

Research Progress on the Treatment of Qi Deficiency and Blood Stasis Type Hand-foot Syndrome by Buyang Huanwu Decoction

Jianmin Qu¹, Gang Wang^{2,*}

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

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

*Correspondence Author

Abstract: *Hand-foot syndrome (HFS) is one of the common adverse reactions in the treatment of malignant tumors, and its incidence is gradually increasing with the widespread use of antitumor drugs. HFS seriously affects patients' daily social and life, and even leads to drug dosage reduction or early discontinuation of medication, which delays treatment. Modern medicine has not yet fully clarified the understanding of its etiology and pathogenesis, the lack of uniform standards for the evaluation of therapeutic efficacy, and the poor effect of targeted systemic therapy. Chinese medicine classifies HFS into the category of "blood paralysis", and considers that the disease is located in the hands and feet, with deficiency as the main cause, and the deficiency as the underlying cause, and the mixture of deficiency and reality. BHD is from the book "Reform and Error Correction of Medical Forests" written by Qing Dynasty physician Wang Qingren, which has the effects of tonifying qi, activating blood and clearing collaterals. The formula is rigorous and well formulated, and is now widely used in all kinds of diseases with qi deficiency and blood stasis, with remarkable results. In recent years, with the rapid development of modern pharmacology, the research on the microscopic mechanism of action of BHD has been developing and deepening, which provides new ideas for the treatment of the disease. In this paper, we review BHD in HFS in the treatment of malignant tumors from the aspects of its formula and modern pharmacological research, with a view to providing clinical basis and reference for the future treatment of HFS of qi deficiency and blood stasis type by BHD.*

Keywords: Buyang Huanwu Decoction, Treatment of malignant tumors, Hand-foot syndrome, Evidence of Qi deficiency and blood stasis, Research progress.

1. Introduction

Hand-foot syndrome (HFS), also known as palmoplantar sensory loss erythema (palmar planter erythrodysesthesia, PPES), is a common cutaneous toxic reaction during the treatment of malignant tumors, with an incidence rate as high as 89% [1]. The main clinical manifestations are symmetrical abnormal sensation, finger (toe) pain, heat, erythematous swelling, preferably in the palms of the hands and soles of the feet, initially manifested as numbness, tingling, dullness of sensation, and gradually developed to desquamation, vesiculation and ulceration, and continue to deteriorate and even the formation of skin blistering lesions, and the disappearance of fingerprints in some patients, which seriously affects the quality of life of the patients, which leads to the reduction of the dose of unintended medications, and even leads to the interruption of the treatment [2], decreasing the therapeutic effect and affecting the long-term survival of patients. Numerous chemotherapeutic agents can cause HFS, such as paclitaxel [3] (docetaxel), antimetabolites (capecitabine, cytarabine, methotrexate), and anthracyclines (adriamycin). The incidence of HFS varies among different chemotherapeutic agents, ranging from 18 to 51.7% for polyethylene glycolized liposomal adriamycin [4], 78.5% for capecitabine [5], and 12.9 to 35% for 5-fluorouracil [6]. It has been found that the higher the drug dose intensity, the higher the severity of HFS, i.e., HFS is a dose-dependent symptom [7]. Molecularly targeted therapies such as tyrosine kinase inhibitors (MTKI), especially regorafenib, sorafenib, axitinib, and sunitinib, etc. [8] can cause hand-foot skin reaction (HFSR) is a kind of HFS, and the incidence rate is as high as 30% [9]. Modern medical knowledge of its etiology and pathogenesis has not been completely clarified, the evaluation

of therapeutic efficacy lacks a unified standard, and systemic treatments such as methyl cobalamin, vitamin B6, vitamin E, reduced glutathione, and cyclo-oxygenase inhibitors are mostly used in the clinic to alleviate the symptoms, but the effect is poor. Currently, there is no standard treatment for HFS. Chinese medicine tends to diversify its understanding of HFS, which has significant efficacy in clinical practice by catching the disease mechanism through identification and treatment. In this paper, we will review the Chinese medical name, etiology and pathogenesis, diagnosis and treatment of HFS, the formula of tonifying yang and restoring five soups, and modern pharmacology, with a view to providing more directions for improving the survival quality of HFS patients with qi deficiency and blood stasis.

2. The Name of HFS in Chinese Medicine

There is no record of the name of HFS in Chinese medicine, modern medical doctors according to the experience of clinical treatment, under the guidance of the dialectical theory of treatment, the disease is mostly attributed to the "blood paralysis" category. "Evil into the yin, then the blood paralysis..... Huai heat too much, or cold folded in the meridians, or wet offenders in the glory and guardianship, and thus the blood fight..... so that the blood can not be glorified outside, the gas can not be nourished in the internal", blood paralysis for the Evil qi attacks the body, into the yin to cause body qi and blood stagnation, meridians and internal and external glorification of the function of the malfunction, the emergence of pain in the limbs, numbness and insensitivity of the skin and other symptoms.

2.1 Etiology and Pathogenesis

HFS is located in the hands and feet, mainly in the virtual, the standard is solid, mixed real and virtual. "All drugs are poisonous and toxic, all can change in people for harm, but also can kill", "long-term use of drugs, the nature of the rigid, even death", the basic mechanism is due to the "drug toxicity" gather The endings of the extremities, to the meridians, collaterals blockage, thus affecting the operation of qi and blood [10], HFS patients because of the metabolic toxicity of antitumor drugs in the hands and feet of the accumulation of obstruction of meridians, so that stasis of blood, phlegm and dampness and other pathological products blocking the meridians, do not glorify the four endings, the appearance of the skin numbness and insensitivity, sensory disorders, and other symptoms, that is, "not through the pain". "There is a gas deficiency can not guide the blood to glorify and nourish the muscles and veins and numbness, there is a blood deficiency to glorify and nourish the muscles and flesh, so as to make the numbness through the tunnel and condensation", patients with malignant tumors, internal organs of the internal organs of qi and blood, yin and yang imbalance, the positive qi has been a deficiency, the end of the limbs can not be moistened and nourished, therefore, "not to glorify the pain".

2.2 Diagnosis and Treatment

There is no uniform standard for TCM diagnosis and typing of HFS, and it is found that chemotherapeutic drugs are mostly cold and cold in nature, and targeted drugs and immunological agents are mostly pungent and hot [11]. Due to the differences between the pharmacological properties of anticancer drugs and the patient's physique, combining with the lesion site and symptoms, TCM diagnosis and typing is carried out on the basis of the systemic clinical manifestations. Jia Liqun was categorized into Yang deficiency and blood stasis syndrome, heat and toxicity accumulation syndrome and blood deficiency and wind dryness syndrome [12]. Zhao Gaofei was classified into Yang deficiency and blood stasis syndrome, Qi deficiency and blood stasis syndrome, stasis-heat interconnection syndrome and blood deficiency and stasis syndrome [13]. Pei Yuying classified into stasis-heat internal stagnation, qi and yin deficiency, qi deficiency and blood stasis, cold congealed meridians, blood-heat and wind exposure, camp injury and blood stasis, qi and blood deficiency, meridian stasis and obstruction, and spleen and stomach weakness, dampness-heat stasis and obstruction [11]. Guo Yong was classified as drug poison violating the spleen, spleen and stomach weakness, qi and blood deficiency, qi deficiency and blood stasis, stasis blocking the veins and channels, drug poison violating the spleen, spleen deficiency generating dampness, phlegm and dampness blocking the channels and channels, drug poison stagnation, liver loss of drainage, unfavorable qi mechanism, and drug poison invasion, cold congealing and blocking the channels and channels [10]. Chu Ruige was divided into qi and blood deficiency evidence, qi and yin injury evidence, blood deficiency and wind dryness evidence and heat and poison embedded in the skin evidence [14]. In summary, each medical practitioner expressed his own opinion and formed his own system. According to the consensus of experts, qi deficiency and blood stasis type is one of the common types of evidence [15].

2.3 Evidence of Qi Deficiency and Blood Stasis

Su Wen - The Theory of Regulating the Menstruation: "The way of the five viscera all comes out of the meridians and tunnels to carry blood and qi; if blood and qi are not harmonized, all diseases are born out of change. If Qi is not harmonized with Blood, Blood is not transported without Qi; Blood stasis is formed by Qi deficiency; Blood stasis produces stasis over time; and stasis follows Qi deficiency." Zhou Yangjun said: "It is the scripture that says blood paralysis, but not gas, I do not know the blood paralysis, due to the injury of the gas is also, into the veins then the blood is condensed and does not flow..... and then the evil can be entered into the", malignant tumors after chemotherapy drug damage to the qi and blood, qi deficiency is to promote the powerlessness of the blood is stagnant and difficult to walk, that is "If Qi does not reach, then numbness occurs; if Blood does not glorify, then numbness occurs." This syndrome is characterized by qi deficiency as the root cause and blood stasis as the target, i.e. "stasis is caused by deficiency". Treatment should be based on tonifying qi, supplemented by activating blood circulation and removing blood stasis. According to the Guiding Principles for Clinical Research of New Traditional Chinese Medicines [16], the main symptoms: localized to "blackness, sores, deficiency, and pain" as the characteristics. Black: skin nail error, skin pigmentation, dark color, bruising, blackening, unclear border, mostly seen in the skin at the interphalangeal joints and nail beds, thickening of finger/toe nails. Sore: dark red patchy rash, mildly on the fingers and soles of the feet, in a scattered distribution of the size of corn grains, severely on the palms of the hands, the backs of the hands and the backs of the feet, fused into patches of dark red patches with unclear boundaries, or accompanied by vesicular eruption. Deficiency: accompanied by dizziness, fatigue, lack of breath and laziness. Pain: pain and numbness in the hands and feet, aggravated by cold, gradually developing with the chemotherapy cycle to affect normal life such as walking and holding objects. The tongue is pale or dull with petechiae. Pulse is stringy or sunken and fine.

3. Buyang Huanwu Decoction (BHD)

Wang Qingren cloud: "half of the body does not reach, loss of vital energy, is its origin, the loss of up to five percent and disease..... vital energy loss of five percent, under the remaining five percent, the flow of the whole body, we will see the loss of qi state..... hair for impotence evidence". Buyang Huanwu Decoction (BHD) is a formula to replenish the deficient yang qi [17], which believes that "if the qi is deficient, it will not be able to reach the blood vessels, and if the blood vessels do not have qi, it will stay and stagnate", and that the deficiency of qi is the basis of this formula, while the blood stasis is the target of this formula, and stagnation of blood is caused by the deficiency, and that "all treatments for paralysis must be to open up the channels so as to allow the qi to flow freely". This formula is a representative formula for Qi deficiency and blood stasis. His book "Medical Forest Correction", the BHD is recorded in detail: "Astragalus (raw) four taels, the tail two money, red peony one and a half money, the ground dragon (remove the soil) one money, Chuanxiong one money, peach kernel one money, safflower one money, pan-fried with water", efficacy: replenish the qi and activate the blood and collaterals, the main treatment of paraplegia, askew mouth and eyes, spoken language, salivation at the corners of the mouth, impotence of the lower limbs Waste,

frequent urination, incontinence. Formula: tonifying yang to return five soup plus reduction, astragalus, peach kernel, safflower, angelica, red peony, chuanxiong, dilong and so on. Treatment: tonifying qi and promoting blood circulation, activating blood circulation and removing blood stasis.

3.1 Explanation

The *Materia Medica Repertoire*: "thieves wind disease, partial in the blood veins and the hands and feet do not follow the person, Astragalus can glorify the sinews and bones; carbuncle and ulcer evidence, pus and blood within the ulcer, yang qi is weak and does not converge the person, Astragalus can be muscle, and yin sores can not be started, yang qi is weak and does not heal the person, Astragalus can be muscle"; can be complementary to the gas to promote the yang, support the sores to produce muscle; "*Materia Medica Compendium*": "*Angelica pinnatifida* breaks blood and flows downward", it can break blood and activate blood circulation, regulate menstruation and relieve pain; "*Justice of the Materia Medica*": "To expel blood and guide blood stasis, to break up stagnation and drain downward flow, red peony is also used", it can clear away heat and cool the blood, dissipate blood stasis and relieve pain; "*Yunnan Materia Medica*": "*Di Long* can dispel wind and treat children's convulsions. It is used in treating children's convulsion and convulsive wind, crooked mouth and eyes, strengthening tendons and treating fistulae", which can dispel wind and activate blood circulation, activate blood circulation and remove blood stasis; "*The Essentials of the Materia Medica*": "*But Chuanxiong* is a qi medication in the blood, so it can be used to disperse pungently and lead blood upward", which can dispel wind and activate blood circulation, and clear blood circulation to relieve pain; "*The Compendium of Famous Medical Doctors*": "*Peach kernel*. Removing blood from strokes, breaking the obstruction in the abdomen, clearing the veins and relieving pain", can activate blood circulation and dispel blood stasis; "*Classic of the Materia Medica*": "The poison of all insect medicines must injure the blood, safflower can move the blood, and if the blood is alive, the poison can be relieved", can activate blood circulation and move the blood, harmonize with the blood and produce the blood.

In this formula, raw astragalus is used to replenish the vital energy, which means that when qi is strong, the blood will flow, and the blood stasis will be removed and the collaterals will be opened, which is the king's medicine; angelica root is long in activating the blood and has the wonderful ability of eliminating blood stasis without hurting the blood, which is the subject's medicine; chuanxiong ligustici, red peony, peach kernel, safflower help angelica root to activate the blood and eliminate the blood stasis, and dilong is the auxiliary drug to activate the collateral and the channels and to promote the power of specialization. The combination of this formula is characterized by a large number of qi tonic drugs and a small number of blood-activating drugs, so that qi and blood to treat the root cause, remove blood stasis to treat the symptoms, the symptoms of both the root cause and the symptoms of the Department of qi congestion, blood does not injure the right to play a total of tonifying qi, blood circulation of the work of the function.

3.2 Modern Pharmacological Studies

Modern pharmacological studies have shown that BHD can significantly inhibit tumor necrosis factor (TNF- α)-induced apoptosis of endothelial cells exerting a protective effect on inflammation, improve cellular activity by regulating the nuclear transcription factor- κ Bp65/NOD-like receptor protein 3 (NF- κ Bp65/NLRP3) signaling pathway reducing reactive oxygen species content, down-regulated the expression of cysteine protease-1, apoptosis-associated speck-like proteins, NLRP3 inflammatory vesicles and NLRP3, and decreased the expression of interleukin-1 β and interleukin-18 thereby exerting a protective effect [18].

3.2.1 Astragalus

Astragalus contains flavonoids, saponins and polysaccharides and other effective components, which inhibit tumor growth through the Wnt/ β -catenin signaling pathway [19]; it can stimulate M1-type macrophages and T cells in the state of immunosuppression, improve anti-tumor ability [20], promote apoptosis of tumor cells, inhibit tumor cell invasion and metastasis, regulate the tumor microenvironment, anti-tumor angiogenesis, and regulate autophagy, inducing macrophage polarization, enhancing body immunity and inhibiting immune escape, and reversing cisplatin resistance [21].

3.2.2 Paeonia lactiflora

Red peony contains active ingredients such as total paeoniflorin, paeoniflorin alcohol, gallic acid, volatile oil and sugar [22], which can inhibit tumor cell proliferation, invasion and metastasis, reduce the expression level of tumor-related genes, interfere with the growth cycle, slow down the rate of reproduction, inhibit migration and infiltration, induce apoptosis of tumor cells, regulate the immune function of the organism, reverse the multi-drug resistance of tumor cells, and inhibit angiogenesis [23].

3.2.3 Chuanxiong

Ligusticum chuanxiong contains active ingredients such as chuanxiong lactone, chuanxiong xizine and phenanthroline [24], which can induce multiple effects such as oxidative stress, disruption of mitochondrial function inducing apoptosis, inhibition of tumor stem cell properties preventing metastasis [25], inhibition of oncogene expression, modulation of hypercoagulable state of the blood, anti-tumor angiogenesis, and enhancement of immunosurveillance.

3.2.4 Angelica sinensis tail

The tail of *Angelica sinensis* contains effective components such as angelica polysaccharides, volatile oils, and amino acids [26], which inhibit tumor cell proliferation and promote tumor cell apoptosis by regulating signaling pathways such as the Bcl-2 family of proteins, the cystatinase signaling pathway, and the transforming growth factor- β pathway, modulate tumor gene expression, and improve the immune response [27], as well as antioxidant, pain relief, reduction of inflammation, effective protection of nerves, and inhibition of Platelet aggregation [28].

3.2.5 Dillan

Dilong contains active proteins, amino acids, peptides, nucleosides and organic acids and other effective components [29], through the regulation of protein tyrosine kinase-transcriptional activator 3-related pathway in order to inhibit the proliferation of tumor cells; it has anticoagulant, antioxidant, promote the development of bone marrow hematopoietic cell progenitor cells, and enhance the immune function of the body [30].

3.2.6 Saffron

Saffron contains quercetin, kaempferol, isorhamnetin, hydroxy saffron yellow pigment A and saffron glycoside I and other active ingredients [31], which may act on the key targets such as AKT1, CCND1, MMP9, EGFR, TP53 and other key targets, and involves the signaling pathway of P53 and tumor necrosis factor (TNF), and inhibits the proliferation of tumor vascular endothelial cells and neoangiogenesis, and induces apoptosis[32], and alleviating the “hypercoagulable blood” state of malignant tumors [33].

3.2.7 Peach kernel

Peach kernel contains liposomes, cyanogenic glycosides, amino acids, peach kernel proteins, volatile oils, steroids, flavonoid glycoside compounds and trace elements and other active ingredients [34], inhibit inflammation vascular permeability; improve body immunity, with anti-tumor effects [35].

Zhao Jing included 42 patients with HFS (qi deficiency and blood stasis type), patients treated with BHD showed a decrease in the grade of HFS, a decrease in the numerical rating scale (NRS) scores of hand and foot skin pain, a significant increase in the scores of the KPS and the skin sensitivity value-16 scales, and significant efficacy in their quality of life, Chinese medicine clinical scores and other therapeutic effects, which made their therapeutic effects satisfactory [36]. Wang Gang selected 32 patients with peripheral nerve damage after chemotherapy and gave them acupuncture combined with BHD, and their therapeutic effects were satisfactory [37]; some studies found that BHD could significantly increase the expression levels of vascular endothelial growth factor and angiopoietin-2 in patients, and improve the neurological deficits. Wu Min selected 60 cases of patients who developed HFS after targeted therapy with oral anrotinib hydrochloride capsules, randomly divided into two groups, the control group was given oral vitamin B6 combined with topical urea Vitamin E ointment treatment, and the treatment group was added with BHD chemically tailored for internal + external use, the effective rate of the treatment group was 90.00%, and the effective rate of the control group was 53.33%; the treatment group was better than the control group in terms of improvement of numbness of the hands and/or feet, tingling of the hands and feet, edema, The improvement of patients' quality of life was better than that of the control group; after treatment, PLT, platelet/lymphocyte ratio (PLR) were significantly reduced, and the levels of WBC, N, and hemoglobin were higher than that of the control group; the sensory conduction velocities (SNCV) of the radial, median, peroneal, and superficial peroneal nerves of the patients of the two groups were higher than that of the control group after treatment [38]. Yang Bing

applied BHD to prevent and control capecitabine-associated HFS, which significantly improved the clinical symptoms of patients with remarkable efficacy [39].

4. Conclusion

In summary, at present, the pathogenesis of HFS has not been completely clarified and still needs to be further explored, there is a lack of uniform standards for the evaluation of efficacy, and Western medicine lacks targeted systemic therapies, and the clinical use of methylcobalamin, vitamin B6, vitamin E, reduced glutathione, COX-2 inhibitors, etc. to alleviate the symptoms, but with poorer results. BHD plays an important role in the treatment of malignant tumors, and its active ingredient, quercetin, lignans and kaempferol may intervene in oxidative stress and inflammatory stress-induced apoptosis, which provides a new perspective for continuing to dig into the specific mechanisms, and is conducive to the exploration of new targets and pathways as well as the development and application of new targets and pathways; however, there are fewer studies on the mechanisms of apoptosis, autophagy, and other related mechanisms of BHD in the treatment of tumors, and glycoside fractions, oxidative damage, bioinformatic analyses, and metabolomics have been the recent hotspot in the field of mechanism of action. And BHD has the advantages of multiple pathways, good efficacy, small side effects, wide range of adaptations, and holistic regulation and flexible dialectical treatment, etc. It can improve the combined symptoms of malignant tumor-related toxicities and side effects, etc. Multi-drug additions and subtractions, and give full play to the advantages of the overall comprehensive conditioning of traditional Chinese medicine to provide more clinical application directions for the slowing down of the tumor pathogenesis process and the improvement of the quality of patient's survival, and it has been commonly used in the clinic, and has achieved a certain degree of therapeutic efficacy ; however, the sample size of cases selected by various investigators is generally small and lacks large-sample clinical randomized controlled trials (RCTs), and supplementing RCT-type studies in the future will help to clarify the evaluation of the efficacy of BHD in the treatment of HFS with qi deficiency and blood stasis.

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