

Progress of Research on the Prevention and Treatment of Chemotherapy-induced Peripheral Neurotoxicity by Traditional Chinese Medicine

Tianqi Chong¹, Yami Zhang^{2,*}

¹Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China

²Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China

*Correspondence Author

Abstract: Chemotherapy-induced peripheral neurotoxicity (CIPN) is a common and serious complication after chemotherapy in patients with malignant tumours, characterized by high incidence, insidious onset, and a lack of effective treatments, which seriously affects the quality of patients' survival. Modern medicine has limited preventive and therapeutic drugs for CIPN, and the clinical practice is based on dose adjustment and symptom management. In Traditional Chinese Medicine (TCM), CIPN is classified as "Bi syndrome" (Bi Zheng) and "blood Bi" (Xue Bi), and the core pathogenesis is "root deficiency and branch excess", which is based on the deficiency of qi and blood stasis, cold and blood stasis and the deficiency of the liver and kidney. In this paper, we systematically review the research progress of Chinese medicine in the prevention and treatment of CIPN, including internal treatment external treatment, and the combined intervention of acupuncture and medicine. Existing studies have shown that TCM can improve clinical symptoms and reduce the incidence of neurotoxicity through multi-targeted and holistic regulation, with high safety and good patient compliance. However, there are still problems such as in-depth exploration of the mechanism and lack of high-quality evidence-based evidence in the current study. In the future, we should further elucidate the mechanism of CIPN, optimize the combination of Chinese and Western medicine, and conduct more real-world studies and randomized controlled trials to enhance the level of clinical evidence and guide the rational use of drugs.

Keywords: Chemotherapy-induced peripheral neurotoxicity, Traditional Chinese medicine, Internal treatment, External treatment.

1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common complications observed in cancer patients following chemotherapy. Epidemiological data indicate that the incidence of CIPN can be as high as 80%. Common chemotherapeutic agents associated with CIPN include platinum-based drugs, taxanes, and vincristine, among others [1]. Clinically, CIPN primarily manifests as dysfunction of the peripheral nervous system, characterized by symmetrical sensory neuropathy. Typical symptoms present as glove-and-stocking distribution paresthesia in the distal extremities, including numbness, burning pain, tingling sensations, thermal hypersensitivity, and reduced sensory perception. In severe cases, patients may develop impaired fine tactile sensation and autonomic nervous system dysfunction. According to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, CIPN is graded from 1 to 4. Notably, grade 3 or 4 neurotoxicity often necessitates dose reduction or even discontinuation of chemotherapy, thereby adversely affecting patient prognosis and quality of life [2].

CIPN has emerged as a critical clinical challenge that significantly compromises patients' quality of life. This is attributed to its insidious onset, irreversible progression, and the paucity of effective therapeutic interventions. Symptoms may persist for months or even years following the cessation of chemotherapy, and in some cases, exhibit a "coasting" phenomenon-defined as the continued worsening or exacerbation of neurotoxic symptoms even after treatment discontinuation [2]. Currently, therapeutic options for CIPN remain limited within Western medicine. Duloxetine is the only agent recommended by the American Society of Clinical Oncology (ASCO) to alleviate CIPN-associated pain;

however, its efficacy is modest and accompanied by potential adverse reactions [3]. The efficacy of other agents, such as calcium and magnesium infusions or pregabalin, remains controversial and lacks consistent validation [4]. Both ASCO and the European Society for Medical Oncology (ESMO) guidelines emphasize that there is currently insufficient evidence to support the use of any pharmacological agent for the prevention of CIPN. Consequently, clinical management primarily relies on dose modification and symptomatic control [2].

No records pertaining to CIPN are found in ancient medical texts. In Traditional Chinese Medicine (TCM), this condition is classified under categories such as "Bi syndrome" (Bi Zheng), "blood Bi" (Xue Bi), "numbness" (Ma Mu), and "cold syncope" (Han Jue). It is believed that chemotherapeutic agents, being predominantly bitter and cold in nature, consume the body's Qi and blood. This leads to impaired circulation, blood stasis obstructing the collaterals, and cold congealing in the meridians, thereby resulting in symptoms such as limb numbness and pain [4]. Relevant studies indicate that TCM demonstrates unique advantages in the prevention and treatment of CIPN. These interventions- including oral herbal medicine and external therapies (such as acupuncture, fumigation, soaking, and topical application)- exhibit characteristics of multi-target regulation and holistic modulation. They are associated with fewer adverse reactions and higher patient acceptance and compliance [4]. In recent years, a large number of clinical studies have confirmed the efficacy of TCM in managing CIPN. However, the quality of these studies varies considerably, and there remains a lack of unified standards.

2. Theoretical Background

2.1 The Understanding of the Pathogenesis of CIPN in Modern Medicine

The pathogenesis of CIPN is complex, involving multiple pathological pathways. Platinum-based agents, taxanes, and vinca alkaloids are common chemotherapeutic drugs known to induce neurotoxicity in clinical settings; the mechanisms underlying this toxicity vary depending on the specific agent. Current studies indicate that platinum-based drugs primarily form DNA adducts that interfere with the proper transcription of ribosomal RNA, thereby damaging dorsal root ganglion (DRG) neurons [5]. Additionally, these agents can bind to mitochondrial DNA (mtDNA); once bound, the mtDNA becomes irreparable, leading to increased reactive oxygen species (ROS) and oxidative stress. Consequently, intracellular enzymes, proteins, and lipids may be damaged by pathological levels of cellular metabolism and ROS, resulting in structural changes in peripheral nerves [6]. Platinum agents can also cause dysfunction of ion channels-particularly sodium channels-leading to acute cold hypersensitivity and chronic cumulative neuropathy [7]. Taxanes stabilize abnormal microtubule bundles in the cytoplasm. While stabilizing microtubules, they concurrently impair axonal transport, which is responsible for carrying essential cellular components via synaptic vesicles; furthermore, they activate inflammatory signaling pathways, leading to nerve damage [8]. Vincristine, a vinca alkaloid, binds to tubulin, inhibiting microtubule polymerization, disrupting axonal transport, and interfering with normal mitochondrial function [4]. Common mechanisms shared among these drugs include mitochondrial dysfunction and oxidative stress, neuroinflammatory responses (activation of microglia and astrocytes), ion channel dysregulation, and downregulation of nerve growth factor (NGF) expression [4].

2.2 The Understanding of the Etiology and Pathogenesis of CIPN in Traditional Chinese Medicine

As stated in Suwen (The Plain Questions) · Treatise on Bi-Syndrome, “In cases where there is no pain but only numbness, it indicates that the disease has penetrated deeply due to its chronic nature; the flow of Ying (Nutritive) and Wei (Defensive) Qi becomes rough, and the meridians and collaterals are occasionally obstructed, hence the absence of pain. When the skin fails to receive nourishment, numbness ensues.” Guided by the principles of holistic concept and treatment based on syndrome differentiation, TCM categorizes this condition under the umbrella of “Bi-Syndrome” (Bizheng). Traditional Chinese Medicine defines its core pathogenesis as “root deficiency with branch excess” (Benxu Biaoshi). Chemotherapeutic agents, mostly classified as cold-natured substances, are potent and damaging to the body’s orthodoxy (Zhengqi); they consume Qi and damage blood, leading to impaired circulation of Qi and blood, obstruction of the vessels, and resulting in numbness and pain [9]. Chen Ting et al. investigating the TCM syndromes associated with oxaliplatin-induced peripheral neurotoxicity in colorectal cancer patients, found that the most prevalent syndrome was Qi deficiency with blood stasis, followed by cold-dampness obstruction and deficiency of both Qi and blood [10]. Huang Junjie et al. summarizing the clinical experience of Professor Lin Lizhu in treating CIPN, proposed understanding CIPN from the perspective of “Cold Deficiency

Bi-Syndrome.” They argued that its core pathogenesis involves Yang Qi deficiency, cold congealing with blood stasis, and meridian obstruction. Consequently, treatment should prioritize “dredging collaterals and eliminating bi-syndrome” as the primary external therapy method, and “regulating Qi and tonifying deficiency” as the fundamental internal therapy [9]. Cao Wen et al. also noted that the pathogenesis of CIPN can be summarized by three characters: “Deficiency (root), Stasis (branch), and Cold (trigger).” Here, deficiency refers to the root cause (Qi-blood deficiency, liver-kidney insufficiency), stasis is the manifestation (blood stasis blocking collaterals), and cold acts as the trigger (cold hypersensitivity induced by oxaliplatin) [11].

2.3 Theoretical Basis of Traditional Chinese Medicine in the Prevention and Treatment of CIPN

Based on the aforementioned understanding of its pathogenesis, the primary therapeutic principles of TCM for the prevention and treatment of CIPN focus on replenishing Qi and blood, activating blood circulation to remove meridian obstruction, warming the meridians to dispel cold, and nourishing the liver and kidneys [11]. Treatment strategies can be categorized into internal and external therapies. Internal therapy adheres to the principle of “treatment based on syndrome differentiation,” utilizing modified formulas such as Buyang Huanwu Decoction and Huangqi Guizhi Wuwu Decoction according to the patient’s specific pattern. External therapies include herbal fumigation, soaking, application, and acupuncture. These methods leverage transdermal absorption and thermal effects to deliver medicinal efficacy directly to the affected sites and improve local microcirculation; alternatively, they stimulate specific acupoints via needling or moxibustion to dredge the meridians and harmonize Qi and blood [12]. Both approaches can be employed independently or in combination, embodying the TCM philosophy of “integrated internal and external treatment”.

3. Literature Review

3.1 Internal Treatment

3.1.1 Application of Classical Formulas

Huangqi Guizhi Wuwu Decoction (HQGZWWD), a classic Traditional Chinese Medicine formula derived from the Synopsis of the Golden Chamber (Jin Kui Yao Lue), is currently one of the most widely used prescriptions. Composed of five herbs-Astragali Radix, Paeoniae Radix, Cinnamomi Ramulus, Zingiberis Rhizoma Recens, and Jujubae Fructus-it functions to replenish Qi, warm the meridians, and harmonize blood to relieve numbness. It is primarily indicated for patients with Qi deficiency and blood stasis syndrome [13]. Recent studies have demonstrated its therapeutic potential in managing CIPN. Wang Xiaorou observed the intervention effects of this formula on breast cancer-related CIPN, reporting that it significantly reduced the incidence of CIPN while improving nerve conduction velocity [13]. Similarly, Dai Lingling utilized Wenjing Tongmai Granules, a modified version of HQGZWWD, to treat oxaliplatin-induced peripheral neurotoxicity. This study not only confirmed the clinical efficacy of the formula but also explored its underlying mechanisms [14]. Furthermore,

multiple studies suggest that the neuroprotective effects of HQGZWW are mediated through various pathways. These include downregulating NR2B expression in the spinal dorsal horn, upregulating phosphorylated neurofilament-H (PNF-H) protein levels in the dorsal root ganglion (DRG), and promoting the expression of nerve growth factor (NGF) [15].

Danggui Sini Decoction is another significant formula. Also originating from the *Treatise on Cold Damage Diseases* (Shang Han Lun), it states: “For cold extremities of the hands and feet with a minute, nearly imperceptible pulse, Danggui Sini Decoction is the principal treatment.” Its composition includes *Angelicae Sinensis Radix*, *Cinnamomi Ramulus*, *Asari Radix et Rhizoma*, *Glycyrrhizae Radix et Rhizoma*, *Paeoniae Radix Alba*, *Jujubae Fructus*, and *Akebiae Caulis*. The formula functions to warm the meridians, dissipate cold, nourish blood, and unblock the vessels, making it suitable for patients presenting with “deficiency of both Qi and blood accompanied by cold congealing in the meridians.” Relevant studies have shown that Luo Hui utilized Sini San combined with modified Danggui Sini Decoction to prevent and treat oxaliplatin-induced peripheral neurotoxicity, thereby verifying its clinical efficacy [16]. Furthermore, this formula has been demonstrated to alleviate symptoms of cold hypersensitivity induced by oxaliplatin [16].

The Buyang Huanwu Decoction (BYHWD) is also among the applicable formulas. With *Astragali Radix* serving as the sovereign herb, this formula is combined with herbs such as *Angelicae Sinensis Radix*, *Persicae Semen*, *Carthami Flos*, *Chuanxiong Rhizoma*, and *Pheretima*. Its function is to replenish Qi, invigorate blood, and unblock collaterals to relieve pain. Clinical studies have shown that BYHWD can alleviate symptoms in CIPN patients, including numbness, tingling, and hypesthesia of the hands and feet. Zhang Yongchao et al. noted that the combination of BYHWD with Western medicine for the treatment of peripheral nerve injury following chemotherapy yields superior overall efficacy compared to Western medicine alone [4].

Beyond these remedies, replenishing formulas like *Ba Zhen Tang* and *Shi Quan Da Bu Tang* are commonly utilized in clinical practice for CIPN cases characterized by a deficiency of both Qi and blood [4].

3.1.2 Research on Empirical Formulas and Self-Formulated Formulas

In addition to classical traditional formulas, numerous empirically derived formulas and practitioner-designed prescriptions have demonstrated favorable clinical outcomes in the intervention and treatment of CIPN. Zeng Chuanxiu conducted a systematic study on the neuro-toxicity following oxaliplatin chemotherapy using the *Yiqi Tongluo* formula combined with acupuncture therapy, evaluating both its clinical efficacy and underlying mechanisms [17]. Huang Junjie selected the *Tongluo Huoxue* formula for experimental trials targeting peripheral nerve injury induced by taxane-based chemotherapeutic drugs; the results validated the clinical effectiveness of this prescription [18]. Zhang Qiao observed that the *Zhimao* formula alleviated symptoms such as limb numbness and paresthesia in patients suffering from oxaliplatin-related peripheral neurotoxicity [19]. Jiao Jiao's

team utilized the *Wenjing Hexue Tongbi* formula to treat oxaliplatin-induced peripheral neurotoxicity in patients diagnosed with Qi and blood deficiency; their findings confirmed that the formula could reduce both the incidence and severity of adverse reactions [20]. Tan Weihang effectively improved oxaliplatin-induced peripheral nerve injury using the *Hezhong* formula [21]. Wu Chao adopted a comprehensive therapeutic approach-involving benefiting Qi, warming Yang, and activating blood circulation-to intervene in oxaliplatin-related neurotoxicity, fully demonstrating the unique advantages of TCM's multi-pathway combination therapy [22]. Yan Juntao employed a self-formulated *Wenyang Buxue Tongluo* formula for the clinical prevention and treatment of oxaliplatin-induced peripheral neurotoxicity; long-term case observations confirmed its precise efficacy and stability [23]. Ji Yuanyuan applied the *Yiqi Jiedu Tongluo* formula to colorectal cancer patients undergoing chemotherapy, intervening proactively to prevent oxaliplatin-induced peripheral nerve damage; her research focused primarily on the preventive efficacy of the formula [24]. Similarly, Xing Yiyang's team emphasized early prevention, utilizing the *Juanbi Huoluo* formula for preemptive intervention, which significantly reduced the incidence of oxaliplatin-induced peripheral neurotoxicity and confirmed the formula's preventive effects [25].

3.1.3 Studies on the Active Ingredients of Chinese Materia Medica

There is a growing focus on the neuroprotective roles of TCM and its bioactive compounds. Specific examples include *Astragaloside IV*, which protects neurons through antioxidant and anti-inflammatory pathways as well as by promoting NGF expression; *Ginsenosides Rg1* and *Rb1*, which prevent neuronal apoptosis and enhance neuroconductivity; *Curcumin*, known for its anti-inflammatory effects and ability to modulate mitochondrial function; and *Tetramethylpyrazine*, which improves microcirculation and suppresses P2X3 receptor activation to relieve neuropathic pain [4]. These studies offer valuable theoretical insights into the mechanisms of TCM compound formulations.

3.2 External Treatment

External therapies of TCM are a vital approach for the prevention and treatment of CIPN. They act directly on the affected areas and offer advantages such as ease of operation, high patient compliance, minimal side effects, and high safety. While the pharmacological mechanisms of external and internal therapies are identical, they differ only in the route of administration. Major modalities include herbal fumigation and soaking, acupuncture, and indirect moxibustion.

3.2.1 External herbal bathing

Liu Yang observed the effects of *External Wash I Formula* used externally to prevent and treat oxaliplatin-induced peripheral neurotoxicity; the results showed that it effectively reduced the incidence of neurotoxicity [26]. Gao Dehui adopted *Qigui Wenyang Tongluo Tincture* for external use combined with TDP irradiation to treat oxaliplatin-induced peripheral neurotoxicity, achieving favorable outcomes. This approach fully demonstrates the integration of external

Chinese medicine therapy with modern physiotherapy techniques [27].

3.2.2 Other therapies

Li Wenxia et al. observed that oxaliplatin-induced peripheral neuropathy (OIPN) predominantly manifests as Qi deficiency and blood stasis syndrome. They validated the therapeutic efficacy of the “Jinlong Tongbi Plaster” (Tendon-Relaxing and Obstruction-Freeing Plaster) in treating this condition [28]. Li Yilan et al. utilized indirect moxibustion at specific acupoints to treat platinum-based chemotherapy-induced peripheral nerve injury, achieving significant symptom relief in patients [29]. Chen Weibin conducted a clinical study involving 80 patients with oxaliplatin-induced peripheral neurotoxicity, administering acupuncture at specific acupoints. The results demonstrated a total effective rate of 70.00% in the observation group compared to 47.50% in the control group, indicating a significant therapeutic effect [30].

3.2.3 Exploration of the Mechanisms of External Therapies

Regarding the mechanisms of TCM external therapy, current understanding primarily encompasses the following aspects. Firstly, after transdermal absorption, medicinal components act directly on the local area to improve microcirculation, while simultaneously exerting anti-inflammatory and analgesic effects and promoting nerve repair. Secondly, the thermal effect accompanying external treatment facilitates vasodilation and accelerates local tissue metabolism, thereby creating a more favorable environment for nerve recovery. Thirdly, acupoint stimulation at specific sites regulates the flow of Qi and blood within the meridian system, reflecting the holistic regulatory characteristic of TCM external therapy [31]. Modern medical research indicates that acupuncture promotes nerve regeneration and functional reconstruction while improving sensory nerve abnormalities through multiple mechanisms. These include improving the microenvironment of peripheral nerve cells, reducing oxidative stress damage in peripheral nerves, regulating brain neuroplasticity, and modulating axonal reflexes [27].

3.3 Combination of Acupuncture, Medicine, and Comprehensive Intervention

Integrating acupuncture with medication has become a vital approach for preventing and treating CIPN in clinical settings. For instance, Zeng Chuanxiu et al. validated the clinical efficacy of the Yiqi Tongluo formula combined with acupuncture against oxaliplatin-induced peripheral neurotoxicity and elucidated its mechanisms, thereby demonstrating a significant synergistic effect [17]. Corroborating these findings, Wang Qian et al. found that such combination therapy outperforms single-modality treatments in mitigating chemotherapy-induced peripheral neurotoxicity [32]. Additionally, Wu Chao utilized an internal-external therapeutic regimen based on Yiqi Wenyang Huoxue to address the same condition, effectively illustrating the holistic nature of TCM treatment [22].

4. Conclusion

In summary, TCM has made certain progress in the prevention

and treatment of CIPN, effectively alleviating clinical symptoms and improving the quality of life for patients. However, several gaps remain in this field. For instance, research on the pathological mechanisms is still lacking in depth, and the mechanisms, targets, and pathways of many effective herbal formulas have yet to be fully elucidated. Furthermore, there is a relative scarcity of high-quality studies based on real-world data, and the overall level of existing evidence remains low. These limitations have, to some extent, hindered the further development of TCM in this area. Therefore, future research should focus on further elucidating the pathogenesis and progression of CIPN and continuing to optimize integrated TCM and Western medicine treatment protocols. Concurrently, there is a need to actively explore novel therapeutic methods and administration routes. The ultimate goal is to provide better guidance for rational clinical drug use and to further enhance patient quality of life [33].

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