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Research Progress of TCM Treatment of Tumor-related Cardiovascular Toxicity

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Abstract: ***Cancer is the second leading cause of death in the world. At present, cardiovascular disease has become the second leading cause of death for tumor survivors following tumor recurrence and metastasis. Early diagnosis and prevention of cardiovascular toxicity that may occur during the treatment of cancer patients. Cardiovascular toxicity related to cancer treatment includes cardiac insufficiency and heart failure (heart failure), coronary heart disease, immune myocarditis, hypertension, thromboembolic disease and other cardiovascular diseases. As a branch of the medical field, Chinese medicine is well known in the prevention and treatment of malignant tumors, and Chinese medicine therapy is a potential candidate for the treatment of tumor-related cardiotoxicity. This article summarizes the recent research progress of TCM therapy for anti-tumor cardiotoxicity related to tumor therapy.***

Keywords: Traditional Chinese medicine, Cardiovascular toxicity, Antitumor therapy, Oncology cardiology.

1. Introduction

Cancer treatment methods include general chemotherapy, radiotherapy, immunotherapy, targeted therapy, etc. All of these therapies can cause cardiovascular toxicity and side effects to a certain extent and even persistent cardiac complications, threatening the life of patients and even causing death, which has attracted increasing attention [1] from relevant experts. In recent years, with the rapid development of anti-tumor drugs and the continuous improvement of the survival rate of cancer patients, the prevention of cardiovascular toxicity and side effects is the focus of anti-tumor drug research. A large number of biomarkers and imaging tests have provided tumor cardiologists with an effective method to monitor the cardiovascular toxicity [2] of antitumor drugs. But there is still no consensus on the best prevention strategy, early diagnosis and intervention to reduce late cardiotoxicity and heart-related events. Although the role of traditional Chinese medicine is still unclear, ensuring the successful completion of treatment for patients can especially reduce the occurrence and development of cardiotoxicity, which may provide ideas and references for the prevention and management of cardiotoxicity events related to anti-tumor therapy. This article makes a systematic review on the current status of clinical research on the prevention and treatment of cardiotoxicity by traditional Chinese medicine.

2. The Understanding of Tumor-related Cardiovascular Toxicity

With the continuous improvement of the level of tumor treatment and the use of new drugs, including surgery, radiotherapy, chemotherapy, endocrine therapy, targeted therapy and immunosuppressive therapy, the survival of tumor patients has been prolonged, and more and more survivors with tumor [3]. At the same time, the number of anti-tumor patients associated with cardiovascular diseases increases, resulting in cancer therapy-related cardiovascular toxicity (CCR-CVT) getting more and more understanding and attention. Ccr-cvt has gradually become one of the most common complications in the process of tumor treatment, even beyond the tumor itself, has become the second largest cause of death in tumor patients except recurrence and metastasis, and seriously affects the survival of patients [4, 5]. In 2021, Chinese experts and scholars wrote for the first time the Chinese Clinical Oncology Society (CSCO) Guidelines for the Prevention, diagnosis, treatment and management of cardiovascular toxicity related to cancer treatment in order to ensure the safety of anti-tumor therapy and improve patient prognosis [6]. Currently, there are too few drugs used to protect the heart damage, and the only protective agent approved by the FDA for the protection of tumor cardiotoxicity, dextropropimide, is expensive and not widely used in China [7]. Therefore, there is an urgent need to develop drugs to protect the heart from damage when potential heart agents are used.

3. Etiology and Pathogenesis of Cardiovascular Toxicity Associated with Cancer Treatment

There is no relevant record of cardiotoxicity of TCM anti-tumor drugs, but according to the clinical manifestations of patients, the blood is weak, the heart is not enough, and the god is disturbed, and it is cardiotoxicity. Combined with modern medical research results, it belongs to the categories [8, 9] of TCM "chest numbness" and "palpitation". "Golden Chamber outline heart code" cloud: "poison, evil gas accumulation is called", due to the needs of anti-tumor treatment, often need multiple courses of treatment, with the extension of drug use time, the accumulation of drug dose, radiation and anti-tumor drugs can be blocked in the heart, after a long time, brewing into "poison", ultimately damage the heart, corrupt shape and quality [10]. The drug poison accumulates in the body internal energy injury Yin, easy and phlegm stasis, obstructing qi and blood, damage the heart collaterals, clinical every see palpitation, chest tightness, shortness of breath, movement is aggravated heart injury signs [11]. Therefore, Qi-Yin deficiency is not only the pathogenesis of malignant tumor, but also the pathogenesis of cardiotoxicity of antitumor drugs; The toxicity of heart and collateral is very important in the cardiotoxicity of anti-tumor drugs, and it is the key link of the cascade of myocardial

damage amplified step by step, and eventually lead to irreversible functional damage [12]. The disease of CTR-CVT is caused by the "drug toxicity" caused by anti-tumor drugs and the Qi-Yin deficiency of tumor patients themselves. The basic pathogenesis of CTR-CVT is the primary deficiency and the standard deficiency is the primary deficiency of Qi-yin deficiency and the standard deficiency is the toxic phlegm congestion.

4. Cardiovascular Toxicity Related to Tumor Treatment

4.1 Cardiac Dysfunction Associated with Cancer Treatment

Cardiac insufficiency is the most common and serious complication of CTR-CVT and has an important impact [13] on the prognosis of patients treated with anthracyclines and anti-HER-2. A decrease in left ventricular ejection fraction (LVEF) is usually the initial presentation with no significant discomfort, and the patient progresses to heart failure [14] with increasing dosage. The main goals for tumor-treatment-related cardiac dysfunction are to maintain normal left ventricular ejection fraction, delay myocardial remodeling, and evaluate risk factors. LVEF should be monitored; It is recommended that all LVEF below 50% or biomarkers (BNP, troponin) elevated should be considered to activate ACEI/ARB/ARNI or β-receptor antagonists, SGLT-2 inhibitors, dexrazoine to protect myocarocytes [15].

The clinical effect of Yiqi Yangxin Decoction on the prevention of cardiotoxicity of anthracyclines during adjuvant chemotherapy in breast cancer patients was studied. The evaluation indexes were TCM symptom score, quality of life, echocardiogram, electrocardiogram changes, and serum troponin (cTnT) and creatine kinase (CK) content changes. The results showed that: cTnT and CK contents in chemotherapy group and combined Yiqi Yangxin decoction group were higher than before [16]. Yiqi Yangxin Decoction could prevent the cardiotoxicity of anthracyclines and improve the quality of life of patients. To observe the clinical efficacy of Qishenyiqi dropping pills in the treatment of anti-tumor drug-related cardiac dysfunction in patients with malignant tumors, the control group was given conventional western medicine treatment, and the observation group was given oral Qishenyiqi dropping pills on the basis of this, the total effective rate of the observation group was 91.0%, higher than that of the control group 74.2%. Moreover, 6min walking distance, BNP, HRV index, cardiac function index, serum hs-CRP, IL-6 and myocardial enzyme index in the observation group after treatment were better than those in the control group. Qishenyiqi dropping pills combined with Western medicine in the treatment of anti-tumor drug-related cardiac dysfunction in patients with malignant tumors were better than those treated with Western medicine alone, and the safety was higher [17]. Sini Decoction is a traditional Chinese medicine, mainly composed of licorice, dried ginger and aconite. The active ingredient in Sini Decoction has been shown [18] to have some protection against the cytotoxicity of anthracyclines, including aconite, which enhances myocardial contractile force.

4.2 Immune-associated Myocarditis

Due to the increasing clinical use of PD-1 and PD-L1 inhibitors, and their cause of cardiotoxicity, especially immune myocarditis, which can be life-threatening, the issue of cardiotoxicity needs to be paid [19] attention to by clinicians. At present, the pathogenesis and etiology of myocarditis associated with immune checkpoint inhibitors (ICIs) have not been clearly defined in clinic, which may be closely [20] related to T cell activation, immune examination, and production of autoantibodies. The clinical manifestations of myocarditis caused by ICIs vary greatly. Dyspnea is the most common clinical symptom, followed by chest pain, palpitation, arrhythmia, heart failure and lower limb edema [21]. In mild cases, there may be only elevated myocardial markers without clinical symptoms, or only non-specific symptoms [22] such as fatigue, fatigue, myalgia, nausea, vomiting, etc. In severe cases, there may be explosive myocarditis, resulting in cardiogenic shock, sudden cardiac death and other serious consequences. Endomyocardial biopsy is the gold standard [23] for diagnosing ICIS-associated myocarditis. However, the real world incidence may be higher because some patients have hidden symptoms and go undiagnosed, resulting in cases being missed. Traditional Chinese medicine is an indispensable part of the comprehensive treatment of cancer. For the cardiotoxicity caused by ICIs, its main therapeutic significance is "attenuated". Traditional Chinese medicine has its potential advantages [24] in the prevention and treatment of cardiotoxicity caused by ICIs.

In the animal studies [25] of Liu Qian et al, anti-PD-1 antibody was given to intervene in immune myocardium, which significantly aggravated myocardial damage. After Shenqi Fuzheng injection was given in advance, the levels of CK-MB and cTNT were significantly reduced, and the levels of IL-1β, TNF-α protein and mRNA were decreased. It was verified that Shenqi Fuzheng injection could prevent anti-PD-1 antibody from aggravating myocarditis injury. Up to now, although there are few reports on the treatment of immune-related myocarditis with traditional Chinese medicine, traditional Chinese medicine has the characteristics of multi-components, multi-targets and multi-approaches. Exploring the application of traditional Chinese medicine in immune-related myocarditis is a new direction to promote the innovation of traditional Chinese medicine.

4.3 Hypertension

High blood pressure is the most common adverse reaction to antivascular targeted drugs. Studies have shown that up to 80% of patients treated with vascular endothelial growth factor (VEGF) inhibitors develop new hypertension or worsen [26] existing hypertension. Patients with antitumor drug use should have their blood pressure monitored regularly once they start taking these drugs that can cause hypertension, especially in the early stages of treatment. The primary goal of controlling hypertension is to reduce the risk [27] of damage to the target organ. In addition, good control and management of blood pressure is a prerequisite to ensure the continued use of antitumor drugs, if the blood pressure is too high or difficult to control will force the termination of tumor treatment. Antihypertensive treatment of tumor treatment-related hypertension is similar [28] to conventional hypertension treatment.

The blood pressure of patients with Apatinib-related hypertension decreased significantly and remained relatively stable 5 days after Wang Tongbiao et [29] al. Guan Xianghua et [30] al. reduced VEGF levels and controlled blood pressure in patients with hypertension complicated with heart failure by supplementing qi and clearing collateral. Ouqiwei [31] used Erchen, salvia miltiornis, Leonurus and other anti-phlegm and collateral-clearing drugs combined with nifedipine controlled release tablets to reduce blood pressure, and also improved the clinical symptoms of patients with dizziness and headache. At the same time, the level of VEGF was reduced, and the vascular endothelial function of patients was improved to a certain extent. Liu Wanmei [32] used acupoint antihypertensive exercises (Fengchi point, Neiguan point, Temple point, Baihui point, Quchi point, Zusanli point) to treat Apatinib complicated with hypertension, which could significantly improve the blood pressure and improve the quality of life of patients. Traditional Chinese medicine treatment can alleviate targeted drug-related hypertension to a certain extent, and patients with hypertension should actively improve bad living habits during treatment, so as to maintain stable blood pressure more effectively and improve health level.

4.4 Coronary Artery Disease

The mechanisms of myocardial ischemia induced by antitumor therapy are varied, including vasospasm, endothelial injury, acute arterial thrombosis, and long-term abnormal lipid metabolism and the subsequent accelerated development of atherosclerosis. Acute myocardial infarction (AMI) and unstable angina pectoris are common coronary heart [33] diseases associated with anticancer therapy. The pathogenesis is mainly vasospasm and vascular endothelial injury, leading to abnormal coagulation function, acute thrombosis, blood vessel stenosis, and eventually coronary [28] heart disease. When evaluating patients with coronary heart disease, it is necessary to comprehensively consider the patient's past history and smoking history, as well as the history of chemotherapy and radiotherapy, because many patients present with asymptomatic coronary heart [34] disease within 10 years after chemoradiotherapy.

Zhu Wei [35] randomly divided 102 patients with coronary microvascular disease (CMVD) into conventional group and research group, with 51 cases in each group. The conventional group was given conventional Western medicine treatment, while the research group was given Xuefu Zhuyu decoction on the basis of conventional group. The course of treatment for both groups was 8 weeks. In addition, both groups can significantly reduce the levels of serum hypersensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and endothelin-1 (ET-1) of patients, improve the level of serum nitric oxide (NO), protect vascular endothelial function, and reduce the level of inflammatory factors in the body. Clinical studies by Zang Quan ET al [36]. Compared with conventional Western treatment, Jianpi Yangxin formula combined with conventional Western treatment can significantly reduce the levels of serum ischao-modified albumin, endothelial cell specific molecule-1 and ET-1 in patients with microvascular angina pectoris ($P<0.05$), protect the vascular endothelial function of patients, and then relieve the symptoms of angina pectoris and improve the quality of life.

4.5 Venous Thromboembolism Disease

The blood of tumor patients is often in a hypercoagulable state, and the veins are the most common site of thromboembolism, which is often found in deep veins and lungs [37]. The content of fibrinogen and the number of platelets in the plasma of patients with malignant tumors are higher than the normal level, but the content of anticoagulant substances such as antithrombin, C protein and S protein is low, which is easy to cause blood hypercoagulability. More and more anti-angiogenic drugs should be used in anti-tumor therapy, which often interfere with the normal blood clotting mechanism of the body, damage the vascular endothelium, and then lead to the destruction of its function, and promote thrombosis [38].

Professor Zhao Yuanhong used Huangqi Guizhi Wuwu Decoction to distinguish the patients with lower extremity venous thrombosis of lung cancer, and then used Huangqi Guizhi Wuwu Decoction and Xiaoqinglong decoction [39]. After 4 weeks of medication, the swelling of the lower extremity of the patients was significantly reduced and the pain was relieved. 3 months later, venous color ultrasound showed no thrombosis in deep veins. To observe the clinical efficacy of Taohong Siwu Decoction in the treatment of deep vein embolism in tumor patients, 48 tumor patients with deep vein embolism were randomly divided into two groups, 24 cases in each group. The treatment group was given Taohong Siwu decoction and the control group was given heparin sodium. The recent curative effect, swelling subside, embolized vein repatency, toxic and side effects were observed. Compared between the treatment group and the control group, swelling, pain disappeared, fever, eczema ulcer healing, venous embolism and other symptoms, the embolized vein reopening, toxic and side effects of the treatment group were significantly superior to the control group [40].

5. Conclusion

Clinical trials of antitumor drugs often underestimate the likelihood of cardiovascular events in the "real world" population. At present, there are more and more studies on the prevention and treatment of tumor cardiotoxicity by traditional Chinese medicine. It is expected that traditional Chinese medicine for the prevention and treatment of tumor cardiotoxicity will enter the era of big data as soon as possible to help the prevention and treatment of tumor cardiotoxicity. The combination of modern Chinese medicine to prevent and cure tumor cardiotoxicity is also the current research direction of oncologists and cardiologists. The treatment of modern medicine has been standardized, but it lacks the characteristics of individual treatment. To realize the treatment mode of combining TCM syndrome differentiation with modern medical disease differentiation, the clinical practice of TCM syndrome differentiation and treatment has been raised to a new height.

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