DOI: 10.53469/jcmp.2024.06(06).40

Progress in Traditional Chinese and Western Medicine Treatment of Chemotherapy-Induced Peripheral Neuropathy

Xin Zhao[1], Lingling Qing[1], Yixuan Cao[1], Hailong Si[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
**Correspondence Author*

Abstract: ***In recent years, the incidence of malignant tumors rising rapidly, as targeted, immune treatment has brought the Gospel at the same time, due to the expensive drug, adapt to the limited, side effects make its clinical application is limited, so chemical therapy is still the cornerstone of the clinical treatment of malignant tumors. Chemotherapy-induced peripheral neuropathy (CIPN) is a common toxic and side effect in the process of chemotherapy. Modern medicine has no good treatment and drugs for modern medicine, mainly prevention. With its unique thinking mode of syndrome differentiation and the multi-target characteristics of Traditional Chinese Medicine (TCM), TCM may provide new ideas for the treatment of CIPN. This paper reviews the pathogenesis of peripheral neurotoxicity induced by chemotherapy drugs and the diagnosis and treatment of traditional Chinese and Western medicine.***

Keywords: Malignant tumor, Chemotherapy drugs, Chemotherapy-induced peripheral neuropathy, Traditional Chinese and western medicine treatment**.**

1. Introduction

Chemotherapy-related CIPN refers to the peripheral neuropathy of the extremities caused by chemotherapy drugs, mainly with sexual sensory and autonomic nerve dysfunction of the distal limb, which is manifested as pain, numbness and excessive sensitivity to temperature [1]. In severe cases, it may involve the proximal limbs, accompanied by the disappearance of tendon reflexes or motor disorders. Its common inducing drugs are paclitaxel, platinum, thalidomide and vincristine. The clinical use of oxaliplatin leads to a higher incidence of CIPN, and the neurotoxicity caused by these drugs is mostly dose-limiting toxicity, and the symptoms will worsen with the continuous accumulation of drug doses. Although relevant studies use methylcobalamin, vitamin, duloxetine and other drugs for prevention and treatment, but little effect, and some treatment methods are easy to cause nausea and vomiting, which did not benefit patients [2]. This study aims to explore the research progress of integrated Chinese and Western medicine, which can provide reference for clinical treatment of CIPN.

2. Mechanism of Action and Clinical Manifestations

The pathogenesis of CIPN is complex, different chemotherapy drugs affect different parts of the peripheral nervous system, patients usually first sensory nerve symptoms, mainly involving the hand and foot, foot symptoms often more obvious hand, by multiple, symmetry is long "gloves and socks" like from the end to the center of the distribution of pain, numbness, touch, temperature abnormalities and vibration damage, etc., to the end of the most obvious [3], in severe cases, these symptoms may develop into sensory ataxia and the loss of perception.

At present, the pathogenesis of CIPN is mainly in the following aspects:

2.1 DRG Harm

DRG is keeping up with the ganglion, spinal nerve for pain conduction of primary neurons, its sensory neurons, and no blood-brain barrier protection, chemotherapy drugs such as paclitaxel, oxaliplatin easy to enter the DRG toxicity, its inhibit the sensory neurons cell body rRNA synthesis, the protein synthesis disorder, sensory neuron organelle abnormal morphological changes and the corresponding functional damage [4]. Platinum drugs can form complexes with intracellular DNA and accumulate in DRG, leading to DRG cell damage and apoptosis [5]. Cisplatin mainly causes symptoms of sensory nervous system damage such as symmetrical distal limb paresthesias, numbness, pain, muscle spasm, disappearance of tendon reflexes, impaired fine movement and ataxia, and generally there is no performance related to motor nervous system damage [6]. The neurological toxicity of carboplatin is similar to that of cisplatin, mainly with sensory neuropathy. The manifestations of peripheral neuropathy caused by oxaliplatin are both acute and chronic. Acute occurs after a few hours, manifested by the end of the limb or perioral area sensory disorders (limb numbness and pain, throat numbness, throat and jaw tightening, tongue sensory abnormalities and language disorders, etc.) or / and sensory abnormalities (ant line sense, foreign body sensation, acupuncture sensation, etc.), the symptoms in the treatment interval usually reduced, reversible, but with the increase of treatment cycle and aggravating [4]. Chronic peripheral neuropathy refers to the peripheral neuropathy with limb numbness and paresthesia as the initial symptoms after several cycles of chemotherapy. With the accumulation of oxaliplatin dose, the decrease of fine touch and proprioceptive sensitivity, ataxia and even somatic dysfunction can occur secondary [7].

2.2 Microtubule Damage

Microtubules are a key structure for neuronal axonal energy

and material transport. Taxane drugs are microtubule inhibitors, and their microtubule condensation may affect the signal transmission and dysfunction of axons by interfering with microtubule formation [8]. The main manifestations are glove-sock-like numbness and burning at the limbs, and in severe cases, distal sensory loss of symmetry and tremor paralysis are the main symptoms [9].

2.3 Mitochondrial Damage and Oxidative Stress

Chemotherapy drugs and mitochondrial permeability conversion pore interaction induce its opening, change the mitochondrial calcium homeostasis and mitochondrial electron transport chain lead to mitochondrial membrane potential abnormalities, increased ROS generation, ATP levels, calcium release [10-12], calcium ion channel and sodium channel change, make the surrounding neurons excitability threshold changes, cause abnormal excitability [13]. The mitochondrial injury produces a large amount of reactive oxygen species, secondary to oxidative stress damage, leading to the occurrence of neurotoxicity.

3. TCM Knowledge of CIPN

There is no description of the name of peripheral nerve toxicity in traditional Chinese medicine according to the ancient books. According to the early symptoms of numbness and pain in the limbs, combined with the thinking mode of grasping the essence of the disease in the Department of Traditional Chinese medicine, CIPN can belong to the categories of "numbness", "bi syndrome" and "impotence syndrome" in traditional Chinese medicine. "Ask · the generation of the five zang" said: "blood coagulation in the skin, for bi." "Neijing" first put forward the name of the disease, and pointed out that the insensitive pathogenesis for "its pain and not benevolence, disease long into deep, rongwei astringent, meridians, so unreasonable; the skin is not camp, so it is not kind". Zhang Zhongjing, a famous doctor in the Eastern Han Dynasty, further explained the etiology and pathogenesis of blood bi: "The Yin and Yang are small, the mouth is small, the ruler is small and tight, the body is not kind, such as fengbi", and created the famous square Astragalus Guizhi soup, which is used today [14].

Modern medicine that chemotherapy drugs are cold, combined with tumor patients itself insufficient vital qi, after entering the body will further damage the body upright, qi, camp, weak, gas deficiency is weak blood astringent stagnation, blood deficiency, glory, blood gas, blood stasis, evil poison stranded, eventually meridians closed obstruction, veins loss, limb endings pain, numbness and other symptoms [15].

4. The Treatment of CIPN Caused by Chemotherapy Drugs

4.1 Western Medicine Treatment

For the patients with CIPN, Generally assessed using subjective scales, The most commonly used scales are EORTC-QLQ-CIPN20 scoring scale and NCI-CTCAE grading scale [16], The EORTC-QLQ-CIPN20 scoring scale assessment is a more comprehensive, Including the motor and sensory nerve symptoms, Autonomic nerve symptoms, The NCI-CTCAE grading scale is based on the assessment scale of healthcare workers, simplicity of operator, Contains both the sensory and motor aspects, Level 1-5 [15], For example, combined pain or anxiety and depression can be assessed by NRS, VAS scale and anxiety and depression scale. Western medicine treatment program mainly includes two aspects: drug therapy and non-drug therapy:

4.1.1 Pharmacotherapy

Clinically, for severe or acute CIPN, usually reduce the dose of chemotherapy drugs or stop therapy. Drug therapy mainly includes: 1) ion channel modulators (carbamazepine, gabapentin, pregabalin, etc. [17]), carbamazepine has many potential side effects, and monitor patient response and serum levels; gabapentin is an anticonvulsant drug, which can cross the blood-brain barrier with protein alphaz-delta of neuronal presynaptic voltage-gated calcium channel, and block nerve synapses without shoot Ca^{2+}Release, relieve the symptoms of mechanical pain sensitivity, but a small number of people taking gabapentin have drowsiness, fatigue and other adverse symptoms [13]. 2) Antioxidants and cytoprotective agents (mainly amifostine, glutathione, B vitamins and E vitamins), research found that glutathione can prevent p53 protein accumulation in the cells, thus blocking cell apoptosis [4], reduce chemotherapy drugs in the dorsal root ganglion accumulation, play the role of nerve protection. 3) Neurotransmitter reuptake inhibitors (duloxetine, venlafaxine, etc.), Duloxitin is a selective inhibitor of serotonin and norepinephrine reuptake [18], Although recognized by the American Clinical Society of Oncology (ASCO) is recommended for use, However, its efficacy on neuropathic pain is limited, To paraesthesia and dysfunction [19], And duloxetine due to its neurological and digestive system side effects such as drowsiness, nausea, vomiting, vertigo and other reverse limited the patient chemotherapy tolerance; Venlafaxine similarly reduces the motor, sensory, and neuropathic pain grades, But less well than duloxetine in reducing pain levels. 4) Neurotrophic agents (vitamins, methocobalamin, fatty acids, etc.) protect the structure and function of nerves by affecting the physiological metabolism of myelin sheath. Several studies [20] showed that the use of vitamin drugs before chemotherapy can significantly reduce the incidence of CIPN; Zhao Yanxia [21] found that chemotherapy combined with methocobalamin can effectively prevent and reduce the incidence of CIPN and delay its occurrence time. 5) The nucleotide drug cytidine triphosphate disodium (CTP) can regulate the synthesis and reconstruction of the biofilm structure of nerve cells by affecting the synthesis of phospholipids, accelerate the recovery of the structure and function of nerve cells, and improve the ability of cells to resist damage. 6) Calcium and magnesium mixture (calcium gluconate and magnesium sulfate), Ca^{2+}Affect the hyperpolarization of cell membranes, thereby promoting the Na^{+} Closing of the channel, so that the Na on the cell membrane + Lower permeability of the channel; magnesium sulfate canTo inhibit the synaptic transmission of the central nervous system and the stress of nervous fibers to reduce the degree of CIPN, He Jingdong et al. [22] reported that the continuous use of calcium gluconate 3 g/d oral administration during chemotherapy could reduce the incidence of neurotoxicity.

4.1.2 Non-drug therapy

General care: ask patients to keep warm and avoid cold irritation; reduce skin friction and contact with irritating fluid; individually adjust the infusion speed and time of chemotherapy drugs, etc. Exercise therapy: including sensorimotor training (SMT), whole body vibration (WBV) and other promote body blood circulation, so as to promote the recovery of diseased nerve, improve nerve conduction speed, relieve nerve numbness, paraesthesia and tingling. Massage therapy: massaging the plantar foot can activate the related sensory and motor areas of the cerebral cortex, and then promote the repair and growth of nerves. Cryotherapy: Studies have shown that low temperature can effectively contract peripheral blood vessels, slow down blood circulation, reduce the contact between chemotherapy drugs and peripheral nerves, and reduce tissue temperature by 10℃ can reduce the tissue metabolic rate by 50%, thus improving the symptoms of CIPN [23], but there is also a risk of cold intolerance and cold-related damage. Pressurization therapy: Kanbayashi et al. [24] found that surgical gloves had the same preventive effect as frozen gloves, and the mechanism was similar to cryotherapy. In addition, there are therapies such as electrical stimulation, photobiological regulation, magnetic field therapy, spoiler treatment and so on, etc. However, this kind of research lacks a large sample size, and further research is still needed to confirm its effectiveness.

4.2 Internal Treatment of TCM Treatment

The main clinical treatment of CIPN internal treatment includes warming meridian and dispersing cold, promoting blood circulation and removing blood stasis, warming Yang, dredging collaterals and tonifying qi and blood, etc. The forms of internal treatment mainly include the use of traditional Chinese medicine and the use of proprietary Chinese patent medicine injection.

4.2.1 Internal administration of traditional Chinese medicine

There are many studies carried out by adding or subtracting prescriptions based on prescription or prescription, and the most widely used clinical prescriptions are mainly Astragalus Guizhi wuwu soup, Yang soup, Angelica soup, etc. Gong Xiaoxia [25] reported that oxaliplatin chemotherapy at the same time oral tonic and five soup, Promote blood circulation and remove blood stasis without hurting the vital qi, To improve the peripheral peripheral and improve the nerve conduction velocity can prevent the occurrence of peripheral neuropathy; Kong Yingze et al. [26] reported that in the treatment of oxaliplatin (L-OHP), Collect Yin and camp, Wen Yang tongwei, tongluo debi, Display efficiency of 81.8% (9/11), Total response rate: 100% (11/11), besides, It can also significantly reduce the incidence of high-grade neurotoxicity, Yu Bin et al. [27] selected 50 patients with malignant tumors, After treatment of Astragalus cassia root soup, The incidence of I and peripheral neurotoxicity was significantly lower than that in the control group. Based on network pharmacology, Shang Zhihao [28] et al. discussed that we could improve neurotoxic damage through multiple ways of preventing oxidative stress and mitochondrial damage, protecting nerve cell apoptosis, and inhibiting inflammatory response. Angelica four inverse soup with temperature by scattered cold, raise blood through pulse for cure, modern experimental research [29] found angelica four inverse soup with anti-inflammatory, analgesic, antispmolysis, anticoagulation and thrombosis, improve peripheral blood circulation and improve nerve conduction velocity, such as Ding Rong[30] study found that angelica four inverse soup may by regulating rat L4~L5 back root ganglion TRPA 1, TRPM 8, TRPV 1 expression and activation of dorsal nerve root cells TRPA 1, TRPM8 two channels, to reduce neurotoxicity caused by oxaliplatin. Professor Zhang Mei [31] believes that the numbness and pain of the limbs of this disease are caused by the loss of cold meridians, fur and skin, or the blocked movement of qi and blood. It is similar to the pathogenesis of Bi syndrome mentioned by Sun Simiao. The treatment of warm Yang has remarkable results. Professor Jiang Yi [32] believes that the pathogenesis of this disease lies in Yang deficiency, blood stasis as the standard, the meridians can not be nurtured, and the meridians are not prosperous. Therefore, "warm Yang tongluo" is the treatment core, combined with various treatment methods such as qi and blood circulation, and the specimens are treated.

4.2.2 Use of Chinese patent medicine injection

Chinese patent medicine injection is mainly astragalus injection, Shenmai injection, Ginseng injection, ligustrazine, etc. Liu Zhanhua et al. [33] reported that by quietly dropping ligustrazine 240mg before L-OHP, the incidence of neurotoxicity was 28% (4/14) after promoting blood circulation and removing blood stasis, and all of them were grade I.

4.3 External Treatment of TCM

Yue Pian Wen, "the principle of external treatment is the principle of internal treatment, and the medicine of external treatment is the medicine of internal treatment; the different, the ear", believing that the principle of drug prescription is consistent between internal and external treatment. That "the disease first from the fur into, medicine can be entered from this". The external treatment of CIPN includes Chinese medicine soaking, acupuncture, Chinese medicine fumigation, acupoint application, directional penetration, Chinese medicine gel application, etc., among which Chinese medicine soaking and acupuncture treatment are the most common.

4.3.1 Traditional Chinese medicine external washing

Related studies show that the external washing treatment of CIPN is mainly to warm Yang, invigorate qi, promote blood circulation and dredging collaterals, supplemented by replenishing qi and blood, removing blood stasis and other warm and dispersing products [34]. The advantage of Chinese medicine bubble washing is that drugs can be directly absorbed from the skin, meridians and acupoints. The local drug concentration of lesions is high, which promotes nerve repair, and it is safe and convenient. Wang Huiling [14] and other studies took the method of warming meridians and activating blood circulation, using traditional Chinese medicine bath prescription composed of cassia branch, Sichuan pepper, Chuanxiong and other drugs to dredge the meridians, promote blood circulation and remove blood stasis,

and CIPN can play a corresponding therapeutic role after chemotherapy. Guan Jieshan et al. [35] treated 30 patients with TCM self-prepared prescriptions (Chuanxiong, red peony root, cassia root, Willingxian, etc.) after albumin-bound paclitaxel injection. The results showed that 93.3% of the patients had limb numbness and pain, CIPN grade decreased, 86.7%, and the score increased. Dong Mengyu [36] and other clinical studies have found that CIPN after chemotherapy has helped to improved the conduction velocity of peripheral nerves and reduced the severity of peripheral nerve toxicity. Zhang Jiali [37] and others took "nourishing blood and tonifying deficiency, dredging collaterals and removing blood stasis" as the treatment method, and the self-nourishing blood prescription (blood vine, safflower, kidney, knotweed, Salvia miltiorrhiza, etc.) can effectively reduce the incidence of high-grade peripheral neurotoxicity caused by oxaliplatin and reduce the severity of CIPN.

4.3.2 Acupuncture and treatment

Acupuncture and moxibustion has the use of dredging meridians and dredging collaterals, fuzheng and dispelling evil. It plays an indispensable role in the clinical treatment of CIPN caused by chemotherapy drugs. Through the coordination of local acupuncture and the selection of acupoints, the operation of local to the whole body is stimulated. The commonly used acupoints are Zusanli and Fenglong of the foot Yangming stomach, the valley and qu chi of the large intestine of the hand Yangming, and the sea of blood and three Yin. CIPN disease position in the limb endings, Belongs to the superficial category of traditional Chinese medicine, "Su · impotence" cloud: "the skin of the lung", Tai Yuan cave, For the infusion (acupoint) of the lung meridian, It has the function of strengthening health and dispelling evil and regulating blood vessels [38]; Hegu acupoint, Where the large intestine is injected through the raw gas, Through the meridian activation, shu tendons and the force is very strong; Blood sea point, For the sea of twelve classics, Where qi and blood converge, Is an important acupoint for the infusion of qi and blood, It has the function of promoting qi and blood circulation [39]; Zusanli can regulate the spleen and stomach, To help the biochemistry of Qi and blood, By regulating qi and blood to dredge the meridian qi; Three Yin intersection can adjust the liver, spleen, kidney three meridian qi and blood, Combining with Zusanli can enhance the effect of regulating the spleen and stomach;

Li Xuemei [40] compared the efficacy of acupuncture and pregabalin alone and pregabalin alone, and found that the effective rate of combined acupuncture was higher than that of pregabalin alone, which could significantly relieve the numbness and tingling feelings of patients. Yan Yu jiang [41] to dredging collaterals, promoting blood stasis, fuzheng dispel evil, for platinum, vincristine and paclitaxel after chemotherapy CIPN patients selected pool, valley, Zusanli acupuncture, western medicine group given B vitamin injection treatment, the results show that the acupuncture group effective rate is 83.33%, significantly higher than the western medicine group of 51.28%. In addition to simple acupuncture treatment, it is also used to output pulse current, with a needle as the conduction medium to stimulate the surrounding microvascular circulation, so as to achieve the effect of analgesia [13]. Wang Bin [42] In the study of CIPN induced by platinum drugs, he concluded that electricity has obvious therapeutic effect on sensory nerve and motor injuries.

4.3.3 Other external treatments

Chinese medicine ta good therapy is a traditional Chinese medicine, the conduction effect of wet compress, so that the drug through the muscle Cou hair into the viscera, direct to the disease, improve the movement of qi and blood, promote the meridians smooth meridians, play a therapeutic role. Li Yilan [43] and other clinical partition moxibustion with cinnamon medicine cake (composed of clove and cassia bark) through the corresponding moxa column fumigation points, to achieve the qi and blood circulation, warm meridians, relieve the numbness and tingling symptoms. Liu Lingling [44] and other clinical studies show that the miltiorrhiza powder in Yongquan point, Laogong point Xing He moxibustion, can reduce the incidence of peripheral neuropathy after chemotherapy, reduce the occurrence of peripheral nerve injury.

5. Discussion

Chemotherapy drugs caused by peripheral neuropathy is the main problem of limiting its clinical application, and symptoms even after the stop, related neuropathy may continue to deteriorate and spread, reduce the quality of life of patients, and the confidence of the follow-up treatment, modern medical treatment to a certain extent, but its treatment effect still has certain limitations. "Theory of" syndrome differentiation " thought of traditional Chinese medicine embodies the advantages of traditional Chinese medicine, the advantage of regulating the overall balance of Yin and Yang, and the advantage of direct disease, make, local to high drug concentration, Chinese medicine outside washing mainly is given priority to, can be combined with methylocobalamin to explore curative effect, acupuncture can be combined with moxibustion method, for CIPN effective external solution to provide more options. The current problem is that most clinical studies have small sample size, lack of large sample randomized controlled trials, large differences in individual drugs, and it is difficult to reach a consensus, and the specific mechanism and target of TCM action on peripheral nerve toxicity still need to be further explored. Therefore, clinically, the advantages of TCM treatment and the efficacy of western medicine treatment should be quickly combined to jointly reduce the symptoms of CIPN patients and improve their quality of life, which still needs to be actively explored.

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