Integrated Medicine for Chemotherapy-Induced Peripheral Neuropathy

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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of typical chemotherapeutics among cancer survivors. Despite the recent progress, the effective prevention and treatment strategies for CIPN remain limited. Better understanding of the pathogenesis of CIPN may provide new niches for developing a new ideal therapeutic strategy. This review summarizes the current understanding of CIPN and current recommendations along with completed/active clinical trials and aims to foster translational research to improve the development of effective strategies for managing CIPN.

Keywords: chemotherapy-induced peripheral neuropathy; cancer survivors; new drug development; alternative and complimentary medicines

1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) often occurs in cancer patients receiving neurotoxic chemotherapies. It often affects sensory neurons resulting in severe pain, which may lead to long-term morbidity in cancer survivors. Owing to the improvement in cancer survival rate, an increase in the prevalence and burden of CIPN is expected. Forty-seven percent of cancer survivors presented persistent neuropathy up to 6 years after chemotherapy completion. They exhibited altered gait patterns with slower and shorter steps, and had a 1.8-fold increase in fall risk than those without CIPN [1]. Additionally, it was reported that 12% of cancer survivors with CIPN fell within three months [2]. These observations highlight the need for an effective treatment for CIPN to improve the quality of life and safety among cancer survivors.

Currently, no treatments have been recommended to prevent CIPN. The lack of a specific target for chemotherapies is a significant challenge in CIPN management. A deeper understanding of the underlying mechanisms of how CIPN develops and progresses may help in developing novel effective strategies for prevention and treatment [3–8]. Additionally, a better way to translate the mechanistic understandings into clinical interventions, which will promote the development of new effective strategies, remains a challenge [9]. Nevertheless, an ideal study design based on known mechanisms will help in addressing the unmet medical need. This review summarizes the current understanding of CIPN and current recommendations based on completed/active clinical trials in Western medicine and alternative and complimentary medicines.
2. The Current Understanding of CIPN: The Pathophysiology and Molecular Mechanisms

CIPN is a common, painful, dose-limiting neurotoxic side effect of chemotherapeutics for breast, gastrointestinal, gynecologic, and hematologic cancers. Its prevalence will increase owing to the improvement in cancer survival. More than 68% of patients suffer from this condition after receiving chemotherapies [6,10–13]. Classical chemotherapeutics, including platinum analogs (cisplatin, carboplatin, and oxaliplatin), antimitotic agents (taxanes and vinca alkaloids), and proteasome inhibitors, have higher risks in the development of CIPN [14]. Typical CIPN symptoms start during the first 2 months of treatment. CIPN progresses during chemotherapy but stabilizes after the completion of treatment. However, many patients experience uninterrupted limb numbness, tightness, and pain, which influences sleep, mood, and quality of life. Although most CIPN occurs in a dose-dependent manner, other drug-specific syndromes such as paclitaxel- and oxaliplatin-induced acute neurotoxicity or cisplatin discontinuation that caused worsening neuropathy were also observed. The most common chemotherapies, their estimated cumulative dose associated with neuropathy, and the drug-specific clinical features in patients with CIPN have been summarized elsewhere [10,15–24] and in Table 1.

| Type | Drug | Mechanism of CIPN | Cumulative and Dose | Incidence of CIPN | Acute Neuropathy | Chronic Neuropathy | Additional Features |
|------|------|-------------------|---------------------|-------------------|-----------------|-------------------|--------------------|
| **Platinum-Based** | Cisplatin | Nuclear and mitochondrial DNA damage | Cisplatin >300 mg/m², Oxaliplatin >800 mg/m² may be needed after the first dose | Cisplatin 49–100%, Carboplatin 13–42%, Oxaliplatin 85–95% | Cold-induced dysesthesias (hand/face), Muscle cramps | Sensory neuropathy/neuronopathy, ataxia | “Coasting”, cranial nerve involvement: hearing loss, tinnitus, ageusia, Lhermitte’s phenomenon |
| | Carboplatin | | | | |
| | Oxaliplatin | | | | |
| **Taxanes** | Docetaxel | Stabilization of microtubule polymers | Docetaxel ~400 mg/m², Paclitaxel ~1000 mg/m²; doses of ≥250 mg/m² may be needed after the first dose | 48.2% | Taste impairment | Sensorimotor neuropathy | Occasionally cranial nerves, mononeuropathies, autonomic features, “coasting” |
| | Paclitaxel | | | | |
| | Nab-paclitaxel | | | | |
| | Cabazitaxel | | | | |
| |  | | | | |
| |  | | | | |
| **Vinca alkaloids** | Vincristine | Destabilization of microtubule polymers | Vincristine >4 mg/m² may be needed after the first dose | 20%; Vincristine 30–40% | Taste impairment | Sensorimotor neuropathy | Occasionally cranial nerves, mononeuropathies, autonomic features, possible ‘coasting’ |
| | Vinblastine | | | | | |
| | Vinorelbine | | | | | |
| | Vindesine | | | | | |
| | Brentuximab vedotin | Destabilization of microtubule polymers | 36–53% | Demyelinating, sensorimotor neuropathy | Autonomic myokymia | Conjugated antibody | |
| | Brentuximab vedotin | | | | | | |
| |  | | | | | | |
| **Epothilones** | Eribulin | Destabilization of microtubule polymers | 25% | NS | Sensorimotor neuropathy | Conjugated antibody | |
| |  | | | | | | |
| **Ado-trastuzumab Emtansine** | Ado-trastuzumab Emtansine | Destabilization of microtubule polymers | 13% after the first dose | NS | Sensorimotor neuropathy | Conjugated antibody | |
| |  | | | | | | |
| **Proteasome inhibitor** | Bortezomib | Proteasome inhibitor | NS | Small fiber neuropathy, Severe polyradiculoneuropathy | Fewer CIPNs with subcutaneous delivery of bortezomib | |
| | Carfilzomib | | | | | |
| | Ixazomib | | | | | |

Abbreviations: NS, not specified.
Because of the absence of the blood–brain barrier and excellent lymphatic drainage, the peripheral nervous system (PNS) develops CIPN much easily than the central nervous system [11,25]. Moreover, it is much easier to penetrate sensory neurons than motor neurons owing to the lesser myelination [10]. The mechanisms are complex with peripheral, spinal, and supraspinal changes, ranging from the alternation of ion channel activity to intracellular signaling systems [26,27]. Common pathological mechanisms may include mitochondrial dysfunction, imbalance in redox homeostasis, inflammation leading to apoptosis, and nerve degeneration [28]. However, drug type, cumulative dosage, clinical features, and the time course of neuropathic symptoms vary among patients. The way of administration may affect the development of CIPN. Methotrexate will be associated with neurotoxicity only with intrathecal administration [29]. Bortezomib-induced CIPN can be reduced using subcutaneous administration [22]. Genetic variations may also set a role in the gene-environment interaction, which may act as predictive CIPN biomarkers [30–43], and are one of the risk factors for developing CIPN. It is recognized that the PNS damage triggers the migration of macrophages and Schwann cells into the lesions to clean up debris, followed by the release of neurotrophic factors by Schwann cells to promote neuroregeneration. Recently, the stimulator of interferon genes-interferon type I (STING–IFN-I) signaling axis was recognized as a critical regulator of physiological nociception and a promising target for treating CIPN [44]. Galactin-3 released by Schwann cells was also reported as a critical factor to cause CIPN [45].

Specific mechanisms of neurotoxic chemotherapies vary but may highly associate with their primary roles in anticancer effects. Platinum agents, such as cisplatin and oxaliplatin, exert damage via DNA cross-linking or oxidative stress, leading to mitochondrial dysfunction and neuronal apoptosis in the dorsal root ganglia [46–49]. Moreover, oxalate metabolized from oxaliplatin prolongs the open state of the voltage-gated sodium channel, extending neuron depolarization and hyperexcitability [50]. It is noted that, unlike cancer cells, cells affected by CIPN are non-dividing. The distinct responses between the high-dividing cancer cells and non-dividing neuronal cells includes the imbalance of proteostasis, pointed a direction to simultaneously prolong neuronal cell survival via improving protein refolding by which to get chance to remove DNA adducts via DNA repair process.

Taxanes inhibit microtubule depolymerization via stabilizing GDP-bound tubulin, leading to mitotic arrest during the cell cycle G2/M phase [51]. Additionally, taxanes disrupt axonal energy supply by targeting mitochondria complexes I and II in primary afferent neurons [52,53]. Furthermore, paclitaxel induces the upregulation of toll-like receptor 4 and monocyte chemotactic protein 1 in the dorsal root ganglion, which triggers macrophage infiltration and corresponding inflammation [54]. Nevertheless, the upregulation of transient receptor potential cation channel subfamily V member 4 in the dorsal root ganglion has been linked to paclitaxel-induced neuropathic pain [55].

Unlike taxanes, vinca alkaloids prevent microtubule polymerization by binding and inhibiting tubulin-dependent GTP hydrolysis [56,57]. Vincristine-induced CIPN has been linked to the reduction of endomorphin-2 levels, thus disrupting its analgesic effect on mu-opioid receptors and subsequently leading to hypersensitivity and CIPN [58]. Additionally, chemotherapeutics-induced reactive oxygen species affect serine protease activity and afferent pain pathways [59,60]. Improved understanding of the underlying mechanisms will help in the development of new therapeutic/preventive approaches for CIPN. However, a better translation of those mechanisms into clinical benefits remains a challenge.

3. Current Treatment of CIPN—In the View of Western Medicine

There are no preventative treatments for CIPN [61,62]. The current primary recommended therapy for CIPN focuses on pain relief and symptom management with analgesics, antidepressants, and antiepileptics in clinical practice [63]. The first-tier choices include duloxetine, pregabalin/gabapentin, or amitriptyline [64]. Pregabalin or gabapentin structurally mimic gamma aminobutyric acid with recognized efficacy in the treatment of both
epilepsy and neuropathic pain. However, unsteadiness, dizziness, edema, somnolence, and loss of concentration are the main problems [7]. Although tricyclic antidepressant amitriptyline is the gold standard for neuropathic pain, urinary retention or severe dizziness may occur in patients with benign prostate hyperplasia or elderly patients [65]. Opioids, such as tramadol or lidocaine patch, used as the second-tier choices only partially relieved neuropathic pain. The adverse effects such as nausea, dizziness, and somnolence have been observed [66,67]. Vitamin B [68,69] or vitamin E [70–75], often prescribed for neuropathic pain or diabetic polyneuropathy, showed no significant improvement in pain management. Other agents have been studied in clinical trials based on postulated effects on underlying mechanisms [7,61,66,67,76–78]. State-of-the-art therapies such as cryotherapy [79] or induced pluripotent stem cells or fibroblast-derived neuronal subtypes, including dorsal root ganglion neurons [80,81], remain to be evaluated. Exercises such as yoga also show benefit for alleviating CIPN [82–85]. Understanding the underlying mechanisms of dual targets of rapidly dividing cancer cells and non-dividing, post-mitotic neurons remain challenging. The current recommendations or completed/active clinical trials for CIPN are summarized in Table 2. In particular, trial specifically for plantinum—especially cisplatin alone—is rare. Lack of obvious study end point may be one reason. In addition, difficulties for specific patient enrollment may be taken into account. Breakthrough for understanding the underlying mechanisms how those plantinum drugs causes neuronal cell death, and a niche for prolonging neuron survival will help to find the critical regulatory target.

Table 2. Current clinical trials for chemotherapy-induced peripheral neuropathy (CIPN).

| Study Title                                                                 | Identifier   | Sponsor                  | Phase | Chemo-Therapeutics         | Cancer Type | Intervention                               |
|---------------------------------------------------------------------------|--------------|--------------------------|-------|----------------------------|-------------|-------------------------------------------|
| Drug repurposing for the prevention of chemotherapy-induced peripheral neuropathy (CIPN) | NCT04780854  | Cairo University         | Phase 2 | Paclitaxel                 | NS          | Metformin vs. placebo                      |
| The preliminary effects of henna on CIPN                                   | NCT04201587  | Selcuk University        | NA    | NS                         | NS          | Henna application vs. control              |
| Effect of tro19622 in the treatment of patients with chemotherapy-induced peripheral neuropathy (CIPN) | NCT00876538  | Hoffmann-La Roche        | Phase 2 | Taxanes                    | NS          | Olesoxime (TRO19622) vs. placebo          |
| Niagen and persistent chemotherapy-induced peripheral neuropathy           | NCT04112641  | University of Iowa       | Phase 2 | Taxanes or Platinum        | NS          | Nicotinamide riboside vs. placebo capsules |
| Suncist: a study of calmangafodipir in healthy Japanese and Caucasian subjects | NCT03430999  | Pledpharma AB            | Phase 1 | NA                         | NA          | Calmangafodipir vs. placebo               |
| Pregabalin in CIPN                                                        | NCT02394951  | Washington University School of Medicine | NA    | Oxaliplatin, Paclitaxel, Docetaxel, or their combinations | NS          | Pregabalin vs. placebo                     |
| Preventive treatment of oxaliplatin-induced peripheral neuropathy in metastatic colorectal cancer (polar-m) | NCT03654729  | Pledpharma AB            | Phase 3 | mFOLFOX6                   | Metastatic colorectal cancer | Calmangafodipir (2 dosages) vs. placebo |
| A study to assess the efficacy and safety of oxycodone/naloxone in Korean patients with chemotherapy-induced peripheral neuropathy (CIPN) | NCT01675531  | Mundipharma Korea Ltd.    | Phase 4 | NS                         | NS          | Targin (oxy-codone/naloxone)              |
| Study Title                                                                 | Identifier      | Sponsor                  | Phase | Chemotherapeutics | Cancer Type                                                                                      | Intervention                                      |
|---------------------------------------------------------------------------|-----------------|--------------------------|-------|-------------------|-----------------------------------------------------------------------------------------------|---------------------------------------------------|
| Effect of hemp-CBD on patients with CIPN                                  | NCT04398446     | Main Line Health         | Phase 2 | NS                | Non-metastatic breast, uterine, ovarian, or colorectal cancers                                | Hemp-based cannabidiol vs. placebo                 |
| Preventive treatment of oxaliplatin-induced peripheral neuropathy in adjuvant colorectal cancer | NCT04034355     | Pledpharma AB            | Phase 3 | mFOLFOX6          | Colorectal cancer                                                                               | Calmangafodipir vs. placebo                       |
| Ozone therapy in chemotherapy-induced peripheral neuropathy: RCT (O3NPIQ)  | NCT04299893     | Bernardino Clavo         | Phase 2, Phase 3 | NS                | Hematopoietic, lymphoid cell, or solid malignant neoplasms                                   | Ozone vs. oxygen                                  |
| Duloxetine and neurofeedback training for the treatment of chemotherapy induced peripheral neuropathy | NCT04560673     | M.D. Anderson Cancer Center | Phase 2 | NS                | Duloxetine vs. neurofeedback training vs. their combination                                  |                                                   |
| Study of nicotine for pain associated with chemotherapy-induced peripheral neuropathy | NCT04468230     | Virginia Commonwealth University | Phase 2 | NS                | Nicotine transdermal patch                                                                     |                                                   |
| Menthol in neuropathy trial (MINT)                                        | NCT04276727     | University of Edinburgh  | Phase 2 | NS                | Menthol vs. placebo                                                                            |                                                   |
| Minocycline hydrochloride in reducing chemotherapy-induced peripheral neuropathy and acute pain in patients with breast cancer undergoing treatment with paclitaxel | NCT02297412     | Academic and Community Cancer Research United | Phase 2 | Paclitaxel        | Breast cancer                                                                                  | Minocycline hydrochloride vs. placebo             |
| Study Title | Identifier | Sponsor | Phase | Chemo-Therapeutics | Cancer Type | Intervention |
|-------------|------------|---------|-------|--------------------|-------------|--------------|
| High dose inorganic selenium for preventing chemotherapy-induced peripheral neuropathy | NCT04201561 | Seoul National University Hospital | Phase 3 | Paclitaxel | Response evaluation criteria in solid tumors (RECIST), or gynecologic, epithelial ovarian, fallopian, or primary peritoneal cancers | Sodium selenite pentahydrate vs. vehicle vs. standard care |
| Chemotherapy-induced peripheral neuropathy-essential oil intervention | NCT03449303 | Augusta University | NA | NS | Breast cancer | Eoil (10% dilution of Curcuma longa, Piper nigrum, Pelargonium asperum, Zingiber officinale, Mentha x piperita, and Rosmarinus officinalis Ct. Cineole in (Simmondsia chinensis) vs. placebo (Simmondsia chinensis) |
| The role of transient receptor potential channels in chemotherapy-induced peripheral neuropathic pain | NCT04415892 | Universitaire Ziekenhuizen Leuven | NA | Paclitaxel or Oxaliplatin | NS | Cinnamaldehyde and capsaicin |
| Cannabinoids for taxane-induced peripheral neuropathy | NCT03782402 | New York State Psychiatric Institute | Phase 2 | Paclitaxel or Docetaxel | Breast cancer | Cannabinoids of various strengths |
| N-acetyl cysteine effect in peripheral neuropathy in cancer patients | NCT03492047 | Ain Shams University | Phase 1, Phase 2 | Paclitaxel | Breast cancer | N-acetylcysteine (low vs. high dose) vs. standard care |
| Lidocaine versus duloxetine for the prevention of taxane-induced peripheral neuropathy in breast cancer patients | NCT04732455 | Gamal Mohamed Taha Abouelmagd | NA | Taxanes | Breast cancer | Lidocaine vs. vehicle vs. duloxetine |
| Study Title                                                                 | Identifier       | Sponsor                         | Phase          | Chemo-Therapeutics | Cancer Type          | Intervention                                |
|---------------------------------------------------------------------------|------------------|---------------------------------|----------------|-------------------|---------------------|---------------------------------------------|
| The potential protective role of venlafaxine versus memantine in paclitaxel-induced peripheral neuropathy | NCT04737967     | Mendel AI                       | Phase 2, Phase 3 | Paclitaxel        | NS                  | Venlafaxine vs. memantine                   |
| NR in chemo-induced peripheral neuropathy                                 | NCT03642990     | Donna Hammond                   | Phase 2        | Paclitaxel        | Metastatic breast cancer | Nicotinamide riboside                       |
| NR in chemo-induced peripheral neuropathy                                 | NCT03642990     | Donna Hammond                   | Phase 2        | Platinum          | Platinum-resistant ovarian, peritoneal, endometrial, fallopian tube, or head and neck cancers | Nicotinamide riboside                       |
| Duloxetine in treating peripheral neuropathy caused by chemotherapy in patients with cancer | NCT00489411     | Alliance for Clinical Trials in Oncology | Phase 3      | Taxanes or Platinum | NS                  | Duloxetine hydrochloride vs. placebo       |
| Vitamin e in preventing peripheral neuropathy caused by chemotherapy in patients receiving chemotherapy for cancer | NCT00363129     | Alliance for Clinical Trials in Oncology | Phase 3      | Taxanes or Platinum | NS                  | Vitamin E vs. placebo                      |
| Lamotrigine in treating peripheral neuropathy caused by chemotherapy in patients with cancer | NCT00068445     | Alliance for Clinical Trials in Oncology | Phase 3      | Taxanes, Platinum, Vinca Alkaloids | NS                  | Lamotrigine vs. placebo                     |
| Clinical study on acetyl-l-carnitine                                      | NCT01526564     | Lee's Pharmaceutical Limited    | Phase 3        | Taxoids, Satraplatin and Vincristine | NS                  | Acetylcarnitine vs. placebo                 |
| Gabapentin in treating peripheral neuropathy in cancer patients undergoing chemotherapy | NCT00027963     | Alliance for Clinical Trials in Oncology | Phase 3      | Taxanes, Platinum, or Vinca alkaloids | NS                  | Gabapentin vs. placebo                      |
Table 2. Cont.

| Study Title                                                                 | Identifier       | Sponsor                                      | Phase      | Chemo-Therapeutics                        | Cancer Type                                                                 | Intervention                                      |
|-----------------------------------------------------------------------------|------------------|----------------------------------------------|------------|-------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|
| Baclofen-amitriptyline hydrochloride-ketamine gel in treating peripheral     | NCT00516503      | Alliance for Clinical Trials in Oncology     | Phase 3    | Chronic myeloproliferative disorders,     | Chronic myeloproliferative disorders, leukemia lymphoma, lymphoproliferative   | Baclofen/amitriptyline/ketamine gel vs. placebo  |
| neuropathy caused by chemotherapy in patients with cancer                   |                  |                                              |            | leukemia lymphoma, lymphoproliferative    | disorders, multiple myeloma and plasma cell neoplasm, myelodysplastic         |                                                  |
|                                                                             |                  |                                              |            | disorders, multiple myeloma and plasma    | syndromes, myelodysplastic/myeloproliferative neoplasms                       |                                                  |
|                                                                             |                  |                                              |            | cell neoplasm                              |                                                                               |                                                  |

Abbreviations: NA, not applicable; NS, not specified.

4. Alternative and Complementary Treatment and Prevention of CIPN

In traditional Chinese medicine (TCM), the primary pathogenesis of CIPN is related to spleen deficiency (Pi xu 脾虚), qi deficiency (Qi xu 氣虛), toxicity (Du 毒), stagnation (Yu 瘀), dampness (Shi 濕), and kidney deficiency (Shen xu 腎虛) [86]. Some herbal medicines, acupuncture, and pharmacopuncture have shown benefits in managing the disease as described below.

4.1. Chinese Herbal Medicine

Goshajinkigan (GJG, Ji Sheng Shen Qi Wan (濟生腎氣丸)) has been used to treat diabetic neuropathy [87,88]. Clinical studies have indicated that GJG is effective against FOLFOX regimen- [89–91], oxaliplatin- [92], and paclitaxel/carboplatin-induced peripheral neuropathy [93]. However, the reproducibility of its effects is challenging [94–96]. Shakuyaku-Kanzo-to (SYKZT, Shao Yao Gan Cao Tang (芍藥甘草湯)) has its benefit for PNS dysfunction in paclitaxel combination therapy [97]. Ogikeishigomotsuto (AC591, Huangqi Guizhi Wuwu decoction (黃耆五物湯)) has been used to treat diabetic neuropathy [98,99]. A randomized controlled study revealed that AC591 prevents oxaliplatin-induced neuropathy without reducing its antitumor activity [100]. Ginkgo biloba (GB, Ying-Shin (銀杏)) has been used for its protective effects on nervous and circulatory systems to treat diseases, including arrhythmias, ischemic heart disease, thromboses, cancer, diabetes, and Alzheimer’s disease, and cognition disorders [101]. A retrospective study revealed that GB reduces the oxaliplatin-caused intensity and duration of acute dysesthesias and yields synergistic effects for anti-tumorigenesis [102].

4.2. Acupuncture

Acupuncture significantly reduces CIPN, such as neuropathic symptoms (pain, tingling, and numbness), quality of life, and nerve conduction, and is considered for treat-
ment/prevention of CIPN. However, the evidence remains to be accumulated [103–105]. Acupuncture might help nerve repair by increasing the limbs’ blood flow [106,107]. A six-week acupuncture course improves pain, numbness, and tingling in patients with grade II CIPN [108]. A randomized controlled trial showed that acupuncture plus methylcobalamin was superior to methylcobalamin alone in providing pain relief and improving the quality of life [109].

4.3. Electroacupuncture

The effects of electroacupuncture on CIPN remain to be evaluated. In a four-arm randomized trial, a comparison of four different treatments, including electro-acupuncture, hydroelectric baths, Vitamin B1/B6 capsules, and placebo groups, in patients with CIPN showed no therapeutic effect of electroacupuncture [14]. Although a randomized controlled trial revealed that an eight-week course of electro-acupuncture relieves CIPN symptoms [110,111], a trial focused on preventing the symptoms of CIPN by electroacupuncture was not as good as expected [112]. Transcutaneous electrical nerve stimulation (TENS) has become an alternative for CIPN treatment; however, it requires empirical clinical evidence. Although some studies have shown efficacy in nerve regeneration and a wireless, home-based TENS may be a feasible device to relieve the symptoms of CIPN such as tingling, numbness, cramping, and pain [113], valid results were not found in a preliminary case-controlled study in clinical conditions [114]. A new approach, acupuncture-like transcutaneous nerve stimulation, applies TENS to the acupoints based on TCM theory and has shown significant improvement in neuropathic pain and numbness [115]. Scrambler therapy, another type of electrical stimulation, showed its benefit for acute or chronic CIPN [116] and quality of life [117,118]. Although a randomized phase II pilot study revealed a superior effect of TENS when compared with scrambler therapy [119], the benefit for the pain score remains to be evaluated [120]. Current completed or active acupuncture clinical trials for CIPN are summarized in Table 3.

| Study Title                                                                 | Identifier       | Sponsor                          | Phase | Chemotherapeutics               | Cancer Type                        | Intervention                                                                 |
|----------------------------------------------------------------------------|------------------|----------------------------------|-------|---------------------------------|-----------------------------------|----------------------------------------------------------------------------|
| Oral Cryotherapy Plus Acupressure and Acupuncture Versus Oral Cryotherapy for Decreasing Chemotherapy-Induced Peripheral Neuropathy From Oxaliplatin-Based Chemotherapy in Patients With Gastrointestinal Cancer | NCT04505553     | University of Washington         | Phase 2 Pilot Study | Oxaliplatin-Based Chemotherapy   | Gastrointestinal Cancer          | Oral cryotherapy vs. oral cryotherapy plus acupuncture/acupressure       |
| Acupuncture in Reducing Chemotherapy-Induced Peripheral Neuropathy in Participants With Stage I-III Breast Cancer | NCT03505671     | Wake Forest University Health Sciences | NA    | NS                             | Breast Cancer                     | Acupuncture vs. standard care                                              |
| Acupuncture for Peripheral Neuropathy Induced by Paclitaxel in Early Stage Breast Cancer | NCT04461977     | Instituto Brasileiro de Controle do Cancer | NA    | NS                             | Breast cancer (stages I, II, III) | Acupuncture vs. sham acupuncture                                          |
| Acupuncture for CIPN in Breast Cancer Patients                          | NCT02615678     | Southern California University of Health Sciences | NA    | NS                             | Breast Cancer                     | Before and after acupuncture                                               |
| Integrative Medicine for Chemotherapy-Induced Peripheral Neuropathy       | NCT03290976     | The Chaim Sheba Medical Center   | NA    | Taxanes                         | 1. Female patients with breast or gynecological cancers | Single vs. multi-modality acupuncture vs. standard care              |
| Integrative Medicine for Chemotherapy-Induced Peripheral Neuropathy       | NCT03290976     | The Chaim Sheba Medical Center   | NA    | NS                             | 2. Patients of either gender with hematological malignancies | Single vs. multi-modality acupuncture vs. standard care  |
### Table 3. Cont.

| Study Title                                                                 | Identifier          | Sponsor                                      | Phase | Cancer Type                                                                 | Intervention                                      |
|---------------------------------------------------------------------------|---------------------|----------------------------------------------|-------|-----------------------------------------------------------------------------|--------------------------------------------------|
| Standard Care Alone or With Acupuncture for CIPN in Breast Cancer and Multiple Myeloma (ACUFOCIN) | NCT02275403         | The Christie NHS Foundation Trust             | Phase 2 NS | Breast cancer, multiple myeloma, gastrointestinal cancer, or gynecological cancer | Acupuncture vs. standard care                    |
| The Use of Acupuncture for Treatment of Chemotherapy-induced Peripheral Neuropathy (CIPN) | NCT02309164         | University of Sao Paulo                       | NA    | NS                                                                          | Acupuncture vs. standard care                    |
| Evaluation of the Efficacy of Acupuncture in Chemotherapy-Induced Peripheral Neuropathy | NCT03626220         | China Medical University Hospital             | NA    | NS                                                                          | Breast cancer                                    |
| The Effectiveness and Cost-Effectiveness of Acupuncture in Managing Chemotherapy-induced Peripheral Neuropathy | NCT02553863         | The Hong Kong Polytechnic University          | NA    | NS                                                                          | Lung, breast, gynecological, or head & neck cancers, or colorectal cancer (stage I, II, III). | Acupuncture vs. standard care                    |
| Efficacy of Acupuncture on Chemotherapy-Induced Peripheral Neuropathy | NCT04739631         | Taipei Veterans General Hospital, Taiwan      | NA    | Taxanes (paclitaxel or docetaxel), platinum (cisplatin, oxaliplatin, carboplatin) | Acupuncture vs. sham acupuncture                 |
| Testing the Effects of Transcutaneous Electrical Nerve Stimulation (TENS) on Chemotherapy-Induced Peripheral Neuropathy (CIPN) | NCT04367480         | University of Rochester NCORP Research Base   | NA    | NS                                                                          | TENS                                             |
| Feasibility Study for Electroacupuncture for Chemotherapy-Induced Peripheral Neuropathy (CIPN) | NCT04092764         | H. Lee Moffitt Cancer Center and Research Institute | NA    | Taxanes or Platinum-Based                                                   | Electroacupuncture vs. NeuroMetrix vs. Rydel-Seiffer tuning fork |
| Acupuncture for Chemotherapy-induced Peripheral Neuropathy | NCT03582423         | Hong Kong Baptist University                  | NA    | Eight cycles of adjuvant oxaliplatin-based chemotherapy                    | Electroacupuncture vs. sham acupuncture          |
| Scrambler Therapy in the Treatment of Chronic Chemotherapy-Induced Peripheral Neuropathy | NCT02111174         | Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins | NA    | NS                                                                          | Scrambler therapy vs. sham therapy               |

Abbreviations: NA, not applicable; NS, not specified; TENS, Transcutaneous Electrical Nerve Stimulation.

#### 4.4. Honeybee Venom Pharmacopuncture

Melittin is a 26 amino acid amphiphilic peptide that accounts for 40–50% dry weight of the venom. It is the vital pharmacological component of honeybee venom [121], with analgesic, anti-inflammatory, and anticancer effects [122]. Combined with the acupoints, pharmacopuncture is suggested to improve CIPN [123–126].
4.5. Challenges of TCM for CIPN

Several challenges remain for applying TCM for CIPN management. TCM syndrome plays a vital role in TCM fundamental theories. The main limit is the high difficulty of comparing alternative medicines with respect to the principles of evidence-based medicine. A precise scientific method to identify specific TCM syndrome and to consider and evaluate clinical trials will be essential. Additionally, the source, process methods, active component identification, and quality control of herbal medicine remain to be standardized. Furthermore, TCM techniques such as acupuncture, concise practitioner training, acupoint selection, deep of needle insertion, and practical protocols will be crucial. Nevertheless, TCM syndrome-specific animal models, effective chemotherapeutic agents, mode of delivery (intravenous rather than intraperitoneal injection), and adequately randomized and blinded studies are needed to represent real clinical situations [4].

5. Conclusions and Future Perspectives

CIPN is a common and persistent side effect of common chemotherapeutics. Currently, there is no intervention available for its prevention, although duloxetine has shown moderate treatment efficacy.

Study details of biological mechanisms attributing to CIPN will be required for finding the therapeutic niches. Additionally, an ideal preclinical model will be needed to better mimic individual differences, age- and gender-dependent phenotypes of interest, and the use of standardized behavioral tests for adequately powered study designs, including appropriate controls and randomization, is needed.

Clinical studies provide additional challenges. The intervention design, eligibility criteria selection, outcome measures and study endpoints, potential effects of an intervention on chemotherapy efficacy, and sample sizes of randomized groups based on anticipated effect size and variability are critical for research success. Systemic and multidisciplinary collaborative research ensure the development of next-generation strategies for CIPN treatment/prevention and provide benefits and better quality of life for cancer survivors suffering from CIPN.

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