

Progress in the Efficacy of Traditional Chinese Medicine Combined with Immune Checkpoint Inhibitors in the Treatment of Patients with Advanced Malignant Tumors

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Abstract

With the continuous increase and improvement of tumor treatment methods, immune checkpoint inhibitor therapy has gained obvious benefits in tumor treatment. Its therapeutic advantages are highlighted while there are certain limitations. With the continuous deepening of research, it is found that there are certain drug side effects and tumor drug resistance. With the continuous development of traditional Chinese medicine, traditional Chinese medicine has shown its unique advantages in the treatment of tumors. Traditional Chinese medicine can make up for the shortcomings of immunotherapy and benefit more tumor patients. The regulation of immune environment and drug side effects of traditional Chinese medicine combined with immunotherapy provides a breakthrough point for the treatment of malignant tumors with integrated traditional Chinese and Western medicine.

Keywords

Traditional Chinese Medicine; Immunotherapy; Integrated Traditional Chinese And Western Medicine; Malignant Tumor ; Summary.

1. Introduction

With the improvement of consumption level, the prevalence of malignant tumors is getting higher and higher, and the treatment of malignant tumors is also increasing. The occurrence and development of tumors are closely related to immunity. With the development of immunology, immunotherapy plays a vital role in the treatment of malignant tumors. However, immune-related adverse reactions, such as rash, hepatitis, gastroenteritis, etc., are inevitable in the treatment. Although most patients have mild immune-related adverse reactions, there will always be a few patients with severe reactions or even death. Tumor immunotherapy, as a systemic treatment, can kill and inhibit the occurrence of tumors by strengthening the immune function of the body. Traditional Chinese medicine treats diseases from the overall concept and has a regulatory effect on the overall microenvironment of the human body. It can inhibit and kill tumor cells by regulating immune cytokines and tumor immune microenvironment. It can also enhance the role of immunotherapy and reduce toxic and side effects [1]. Traditional Chinese medicine treatment is mainly based on symptoms, which can reduce the immune-related adverse reactions during immunotherapy, and greatly avoid the treatment interruption caused by immune adverse reactions during treatment [2]. It can participate in the whole process of anti-tumor treatment.

2. The pathogenesis of traditional Chinese medicine tumor

Traditional Chinese medicine advocates 'harmony between man and nature', regards man as a whole, and believes that the treatment of diseases should start from the overall concept. First of all, starting from the 'yin and yang theory' of traditional Chinese medicine, the human body is divided into yin and yang, and the two are opposite to each other, restricting each other to maintain the objective law of human life activities [3], which fully reflects the overall connection of the human body 'correspondence between man and nature' and promotes the further development of the theoretical system of traditional Chinese medicine. The relative properties of yin and yang in clinical manifestations, yang has a positive effect, such as promoting, warming, exciting role, and yin has a negative effect, such as cohesion, moistening, inhibition. 'Leijing Fuyi' points out that the dynamic person is calm, and the yin-hyperactivity person is better than the yang. This sentence reflects the result of the struggle between yin and yang, and the balance between the two sides, so as to promote the continuous development of things. For the human body, the balance between yin and yang remains normal, known as the physiological state. If disturbed by external factors, the balanced relationship between yin and yang is broken, and a certain aspect of yin and yang will be strong at any time, resulting in a pathological state in which the balance of their relationship is broken, and various diseases arise. On the other hand, for traditional Chinese medicine, the emergence and development of a disease depends on whether the body's yin and yang are balanced. The healthy qi belongs to the yang side, and its deficiency is the root cause of tumor development. The rise and fall of evil is also the embodiment of the balance of yin and yang. 'Suwen · needling theory' believes that the body's healthy qi is strong and the blood gas is sufficient, so that the human body's defensive qi is sufficient, then the evil qi is difficult to enter the human body, and the disease can not occur [4]. On the contrary, the body's yang qi is the vital qi is weak due to various reasons, the body's defensive qi is insufficient, unable to resist the invasion of evil qi, evil qi take advantage of the virtual, leading to a series of dysfunction of the body, the balance of yin and yang is broken, leading to the occurrence of disease, the pathogenesis of malignant tumor is the yang qi is the vital qi deficiency [6], the external evil qi invasion of the human body leads to the balance of the body function is broken [5], qi and blood stasis, phlegm and toxin accumulation.

3. Chinese medicine immune regulation

In traditional Chinese medicine, it is proposed that the imbalance of yin and yang, the deficiency of healthy qi and the abundance of pathogenic factors are the key causes of tumor development. Therefore, strengthening the body resistance to eliminate pathogenic factors and adjusting yin and yang are the basic principles in the treatment of tumors [7]. This treatment method can be used in the whole treatment process of tumors, which is the clinical manifestation of traditional Chinese medicine in the treatment of tumors. Due to the slow onset of the tumor, the course of the disease is long, especially in the middle and advanced cancer patients or cancer patients after treatment are mostly manifested as deficiency syndrome, that is, the body's immune function is low in western medicine [8]. Under the guidance of the idea of supporting healthy qi to treat tumors, this series of treatments can promote the healthy qi of the human body, adjust the balance of yin and yang, and correct the weak state of yang qi of the human body, so as to improve the immune function of the body, strengthen the ability of the healthy qi of the human body to expel foreign pathogens, and control the occurrence and development of tumors from the source. The focus of tumor treatment is to promote the balance of yin and yang, and to help the healthy qi to resist external evils. Through a variety of ways to make Yin and Yang restrict each other, so that the balance between Yin and Yang to achieve the balance of Yin and Yang secret, righteousness can restrict the balance of external evils, and achieve the purpose of inhibiting the growth of tumor cells, alleviating the clinical symptoms of tumor patients, and

improving the quality of life of patients [9]. Early scholars have proposed that modern oncogenes and tumor suppressor genes represent the yin and yang in traditional Chinese medicine respectively, and their dynamic balance is inseparable from yin and yang. According to the different attributes of yin and yang, oncogenes and tumor suppressor genes are considered to belong to yin and yang. The conditions under which tumors can occur are that the balance of yin and yang is broken, that is, the balance of oncogenes and tumor suppressor genes [10]. According to the records in the classics of traditional Chinese medicine, the deficiency of vital qi in tumor patients is mainly manifested in the deficiency of 'qi' and 'blood' [11], while the external evils are mainly manifested in qi stagnation, blood stasis and damp heat. Therefore, tonic drugs are commonly used in traditional Chinese medicine to help vital qi, and qi-regulating drugs, blood-activating and stasis-resolving drugs and heat-clearing drugs are commonly used to eliminate pathogenic factors.

4. TCM immune-related adverse reactions

The common side effects of immunotherapy include skin toxicity, gastrointestinal toxicity and liver toxicity. Skin toxicity is mostly manifested as maculopapules, itching, etc. Gastrointestinal toxicity is mainly diarrhea, and abdominal pain, bloating, loss of appetite, etc. may also occur. From the perspective of traditional Chinese medicine, immune-related adverse reactions are viewed. Skin toxicity is summarized as 'drug rash' of traditional Chinese medicine. The pathogenic factors are often wind, heat, toxin and dampness. The pathogenesis is caused by wind, heat, toxin and dampness reaching the surface of the muscle. The treatment is mainly based on clearing heat and detoxifying, drying dampness and relieving itching [12]. Gastrointestinal reaction is the most common diarrhea. From the perspective of traditional Chinese medicine, spleen deficiency and dampness are the causes of diarrhea, mainly manifested as loss of appetite, abdominal distension and other symptoms. In terms of liver toxicity, traditional Chinese medicine and western medicine have essential differences. Traditional Chinese medicine believes that liver has the function of dredging and storing blood, which is mainly manifested in regulating emotions, promoting digestion, dredging qi and hematopoietic function. Liver toxicity can be manifested as liver dysfunction. The common syndrome type of advanced cancer patients is liver and kidney deficiency, and traditional Chinese medicine is commonly used to nourish liver and kidney.

5. Advantages of traditional Chinese medicine in immunotherapy

Traditional western medicine tumor immunotherapy refers to a treatment method that kills and inhibits tumor cells by enhancing the body's immune function. At present, the commonly used immune checkpoint inhibitors in clinical practice are mainly PD-1 monoclonal antibody, PD-L1 monoclonal antibody and CTLA-4 inhibitor. Its mechanism of action is to enhance the body's immune response ability, reduce the immunosuppressive effect, activate the body's immune system to kill tumor cells, so as to achieve the purpose of treating tumors. This mechanism is reflected in traditional Chinese medicine, which can play a role in treating tumors by regulating the body's immune microenvironment. The ideological theory of 'Fuzheng Kangxie' is similar to the principle of immune checkpoint inhibitors, and the academic thought of 'preventive treatment of disease' also assists the treatment of cancer patients [13]. This model is basically consistent with the traditional western medicine immunotherapy in the treatment of tumors, which breaks the body's immune tolerance, reverses immune escape, restores the body's normal immune function, and stimulates the body to kill tumor cells [14]. Therefore, the common drugs in the adjuvant treatment of tumors in traditional Chinese medicine are divided into the following [15]: 1. Tonifying drugs, that is, to supplement the body's healthy qi drugs, namely qi, blood, etc., by regulating and improving the function of zang-fu

organs, enhancing the body's ability to resist diseases, and treating various weak diseases. 2, promoting blood circulation and removing blood stasis drugs, to dredge blood vessels, promote blood circulation as the main effect. 3. Heat-clearing drugs, with clearing heat as the main role, its medicinal properties are mostly cold, with heat-clearing and detoxifying, purging fire, and other effects. According to the study, these drugs play a therapeutic role through different targets and pathways. 'Kidney is the congenital foundation and spleen and stomach are the acquired foundation. ' Spleen and kidney are closely related to the healthy qi of human body. Whether the spleen and kidney function are normal is closely related to the normal immune cells of the body and whether the immune function can play a role in killing tumor cells [16]. Deficiency of spleen function can reduce the cellular immune function of tumor patients, and deficiency of kidney can often lead to deficiency of healthy qi of the body. Patients with advanced malignant tumors often have five internal organs and yin and yang qi and blood deficiency, so the treatment is mainly based on tonifying spleen and kidney [17]. By observing the relevant indicators of 100 patients with paraneoplastic syndrome before and after treatment, Zhao et al., concluded that the treatment effect of traditional Chinese medicine combined with immunosuppressive agents was better than that of immunosuppressive agents alone [18].

6. The advantages of traditional Chinese medicine in the treatment of immune-related adverse reactions

Immunotherapy has a significant effect on prolonging the survival of patients during tumor treatment, but it will damage normal tissues during treatment and cause certain autoimmune-related side effects. The immune-related side effects caused by PD-1 / PD-L1 monoclonal antibody are similar to those caused by CTLA-4 monoclonal antibody, but the incidence and severity of PD-1 / PD-L1 are lower than those of CTLA-4 monoclonal antibody [19-20]. In clinical observation, the advantages of traditional Chinese medicine in alleviating common immune-related toxic and side effects are increasingly prominent.

6.1. Skin toxicity

From the perspective of traditional Chinese medicine, the common pathogenic factors causing skin toxicity are wind, heat, toxin and dampness. Therefore, the treatment methods of clearing heat and detoxifying, dispelling wind and removing dampness, relieving itching and so on are adopted. The commonly used traditional Chinese medicines in clinic are wild chrysanthemum, white fresh skin, sophora flavescens, honeysuckle, scutellaria baicalensis, etc. In the clinical study, it was found that the effect of skin itching and other skin adverse reactions caused by oral antipruritic agent or external application of PD-1 inhibitor with honeysuckle water was obvious [21]. It is fully proved that traditional Chinese medicine has a unique therapeutic effect in the process of tumor immunotherapy.

6.2. Gastrointestinal toxicity

From the perspective of traditional Chinese medicine, the pathogenesis of gastrointestinal toxicity in patients with middle and advanced cancer is spleen deficiency and dampness. The corresponding treatment is invigorating spleen and removing dampness. *Atractylodes macrocephala* is the representative drug of invigorating spleen and removing dampness. It is clinically confirmed that *Atractylodes macrocephala* has a certain effect in promoting the recovery of gastrointestinal function [22]. The common representative prescriptions are Sijunzi Decoction, Shenling Baizhu Powder and so on. Zhang Fan et al. found that Huangqin Decoction has the function of gastrointestinal discomfort through clinical observation, which can shorten the duration of diarrhea caused by sorafenib and reduce the degree of diarrhea, and significantly improve the clinical efficacy of tumor patients [23]. The use of traditional

Chinese medicine to alleviate the gastrointestinal toxicity caused by immunotherapy avoids the conflict between the effects of several drugs in the treatment and hinders the smooth progress of tumor treatment.

6.3. Hepatotoxicity

Liver toxicity is one of the common side effects of tumor immunotherapy, mostly manifested as liver dysfunction symptoms, and malignant tumors are chronic wasting diseases. Therefore, the TCM syndromes of patients with middle and late malignant tumors are mostly liver and kidney deficiency. Commonly used Chinese medicines are Schisandra, Bupleurum, Artemisia capillaris, etc. According to research, it has the effect of reducing transaminases. The commonly used prescriptions for treating liver and kidney deficiency are Xiaoyao Powder, Duzhong Dihuang Pills, etc. Traditional Chinese medicine can play a good auxiliary role in the treatment of liver toxicity, and the combination of traditional Chinese and Western medicine is more effective.

7. Summary and prospect

In the treatment of malignant tumors, before the emergence of immunotherapy, it has been committed to the killing of tumor cells, and the immune aspects of the body have not been further studied. The balance of the human immune system plays an important role in the occurrence, development and prognosis of tumors [24]. In recent years, with the continuous development of immunology, the advantages of immunotherapy in tumor treatment have become increasingly prominent. The therapeutic principle is to activate or enhance the human immune system so that it can recognize and kill tumor cells, so as to achieve the purpose of treating tumors. This treatment treats people as a whole and is committed to the human immune system. By maintaining the normal immune function of the human body and the normal expression of tumor microenvironment-related factors, it enhances the immune function of the body, avoids immune tolerance during the treatment process, and inhibits tumor immune escape. Inhibition and killing of tumor cells. This coincides with the overall concept of traditional Chinese medicine in the treatment of diseases. Traditional Chinese medicine believes that people are an organic and unified whole. Therefore, the occurrence and development of a disease is not only related to the accumulation of local cancer toxins, but also to whether the body's yin and yang is balanced, whether the vital qi is full, and whether the operation of qi and blood is normal. Inextricably linked, so in the treatment of diseases, we should not only pay attention to the local but also look at the whole. While treating local problems of tumors, we should pay more attention to the balance of all aspects of the body. With the continuous development of traditional Chinese medicine, the syndrome differentiation and treatment of traditional Chinese medicine is indispensable in the treatment of tumors, especially the toxic and side effects of drugs shown in the process of immunotherapy. Due to individual differences, the symptoms of tumor patients are different, and the syndrome differentiation and treatment of traditional Chinese medicine is particularly important [25]. The holistic concept of traditional Chinese medicine and the theory of yin and yang provide a good idea for the development of tumor immunotherapy. The whole of traditional Chinese medicine provides a theoretical basis for tumor immunotherapy and provides a new direction for the treatment of tumors with integrated traditional Chinese and Western medicine. The combination of traditional Chinese and Western medicine has obvious advantages in the treatment of diseases in clinical practice, especially in the use of immune checkpoint inhibitors, which makes the theory of yin and yang of traditional Chinese medicine and the theory of strengthening the body and dispelling evils reflected in the treatment of Western medicine [26]. Although traditional Chinese medicine has achieved certain results in the clinical research of integrated traditional Chinese and Western medicine for malignant tumors, the mechanism of traditional Chinese medicine combined with immunotherapy for tumors is still unclear, and

its development is still in the basic stage. In addition, the composition of traditional Chinese medicine is complex, and how to avoid its toxic and side effects is still unclear [24]. Continuous clinical research and experiments are needed to provide more powerful evidence for traditional Chinese medicine in the treatment of malignant tumors. It is helpful for the more extensive application of integrated traditional Chinese and western medicine in clinical practice.

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