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REVIEW

A Review on Probable Causes of Cardiotoxicity Caused by Common Cancer Drugs and the Role of Traditional Chinese Medicine in Prevention and Treatment

Miao Zhou[1],*, Wenyan Wang[2],*, Jiahao Weng[1], Zhikun Lai[1]

[1]Department of Cardiology, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China; [2]Department of Endocrinology, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jiahao Weng, Department of Cardiology, Shanghai municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, No. 274 Zhijiang Middle Road, Jingan District, Shanghai, 200071, People's Republic of China, Tel +86 13916958289, Email jiahaowengwjh@126.com

Abstract: Cancer is a widespread disease in our nation, characterized by a high occurrence rate. The use of tumor medications has been linked to an increased chance of cardiovascular complications, including a notable occurrence of heart toxicity. This has caused significant concern among healthcare professionals. This article provides a comprehensive compilation of drugs recognized for their potential to cause heart toxicity. Furthermore, extensive research has been conducted to investigate and categorize the effects of heart toxicity, with the purpose of promoting awareness, facilitating early intervention, and ultimately reducing the occurrence of heart toxicity. At the same time, there is an anticipation that Traditional Chinese Medicine (TCM) can capitalize on its unique attributes to address such ailments. To establish its effectiveness, it is crucial to carry out extensive clinical trials or retrospective analyses. The purpose of this article is to summarize the possible mechanisms of cardiac toxicity caused by commonly used chemotherapy drugs and summarize the possible mechanisms of adverse cardiac toxicity, laying the groundwork for subsequent research.

Keywords: chemotherapeutic drugs, cardiotoxicity, mechanisms, TCM intervention

Introduction

The increase in chronic illnesses, particularly cancer, has become a major concern for the well-being of the Chinese population due to factors such as the aging population, mounting living pressures, unhealthy lifestyles, and various other contributors. This worrying trend has been identified as a significant threat to the health of the Chinese people. According to the Global Burden of Disease 2019 (GBD2019) report, cancer was responsible for the death of 2.72 million individuals in China in 2019, accounting for nearly a quarter of all deaths that occurred in the country that year.[1]

Contemporary scientific research has made significant progress in the timely detection, management, and overall survival rates of neoplastic diseases. However, individuals diagnosed with tumors or precancerous conditions now face an increased risk of experiencing cardiovascular health issues after undergoing cancer treatment.[2] In the past, this risk was not as apparent due to the shorter life expectancy of patients, which limited the time available for cardiovascular complications to arise and become a major concern. With the growing longevity of cancer patients, there is now a heightened concern regarding the cardiovascular complications associated with cancer treatments. Studies have revealed that subclinical cardiotoxicity caused by chemotherapy drugs affects up to 18% of patients, while clinical cardiotoxicity occurs in as many as 6% of cases.[3] The emergence of cardiotoxicity as a side effect of chemotherapy drugs poses a new challenge in terms of clinical diagnosis and treatment.[3] The

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purpose of this article is to summarize the possible mechanisms of cardiac toxicity caused by commonly used chemotherapy drugs and summarize the possible mechanisms of adverse cardiac toxicity, laying the groundwork for subsequent research.

Potential Mechanisms of Cardiotoxicity Induced by Common Drugs

Bevacizumab - A Vascular Endothelial Growth Factor Inhibitor

Bevacizumab (BVZ) is a type of antibody that is created using human genes and is designed to specifically target and block the function of vascular endothelial growth factor (VEGF). This action prevents the formation of new blood vessels (angiogenesis), which hampers the growth of cancerous cells and stops the spread of tumors.[4,5] As a result, it serves as an effective treatment option for various types of tumors such as colorectal cancer, lung cancer, breast cancer, cervical cancer, and more. The extensive utilization of Bevacizumab in clinical anti-tumor therapy highlights its significant value in achieving the goal of combating cancer.

BVZ Induced Hypertension in a Dose-Dependent Manner

Various clinical trials have reported that the prevalence of BVZ-related hypertension ranges from 16% to 47%.[6,7] Moreover, the frequency of hypertension was found to be influenced by the dosage of BVZ given.[8] Individuals receiving a high dosage of BVZ experienced a more notable rise in blood pressure compared to those given a low dosage (see Figure 1).

Hypertension may arise due to the interaction between cardiac output and peripheral vascular resistance. By inhibiting VEGF, BVZ has the potential to promote the growth of vascular smooth muscle cells and reduce the production of nitric oxide.[9,10] These actions can cause the thickening of the blood vessel walls, narrowing of the vessel opening, decreased vasodilation capacity, and heightened vascular resistance. Consequently, these factors contribute to the development of hypertension.

BVZ Induced Elevation of Blood Pressure and Myocardial Ischemia Leading to Chronic Heart Failure

Chronic heart failure (CHF) often occurs in conjunction with heightened blood pressure and myocardial ischemia caused by prolonged narrowing of blood vessels. Previous studies have indicated that the administration of BVZ can raise average arterial blood pressure during treatment.[6,7] Sustained hypertension can lead to the enlargement of the heart muscle towards its center (myocardial centripetal hypertrophy), which can result in impaired function of the heart's ventricles during contraction and/or relaxation.

The mechanism involved in ischemic heart disease involves alterations in VEGF that lead to dysfunction of the cells lining the blood vessels (vascular endothelial cells) and hindered reconstruction of blood vessels. Inhibiting VEGF has been demonstrated to

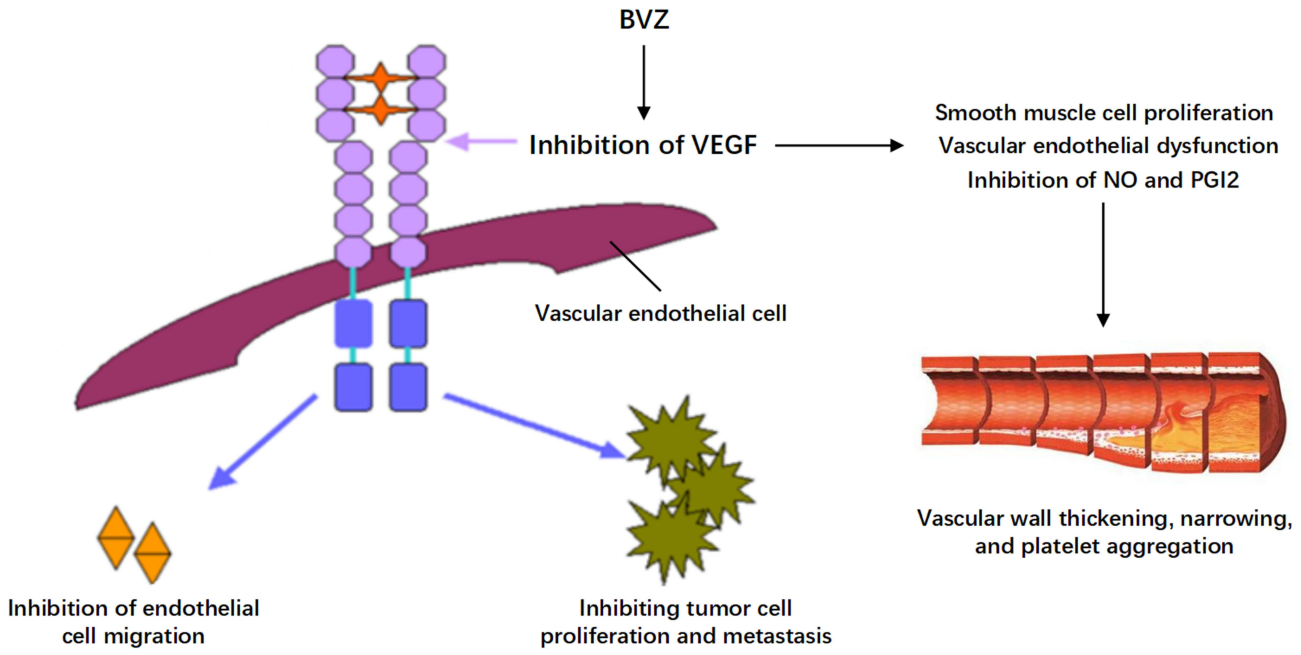

Figure 1 Schematic diagram of cardiac toxicity caused by bevacizumab.

prevent the formation of alternative blood vessels,[11] thus obstructing blood supply and interfering with the healing of myocardial damage. Several factors have been identified as potential contributors to the development of cardiac dysfunction and CHF.

BVZ Promotes Arterial Thrombosis

Thromboembolism is a significant occurrence that can be extremely dangerous and even fatal. When combination chemotherapy is given, the likelihood of developing arterial thromboembolism is greater compared to receiving chemotherapy alone. Additionally, the dosage of BVZ has been recognized as a potential contributing factor to this risk.

Nitric oxide (NO) and prostacyclin I2 (PGI2) production are both increased as a result of VEGF's suppression of platelet aggregation. On the other hand, unstable atherosclerotic plaques, bleeding from plaque ruptures, and stimulated platelet aggregation are frequently responsible for arterial thromboembolism. The BVZ-induced VEGF suppression has the potential to alter vascular homeostasis, which could lead to a reduction in the stability of atherosclerotic plaques. This can then result in plaque rupture and a decrease in the synthesis of essential VEGF-stimulated platelet inhibitors such NO and PGI2. As a result, arterial thrombosis might be encouraged.[12–14]

Anthracyclines - Doxorubicin

Anthracyclines (ANT) are a significant group of cancer-fighting medications that were created in the 1970s. Within the ANT class, there are drugs like Doxorubicin (DOX) and Daunorubicin (DNR) that are considered non-specific chemotherapy agents, affecting the cell cycle. Presently, these drugs have been widely used in medical settings. They possess a wide range of effectiveness against various malignant tumors, such as lung cancer, breast cancer, and lymphoma. They are an essential part of many chemotherapy treatment plans.

DOX Significantly Increases the Incidence of Heart Failure

Von Hoff et al conducted a retrospective analysis involving more than 4000 patients who received DOX treatment. The analysis revealed a significant increase in the risk of heart failure when the cumulative dose of DOX reached 550 mg/m^2. Previous studies[15,16] have identified DOX as a primary factor contributing to ANT-induced heart failure. To further investigate the incidence of DOX-associated congestive heart failure (CHF), three clinical trials were conducted between 1988 and 1992. The results indicated that CHF occurred in 5% of patients when the cumulative dose of DOX reached 400 mg/m^2, 16% at 500 mg/m^2, and 26% at 550 mg/m^2. Notably, even patients who received as little as 240 mg/m^2 of DOX showed histopathological alterations in their endometrial biopsy samples. Studies[17,18] have also reported impaired cardiac function in individuals administered doses as low as 100 mg/m^2. These findings suggest that the administration of any dosage level of ANT may not be considered safe, emphasizing the relevance of an individual's susceptibility to myocardial damage.

DOX exerts its cytotoxic effects on tumors by inhibiting the activity of recombinant topoisomerase (Top), as stated in reference.[19] (see Figure 2) In cells that have completed cell division (post-mitotic cells), such as adult cardiomyocytes, the expression of Top IIβ is high, while Top IIα is not expressed.[20] Top IIβ is found in the nucleus and mitochondria.[21] When DOX binds to Top IIβ and deoxyribonucleic acid (DNA),[22] it forms protein DNA adducts, which cause double-strand breaks in both nuclear DNA and mitochondrial DNA. This leads to the activation of DNA damage and apoptotic responses.[23] DOX acts quickly by integrating into mitochondrial DNA, thereby inhibiting its synthesis and depleting its levels (Figure 2). Mitochondrial DNA is a significant target for DOX, and its interaction with mitochondria may contribute to the development of cardiotoxicity associated with DOX administration.[24]

It is commonly acknowledged that the pathophysiology of cardiotoxicity caused by DOX is a complicated process involving several signaling channels and interactions between different cell types.[25]

DOX May Cause Ventricular Arrhythmias

Cardiac injury caused by ANT has been demonstrated through various mechanisms, such as autonomic nerve dysfunction, oxidative stress, mitochondrial damage, imbalance in iron metabolism, and inflammatory response. These pathways have been shown to potentially elevate the heart's electrical unpredictability, leading to the development of ventricular arrhythmia. However, the precise underlying mechanism remains incompletely understood.[26]

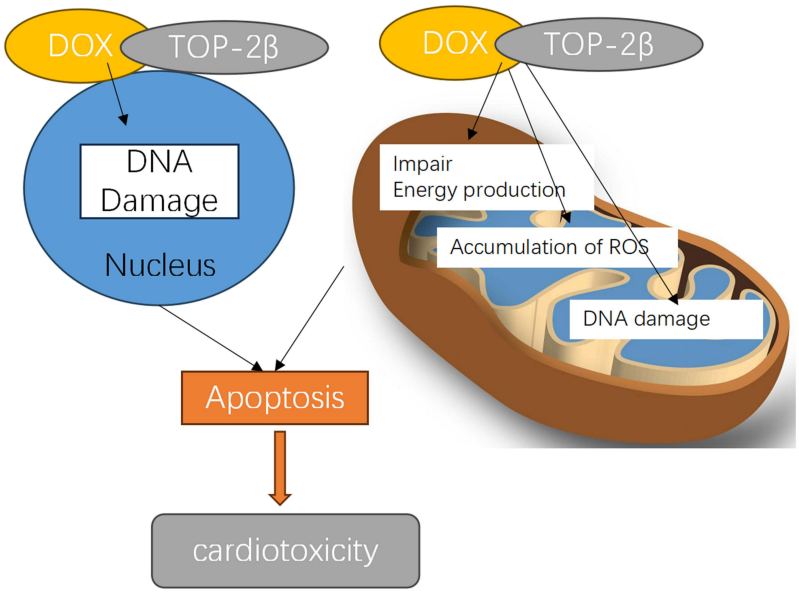

Figure 2 Schematic diagram of cardiotoxicity caused by anthracyclines.

HER2-Targeted Therapy - Trastuzumab

Trastuzumab is a type of monoclonal antibody that has been modified to specifically focus on the outer part of the human epidermal growth factor receptor-2 (HER-2). By attaching to the outer part of HER-2, this antibody selectively blocks the signaling pathways associated with HER-2. Currently, the medical community recognizes the importance of using Trastuzumab in postoperative adjuvant therapy and as the primary treatment for metastatic HER-2 positive breast cancer.

Trastuzumab Triggers Heart Failure and May Trigger Cardiomyopathy

The aim of this research is to evaluate the effectiveness of trastuzumab in breast cancer patients by conducting a critical Phase III clinical trial. The administration of trastuzumab yielded a noticeable improvement in the survival rate among the group of patients. However, it was observed that 27% of the patients who received trastuzumab developed heart failure, as mentioned in reference.[27] Several important clinical trials have confirmed the significant role of trastuzumab in improving cancer patients' survival rates. Nonetheless, these trials have also established a link between trastuzumab and heart failure, as demonstrated by studies.[11,28] Therefore, it is plausible to suggest that trastuzumab may contribute to the development of cardiomyopathy (see Figure 3).

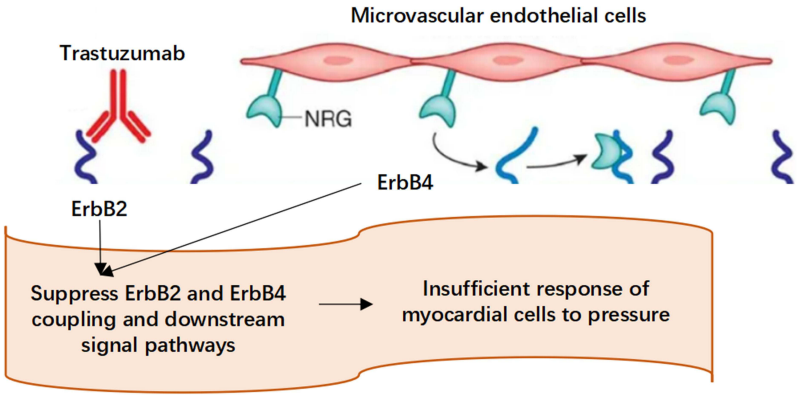

Figure 3 Schematic diagram of cardiac toxicity caused by trastuzumab.

Trastuzumab disrupts the communication pathway between HER-2 and HER-4 heterodimers that is activated by neuregulin-I. This pathway is important for the proper functioning of cardiomyocytes and the repair of heart damage. Neuregulin-I has been shown to have protective effects on the heart through several mechanisms. These include promoting the survival, growth, and reproduction of cardiomyocytes, maintaining a balance in the effects of beta-adrenergic signaling, regulating calcium levels, promoting angiogenesis, and encouraging the differentiation of stem cells into cardiomyocytes. Disrupting these signals could potentially impair heart function and lead to heart failure.[29] Trastuzumab has been shown to decrease the levels of an anti-cell death protein called B-cell lymphoma-xl (Bcl-xl) and increase the levels of a pro-cell death protein called Bcl-xs. This mechanism leads to the breakdown of the protective membrane of mitochondria, disruption of electron transport, generation of harmful free radicals, and reduced production of adenosine triphosphate (ATP), ultimately causing damage to heart muscle cells.[30] Additionally, it's important to note that trastuzumab can affect the function of mitochondria by influencing downstream signaling pathways activated by HER-2, such as the phosphatidylinositol 3-kinase (PI3K)-protein kinase B (AKT) and extracellular regulatory protein kinase (ERK)-mitogen-activated protein kinase (MAPK) pathways. Previous research has shown that damage and potential cell death can occur in myocardial microcells.[31]

In summary, trastuzumab disrupts the communication between HER-2 and HER-4 proteins, affecting the important neuregulin-I signaling pathway in cardiomyocytes. This disruption can hinder heart function, leading to heart failure. Trastuzumab also affects mitochondrial integrity and function, causing damage to heart muscle cells. These effects are mediated through various signaling pathways, including PI3K-AKT and ERK-MAPK.

Antimetabolic Drug - 5-Fluorouracil

5-Fluorouracil (5-FU) is an uracil derivative that contains a fluorine atom replacing the hydrogen atom at the 5' position. Although widely used as the main therapy for gastrointestinal cancers, either alone or in combination with other drugs, 5-FU demonstrates a relatively low success rate in terms of effectiveness. The reason behind this is the frequent occurrence of drug resistance in patients, leading to reduced efficacy.

The risk of myocardial ischemia caused by 5-FU is related to the dosage of medication, and coronary heart disease is a risk factor

Myocardial ischemia has been reported to occur in 1.2% to 1.6% of individuals receiving 5-FU medication, with some studies reporting a greater prevalence of up to 68%.[32–34] These findings demonstrate an increasing trend in correlation with the dosage administered, showing a rise of about 10% at a dose of 800 mg/m^2.[31] The frequency of this condition is notably higher in individuals with a previous history of coronary heart disease, exhibiting an increase of approximately 5 to 10 times compared to those without such a history.[35,36]

Cardiomyocytes and endothelial cells may potentially undergo apoptosis as a result of the cardiotoxicity caused by 5-FU, which might then result in the emergence of inflammatory lesions that resemble those seen in cases of toxic myocarditis. Regarding the effectiveness of this practice, there are still questions. Other potential mechanisms include increased hypercoagulability, immunological reactions, and direct myocardial damage.[37–39] In summary, the specific mechanism is still unknown.

Immunomodulatory Agent - Thalidomide

Originally introduced as a medicine for its ability to induce vomiting and promote sedation, Thalidomide, scientifically referred to as α-N-phthalimide-glutamine, was later discovered to possess immunosuppressive and antiangiogenic properties. These effects are achieved by inhibiting the uptake of inflammatory cells and reducing the production of cytokines such as tumor necrosis factor-α (TNF-α).[40,41] Thalidomide has proven to be an effective treatment for cancer and is now recognized as one of the anti-tumor drugs used in the management of multiple myeloma.[42]

Arrhythmias Caused by Thalidomide are Reversible

In a prospective analysis of 200 patients participating in a Phase III clinical trial for multiple myeloma, Fahdi et al discovered that a considerable number (53%) of patients who were given thalidomide treatment experienced bradycardia.

This outcome remained significant even after considering the impact of β-blockers or electrolyte imbalances. It is worth noting that 10% of these patients needed to undergo permanent pacemaker implants.[43]

It is believed that thalidomide works by blocking the production and function of TNF, which leads to an increased activity in the parasympathetic nervous system. This heightened activity can cause a slow heart rate known as bradycardia.[42] By decreasing the dosage or discontinuing thalidomide, the bradycardia can be reduced, suggesting that the heart rhythm disturbances caused by thalidomide may be reversible.

Thalidomide Promotes Venous Thrombosis

The use of thalidomide alone for treating myeloma patients carried a risk of developing venous thromboembolism (VTE) that was less than 5%. However, when thalidomide was used in combination with other chemotherapy treatments, the risk of adverse effects significantly increased. For instance, the incidence of thrombosis was estimated to be between 10–20% in patients receiving dexamethasone treatment,[44] and between 20–40% in patients receiving Adriamycin.[45,46] In Phase II clinical trials involving patients with metastatic renal cell carcinoma, who were treated with a combination of gemcitabine and continuous fluorouracil, VTE occurred in as many as 43% of the cases.[47]

Thalidomide-induced blood clots are not entirely recognized to be the result of a specific process. One hypothesis suggests that the combination of thalidomide and other chemotherapy drugs may harm endothelial cells, resulting in malfunction and increased blood clotting.[48] However, there is currently not enough empirical evidence to support this claim.

Platinum-Based Chemotherapy Drugs - Cisplatin

Platinoid medications belong to a group of drugs that are not specific to any particular stage of the cell cycle. Their main function is to trigger apoptosis, or programmed cell death, in tumor cells by hindering the process of DNA transcription and replication. Consequently, they demonstrate anti-cancer properties. Platinum-based chemotherapy drugs find wide application in medical settings for the treatment of different cancer types. These include lung cancer, bladder cancer, ovarian cancer, cervical cancer, esophageal cancer, stomach cancer, colorectal cancer, head and neck tumors, as well as other common malignant conditions.

Cisplatin Promotes Thrombosis

Individuals diagnosed with non-small cell lung cancer who received Cisplatin and Gemcitabine treatment experienced a higher occurrence of a condition, known as embolization, as observed in 17.6% of cases.[49] Among patients with invasive cervix, the occurrence of VTE was found to be 16.7% in those who underwent radiotherapy along with low-dose Cisplatin. Moreover, when Cisplatin was administered, the prevalence of ovarian cancer was recorded at 10.6%.[50] Additionally, there have been reports indicating a connection between Cisplatin and various thrombotic events such as stroke, recurrent peripheral artery thrombosis, and aortic thrombosis.[51]

The specific process responsible for the blood clotting effects of Cisplatin has not been thoroughly explored in existing literature. Studies have shown that the use of Cisplatin may activate platelets,[52] increase the presence of von Willebrand factor (vWF),[53] and cause endothelial cells to undergo apoptosis. This pathway ultimately leads to the release of procoagulant particles from the endothelial cells, which can generate thrombin via a pathway unrelated to tissue factor.

The main detrimental impacts of chemotherapy medications on the heart encompass high blood pressure, irregular heartbeat, cardiac insufficiency, and the development of blood clots, among other effects (see Table 1). While the causes of some of these conditions have been adequately understood, in certain cases, the first step is to recognize and identify adverse drug reactions. Exploring strategies for prevention, control, and treatment of these diseases is of utmost importance and warrants additional research.

The Comprehension and Management of Cardiotoxicity Induced by Chemotherapeutic Drugs in TCM

According to TCM theory, anticancer drugs have harmful effects on the cardiovascular system. Cardiovascular toxicity is a type of medication toxicity that might show itself as symptoms like palpitations and chest blockage. The absence of healthy Qi (essential energy) and the malfunction of Zang-Fu organs (internal organs) are the primary internal factors for

Table 1 The Effects and Cardiotoxicity of Commonly Used Chemotherapy Drugs

Chemotherapy Drugs	Indications	Adverse Reactions				
		Hypertension	Heart Failure	Thrombus	Arrhythmias	Cardiomyopathy
Bevacizumab (BVZ)	Mainly used for the treatment of various solid tumors such as metastatic colorectal cancer, non-small cell lung cancer, hepatocellular carcinoma, glioblastoma, ovarian cancer, fallopian tube cancer, peritoneal cancer, cervical cancer, etc	✓	✓	✓		
Doxorubicin (DOX)	Mainly used to treat acute leukemia, lymphoma, neuroblastoma, breast cancer, ovarian cancer and other malignant tumors		✓		✓	
Trastuzumab	Used to treat HER2 positive breast cancer and gastric cancer		✓			✓
5-fluorouracil (5-FU)	Mainly used to treat colorectal cancer, gastric cancer, breast cancer and other gastrointestinal tumors					✓
Thalidomide	Mainly used for the treatment of metastatic or unresectable gastrointestinal stromal tumors (GIST) and metastatic or unresectable pancreatic islet cell tumors			✓	✓	
Cisplatin	Mainly used to treat ovarian cancer, testicular cancer, bladder cancer cancer, head and neck cancer and other solid tumors			✓		

tumor development. The negative consequences of medication toxicity can be related to the decreased Qi and blood circulation in these organs. It is commonly acknowledged in TCM's Golden Mirror of Medicine that Qi defeats poison and has the power to control its effects. Ingesting poisons might result in an accumulation of Qi, which is necessary for the body's energy.

However, the accumulation of this condition can lead to the erosion of Qi and eventually its depletion. TCM states that the underlying cause of this illness lies in the weakening of healthy energy and the strengthening of pathogenic factors, resulting in a combination of deficiency and excess. TCM categorizes chemotherapy drugs as heat-toxic substances, which have the potential to deplete Qi and harm Yin. This is particularly worrisome for cancer patients who may already have impaired Qi and blood circulation, as well as symptoms such as weak Qi, Qi deficiency, blood stagnation, and damage to the heart and blood vessels. These symptoms can ultimately lead to cardiac toxicity.

Tonifying deficiency drugs were the most commonly employed in the prevention and treatment of chemotherapy-induced cardiotoxicity, followed by drugs that enhance blood circulation and remove blood blockages, alleviate internal heat, and warm internal coldness. The combined occurrence of these initial four drug categories constituted 76.7% of the overall frequency of usage. *Ginseng* and *astragalus* are well-known herbs in the field of replenishing Qi and are frequently utilized for tonifying deficiency. *Salvia miltiorrhiza* and *Ligusticum Chuanxiong* are commonly employed to improve blood circulation and eliminate blood stasis, while *sophora flavescens* is often used to alleviate internal heat.[54]

The management of cardiotoxicity involves addressing the development of TCM compound preparation, which is primarily characterized by a deficiency in Qi and Yin. The medications used in this treatment approach primarily aim to replenish Qi and Yin. Several commonly used basic formulas have been identified, including the prepared licorice decoction known as Zhigancao Decoction, the antioxidant prescription called Sanhuang, and the Qi and heart nourishing decoction known as Yiqi Yangxin Decoction.[55,56] TCM injections such as Xinmailong injection, Danshen injection containing Sulfotanshinone Sodium, Shenqi Fuzheng injection, and Sophora flavescens injection have been reported in the literature.[57]

Numerous studies have conducted thorough assessments of the harmful effects on the heart caused by Traditional Chinese Medicine (TCM) mixtures when used alongside chemotherapy drugs. Through a comprehensive analysis of multiple studies, it has been found that incorporating TCM mixtures into supplementary treatment alongside chemotherapy significantly enhances the parameters of cardiac function, myocardial enzyme spectrum, electrocardiogram, and cardiac color ultrasound for patients.[58]

The advantage of TCM in treating cardiotoxicity caused by chemotherapy drugs is that it can be individualized according to the patient's constitution, syndrome type and condition, regulate the overall balance of the body, and improve the body's tolerance and sensitivity to chemotherapy drugs. However, there are also many shortcomings. TCM treatment takes effect slowly, for which it is not suitable for acute or severe cardiac toxicity patients. At the present stage, there is a lack of unified standards and norms for TCM treatment, and there may be differences in medication among different doctors, which affects the evaluation and comparison of clinical effects. There is also a lack of sufficient evidence-based medical evidence to support the treatment of such diseases by TCM. Most studies are observational or retrospective studies, lacking high-quality randomized controlled trials and systematic reviews.

The study has some limitations. Most of the current research is limited to small-scale studies conducted in a single location. The goal of monitoring chemotherapy-induced heart toxicity is to reduce the occurrence of related illnesses and gather data on associated symptoms. Considering the underlying mechanism, it is expected that conducting larger-scale randomized controlled trials across multiple centers will advance the progress of research on this condition. Additionally, further studies investigating mechanisms of TCM in treating cardiotoxicity caused by common cancer drugs are needed.

Prospect

The problem of heart toxicity caused by chemotherapy medications is an urgent matter that requires immediate focus. To address the changing needs of the field, it is crucial not only to develop new ideas but also to reform existing treatment approaches. This requires a collaborative effort involving different fields of expertise. Currently, there is solid evidence demonstrating the heart toxicity caused by chemotherapy drugs. These effects can significantly affect a patient's quality of life and prognosis during or for years after chemotherapy ends. Both TCM and Western medicine have their own advantages and disadvantages in treating cardiotoxicity caused by chemotherapeutic drugs. Western medicine treatment mainly through drugs, physical and other means, to prevent or treat cardiotoxicity in different mechanisms. TCM treatment mainly regulates the balance of Yin and Yang of the body, enhances the anti-damage ability of the heart, and reduces the toxic side effects of chemotherapy drugs. TCM treatment has the characteristics of individualization, comprehensiveness and high safety, but its mechanism is not clear and clinical evidence is insufficient. At present, the pathogenesis of such diseases and the formulation of treatment plans have been investigated by traditional herbalist doctors, but the research is still more common in single-center with small sample. The future direction may be the combination of Chinese and western medicine to treat the cardiotoxicity caused by chemotherapy drugs, give full play to their respective advantages, and achieve the best treatment effect and minimal side effects. At present, some treatment schemes of integrated Chinese and western medicine have been evaluated in clinical trials, but more basic and clinical studies are needed to explore the optimal scheme and mechanism, and it is hoped that more large-scale randomized controlled studies with many centers can enrich the research progress of this disease.

Abbreviations

BVZ, Bevacizumab; VEGF, vascular endothelial growth factor; CHF, Chronic heart failure; PGI2, Prostacyclin I2; NO, Nitric Oxide; ANT, Anthracyclines; DOX, doxorubicin; HER-2, human epidermal growth factor receptor-2; Bcl, B-cell lymphoma; ATP, Adenosine triphosphate; PI3K, Phosphatidylinositol3-kinase; AKT, Australasian Kidney Trials; ERK, extracellular regulated protein kinases; MAPK, mitogen-activated protein kinase; 5-FU, 5-fluorouracil; DNA, DeoxyriboNucleic Acid; Top, Recombinant Topoisomerase; TNF-α, Tumour necrosis factor-α; VTE, Venous Thromboembolism.

Data Sharing Statement

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request. We declared that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki.

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Disclosure

The authors declare that they have no competing interests in this work.

References

1. Fu YH, Rao ZZ, Li RT, et al. Prediction of disease burden caused by malignant cancer in the context of risk factor control in China, 2030. *Chine J Epidemiol*. 2022;43(1):7. doi:10.3760/cma.j.cn112338-20210902-00705
2. Chang H-M, Moudgil R, Scarabelli T, Okwuosa TM, Yeh ETH. Cardiovascular Complications of Cancer Therapy: best Practices in Diagnosis, Prevention, and Management: part 2. *J Am Coll Cardiol*. 2017;70(20):2536–2551. doi:10.1016/j.jacc.2017.09.1096
3. Herrmann J. Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. *Nat Rev Cardiol*. 2020;17(8):474–502. doi:10.1038/s41569-020-0348-1
4. Dvorak HF. Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. *J Clin Oncol*. 2002;20(21):4368–4380. doi:10.1200/JCO.2002.10.088
5. Pavlidis ET, Pavlidis TE. Role of bevacizumab in colorectal cancer growth and its adverse effects: a review. *World J Gastroenterol*. 2013;19(31):5051–5060. doi:10.3748/wjg.v19.i31.5051
6. Hurwitz HI, Fehrenbacher L, Hainsworth JD, et al. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. *J Clin Oncol*. 2005;23(15):3502–3508. doi:10.1200/JCO.2005.10.017
7. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol*. 2005;23(4):792–799. doi:10.1200/JCO.2005.05.098
8. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 2004;22(11):2184–2191. doi:10.1200/JCO.2004.11.022
9. Laitinen M, Zachary I, Breier G, et al. VEGF gene transfer reduces intimal thickening via increased production of nitric oxide in carotid arteries. *Hum Gene Ther*. 1997;8(15):1737–1744. doi:10.1089/hum.1997.8.15-1737
10. Levy BI, Ambrosio G, Pries AR, et al. Microcirculation in hypertension: a new target for treatment? *Circulation*. 2001;104(6):735–740. doi:10.1161/hc3101.091158
11. Bird BR, Swain SM. Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. *Clin Cancer Res*. 2008;14:14–24. doi:10.1158/1078-0432.CCR-07-1033
12. Tsai HT, Marshall JL, Weiss SR, et al. Bevacizumab use and risk of cardiovascular adverse events among elderly patients with colorectal cancer receiving chemotherapy: a population-based study. *Ann Oncol*. 2013;24(6):1574–1579. doi:10.1093/annonc/mdt019
13. Zachary I, Gliki G. Signaling transduction mechanisms mediating biological actions of the vascular endothelial growth factor family. *Cardiovasc Res*. 2001;49(3):568–581. doi:10.1016/S0008-6363(00)00268-6
14. Meyer T, Robles-Carrillo L, Robson T, et al. Bevacizumab immune complexes activate platelets and induce thrombosis in FCGR2A transgenic mice. *J Thromb Haemost*. 2009;7(1):171–181. doi:10.1111/j.1538-7836.2008.03212.x
15. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med*. 1979;91:710–717. doi:10.7326/0003-4819-91-5-710
16. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer*. 2003;97(11):2869–2879. doi:10.1002/cncr.11407
17. Nysom K, Holm K, Lipsitz SR, et al. Relationship between cumulative anthracycline dose and late cardiotoxicity in childhood acute lymphoblastic leukemia. *J Clin Oncol*. 1998;16(2):545–550. doi:10.1200/JCO.1998.16.2.545
18. van der Pal HJ, van Dalen EC, Hauptmann M, et al. Cardiac function in 5-year survivors of childhood cancer: a long-term follow-up study. *Arch Intern Med*. 2010;170(14):1247–1255. doi:10.1001/archinternmed.2010.233
19. Bodley A, Liu LF, Israel M, et al. DNA topoisomerase II-mediated interaction of doxorubicin and daunorubicin congeners with DNA. *Cancer Res*. 1989;49(21):5969–5978.
20. Avci H, Epikmen ET, Ipek E, et al. Protective effects of silymarin and curcumin on cyclophosphamide-induced cardiotoxicity. *Exp Toxicol Pathol*. 2017;69(5):317–327. doi:10.1016/j.etp.2017.02.002
21. Iqubal A, Sharma S, Ansari MA, et al. Nerolidol attenuates cyclophosphamide-induced cardiac inflammation, apoptosis and fibrosis in Swiss Albino mice. *Eur J Pharmacol*. 2019;863:172666. doi:10.1016/j.ejphar.2019.172666
22. Abushouk AI, Ismail A, Salem AM, Afifi AM, Abdel-Daim MM. Cardioprotective mechanisms of phytochemicals against doxorubicin-induced cardiotoxicity. *Biomed Pharmacother*. 2017;90:935–946. doi:10.1016/j.biopha.2017.04.033
23. Gunes S, Sahinturk V, Karasati P, Sahin IK, Ayhanci A. Cardioprotective effect of selenium against cyclophosphamide-induced cardiotoxicity in rats. *Biol Trace Elem Res*. 2017;177:107–114. doi:10.1007/s12011-016-0858-1

24. Gazia MA, El-Magd MA. Ameliorative effect of cardamom aqueous extract on doxorubicin-induced cardiotoxicity in rats. *Cells Tissues Organs*. 2018;206(1–2):62–72. doi:10.1159/000496109
25. Songbo M, Lang H, Xinyong C, Bin X, Ping Z, Liang S. Oxidative stress injury in doxorubicin-induced cardiotoxicity. *Toxicol Lett*. 2019;307:41–48. doi:10.1016/j.toxlet.2019.02.013
26. Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of anthracyclines. *Front Cardiovasc Med*. 2020;7:26. doi:10.3389/fcvm.2020.00026
27. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344(11):783–792. doi:10.1056/NEJM200103153441101
28. Hudis CA. Trastuzumab–mechanism of action and use in clinical practice. *N Engl J Med*. 2007;357(1):39–51. doi:10.1056/NEJMra043186
29. Dias A, Claudino W, Sinha R, et al. Human epidermal growth factor antagonists and cardiotoxicity—a short review of the problem and preventative measures. *Crit Rev Oncol Hematol*. 2016;104:42–51. doi:10.1016/j.critrevonc.2016.04.015
30. Albini A, Cesana E, Donatelli F, et al. Cardio-oncology in targeting the HER receptor family: the puzzle of different cardiotoxicities of HER2 inhibitors. *Future Cardiol*. 2011;7(5):693–704. doi:10.2217/fca.11.54
31. Nemeth BT, Varga ZV, Wu WJ, et al. Trastuzumab cardiotoxicity: from clinical trials to experimental studies. *Br J Pharmacol*. 2017;174 (21):3727–3748. doi:10.1111/bph.13643
32. de Forni M, Malet-Martino MC, Jaillais P, et al. Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. *J Clin Oncol*. 1992;10(11):1795–1801. doi:10.1200/JCO.1992.10.11.1795
33. Meyer CC, Calis KA, Burke LB, Walawander CA, Grasela TH. Symptomatic cardiotoxicity associated with 5-fluorouracil. *Pharmacotherapy*. 1997;17(4):729–736. doi:10.1002/j.1875-9114.1997.tb03748.x
34. Robben NC, Pippas AW, Moore JO. The syndrome of 5-fluorouracil cardiotoxicity. An elusive cardiopathy. *Cancer*. 1993;71(2):493–509. doi:10.1002/1097-0142(19930115)71:2<493::AID-CNCR2820710235>3.0.CO;2-C
35. Labianca R, Beretta G, Clerici M, Fraschini P, Luporini G. Cardiac toxicity of 5-fluorouracil: a study on 1083 patients. *Tumori*. 1982;68:505–510. doi:10.1177/030089168206800609
36. Schober C, Papageorgiou E, Harstrick A, et al. Cardiotoxicity of 5-fluorouracil in combination with folinic acid in patients with gastrointestinal cancer. *Cancer*. 1993;72(7):2242–2247. doi:10.1002/1097-0142(19931001)72:7<2242::AID-CNCR2820720730>3.0.CO;2-E
37. Frickhofen N, Beck FJ, Jung B, Fuhr HG, Andrasch H, Sigmund M. Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil. *Ann Oncol*. 2002;13(5):797–801. doi:10.1093/annonc/mdf035
38. Saif MW, Tomita M, Ledbetter L, Diasio RB. Capecitabine-related cardiotoxicity: recognition and management. *J Support Oncol*. 2008;6(1):41–48.
39. Kosmas C, Kallistratos MS, Kopterides P, et al. Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. *J Cancer Res Clin Oncol*. 2008;134(1):75–82. doi:10.1007/s00432-007-0250-9
40. D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci U S A*. 1994;91(9):4082–4085. doi:10.1073/pnas.91.9.4082
41. Moreira AL, Sampaio EP, Zmuidzinas A, Frindt P, Smith KA, Kaplan G. Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. *J Exp Med*. 1993;177:1675–1680. doi:10.1084/jem.177.6.1675
42. Barlogie B, Desikan R, Eddlemon P, et al. Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: identification of prognostic factors in a Phase 2 study of 169 patients. *Blood*. 2001;98(2):492–494. doi:10.1182/blood.V98.2.492
43. Fahdi IE, Gaddam V, Saucedo JF, et al. Bradycardia during therapy for multiple myeloma with thalidomide. *Am J Cardiol*. 2004;93(8):1052–1055. doi:10.1016/j.amjcard.2003.12.061
44. Zangari M, Anaissie E, Barlogie B, et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. *Blood*. 2001;98(5):1614–1615. doi:10.1182/blood.V98.5.1614
45. Zangari M, Siegel E, Barlogie B, et al. Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy. *Blood*. 2002;100(4):1168–1171. doi:10.1182/blood-2002-01-0335
46. Desai AA, Vogelzang NJ, Rini BI, Ansari R, Krauss S, Stadler WM. A high rate of venous thromboembolism in a multi-institutional phase II trial of weekly intravenous gemcitabine with continuous infusion fluorouracil and daily thalidomide in patients with metastatic renal cell carcinoma. *Cancer*. 2002;95(8):1629–1636. doi:10.1002/cncr.10847
47. Kaushal V, Kohli M, Zangari M, Fink L, Mehta P. Endothelial dysfunction in antiangiogenesis-associated thrombosis. *J Clin Oncol*. 2002;20 (13):3042. doi:10.1200/JCO.2002.20.13.3042
48. Numico G, Garrone O, Dongiovanni V, et al. Prospective evaluation of major vascular events in patients with nonsmall cell lung carcinoma treated with cisplatin and gemcitabine. *Cancer*. 2005;103(5):994–999. doi:10.1002/cncr.20893
49. Jacobson GM, Kamath RS, Smith BJ, Goodheart MJ. Thromboembolic events in patients treated with definitive chemotherapy and radiation therapy for invasive cervical cancer. *Gynecol Oncol*. 2005;96(2):470–474. doi:10.1016/j.ygyno.2004.10.023
50. Apiyasawat S, Wongpraparut N, Jacobson L, Berkowitz H, Jacobs LE, Kotler MN. Cisplatin induced localized aortic thrombus. *Echocardiography*. 2003;20(2):199–200. doi:10.1046/j.1540-8175.2003.03002.x
51. Togna GI, Togna AR, Franconi M, Caprino L. Cisplatin triggers platelet activation. *Thromb Res*. 2000;99(5):503–509. doi:10.1016/S0049-3848(00) 00294-2
52. Cool RM, Herrington JD, Wong L. Recurrent peripheral arterial thrombosis induced by cisplatin and etoposide. *Pharmacotherapy*. 2002;22 (9):1200–1204. doi:10.1592/phco.22.13.1200.33524
53. Licciardello JT, Moake JL, Rudy CK, Karp DD, Hong WK. Elevated plasma von Willebrand factor levels and arterial occlusive complications associated with cisplatin-based chemotherapy. *Oncology*. 1985;42:296–300. doi:10.1159/000226049
54. Lv XF, Wen RQ, Liu K, et al. Role and molecular mechanism of traditional Chinese medicine in preventing cardiotoxicity associated with chemoradiotherapy. *Front Cardiovasc Med*. 2022;9:1047700. doi:10.3389/fcvm.2022.1047700
55. Sagaonkar PS, Pattanshetty R. Effect of medical qigong therapy on distress, fatigue, and quality of life in head and neck cancer patients undergoing intensity-modulated radiation therapy: a single arm clinical trial. *World J Tradit Chin Med*. 2021;7:427–435. doi:10.4103/wjtcm.wjtcm_15_21
56. Zheng XY, Zhang YH, Song WT, Chang D, Liu JX. Research progress on the pharmacological mechanisms of Chinese medicines that tonify Qi and activate blood against cerebral ischemia/ reperfusion injury. *World J Tradit Chin Med*. 2022;8:225–235. doi:10.4103/wjtcm.wjtcm_21_21
57. Guo D, Cai Y, Chai D, et al. The cardiotoxicity of macrolides: a systematic review. *Pharmazie*. 2010;65(9):631–640.
58. Bhagat A, Kleinerman ES. Anthracycline-Induced Cardiotoxicity: causes, Mechanisms, and Prevention. *Adv Exp Med Biol*. 2020;1257:181–192.