

# Progress in TCM Treatment of Chemotherapy-induced Hand-foot Syndrome in Malignant Tumors

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**Abstract:** Antineoplastic drugs are easy to cause hand-foot syndrome in patients, seriously affect the quality of life, and even affect the dose or course of chemotherapy, and then affect the therapeutic effect. At present, there is no unified treatment standard in western medicine. Some studies have confirmed that the hand and foot of traditional Chinese medicine has a certain clinical effect on hand and foot syndrome. This paper mainly summarizes the clinical research results of traditional Chinese medicine on malignant tumor chemotherapy hand and foot syndrome by consulting the relevant literature, in order to provide reference for clinical drug use.

**Keywords:** Hand and foot syndrome; TCM treatment; Review

## 1. Introduction

The most common adverse reaction after antineoplastic therapy is hand-foot syndrome (HFS) after chemotherapy [1]. Although HFS does not endanger the life of patients, it seriously affects the quality of life of patients, serious HFS life is difficult to take care of themselves, in addition, serious HFS can lead to chemotherapy dose reduction or stop treatment, thus affecting the efficacy of tumor [2]. Western medicine uses high-dose vitamin B6. COX-2 inhibitor celecoxib, glucocorticoid, urea cream and other treatment, the effect is not good. Since ancient times, there have been a large number of traditional Chinese medicine for the diagnosis and treatment of hand and foot skin damage, and now there are many clinical studies show that traditional Chinese medicine treatment has a good effect on HFS.

## 2. Hand and foot syndrome

Hand and foot syndrome [3] (HFS), also known as palmoplantar erythema, limb erythema and chemotherapy-induced erythema, is a characteristic skin toxic reaction, mainly manifested as palmar and toe tingling pain, burning pain and bilateral symmetrical swelling, severe pain, desquamation, ulcers and so on, which have a great impact on the daily life of patients. In 1984, Lokich of Harvard Medical School reported that 5-fluorouracil and its metabolites could cause HFS [4], which showed dose-limited toxicity, which mainly occurred in the compressed area. The common chemotherapeutic drugs in HFS were capecitabine, fluorouracil, liposome doxorubicin and so on. Among them, 17% had severe HFS [5].

HFS usually occurs 2-21 days after treatment, and can be as late as 10 months [6]. The clinical manifestations are different, such as numbness and dullness of hands and feet, skin pigmentation [7] and itching of hands and feet [8]. In severe cases, erythema, swelling, desquamation, chapping, knot-like blisters or severe pain may occur in people with dark skin. Skin pigmentation of the palm and foot is more common, in addition, pigmentation after inflammation is also more common, especially capecitabine, diffuse or distributed along the palmprint in the palm and sole of the foot [6]. At present, it is roughly divided into 3 degrees in clinic. Degree I: numbness, insensitivity, painless swelling or erythema, which does not affect daily life; degree II: painful swelling or erythema, which affects daily life; degree III: wet desquamation, ulcer, blisters or pain, which seriously affects daily life. In severe cases, drug withdrawal is often used clinically, although the effect of this method is good, but it disturbs the regular treatment of patients. At present, the mechanism of antineoplastic drugs causing HFS is not clear, but it has been reported that antineoplastic drugs may cause HFS due to peak plasma concentration or excessive cumulative dose of drugs in vivo, or it may be related to rich blood, developed sweat glands, high temperature, local pressure, low skin dihydropyrimidine dehydrogenase activity and high expression of thymidine phosphorylase in feet and hands [9-10]. If it is not treated in a timely manner, the medication

of the patient will be interrupted.

### **3. Western medical treatment of hand and foot syndrome**

Western medicine mainly takes high-dose vitamin B6, COX-2 inhibitor celecoxib, glucocorticoid and other treatments for HFS. Oral vitamin B6 is often used as a method for the prevention and treatment of HFS. Chen Delian [11] observed the efficacy of vitamin B6 combined with apatinib in the treatment of advanced non-small cell lung cancer. The results showed that oral apatinib plus vitamin B6 could reduce the incidence of oral mucositis and HFS. Celecoxib capsule is the most commonly used COX-2 inhibitor in clinic. It is reported that celecoxib is the most statistically significant and promising method for the prevention and treatment of HFS in clinic. Tian Dan et al. [12] 48 patients with advanced gastric cancer were treated with celecoxib combined with XELOX regimen. The results showed that the incidence of HFS in celecoxib group was significantly lower, and all of them were grade 1 reaction. However, compared with placebo group, cardiovascular events are easy to occur [13]. An Linjing et al. [14] prospective randomized controlled trials showed that urea cream could reduce the incidence of sorafenib-induced HFS and improve the tolerance of patients to sorafenib.

### **4. Understanding and treatment of hand-foot syndrome in traditional Chinese medicine**

#### ***4.1. Understanding of hand-foot syndrome in traditional Chinese medicine***

Traditional Chinese medicine believes that HFS is equivalent to the category of "erotic sore", "furuncle", "goose palm wind", "arthralgia syndrome" and "blood arthralgia" in TCM. The side effects of antineoplastic drugs belong to the category of "drug toxicity" in traditional Chinese medicine [15]. The toxicity stagnates heat, causes local skin redness, swelling and heat pain, heat pathogen accumulates for a long time, leads to pustule formation, heat burns Yin fluid, blood deficiency and loss of nourishment, skin loss in osmosis, local skin desquamation and chapping, lack of pubic fluid, fire pathogen is easy to cause wind and blood, heat pathogen consumes qi and injures yin, Yin blood does not follow the usual way, heat forces blood in vain, blood overflow outside the pulse, blood stasis blocks meridians and collaterals. If you can't get through, you will feel pain, tingling, etc. The blood stasis does not disperse, the new blood does not give birth, the qi and blood is unfavorable, and the limb loss leads to the numbness of the hands and feet. the treatment is mainly detoxification, supplemented by nourishing blood, removing blood stasis and dredging collaterals. Studies have shown that traditional Chinese medicine can significantly improve the side effects of hands and feet, and provide a guarantee for regular treatment of patients [16]. With the development of traditional Chinese medicine, many treatment methods of HFS have emerged in traditional Chinese medicine, and the curative effect is more significant [17-18]. The intervention of traditional Chinese medicine can reduce the discomfort and pain of HFS patients, improve their quality of life, effectively alleviate the non-disease progressive withdrawal of drugs in HFS patients, and provide the possibility for patients to continue treatment. The main treatment methods are internal administration of traditional Chinese medicine, external use of traditional Chinese medicine and acupuncture treatment.

#### ***4.2. Internal administration of traditional Chinese medicine***

Liu Keqi et al. [19] observing the therapeutic effect of Jiawei Xiexin decoction on HFS, 80 patients were randomly divided into two groups. The treatment group was treated with Jiawei Xiexin decoction and external application of Arnebia olive oil, while the control group only received routine chemotherapy. The results showed that the total effective rate and treatment satisfaction rate of the treatment group were higher than those of the control group, and the incidence of HFS in the treatment group was lower than that of the control group. Gong Jian [20] selected 64 patients with colorectal cancer who received capecitabine-based chemotherapy and randomly divided them into two groups. The treatment group was given Sanbi Decoction orally on the basis of chemotherapy. After 6 cycles, the incidence of HFS in the control group and treatment group was 56.25% and 28.12%, respectively. And the improvement of TCM symptoms in the treatment group is more obvious. Xie Yanhua et al.[21]in order to explore the treatment and prognosis of Xuefuzhuyu decoction combined with oral capecitabine for colorectal cancer, 98 patients with colorectal cancer were randomly divided into observation group and control group. The control group was given oral capecitabine, and the observation group was treated with Xuefuzhuyu decoction. After treatment, the incidence of HFS in the observation group was 10.20%, which was significantly lower than 38.78% in the control group. Zou Jinlin et al. [22] randomly divided 120 patients

with chemotherapy-related hand and foot syndrome after colon cancer operation into the control group and the observation group. The control group was treated with oral vitamin B6 and mecobalamin tablets. The observation group was again treated with Yiqi Tongbi traditional Chinese medicine and Siwu decoction. After 2 courses of treatment, the effective rate of the control group was 88.33%, which was lower than 91.67% of the observation group.

#### ***4.3. External use of traditional Chinese medicine Internal administration of traditional Chinese medicine***

Zhao Hui [23] selected a total of 82 patients who received capecitabine chemotherapy and were randomly divided into two groups. All patients were given routine treatment with western medicine. The observation group was treated with Huangqi Guizhi Wuwu decoction on the basis of the above treatment. The results showed that the incidence of hand and foot syndrome in the observation group was significantly lower than that in the control group (37.5% vs 70%). Zhu Xiaojuan et al. [24] divided the patients with HFS into two groups: the control group was treated with matrix medicine, and the experimental group was treated with ginseng hand and foot moisturizing ointment. After 2 weeks of treatment, the experimental group was superior to the control group in the aspects of hand and foot pigmentation, sensory dullness, numbness, needling, burning, erythema, swelling, desquamation, ulcer, pain and total score. Wei Weii et al. [25] divided 60 patients who received capecitabine chemotherapy into two groups. The control group was treated with vitamin B6 orally, and the treatment group was treated with governor pulse moxibustion (0.05g, 1.5g, cinnamon 2g, musk 0.1g, Chuanxiong 1g) combined with traditional Chinese medicine soaking (geranium 60g, epimedium 20g, red peony 15g, cassia twig 15g). Both groups took 21 days as a course of treatment, with a total of 4 courses of treatment. The results showed that the incidence and severity of HFS in the treatment group were slighter than those in the control group, and the symptom scores and pain NRS scores in the treatment group were lower than those in the control group. Xu Na [26] observed the efficacy of Qigui external washing prescription in improving hand and foot syndrome in patients with malignant tumor chemotherapy. 72 patients with malignant tumor were divided into study group and control group. After 2 cycles of chemotherapy, the comparison of the curative effect between the two groups showed that the HFS grade and total effective rate of the study group were significantly improved, the NRS score of the study group was lower than that of the control group, and the change of QOL score of the study group was better than that of the control group. Guo Ting et al. [27] selected 70 HFS patients and divided them into treatment group (n = 35) and control group (n = 35). Compound Phellodendron Phellodendri liquid was used in the treatment group, and self-made solution was given in the control group (0.9% sodium chloride injection 100ml, 2% lidocaine 5ml + gentamicin 80000 U). After one week of intervention, the total effective rate of the treatment group was 97.14%, and that of the control group was 80%. The total effective rate of the treatment group was significantly higher than that of the control group, and the quality of life and pain relief rate were significantly improved compared with the control group. Li Zhiming et al. [28] adopted the method of self-control before and after treatment. 30 patients with HFS were treated with Jiawei Xianliuoyin decoction for warm bath and external application of medicine bag. After 14 days of treatment, the TCM syndrome score and general state score were significantly improved as compared with those before treatment. Among them, the symptoms of hands and feet (dry skin, skin erythema, swelling, burning, skin numbness and itching) were alleviated in varying degrees, and the total effective rate was 86.67%; the general state of patients (mental state, emotion, appetite and sleep) was effectively improved, and the total effective rate was 80.00%.

#### ***4.4. Acupuncture treatment***

Yang Zepi [29] adopted a prospective study method, including 24 patients with HFS treated with acupoint acupuncture for 3 weeks. The results showed that before and after treatment, the clinical symptoms of HFS were completely relieved in 2 patients, HFS grade decreased in 12 patients, and 6 patients maintained a stable state. The total effective rate was 70%. Chen Lixia et al. [30] randomly divided 70 HFS patients caused by capecitabine chemotherapy into the control group and the observation group to study the clinical efficacy of thunderfire moxibustion combined with vitamin B6 in the treatment of capecitabine chemotherapy-induced hand and foot syndrome (HFS). Both groups were given oral vitamin B6. On this basis, the observation group was supplemented with thunder-fire moxibustion and selected acupoints Hegu (double), Sanyinjiao (double) and Taichong (double). After 6 weeks of treatment, the results showed that the total effective rate was 57.58% in the control group and 85.29% in the observation group. The scores of NRS and KPS in the control group were higher than those in the control group, and the improvement effect of COX-2 and VEGF in the observation group was better than that in

the control group.

## 5. Conclusion

The mechanism of HFS is not clear. For a long time, scholars believe that the occurrence of HFS is related to vitamin B6 deficiency. With its unique advantages, traditional Chinese medicine plays an important role in anti-tumor, improving clinical symptoms of HFS and ensuring the normal progress of chemotherapy, which makes up for the deficiency of western medicine. Many clinical trials have confirmed that traditional Chinese medicine for internal administration, external use and acupuncture treatment of HFS have good clinical effects. Although traditional Chinese medicine is effective in preventing hand-foot syndrome, there are still many shortcomings, such as the observed chemotherapy cycle is short, there is no specific clinical efficacy evaluation index, and the cumulative effect of chemotherapeutic drug toxicity is not considered. Therefore, in the future research, we should prolong the observation cycle, establish a unified evaluation standard of curative effect, and increase the support of basic research as the direction of its exploration, so as to better guide its clinical treatment.

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## References

- [1] Guo Ting, He Hong, Hu Fengyang, Mei Mengxue, Liu Peirong. (2018) *Effect of Compound Cortex Phellodendri Liquid in the treatment of Capecitabine-induced hand-foot syndrome*. *China Medical Herald*, 15(26), 125-128.
- [2] Cui Yongjia, Weng Jieqiong, Lu Wenping. (2021) *Treatment of Hand and Foot Skin Adverse Reactions Caused by Anticancer Drugs Based on Syndrome Differentiation of "Dryness and Dampness"*. *Modernization of Traditional Chinese Medicine and Materia Medica-World Science and Technology*, 23(07), 2487-2491.
- [3] Lu Shujiao, Mao Shiwang, Shi Yong. (2017) *Clinical Manifestations in Five Cases of Hand-foot Syndrome Induced by Apatinib Mesylate*. *Chinese General Practice*, 20(18), 2267-2270.
- [4] Lokich J J, Moore C. (1984) *Chemotherapy-associated pal-mar-planter erythrodysesthesia syndrome*. *Ann Intern Med*, 101(6), 798-799.
- [5] Lou Y, Wang Q, Zheng J, et al. (2016) *Possible pathways of capecitabine-induced hand-foot syndrome*. *Chem Res Toxicol*, 29(10), 1591-1601.
- [6] Nikolaou V, Syrigos K, Saif M W. (2016) *Incidence and implications of chemotherapy related hand-foot syndrome*. *Expert Opin Drug Saf*, 15(12), 1625-1633.
- [7] Miller K K, Gorcey L, McLellan B N. (2014) *Chemotherapy-induced handfoot syndrome and nail changes: a review of clinical presentation, etiology, pathogenesis, and management*. *J Am Acad Dermatol*, 71(4), 787-794.
- [8] Lou Yanni, Jia Liqun. (2008) *Occurrence regularity and treatment progress of hand and foot syndrome caused by capecitabine*. *Journal of China-Japan Friendship Hospital*, 3, 176-178.
- [9] Tong Zhuyue, Wang Binbin. (2017) *The latest research progress of hand and foot syndrome*. *Zhejiang Clinical Medical Journal*, 19(3), 581-583.
- [10] Zhong Meihua, Mu Leilei, Liu Dongmei. (2017) *Study on the efficacy of mucopolysaccharide polysulfonate cream in the prevention and treatment of hand and foot syndrome by ultrasonic conductivity combined with nursing intervention*. *Chinese Journal of Modern Nursing*, 23(15), 1987-1990.
- [11] Chen Delian, Chen Mingcong, Jiang Huihong. (2018) *Clinical observation of high-dose vitamin B6 combined with apatinib in the treatment of advanced non-small cell lung cancer*. *Zhejiang Medicine*, 40(3), 291-293.
- [12] Tian Dan, Wang Shenming. (2017) *Clinical study on celecoxib combined with XELOX regimen in the treatment of advanced gastric cancers*. *Academic Journal of Guangzhou Medical University*, 45(1), 63-65.
- [13] De Vecchis R, Baldi C, Di Biase G, et al. (2014) *Cardiovascular risk associated with celecoxib or etoricoxib: a meta-analysis of randomized controlled trials which adopted comparison with placebo or naproxen*. *Minerva Cardioangiol*, 62(6), 437-448.

- [14] An Linjing, Zhang Xin, Zhang Lina, et al. (2014) Randomized controlled trial of nurse intervention of urea-based cream on sorafenib-associated hand-foot skin reactions of patients. *Journal of Clinical Medicine in Practice*, 18(22), 45-47, 54
- [15] Guo Zhongning, Yang Yufei. (2005) Traditional Chinese Medicine Drug Huwei Yufu Decoction for the Treatment of Xeloda Related Hand-foot Syndrome in 33 Cases. *China Cancer*, 14(9), 625-627.
- [16] Yan Ruyi, Yu Lanchu, Liu Ping. (2017) Observation on the efficacy of traditional Chinese medicine fumigation in the treatment of second degree hand foot syndrome caused by capecitabine. *Qinghai Medical Journal*, 47(7), 68-70.
- [17] Huang Yu, Wang Shaoxia. (2018) A study on treating hand and foot syndrome caused by chemotherapy in malignant tumors at home and abroad. *Clinical Journal of Chinese Medicine*, 10(3), 86-89.
- [18] Wu Wei, Chu Binbin, Liang Linchun, et al. (2019) Clinical observation of traditional Chinese medicine fumigation and washing combined with vitamin B6 in the prevention and treatment of apatinib-induced hand and foot syndrome. *Modern Practical Medicine*, 31(2), 206-207.
- [19] Liu Keqi, Sun Tian, Xu Xianggui, Zhong Li, Qiu Yulian. (2018) Clinical Observation of Using Modified Xiexin Decoction Combined with Porphyra Olive Oil External Use in the Prevention and Treatment of 80 Cases of Kababine Related Hand Foot Syndrome. *Journal of Sichuan of Traditional Chinese Medicine*, 36(09), 119-121.
- [20] Gong Jian. (2018) Prevention and treatment of capecitabine-related hand and foot syndrome with Sanbi decoction: a report of 32 cases. *Fujian Journal of TCM*, 49(04), 16-17+20.
- [21] Xie Yanhua, Wang Songhai, Li Linchan, Miao Wenhong. (2020) Effect of Xuefu Zhuyu Decoction on hand-foot syndrome and prognosis after oral capecitabine in colorectal cancer. *Journal of Yanan University (Med Sci)*, 18(04) 77-80.
- [22] Zou Jinlin, Lin Zhidong, Niu Bin, Mou Xiangqiong. (2019) Clinical Study of Yiqi Tongbi Prescription Combined with Siwu Decoction in Treatment of Colon Cancer Patientspostoperative Chemotherapy Related Hand Foot Syndrome. *Chinese Archives Of Traditional Chinese Medicine*, 37(08), 1906-1909.
- [23] Zhao Hui. (2019) The protective effects of the Huangqi Guizhi Wuwu decoction on capecitabine associated hand and foot syndrome. *Clinical Journal of Chinese Medicine*, 11(07), 77-79.
- [24] Zhu Xiaojuan, Li Jie. (2019) Clinical randomized double-blind controlled trial of Shencao hand-foot cream in the treatment of hand-foot syndrome. *China Journal of Traditional Chinese Medicine and Pharmacy*, 34(08), 3825-3828.
- [25] Wei Wei, Huang Bo, Li Zhiyuan, Li Xiaofei, Mo Liuqing. (2021) Preventive and therapeutic effect of du pulse moxibustion combined with traditional Chinese medicine soaking on capecitabine associated hand and foot syndrome. *Hebei J TCM*, 43(03), 423-425+429.
- [26] Xu Na. (2019) Observation on the Therapeutic effect of Comprehensive Nursing of traditional Chinese and Western Medicine on hand and foot Syndrome in patients with malignant tumor undergoing chemotherapy. *Today Nurse*, 26(11), 71-73.
- [27] Guo Ting, He Hong, (2019) Hu Fengyang, Mei Mengxue, Liu Peirong. Efficacy observation of Fufang Huangbai Liquid in treating hand-foot syndrome caused by capecitabine. *China Journal of Traditional Chinese Medicine and Pharmacy*, 34(06), 2829-2832.
- [28] Li Zhiming, Wang Fen, Fan Yinan, Song Fengli, Wang Aili, Kang Ning, Li Tong. (2020) Clinical study on external application of Jiawei Xianfang Huoming Yin in the treatment of hand-foot syndrome with stasis-heat entering collaterals. *China Journal of Traditional Chinese Medicine and Pharmacy*, 35(04), 2133-2136.
- [29] Yang Zepei, (2020) Prospective and open clinical study of acupuncture in the treatment of hand and foot syndrome. *Beijing University of Chinese Medicine*.
- [30] Chen Lixia, Yan Feng. (2020) Clinical Study of Thunder-fire Moxibustion Combined with Vitamin B6 in Treating Hand-foot Syndrome Caused by Capecitabine Chemotherapy. *Journal Of Shandong University Of TCM*, 44(06), 674-678.