

Original Paper

Research Progress on Chemotherapy-Induced Peripheral Neuropathy in Traditional Chinese and Western Medicine

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Abstract

Chemotherapy-Induced Peripheral Neuropathy (CIPN) is one of the common adverse reactions in the treatment of malignant tumors. Among them, drugs such as taxanes, platinumines and vincristine have a relatively high induction rate, which not only affects the quality of life of patients, It also interferes with the normal progress of clinical treatment. At present, its pathogenesis is complex and there is no effective prevention plan. By analyzing and integrating relevant literature at home and abroad, this paper summarizes the pathogenesis of CIPN, and concludes the prevention and intervention methods of traditional Chinese and Western medicine to provide systematic theoretical support for further exploration of the pathogenesis of CIPN and clinical diagnosis and treatment.

Keywords

Chemotherapy, Peripheral neuropathy, Chinese and Western Medicine, Research Progress

1. Introduction

Chemotherapy, as a core approach to comprehensive treatment of malignant tumors, can effectively prolong the survival period of patients. But the various toxic reactions it brings are hard to avoid. Among them, chemotherapy-induced peripheral neuropathy, with its high incidence, persistence and even irreversibility, has become a major difficulty in clinical diagnosis and treatment. In Western medicine, vitamin and neurotrophic drugs are often used, but their overall improvement ability is limited^[1]. Traditional Chinese medicine has obvious advantages in the prevention and treatment of peripheral neuropathy, and various regimens can prevent and treat chemotherapy-induced nerve damage symptoms^[2] in a short time. This article series reviews the pathological mechanisms related to CIPN and the treatment

methods of traditional Chinese and Western medicine, with the aim of providing a reference for the development of new prevention and treatment strategies.

2. Pathogenesis of CIPN

2.1 DRG Injury Induces Sensory Abnormalities

Abnormal signals such as dullness, numbness, and neuralgia are conducted to the central nervous system through the Dorsal root ganglion (DRG) of the peripheral nerves, which lacks the protection of the blood-brain barrier and lymphatic system, where chemotherapy drugs accumulate and produce cytotoxicity^[3]. Platinum-based drugs can bind to DNA inside neurons to form complexes that accumulate in DRG tissues, causing neuronal damage and apoptosis^[4]. Chemotherapy drugs such as paclitaxel, vincristine, thalidomide and bortezomib can also cause DRG damage^[5-7].

2.2 Mitochondrial Dysfunction and Oxidative Stress Response

Mitochondria are primarily responsible for regulating normal energy metabolism in the body and are involved in multiple physiological and pathological regulatory processes. Anti-tumor drugs can disrupt normal mitochondrial function^[8] through multiple pathways. Platinum-based drugs disrupt mitochondrial DNA replication, transcription and protein synthesis by binding to it, thereby causing a decrease in cellular metabolism, an increase in oxidative stress response and peripheral nerve damage^[9-11]. Paclitaxel drugs are involved in the entire ^[12] process of CIPN occurrence and development by altering the permeability pores of the mitochondrial membrane, promoting the release of large amounts of calcium ions, activating calprotease, degrading proteins such as neuronal calcium sensors, causing mitochondrial depolarization, energy and neuronal dysfunction.

2.3 Abnormal Function of Cell Membrane Channels

After chemotherapy drugs invade the peripheral nervous system, the functions and expressions of multiple cell membrane channels are altered, and neural signal transduction is disrupted. The related channels are mainly divided into two categories: one category regulates nerve excitation conduction, including voltage-gated sodium, potassium, calcium ion channels, etc. After paclitaxel treatment, the expression level of sodium channels in the dorsal root ganglion is increased, resulting in overexcitation^[13] of neurons. After treatment with oxaliplatin, potassium channel expression is significantly downregulated and neuronal membrane excit ^[14] ability is enhanced. Chemotherapy drugs also up-modulate voltage-gated calcium channels, lower the threshold for action potential initiation, and persistently cause abnormal neural excitation^[15]. Another class is responsible for regulating the drug transmembrane transport process, such as transporters like OCT2, Atp7a, Mate1, etc^[16]. It directly affects the accumulation of drugs in neuronal cells.

3. Prevention and treatment of CIPN

3.1 General Measures

① Strengthen health education and daily care, remind patients to rest well and keep warm, and try to

avoid contact with cold items, metal objects, cold air, etc. ② Have a light diet and strictly avoid spicy and irritating foods; ③ Reduce skin friction and irritation and avoid using irritating topical products; ④ Prioritize central intravenous infusion of chemotherapy drugs to reduce the risk of peripheral intravenous infusion; ⑤ Moderately extend the duration of intravenous infusion to alleviate drug toxicity; ⑥ Once neurotoxic symptoms occur, the medication should be immediately suspended, the dosage reduced, or the treatment interval increased based on the individual condition of the patient. Symptomatic treatment should be provided for symptom improvement, and the chemotherapy plan should be resumed after evaluation.

3.2 Medication Treatment

3.2.1 Mecobalamin

Mecobalamin, an activated form of vitamin B12 that can regenerate and repair damaged peripheral nerves and reduce the neurotoxicity caused by glutamic acid, is often clinically considered safe, effective and well^[17] tolerated by patients. Studies have confirmed ^[18] that mecobalamin can effectively relieve vincristine-induced neuralgia, reduce mitochondrial damage, inhibit the activation of the oxidase pathway, and balance pro-inflammatory and anti-inflammatory cytokines in the spinal dorsal horn. These findings provide new research targets for the prevention and control of chemotherapy-related neuralgia.

3.2.2 Lidocaine and Methicilline

Both lidocaine and mesetine are sodium channel bloc^[19] kers that improve neuropathic pain caused by various etiology, including CIPN. Clinical data showed that among 9 CIPN patients treated with intravenous lidocaine, 8 patients experienced transient relief of abnormal pain and 5 patients achieved long-lasting analgesic effects^[20]. In clinical practice, if adverse reactions such as irritation and discomfort occur at the injection site after lidocaine injection, oral methicilline treatment can be promptly switched.

3.2.3 Calcium and Magnesium Infusion

Calcium and magnesium preparations can regulate nerve conduction, maintain a stable intracellular environment, and alleviate chemotherapy-induced neuralgia. Existing studies have confirmed that calcium-magnesium infusion can significantly improve grade II neurotoxic damage caused by oxaliplatin, which can be significantly improved ^[21] by calcium-magnesium infusion, but the exact value still needs to be verified by clinical trials.

3.2.4 Venlafaxine and Duloxetine

These two classes of drugs are often used in clinical practice to treat major depressive disorder by blocking the reuptake process of serotonin and norepinephrine on the postsynaptic membrane and increasing the concentration ^[22] of neurotransmitters in the synaptic cleft. Controlled clinical trials ^[22] divided CIPN patients into three groups: venlafaxine, duloxetine, and placebo. The results showed that both drugs could significantly lower neuralgia scores, with duloxetine having a more prominent overall effect in improving chemotherapy-related neuropathy.

3.2.5 Other Drugs

In clinical practice, other drugs such as ganglioside, amitriptyline, gabapentin, etc. have also been used

for the treatment of CIPN, but the current research is limited and more large-sample clinical data are needed to evaluate the efficacy.

4. Understanding of CIPN in Traditional Chinese Medicine

Modern Chinese medicine theory classifies symptoms such as numbness, cold pain, and abnormal sensations in the extremities of CIPN into the category of "bi syndrome". The core pathogenic factors of CIPN are invasion of drug toxins, deficiency of vital energy, and obstruction of blood vessels. Regarding pathogenesis and treatment, the external cause is the invasion of bitter and cold chemotherapy drugs, the internal deficiency of Yang qi syndrome, the combination of internal and external pathogenic factors leads to Yang qi not reaching the extremities, insufficient warmth of the extremities, cold coagulation of the meridians, blood stasis obstruction, resulting in cold pain and abnormal sensations in the extremities. The main clinical syndrome types are qi deficiency and blood stasis type, cold coagulation and blood stasis type, and qi and blood deficiency type, and the corresponding treatment methods are tonifying qi and activating blood to unblock meridians, warming Yang and activating blood to unblock meridians, and tonifying qi and nourishing blood to unblock meridians.

There are mainly two types of traditional Chinese medicine intervention methods for CIPN, one is internal treatment and the other is external treatment. The internal treatment is mainly based on Chinese herbal decoctions and Chinese herbal injections. The classic representative prescriptions include Huangqi Guizhi Wuwu Decoction, Buyang Huanwu Decoction, Danggui Sini Decoction, Yanghe Decoction, etc. External treatments include Chinese herbal external washing, acupoint application, acupuncture, auricular point pressing, massage, wax therapy, etc. The forms of treatment are diverse.

4.1 Internal Treatment Methods in Traditional Chinese Medicine

4.1.1 Oral Administration of Chinese Herbal Decoctions

1) Huangqi Guizhi Wuwu Decoction

This prescription is from "Essential Prescriptions from the Golden Cabinet: Combined Treatment of Pulse and Syndrome of Blood Arthralgia and Debility". It is a special prescription for blood arthralgia, and its core efficacy lies in harmonizing ying and Wei, tonifying qi and promoting blood circulation, and unblocking meridians. Modern pharmacological studies have shown that Huangqi Guizhi Wuwu Decoction can accelerate the regeneration^{[23][24]} of damaged nerves by improving limb microcirculation, eliminating free radicals, protecting neuronal structure, and regulating the expression of genes and proteins related to nerve repair. A controlled trial of gastric cancer patients receiving oxaliplatin chemotherapy found ^[25]that chemotherapy combined with modified Huangqi Guizhi Wuwu Decoction significantly reduced the incidence of neurotoxicity and injury grade. All observation indicators in the observation group were superior to those in the chemotherapy alone group, and the differences between the groups were statistically significant.

2) Buyang Huanwu Decoction

This prescription originated from "Medical Forest Correction" and is a representative prescription for qi

deficiency and blood stasis syndrome, with the effects of tonifying qi, promoting blood circulation and unblocking meridians. It is suitable for symptoms such as paralysis, numbness, weakness and pain of the limbs. The formula uses a large amount of qi-tonifying drugs and a small amount of blood-activating drugs, with qi-tonifying as the main and meridian-activating blood as the secondary, to achieve the effect that qi is abundant and blood flows, and stasis is dispersed and meridians are unobstructed. A meta-analysis that^[26] included eight randomized controlled trials showed that oral Buyang Huanwu Decoction could effectively prevent CIPN, reduce neurotoxic symptoms, decrease its incidence, and was safe to use. Pharmacological studies have found that Buyang Huanwu Decoction can also improve nerve microcirculation at the site of injury, promote Schwann cell proliferation, and assist in peripheral nerve repair^[27].

3) Dangui Sini Decoction

This prescription is from *Treatise on Cold Damage Disorders*. It is used to treat blood deficiency and cold convulsions. It is warm but not dry, tonifying but not blocked. It takes into account warming Yang and dispelling cold, tonifying qi and nourishing blood, promoting qi and activating blood, and regulating qi and blood simultaneously. Animal studies have found^[28] that the protein expression of TRP in the dorsal root ganglion of rats administered Dangui Sini Decoction decreased significantly, and the reduced protein level can relieve chemochem-induced limb cold sensitivity and neuropathic pain, confirming the practical value of this formula for CIPN.

4) Yanghe Decoction

The Yanghe Decoction, derived from the *Complete Collection of Surgical Syndromes and treatments*, was originally used to treat the Yin syndrome of outer shell sores and ulcers. Modern physicians have expanded its application scope based on its characteristics of "warming Yang and tonifying blood, dispelling cold and benefiting qi and promoting blood circulation" to treat CIPN by warming and tonifying the primordial Yang in the kidney and dispelling cold and dampness. Clinical observations show that the modified Yanghe Decoction can significantly reduce limb numbness and pain caused by chemotherapy. It reduces the probability of neurotoxicity and improves patients' tolerance to chemotherapy and quality^[29] of life.

4.1.2 Traditional Chinese Medicine Injection

Controlled studies on platinum-based chemotherapy-induced nerve injury showed^[30] that mecobalamin combined with Shenfu injection had a significantly better effect on improving pain, limb sensory abnormalities, and emotional state than the mecobalamin regimen alone; Shenqi Fuzheng injection combined with neurotolepin for patients undergoing oxaliplatin chemotherapy can effectively reduce accumulated peripheral neurotoxicity and lower oxidative stress levels, with prominent ^[31]clinical synergistic intervention advantages.

4.2 External Treatment of Traditional Chinese Medicine

4.2.1 External Washing with Chinese Herbal Medicine

Chinese herbal external wash works by transdermal absorption through the skin, acupoints, meridians,

etc., directly acting on the lesion site, making the drug more concentrated and effective. Clinical studies have shown^{[32][33]} that the Juanbi Huolue formula wash combined with Leihuo moxibustion can reduce oxaliplatin-induced neurotoxicity and protect peripheral nerve function; The modified Huangqi Guizhi Wuwu Decoction for fumigation and washing of CIPN in patients with gynecological malignancies can improve the quality of life of tumor patients without obvious adverse reactions.

4.2.2 Acupoint Application

Acupoint application therapy was first recorded in "Fifty-Two Prescriptions for Diseases". It relies on stimulating local acupoints to unblock the meridians throughout the body, regulate the functions of qi and blood in the internal organs, and enable the drugs to directly penetrate the skin surface, reducing the metabolic burden on the liver and kidneys caused by oral medication. In patients with paclitaxel-induced neuropathy, after applying Guizhi Fuzi Decoction to acupoints, the sensory and motor conduction velocities of the median nerve and common peroneal nerve were significantly improved, and the overall treatment effectiveness exceeded that of the group^[34] treated with Western medicine alone.

4.2.3 Acupuncture

Acupuncture works by needling specific points to unblock meridians, harmonize Yin and Yang in the body, and stimulate and regulate the circulation of essence, qi and blood in the patient's local area and throughout the body to improve various symptoms of CIPN. In the treatment of patients^[35] with peripheral neurotoxicity after oxaliplatin chemotherapy, Buyang Huanwu Decoction combined with acupuncture and blood release can improve the KPS physical condition score, reduce the neurotoxicity grade, and accelerate the recovery of nerve conduction function; When Hegu, Taichong, Zusanli and other acupoints are selected for treatment^[36], the improvement effect on paclitaxel-induced nerve injury is better than that on oxaliplatin-induced lesions. The core mechanism of acupuncture analgesia has been confirmed^[37] in animal studies, which can induce the release of endorphins and enkephalins related to muscle nerves and regulate the pain conduction pathways at the spinal cord, midbrain, and hypothalamic-pituitary levels.

4.2.4 Other External Treatments

Auricular points, massage, wax therapy and other traditional Chinese medicine treatments also have multiple advantages. Studies have shown that auricular point pressing combined with external Chinese herbal washing can reduce the incidence^[38] of neurotoxicity; Massage techniques can relieve the stabbing and numbness^[39] of grade 2 CIPN; Wax therapy, with its warming effect, accelerates local blood circulation and promotes the metabolism of pain-causing substances. When combined with mecobalamin to treat albumin-paclitaxel-associated neuropathy, the clinical total effective rate can be increased from 77% to 95%, and the nerve conduction velocity can also be significantly optimized^[40].

5. Conclusion

At present, CIPN remains a major challenge in clinical oncology diagnosis and treatment. To effectively address this issue, it is necessary to conduct more rigorous basic and clinical research, develop effective

and safe drugs to serve patients, apply traditional Chinese medicine, intervene through multiple channels and means, provide new breakthroughs for diagnosis and treatment, and establish a systematic and scientific comprehensive prevention and treatment system for CIPN.

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