

Research progress on bone marrow suppression after radiotherapy and chemotherapy for gynecological malignant tumors using TCM internal and external treatment methods

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Abstract: Gynecological malignancies are currently one of the most common malignant tumors faced by women, including cervical malignancies, endometrial malignancies, ovarian malignancies, vulvar malignancies, etc. In recent years, for the treatment of gynecological malignant tumors with Western medicine, surgery combined with postoperative radiotherapy and chemotherapy has been commonly used in clinical practice. Although it can effectively eliminate cancerous cells and improve patients' clinical symptoms, it not only kills cancer cells but also leads to serious adverse reactions such as bone marrow suppression. This article discusses the use of traditional Chinese medicine in the treatment of gynecological malignant tumors and radiochemotherapy. From the perspectives of internal and external treatment, it summarizes the research progress of traditional Chinese medicine in improving bone marrow suppression after radiotherapy and chemotherapy, providing corresponding reference for future clinical treatment.

Keywords: Traditional Chinese medicine internal and external treatment methods; Gynecological malignant tumors; Bone marrow suppression; Radiochemotherapy

1. Introduction

Bone marrow suppression is the most common and severe adverse reaction after radiotherapy and chemotherapy for gynecological malignant tumors. It not only directly reduces the quality of life of patients, but also may affect the progress and effectiveness of later treatment^[1,2]. Its occurrence is due to the lack of targeted radiotherapy and chemotherapy, which not only kills cancer cells but also damages normal cells that proliferate rapidly in the body. Therefore, it leads to damage to hematopoietic stem cells and hematopoietic progenitor cells that proliferate rapidly in blood cells, leading to potential bone marrow damage, as shown in Figure 1.

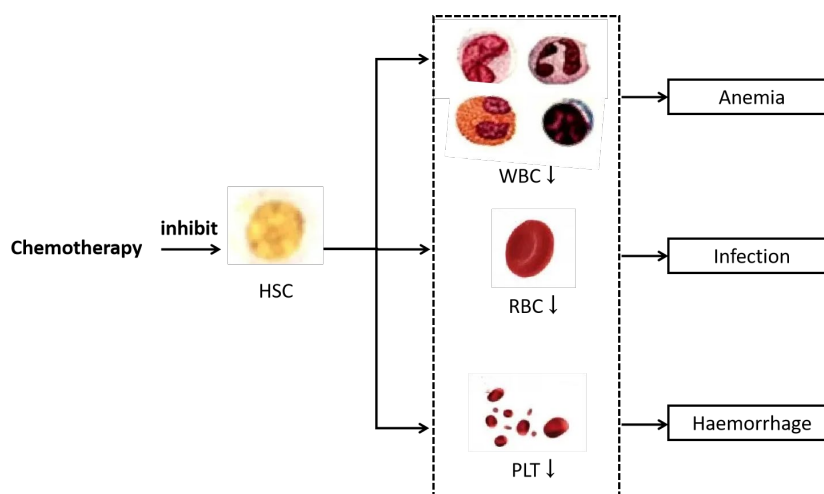


Figure 1: Inhibition of HSC by Chemotherapy

Traditional Chinese medicine believes that gynecological malignant tumors are caused by qi stagnation and blood stasis, and proposes a dialectical treatment method for gynecological tumors. This article reviews the research progress of traditional Chinese medicine internal and external treatment methods for bone marrow suppression after radiotherapy and chemotherapy for gynecological malignant tumors.

2. Traditional Chinese Medicine's Understanding of Gynecological Malignant Tumors

Regarding the understanding of tumors, traditional Chinese medicine has a precise and detailed summary of the biological meaning of tumors in the "Shengji Zonglu", which states that "tumors are the meaning that cannot be left behind. The word "cancer" first appeared in the "Wei Jibao Book" published in the Song Dynasty, which regarded cancer as one of the five causes of carbuncle and gangrene. Traditional Chinese medicine believes that gynecological malignant tumors belong to the categories of "stone mass", "metrorrhagia and leakage", "five color band", "accumulation", "micro mass" and other symptoms. The pathogenesis of gynecological tumors has been explored in the "Shen Nong Ben Cao Jing" and "Jin Kui Yao Lue ". Traditional Chinese medicine believes that the occurrence of gynecological tumors is the result of the combined action of internal and external factors in the body. The main pathogenesis of this disease should be attributed to the deficiency of qi, blood, yin, yang, and body fluids of the internal organs, while the deficiency of qi mainly refers to the accumulation of pathogenic factors such as phlegm dampness, heat toxicity, blood stasis, and qi stagnation. The principle of treatment should be to support the right and eliminate pathogenic factors, apply both attack and supplement, support the right without retaining pathogenic factors, and eliminate pathogenic factors without harming the right. The mechanism of the occurrence of gynecological malignant tumors is also described in the "Complete Book of Jingyue: Women's Regulations" Stagnation of blood stasis is a symptom that only women have. Its symptoms may arise during menstruation or postpartum, from internal injuries causing coldness, from external exposure to wind and cold, from anger causing liver damage, from qi inversion leading to blood retention, or from worry causing spleen damage, from qi deficiency leading to blood stagnation, or from accumulated fatigue and weakness, from weak qi leading to failure. It is always caused by blood movement, and the remaining blood is not purified. However, if there is a slight reversal, the stagnation gradually accumulates and becomes a symptom.

2.1. *Understanding of the etiology and pathogenesis of gynecological malignant tumors after radiotherapy and chemotherapy in traditional Chinese medicine*

In terms of the harm and mechanism of postoperative radiotherapy and chemotherapy to the body of gynecological malignant tumors, there is almost no difference. From the perspective of traditional Chinese medicine, radiotherapy is done through radiation with strong killing power of fire heat toxin [3,4]. After acting on the body, the fire heat toxin is abundant, burning the body's blood, consuming qi and damaging essence, burning the yin, leading to deficiency of both qi and blood, deficiency of liver and kidney, imbalance of spleen and stomach, and imbalance of yin and yang. Chemotherapy involves killing cancerous cells with drugs that possess the toxic effects of fire and heat. However, due to insufficient targeting, it can also kill normal cells and tissues, leading to a series of adverse reactions. And these drugs and treatment methods that harm the body are referred to in traditional Chinese medicine as the pathogenic factors of toxins, namely the "use poison to attack poison" method [5-7]. The treatment methods of radiotherapy and chemotherapy often involve the viscera, consume qi and blood, damage the normal qi, and cause kidney deficiency and marrow deficiency by damaging the innate essence of the kidney, and then damage the acquired spleen and stomach, resulting in a lack of blood and gas source. Due to the belief that 'positive qi exists within, evil cannot be interfered with', it can be inferred that tumor patients must have an internal factor of insufficient positive qi. Insufficient positive qi and the combination of toxin and evil manifest as various toxic side effects. The "Su Wen" says: "When evil gathers, its qi will be depleted. Malignant tumor patients are already physically deficient, and combined with radiation therapy and chemotherapy, the body is suddenly attacked by fire, heat, and toxins, making the healthy qi weak and unable to resist the toxins, resulting in the residual toxins in the body. After multiple rounds of chemotherapy, toxic toxins remain in the body and can develop into latent toxins over time. Whether caused by internal imbalance of qi, blood, yin, and yang in the body or external radiation and chemotherapy, the deficiency of qi is the fundamental cause of the occurrence and development of gynecological malignant tumors and the occurrence of toxic side effects after radiation and chemotherapy.

2.2. Traditional Chinese Medicine's Understanding of Differentiation and Treatment of Bone Marrow Inhibition after Radiochemotherapy in Gynecological Malignant Tumors

Although there is no mention of bone marrow suppression in traditional Chinese medicine, clinical symptoms such as dizziness, fatigue, and lack of breath can be classified as "blood fatigue" and "deficiency fatigue" [8,9]. The principle of its treatment mainly adopts the methods of "supplementing deficiency" and "warming fatigue" [10]. In recent years, many doctors have proposed their own ideas on the treatment of bone marrow suppression. Overall, during the radiotherapy and chemotherapy process of gynecological malignant tumors, due to insufficient targeting of cancer cells by radiation and chemotherapy drugs, while clearing cancer cells, it can also damage some normal cells and tissues in the body, leading to bone marrow suppression, with the most significant reduction in white blood cells. Chemotherapy drugs and radiation therapy belong to the category of fire heat toxin in traditional Chinese medicine. When they suddenly attack the human body, they will cause the body's fire heat toxin to accumulate, consume qi and damage essence, burn body fluids, and cause dysfunction of the internal organs, resulting in deficiency of both qi and yin. Therefore, it is recommended to strengthen the spleen and replenish qi for treatment.

The main damage caused by radiotherapy and chemotherapy is the bone marrow. Liver is congenital foundation for woman. Both physiological characteristics that the blood of female is not enough commonly and the pathological changes that qi is superfluous generally have close connection with the liver. The spleen is the foundation of acquired life and the source of qi and blood biochemistry. And the kidney is responsible for bone and marrow production, as well as for storing essence. Essence and blood are homologous [11]. If kidney deficiency occurs, the marrow cannot be produced, the essence cannot be stored, and blood cannot be transformed. Therefore, nourishing the liver, spleen, and kidney should be one of the principles of treatment [12]. In addition, traditional Chinese medicine believes that the basis for the occurrence of malignant tumors is the deficiency of the body's vital energy, which cannot promote the normal operation of the body's blood or the inability of qi deficiency to control the whole body's blood, leading to delayed blood circulation or blood overflow beyond the meridians, leading to the formation of blood stasis in the body. The reason why the body suffers from malignant tumors is because the cancer toxin is embedded in the body, blocking the normal operation of the meridians and blood in the organs, leading to the occurrence of qi stagnation and blood stasis. Therefore, it is also more likely to lead to the coexistence of cancer toxin and qi stagnation and blood stasis in the body. It is difficult to achieve good therapeutic effects solely by using tonics, and it is necessary to take a stronger treatment method [13]. The various drugs and toxins in chemotherapy, as external pathogens in the cognitive category of traditional Chinese medicine, can exacerbate the chronic pathological process of internal stasis and toxin accumulation, becoming a major factor in aggravating the spleen and kidney deficiency of the body. At the same time, spleen and kidney deficiency can also lead to the formation of blood stasis, so detoxification and blood stasis should be treated [14]. In summary, traditional Chinese medicine believes that the basic treatment principles for bone marrow suppression caused by radiotherapy and chemotherapy should be based on strengthening the spleen and supplementing qi, nourishing the liver, spleen, and kidney, and detoxifying and removing blood stasis.

3. Clinical Study on the Effect of Traditional Chinese Medicine Internal and External Treatments on Bone Marrow Inhibition after Radiochemotherapy in Gynecological Malignant Tumors

3.1. Clinical status of traditional Chinese medicine internal treatment for bone marrow suppression after radiotherapy and chemotherapy

Many traditional Chinese medicine researchers have proposed different treatment methods for bone marrow suppression caused by postoperative radiotherapy and chemotherapy in gynecological malignant tumors. However, overall, the principle is still to strengthen the spleen and kidney, replenish qi and generate blood. Zhu Jiangfeng et al. used traditional Chinese medicine Fuzheng ointment to tonify the liver and kidney, spleen and stomach, and found that it can significantly increase the number of white blood cells in patients with gynecological tumors after radiotherapy and chemotherapy ($P < 0.05$) [15]. Kong Shoufang et al used Yiyuan Tang with an added or reduced dosage, one dose per day, decocted in water, to tonify the spleen and kidney, promote blood circulation, and nourish blood. Combined with the injection of human granulocyte colony stimulating factor for treatment, case control studies showed that compared to the control group, the inhibitory effect of chemotherapy drugs on bone marrow production in the case group patients was significantly reduced, and the duration of severe

white blood cell reduction was shortened, which can effectively improve the cure rate and reduce the recurrence rate [16]. Liu Qingyuan based on the experience of his teacher He Ruoping, focused on "treating diseases to seek the root cause", closely guarding the spleen and kidneys, and using the Four Gentlemen's Decoction and Huangqi as the main formula. According to the location of deficiency and damage, timely adjustments should be made. He emphasized that strengthening the spleen and tonifying the kidneys should focus on the spleen and stomach, as both diet and medication are absorbed through the spleen and stomach. If used specifically for tonifying during treatment, it is easy to breed phlegm and dampness. Therefore, when treating symptoms, the spleen and stomach should be primarily cared for, so that the function of spleen and stomach circulation is normal, water and grain are dissipated, and there is no stagnation in emptying. The qi and blood are full, the essence is raised, and the muscles and muscles are nourished. The case study found that this prescription can effectively improve the patient's blood routine indicators and the tumor does not recur [17]. Zhao Minmin based on the experience of his teacher Lu Su, used the method of calming and tonifying yin and yang, while also regulating the heart, kidney, and spleen. He developed his own formula for nourishing the body and promoting white blood (Sanguisorba officinalis, Shiwei, Xianmao, Morinda officinalis, Ligustrum lucidum, Eclipta, Codonopsis pilosula, and Atractylodes macrocephala) through dialectical addition and subtraction. For premenopausal women, he added Astragalus membranaceus, Angelica sinensis, and Radix Pseudostellariae to tonify qi and blood. The addition of nourishing yin and nourishing blood to the glans penis, caulis spatholobi, and roasted semen polygonatum was used to treat premenopausal women, and good therapeutic effects were observed in individual cases [18]. Fan Zhixia applied the basic theory of traditional Chinese medicine to differentiate and treat leukopenia after radiotherapy and chemotherapy in gynecological malignant tumors. In the control group, on the basis of intramuscular injection of colony-stimulating factor, traditional Chinese medicine Fuzheng Buqi and Fuzheng Buyin were added. Qi deficiency syndrome was treated with modified Buzhong Yiqi decoction, while Yin deficiency syndrome was treated with modified Liangdi Tang combined with Erzhi Wan, with an effective rate of 95% [19]. Li Shuang used the traditional TP chemotherapy regimen while also adding Shengxue Yisui Tang, which was decocted to 200ml in water and taken separately in the morning and evening. A case control study found that this formula reduced the incidence of bone marrow suppression after TP chemotherapy to a certain extent, and could effectively reduce chemotherapy toxicity and improve the quality of life of tumor patients after chemotherapy [20]. Yan Xuezhao used both traditional TC chemotherapy regimen and modified Yiqi Xiaoji Formula as an adjuvant therapy to achieve the effects of supplementing qi, strengthening spleen, and strengthening the body against cancer. The results of 94 intervention studies showed that it has a good preventive and therapeutic effect on bone marrow suppression after radiotherapy, and can reduce the use of recombinant human granulocyte stimulating factors [21]. Zheng Jianbo and others used self-prepared Xianhuang Decoction (Agrimony, Astragalus, Codonopsis, prepared root, Atractylodes macrocephala, ass hide glue, angelica, ligustrum lucidum, liquorice, dodder seed, deer antler tablet) for patients with leukopenia due to deficiency of spleen and kidney qi (yang) after radiotherapy and chemotherapy. They took it separately in the morning and in the evening, combined with moxibustion at Zusanli, Shenshu, Pishu, Xuehai and other points for 30min/time. The result was better than that of the control group who only took orally Diyushengbai tablet and Sharganol tablet [22]. Yang Luyin et al targeted patients with stage III-IV cervical cancer who were diagnosed with spleen and kidney deficiency combined with heat toxicity syndrome based on the basic theory of traditional Chinese medicine. On the basis of combined synchronous radiotherapy and chemotherapy, they were treated with tonifying the spleen and kidney, clearing heat and detoxifying, and dissipating symptoms and dispersing nodules. They also used Zhenqi Liuju Cancer Inhibition Decoction. They started taking water one day before radiotherapy, three times a day, and took it continuously for 6 weeks. The results showed that the incidence of bone marrow suppression was significantly reduced compared to the control group [23]. Kang Nan et al used the method of tonifying the kidney and strengthening the spleen to treat postoperative leukopenia in cervical cancer. Based on the basic formula of Bazhen Tang, Huangqi, and Ligustrum lucidum, dialectical addition and subtraction of medication according to clinical symptoms can effectively improve the patient's bone marrow suppression [24]. Li Rongrong based on the experience of his mentor Pei Zhengxue, randomly divided 60 patients with stage IIB, III, and IIIA cervical cancer of Qi deficiency and blood stasis type into two groups. The treatment group was treated with Pei's cervical cancer formula in addition to routine synchronous radiotherapy and chemotherapy, and started taking one dose daily three days before radiotherapy and chemotherapy for one month. It was found that the incidence of bone marrow suppression decreased from 76.67% to 36.67% [25]. Du Kunyi [26] treated patients with bone marrow suppression after radiotherapy and chemotherapy for malignant tumors with self-made Yangxue Fuzheng Pill. It can strengthen the spleen, promote blood circulation, and tonify the kidney on the basis of routine supportive therapy and symptomatic treatment. Each dose was

10g, 3 times per day. Peripheral blood neutrophils, hemoglobin, and platelets were detected to be higher than before treatment.

3.2. Clinical Status of Traditional Chinese Medicine External Treatment for Bone Marrow Inhibition after Radiochemotherapy

The meridian and acupoint theory of traditional Chinese medicine also points out new ideas for the treatment of bone marrow regeneration inhibition after radiotherapy and chemotherapy for gynecological malignant tumors. According to the theory of traditional Chinese medicine, meridian and acupoints are distributed throughout the entire body. Choosing appropriate parts of the body's meridian and acupoints and performing various stimuli can effectively promote the production and normal operation of body qi, blood, body fluids, etc., thereby promoting the body to achieve the ideal state of "Yin Ping Yang Mi" [27]. Gong Yanqing used acupoint ginger separated moxibustion to warm yang, dispel cold, and strengthen spleen and replenish qi for patients with degree I and II bone marrow suppression. Ginger was cut into thin slices, fine needles were punctured for several holes, and Ai Zhu was placed at the corresponding acupoints (Shenque, Qihai, Guanyuan). After repeated treatment for one course, the intervention research results of 100 cases showed that ginger separated moxibustion can effectively improve the symptoms of qi and yin deficiency in patients and increase white blood cell count [28]. Wang Xiacong et al. divided 60 patients with solid tumors who were scheduled for systemic chemotherapy into groups, and began administering Ganshu, Pishu, and Shenshu traditional Chinese medicine hard ointments (Huangqi, Codonopsis pilosula, yam, Radix Rehmanniae, Radix Rehmanniae, Fructus Psoraleae, Fructus Lycii, Cinnamomum cassia, Eucommia ulmoides, etc.) to the treatment group one week before chemotherapy. They found that preoperative traditional Chinese medicine treatment can effectively reduce the incidence of bone marrow suppression after chemotherapy [29]. Yang Ronghua conducted an experimental study on 114 ovarian cancer patients. The experimental group inhaled 20ml of Huangqi injection with a syringe one day before chemotherapy, inserted it into the Zusanli point to a certain depth, and then lifted and inserted it for tonifying and reducing. After gaining qi, the Huangqi injection was slowly pushed in once a day, lasting until one day after the end of chemotherapy as a course of treatment. The results showed that acupoint injection of Huangqi injection has an effective protective effect on bone marrow suppression after chemotherapy [30]. Li Bo et al treated patients with thrombocytopenia after chemotherapy with acupoints such as Ganshu and Pishu puncturing and retaining cupping for 8-10min, with 5-8ml of bleeding per cupping, once every 3 days. The results showed that their platelet rebound rate was faster, and most patients achieved a significant rebound after the first puncture and cupping treatment [31].

4. Conclusion and Outlook

Chemotherapy and radiation therapy are currently common and irreplaceable treatment methods for malignant tumors. However, due to their severe adverse reactions, they often affect the treatment process of patients, and even lead to hospital infections and anemia, promoting the emergence of cachexia. In recent years, research on the application of traditional Chinese medicine alone or in combination with Western medicine has observed the role of traditional Chinese medicine internal and external treatment in preventing postoperative bone marrow suppression and improving clinical symptoms of patients. At the same time, it has its unique efficacy in improving patients' quality of life and other aspects, with minimal toxic and side effects. The traditional Chinese medicine treatment method has a long history and is simple and convenient. From the perspective of diagnosis and treatment, it adheres to the principle of "seeking the root of the disease". It advocates the preventive concept of "preventing disease before it occurs, and preventing disease from changing". Therefore, the internal and external treatment methods of traditional Chinese medicine are particularly effective in preventing bone marrow suppression after radiotherapy and chemotherapy. At present, there is still a lack of unified treatment standards for gynecological malignant tumors treated with traditional Chinese medicine, and most studies have a small sample size. It is expected that in the future, in addition to radiotherapy and chemotherapy for gynecological malignant tumors, appropriate dialectical treatment can be combined with the theoretical internal and external treatment methods of traditional Chinese medicine to provide patients with preventive treatment of traditional Chinese medicine throughout the entire course of the disease. In addition, by conducting specific mechanisms of traditional Chinese medicine prevention and treatment and conducting large-scale intervention studies, we aim to provide more scientific basis for traditional Chinese medicine prevention and treatment of gynecological malignant tumors while preventing bone marrow suppression and alleviating patient symptoms after

radiotherapy and chemotherapy.

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