Research on the Mechanism of Traditional Chinese Medicine in Treating Chemotherapy Induced Peripheral Neuropathy

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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) is characterized by numbness, paresthesia and hyperalgesia at the extremities. It is a common side effect of tumor therapy and the main cause of tumor treatment failure and poor quality of life. Duloxetine is the only first-line drug recommended by the latest CIPN treatment guidelines, but its efficacy is not ideal. Modern studies show that CIPN pathogenesis is numerous, and the treatment of CIPN is still limited to a single mechanism and the treatment effect is not ideal. Clinical practice observed that Chinese medicine treatment CIPN patients can obviously alleviate pain, and modern pharmacological studies show that Chinese medicine can alleviate CIPN symptoms through a variety of mechanisms, this study on the CIPN protection mechanism and Chinese medicine treatment CIPN mechanism to do a summary.

Keywords: Chemotherapy-induced peripheral neuropathy; Traditional Chinese medicine; Mechanism

1. Introduction

Chemotherapy Induced Peripheral Neuropathy is a dose-related side effect caused by neurotoxic chemical drugs used in cancer treatment [1]. The main clinical manifestations are numbness of distal limbs, sensory disturbance and allodynia, which are distributed in stockings and gloves. With the continuous use of chemical drugs, CIPN has the characteristics of persistence, progressive aggravation and irreversibility. For most patients, CIPN becomes a chronic disease, and symptoms persist for several months or even progress after the end of treatment, seriously affecting the normal use of chemotherapy drugs and the quality of life of patients [2]. According to relevant reports, about 80% of patients are affected by CIPN in the course of tumor treatment, and 30%~40% of patients suffer from pain caused by CIPN for a long time. At present, only duloxetine is recommended as the first-line drug in CIPN treatment guidelines [3], but the benefit rate of patients is not completely covered. With the aging of the world, the number of cancer patients is increasing day by day. In order to prolong the survival time and improve the quality of life of patients, CIPN mechanism research and treatment have attracted extensive attention. Contradictory is that different chemotherapy drugs produce CIPN mechanism is different, one drug can not completely cover different mechanisms, leading to CIPN treatment effect is not ideal, and Chinese herbal medicine composition is complex, the same Chinese herbal medicine can play a therapeutic role from multiple mechanisms, this article, on CIPN protection mechanism and Chinese herbal medicine treatment CIPN mechanism to do a review.

2. Protection mechanism of CIPN

Chemotherapy-induced peripheral neuropathy has many mechanisms, including active oxygen generation, hypoxia, neuroinflammation, mitochondrial damage and/or apoptosis, ion channel disorder, myelin sheath damage, microtubule damage, nerve fiber cell capillary damage and nerve cell apoptosis [4], etc, and treatment ideas should be considered according to its pathogenic mechanism.

2.1. Antioxidant stress

Chemotherapeutics induce reactive oxygen species (ROS) to generate further oxidative stress (OS) leading to CIPN. This pathogenic mechanism exists in most chemotherapeutic drugs. The contradiction
is that the generation of ROS plays a therapeutic role on the one hand, i.e., enhances the antitumor effect of chemotherapeutic drugs, and on the other hand, it has its side effects. Therefore, it is important to reduce or avoid CIPN without interfering with the therapeutic effect of tumor [5]. There are many mechanisms for the production of reactive oxygen species, and one of the essential pathways is the production of reactive oxygen species in mitochondria through oxidative phosphorylation. The common side effect of paclitaxel drugs is peripheral neuropathy, which does not directly produce reactive oxygen species to cause CIPN, but acts on mitochondria, leading to mitochondrial swelling and vacuole formation, which in turn causes mitochondrial insufficiency, and the reduction of metabolism produces ROS to cause oxidative stress, which finally leads to the formation of CIPN [6]. Many studies [7] show that the important mechanism of CIPN induced by oxaliplatin and cisplatin is mitochondrial damage and active oxygen generation. Oxaliplatin and cisplatin combine with mitochondrial DNA to form mDNA adducts. Platinum-mDNA adducts affect mitochondrial replication and transcription, but mitochondria do not have DNA self-repair ability, and abnormal proteins are produced. Mitochondrial physiological functions are impaired. The production of ROS in turn acts on mitochondria to further aggravate mitochondrial damage, which leads to the aggravation of CIPN. Clavo et al. [8] proposed to treat CIPN through antioxidant stress pathway. Patients secondary to grade II or III CIPN pain were treated by rectal ozone blowing. Most patients had obvious improvement in chronic pain. Clavo also proposed that ozone treatment defects were not obvious when using low dose ozone treatment, but the treatment effect was opposite when using high dose ozone treatment. Moreover, the use of ozone therapy required professional operation. At present, ozone treatment of CIPN still needs large-scale experiments to verify whether it can be widely used in clinical practice. At present, N-acetylcysteine and glutathione are often mentioned in CIPN treatment [9]. N-acetylcysteine acts on glutathione peroxidase as an antioxidant, causing an increase in glutathione whole blood concentration. Glutathione has a high affinity for heavy metal ions. Glutamine increases the binding of platinum drugs, reduces the binding of platinum drugs and mitochondria, and reduces the damage of platinum chemotherapy drugs to peripheral nerves. However, considering that the experimental participants are few, whether N-acetylcysteine and glutathione can be widely used in clinical patients needs further verification.

### 2.2. Anti-inflammatory

Studies have shown that neuroinflammation plays an important role in CIPN. Chemotherapy was previously thought to play an anti-tumor role by inhibiting immune function. Recently, a large number of experiments have shown that chemotherapy can cooperate with immune cells to treat tumors, but it will lead to the regulation of immune system elements, causing the secretion and release of inflammatory mediators (tumor necrosis factor-α (TNF-α), interleukin-1 β (IL-1β), and interleukin-6 (IL-6)) and neurosensory system allergy, resulting in neuroinflammation and peripheral nerve symptoms. Study [10] also found that the symptoms of peripheral neuropathy caused by different drugs are different, and their characteristics vary according to the type of drug (platinum derivatives, taxanes, vinblastine and protease inhibitors), even if they are the same platinum derivatives, cisplatin and oxaliplatin cause peripheral neuropathy symptoms. Cavaletti and Marmiroli’s study [11] showed that with the continuous use of drugs (cisplatin, oxaliplatin), chronic neurotoxicity gradually manifests as fine sensorimotor coordination disorders, numbness, and sensory disorders. In addition to chronic neurological symptoms, acute neuropathic symptoms of oxaliplatin usually occur several hours after drug use, characterized by intensified cold exposure, sensory disorders, and sensory abnormalities, as proposed by Fumagalli et al. Even though there are significant differences in the neuroinflammatory pathways of different chemotherapy drugs, different CIPN inducers seem to have the same immunosuppressive targets. CIPN immunomodulatory therapy can inhibit the neuroinflammatory pathways to prevent and improve chemotherapy induced neuropathy, while clarifying the unique pathways of different neuroinflammatory pathways to target and improve the symptoms is also one of the traditional ideas.

### 2.3. Protecting mitochondrial

When it comes to the damage mechanism of CIPN, whether it is inflammation, oxidative stress, ion channel disruption, or direct action of cytotoxic drugs on mitochondria, it can lead to mitochondrial dysfunction. Insufficient generation of mitochondrial adenosine triphosphate (ATP) leads to damage to the electron transfer chain, causing extensive axonal damage and resulting in the occurrence of CIPN. Even though different neurotoxic drugs have different pathogenic mechanisms, most drugs can cause mitochondrial damage from different levels, leading to CIPN. Therefore, repairing mitochondria can prevent and improve chemotherapy induced neuropathy. Oxidative stress is the main pathway leading to mitochondrial dysfunction. On the one hand, neutralizing reactive oxygen species can be considered to
indirectly repair mitochondria. The POLAR team’s research on magnetic resonance imaging contrast agents Calmanga fripir and ARETI \cite{12} commonly used in antihypertensive and cardioprotective drugs Carvedilol uses the mechanism of mitochondrial superoxide dismutase to prevent and improve CIPN. Clinical research is currently underway. On the other hand, it can directly repair mitochondria \cite{13}. Ronnie et al. used protein deacetylase 6 (HDAC6) inhibitors to directly restore axonal mitochondrial health.

2.4. Maintaining ion channel stability

Ion channel disorder is also one of the damage mechanisms that cannot be ignored. Paclitaxel is a microtubule-targeted chemotherapeutic agent that alters ATP-induced calcium release, depletion of calcium channels and inhibition of calcium-dependent calpain enzymes in primary cultures of neuroblastoma cells and dorsal root ganglia (DRG), all of which prevent paclitaxel-induced axonal degeneration \cite{12}. The Waller denaturation experiment has confirmed sterility α. The Toll/interleukin-1 receptor (TIR) motif containing 1 (Sarm1) is a key mediator of damage induced axonal degeneration. Sarm1 produces the marker intracellular adenosine diphosphate sugar (cADPR), which was mentioned in this experiment as not inducing axonal degeneration \cite{14}. Other studies have shown that cADPR is a calcium mobilization agent, and cADPRN can regulate intracellular calcium release through Ryanodine receptors (RyRs). At the same time, cADPR can also activate the transient receptor potential channel (TRPM2) associated with melatonin, a non-specific cation channel mainly located on the plasma membrane for calcium permeation \cite{15}. These studies indicate that cADPR not only serves as a marker for Sarm1, but also has the potential to induce axonal calcium ion imbalance and axonal degeneration. Based on this theory, Li et al. \cite{16} studied drugs aimed at improving paclitaxel induced neuropathy using Sarm1 and cADPR as targets, and proposed that the cADPR competitive antagonist 8-Br-cADPR can be used to improve peripheral nervous symptoms. Small molecule inhibitors targeting Sarm1 also have great research potential. When it comes to ion channel dysregulation, Na+ channel disorder cannot be ignored. Voltage gated sodium ion channel 1.7 (Nav1.7) plays an important role in neuropathic pain, and its gene expression increases in the dorsal root ganglia (DRGs) of rats treated with paclitaxel. Li et al.’s research has shown that voltage gated sodium ion channels can serve as a new target for treating neuropathic pain. At present, small molecule drugs directly targeting Nav1.7 are still under research. Gomez et al. \cite{17} added small modifications to the cytoplasmic tissue protease reactive mediator protein 2 (CRMP2) that interacts with Nav1.7, blocking the function of NaV1.7. They showed anti nociceptive sensation in animal models of neuropathic pain and found that the regulatory sequence (CRS) of CRMP2 unique to Nav1.7 can be used as a therapeutic target for neuropathic pain.

3. TCM knowledge of CIPN

According to the clinical symptoms of CIPN, numbness, paresthesia and even muscular atrophy of distal extremities can be attributed to "Bi syndrome and Wei syndrome" of TCM. "Lingshu" said: "striae and flesh is not firm, good disease arthralgia." "Jing Sheng Fang Zhu Bi Men" says: "all due to physical weakness, empty striae, due to wind and cold moisture and become arthralgia also", in summary, doctors said: arthralgia, qi deficiency, loose striae. Tumor patients, originally due to disease caused by deficiency, on the basis of the use of cytotoxic drugs, the patient's healthy qi loss is more serious, so healthy qi deficiency. "Jingyue Quanshu" said: "Cover arthralgia closed also, with blood gas closed by evil, can not walk and disease also. " And he said, "The only thing wrong with this is that it's not the blood, it's the cold, it's the cold, it's the meridians, it's the pain. " It is pointed out that Bi syndrome is due to the invasion of external pathogens into meridians due to deficiency of body, resulting in obstruction of meridians. Many modern doctors \cite{18} believe that the core pathogenesis of CIPN is the invasion of qi deficiency and pathogenic factors and the blockage of collaterals. The treatment is to replenish qi and blood, warm meridians and open meridians. However, some doctors \cite{19}, based on the Zangxiang theory and holistic view of TCM, believe that the pathogenesis of CIPN is liver yang deficiency, and improve the pain of patients by ascending liver yang and regulating liver qi. This article will record CIPN treated by TCM and its mechanism from the point of view of "the same syndrome is different, the combination of disease and syndrome".
4. Study on the mechanism of CIPN treated with Chinese herbs

4.1. Traditional Chinese Medicine prescription

4.1.1. Qi deficiency and blood stasis, meridian obstruction

The patient has numbness of limbs, fatigue, difficulty in lifting up, progressive aggravation, thin white or yellow tongue, astringent or tight pulse, syndrome differentiation for qi deficiency and blood stasis, treatment for invigorating qi and activating blood circulation and dredging collaterals, prescription selection Buyang Huanwu Decoction, oral administration and external fumigation combined. Astragalus membranaceus is a monarch medicine, slightly warm in nature, returning to lung and spleen meridians, enhancing the function of spleen and stomach. Spleen and stomach are the foundation of acquired life, the source of qi and blood biochemistry, enhancing lung qi, relying on the power of lung to regulate festival, transporting essence to the whole body. "Medical Lin Gaicuo" selected Angelica sinensis as a minister medicine, blood circulation and blood. Red peony root, Szechuan lovage rhizome, peach kernel, safflower and earthworm are taken to activate blood circulation and remove blood stasis, and the five drugs are adjuvant drugs. Zhou Xiaoyan et al. [20] divided 80 CIPN patients into two groups according to random grouping method. The control group was given oral mecobalamin, and the study group was given modified Buyang Huanwu Decoction on the basis of mecobalamin. After one course of treatment, the curative effect was evaluated P<0.05. The curative effect of the study group was significantly better than that of the control group, indicating that modified Buyang Huanwu Decoction could improve CIPN symptoms. In the rat model of nerve transection and junction (NTC) [21], BYHWD reduced the release of inflammatory cytokines (IL-1β, TNF-α) at the rejunction, regenerated axonal cells of NTC, and improved functional activity in rats after nerve injury. In a controlled study of patients with acute cerebral infarction [22], Buyang Huanwu Decoction improved blood viscosity and hemodynamics more than aspirin, improving symptoms by improving hypoxia.

4.1.2. Yang deficiency cold coagulation, meridian obstruction

The patient has tingling pain at the ends of limbs, aggravated by cold, limbs are not warm, limbs are not flexible, or accompanied by stomach distension, weak mouth, thin white fur, thin and weak pulse. Syndrome differentiation for blood deficiency cold coagulation, meridian obstruction, treatment to promote blood circulation and nourish blood, dispel cold collaterals, Fang selected Danggui Sini Tang Hua Cai. Chemotherapy drugs are bitter and cold in nature, damaging their vital qi, damaging their yang qi, consuming their yin blood, resulting in meridian obstruction. Clinically, if bitter and cold is used, pungent and warm medicine should be added to warm the tendons and meridians. If the obstruction is severe, insect medicine should be used to clear the meridians. At the same time, attention should be paid not to be too warm and dry to prevent yin blood consumption and aggravate meridian obstruction. The prescription angelica bitter, spicy, sweet and warm, can supplement the deficiency of Ying blood, but also can be astringent blood vessels. Cinnamomum cassia is pungent and warm, red in color and enters the heart. The heart governs the blood vessels, which warms the meridians and dispels cold, activates blood circulation and unblocks the meridians. It can also help Angelica warm and unblock the blood vessels. peony acid bitter slightly cold, benefit yin astringe camp, and angelica consistent, nourishing blood and blood, and cassia twig consistent, adjust ying wei. Asarum is pungent and warm, and its shape is as thin as a sword. It can remove cold evil through muscle surface and warm meridians and dissipate cold. Akebia is cold in nature, but after getting cassia twig and asarum, its bitter cold can be restricted, and its effect of opening up blood stasis can be exerted, so that qi and blood are unobstructed. Jujube, licorice combined to strengthen the spleen of the source, tonify blood, Tongyang. Ding Rong et al. [23] clinical observation showed that Danggui Sini Decoction can significantly improve peripheral neuropathy caused by oxaliplatin. Dorsal root ganglia (DRG) is the first-order neuron of pain input. DRG synthesizes N-methyl-D-aspartate receptor subunit 2B (NR2B), and inhibition of NR2B has neuroprotective effects [24]. Animal experimental model [24] showed that long-term injection of oxaliplatin into rats could increase NR2B synthesis in DRG of spinal dorsal horn of rats, and rats showed hyperalgesia. After injection of Danggui Sini Decoction, pain was reduced in rats, and NR2B decreased, indicating that Danggui Sini Decoction had neuroprotective effect. Clinical trials [26] have also shown that Danggui Sini Decoction combined with Yanghe Decoction can reduce oxaliplatin-induced peripheral neurotoxicity, increase motor and sensory nerve conduction velocity, and improve hemodynamic indicators.

4.1.3. Qi deficiency and blood weakness, disharmony between camp and health

Patients may experience skin numbness, accompanied by dull pain at the end of the limbs, weakness
in the limbs, and lack of flexibility in movement, or accompanied by a feeling of ant movement. The tongue may be dull, and the pulse may be slightly astringent and tight. Dialectically, it is characterized by Qi deficiency and blood stasis, cold coagulation of the meridians, and treatment with nourishing Qi and promoting blood circulation, warming and unblocking the meridians. Fang Xuan Huangqi Guizhi Wuwu Tang. Astragalus membranaceus is a medicinal herb that nourishes qi. Stir frying honey with warm ingredients is beneficial for strengthening the spleen and stomach, and can nourish the qi of the spleen and stomach while keeping it warm. Guizhi is a medicinal herb used by officials, with a spicy and warm nature. It can warm and unblock meridians, assist in the transformation of yang and qi, unblock the meridians, disperse cold and dampness, and introduce yang qi into the meridians, supplemented by ginger. Paeonia lactiflora is used together with osmanthus twig to nourish blood and promote blood circulation, while jujube is also used as an adjunct to nourish blood. Methylcobalamin, also known as methylvitamin B12, is a metabolite of vitamin B12 in the human body. It can promote the synthesis of nuclear acid synthesis proteins in nerve cells, promote the regeneration of nerve myelin axons, and is often used to treat peripheral neuropathy. By comparing the effects of Huangqi Guizhi Wuwu Tang and Mecobalamin on peripheral neuropathy caused by oxaliplatin [27], the study showed that both can improve peripheral nerve symptoms in patients, and oral Chinese medicine has a particularly good therapeutic effect. At the same time, it was found that both can also improve the sensory nerve conduction velocity of patients, and Huangqi Guizhi Wuwu Tang is more pronounced. Animal model [29] shows that Huangqi Guizhi Wuwu Tang can promote the repair of the sciatic nerve in rats with peripheral neuropathy caused by oxaliplatin, improve sciatic nerve conduction velocity, and shorten injury time. Jiawei Huangqi Guizhi Wuwu Tang [29] can also improve mitochondrial function and improve peripheral neuropathy in patients by inhibiting oxidative stress and regulating the expression of mitochondrial apoptotic protein P53. The latest study shows that Huangqi Guizhi Wuwu Tang can also improve CIPN symptoms by regulating the composition of intestinal microbiota.

4.2. Single drug of traditional Chinese medicine

4.2.1. Astragalus membranaceus

Modern research shows that Astragalus membranaceus can be isolated from more than 60 chemical components, and its pharmacological effects focus on many aspects such as anti-tumor, improving immunity, anti-inflammatory, anti-oxidation, lowering blood sugar, diuresis and protecting heart function [30]. Astragalus polysaccharides is one of the effective components isolated from Astragalus membranaceus, which plays an antioxidant role through various mechanisms. Liang Wannian et al. [31] isolated Astragalus polysaccharides from Astragalus membranaceus by high pressure crushing extraction process in vitro, and verified that Astragalus polysaccharides had scavenging ability on free radicals by in vitro antioxidant experiment. Hou Minna et al. [32] isolated Astragalus polysaccharides and saponins from Astragalus membranaceus can play an antioxidant role by scavenging free radicals. There are also studies [33] suggesting that APS acts as an antioxidant in vitro by scavenging superoxide anions. Astragalus polysaccharides [34] can not only play an antioxidant role by scavenging oxygen free radicals and superoxide anions, but also improve microcirculation nervous system diseases by reducing the release of neuroinflammatory factors. Quercetin [35] is also one of the active ingredients isolated from Astragalus membranaceus, and in animal experiments quercetin has neuroprotective effects by increasing the length and number of axons in mice. In the diabetic animal model experiment, Astragaloside IV can improve mitochondrial dysfunction by inhibiting Notch pathway activation, which also provides a mechanism for Astragaloside IV to treat CIPN.

4.2.2. Angelica sinensis

Angelica sinensis is often used in prescriptions to improve CIPN, and modern studies have shown that Angelica sinensis improves CIPN through anti-inflammatory and anti-oxidative stress mechanisms. Ligustilide is the component with the most volatile oil content in Angelica sinensis. LYU et al. [36] studied the effect of ligustilide on pain rat model in animal experiments. The study showed that ligustilide could reduce the nerve damage caused by inflammation by reducing (IL-1β) and TNF-α, and the pain of rats was reduced. Ligustilide has also been shown to exert anti-inflammatory and analgesic effects by inhibiting nuclear factor-kB (NF-kB)-mediated cytokine production [37]. SOD and CAT are antioxidant enzymes. The degree of oxidative stress can be reflected by detecting the SOD and CAT contents in the body. Angelica sinensis polysaccharide isolated from Angelica sinensis can increase the contents of SOD and CAT in OA rats, thus improving the soft tissue symptoms of OA rats through antioxidant stress [38], which provides theoretical basis for Angelica sinensis polysaccharide to improve CIPN from antioxidant stress. Angelica sinensis and Astragalus membranaceus both have antioxidant stress effect, usually appear as anti-drug in the treatment of CIPN prescription, research found that the use of two drugs at the
same time to enhance antioxidant activity, of which Angelica ratio is higher than Astragalus membranaceus, its antioxidant activity is the strongest, but the optimal ratio has not been studied [39].

4.2.3. Peony

Paeoniflorin is derived from the dry root of paeonia lactiflora of Ranunculaceae. Modern pharmacological studies show that paeoniflorin has anti-inflammatory, analgesic and antioxidant effects. Paeoniflorin has been shown to ameliorate bortezomib-induced peripheral neurotoxicity by reducing IL-6 without affecting bortezomib antitumor efficacy [40]. Adenosine A1 receptor plays an important role in pain transduction pathway and is closely related to analgesia. Animal models of inflammatory pain and neuropathic pain in rats showed that paeoniflorin could alleviate thermal pain and mechanical pain sensation in rats of both models by increasing adenosine A1 receptor expression in dorsal horn of spinal cord [41]. It has also been shown that paeoniflorin can resist oxidative stress, and paeoniflorin protects skin cells from hypoxia damage by increasing NO production and decreasing the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [42]. Therefore, paeoniflorin can also improve CIPN symptoms by resisting oxidative stress.

4.2.4. Rhizoma Chuanxiong

Chuanxiong has anti-inflammatory, antioxidant stress, mitochondrial protection, and anti neurotoxicity properties, and can be used to treat CIPN through multiple mechanisms. Ligusticum chuanxiong protein (LCP) is a potent antioxidant isolated from Ligusticum chuanxiong, but due to its poor solubility, it is difficult to be widely used in the food processing industry. The reducing agent glucan and Chuanxiong protein are covalently combined to form a glucan Chuanxiong protein copolymer (GLCP). In vitro experiments have shown that both LCP and GLCP can scavenge ABTS+ free radicals, and GLCP has a higher clearance rate compared to LCP [43]. There are also studies showing that extracts of Ligusticum chuanxiong and Angelica sinensis have antioxidant effects by inhibiting the production of ROS [44]. Modern research has shown that Chuanxiong extract also has protective effects on mitochondria and anti neurotoxicity.

5. Summary

With the aging of the world, the number of cancer patients continues to rise. Chemotherapy is still widely used as the cornerstone of tumor treatment. However, CIPN caused by chemotherapy has complex mechanism and no specific drug has been found, which puzzles patients and medical staff. In clinical practice, traditional Chinese medicine has obvious advantages in the treatment of CIPN, partly due to the complexity of Chinese herbal components, which can play a therapeutic role from multiple mechanisms, but considering from the modern pharmacology, complex components have also become difficult to study. At present, the research focus of Chinese medicine treatment of CIPN lies in what mechanism a certain component of Chinese herbal medicine treats diseases, and there is not much research on what pathway or target the component passes through. From the perspective of modern pharmacology, Chinese herbal medicine provides a direction for precise treatment of CIPN. This article summarizes the mechanism of CIPN treatment by several common Chinese herbal medicines and single Chinese herbal medicines. Future research on the pathway and target of CIPN treatment may be continued in order to find new treatment methods to relieve patients' pain.

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