

A Randomized Assessor-Blinded Wait-List-Controlled Trial to Assess the Effectiveness of Acupuncture in the Management of Chemotherapy-Induced Peripheral Neuropathy

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Alexander Molassiotis, RN, PhD¹, Lorna K. P. Suen, RN, PhD¹,
Hui Lin Cheng, RN, PhD¹, T. S. K. Mok, MD², Sara C. Y. Lee, MSc¹,
C. H. Wang, MD², Paul Lee, PhD¹, Howan Leung, MBBS²,
V. Chan, MD², T. K. H. Lau, MD², and Winnie Yeo, MD²

Abstract

Purpose: Chemotherapy-induced peripheral neuropathy is a complex side effect with few available treatment options. The aim of the study was to test the effectiveness of an 8-week course of acupuncture in the management of chemotherapy-induced peripheral neuropathy in cancer patients who were receiving or had received neurotoxic chemotherapy. **Methods:** Randomized assessor-blinded controlled trial with 2 arms; one arm received acupuncture twice weekly for 8 weeks, while the other arm was a wait-list control group receiving only standard care. Primary outcome was pain intensity and interference over the past week using the Brief Pain Inventory at the end of the intervention. Secondary outcomes included clinical assessment (CTCAE [Common Toxicity Criteria for Adverse Events] grading and Total Neuropathy Score—Clinical Version) and nerve conduction studies; and patient-reported outcome measures (Functional Assessment of Cancer Therapy—Gynecologic Oncology Group—Neurotoxicity Quality of Life scale and Symptom Distress Scale) assessed at baseline, end of treatment (8 weeks), week 14, and week 20 from the beginning of treatment. **Results:** Eighty-seven patients were randomized to the experimental arm ($n = 44$) and to the standard care wait-list control arm ($n = 43$). Significant changes at 8 weeks were detected in relation to primary outcome (pain), the clinical neurological assessment, quality of life domains, and symptom distress (all $P < .05$). Improvements in pain interference, neurotoxicity-related symptoms, and functional aspects of quality of life were sustained in the 14-week assessment ($P < .05$), as were physical and functional well-being at the 20-week assessment ($P < .05$). **Conclusions:** Acupuncture is an effective intervention for treating chemotherapy-induced peripheral neuropathy and improving patients' quality of life and experience with neurotoxicity-related symptoms with longer term effects evident.

Keywords

acupuncture, chemotherapy-induced peripheral neuropathy, cancer, neurotoxicity, quality of life, pain

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a derangement in structure and function of peripheral motor, sensory, and autonomic neurons, causing peripheral neuropathic signs and symptoms.¹ Depending on the chemotherapy used, a pure sensory and painful neuropathy (with platinum analogues, ie, cisplatin, oxaliplatin, and carboplatin) or a mixed sensory motor neuropathy with or without involvement of the autonomic nervous system (with vinca

alkaloids, ie, vincristine, or taxanes, ie, paclitaxel) can ensue. The overall incidence of CIPN is not clear, but it is estimated

¹The Hong Kong Polytechnic University, Kowloon, Hong Kong SAR

²Prince of Wales Hospital, Sha Tin, Hong Kong SAR

Corresponding Author:

Alexander Molassiotis, School of Nursing, The Hong Kong Polytechnic University, No. 11 Yuk Choi Road, Hung Hom, Kowloon, Hong Kong SAR.

Email: alex.molassiotis@polyu.edu.hk



to occur in 10% to 20% of patients during treatment and it may be as high as 100%, depending on the chemotherapy drug, dose intensity, cumulative dose, and other as yet unidentified risk factors.¹⁻⁴ The implications of CIPN on the quality of life of cancer patients are significant, including dysfunction in daily activities, social well-being, work reintegration, and physical impairments including pain.⁵ There is a considerable impact on health care resource utilization too, with those experiencing CIPN having more frequent outpatient visits and medication use, estimated to be at US\$17 000 more in patients with CIPN than non-CIPN cancer patients.⁶

Attempts to manage this complex symptom with any interventions have been largely unsuccessful with low level of evidence,⁷ and interventional research for this symptom is currently minimal. The American Society of Clinical Oncology guidelines provide no recommendation for preventing CIPN, a moderate recommendation for duloxetine in the treatment of CIPN, and a few treatment options that have inconclusive evidence for CIPN, but which are considered on the basis of their effect on other neuropathic pain conditions.⁷ In this clinical area of limited treatment options, acupuncture may be considered for treating CIPN, with small-scale pilot studies ($N < 30$) or case series providing some initial evidence of effect, particularly in decreasing neuropathic pain.⁸⁻¹⁴ A systematic review identified 3 such trials, which all used a different approach (acupuncture, auricular acupuncture, and acupuncture with moxibustion).¹⁵ Although these mostly uncontrolled or underpowered studies are positive and encouraging, they suggest that acupuncture could be an option for these patients and that controlled trials using validated patient-reported outcome measures are justified.

Aims

The aim of the study is to test the effectiveness (in terms of neuropathic pain, other neurological sensations, and overall quality of life) of an 8-week course of acupuncture in the management of CIPN in cancer patients who are receiving or have received neurotoxic chemotherapy.

Methods

Design

The design of the study involves a pragmatic randomized assessor-blinded controlled trial. Clinicians, researchers, and those assessing the patients and obtaining patient data were blinded to the allocation (but not the patients nor the acupuncturists). A 2-group design is used with the experimental group receiving a course of acupuncture in addition to standard care and a wait-list control arm receiving standard care only.

Participants and Settings

Patients with breast, head and neck, colorectal, multiple myeloma, or gynecological cancer receiving taxane-based, bortezomib, capecitabine, or platinum-based chemotherapy experiencing CIPN during or after the end of chemotherapy were recruited. The study took place in 2 large cancer centers in the Hong Kong territory.

Inclusion Criteria

- Patients with diagnosis of breast, gynecological, colorectal, or head and neck cancer, and multiple myeloma with life expectancy (as judged by the clinician) longer than 5 months.
- Patients with cancer stages I to IV; Karnofsky Performance score 80 to 100.
- Currently receiving or having received neurotoxic chemotherapy (taxanes, cisplatin, oxaliplatin, bortezomib, etc).
- Reporting tingling in hands or feet and other clinical indications of CIPN after initiation of cancer treatments, confirmed to be indicative of CIPN by a medical consultant, often through brief neurological examination but at times based only on clinical signs.
- Not using any medication for the prevention or treatment of CIPN for the past 3 months.
- Willing to participate and be randomized to one of the study groups.
- No previously established peripheral neuropathy.

Exclusion Criteria

Patients with needle phobia; patients with low platelet count ($< 50\,000$); comorbidity with a bleeding disorder or coagulopathy; pregnancy, or having received acupuncture treatment in the past 3 months; patients with lymphedematous limbs or who have undergone axillary dissection; and patients with metastatic bone disease or metastatic involvement of the neural system.

Recruitment

Potential subjects were identified (through clinic lists and databases of patients who were undergoing treatment or attending follow-up visits), were approached initially by the relevant clinical team, and then screened by research staff.

Randomization

Patients were allocated to study groups through computer-generated randomization carried out by the Prince of Wales Hospital clinical trials unit in Hong Kong. Randomization consisted of minimization with a random element (stochastic

minimization), balancing for the treatment types (taxanes or platinum analogues or bortezomib/thalidomide received).

Intervention

The acupuncture intervention is described below based on the STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) recommendations for reporting acupuncture trials. In the acupuncture group, patients received, in addition to standard care, a standardized 30-minute acupuncture session needling specific body points; there was flexibility in case some points could not be punctured (ie, in case of lymphedema), and alternative points (as in routine practice) were selected by the therapists using their discretion to maintain an equal dose of treatment to all patients. The points were standardized according to the clinical manifestations of the subjects: if upper limbs were involved, we used LI4, LI11, PC7, TE5, and/or Baxie points (Ex-UE9; since the effect of Ex-UE9, PC7, and TE5 are similar, only 1 out of the 3 was chosen); if lower limbs were affected (most common), we used SP6, ST36, LV3, ST41, and/or Bafeng (Ex-LE10; since the effect of LV3, Ex-LE10, and ST41 are similar, only 1 out of the 3 was chosen) reflecting a traditional Chinese medicine diagnosis of “blood and qi stagnation and accumulation of dampness.” If the pain threshold of the patients was low, TE5 for upper limbs and/or ST41 for lower limbs were chosen. An equal “dose” of points was used for all patients (4 points bilaterally). Stimulation of the acupoints to achieve de qi sensation was done manually through rotation of the needle backward and forward for a few seconds, done twice during each treatment session (just after inserting the needle and before removing the needle). This approach to treatment mimics current acupuncture practices and is based on the literature^{12,13,16}; we have discussed this with experienced acupuncturists and used earlier data¹³ and experience from the acupuncturists in the trial team. Acupuncture sessions were carried out twice weekly for 8 weeks (= a total of 16 sessions). Points were punctured to a depth of 0.5 to 1.2 cm depending on the patients’ size, sensitivity, and state of health. The needles were Hwato sterile needles for single use, size 0.25 × 40 mm. Each session was based on a strict protocol followed by all therapists. Immediately after each session, the therapist completed an intervention monitoring form verifying the exact treatment given and any other issues that needed to be reported (ie, any side effects). Forms were checked regularly by the investigators for consistency across therapists. No other complementary therapy use was recommended during the course of acupuncture. Therapists were Chinese medicine practitioners, registered with their professional body in Hong Kong and had a minimum of 2 years’ experience in working with patients.

Standard Care

The comparison arm was a standard care control arm that received pain medication, vitamin B₁₂/B₆, or other medication as deemed necessary by the doctor. This group was offered acupuncture for their CIPN at the end of the trial after they completed week 20 assessments. Treatment was given as per in the intervention group above.

Study Duration

Treatment duration was 8 weeks. The duration of each patient’s involvement in the study was 20 weeks (5 months) with assessments at baseline, end of 8-week treatment, 14 weeks, and 20 weeks (the latter 2 to assess possible longer term effects).

Outcome Measures

Primary outcome at 8 weeks (end of acupuncture treatment): pain: “worst pain during past week” was measured using the Brief Pain Inventory (BPI).¹⁷ The BPI measures pain intensity (worst pain; pain in last 24 hours; average pain; and pain right now) on a 10-point scale (from 0-10) and its interference with 7 functions (ie, sleep or walking ability) also on a 10-point scale. Higher scores indicate worse pain intensity and/or interference.

Secondary Outcomes

- Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx) is a 38-item self-reported questionnaire: the 27-item general assessment of Quality of Life scale (FACT-G) alongside its 11-item neurotoxicity-specific module.¹⁸ Higher scores indicate better quality of life outcomes.
- The presence of other related symptoms (ie, fatigue, sleep, etc) was assessed using the 10-item Symptom Distress scale.¹⁹ Higher scores indicate more distress with symptoms.

Completion of the self-report questionnaires was done at home and these were posted back to the researchers using prepaid envelopes.

Neurotoxicity examination: baseline and at the end of acupuncture course.

A nurse not involved in the study and without knowing the patient allocation performed the neurological assessment. This was the same person for all patients, and training was provided for neurological assessments.

- The 7-domain Total Neuropathy Score–Clinical Version (TNSc). The TNSc provides a composite score based on clinical neurological examination obtained from grading of symptoms (including autonomic ones), signs, and quantitative sensory tests

(tendon reflexes; strength; vibration sensibility, pin sensibility; and 10-g monofilament), and provides a single measure to quantify neuropathy.²⁰

- The National Cancer Institute–Common Toxicity Criteria for Adverse Events (CTCAE) v.4.0, is a physician-rated grading system that includes criteria and definitions for quantifying and grading CIPN (both neurosensory and neuromotor components) utilizing a 5-point scale ranging from grade 1 to grade 5.
- Neurophysiological testing included a detailed motor nerve conduction study (NCS) in a subsample of the patients of the following nerves on the affected limbs: for upper limbs, the test included median nerve (bilateral) and ulnar nerve (bilateral). For lower limbs, the test included peroneal nerve (bilateral) and tibial nerve (bilateral). There was provision of the most sensitive parameters to register any axonopathy or demyelination. Distal latencies, amplitudes, and conduction velocities were measured as well as F-waves. For the sensory nerve conduction part of the neurophysiological assessment (NCS), the following nerves were studied: for upper limbs, the test included median nerve (bilateral) and ulnar nerve (bilateral). For lower limbs, it included sural nerve (bilateral). Neurophysiological testing was offered to each patient before and after treatment but only a subgroup of patients could attend one or all of the sessions owing to the concurrent need of chemotherapy, acupuncture treatment, discomfort from the assessment, and travel logistic issues.
- Sociodemographic and treatment characteristics were obtained from the patients' records or patients themselves. Patients were asked at baseline about treatment expectations, how much they believed this method will help them alleviate their neuropathy/pain, and how much faith they have in acupuncture (10-point Visual Analogue Score scales), alongside information if they have used any complementary therapies in the past and how much faith they have on complementary therapies. Chemotherapy dosage documentation (cumulative dosage received, completed number of cycles, and chemotherapy type) were also collected. Adverse effects were monitored at each clinic visit for the duration of the acupuncture treatment (although none reported).

Ethical approval from the Human Research Ethics Review Committee of the Hong Kong Polytechnic University (HSEARS20141011004) and the study hospitals (CREC Ref. 2014.529-T) was obtained. All patients signed a consent form.

Sample Size

Based on a randomized control trial on auricular acupuncture for cancer chronic peripheral or central neuropathic pain,²¹ a 30-day trial could reduce the pain intensity of the cancer patients from a Visual Analogue score (0-100) of 58 to 44 (standard deviation = 19). This effect corresponds to a Cohen's *d* of 0.74, and 39 patients per arm were required to achieve significance level of .05 and power of 0.90. It is prudent to inflate this figure further as follows: (1) the score distributions are likely to be fairly skewed and a Wilcoxon rank sum test may be more appropriate than a *t* test; (2) some dropout is likely, and though appropriate to use a last value carried forward (LVCF) approach, a completers analysis is also likely to be performed. Taking these 2 factors into account indicates aiming for a sample size of 44 in each arm.

Data Analysis

Analyses included descriptive statistics to summarize the data, analysis of variance to assess between-groups differences for primary and each of the secondary outcomes, and generalized linear model (analysis of covariance [ANCOVA]) using the baseline pain score as covariate. Ninety-five percent confidence intervals were also calculated. In more detail, while a *t* test is adequate for analysis, ANCOVA was used with the baseline score for each dependent variable as a covariate, and center and trial arm as grouping factors. Dropout cases and nonrespondents were asked to complete the primary outcome scale (1 item) and the 2 items of the CTCAE scale on CIPN in order to capture outcomes in as many patients as possible, and if this was not feasible, we used data imputation (LVCF). An intention-to-treat analysis was carried out. Sensitivity analysis in the primary outcome variables (where there were missing values) repeating the ANCOVA after using LVCF was also carried out as well as with GEE (generalized estimating equation) for all variables.

Results

Sample Characteristics

Eighty-seven Chinese patients with CIPN were recruited, 43 randomized to the control arm and 44 to the acupuncture arm. Their mean age was 57.1 years (SD = 7.7 years). The majority (72.4%) were females, had breast (42.5%) or colorectal (34.5%) cancer, were off treatment (90%), and an average of 15.3 months experiencing CIPN (range = 1-81 months). Detailed characteristics are shown in Table 1. There were no differences in sample characteristics between the 2 groups at inclusion. The CONSORT (Consolidated Standards of Reporting Trials) diagram of the patients' participation to the trial is shown in Figure 1.

Table I. Sample Characteristics.

Variable	Control Arm (N = 43), n (%)	Intervention Arm (N = 44), n (%)	Overall (N = 87), n (%)
Sex (<i>P</i> = .13)			
Male	15 (34.9%)	9 (20.5%)	24 (27.6%)
Female	28 (65.1%)	35 (79.5%)	63 (72.4%)
Marital status (<i>P</i> = .997)			
Never married	7 (16.3%)	8 (18.2%)	15 (17.2%)
Married	31 (72.1%)	31 (70.5%)	62 (71.3%)
Widower/widow	1 (2.3%)	1 (2.3%)	2 (2.3%)
Divorced	4 (9.3%)	4 (9.1%)	8 (9.2%)
Education level (<i>P</i> = .30)			
Nil	2 (4.7%)	0 (0.0%)	2 (2.3%)
Primary	13 (30.2%)	9 (20.5%)	22 (25.3%)
Secondary	23 (53.5%)	30 (68.2%)	53 (60.9%)
Post-secondary	5 (11.6%)	5 (11.4%)	10 (11.5%)
Economic status (<i>P</i> = .79)			
Full-time worker	21 (48.8%)	22 (50.0%)	43 (49.4%)
Taking care of family	11 (25.6%)	11 (25.0%)	22 (25.3%)
Retired	11 (25.6%)	10 (22.7%)	21 (24.1%)
Others	0 (0.0%)	1 (2.3%)	1 (1.1%)
Major income source (<i>P</i> = .12)			
Government	4 (9.3%)	1 (2.3%)	5 (5.7%)
Family	23 (53.5%)	19 (43.2%)	42 (48.3%)
Personal income	16 (37.2%)	21 (47.7%)	37 (42.5%)
Savings	0 (0.0%)	3 (6.8%)	3 (3.4%)
Personal monthly income (HK\$, 1 US\$ = 7.8 HK\$)			
<\$10 000	27 (62.7%)	29 (65.9%)	56 (62.5%)
\$10 000-\$19 999	10 (23.3%)	10 (22.7%)	20 (22.9%)
\$20 000 or above	6 (14.0%)	5 (11.4%)	11 (12.6%)
Diabetes (<i>P</i> = .97)			
Yes	4 (9.3%)	4 (9.1%)	8 (9.2%)
Cancer stage (<i>P</i> = .30)			
I	10 (23.3%)	4 (9.1%)	14 (16.1%)
II	10 (23.3%)	15 (34.1%)	25 (28.7%)
III	20 (46.5%)	22 (50.0%)	42 (48.3%)
IV	3 (7.0%)	3 (6.8%)	6 (6.9%)
Type of cancer (<i>P</i> = .74)			
Ovarian	8 (18.6%)	4 (9.1%)	12 (13.8%)
Head and neck	3 (7.0%)	3 (6.8%)	6 (6.9%)
Breast	16 (37.2%)	21 (47.7%)	37 (42.5%)
Colorectal	15 (34.9%)	15 (34.1%)	30 (34.5%)
Myeloma	1 (2.3%)	1 (2.3%)	2 (2.3%)
Currently receiving chemotherapy	4 (9.2%)	5 (11.4%)	9 (10.3%)
Post chemotherapy	40 (90.8%)	38 (88.6%)	78 (89.7%)
	N; Mean (SD)	N, Mean (SD)	N, Mean (SD)
Chemotherapy received and cumulative dose			
Oxaliplatin-based regimens (mg/m ²) (<i>P</i> = .42)	N = 14; 945.1 (78.3)	N = 15; 900.1 (192.7)	N = 29; 921.8 (148.1)
Carboplatin and total area under the curve (<i>P</i> = .34)	N = 8; 29.4 (3.2)	N = 5; 25.0 (12.4)	N = 13; 27.7 (7.8)
Cisplatin-based regimens (mg/m ²) (<i>P</i> = .29)	N = 4; 639.0 (198.0)	N = 3; 500.0 (40.0)	N = 7; 579.4 (160.2)
Paclitaxel-based regimen (mg/m ²) (<i>P</i> = .15)	N = 12; 878.1 (279.3)	N = 17; 760.1 (151.9)	N = 29; 809.0 (217.5)
Docetaxel-based regimens (mg/m ²) (<i>P</i> = .51)	N = 12; 350.0 (52.2)	N = 8; 367.8 (65.5)	N = 20; 357.1 (56.9)
Capecitabine (mg/m ²) (<i>P</i> = .97)	N = 15; 122826.7 (34820.2)	N = 14; 123372.0 (42613.4)	N = 29; 123089.9 (38071.0)
Bortezomib (mg/m ²)	N = 1; 10.4	N = 1; 36.0	N = 2; 23.2 (18.1)
Number of chemotherapy cycles received (<i>P</i> = .81)	6.0 (1.9)	6.1 (3.3)	6.0 (2.7)
Number of chemotherapy cycles received (oral chemotherapy) (<i>P</i> = .77)	N = 15; 8.1 (1.7)	N = 14; 7.9 (0.3)	N = 29; 8.0 (1.2)
Days since the last chemotherapy cycle (<i>P</i> = .54), mean (SD)	459 (399)	401 (176)	430 (438)
Used complementary therapies in the past (<i>P</i> = .32); yes, N (%)	27 (62.8%)	23 (52.3%)	50 (57.5%)
Belief that acupuncture will help you manage your problem (10-point scale) (<i>P</i> = .56), mean (SD)	6.9 (1.8)	6.6 (2.1)	6.7 (2.0)
How much faith do you have in complementary therapies in general? (10-point scale) (<i>P</i> = .43), mean (SD)	6.7 (2.2)	6.4 (2.3)	6.6 (2.3)

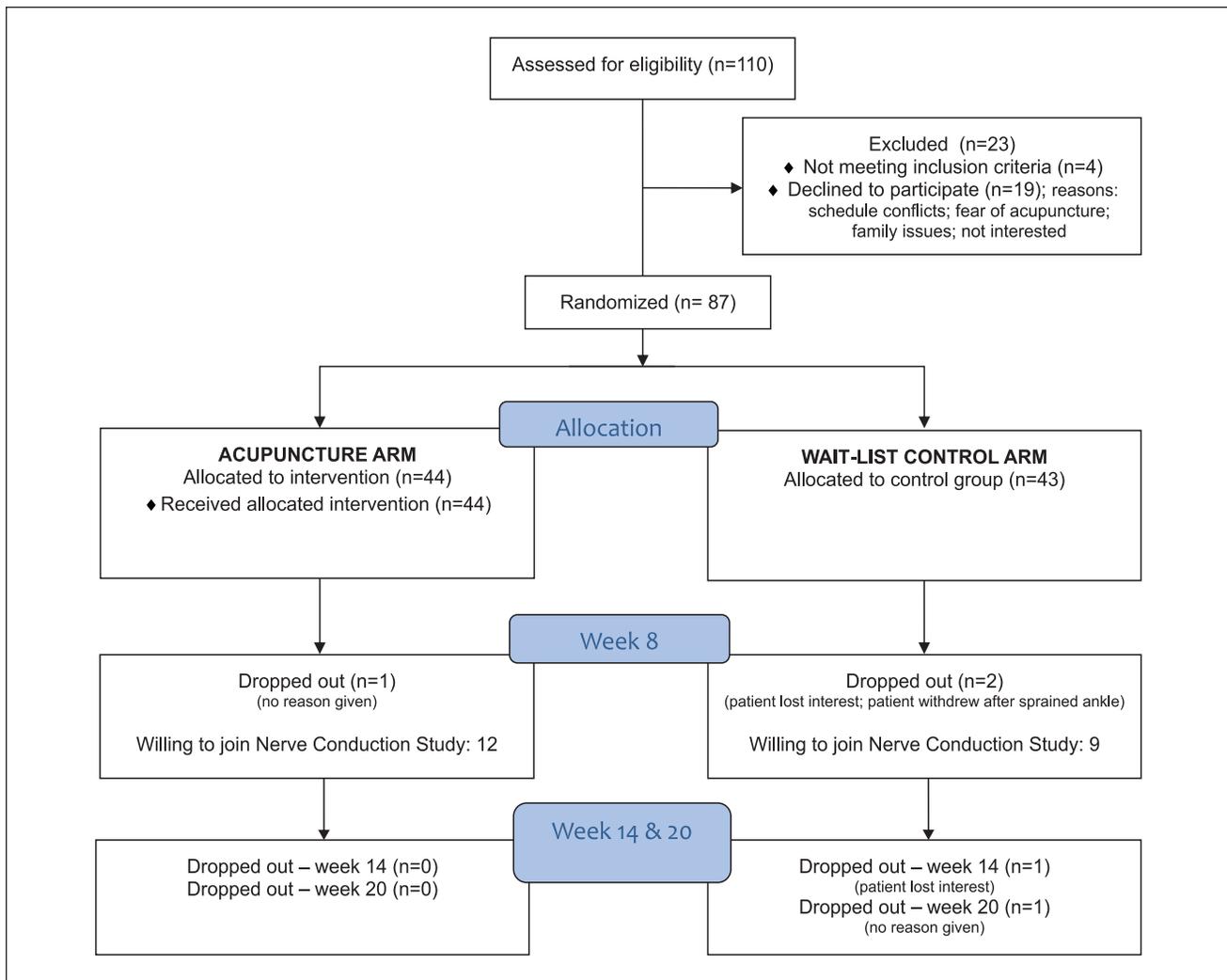


Figure 1. CONSORT diagram of the trial flow.

The vast majority had moderate/severe CIPN (56/87 patients with signs of sensory neuropathy and 63/87 patients with signs of motor neuropathy as per CTCAE scale at entry to trial).

Outcomes

Detailed outcome analysis is shown in Table 2. The primary outcome (pain intensity and pain interference) was significantly better at the end of the intervention in the acupuncture arm than the control arm ($P < .05$ and $P < .01$, respectively). Pain intensity remained lower in the acupuncture arm at the 14-week assessment ($P < .05$; see Figure 2). Statistically significant differences were still present in pain interference ($P < .01$) at 14 weeks. At week 20, the BPI score had a 0.7-point difference from the control group, but this did not reach statistical significance as less than half of the patients actually reported pain. Use of concomitant

medication for CIPN at week 8 was minimal and included 6 participants in the control arm and 3 participants in the experimental group, 1 massaging hands, 1 using Panadol, and traditional Chinese medicine.

The TNSc (combination of sensory tests/neurological assessment, signs and symptoms) was significantly improved at the end of the intervention in the acupuncture arm ($P < .05$). Also, significant improvements were seen in the sensory CTCAE item ($P < .05$) but not the motor item, although the latter had a 17% difference in prevalence at week 8 between the 2 groups (or 22% difference from baseline), with the lower prevalence being in the acupuncture group.

Quality of life was also significantly better in the acupuncture arm at the end of the intervention, particularly in terms of physical well-being ($P < .01$), functional well-being ($P < .05$), neurotoxicity subscale score ($P < .01$), the FACT/GOG-Ntx Trial Outcome Index (TOI; $P < .001$), the

Table 2. Trial Outcomes Between Control and Intervention Groups Over Time^a.

		Baseline	8 Weeks	<i>p</i> ^b	14 Weeks	<i>p</i> ^b	20 Weeks	<i>p</i> ^b
Brief Pain Inventory								
Pain intensity (worst pain; <i>P</i> for group by time interaction .03)	Control group	1.3 (0.4)	1.7 (0.4)	.31	2.2 (0.4)	.06	2.3 (0.4)	.03
	Intervention group	2.1 (0.5)	1.0 (0.3)	.008	1.5 (0.4)	.13	1.8 (0.3)	.49
	Effect size		0.26		0.26		0.17	
<i>P</i> value ^c		.20	.14		.18		.35	
Pain intensity (mild pain or more severe; <i>P</i> for group by time interaction .01)	Control group	N = 10 (23%)	N = 16 (37%)	.07	N = 21 (51%)	.001	N = 22 (55%)	<.001
	Intervention group	N = 15 (34%)	N = 8 (18%)	.03	N = 13 (32%)	.76	N = 20 (46%)	.13
	Effect size		.04		.07		.44	
<i>P</i> value ^c		.26	.04		.07		.44	
Pain interference (<i>P</i> for group by time interaction .04)	Control group	0.9 (0.3)	1.3 (0.3)	.33	1.7 (0.3) ^c	.04	2.0 (0.4)	.007
	Intervention group	1.5 (0.3)	0.5 (0.2)	.001	1.5 (0.4)	.94	1.6 (0.3)	.75
	Effect size		0.36		0.11		0.19	
<i>P</i> value ^c		.25	.04		.66		.42	
Pain interference (mild pain or more severe) (<i>P</i> for group by time interaction .02)	Control group	N = 9 (21%)	N = 16 (37%)	.04	N = 24 (48%)	.001	N = 22 (55%)	<.001
	Intervention group	N = 5 (34%)	N = 8 (18%)	.03	N = 20 (32%)	.76	N = 19 (44%)	.21
	Effect size		.04		.12		.32	
<i>P</i> value ^c		.16	.04		.12		.32	
FACT								
Physical well-being (<i>P</i> for group by time interaction .006)	Control group	21.6 (0.8)	20.9 (0.8)	.37	20.1 (0.9)	.047	19.1 (0.9)	.007
	Intervention group	20.5 (0.8)	23.5 (0.5)	<.001	21.7 (0.8)	.22	21.6 (0.7)	.21
	Effect size		0.46		0.28		0.46	
<i>P</i> value ^c		.38	.01		.19		.02	
Social/family well-being (<i>P</i> for group by time interaction .53)	Control group	20.7 (1.0)	20.3 (0.9)	.63	18.5 (0.9)	.05	18.4 (1.2)	.03
	Intervention group	20.0 (0.7)	20.5 (0.7)	.49	19.7 (0.9)	.69	19.3 (0.8)	.40
	Effect size		0.03		0.21		0.16	
<i>P</i> value ^c		.55	.87		.35		.51	
Emotional well-being (<i>P</i> for group by time interaction .86)	Control group	13.3 (0.6)	13.2 (0.7)	.86	13.0 (0.6)	.61	13.1 (0.7)	.77
	Intervention group	14.0 (0.6)	13.9 (0.5)	.90	13.8 (0.6)	.76	13.3 (0.7)	.25
	Effect size		0.18		0.20		0.04	
<i>P</i> value ^c		.41	.41		.39		.87	
Functional well-being (<i>P</i> for group by time interaction .12)	Control group	17.3 (0.9)	16.3 (0.8)	.26	16.8 (0.9)	.51	16.0 (1.0)	.23
	Intervention group	17.0 (0.6)	18.8 (0.7)	.03	17.6 (0.7)	.48	17.9 (0.9)	.36
	Effect size		0.51		0.16		0.38	
<i>P</i> value ^c		.78	.02		.50		.16	
Neurotoxicity subscale (<i>P</i> for group by time interaction .04)	Control group	26.5 (1.2)	28.2 (1.1)	.06	27.4 (1.0)	.30	28.0 (1.1)	.18
	Intervention group	27.4 (0.9)	32.2 (1.1)	<.001	30.6 (1.2)	<.001	30.3 (1.3)	.003
	Effect size		0.56		0.45		0.32	
<i>P</i> value ^c		.56	.01		.04		.18	
FACT/GOG-Ntx Trial Outcome Index (<i>P</i> for group by time interaction 0.001)	Control group	65.3 (2.4)	65.4 (2.2)	.98	64.4 (2.0)	.60	63.1 (2.4)	.34
	Intervention group	64.9 (1.8)	74.5 (1.8)	<.001	69.9 (2.3)	.006	69.8 (2.4)	.01
	Effect size		0.65		0.39		0.48	
<i>P</i> value ^c		.88	.001		.07		.047	
FACT-G total score (<i>P</i> for group by time interaction .049)	Control group	72.9 (2.4)	70.7 (2.5)	.27	68.4 (2.4)	.03	66.8 (2.2)	.02
	Intervention group	71.5 (1.8)	76.7 (1.7)	.004	73.4 (1.9)	.54	72.4 (2.1)	.79
	Effect size		0.42		0.31		0.38	
<i>P</i> value ^c		.64	.045		.19		.12	
FACT/GOGNtx_total (<i>P</i> for group by time interaction .01)	Control group	99.4 (3.1)	98.9 (3.1)	.85	96.0 (2.9)	.18	94.7 (3.3)	.15
	Intervention group	98.9 (2.3)	108.9 (2.2)	<.001	103.3 (3.0)	.06	102.4 (3.1)	.16
	Effect size		0.55		0.41		0.42	
<i>P</i> value ^c		.90	.009		.08		.09	
Symptom Distress Scale total score (<i>P</i> for group by time interaction .15)	Control group	17.6 (0.9)	17.6 (0.9)	.995	18.4 (0.9)	.28	19.4 (0.9)	.06
	Intervention group	16.6 (0.7)	14.6 (0.6)	.001	17.1 (0.9)	.49	18.5 (0.9)	.004
	Effect size		0.54		0.24		0.16	
<i>P</i> value ^c		.42	.009		.29		.49	
Total Neuropathy Score (<i>P</i> for group by time interaction .01)	Control group	7.6 (0.5)	7.6 (0.6)	.92	—	—	—	—
	Intervention group	8.1 (0.5)	6.2 (0.5)	<.001	—	—	—	—
	Effect size		0.42		—		—	
<i>P</i> value ^c		.43	.10		—		—	
NCI-CTCAE-sensory (moderate/severe) (<i>P</i> for group by time interaction 0.046)	Control group	N = 27 (63%)	N = 26 (62%)	.91	—	—	—	—
	Intervention group	N = 29 (66%)	N = 16 (37%)	.001	—	—	—	—
	Effect size		.76		—		—	—
<i>P</i> value ^c		.76	.02		—		—	
NCI-CTCAE motor (moderate/severe) (<i>P</i> for group by time interaction .07)	Control group	N = 30 (70%)	N = 28 (67%)	.62	—	—	—	—
	Intervention group	N = 33 (75%)	N = 21 (50%)	.003	—	—	—	—
	Effect size		.59		—		—	—
<i>P</i> value ^c		.59	.11		—		—	

Abbreviations: FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity; NCI-CTCAE, National Cancer Institute–Common Toxicity Criteria for Adverse Events.

^aMarginal mean (standard error) estimated with ANCOVA and GEE.

^bComparison with baseline.

^cControl versus intervention group comparison.

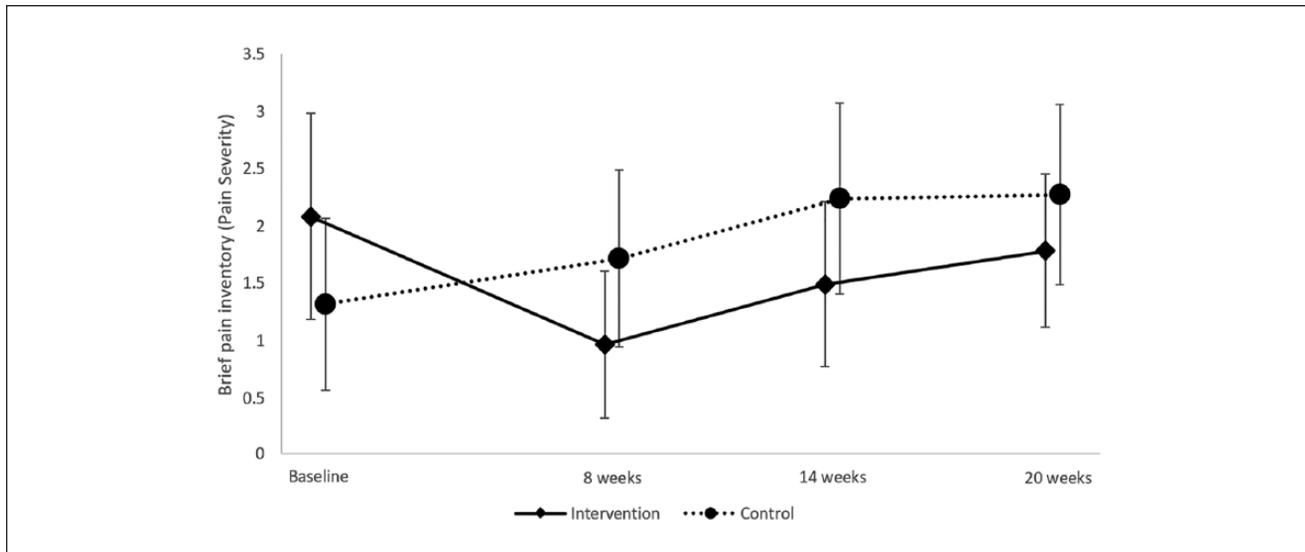


Figure 2. Worst pain intensity score changes over time.

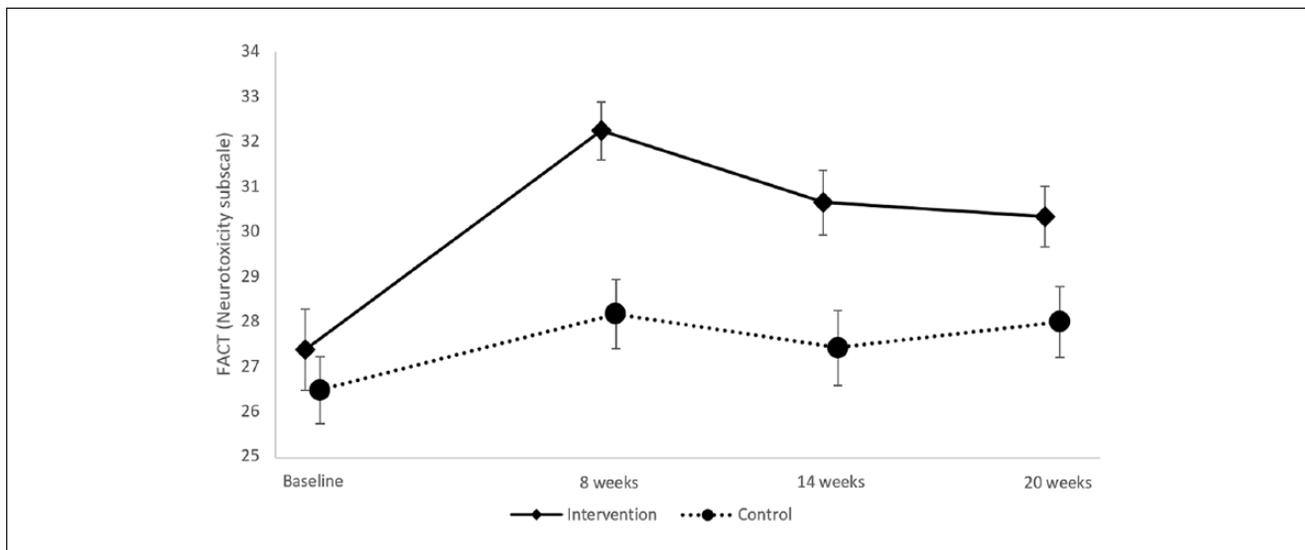


Figure 3. FACT-G Neurotoxicity scale (total score) changes over time.

FACT-G total score ($P < .01$), and the total score for the FACT/GOG-Ntx scale ($P < .01$; see Figure 3). The neurotoxicity subscale score, the FACT/GOG-Ntx TOI score, and FACT/GOG-Ntx total score remained significantly better in the acupuncture arm at the 14-week assessment, and at 20 weeks, physical well-being and FACT/GOG-Ntx TOI score continued to remain better in the acupuncture arm (Table 2 and Figure 4). Overall symptom distress was also lower in the acupuncture arm at the end of the intervention ($P < .01$).

Sensitivity analysis showed that the results were sustained when LVCF was used. The effect size estimation from ANCOVA and GEE were also similar, although the GEE had larger standard error (due to its complexity) hence

some significant effects in the ANCOVA model became insignificant in the GEE model.

The NCS showed values largely within the normal ranges or borderline ones for all parameters at baseline (Table 3). At 8 weeks, there was no significant difference from baseline.

We examined if there was a correlation between outcomes and expectations, faith in the treatment, and faith in complementary therapies. There were no significant correlations in any of the outcome variables and these beliefs, except in the case of symptom distress score at 14 weeks, which was correlated with faith in complementary therapies ($r = 0.31$, $P < .05$) and also had an inverse correlation with

Table 3. Median Values of Nerve Conduction Studies for Combined Right and Left Foot at Week 8 Between Control and Experimental Groups.

Variable	Control (n = 8)	Intervention (n = 9)	P ^a
Sum of both foots in peroneal, motor (extensor digitorum brevis)—distal latency (ms)	6.6	7.1	.83
Sum of both foots in peroneal, motor (extensor digitorum brevis)—amplitude (μV)—first recording	13.8	16.1	.68
Sum of both foots in peroneal, motor (extensor digitorum brevis)—amplitude (μV)—second recording	12.6	14.7	.63
Sum of both foots in peroneal, motor (extensor digitorum brevis)—velocity (m/s)	90.5	93.0	.75
Sum of both foots in tibial, motor (abductor hallucis brevis)—distal latency (ms)	8.6	9.2	.82
Sum of both foots in tibial, motor (abductor hallucis brevis)—amplitude (μV)—first recording	27.2	33.3	.30 ^b
Sum of both foots in tibial, motor (abductor hallucis brevis)—amplitude (μV)—second recording	20.2	26.2	.06
Sum of both foots in tibial, motor (abductor hallucis brevis)—velocity (m/s)	89.5	93.0	.33
Sum of both foots in sural, sensory (behind malleolus)—distal latency(ms)	4.2	4.4	.25
Sum of both foots in sural, sensory (behind malleolus)—amplitude (μV)	14.0	13.0	.71
Sum of both foots in sural, sensory (behind malleolus)—velocity (m/s)	100.0	87.0	.27

^aAdjusted for baseline scores.

^bP = .04 when only the values for the right foot were assessed.

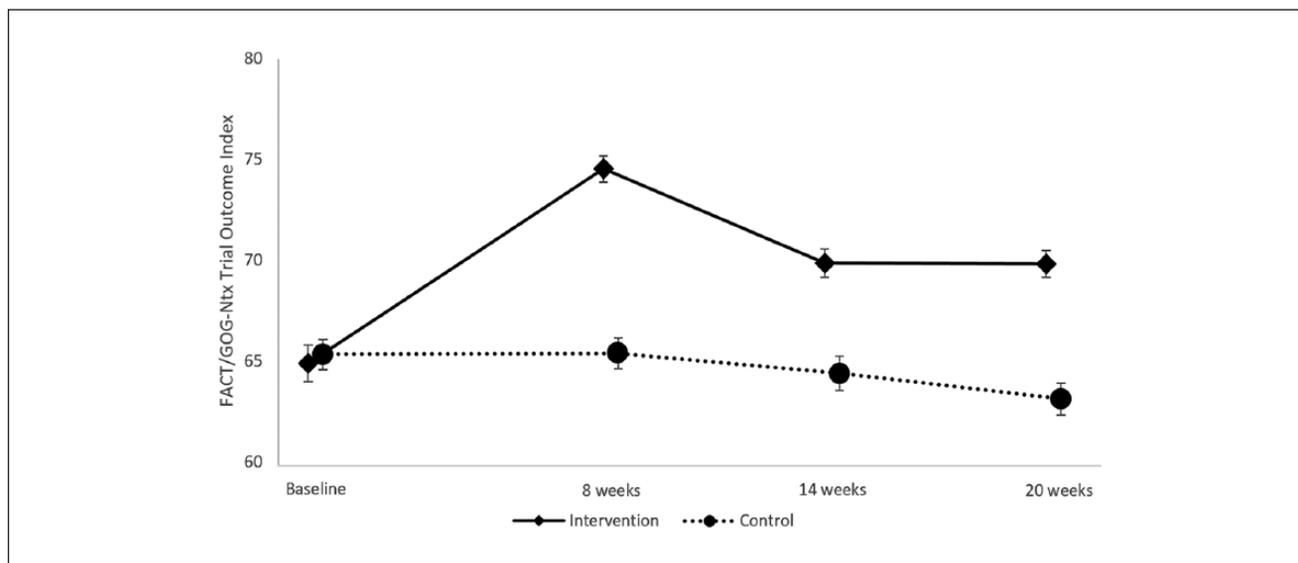


Figure 4. FACT/COG-Ntx Trial Outcome Index changes over time.

expectations ($r = -0.32, P < .05$). Furthermore, no adverse effects were reported after checking the therapists’ records.

Discussion

This is the first fully powered trial using acupuncture to treat CIPN, showing, both through patient-reported outcomes and clinical neurological assessment, that it significantly improved CIPN in the acupuncture group compared with the standard care wait-list control group. The current findings alongside available small-scale pilot/feasibility trials or uncontrolled trials and case series⁸⁻¹⁴ confirm the beneficial effect of acupuncture in treating CIPN. This is

exciting as there are limited treatment options available for managing CIPN.⁷

Clinical assessment that combines touch perceptions and deep nerve impairment at week 8 (primary outcome assessment) by blinded assessors clearly shows significant improvements. This is further supported by the clinician-rated CTCAE where significant sensory changes were also detected. For the CTCAE motor item, statistically significant differences were not shown, although the numeric difference in favor of the acupuncture group was 22%; when we assessed individual limb score changes, the left hand motor impairment was also improved in the acupuncture group ($P < .05$). This may also indicate that acupuncture

may be more effective in dealing with sensory impairment than motor.

Pain intensity and pain interference with daily life were significantly better in the acupuncture arm, despite the small number of patients who experienced (mostly mild) pain in the overall sample, suggesting a strong effect. The change in intensity in the acupuncture group was 38% from baseline, whereas in the control group, pain intensity slightly increased. The impact of the improvement was notable, as most patient-reported outcomes in the study, including overall quality of life, neurotoxicity-related symptoms (ie, tingling/numbness in the hands/feet), physical well-being, and functional well-being, were enhanced in the acupuncture group. The change in pain interference (1 point in the acupuncture group) is also consistent with minimal clinically important differences (MCIDs) reported in past studies of 0.5 to 1 point in a group of patients with bone metastasis showing improvement (although MCIDs for those deteriorating were 1.4-2.3 points).²² However, another study on bone metastasis patients showed that MCID for pain interference is 2 to 3.5 points in those with complete/partial response or 0.5 to 2.2 points in those with indeterminate response, and in our study the change was 1 point only.²³ Quality of life indicators, such as neurotoxicity subscales, neurotoxicity TOI, physical well-being, and functional well-being, also showed highly statistically significant improvements in the acupuncture group. Published MCIDs for the FACT physical well-being and functional well-being are around 2 to 3 points of change,²⁴ and our data showed change of 3 and 1.8, respectively, at the end of intervention, although there are no established MCID values for neurotoxicity subscale scores. It is interesting to see that symptom distress from multiple symptoms also improved, suggesting that acupuncture for CIPN can impact on a wider range of symptoms, perhaps as a result of some acupoints used not being specific only to CIPN. Improvements were sustained for longer term albeit not in all outcomes assessed, but primarily in physical and functional well-being and neurotoxicity-related symptoms. It may be prudent to provide patients with additional less frequent “boosting” sessions to maintain the initial effect, a common practice among therapists, although this may need testing in the future.

The NCS was not a useful test in this study, as most patients had no evidence of neurophysiological impairment, with values in the nerves assessed being often within normal ranges. Perhaps CIPN affects more small nerve fibers (ie, A-delta fibers or C fibers), whereas NCS is able to measure primarily large nerve fibers with routine electrodiagnostic tests being mostly normal in patients with small fiber neuropathies.²⁵ The role of NCS and other neurophysiological tests in the diagnosis of CIPN needs further investigation. The small number of patients undergoing NCS is a limitation; however, the test

is expensive as well as uncomfortable and time-consuming for the patients, hence we allowed this part of the study to be on a voluntary basis.

There is debate in the literature if the results of acupuncture are due to placebo effects and the need for a sham group in acupuncture trials. The current study answers an effectiveness research question using a pragmatic trial design. The decision not to use a sham-control methods in this study was not taken lightly and considered a number of aspects, including the difficulty in masking acupuncture in very “acupuncture-experienced” people like the Chinese and the ethics of using shams and having to attend for treatment for 8 weeks while still continuing to experience discomfort. Also, a crucial question is whether various sham methods can elicit a therapeutic effect and criticisms of shams in acupuncture trials have been previously discussed by ourselves²⁶ and other researchers.^{27,28} In the revised CONSORT standards for reporting acupuncture trials, it is also highlighted that sham needling techniques may evoke neurophysiological and other responses, an area for which we have lack of knowledge, leading to compromises in the interpretation of results.²⁹ Until this debate is resolved, we should not deny patients from the opportunity of symptom improvement using acupuncture, if they prefer or have access to use it. In the current trial, we decreased placebo effects by minimizing interactions and communication between the therapist and the patients, using a wait-list control arm, assessing the role of patient expectations from treatment and using both objective and subjective outcome measures.

Study limitations may include the small sample size (although this was a fully powered trial), the use of CTCAE as one of the objective measures that has been criticized as a scale that can misdiagnose CIPN,³⁰ the lack of sham- or attention-control methods, and use of multiple secondary outcomes at multiple time-points. Also, it is not clear if the duration of effect can extend beyond 20 weeks, as we have not used “booster sessions,” a common practice in acupuncture treatments. However, our previous research in relation to cancer-related fatigue showed that such booster sessions may not enhance or extend the acupuncture effect.³¹ Pain, as an outcome for CIPN trials, may also not be the most appropriate primary endpoint as highlighted in the literature,³² as the CIPN experience is wider than pain and involves many other sensations that are more commonly present in CIPN. Indeed, in our trial pain was not the most frequently reported experience, with less than half the patients experiencing mild-to-moderate pain. Also, the neurotoxicity-related (secondary) outcomes were the ones to show consistently and more long-term improvements after the intervention.

Acupuncture can be a treatment option for patients experiencing CIPN, although access to such a service and costs for private treatments may affect the uptake of acupuncture

from patients. Specific attention should be paid to the “dose” and duration of treatment and the specific acupoints used. Further trials in a wide range of participants should be carried out to confirm the results of the present study.

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