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Cognitive Impairment from Breast Cancer Chemotherapy in the Perspective of Traditional Chinese Medicine

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ABSTRACT

In recent years, the incidence of breast cancer has been on the rise globally and in China. The conventional treatment methods for breast cancer include surgery, radiotherapy, chemotherapy, endocrine therapy, targeted therapy, traditional Chinese medicine, and other biological immunotherapy. In the treatment of breast cancer, the status of chemotherapy drugs is unshakable, and the related toxic side effects have gradually attracted people's attention. Doxorubicin is an anthracycline drug, which is the cornerstone drug for adjuvant chemotherapy for breast cancer. It exerts anti-tumor effects by inserting DNA and inhibiting topoisomerase II, but it can also cause severe neurotoxicity by crossing the blood-brain barrier, clinically manifested as memory and executive function decline, etc., which has a huge impact on the patient's work and life. With the development of modern medicine, the advantages of traditional Chinese medicine in preventing and treating adverse reactions related to breast cancer and improving patients' quality of life are increasingly being recognized. Traditional Chinese medicine classifies chemotherapy-induced cognitive impairment into related diseases such as "dementia", "brain marrow depletion", and "forgetfulness" based on its main clinical symptoms, and achieves the therapeutic effect of improving chemotherapy-induced cognitive impairment through clinical differentiation and coordinating relevant therapies, providing a scientific basis for the treatment of adverse reactions related to malignant tumors by traditional Chinese medicine in radiotherapy and chemotherapy.

KEYWORDS

Breast Cancer; Traditional Chinese Medicine; Chemotherapy; Cognitive impairment

1. THE TREND OF BREAST CANCER INCIDENCE IS NOT OPTIMISTIC

In recent years, the incidence of breast cancer globally and in China has been on the rise, with the incidence of breast cancer surpassing that of lung cancer for the first time in 2020, becoming the world's No. 1 cancer. Data from the Global Cancer Observatory, a branch of the World Health Organization, show that in 2020 alone, there were 2.26 million new cases of breast cancer globally, with 685,000 deaths. Both the incidence and mortality rates of breast cancer in women rank first globally. In terms of China, the incidence of breast cancer grows at a higher rate than the global average. According to statistics from the World Health Organization, in 2020, 2.09 million new cancer cases were reported in Chinese women, of which nearly 420,000 were breast cancer patients, accounting for 20%. According to statistics from the International Agency for Research on Cancer (IARC), in 2020, 2.09 million new cases of breast cancer were reported in Chinese women, of which nearly 420,000 were breast cancer patients, accounting for 20%. According to IARC statistics, in 2020, over 416,000 new cases of breast cancer were reported in China, with an incidence rate of 39.1/100,000, and over 117,000 deaths.

2. DEFINITION AND CLINICAL MANIFESTATIONS OF COGNITIVE IMPAIRMENT AFTER BREAST CANCER CHEMOTHERAPY

With the continuous improvement of clinical diagnosis and treatment, the survival rate of breast cancer patients has improved significantly, and the survival time has been significantly extended. The conventional treatment methods for breast cancer include surgical treatment, radiotherapy and chemotherapy, endocrine therapy, targeted therapy, traditional Chinese medicine and other biological immunotherapy. In the treatment of breast cancer, the status of chemotherapy drugs cannot be shaken. At the same time, the attention paid to chemotherapy-related adverse reactions has gradually increased. For example, doxorubicin is a type of anthracycline drug, which is the cornerstone drug for breast cancer adjuvant chemotherapy. It works by inserting DNA and inhibiting topoisomerase II to exert antitumor effects, but it can also cause severe neurotoxicity by crossing the blood-brain barrier, leading to clinical symptoms such as memory and executive function impairment, which have a huge impact on the patient's work and life. In 1983, Silberfarb et al. first proposed the concept of Chemotherapy Related Cognitive Impairment (CRCI), which is a common side effect of chemotherapy, and some scholars also named it Chemotherapy Induced Cognitive Impairment (CICI), also known as "Chemobrain" or "Chemofog". It is a clinical syndrome characterized by memory, learning, and motor function impairment [1]. Clinical findings suggest that approximately 80% of breast cancer patients experience varying degrees of cognitive impairment after surgery, radiation therapy, chemotherapy, and endocrine therapy [2].

3. CURRENT TREATMENT METHODS AND EXISTING PROBLEMS FOR COGNITIVE IMPAIRMENT AFTER CHEMOTHERAPY FOR BREAST CANCER IN CHINA AND ABROAD

Despite being one of the most common symptoms in cancer patients, CRCI has not received sufficient attention in the past as it was mostly attributed to cancer or unavoidable side effects of treatment. Currently, clinical interventions for CRCI mainly involve drug therapy and cognitive behavioral therapy. Common Western drugs include modafinil, methylphenidate, donepezil, astaxanthin, resveratrol, catechin, and ginkgo biloba. In addition to drug therapy, non-pharmacological treatments such as psychotherapy, yoga therapy, and rehabilitation therapy are also used abroad, which can also alleviate symptoms to some extent. In China, cancer-related adverse reactions such as CRCI are mostly treated with traditional Chinese medicine and other methods, which can achieve good therapeutic effects. However, even if these symptoms are corrected, it is only simple symptomatic treatment, and there is still a lack of effective treatments for the underlying causes of CRCI.

4. THE ASSOCIATED MECHANISMS OF COGNITIVE DYSFUNCTION CAUSED BY CHEMOTHERAPY DRUGS

Chemotherapy drugs not only cause functional disorders, but also directly damage the nervous system. Studies have shown that a variety of chemotherapy drugs used in breast cancer treatment, including paclitaxel, cisplatin, doxorubicin, and 5-fluorouracil, can have an impact on the central nervous system to some extent [3, 4]. Meanwhile, the central nervous system DNA damage and defects in DNA repair mechanisms caused by chemotherapy may be one of the important mechanisms behind chemotherapy-induced brain injury.Ahles et al. [5] found that chemotherapy drugs reduce the synthesis of neurotransmitters and oxidative stress, which impairs DNA damage repair and accelerates telomere shortening.Krynetskiy et al. [6] conducted animal experiments to find that DNA in mouse brain cells underwent single and double strand breaks after chemotherapy, which was related to the decline in cognitive function. DNA damage can cause a decrease in antioxidant capacity, thus increasing DNA oxidative stress levels and accelerating cell aging and degeneration, leading to

changes in memory and other cognitive functions [7]. In cognitive disorders such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis, there is an increase in the levels of cytokines in cerebrospinal fluid, peripheral blood, and inflammatory chemokines [8]. Some chemotherapy drugs can increase levels of cytokines such as interleukin and tumor necrosis factor. Related studies have found that cytokines are related to the occurrence of cognitive impairment after chemotherapy, and that the large amount of TNFα after chemotherapy promotes the progression of CRCI in patients [9, 10].

5. TRADITIONAL CHINESE MEDICINE'S UNDERSTANDING OF BREAST CANCER

Breast cancer is one of the most common malignant tumors in women, with names such as "breast stone abscess," "stone milk," and "breast nut," and belongs to the scope of traditional Chinese medicine's "breast rock." Traditional Chinese medicine believes that the occurrence of breast cancer is closely related to the weakening of the body's vital energy and the invasion of pathogenic toxins. A weakened vital energy and dysfunction of the internal organs' yin and yang are the main foundations for contracting this disease.There have been many records by medical practitioners on the causes and pathogenesis of breast cancer. For example, in the "Acupuncture Theory" of the Inner Canon of Huangdi, "If one has a strong constitution, external pathogens cannot harm one." In the "Discussion on Hot Diseases" of the Inner Canon of Huangdi, "Where pathogens gather, the body's vital energy must be weak." This indicates that the basic cause and determining factor of the disease is the weakness of the body's vital energy, including qi, blood, yin and yang, and the decline of the functions of the internal organs, which leads to the invasion of pathogens in the breast meridians. The weakness of the body's vital energy mainly refers to the insufficiency of yang qi, There have been many records by medical practitioners on the causes and pathogenesis of breast cancer. For example, in the "Acupuncture Theory" of the Inner Canon of Huangdi, "If one has a strong constitution, external pathogens cannot harm one." In the "Discussion on Hot Diseases" of the Inner Canon of Huangdi, "Where pathogens gather, the body's vital energy must be weak." This indicates that the basic cause and determining factor of the disease is the weakness of the body's vital energy, including qi, blood, yin and yang, and the decline of the functions of the internal organs, which leads to the invasion of pathogens in the breast meridians. The weakness of the body's vital energy mainly refers to the insufficiency of yang qi, and the insufficiency of shen yang, which cannot vaporize and transform the essence of food and drink. If the spleen is not strong enough to transport the body fluids for the stomach, the body fluids will accumulate to form phlegm. which cannot vaporize and transform the essence of food and drink. If the spleen is not strong enough to transport the body fluids for the stomach, the body fluids will accumulate to form phlegm.Additionally, kidney yang deficiency and water retention can also cause phlegm to form, and phlegm is primarily produced by spleen and kidney yang deficiency. Yang deficiency leads to a low level of warmth and vitality, causing blood vessel blockage and poor blood flow, resulting in "stasis," and phlegm and stasis adhere to the breast, leading to the formation of breast cancer. As the breast cancer progresses, the yang energy becomes increasingly deficient, while the pathogenic heat becomes more severe, causing the yang energy deficiency of all the internal organs.

Breast cancer is closely related to emotions. If one's emotions are suppressed, the liver will lose its smooth flow, leading to stagnation of qi and blood. When qi stagnates, blood stasis occurs. When the liver is agitated, it will invade the spleen, causing the spleen's function to be disrupted, leading to the formation of phlegm. Phlegm is the carrier of toxins, and it can invade and spread to other organs, causing dysfunction in the five internal organs, leading to the formation of lumps in the breast's lymphatic vessels due to phlegm, blood stasis, and toxins. According to the theory of traditional Chinese medicine's meridians, the nipple and breasts are respectively associated with the liver, gallbladder, and stomach meridians, and the nipple is the confluence of the liver and kidney meridians. The breasts are the gathering place of yang ming qi and blood. The meridians in the breast area rely

on the liver's dispersal and the yang ming's regulation.The liver is in charge of blood and qi, regulating emotions and coordinating menstrual and breast gland functions. The breast gland is closely related to the liver, spleen, and kidneys. Dysfunctions of these three organs are not only an important pathogenic mechanism for breast cancer, but also one of the key factors that promote its progression.

6. COGNITIVE IMPAIRMENT FROM CHEMOTHERAPY IN THE PERSPECTIVE OF TRADITIONAL CHINESE MEDICINE

With the development of modern medicine, the advantages of traditional Chinese medicine in preventing and treating adverse reactions related to cancer and improving patients' quality of life are increasingly being recognized. In traditional Chinese medicine, CRCI is classified under the scope of related diseases such as "dementia", "depletion of brain marrow", and "forgetting things", and treatment should be based on replenishment. Cognitive impairment also belongs to the category of mental disorders in traditional Chinese medicine, which is different from traditional Chinese medicine's "epilepsy" and "mania", but it cannot be separated from the discussion of mental disorders in traditional Chinese medicine.The core concept in traditional Chinese medicine's theory of consciousness is "shen," and the term "shen" in traditional Chinese medicine has both a "broad" and a "narrow" meaning. The broad meaning of "shen" refers to the master and overall external manifestation of human life activities, including aspects such as appearance, eyes, speech, expressions, responses, movements, spirit, emotions, breathing, pulse, etc. The narrow meaning of "shen" refers to consciousness, thinking, and emotions, etc. Both are closely related to the functions of the five internal organs, and people have the five internal organs that generate five kinds of qi to produce the seven emotions. The seven emotions are the external manifestations of consciousness, and consciousness is the inner basis of the seven emotions.In the "Ling Lan Ming Di Lun" section of the "Su Wen" (Classic of Medicine), it is stated that "the heart is the organ of the emperor, where the spirit resides," meaning that the heart is the source of spiritual energy and plays a leading role in the human body. The term "spiritual energy" in the Inner Canon of Huangdi can be summarized as the essence of yin and yang, or the ruler of life activities and their external manifestations, etc [11]. In ancient philosophy, the concept of "shen" was understood to refer to a person's "spirit," which was associated with the mind, soul, and wisdom [12]. The abnormality of "shen" caused by chemotherapy drugs represents an imbalance of yin and yang on one hand, and the abnormality of the life activity master "spirit" and its external manifestation on the other hand.

Therefore, in clinical treatment, we cannot simply limit CRCI of breast cancer to a single syndrome and prescription. We should start from the complex symptoms, unravel the causes, identify the main syndrome, and differentiate syndromes to treat diseases. Only by doing so can we achieve good therapeutic effects. Traditional Chinese medicine emphasizes the concept of adjusting the body as a whole. Starting from the whole, we can differentiate syndromes according to the different clinical symptoms of each patient and treat diseases by prescribing medication. In improving CRCI, we can also alleviate the somatic symptoms of patients.At present, traditional Chinese medicine has achieved significant success in interventions for cognitive impairment and abnormal emotions. Modern laboratory research has found that many single herbs and compound Chinese medicines have been effective in improving cognitive function, including Polygala tenuifolia [13], Acorus calamus [14], Ginkgo biloba [15], and Panax ginseng [16] as single herbs, and Kaixin Powder Classical Prescriptions [17], Guipi Decoction [18], and Clearing Heart as compound prescriptions. There have also been clinical studies showing that traditional Chinese medicine can improve cognitive impairment caused by chemotherapy in breast cancer patients [19].

7. SUMMARY

In summary, cognitive dysfunction caused by chemotherapy for breast cancer is mainly caused by the mechanisms of inducing neurological system inflammation, oxidative stress, neuronal cell damage, and inhibiting neurogenesis induced by chemotherapy drugs. At present, the evaluation, diagnosis, and related treatment of CRCI are still under exploration, and no unified and standardized treatment protocols have been established.The value and status of chemotherapy in the treatment of breast cancer far exceed its adverse effects, and traditional Chinese medicine plays an important role in the treatment of malignant tumors. It also plays an indispensable role in enhancing the efficacy and reducing the toxicity of chemotherapy in breast cancer patients. Traditional Chinese medicine, with its unique advantages of differential diagnosis and holistic view, can combine the symptoms and physical signs of patients in different stages of breast cancer treatment, look beyond the surface to grasp the essence of the disease, analyze the disease from complex symptoms, and combine disease and syndrome to regulate the functions of internal organs, thus achieving good therapeutic effects. At the same time, it provides scientific evidence for improving cognitive impairment after chemotherapy in breast cancer patients, which has important practical significance for improving the quality of life of cancer patients.

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