

Research Progress of Traditional Chinese Medicine Therapy of Malignant Tumors Cancerous Cachexia

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Abstract: *Cancer cachexia (CC) is a syndrome of metabolic disorders caused by multiple pathogenic factors, which is characterized by chronic consumption and is a common complication leading to death in patients with advanced tumors. In clinical practice, there are many conventional therapy for CC patients with malignant tumors, will have a large adverse reaction on the patients, and long-term use of these drugs are prone to drug resistance, which affect the therapeutic effect. In Traditional Chinese Medicine theory, many clinical symptoms of CC patients can be summarized by the name of "Xu Lao" in Chinese medicine. Through the use of Traditional Chinese Medicine and modern medical theories to discuss the pathogenesis of cancer cachexia, introducing the treatment principles of Xu Lao of medical practitioners, emphasizing the importance of invigorating qi and blood, and taking care of the spleen and kidneys, and summarizing the therapeutic effects of Chinese medicine on patients with different types of CC, so as to provide more therapeutic ideas for the clinical practice of Chinese medicine in treating patients with malignant tumors and carcinoma cachexia in the future.*

Keywords: Malignant tumors, Cancer cachexia, Xu Lao, TCM therapy.

1. Introduction

Cancer cachexia (CC) is a metabolic disorder syndrome characterized by chronic wasting and depletion caused by multiple factors such as reduced nutritional intake, neuroendocrine dysfunction, and abnormal metabolic function [1]. And its clinical symptoms mainly include muscular depletion, gradual decline in physical strength, abnormal nutritional metabolism, destruction of immune function, anorexia, mental depression and so on. As the most commonly lethal factor in patients of advanced tumors, CC can lead to decreased tolerance of drugs, increasingly psychological problems, diminished quality of life, shorter living period, poorer prognosis, and increased healthcare costs [2]. Clinical treatments for CC mostly use drugs such as anti-tumor, appetite stimulation, increased nutrition, and inhibition of protein degradation, but the efficacy is unsatisfactory due to the possible problems, such as the toxicity and side, the induction of multiple complications, the susceptibility to drug resistance and the poor patient clinical adherence to the treatment. Therefore, in recent years, extensive attention has been paid to the treatment of CC with TCM with a view to obtaining higher clinical therapeutic efficacy.

In Traditional Chinese Medicine, there is no such disease name as cancer cachexia, but the common clinical manifestations of CC patients are consistent with diseases of TCM, such as "Xu Lao", "Shi Rong", and "impotence", etc. As early as in "Su Wen - Yu Ji Zhen Zang Lun", it is written that "the major bones are withered, the major muscles are sunken, and the movements are weakened, the shoulder marrow is eliminated, the movement is weakened.....", which described the onset of symptoms similar to those of CC patients in modern medicine, such as the progressive muscle depletion, severe malnutrition, and the decline of various

internal organs functions [3]; The "Wai Ke Xin Fa Yao Jue" recorded that "Shi Rong beside the ear, the neck and shoulder, starting like phlegm and nucleus not moving firmly..... for a long time, the shape of the Qi decline and thinness, the more ulcerated and hardened and the purple spot, the rotting and dipping and bleeding.....", which was consistent with the symptoms of CC of head and neck in the modern medicine, such as thinness and reduced function of various organs. In the comprehensive statistical study on the clinical manifestations, quality of life, survival period and treatment method, we can find that the symptoms of CC are consistent with the characteristics of Chinese medicine disease "Xu Lao". For Synopsis of Golden Chamber, Zhang Zhongjing for the first time treated "Xu Lao" as a separate disease, pointing out that this disease can be caused by the accumulation of gradual formation, and describing the theory of emaciation due to blood disorders to cause the Xu Lao and the treatment of eliminating blood stasis to generate new, which had a profound impact on the research and treatment of "Xu Lao" by scholars of later generations [4]. The treatments of Xu Lao in TCM are based on the basic principle of supporting the healthy energy and stressing the importance of protecting the four aspects of qi, blood, spleen and kidney. Specifically, the methods of benefiting Qi and nourishing blood, nourishing the spleen and stomach, warming the kidneys and strengthening the spleen, as well as nourishing the kidneys and filling up the vital essence are used. These treatments are also combined with modern medical therapies in order to slowing down the progression of the disease, improving the quality of life and lengthening survival period.

Based on above discussion, this paper will review the research progress on the etiology and pathogenesis of cancer cachexia, and the formation of malignant tumors by combining theories of TCM and clinical studies with the results of various modern basic.

2. The Etiology and Pathogenesis of Cancer Cachexia

2.1 The Etiology and Pathogenesis of Cancer Cachexia in Traditional Chinese Medicine

2.1.1 Etiology

As early as the "Huangdi Neijing", there is, "the causes of deficiency is wine, sex, fatigue, the seven emotions caused by food and drink.....", and "modern people which use wine as a syrup, take delusion as a norm, get drunk to sleep, which leading to exhaust their essence and dissipate their root". They propose that factors such as uncontrolled wine and sex, emotional stimulation, unclean diet, and exhaustion can lead to body depletion; and emphasize the key role of taking care of the Jing Qi in the process of preventing and treating the disease of fatigue. Ge Hong has recorded that "all the symptoms of the solid start, more gradual growth..... the problem of accumulation in the abdomen will harm the diet and make people turn thin" [5]. He pointed out that the abdominal accumulation was easy to consume the human body Qi, blood, Yin and Yang, but also because of the anti-tumor treatments for the body visceral vital energy, the constant depletion of anti-tumor treatment for internal organs and vital essence, the patient's internal organs's physiological function weakness, decreased appetite resulting in a reduction in the amount of food, the body's ability to carry out the absorption of essence and micro-substances was insufficient and the body could not get enough nutrients, resulting in the gradual weakening of the body. "He recorded: "the formation of Xu Lao, was caused by internal injuries to the internal organs due to pressure and anger which could be caused by disease", pointing out that the etiology of Xu Lao was related to the seven emotions of internal injuries [6]. According to "Jing Yue's Complete Work", "the mistreatment and failure to regulate the person, after the disease more into the deficiency", emphasizing the disease or sickness mismanagement, the body of Zheng Qi insufficiency, Yin and blood depletion, compounding the sense of external evil and the evil over the positive decline could cause Xu Lao. Xue Shengbai described "the deficiency of the lady, there were innate deficiencies and acquired deficiencies, and innate due to the endowment". He suggested that the endowment weakness due to the lack of innate endowment of the parents, the lack of maintenance in the fetus and other factors were also the causes of Xu Lao. It can be seen that the innate deficiency of kidney Qi, acquired dietary indiscretion, the seven feelings, long illnesses and untreated treatment could lead to the occurrence of deficiency diseases.

2.1.2 Pathogenesis

According to TCM, the basic pathogenesis of Xu Lao are the deficiency of Qi, blood, Yin and Yang of the internal organs. Loss of Qi and blood in the internal organs, the dysfunction of the spleen and stomach, the symptoms of muscle impotence and general weakness as well as mental exhaustion will eventually appear if they are not restored. Although the main locations of Xu Lao are in the spleen, stomach and kidney [7].

But because of the interaction between the body's internal organs, a visceral lesion may cause other visceral dysfunction. So the course of the disease still involves the liver, heart, lungs and other organs. Ancient medical practitioners have different opinions on the pathogenesis of fatigue disease, but after summarization, it is no more than the four aspects of deficiency: Qi, Blood, Yin and Yang. Shen Jinao wrote that [8] "Yang qi, essence and blood were not separated from Qi and Blood. And when the water and fire got Zheng qi, they became essence and Qi. This was the generalization of the deficiency", which emphasized that patients with advanced cancerous malignant disease were mostly weak in both Qi and Blood. When evil Qi infests the lung and spleen, the efficacy the organs in spreading and transferring fluid is impaired, so that the fluid gathers into phlegm and dampness. The phlegm and dampness in turn trap the spleen, which further affect the transportation and absorption of the body's water and grain essence. Clinical treatments are specialized for different patients due to different factors such as tumor type, location, staging and individual physique.

If the identification from the internal organs, the deficiency of the internal organs is the main cause of the disease of fatigue. "Theory of Spleen and Stomach" said "Internal injury to the spleen and stomach, all birthed diseases". There were also the Neijing said "the spleen was the source of qi and blood"; "Spleen mastered the body's muscles"; "all the limbs were endowed with Qi in the stomach..... must be due to the spleen. "These were emphasized that the spleen was the master of the four end and the muscles of the body [9]. If the spleen and stomach are healthy, the internal organs are full of Qi and Blood. Zhang Xichun advanced patients with progressive muscle wasting, loss of appetite, energy consumption and other symptoms attributed to spleen deficiency, advocating the treatment of deficiency from the spleen and emphasizing the main focus on taking care of the spleen and stomach in the treatment.

Neijing put forward: "the kidney was the foundation of the innate and mastered bone marrow", emphasizing that the kidney was the master of the five viscera and six bowels. Its function is closely related to the life activities of human beings. The spleen is the foundation of the nature, and spleen and kidney complement each other to influence the development of diseases. "Essential Readings for Medical Professionals" [10] emphasized that the formation of weakness symptoms was relevant to the spleen and kidneys. TCM thinks that the kidney is the main body of the essence. Kidney essence is the material basis of human life activities. Zhang Jingyue believed that the kidney Yang was "the fire of life", which was the basis of the body's Yang. The deficiency of kidney Yang can also make the spleen and stomach not to transport the essence. The body viscera are not nourished, and the physiological function of each viscus is difficult to maintain, which results in the appearance of tiredness, weakness, loss of appetite, thin limbs, lumbar and knee pain, dizziness, energy metabolism abnormalities and other typical malignant clinical manifestations. Wang Haogu also summarized this kind of malignant manifestation as the evidence of "Yang from the internal elimination of Yang" [11], which could be interpreted by modern medicine as the excessive decomposition of muscle proteins and synthesis disorders, metabolic function disorders, reduction of immune

function, immunity function reduction and other clinical manifestations.

2.2 Pathogenesis of Cancer Cachexia in Modern Medicine

2.2.1 Anorexia

There are two mechanisms of anorexia: primary and secondary. The primary mechanism is that the tumor and the active substances released by the cancerous body tissues, such as tumor necrosis factor- α and interaction with the nerve center, resulting in the disruption of the signaling pathway in charge of food intake and the emergence of anorexia symptoms [12]. In addition, the local compression of digestive tract tumors can lead to decrease in gastrointestinal dynamics, digestive and absorption function disorders and reduce food intake. The secondary mechanisms mainly include the structural and functional changes of the digestive system caused by surgery and chemotherapeutic drugs cause patients to have taste disorders [13], and emotions such as repression and anxiety may lead to decreased appetite.

2.2.2 Abnormalities in protein metabolism

Increased proteolysis can be seen early in CC patients and can progress to increased skeletal muscle catabolism and decreased synthesis and hypoproteinemia. Increased proteolysis in patients can involve two systems, the autophagy lysosome system (ALS) and the ATP-ubiquitin proteasome system (UPS). Studies have demonstrated that ubiquitin-specific peptidases (USPs), which promoted proteolysis by up-regulated in CC and other chronic wasting diseases. In addition, pro-inflammatory factors promote proteolysis and the development of an inflammatory response in the body, leading to exacerbation of the progression of malignant symptoms [14].

2.2.3 Abnormalities in lipid metabolism

Tumor patients have increased fat mobilization, fat conversion rate, fatty acid oxidation, and decreased fat storage. This process mainly involves the following aspects: 1) Inhibition of fat synthesis and storage: the expression of adipogenic transcription factors and genes related to fat uptake and synthesis are down-regulated in patients, and the activity of lipoprotein lipase (LPL) is reduced in the body. As a result, fat synthesis and storage are inhibited. 2) Enhancement of fat degradation: the expression of perilipin1 was significantly reduced in CC patients, which resulted in a decrease in fat synthesis and storage [15]. 3) Enhancement of white adipose tissue (WAT) browning [16]: parathyroid hormone related protein (PTHrP) and cytokines can promote adipose tissue browning, and convert subcutaneous white fat into beige fat. 4) Enhancement of systemic inflammation: Lipomobilizing factor (LMF) can sensitize adipocytes to lipolytic hormones in order to induce fat mobilization in the body [17].

2.2.4 Abnormalities in glucose metabolism

Sugar degradation and gluconeogenesis are enhanced in tumor patients, and the only way to obtain energy is gluconeogenesis, so their glucose oxidation and utilization are

reduced. The large amount of lactic acid produced by glucose degradation in patients with CC is re-synthesized into glucose in the liver, which is then re-synthesized into lactic acid by the tumor cells.

2.2.5 Increase in energy consumption

Increased metabolic rate in patients with malignant tumors leads to progressive tissue depletion in the body. Tumor patients are in a high metabolism state, and the content of fats and muscles in their bodies decreases significantly. In addition, different tissue types and growth sites of tumors have different degrees of energy consumption, and those with more obvious energy consumption have higher rates of malnutrition, weight loss and malignant disease than other tumor patients.

3. Traditional Chinese Medicine Treatment of Carcinoma Malignancy

The basic principle of treatment for Xu Lao is to "strengthen the body and cultivate the root". However, the prerequisite for applying the method of tonification is to clearly identify the degree and predominance of deficiency of qi, blood, yin and yang of the patient. Clinical treatment is always based on the method of cultivating the soil and consolidating the root, emphasizing the harmonization of qi and blood and tonifying the spleen and kidney. Specific treatments include benefiting qi and strengthening the spleen, strengthening the spleen and stomach, tonifying the kidney and filling up the essence, tonifying the kidney and strengthening the spleen, benefiting qi and nourishing yin, and tonifying both qi and blood, etc. Meanwhile, we do not forget to identify the symptoms according to the actual clinical symptoms of the patients, in order to combine detoxification, activation of blood circulation and elimination of blood stasis, the promotion of qi and elimination of phlegm and other methods of comprehensive treatment.

3.1 Treatment from Qi and Blood Theory

Qi and blood are the important material basis for maintaining human life activities. "Qi is the commander of blood, blood is the mother of Qi", one side of Qi or blood is often damaged to the other side, resulting in evidence of deficiency of Qi and blood. Neijing records, the Wei Qi's effects are "warming flesh, filling the skin, fattening coupling, as well as the Division of the opening and closing"; Ying Yin's effects are "urination of fluids, injecting in the veins, turning into blood, in order to glorify the four end". Qi and blood are full of Ying and Wei together, so the function of the internal organs can run normally [18]; not enough qi and blood, Ying and Wei are not harmonious, the body's skin shall not be full of nutrients, the couper shall not be dense, and the internal organs are not warmed up. These result in the typical clinical symptoms of malignant pathology, such as the body emaciation, fatigue and sleepiness, and the deterioration of shape and spirit. In addition, if the operation of Ying and Wei is not smooth, Qi, blood, essence will transmit unsmoothly. Long-term accumulation of Qi and blood will produce phlegm and stagnation, which will further impede the Qi flow. That is what Cheng Wuji [19] said, "strong was circulation of Rong and Wei, matching of rigidity and flexibility." "Living

Method Essentials" also says, "Weakness of the spleen and stomach, the decline of qi and blood, and the sensation of the four seasons can lead to accumulation" [20]. Patients have insufficient Qi in their body, and if they undergo radiotherapy, targeted and immunotherapy, they will suffer more damage to the spleen and stomach as well as Ying and Wei. These could cause the Wei Qi to be disordered outside the vein, the Ying Xue to be stagnant inside the vein, the lack of nutrients in the body and the loss of nutrition of the muscles, which would make the symptoms of the disease more complicated, and the patients have poor prognosis.

For treatment, the main focus should be on tonifying Qi and Xue and harmonizing Ying and Wei. Xiao Jian Zhong Tang is a representative formula for treating deficiency labor. This formula is composed of Gui Zhi Tang and doubled with Paeonia and added Jiaoyi. The king drug, cerealose, is used to tonify the Zhongjiao and benefit the Qi and Ying. In this formula, drugs are used to tonify the Yin and Yang, in order to obtain the heat of Yang to vaporize the Yinjing, and restore the function of the Spleen and Stomach. So that the Qi and blood can be generated by itself and the Yin and Yang can be regulated [21]. Huang Qi Jian Zhong Tang is more powerful than Xiao Jian Zhong Tang in benefiting Qi, building the center and easing the emergency. This formula can make Yang and Yin grow, and be good at treating all the deficiency cases. Zhi Gan Cao Tang is made of Sheng Di Huang as the monarch drug, together with Ejiao and ophiopogon japonicus to nourish Yin and blood. Cassia twig and Ginger warm the Yang. Researches have proved that Zhi Gan Cao Tang can enhance the hematopoietic function of the body and increase the level of blood cells in the body. The first book of "Zheng Ti Lei Yao" contains the Gui Spleen Tang, which emphasizes the treatment of the heart and spleen, and the supplementation of both Qi and blood, in order to "make the spleen strong, so that Qi and blood will have a source of biochemistry".

3.2 Treatment from Spleen and Kidneys

Spleen masters the limbs and muscles; stomach is the ocean of Qi and blood and the functions of each viscera is performed by stomach Qi. In clinical patients, if the stomach Qi is damaged, the Qi and blood will lack a source, the stomach Qi will be destroyed, so the prognosis of the disease will be poor [22]. The transport function of then is impaired, the water and grain essence is insufficient, the limbs and muscles and internal organs are not nourished, and symptoms such as fatigue, tiredness and laziness often occur. Shen Ling Bai Zhu San has effects of benefiting qi and strengthening the spleen and seeping dampness, in which ginseng greatly replenishes the Qi of spleen and stomach. Baizhu and Fuling strengthen the spleen and seep away dampness. This formula uses the sweet and warm to replenish the spleen, and the products of aromatic and seeping dampness to help transportation and digestion. Clinical application can significantly improve the symptoms of CC patients, such as loss of appetite, body fatigue and so on. Ye Tianshi puts forward the theory of division of the spleen and stomach [23]: Spleen Yang deficiency is treated with sweet and warm to benefit Qi and Yang, in order to strengthen the spleen and stomach and nourish essence and blood; Stomach Yin deficiency is treated with sweet and cold to clear and nourish the stomach and nourish the Yin. Emphasizing that it is easy to deplete the Qi

after a long period of time, and some products such as Sheng Di Huang, Maidong and other sweet and cold products are benefit in Qi. Si Jun Zi Tang can also be used to regulate the function of the spleen and stomach [24].

Li Xu Yuan Jian believes that the treatment of fatigue disease should emphasize the regulation of the lungs, spleen and kidneys [25]. Li Zhongzi also suggested that "if the spleen and kidneys were peaceful, the whole body would be cured, and all kinds of diseases would not occur". Clinical studies have found that tonifying the kidneys and strengthening the spleen can increase the levels of serum hemoglobin and albumin in patients, and improve the state of fatigue and poor diet [26]. Zhang Jingyue believes that the illness of Xu Lao is in the Yin part of the body, the essence is "Yang is not surplus" and the treatment is based on solidifying "true Yin". By filling the true Yin of the kidneys, it can generate essence and nourish the five viscera and six bowels. For Da Bu Yuan Jian, ginseng was used together with Shu Di in stronger dosage to maximize the mutual rooting of essence and Qi. Zhang Jingyue suggested that treatment should be based on tonifying the body's Yin and Yang [27]. Yang deficiency is treated with pungent, sweet, warm and dry agents to replenish Yang Qi; Yin deficiency is treated with sweet, cool, mellow and quiet products to nourish Yin [28]. Zhang made good use of Shu Di to nourish blood and fill the essence of nourishing Yin, as well as ginseng and other products to warm the Yang, and said "Shu Di was the first product of the pure and thick drugs [29]". He followed the theory of "seeking Yin in Yang, seeking Yang in Yin", and used a few warming and benefiting drugs to tonify the true Yin of the liver and kidney among the drugs which nourished Yin and filled up the essence. "The use of eight liang of Shu Di to nourish the kidney and benefit the essence. The application of the turtle and deer gum to nourish essence of the marrow, and the combination of all the medicines is to enhance the power of the birth of the essence by seeking the Yin in the Yang. The combination of all medicines in this formula tonifies kidney Yang without damaging the true Yin, so that Yin and Yang of the organism are in harmony.

4. Summary and Outlook

Cancer cachexia is a kind of metabolic syndrome with complex pathogenesis and poor clinical efficacy. Improving nutrition, increasing appetite and reducing muscle catabolism are not enough to change the high metabolic state of patients. In TCM, the principle of treating "Xu Lao" is always to "support the body and cultivate the root", emphasizing the leading role of Qi, blood, spleen and kidney. At the same time, don't forget to take into account other organs and balance attack and tonicity, in order to achieve better clinical effects and therapeutic concepts.

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