

# *Progress in the Prevention and Treatment of Peripheral Neurotoxicity Induced by Chemotherapy with Traditional Chinese and Western Medicine*

Ming Zou<sup>1,a</sup>, Yiduo Wang<sup>1,b</sup>, Pengli Wang<sup>2,c,\*</sup>

<sup>1</sup>*Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China*

<sup>2</sup>*Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712000, China*  
*<sup>a</sup>969828898@qq.com, <sup>b</sup>321639822@qq.com, <sup>c</sup>wplx0421@163.com*

*\*Corresponding author*

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**Abstract:** Chemotherapy induced peripheral neuropathy (CIPN) is one of the common toxic side effects of chemotherapy drugs for malignant tumors. There is no clear standard or guideline for the diagnosis and treatment of CIPN in Western medicine, and most of them are empirical drugs that have achieved certain therapeutic effects. On the basis of modern medicine, traditional Chinese medicine has continuously explored and attempted to find that traditional Chinese medicine treatment has excellent efficacy in preventing and treating CIPN. This article reviews the research progress in the prevention and treatment of CIPN in recent years by analyzing the pathogenesis of CIPN in traditional Chinese and Western medicine, in order to provide clinical workers with clinical diagnosis and treatment ideas.

## 1. Introduction

Chemotherapy induced peripheral neurotoxicity (CIPN) is one of the common Adverse drug reaction of chemotherapy drugs. It is often manifested as swelling pain, numbness and discomfort of the distal extremities, as well as abnormal tactile and thermal sensations. The symptoms are often symmetrical, even involving the proximal extremities, and tendon reflexes disappear or movement disorders occur. During the chemotherapy cycle of malignant tumor systems, if severe neuropathic symptoms occur, which are difficult for patients to tolerate, it often leads to a reduction in the dosage of chemotherapy drugs, or even cessation or change of medication. This not only affects the continuity of the treatment cycle, but also affects the efficacy; It will also reduce patients' daily life treatment, increase their psychological burden and stress. According to the different types of chemotherapy drugs, sometimes the severity of CIPN symptoms will gradually increase with the accumulation of chemotherapy drugs and the increase of treatment cycle, and even the symptoms will still exist after the end of chemotherapy. Therefore, for malignant tumor chemotherapy patients, CIPN is an important issue that cannot be ignored and urgently needs to be solved. According to research in recent years, both Western medicine and traditional Chinese and Western treatment have shown efficacy in preventing and treating CIPN.

## 2. Pathogenic mechanism of CIPN in Western medicine

The common chemotherapeutic drugs that cause peripheral neuropathy include platinum (such as Oxaliplatin, cisplatin, etc.), Vincristine, taxus, etc. At present, its pathogenesis has not been determined, which may be related to the sensory neurons on the Dorsal root ganglion (DRG) of the peripheral nerve injured by chemotherapy drugs. At the same time, factors such as dosage, treatment cycle, severity of disease and individual differences will also affect the occurrence and development of the disease.

The peripheral neurotoxicity of platinum chemotherapy drugs can be divided into acute and chronic [1]. The pathogenesis of platinum induced acute neurotoxicity is related to the changes of axonal Ion channel on neurons. Krishnan AV et al. [2] showed that Oxaliplatin can increase the Na<sup>+</sup>outflow of DRG cells, relatively reduce the inward flow, increase the negative value of Membrane potential, weaken the Action potential, lead to increased sensitivity and excitability of peripheral nerves, and mediate acute disease. However, the pathogenesis of chronic peripheral neurotoxicity of Oxaliplatin is believed by most scholars to be the result of the continuous accumulation of drugs in the body, from quantitative change to qualitative change, which is related to its influence on RNA synthesis and protein translation of neurons and the lack of axon function [3]. McDonald ES et al. [4] found through in vitro and in vivo experiments that platinum drugs can hydrate DNA, which can damage DRG cells and cause apoptosis, leading to axonal decay and neurotoxicity. Platinum drugs can also inhibit the replication of Mitochondrial DNA in DRG neurons, increase the active oxygen in vivo, lead to the imbalance of the body's protective system, and activate oxidative stress response mediated CIPN [5]. Taxus and vinblastine belong to Tubulin inhibitor drugs, both of which are dose dependent drugs. The mechanism of peripheral neuropathy of the two drugs is much the same, and both can mediate CPIN by influencing the structure of axonal microtubules. Vinblastine drugs can combine with Tubulin dimer, which hinders the synthesis of microtubule, resulting in incomplete axonal microtubule structure [6]; However, paclitaxel drugs have relatively high DRG concentrations and can affect the formation of microtubule structures by reducing the activity of ganglion cells [7], leading to abnormal signal transduction and resulting in neurotoxicity. Other studies have shown that paclitaxel and Vincristine can activate Langerhans cell, make Phagocyte gather around the nerve, promote the production and release of inflammatory mediators, and act on Free nerve ending pain receptors to trigger CIPN [8, 9].

## 3. Understanding the etiology and pathogenesis of CIPN in traditional Chinese medicine

There is no name of peripheral neurotoxicity caused by chemotherapy in the classic ancient books of Chinese medicine. According to the symptoms such as numbness, tingling, decreased sensation or loss of extremities, it can be classified into the categories of "bi syndrome", "flaccidity" and "inhumanity" in Traditional Chinese medicine. The etiology and pathogenesis of Bi syndrome are recorded in many classic ancient Chinese medicine books. "Su Wen": "Blood and Qi are all scarce... If one feels cold and dampness, it is good for Bi bone pain." "Su Wen Bi Lun": "Wind, cold, and dampness are mixed together to form Bi. The pathogenesis of tumor patients is always based on the principle of deficiency and excess, and chemotherapy drugs are all toxic substances, which further damage the vital energy. The vital energy is weak, and wind, cold, dampness, and evil enter by taking advantage of deficiency, leading to the onset of the disease; Cold evil dominates stagnation, and cold toxin is prone to stagnation, blocking the meridians. If the meridians are blocked, pain or reduced sensation may occur. The Five Changes of Lingshu: "Those who are rough in texture but not firm in flesh are good at disease and arthralgia. Chemotherapy drugs are cold and cold. Cold and cold products can easily damage the body's yang qi, especially the yang of the spleen and kidney. In addition, the spleen and stomach are the acquired foundation and the source of qi and blood

biochemistry. The spleen yang is insufficient, causing the spleen to lose its healthy circulation, the production of water and grain essence to be insufficient, and the deficiency of qi and blood leads to the loss of nourishment in the tendons, veins, bones, and meat, resulting in numbness and pain. The book "Su Wen · Generation of the Five Zang Organs" states: "Those whose blood clots on the skin are called Bi. Qi is the commander-in-chief of blood. Chemotherapy drugs consume Qi and damage Yin. Qi deficiency leads to weak blood circulation and poor blood circulation. Blood clots on the meridians, but blockage leads to pain; If the muscles and muscles lose their pride, it will cause pain if not honored. The neurotoxicity mechanism of chemotherapy drugs is complex, and most tumors suffer from insufficient qi and blood, with deficiency of the original qi, prolonged stagnation of blood stasis, phlegm dampness, and qi stagnation, all of which belong to the principle of deficiency and excess; Chemotherapy drugs are toxic, with a cold and cold taste, consuming qi and blood, damaging normal qi, and invading evil toxins, resulting in the loss of skin and muscles, stagnation of blood stasis and toxins, and numbness and pain in the limbs.

#### **4. Western medicine treatment**

At present, although a large number of drugs have been used for clinical efficacy research in the prevention and treatment of CIPN, and certain results have been achieved, there is no clear and detailed diagnostic and treatment standards and guidelines for the Western medicine treatment plan of CIPN. Therefore, the clinical treatment of peripheral neuropathy caused by chemotherapy is mostly empirical, and there are significant individualized differences in efficacy. The Western medicine treatment methods for CIPN can be roughly divided into general treatment and drug treatment.

##### **4.1. General treatment**

(1) Eat a light diet, strengthen the intake of high-quality protein, prohibit spicy and stimulating foods, pay attention to rest, maintain a happy mood, and enhance the body's immune system. (2) Pay attention to keeping your hands, feet, and limbs warm. You can use hand warmers or wear gloves to avoid contact with items that are too cold or too hot, metal aluminum products, and irritating liquids. (3) Reduce limb movement and weight bearing, do not stand, walk, etc. for a long time, do not carry heavy objects, etc., reduce skin friction on limbs, and keep local skin clean and dry. (4) Establish a central venous pathway to reduce the damage of chemotherapy toxic drugs to peripheral venous vessels. (5) According to the actual situation of the patient, appropriate choices should be made to extend the administration time, reduce the dosage, or even stop or change the medication.

##### **4.2. Drug treatment**

Apart from general treatment measures, drug prevention and treatment are also very important. At present, drugs commonly used in clinical treatment are as follows: (1) Ion channel regulators and antiepileptics: including calcium magnesium mixture, Gabapentin, Carbamazepine, Pregabalin, etc. The calcium ion in calcium magnesium mixture can be closed by changing the voltage dependent Sodium channel, while magnesium ion can promote sodium pump transport by restoring ATP function [10], thus reducing the incidence of acute peripheral neurotoxicity, which is commonly used to prevent and treat the neurotoxicity caused by Oxaliplatin. Pregabalin is commonly used in the treatment of peripheral Neuralgia and epilepsy. (2) Neurotrophic agents: Neural cells have a certain degree of self-healing ability, so providing them with sufficient raw materials and energy can indirectly promote the self-repair of neural cells, thereby achieving the goal of prevention and treatment. Therefore, neurotrophic drugs are widely used for the prevention and treatment of CIPN, with representative drugs such as methylcobalamin and vitamin drugs. Mecobalamin can promote the

formation of lecithin in the body, thus promoting the formation of medullary cavity, which is conducive to repairing myelin sheath damage, improving Nervous tissue transmission [11],and improving clinical symptoms. (3) Antioxidants: mainly including vitamin E,vitamin B, reduced glutathione, etc. Vitamin E and reduced glutathione are internationally recognized anti oxygen free radical drugs. Reduced glutathione can bind with free radicals in the body and convert them into easily metabolized acids, thereby promoting the excretion of free radicals and achieving antioxidant effects. At the same time, it can enhance the recovery of nerve cell function and reduce the neurotoxicity of chemotherapy drugs[12].(4)Tricyclic antidepressant: nortriptyline, amitriptyline, duloxetine, etc. Some studies have shown that duloxetine can effectively reduce the incidence of peripheral neuropathy [13], and it is the only drug recommended in the current guidelines that can be used to treat peripheral neuralgia caused by CIPN. Although there is currently no clear diagnostic and treatment standard for the treatment of CIPN, and many western medicine drugs have shown certain clinical efficacy in preventing and treating the disease, benefiting patients, the prevention and treatment measures for CIPN still need to be continuously explored and explored.

## **5. Traditional Chinese Medicine Internal Therapy**

The traditional Chinese medicine internal treatment method is one of the important components of traditional Chinese medicine treatment methods, which mainly involves absorbing traditional Chinese medicine preparations into the human body through oral, intravenous infusion, and other methods to exert their effects. The traditional Chinese medicine internal treatment method has a significant therapeutic effect on the prevention and treatment of CIPN. The following will explain and discuss from the aspects of classic traditional Chinese medicine decoction, self formulated compound formula, traditional Chinese medicine formula granules, and traditional Chinese medicine injection.

### **5.1. Classic Traditional Chinese Medicine Decoction**

#### **5.1.1. Danggui Sini Tang**

Modern research has shown that Danggui Sini Tang can also inhibit platelet aggregation, prevent venous thrombosis, and improve peripheral blood circulation and terminal microcirculation by altering blood rheology [14, 15]. Rong Ding et al. [16] randomly divided 48 cases of malignant tumor patients receiving Oxaliplatin chemotherapy into the experimental group (chemotherapy+traditional Chinese medicine) and the control group (chemotherapy), 24 cases each, and observed the efficacy after 4 consecutive chemotherapy cycles of traditional Chinese medicine. The results showed that the incidence of peripheral neuropathy in the experimental group was significantly lower than that in the control group ( $P<0.05$ ).

#### **5.1.2. Buyang Huanwu Tang**

Xuan Sun et al. [17] believed that Buyang Huanwu Decoction can promote the proliferation of Glia after injury, improve the microcirculation around the nerve injury, and has protective, repair and regeneration effects on the injured nerve. Modern medical research shows that Buyang Huanwu Decoction can change blood rheology, inhibit the formation of platelets and thrombus, prevent blood stasis, improve microcirculation of injured nerves, promote capillary growth, and repair damaged nerves [18]. Yumin Liu [19] found in the clinical experiment of observing the therapeutic effect of Buyang Huanwu Tang on CIPNL that the effective rate of the Chinese medicine combined with Western medicine experimental group was significantly higher than that of the Western medicine control group ( $P<0.05$ ).

### 5.1.3. Huangqi Guizhi Wuwu Tang

An animal experimental study has confirmed that Huangqi Guizhi Wuwu Tang can protect and repair peripheral nerve damage by downregulating the expression of NR2B in the 4th, 5th, and 6th lumbar spinal cord of rats and upregulating the level of pNF-H protein in DRG [20]. Yang Yang [21] observed the clinical efficacy of Huangqi Guizhi Wuwu Decoction in the prevention and treatment of peripheral neurotoxicity caused by oxaliplatin, and found that Huangqi Guizhi Wuwu Decoction can reduce the incidence rate of peripheral neuropathy caused by chemotherapy, and the neurological symptoms are relatively mild.

## 5.2. Self formulated compound formula

Xiaojuan Tang [22] randomly divided 60 patients into an experimental group and a control group with 30 cases each. On the basis of chemotherapy, the experimental group was added with a prescription for tonifying the kidney, removing blood stasis and detoxification (composed of cullen corylifolium, cinnamon, astragalus, zedoary turmeric, rhubarb, chuanxiong, caulis spatholobi, and stephania tetrandra) for oral administration, and the control group was given chemotherapy plus micobao tablet for oral administration. The results showed that the formula for tonifying the kidney, resolving blood stasis, and detoxifying can reduce the incidence and severity of CIPN, with a significant difference compared to the control group ( $P < 0.05$ ).

Weiyang Wang et al. [23] treated 56 malignant tumor patients who received chemotherapy with OXA containing regimen with self-made Huoxue Huayu Tang. The treatment group received oral administration of Huoxue Huayu Tang and traditional Chinese medicine fumigation to wash hands and feet on the basis of chemotherapy, while the control group received chemotherapy alone. The experimental results showed that the incidence and severity of neurotoxicity in the Huoxue Huayu Tang group were lower than those in the chemotherapy alone group. This study confirms that oral administration of traditional Chinese medicine combined with traditional Chinese medicine fumigation and washing can effectively prevent and treat neurotoxicity induced by OXA.

Lizhu Yan et al. [24] believe that yang deficiency and blood stasis are the basic pathogenesis of CIPN. Therefore, the treatment method is to warm yang, promote blood circulation, and dissipate blood stasis. They have developed a self-designed cancer rehabilitation I formula to treat peripheral neuropathy caused by OXA. The experimental results show that this formula can effectively prevent and treat chemotherapy induced peripheral neurotoxicity.

## 5.3. Traditional Chinese Medicine Formula Granules

### 5.3.1. Flavored Huangqi Guizhi Wuwu Formula Granules

Jun Ma et al. [25] divided 64 patients with postoperative adjuvant chemotherapy for colorectal cancer into an experimental group of 32 cases and a control group of 32 cases. The control group received a standard chemotherapy regimen, while the experimental group received a combination of modified Huangqi Guizhi Wuwu formula granules orally on the basis of chemotherapy, taking one dose daily, twice daily, for six consecutive courses of treatment. 56 cases were actually completed, with 28 cases in the control group and 28 cases in the experimental group. The results showed that the modified Huangqi Guizhi Wuwu formula granule could prevent and treat the peripheral neuropathy caused by oxaliplatin.

### 5.3.2. Shengyang Yiwei Granules

Jingru Cheng et al. [26] randomly divided 64 patients with malignant tumors into a control group

and a treatment group, with 32 cases in each group. The control group received basic chemotherapy, while the treatment group received oral administration of Shengyang Yiwei granules on the basis of chemotherapy. The results showed that the incidence of chronic nerve injury caused by chemotherapy in the treatment group was lower than that in the control group ( $P < 0.05$ ). Shengyang Yiwei Granule has good efficacy and safety in the prevention and treatment of peripheral nerve injury (spleen deficiency and phlegm turbidity type) caused by Oxaliplatin. Shengyang Yiwei Granules can significantly improve the symptoms of peripheral nerve injury, especially hand and foot numbness, and improve the overall treatment effect of primary malignant tumors, further improving the quality of life of patients.

## **5.4. Traditional Chinese Medicine Injection**

### **5.4.1. Huangqi Injection**

The active ingredient of astragalus injection is mainly astragalus extract. Some studies have shown that astragalus can protect the nerve injury caused by ischemia and reperfusion injury, strengthen the injured nerve fibers, and protect and repair the peripheral nerve fibers [27, 28]. Huijuan Cui et al. [29] observed the efficacy of astragalus injection in preventing neuropathy caused by chemotherapy containing oxaliplatin in 40 cases, suggesting that astragalus injection can effectively reduce the incidence of peripheral neurotoxicity caused by oxaliplatin chemotherapy ( $P < 0.01$ ).

### **5.4.2. Shenfu Injection**

A meta-analysis [30] showed that Shenfu injection has a certain preventive and therapeutic effect on peripheral neuropathy after chemotherapy, and can significantly reduce its incidence. Jingjuan Zhu et al. [31] observed the clinical efficacy of Shenfu injection in preventing peripheral neuropathy caused by chemotherapy containing oxaliplatin, and found that the incidence rate of neuropathy in the Shenfu injection treatment group was significantly lower than that in the control group (45.0% vs 72.5%,  $P < 0.01$ ).

### **5.4.3. Shenmai Injection**

Ginsenoside in Shenmai injection can regulate the metabolism of ganglion neurons to repair damaged neurons [32]. Fengqi Fang et al. [33] found that Shenmai Injection can reduce the incidence of neurotoxicity after platinum chemotherapy in 96 patients who received platinum containing chemotherapy combined with Shenmai injection.

## **6. Traditional Chinese Medicine External Therapy**

In addition to the internal treatment of traditional Chinese medicine, which can effectively prevent and treat peripheral neuropathy after chemotherapy, the external treatment of traditional Chinese medicine also shows its unique treatment methods and advantages in the prevention and treatment of CIPN, which mainly includes the fumigation and washing therapy of traditional Chinese medicine and acupuncture and moxibustion therapy.

### **6.1. Traditional Chinese Medicine Fumigation and Washing Therapy**

Li Wang [34] randomly divided 80 patients with CIPN into a control group and a treatment group with 40 cases each. The control group was given oral methylcobalamin capsules, while the treatment group was given fumigation and washing with water decoction of Xionggui Juanbi Formula, with a

cycle of 21 days. The therapeutic effect was observed after 4 cycles. Finally, a total of 77 patients (39 in the control group and 38 in the treatment group) were actually completed. The results showed that the therapeutic effect of the experimental group was greater than that of the control group after treatment ( $P < 0.05$ ). Yue Shi [35] randomly divided 60 chemotherapy patients containing drugs that cause changes in peripheral neuropathy into a treatment group (chemotherapy+external washing with traditional Chinese medicine) and a control group (chemotherapy+mecobalamin), with 30 cases in each group. After 14 consecutive days of treatment, the therapeutic effects of the two groups were observed. The results showed that external washing with Tongluo Juanbi Tang can effectively reduce the incidence of chemotherapy induced neurotoxicity. Anmei Wang [36] randomly divided 70 patients with colorectal cancer into a treatment group and a control group of 35 cases each: the control group received chemotherapy alone, while the treatment group received chemotherapy combined with Wenjing Huoxue Tang fumigation. The results indicate that fumigation with Wenjing Huoxue Tang can effectively reduce the incidence and severity grading level of CIPN.

## 6.2. Acupuncture and moxibustion therapy

Acupuncture and moxibustion, as an important part of traditional Chinese medicine therapy in China, has shown good efficacy in the clinical diagnosis and treatment of many diseases. At the same time, acupuncture and moxibustion has remarkable efficacy in improving CIPN. Some studies have shown that acupuncture can improve peripheral neuropathy, and its mechanism may be related to its ability to regulate the ion concentration in nerve cells, affect the transport of Ion channel, thereby enhancing the antioxidant capacity of neurons, and clearing excess free radicals inside and outside cells [37]. A meta-analysis [38] found that acupuncture treatment for CIPN received a "moderate" recommendation in terms of overall effective rate; acupuncture and moxibustion is also used to prevent and cure CIPN. Yangming Meridian is the main acupoint selected, and Zusanli, Hegu, Taichong, Quchi and Yanglingquan are commonly used acupoints.

Hongzhao Tian [39] randomly divided 60 patients with peripheral neuropathy who underwent FOL-FOX4 chemotherapy into a treatment group (acupuncture treatment) and a control group (intramuscular injection of 1mg of adenosorbide), with 30 patients in each group. The patients were treated continuously for 14 days, once a day. The results show that acupuncture can improve the peripheral neuropathy caused by chemotherapy, mainly Sensory nerve disorders, and can significantly improve the quality of life of patients. Zijian Su et al. [40] found in the observation of the clinical efficacy of intradermal acupuncture on peripheral neuropathy caused by chemotherapy that intradermal acupuncture can not only reduce the incidence rate and severity of peripheral nerve injury caused by oxaliplatin, but also delay the occurrence of peripheral neuropathy.

## 7. Summary

Peripheral neurotoxicity caused by chemotherapy is widely present in malignant tumor patients during the chemotherapy cycle, and its harm is increasingly being valued. Against the backdrop of poor efficacy in Western medicine treatment of CIPN, with the continuous attempts and explorations of traditional Chinese medicine in the prevention and treatment of CIPN, its internal and external treatment methods have achieved good efficacy in preventing and treating CIPN. In the future clinical diagnosis and treatment of CIPN, a combination of traditional Chinese and Western medicine can be used to demonstrate better clinical efficacy. Although the traditional Chinese and Western medicine treatment strategies for CIPN are becoming increasingly mature, there are still many shortcomings that need to be further explored and improved by more scholars.

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