


Acupuncture and Reflexology for Chemotherapy-Induced Peripheral Neuropathy in Breast Cancer

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Abstract

Background: Treatment of chemotherapy-induced peripheral neuropathy (CIPN), which affects approximately 30% to 40% of patients treated with neuropathy-causing agents, is mainly symptomatic. Currently available interventions are of little benefit. **Study Design:** This study was conducted as a retrospective analysis of the efficacy of acupuncture and reflexology in alleviating CIPN in breast cancer patients. **Methods:** Medical records of 30 consecutive breast cancer patients who received both chemotherapy and treatment for CIPN according to our Acupuncture and Reflexology Treatment for Neuropathy (ART-N) protocol between 2011 and 2012 were reviewed. Symptom severity was rated at baseline, during, and after treatment. **Results:** The records of 30 breast cancer patients who had been concomitantly treated with chemotherapy and ART-N for CIPN were retrieved. Two records were incomplete, leaving a total of 28 patients who were enrolled into the study. Twenty patients (71%) had sensory neuropathy, 7 (25%) had motor neuropathy, and 1 (4%) had both sensory and motor neuropathy. Only 2 (10%) of the 20 patients with grades 1 to 2 neuropathy still reported symptoms at 12 months since starting the ART-N protocol. All 8 patients who presented with grades 3 to 4 neuropathy were symptom-free at the 12-month evaluation. Overall, 26 patients (93%) had complete resolution of CIPN symptoms. **Conclusion:** The results of this study demonstrated that a joint protocol of acupuncture and reflexology has a potential to improve symptoms of CIPN in breast cancer patients. The protocol should be validated on a larger cohort with a control group. It also warrants testing as a preventive intervention.

Keywords

peripheral neuropathy, breast cancer, acupuncture, reflexology, chemotherapy

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a potentially dose-limiting adverse event of a wide variety of anticancer agents, including taxanes and platinum analogues.¹ The mechanism of injury varies between the different drugs. Taxanes are tubulin inhibitors that damage neuronal axons, while platinum analogues accumulate in the cell body of sensory nerves and cause DNA damage.² Regardless of the mechanism, CIPN can manifest as paresthesias, pain, sensory deficits, and rarely as motor weakness. Sensory loss in the feet can lead to ataxia and gait disorders, and reflexes can be absent on physical examination.

The incidence of CIPN is not well-established partly due to the lack of a simple and reproducible assessment tool,³ but is estimated at 30% to 40% of patients treated with at least one of the offending agents.⁴ Factors predisposing to

CIPN are believed to be preexisting neuropathy, such as diabetic neuropathy, prior chemotherapy exposure, and age-related axonal loss.⁵ The neurological deficits caused by CIPN can be severe, long-lasting, and affect the individual's quality of life.⁶ These deficits can also lead to dose reductions and, therefore, to potentially less effective anticancer treatment.⁷

Although attempts have recently been made to apply preventive treatment consisting of anticonvulsants, antidepressants, and opioids to patients at risk,⁸ they proved to be

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unsuccessful in preventing CIPN. As such, treatment remains symptomatic. Physiotherapy and occupational therapy have also been used when proprioception was affected. However, none of those approaches has proven to be very efficacious.⁹ Since Western medicine has little to offer as remedy, it is not surprising that a European study¹⁰ showed that the use of complementary medicine of various kinds is widespread among cancer patients, with a prevalence of 35.9%.

Acupuncture has been shown to be especially effective for chemotherapy-induced nausea and vomiting,¹¹ fatigue,¹² anxiety, depression, and insomnia.¹³ Its role in the treatment of CIPN was also of some benefit in mainly small works. One retrospective case series that included 18 patients with CIPN followed a protocol of 6 weekly acupuncture sessions: 14 patients (82%) reported a symptomatic improvement after 6 weeks.¹⁴ One case report described a patient with multiple myeloma and CIPN who was treated with weekly sessions of acupuncture and electrical stimulation: the patient reported lower pain scores and was able to stop pain medication after 6 treatments.¹⁵

Reflexology has been used in the palliative treatment of cancer patients mainly for postsurgical lymphedema. The evidence supporting its use for CIPN is limited: the single published study reported a decrease in the quality of life in 24 patients with CIPN who were treated with foot massage,¹⁶ while a case report documented a reduction of CIPN symptoms from grade 2 to grade 1 in a patient with advanced esophageal cancer.¹⁷ Given the paucity of information on these issues, this retrospective study aimed to evaluate the efficacy of an acupuncture and reflexology protocol on CIPN in breast cancer patients who were concomitantly treated with chemotherapy.

Methods

The medical records of all consecutive breast cancer patients with histologically proven stage Ia to IV invasive breast carcinoma were reviewed. They had all been treated with cytotoxic chemotherapy between 2011 and 2012 at our institution's oncology day care facility with agents considered as being neurotoxic. All drug regimens were given at standard doses, unless dose reductions were necessary due to toxicity.

The same patients were treated according to the Acupuncture and Reflexology Treatment for Neuropathy (ART-N) protocol that had been developed in our Center for Complementary and Integrative Medicine (CCIM). Therapy was administered by a single experienced practitioner, certified by the national association of traditional Chinese medicine and with more than 5 years of clinical practice. All sessions took place at the CCIM. The protocol includes 1 to 2 weekly sessions of acupuncture (20 minutes) and reflexology (30-40 minutes). The acupuncture phase

consisted of needling Jing-Well points in the hands and feet according to traditional Chinese medicine diagnosis. Additional individualized points were allowed to use if needed according to patient presentation and secondary symptoms (such as fatigue or insomnia). Disposable sterile 0.16 mm × 0.20 mm needles were inserted after the skin was wiped with alcohol. The depth of insertion was determined by reaching the De Qi, that is, "the arrival of vital energy," which is described as a tingling, numbness, and other unique feelings, occurring after an acupuncture needle has been properly placed in the body.¹⁸ In acute cases of deep neuropathy and numbness, adding needle stimulation of qi is required.

Reflexology consisted of the following elements: (1) deep massage of the feet and hands in order to remove the stagnation and regulate a smooth flow of Qi and blood through the meridians (the massage was performed both in the meridians' flow direction and against it), (2) *gha sha* (*Guasha*) rubbing in the arms and ankles of the involved meridians, (3) deep massage of the feet cushions, and (4) rotations of the wrists, hands, ankles and feet.

CIPN symptoms and their severity were assessed by the treating physician at baseline and at regular intervals as part of routine follow-up visits during and after ART-N treatment. Symptom severity was categorized according to Common Terminology Criteria for Adverse Events, version 4, as either grades 1 to 2 or grades 3 to 4 based on patients' complaints and physical examination. Specifically, sensory and motor neuropathies were classified as grade 1 (loss of deep tendon reflexes, intervention not indicated), grade 2 (moderate symptoms, limiting instrumental activities of daily living), grade 3 (severe symptoms, limiting self-care), and grade 4 (life-threatening consequences, urgent intervention indicated). Additional recorded information included type of neuropathy, anticancer agents used and the total doses administered, and disease stage, including the presence and location of metastases.

Statistical Analysis

Statistical analysis was performed using descriptive statistical tools. Continuous data were summarized using the median, mean, and range. Categorical variables were compared between groups using Student's *t* test. The study was approved by the institutional review board, which waived informed consent for this retrospective record review.

Results

The medical records of 30 consecutive patients treated concomitantly for breast cancer and for CIPN were reviewed. Two patients' records lacked sufficient information for evaluation and were not included in the final analysis. All the patients in the study cohort were females and

Table 1. Baseline Characteristics.

Variables	n (%)
Age group	
30-39	9 (32)
40-49	12 (43)
50-59	5 (18)
60-69	2 (7)
Stage	
Ia	4 (14)
Ib	2 (7)
IIa	9 (32)
IIb	5 (18)
IIIa	2 (7)
IIIb	2 (7)
IV	4 (14)
Neuropathy	
Sensory	20 (71)
Motor	7 (25)
Not specified	2 (7)

their median age was 44 years (range 31-69). The median age was 41 years (32-69) for patients with grades 1 to 2 neuropathy and 45 years (44-58) for patients with grades 3 to 4 neuropathy. The mean age in both groups was 49. Twenty patients (71%) had early-stage disease (stages I-II), while 8 (29%) had locally advanced or metastatic disease (stages III-IV; Table 1). Two of the 4 patients with stage IV disease had lung metastases, and the other 2 had skeletal disease. In no patient was the disease a recurrence of earlier malignancy.

Twenty-seven patients (96%) received combination chemotherapy prior to beginning acupuncture and continued it concomitantly with the ART-N protocol. Fifteen of them (54%) received doxorubicin and cyclophosphamide. Each of the following protocols was given to 4 (14%) patients: vinorelbine ± trastuzumab, docetaxel, carboplatin ± trastuzumab, or carboplatin ± paclitaxel. The chemotherapy was changed in 16 (60%) of the patients who started chemotherapy before the ART-N protocol. All changes were pre-planned as part of routine 2-tier breast cancer protocols with standard doses (Tables 2 and 3). The patients were treated with either biological or hormonal therapy, as indicated by the immunohistological stains in the pathological reports. On average, the patients started the ART-N protocol 105 days after initiation of the course of chemotherapy. The average number of ART-N sessions was 10.8 (4-32).

Twenty patients (71%) had sensory neuropathy, 7 (25%) had motor neuropathy, and the neuropathy could not be classified in 2 (7%). One patient had both motor and sensory neuropathy at presentation. The neuropathy was grades 1 to 2 at the time of referral to the CCIM in 21 patients (75%) and grades 3 to 4 in 7 patients (25%).

Table 2. Chemotherapy Drug Exposure Before Acupuncture + Reflexology Therapy.

Drug	Average Number of Cycles (n)	Average Cumulative Dose (mg)
Adriamycin	2.6	260.3
Capecitabine	1	3000
Carboplatin	5.5	1670
Cyclophosphamide	206	2603
Docetaxel	1	118
Paclitaxel	10	1475
Trastuzumab	6.5	1202
Vinorelbine	9	459

Table 3. Chemotherapy Drug Exposure During Acupuncture + Reflexology Therapy.

Drug	Average Number of Cycles (n)	Average Cumulative Dose (mg)
Adriamycin	2.8	266
Carboplatin	7.3	1884.5
Cyclophosphamide	2.8	2660
Docetaxel	3	354
Paclitaxel	10	1407
Trastuzumab	30.5	9208
Vinorelbine	29	1444

Figure 1 illustrates the change in neuropathy severity in patients who presented with grades 1 to 2 neuropathy. While 16 (76%) patients experienced no change after 3 months, only 2 patients (10%) reported neuropathic symptoms of persistent severity at the 12-month evaluation. Those 2 patients were still symptomatic at the 18-month evaluation as well (data not shown). The 5 patients who were symptom-free at 3 months had received an average of 4.6 chemotherapy cycles prior to beginning the ART-N protocol. For patients with no change in neuropathy severity the average was 3.8 ($P = .75$). Likewise, there was no significant difference in the number of chemotherapy cycles given after the start of the ART-N protocol between these 2 groups ($P = .51$). Of the 5 patients with grades 1 to 2 motor neuropathy at presentation, none improved at the 3-month evaluation, and one remained symptomatic at the 12-month evaluation.

All 7 patients who presented with grades 3 to 4 neuropathy reported grades 1 to 2 symptoms at the 3-month evaluation, and no symptoms at the 6-month evaluation or thereafter. There was no difference between patients with sensory or motor neuropathy. Overall, 26 patients (93%) had complete resolution of CIPN symptoms after 12 months of therapy with the ART-N protocol.

Four of the 28 study patients had metastatic disease. Unlike the majority of patients with localized or locally advanced disease, who presented with grades 1 to 2

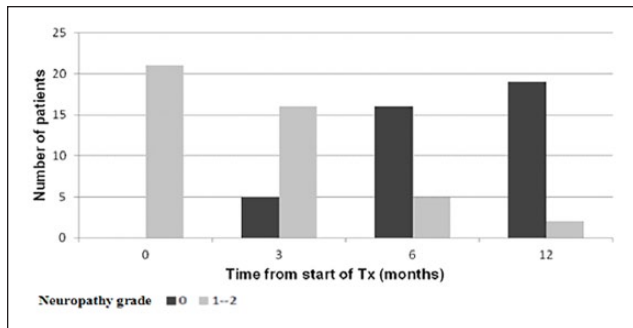


Figure 1. Patients with grades 1 to 2 neuropathy at baseline and at different time intervals from the initiation of acupuncture + reflexology therapy. Tx, treatment.

neuropathy, the 2 patients with metastatic disease and grades 1 to 2 neuropathy were symptom-free at the 3-month evaluation. The 2 patients with metastatic disease and grades 3 to 4 neuropathy had no change in symptoms after 3 months, but they reported no symptoms at the 6-month evaluation, similarly to the patients with grades 3 to 4 neuropathy who did not have metastatic disease.

Discussion

To the best of our knowledge, this pilot study is the first to test the effect of a joint protocol of acupuncture and reflexology on CIPN severity in breast cancer patients. Our results show that 16 of the 21 patients who presented with grades 1 to 2 neuropathy and all 7 patients with grades 3 to 4 neuropathy at presentation, 23 patients (82%) in total, were symptom-free at 6 months after starting the ART-N protocol. At the 12-month evaluation, 26 (93%) patients with grades 1 to 4 sensory or motor neuropathy reported complete resolution of CIPN symptoms. Only 2 (7%) patients were symptomatic at the 12-month follow-up. It is unlikely that the improvement was part of the natural history of CIPN and therefore unrelated to the intervention described. A meta-analysis examining the prevalence of CIPN in over 4000 patients, excluding treatment or prevention trials, demonstrated a CIPN prevalence of 68% in the first month after chemotherapy and 30% at 6 months or more.¹⁹

The presence of metastases was not an adverse predictive sign for response to the ART-N protocol.

The absence of other works on the combined use of both acupuncture and reflexology precludes our ability to compare our results to those of others. The reported results on the use of acupuncture alone, however, are consistent with our findings. Wong and Sagar²⁰ demonstrated improvement in gait, balance, and sensation in 5 consecutive patients treated with a weekly schedule of acupuncture for 12 weeks. Similarly, Xu et al²¹ studied 64 patients with paclitaxel- or oxaliplatin-induced CIPN who had been randomized to either acupuncture or intramuscular cobamamide. There

was a significant improvement in all 20 patients in the acupuncture arm compared to 27% of patients receiving cobamamide. In a report of a study that examined the effect of acupuncture on nerve conduction in patients with sensory CIPN with various malignancies, both solid and hematological, all 6 patients in the treatment arm showed improvement in nerve conduction studies.²² Clinical data regarding symptoms were not provided, but the 5 patients in the control arm who had not received any specific treatment for CIPN showed no improvement in their nerve conduction studies. Our search of the English literature failed to yield any publication on the application of reflexology as treatment for CIPN in the setting of chemotherapy for breast cancer.

National Comprehensive Cancer Network guidelines recommend anticonvulsants and antidepressants as first-line palliative treatment for CIPN,²³ although acknowledging that no pharmacologic treatment can repair nerve damage. Smith et al²⁴ recently randomized 231 patients with grade 1 or higher sensory neuropathy after taxane or oxaliplatin therapy to either daily duloxetine, a serotonin-norepinephrine reuptake inhibitor, or to placebo. Similar to our ratio, 75% of their patients had grades 1 to 2 neuropathy. After 5 weeks, 59% of the patients who received duloxetine reported decreased pain compared to 38% of the patients who received placebo. Duloxetine also decreased numbness and tingling, and the patients reported less use of concomitant medications. It is unknown if the reported CIPN symptoms persisted since there were no longer follow-up findings.

Another oral agent, a cannabinoid extract, failed to show a significant difference compared to placebo in reducing the pain score in a double-blind, placebo-controlled pilot trial.²⁵ That study randomized 18 patients with various malignancies, and the authors recorded a clinically significant improvement in 5 patients, thus indicating that there might be a subgroup of patients who may benefit from the drug. Medication-related side effects (mainly fatigue, dizziness, and nausea) were reported by most of the patients in the treatment arm, though most were mild and did not lead to discontinuation of the medication.

All 28 of our patients completed the acupuncture and reflexology protocol without any adverse events. This is in contrast to the known pharmacological side effects of treatment with anticonvulsants and antidepressants, events that may require dose reductions. Moreover, 23% of the patients in the study by Smith et al who had been treated with duloxetine²⁴ reported grades 2 to 3 adverse events (mainly fatigue and insomnia), and 12 patients discontinued treatment due to toxicity.

We are aware of several limitations of our study. Primarily, they are the study's retrospective nature, lack of randomization, and small sample size that allow for uncontrolled biases. However, since the patients were all followed

by the same physician, there is no potential bias in the evaluation of patients and in the quantification of their neuropathy severity. Though some might claim the absence of symptoms at the 12-month evaluation could be a result of the natural progression of CIPN, we feel that though this cannot be ruled out the data itself hint at the benefit of the ART-N protocol as patients with grades 3 to 4 neuropathy rarely report no symptoms after 6 months nor such a high percentage of patients, all grades included, report absence of symptoms even after 12 months. Finally, the relatively high percentage of motor neuropathy in our cohort may indicate that it might not be representative of the larger CIPN-affected population, although no difference was noted in response to therapy between patients with motor or sensory neuropathy.

Conclusions

The high rate of complete symptom resolution, long duration of response, and tolerability of the protocol, as reflected by the high completion rate, attest to the possible role of a joint protocol of acupuncture and reflexology in the treatment of CIPN. Future work should include a larger, randomized controlled trial to validate our results and examine the protocol for use as a preventive therapy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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