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REVIEW

TMR Non-Drug Therapy

The effects of Chinese herbal fumigation on the prevention of peripheral neurotoxicity caused by chemotherapy: a meta-analysis

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Highlights

The study evaluated the clinical efficacy of Chinese herbal fumigation in the past five years to prevent peripheral neurotoxicity caused by chemotherapy. Five Chinese literatures, with a total of 331 patients, were eventually included. Meta-analysis results demonstrate that herbal fumigation can effectively prevent the occurrence of peripheral neurotoxicity caused by chemotherapy without obvious adverse reactions.

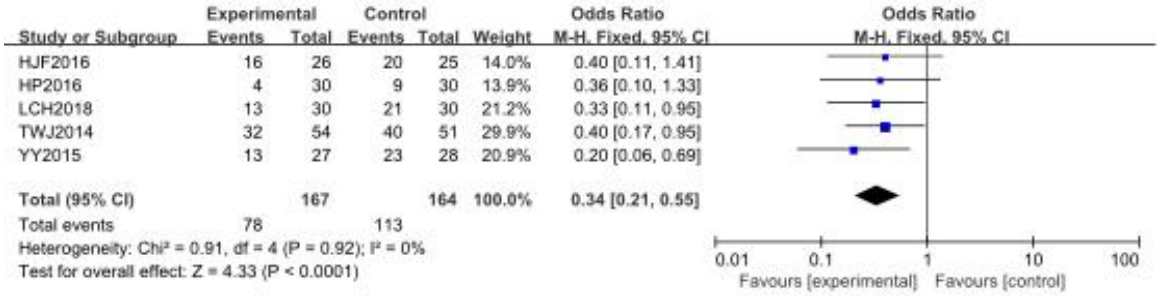

Figure 2 Effect of the Chinese herbal fumigation on preventing peripheral neurotoxicity caused by chemotherapy

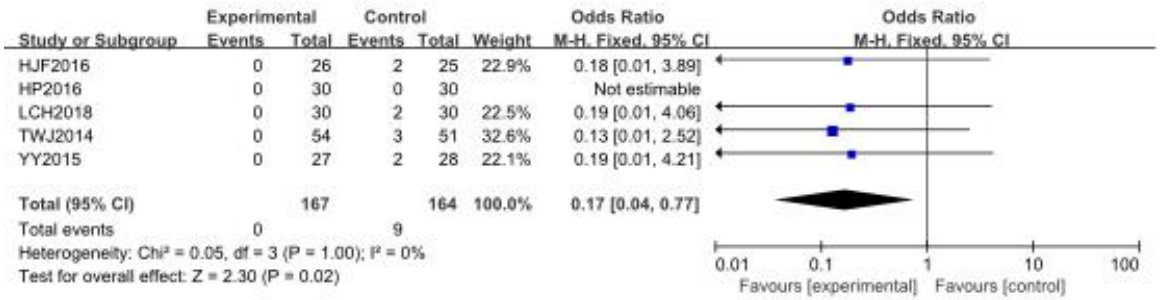

Figure 3 Curative effect of the Chinese herbal fumigation on preventing grade 2 peripheral neurotoxicity caused by chemotherapy

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Abstract

Backgroud: To evaluate the clinical efficacy of Chinese herbal fumigation to prevent peripheral neurotoxicity caused by chemotherapy. **Methods:** CNKI, VIP Database, Wanfang Database, PubMed and Cochrane Databases were searched from January 2014 to July 2019 for randomized controlled trials (RCTs) of herbal fumigation to prevent peripheral neurotoxicity caused by chemotherapy. The RCTs were selected according to the inclusion and exclusion criteria, and the data extraction and bias risk assessment were performed. RevMan 5.3 software was used for statistical analysis. **Results:** Five Chinese RCTs were eventually included, with a total of 331 patients. Meta-analysis showed that compared with the control group, herbal fumigation could significantly reduce the incidence of peripheral neurotoxicity induced by chemotherapy (OR = 0.34, 95% CI (0.21, 0.55), $P < 0.01$). Moreover, herbal fumigation could also reduce the incidence of peripheral neurotoxicity above grade 2 (OR = 0.17, 95% CI (0.04, 0.77) $P = 0.02$). **Conclusion:** Herbal fumigation can effectively prevent the occurrence of peripheral neurotoxicity caused by chemotherapy without obvious adverse reactions.

Keywords: Chinese herbal fumigation, Chemotherapy, Peripheral neurotoxicity, Meta-analysis

***Abbreviations*:**

RCTs, randomized controlled trials; WHO, World Health Organization; OR, odds ratio; CI, confidence interval.

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***Competing interests*:**

The authors declare that there is no conflict of interest.

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Background

Chemotherapy often causes a series of toxic and side effects in tumor patients, among which peripheral neurotoxicity is one of the common clinical adverse reactions. According to statistics, about 20% to 40% of patients will develop peripheral neuropathy after using neurotoxic chemotherapy drugs, and the incidence is proportional to the dose of chemotherapy drugs [1]. It can be seen that prevention is particularly important in this disease. Western medicine has not yet found the exact pathogenesis of the disease, so it is not effective in prevention and treatment. According to the clinical manifestations of this disease, sensory and motor abnormalities, such as numbness in the limbs and cold pain sensitivity, are segmented in the form of "gloves and stockings", which is classified as "biological syndrome" by Chinese medicine [2]. In the theory of traditional Chinese medicine, it believes that chemotherapeutic drugs fall into the category of "drug poisons and evil poisons". Tumor patients have a long history of illness, and their vitality is deficient. Exogenous pathogenic factors lead to dysfunction of the meridians. Therefore, dredging meridian can improve the symptoms. In recent years, the traditional Chinese herbal fumigation has been widely used to dredge the channels and collaterals, which could increase the body's blood with effectively regulating the nervous system. The commonly used herbs include Honghua (*Carthamus Tinctorius*), Weilingxian (*Radix Clematidis*), Aiye (*Artemisia Argyi*), and Guizhi (*Cassia Twig*) etc. Cancer patients who are unwilling to take traditional Chinese medicine or cannot receive acupuncture or acupoint injection are advised for Chinese herbal fumigation. But there are little researches about the clinical efficiency and safety. Therefore, this article conducts a meta-analysis to review the advancement of drug therapy for peripheral neuropathy and evaluate clinical efficacy and the safety.

Materials and methods

Literature search

CNKI, VIP, Wanfang database, PubMed and Cochrane were used to search clinically published randomized controlled trials (RCTs) in the period from January 2014 to September 2019 for studies about the effects of Chinese herbal fumigation to prevent chemotherapy-induced peripheral neurotoxicity. The search terms were as follows: "Chinese herbal fumigation and washing" and "chemotherapy" and "oxaliplatin or cisplatin or paclitaxel, oxaliplatin" and "peripheral neurotoxicity or peripheral neuropathy".

Inclusion criteria

(1) Participants: patients who were given chemotherapy drugs containing peripheral neurotoxicity; Karnofsky performance status score > 60; life expectancy were more than 3 months; no other neurological diseases before treatment; having intact skin of limbs without potential lesions; no history of drug exposure allergy; without limitation of cancer types; (2) interventions: Chinese herbal fumigation combined with chemotherapy (the water temperature is controlled at about 40 ℃, 1–2 times/day, about 30 min each time; the course of treatment is synchronized with the time of chemotherapy); with or without mecobalamin symptomatic treatment; (3) control group: chemotherapy with or without mecobalamin/warm water treatment; (4) study type: RCTs, whether adopting blind methods or allocation concealment, with the language of Chinese and English; (5) peripheral neurotoxicity grading diagnostic criteria uniformly adopt the globally recognized and authoritative World Health Organization (WHO) specific criteria: grade 0, normal; grade I, short-term paresthesia and numbness; grade II, paresthesia and numbness persisted during 2 weeks of treatment; grade III, dysfunction caused by paresthesia and numbness; grade IV, paralysis.

Exclusion criteria

(1) Non-RCT; (2) patients with primary tumor or metastases directly invading peripheral nerves; (3) retrospective studies, animal experiments, reviews, scientific and technological achievements, patent reports, and repeated reports, etc.; (4) the experimental group applies other drugs on the basis of conventional treatment and seriously affects the efficacy; (5) the lack of this article relevant outcome indicators, or outcome indicators using non-peripheral neurotoxicity grade WHO specific versions; (6) original motor system disease or/and limb compression symptoms due to limb metastasis, alcoholism, heavy metal poisoning, HIV infection and other systems (inflammatory, metabolic, ischemic, tumor parasitic syndrome, etc.) disease causing neurological disease; electrolyte disorders such as hypermagnesium or/and hypercalcemia; severe diabetic patients who may cause peripheral paresthesia; patients who have poorly controlled hypertension or/and cerebrovascular disease; those with skin lesions of the hands and feet.

Outcome indicators

(1) The total incidence of peripheral neurotoxicity; (2) the incidence of peripheral neurotoxicity above grade 2; (3) the incidence of adverse reactions; (4) medication regularity of Chinese herbal fumigation to prevent peripheral neurotoxicity caused by chemotherapy.

Literature screening, general data extraction and quality evaluation

Two professional researchers conducted literature screening and cross-checking according to the

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inclusion criteria. If there were inconsistent opinions, they were discussed and resolved to determine the final included literature. General data extraction includes study authors, year, sample size (experimental group/control group), observation time, outcome indicators, adverse reactions, etc. A unified and standardized data extraction form was developed, and the improved Jadad scale was used for quality evaluation (1–2 points for low-quality studies, 3–4 points for higher-quality studies, and 5 points for high-quality studies).

Statistical methods

Meta-analysis was performed by RevMan 5.3 software and the final extracted data was used for statistics. Odds ratio (OR) was used as the effect amount, and the 95% confidence interval (CI) was used. When $P > 0.05$ and $I^2 \leq 50\%$, there was no statistical difference between studies. Meta-analysis was performed by a fixed-effects model. When $P < 0.05$, there were statistical differences between studies. A random-effect model was used for meta-analysis.

Results

Characteristics of included studies

After preliminary search, 94 Chinese and English literatures related to this study were obtained. After reading the full text, according to the inclusion criteria, 5 literatures were included [3–7] (Figure 1). There are 331 patients, including 167 patients in the experimental group (simultaneously with chemotherapy plus fumigation with Chinese medicine) and 164 patients in the control group (single chemotherapy, or simultaneous treatment with mecobalamin or (and) warm water), the general situation of the literature is shown in Table 1.

Law of Chinese herbal fumigation

Through the ancient and modern medical case cloud platform V1.6.1 software, the clinical application rule of herbal fumigationto prevent peripheral neurotoxicity caused by chemotherapy was discussed. The result of data mining analysis show that among the 30 flavors of traditional Chinese medicines involved, the top 10 traditional Chinese medicines in use rate are: Honghua (*Flos Carthami*), Weilingxian (*Radix Clematidis*), Aiye (*Folium Artemisiae Argyi*), Danggui (*Radix Angelicae Sinensis*), Guizhi (*Ramulus Cinnamomi*), Taoren (*Semen Persicae*), Huaqi (*Radix Astragali*), Xixin (*Herba Asari*), Chishao (*Radix Paeoniae Rubra*), Jixueteng (*Caulis Spatholobi*).

Meta-analysis results

The incidence of peripheral neurotoxicity caused by chemotherapy. In view of the prevention and treatment of peripheral neurotoxicity caused by chemotherapy with Chinese herbal fumigation, the peripheral neurotoxicity classification WHO specific standard was used for evaluation after the corresponding cycle of treatment. Five articles were included in this study [3–7]. The heterogeneity test results showed that $P = 0.92 > 0.05$, $I^2 = 0\% < 50\%$, so the fixed effect model was used to calculate the combined effect amount. Meta-analysis results showed OR = 0.34, 95% CI (0.21, 0.55) $P < 0.0001$), indicating that the experimental group and the control group had statistical significance in the incidence of peripheral neurotoxicity caused by chemotherapy (Figure 2).

Curative effect of the herbal fumigation to prevent grade 2 peripheral neurotoxicity caused by chemotherapy. After treatment, the incidence of severe peripheral neurotoxicity in the test group above level 2 was significantly lower than that in the control group. The results of heterogeneity tests showed that $P = 1.00 > 0.05$, $I^2 = 0\% < 50\%$, which showed good homogeneity between studies. So the fixed effect model was used to calculate the combined effect amount. Meta-analysis results showed that there was a difference in the incidence of severe peripheral neurotoxicity between the experimental group and the control group, which was statistically significant (OR = 0.17, 95% CI (0.04, 0.77) $P = 0.02$) (Figure 3)

Analysis of adverse reactions. In the five studies included [3–7], three studies [4, 6, 7] clearly reported adverse reaction results. In one of the studies [7], there were no adverse reactions in the experimental group after fumigation and washing with traditional Chinese medicine. But in other two studies [4, 6], the adverse effects occurred in the test group after fumigation and washing with traditional Chinese medicine. One case [4] showed skin discomfort, and the other two cases [6] showed foot skin irritation, which was manifested by redness and itching of the foot skin and was improved after stopping the traditional Chinese medicine fumigation and washing. There were no cases lost to follow-up in the literature or it was clearly stated that the cause lost to follow-up was not a toxic side effect of external washing of Chinese medicine. Due to two research subjects ($P = 0.85$, $I^2 = 0\%$), a fixed effect model was used for meta-analysis. The results suggest that ($P = 0.21$) is not heterogeneous which indicates that Chinese medicine fumigation and washing is safe in preventing peripheral neurotoxicity caused by chemotherapy. (See Table 2 and Figure 4).

Discussions

The incidence of peripheral neurotoxicity caused by chemotherapeutic drugs is directly proportional to the dose of chemotherapeutic drugs. The degree of injury increases with the increase of dose and the time of injury also prolongs. Therefore, it is important to control the dose of chemotherapeutic drugs, but the clinical situation is still not ideal. Chemotherapy is of

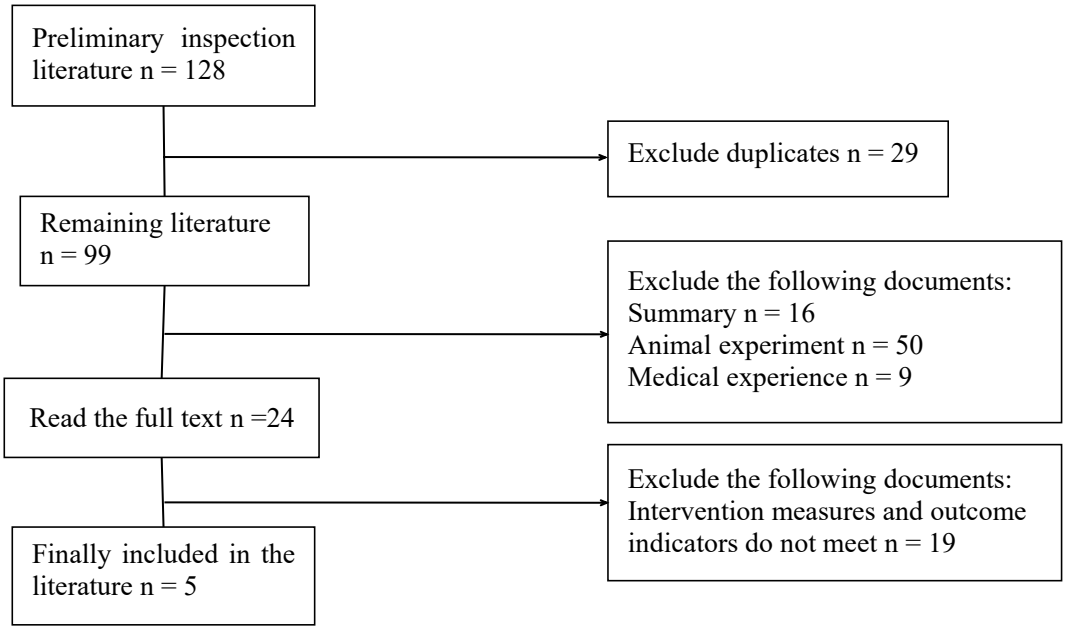

Figure 1 Literature screening process

Table 1 General information of included cases

Author + Years	Sample size (T/C)	Control group	Experimental group	Time	Index	Jadad
TWJ 2014	105 (54/51)	XELOX/FOLFOX4/FOLFOX6/L-OHP + S1	Control plus herbal fumigation (Huangqi (*Radix Astragali*), Danggui (*Radix Angelicae Sinensis*), Wutou (*Aconite*), Jixueteng (*Caulis Spatholobi*), Aiye (*Folium Artemisiae Argyi*) etc.)	3 weeks	①②	4
YY 2015	55 (27/28)	FOLFOX4/FOLFOX6/XELOX/L-OHP + S1	Control plus herbal fumigation (Huangqi (*Radix Astragali*), Taoren (*Semen Persicae*), Honghua (*Flos Carthami*), Chishao (*Radix Paeoniae Rubra*), Ezhu (*Curcuma Zedoary*) etc.)	8 weeks	①②	4
HP 2016	60 (30/30)	FOLFOX/5-FU	Control plus herbal fumigation (Danggui (*Radix Angelicae Sinensis*), Huangqi (*Radix Astragali*), Chishao (*Radix Paeoniae Rubra*), Chuanniuxi (Radix cyathulae), Duhuo (*Radix Angelicae Tuhuo*) etc.)	3 weeks	①②	4
HJF 2016	51 (26/25)	Paclitaxel + mecobalamin	Control plus herbal fumigation (Jixueteng (*Caulis Spatholobi*), Luoshiteng (*Caulis Trachelospermi*), Huzhang (*Polygonum Cuspidatum*), Huangqi (*Radix Astragali*), Guizhi (*Ramulus Cinnamomi*) etc.)	3 weeks	①	4
LCH 2018	60 (30/30)	XELOX	Control plus herbal fumigation (Huangqi (*Radix Astragali*), Guizhi (*Ramulus Cinnamomi*), Aiye (*Folium Artemisiae Argyi*), Honghua (*Flos Carthami*), Chishao (*Radix Paeoniae Rubra*) etc.)	3 weeks	①	3

Note: ① WHO special edition for peripheral neurotoxicity; ② Incidence of adverse reactions.

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Table 2 Adverse reactions

Author + Years	Sample size of experimental	Number of adverse reactions	Incidence (%)	Adverse reaction performance
TWJ 2014	54	2 cases	3.70	Redness and itching on the skin of the feet
YY 2015	27	1 case	3.70	Skin discomfort

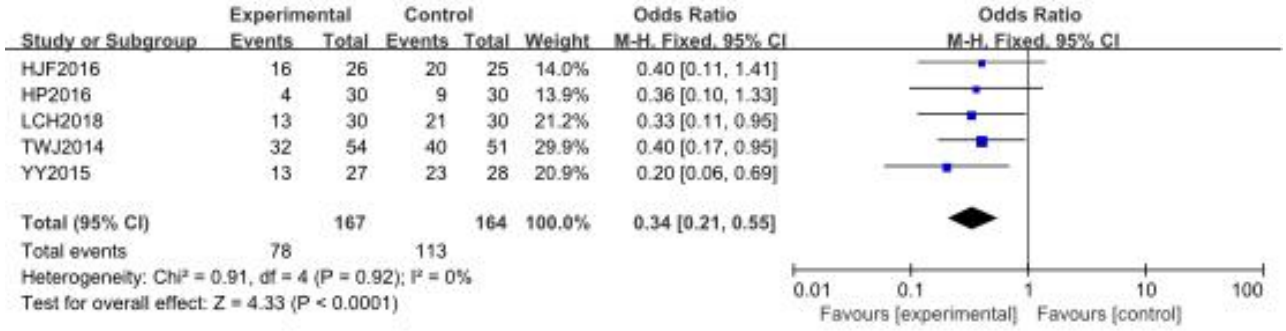

Figure 2 Effect of the Chinese herbal fumigation on preventing peripheral neurotoxicity caused by chemotherapy

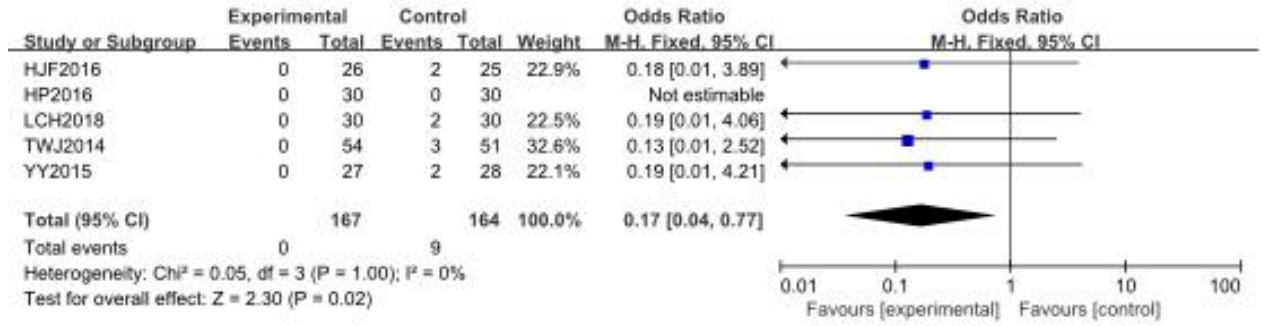

Figure 3 Curative effect of the Chinese herbal fumigation on preventing grade 2 peripheral neurotoxicity caused by chemotherapy

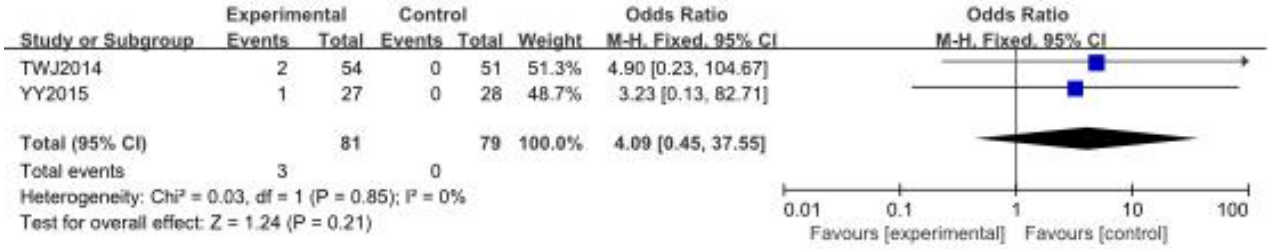

Figure 4 Adverse reactions of the Chinese herbal fumigation

clinical significance to most tumor patients, but its toxic and side effects are common in the clinic. Thus, it is particularly important to cooperate with Chinese medicine in the treatment of chemotherapy.

Traditional Chinese medicine classifies the peripheral neurotoxicity caused by chemotherapy into the category of "arthralgia syndrome". As early as in the ancient book of Chinese medicine *Huangdi Neijing* (*Yellow Emperor's Canon of Internal Classic*; 221 B.C.E.–220 C.E.), there have been specific articles on arthralgia, including etiology, pathogenesis, symptoms, and prognosis. The ancient book of Chinese medicine *Jingui Yaolue* (*Synopsis of the Golden Chamber*; 200 C.E.) clearly contains the names of dampness

arthralgia, blood arthralgia, and calendar festival, among which classic ancient prescription Guizhi Shaoyao Zhimu decoction and Wutou decoction are still commonly used in clinic. In the *Linzheng Zhinan Yian* (*Clinical Guidline of Medical Record*; 1764 C.E.), Ye Tianshi stressed many times that the method should slightly channel its Yang in order to achieve the effects of dredging collaterals and removing arthralgia for patients with arthralgia. Chinese herbal fumigation is a common method in external treatment. Through local fumigation, the herbal works through the skin and circulates through the meridians or blood. The clinical application of fumigation was first recorded in the ancient book of Chinese medicine *Jingui Yaolue* (*Synopsis of the Golden Chamber*; 200 C.E.), which was gradually widely used in all kinds of clinical diseases. In addition, Chinese herbal fumigation can also avoid the irritant response of the herbal to the gastrointestinal tract [8].

This article analyzes the clinical use of Chinese herbal fumigation to prevent peripheral neurotoxicity caused by chemotherapy. The heterogeneity test results showed that, Chinese herbal fumigation could prevent peripheral nerve toxicity caused by chemotherapy (OR = 0.34, 95% CI (0.21, 0.55) $P < 0.01$). In terms of statistical significance, the efficacy of the experimental group was greater than that of the control group. At the same time, Chinese herbal fumigation was used to prevent severe peripheral neurotoxicity above level 2, and results showed that Chinese herbal fumigation was used to prevent severe surroundings of level 2 and above caused by chemotherapy. In the literature included in this article, a total of 331 people, only 3 of them had adverse reactions, that is, the common adverse reactions of Chinese herbal fumigation, localized skin redness and itching, was stopped after the Chinese herbal fumigation, indicating that the Chinese herbal fumigation has small adverse reactions.

Other than that, the results of data mining by V1.6.1 software can be seen that the skin microcirculation is improved by the active substances in the patients with peripheral neurotoxicity caused by chemotherapy [9]. The safflower yellow pigment in safflower can not only protect neurons from injury, but also make the decreased neurotransmitters recover or even close to normal [3]. Weilingxian (*Radix Clematidis*) is warm in nature and acrid in taste. It is easy to circulate into the body. It can be used to disperse wind and is apt to enter tendons and muscles [10]. Aiye (*Folium Artemisiae Argyi*) and Guizhi (*Ramulus Cinnamomi*) are used to specialize in warming meridians, dissipating cold, and stopping arthralgia; Huaqi (*Radix Astragali*) membranaceus internal and external application, with cassia twig branch, can benefit Qi and activate Yang; Danggui (*Radix Angelicae Sinensis*) has the effect of activating blood circulation and nourishing blood; Chishao (*Radix Paeoniae Rubra*) and Honghua (*Flos Carthami*) can improve the circulation of the body and protect the nervous system [3].

Professor Jia Yingjie pointed out that Chinese herbal fumigation should not be separated from dialectics in specific clinical applications. According to the clinical manifestations of patients with peripheral neurotoxicity caused by chemotherapy, three types of syndromes and corresponding selection methods are used as follows: (1) prescription with Yiguan decoction combined with Zuogui pills are used in patients with deficiency of liver and kidney; (2) Huangqi Guizhi Wuwu decoction is used in patients with cold condensed tendons pulse syndrome; (3) Buyang Huanwu decoction is used in patients with choroid stasis syndrome [11]. Professor Lin Hongsheng was willing to use self-made external washing formula. This formula is on the basis of Huangqi Guizhi Wuwu decoction, reusing Huaqi (*Radix Astragali*) to supplement Qi and help Yang. And then combining with blood-activating herbal which has a good clinical effect on the numbness and uncomfortable caused by deficiency of Qi and blood after chemotherapy and imbrosition of vein [12].

However, this article has conducted a meta-analysis of 5 randomized controlled literatures that used Chinese herbal fumigation to prevent chemotherapy-induced peripheral neurotoxicity in the past 5 years, and concludes that Chinese herbal fumigation can significantly reduce the incidence of peripheral neurotoxicity caused by chemotherapy with small adverse reactions. Traditional Chinese herbal fumigation has its unique advantages in this respect and can avoid gastrointestinal tract and liver damage that may be caused by oral administration, achieving the effects by external treatment. What's more, traditional Chinese herbal fumigation, with the effect of improving the quality of life of cancer patients and escorting chemotherapy smoothly, is worthy of clinical promotion and application.

References

1. Smith EML, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA 2013, 309: 1359–1367.
2. Argyriou AA, Bruna J, Marmiroli P, et al. Chemotherapy-induced peripheral neurotoxicity (CIPN): an update. Crit Rev Oncol Hematol 2012, 82: 51–77.
3. Li CH, Shi Y, Huang RB, et al. Clinical observation on external washing of Tongluo Bibi decoction in preventing and treating chemotherapy-induced peripheral neurotoxicity. Liaoning J Tradit Chin Med 2018, 45: 735–737.
4. Yuan Y. Clinical study on the prevention and treatment of oxaliplatin-induced neurotoxicity by Chinese herbal medicine Huoxue Tongjing decoction. Liaoning Univ Tradit Chin Med, 2015.

doi: 10.12032/TMRND20200301004

5. Huang JF, Guo Y. Self-made Huoxue Tongluo Fang bubble wash for prevention and treatment of 26 cases of peripheral neurotoxicity induced by paclitaxel. J Gansu Univ Chin Med 2016, 33: 48–50.
6. Tang WJ, Xin B, Deng C, et al. Clinical observation on 54 cases of nourishing blood and warming meridian Tongluo traditional Chinese medicine to prevent and cure neurotoxicity caused by platinum oxalate. J Tradit Chin Med 2014, 55: 2007–2010.
7. Huang P, Pan YY, Liu LF. Clinical observation of Chinese herbal medicine foot bath in preventing and treating oxaliplatin neurotoxicity. Shandong J Tradit Chin Med 2016, 35: 136–137.
8. Wang Y, Wang MM, Sun ZL, et al. Experimental study on the optimal scheme of Chinese herbal fumigation for rheumatoid arthritis. Chin Arch Traditl Chin Med 2018, 36: 1609–1612 + 1801.
9. Nie YJZ, Luo Y, Li XY, et al. Extraction of safflower active ingredients and evaluation of its effect on improving skin microcirculation. Chin Surf Deterg Cosmet 2019, 49: 304–309.
10. Jia Yumei. Notes on the examination of plant names and realities. Henan: Henan Science and Technology Press, 2015.
11. Li BL, Li XJ. Jia Yingjie's experience in treating neurotoxicity caused by oxaliplatin. Shandong J Tradit Chin Med 2010, 29: 491–492.
12. Qin YG, Lin HS, Hua BJ. Clinical observation on 34 cases of peripheral neuropathy caused by chemotherapy with Waixi Tongluo recipe. J Tradit Chin Med 2012, 53: 2014–2016.