact of CIPN on patient QoL. The ethics committee of the participating institution approved the study protocol (approval number 4034, date 21 April 2020).

Patients

The study population comprised breast, gynaecological and pancreatic cancer patients scheduled to receive neoadjuvant, adjuvant or palliative taxane-based chemotherapy during the period from April 2019 to November 2019. The inclusion criteria were as follows: age range, 20-80 years and ECOG performance status, 0-2; the exclusion criteria were as follows: no chemotherapy cycle carried out, disease progression before the start of treatment, need to change hospital to continue treatment. The patients with other pathologies that may give peripheral neuropathy have not been excluded.

Interventions

The patients were treated with different intravenous chemotherapy schedules: weekly PTX (80 mg/m^2) for 12 cycles following standard anthracycline-based chemotherapy for breast cancer; 3-week PTX (175-225 mg/m^2) plus carboplatin for 6 cycles for gynaecological cancer and weekly nab-PTX (125 mg/m^2) plus gemcitabine (on days 1,8, and 15 of each 28- days) for a maximum of 6 cycles for pancreatic cancer. During every cycle of chemotherapy, premedication drugs (corticosteroids, H1- antagonist/H2-antagonist, and antiemetics) were administered 30 minutes prior to PTX infusion. A total

of 80 mg/m^2 PTX per week was administered as a 1- hour infusion; 175-225 mg/m^2 of PTX was administered in 3- hour infusion followed by carboplatin; 125 mg/m^2 nab-PTX was administered over a 30-40minute cycle followed by gemcitabine (infused over 30-40 minutes).

Regional cooling method

Regional cooling was performed using a regional hands and feet cooling system, which works with the Hilotherm® and forms a closed-loop system with cuffs and tubes, through which a coolant flows at a temperature of 10°C (figure 1). The insulators were fitted on both hands and feet for 30 minutes before and 60 minutes after PTX/nab-PTX administration.

Outcomes

Patient safety,Quality of Life and tolerance to cooling were measured using three validated scales: a visual analog scale (VAS) for pain, subjective tolerance scale and symptom questionnaire (EORTC QLQ-C30; edition 3.0). The severity of PN was evaluated by a nurse using the CTCAE (Table 4.03, 2017). The patients were assessed before each treatment cycle, and on day 90 after the completion of treatment. It is too early to evaluate the whole sample for CIPN at 6 months.

Statistical methods

The background information of the patients such as age, sex and risk factors were presented as counts (percentages). The incidence of PN per cycle according to CTCAE v.4.0, reasons for early Hilotherapy discontinuation and chemotherapy (PTX) dose changes during Hilotherapy treatment are shown as counts (percentages). Statistical analyses were performed using STATA 13.0 (StataCorp LP, Collage Station, TX, USA).

RESULTS

Sixty-four consecutive cancer patients were enrolled in the study. The patient characteristics and risk factors are reported in Table 1. All patients were women (100%): 42 (65.6%) patients had breast cancer, 20 (31.3%) patients had gynaecological cancer, and 2 (3.1%) patients had pancreatic cancer. The mean age was 57 years (Interquantile

range (IQR)=19.25): 1 patient had previously received cisplatin-based treatment, and no patients had received taxanes. Of these 64 patients, 54 (84%) completed all cycles of cooling with the hands and feet system.

Table 1 Patients characteristics (n = 64)

Characteristics	**No. (%)**
Age mean (IQR)	57 (19.25)
Breast cancer	42 (65.6)
Gynecologic cancer	20 (31.3)
Pancreatic cancer	2 (3.1)
Sex	
Female	64 (100)
Male	0 (0)
Risk factors	
None	60 (93.8)
Diabetes	3 (4.7)
Arthrosis	1 (1.5)

IQR= interquartile range

Safety and tolerability

Continuous cooling was well tolerated by all patients. Premature Hilotherapy termination was necessary in 10 (23.8%) patients treated with PTX because of: excessive coldness - 1 patient (2.4%); grade 2 paronychia of the fingernails and grade 1 CIPN - 2 patients (4.8%), toxicity related to PTX administration – 2 patients (4.8%), dysgeusia and asthenia - 1 patient (2.4%), hospitalization - 3 patients (7.1%) and disease progression - 1 patient (2.4%). In this group, 1 patient refused Hilotherapy. Among the 20 patients treated with the combination of PTX/carboplatin, 5 patients (25%) stopped Hilotherm because of: excessive coldness - 1 patient (5%); PTX infusional reactions - 1 patient (5%), haematological toxicities – 1 patient (5%), and disease progression - 2 patients (10%). Three patients treated with the combination of PTX/carboplatin refused Hilotherapy. All data are shown in Table 2.

Table 2 Reasons for early Hilotherapy discontinuation

Early Hilotherapy discontinuation	Breast cancer (n = 42)	Gynecologic cancer (n = 20)
Excessive coldness	1 (2.4)	1 (5)
Fingernails paronychia	2 (4.8)	0 (0)
PTX infusional reactions	2 (4.8)	1 (5)
Hematological toxicity	0 (0)	1 (5)
Dysgeusia and asthenia	1 (2.4)	0 (0)
Hospitalization/ Surgery	3 (7.1)	0 (0)
Disease progression	1 (2.4)	2 (10)
Patient refusal (not included in the analysis)	1	3

No patient had grade > 2 CIPN. Table 3 reports the incidence of PN evaluated according to CTCAE v. 4.0 at the end of each cooling session for each treatment group. Minimal discomfort was reported at the end of each cooling session. No serious or lasting AEs as a result of Hilotherapy were encountered. In addition, no dermatological AEs related to its use were observed.

Table 3 Peripheral neuropathy (PN) per cycle in each treatment groups according to CTCAE v. 4.0

Peripheral neuropathy (PN) CTCAE v. 4.0	**Breast cancer (n = 42)**	**Gynecologic cancer (n = 20)**	**Pancreatic cancer (n = 2)**
Cycle 1 n (%)			
Grade 0	42 (100)	20 (100)	2 (100)
Grade1	0 (0)	0 (0)	0 (0)

Cycle 2 n (%)			
Grade 0	41 (97.6)	20 (100)	2 (100)
Grade1	0 (0)	0 (0)	0 (0)
Treatment discontinuation	1 (2.4)	0 (0)	0 (0)
Cycle 3 n (%)	N=41		
Grade 0	40 (97.6)	18 (90)	2 (100)
Grade1	1 (2.4)	1 (5)	0 (0)
Treatment discontinuation	0 (0)	1 (5)	0 (0)
Cycle 4 n (%)		N=19	
Grade 0	37 (90.2)	13 (68.4)	2 (100)
Grade1	2 (4.9)	1 (5.3)	0 (0)
Treatment discontinuation	2 (4.9)	5 (26.3)	0 (0)
Cycle 5 n (%)	N=39	N=14	
Grade 0	37 (94.9)	7 (50)	1 (50)
Grade1	2 (5.1)	1 (7.1)	0 (0)
Treatment discontinuation	0 (0)	6 (42.9)	1 (50)
Cycle 6 n (%)		N=8	
Grade 0	35 (89.8)	6 (75)	1 (100)
Grade1	2 (5.1)	1 (12.5)	0 (0)
Treatment discontinuation	2 (5.1)	1 (12.5)	0 (0)
Cycle 7 n (%)	N=37		
Grade 0	35 (94.6)		
Grade1	2 (5.4)		
Treatment discontinuation	0 (0)		
Cycle 8 n (%)			
Grade 0	27 (73)		
Grade1	10 (27)		
Treatment discontinuation	0 (0)		
Cycle 9 n (%)			
Grade 0	24 (64.9)		
Grade 1	9 (24.3)		
Grade 2	1 (2.7)		
Treatment discontinuation	3 (8.1)		
Cycle 10 n (%)	N=34		
Grade 0	21 (61.8)		
Grade 1	11 (32.4)		

Grade 2 Treatment discontinuation	2 (5.8) 0 (0)		
Cycle 11 n (%) Grade 0 Grade1 Grade 2 Treatment discontinuation	 14 (41.2) 14 (41.2) 1 (2.9) 5 (14.7)		
Cycle 12 n (%) Grade 0 Grade1 Treatment discontinuation	N=29 11 (37.9) 11 (37.9) 7 (24.2)		
Scheduled cycles	12	6	6
Cycles completed, mean (range)	10 (1 -12)	4 (2 – 6)	5 (4 - 6)

CTCAE, Common Terminology Criteria for Adverse Event

The median time of CIPN onset was 77 days for the entire population: 77 and 89 days in breast and gynaecological cancer patients, respectively. During treatment, it was observed that few patients required a PTX dose reduction due to the following reasons: haematological toxicity; 1 (= 2.4%) patient in the breast cancer group and 3 (= 15%) patients in the gynaecological group; PTX toxicity; 1 (= 2.4%) patient in the breast cancer group and 2 (=10%) patients in the gynaecological group; infection; 1 (= 2.4%) patient with breast cancer; and disease progression; 1 (= 5%) patient in the gynaecological group and 1 (= 50%) patient with pancreatic cancer (Table 4).

Table 4 Chemotherapy (paclitaxel) dose changes during Hilotherapy treatment

Dosage	**Breast cancer (Paclitaxel alone)*** **Pts 41**	**Gynecologic cancer (Carboplatin/ paclitaxel) ** **Pts 20**	**Pancreatic cancer (Nab-paclitaxel/ gemcitabine)*** **Pts 2**
Scheduled paclitaxel, n (%)	38 (92.8)	14 (70)	1 (50)

Paclitaxel dose reduction, n(%)	3 (7.2)	6 (30)	1 (50)
Reason for paclitaxel reduction/discontinuation	1(2.4) haematological toxicity 1 (2.4) paclitaxel toxicity 1 (2.4) infection	3 (15) hematological toxicity 2 (10) paclitaxel toxicity 1 (5) progressive disease	1 (50) progressive disease

* weekly for 12 cycles

** 3-week carboplatin + paclitaxel for 6 cycles

*** weekly nab-paclitaxel + gemcitabine for 8 cycles

DISCUSSION

CIPN is a valid problem regarding patient QoL during or after the completion of chemotherapy. With taxane regimes CIPN occurs very frequently. Tanabe et al. [42] identified 219 breast cancer patients who received PTX as adjuvant chemotherapy. CIPN developed in 212 (97%) patients, and the median time to neuropathy onset was 21 days for the entire patient population: 35 days for a weekly administration and 21 days every 3-week administration. CIPN caused PTX treatment to be terminated in 7 patients (4%). The median duration of CIPN was 727 days, and the symptoms persisted in 64% of the patients after 1 year from the start of PTX and the 41% of them manifested these symptoms also after 3 years [42].

According to the guidelines of the American Society of Clinical Oncology (ASCO) 2014 [32], no established prophylaxis therapies for CIPN are suggested except for duloxetine, but this drug has limited efficacy in the reduction of chemotherapy induced neuropathic pain and no effect on numbness or functional disability.

Many antidepressants, anticonvulsants, topical gels and other substances did not show any benefit in prevention and treatment of CIPN, so an increased interest arose over complementary approaches that could control the symptoms in a mechanical way. One

positive study recently reported the use of ganglioside-monosialic acid (GM). This ganglioside, which previously showed an ability to reduce in the severity of oxaliplatin-induced neurotoxicity in patients with gastrointestinal cancers [43], was also tested in patients with breast cancer treated with PTX. Compared to those who used placebo, patients who used of GM showed a lower incidence of peripheral neurotoxicity grade 1 or higher in the CTCAE v4.0 scale (14.3% vs 100.0%, P <0.001) both as sensory neuropathy (26, 4% vs 97.8%, P <0.001) and as a motor neuropathy (20.9% vs 81.5%, P <0.001) [44].

Regarding the use of the mechanical system to prevent the onset of CIPN, a phase IIA single-arm clinical trial, tested the use of weekly acupuncture in breast cancer patients who developed CIPN > grade 2 after receiving neoadjuvant/adjuvant weekly PTX. Acupuncture was associated with low rates of grade 3 CIPN and the stabilization of CIPN symptoms [45].

Clinical studies [46-51] have reported the effect of transcutaneous electrical nerve stimulation (scrambler therapy) on relieving symptoms related to CIPN. The results showed significant reduction in CIPN symptoms (53% reduction in pain, 44% reduction in tingling and a 37% reduction in numbness [47]) and a long-term effect that was maintained at each follow-up at 5 weeks [47], 10 weeks [48], and 3 months [50]. Recently, a study is still recruiting breast cancer patients with CIPN after chemotherapy who are randomized to receive, in addition to duloxetine or pregabalin, low-frequency electrostimulation generated by a wristband or a "placebo" bracelet [52].

Tsuyuki et al. investigated, in a phase 2 study, the efficacy of using surgical glove (SG) compression therapy for nab-PTX-induced peripheral neuropathy [53]. Surgical glove compression reduced microvascular flow to the fingertips and it significantly reduced the overall incidence of grade 2 or higher nab-PTX-induced CIPN. The patients wore a surgical glove one size smaller than the size that fit their dominant hand, for only 90 min; the other hand was used as a control. The incidence of grade 2 or higher CIPN was lowered from 76.1% to 21.4% compared with the control hand. With that result Tsuyuki et al. performed another prospective single-arm study [54], with early primary breast cancer

patients, but this time, patients wore SGs on both hands. The study showed that the overall incidence of grade 2 or higher sensory CIPN, according to CTCAE, with SG compression therapy was low at 13.8%, and the rate was significantly lower than that of the control group in the prior study (44.1%), with a complete absence of grade 3 CIPN over time [54].

Another way to reduce microvascular perfusion is using cold temperature, which is called "therapeutic regional hypothermia" or "cryotherapy"[55, 56]. Various limb cooling modalities have been used, most of which involve the direct application of ice or frozen gloves and cause rapid cooling gradients with varied and often poor tolerability [57]. Large cooling gradients permit only intermittent coolant application and are limited by significant intolerance and sometimes frostbite [58, 59]. The use of frozen gloves and socks was shown to prevent docetaxel-induced nail and skin toxicity; the control arm was the nonprotected side [60, 61]. The discomfort due to cold intolerance made 11% of patients drop out of Scotte et al.'s study [60]. In a retrospective study, the incidence of docetaxel-induced PN was lower in the patients who used frozen gloves and socks than in patients who did not wear them (35% vs. 57%) [61].

Breast cancer patients court treated with weekly PTX tested the use of frozen flexible gloves and socks. The patients wore gloves and socks on the dominant hand and foot starting 15 minutes before to 15 minutes after the paclitaxel infusion (90 minutes in total), and the nondominant side acted as a control. The frozen gloves were replaced after the first 45 minutes. The incidence of CIPN signs was clinically and significantly lower on the intervention side than on the control side (hand tactile sensitivity 27.8% vs 80.6%, foot tactile sensitivity 25.0% vs 63.9%) [62]. A small study, in the same setting of patients, randomized 29 women to wear cooled gloves/socks on either dominant or non-dominant hand/foot. In this study, the dropout rate was high, due to cryotherapy discomfort, in fact only seven participants (4%) completed the treatment and the postchemotherapy sensory tests [63]. Similarly, the use of cryotherapy by cooling the patients' hands and feet with crushed ice during PTX administration was investigated. Cryotherapy was well tolerated, but the CIPN sensory scores over 12 weeks of PTX were not found to differ between the study arms (mean difference 3.45, 95% CI -3.13 to 10.02, P = 0.26). However, the control arm of the current trial experienced less neuropathy than the placebo arms of previous

similar trials [64]. Even a study that compared cryotherapy, using a frozen glove, and compression therapy, using a surgical glove, to prevent nab-PTX-induced PN, did not find a difference of outcomes with either the systems used [65]. Instead, the study by Rosenbaek et al. [66] demonstrated that the prophylactic use of cryotherapy for PTX treatment to treat early-stage breast cancer in the adjuvant setting had the potential to reduce the risk of a dose-limiting toxicity due to CIPN and increase the proportion of patients who can receive the planned chemotherapy dose (77% of patients).

Compression therapy and cryotherapy share an analogous mechanism of reduced drug exposure due to vasoconstriction during PTX infusion. The low temperature associated with cryotherapy may also reduce the uptake of PTX, damage to neurons or mechanic transductions, which might be related to reduced CIPN symptom [60]. However, the limits of frozen glove use are the preparation of frozen gloves, which is time consuming and costly (the frozen gloves need to be dried overnight or longer in a special freezer), the cold intolerance and the cold-related injuries.

A small study investigated the neuroprotective effect of continuous-flow limb hypothermia, at a coolant temperature of 22°C, in 20 breast cancer patients who received weekly PTX and showed that the CIPN was grade 3 in two patients (10%), grade 2 in two patients (10%), grade 1 in 12 patients (60%), and grade 0 in four patients (20%) [67].

All the results are presented in Table 5.

Table 5 Non-pharmacologic interventions for CIPN prevention/treatment

Non-pharmacologic intervention	**Type of pts**	**Chemotherapy regimen**	**Results**
Acupuncture [45]	Breast cancer	Weekly PTX	28/104 treated patients (27%) developed grade 2 CIPN; 27 patients received acupuncture, 26 completed paclitaxel treatment without developing grade 3 CIPN [45]

Electrocutaneous nerve stimulation [47]	Patients who suffer from various pain syndromes (CIPN, benign low back pain, or postherpetic neuralgia)	Weekly PTX	53% reduction in pain, 44% reduction in tingling and a 37% reduction in numbness [47]
Surgical glove compression [53, 54]	Breast cancer	Weekly nab-PTX	CIPN grade ≥2 (%) after treatment *vs* that in a control group from the literature 13.8 *vs* 44.1 [54] CIPN grade ≥2 (%) after treatment *vs* that of a control on their contralateral side 21.4 *vs* 76.1 [53]
Frozen gloves and socks hypothermia [61, 63]	Breast cancer	Weekly PTX 3-week docetaxel	CIPN grade ≥2 (%) after treatment *vs* that of a control on the contralateral side 27.8 *vs* 80.6 (hand) 25.0 *vs* 63.9 (foot) [63] CIPN grade ≥2 (%) after treatment *vs* that in a control group 35.0 *vs* 57.0 [61]
Continuous-flow limb hypothermia [67]	Breast cancer	Weekly PTX	Grade 3 (10%), grade 2 (10%), grade 1 (60%), and grade 0 (20%) CIPN [67]
Hilotherapy	Breast, gynecologic,	Weekly PTX/ 3-week PTX plus carboplatin/	CIPN grade ≥2 (%) after treatment 6.25% Completed treatment 46.9%

	pancreatic cancer	weekly nab-PTX plus gemcitabine	Dose reduction 15.6%

PTX= paclitaxel; CIPN= chemotherapy-induced peripheral neuropathy

In our study we investigated the effects of cooling the hands and feet for the prevention and symptomatic relief of CIPN. Our study shows that continuous cooling using a coolant temperature of 10°C that lasted the duration of chemotherapy is well tolerated and safe. Our results show good tolerability (Table 3) and, importantly, few early terminations of the cooling protocol (Table 2). In contrast to those of ice or frozen gloves, the advantages of continuous cooling are the controlled manner and more tolerable temperature reduction for the duration of chemotherapy infusion with better outcomes. There is not a placebo effect (related to the use of the control side hand and foot as a comparator) that could make difference in the expected results. The patient-reported outcomes are all standard, reproducible, and valid. Moreover, the development of additional CIPN signs could be revealed only with a long-term follow-up so we followed the patients in order to show the effects of Hilotherapy on preventing late CIPN signs and symptoms. The study limitations are: single-arm trial without a direct comparator, a comparison between patients with and without intervention could check the difference in CIPN incidence and physiological response to treatment; patients come from a single centre, it would be interesting to check whether the same incidence of CIPN is also reported in other centres to check the accuracy of the cooling procedure, for this reason we believe the data from the German centre[68] will be very useful for a future comparison. We used a group of patients not homogeneous for pathology and treatment to widen the sample, an extension of the study could favour a better analysis of subgroup by pathology, stage and treatment; obviously the number of analysed patients today represents a limit, which we hope to overcome with an extension of the enrolment. Moreover, the premature termination of hiloterm before the end of the treatment, although it occurred in a few cases, cannot be neglected; it is necessary to analyse what the individual factors or related chemotherapy factors predisposing to a failure of the method may be. The development of additional CIPN signs is rare after cessation of chemotherapy, but a long-term follow-up would

reveal the effects of the treatment on the natural course of CIPN signs and symptoms. The strength of this study is that it used patient-reported toxicity outcome measures and the data reflect a real-world setting of an unselected patient group.

CONCLUSIONS

CIPN is a serious consequence of chemotherapy, particularly impairing the quality of life of cancer patients. Strategies to prevent CIPN are urgently needed. The regional cooling of hands and feet might have good effectiveness and tolerability, and seems to be able to prevent and reduce the symptoms of CIPN. Other German hospitals are experimenting whit this device and have found comparable results[68]. We are still recruiting patients to obtain more data and to collect data at the second follow-up point (T2) 3 months after the end of chemotherapy, with considerations of the low number of evaluable patients six months after the end of chemotherapy. Furthermore, we will enrich our results with a deeper overview of the impact of CIPN on patients' daily lives and on their perceptions and expectations. In conclusion, albeit limited by the low number of patients enrolled so far, we think that Hilotherm device warrants further attention and validation in CIPN prevention.

Disclosure statement

The authors declare that they have no conflict of interest.

Ethics approval

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethics committee of the participating institution approved the study protocol.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

The authors affirm that human research participant provided informed consent for publication of the images in Figure 1.

Authors' contributions

Ester Oneda: the author has dealt with the interpretation of data and in the drafting of the article

Fausto Meriggi: the author has dealt with the interpretation of data and in the revision of the article

Laura Zanotti: the author has dealt with the analysis of data

Elisabetta Zaina: the author has dealt with the acquisition and the interpretation of data

Sara Bighè: the author has dealt with the acquisition of data

Federica Andreis: the author has dealt with the acquisition of data

Sabogal Rueda: the author has dealt with the acquisition of data

Alberto Zaniboni: the author has dealt with the conception and the design of the study, with the revision of the article and with the approval of the final version.

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FIGURES

Fig. 1 The Hilotherm device