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Review article

# Role of oxidative stress in cardiotoxicity of antineoplastic drugs

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ABSTRACT

Tumors and heart disease are two of the leading causes of human death. With the development of anti-cancer therapy, the survival rate of cancer patients has been significantly improved. But at the same time, the incidence of cardiovascular adverse events caused by cancer treatment has also been considerably increased, such as arrhythmia, left ventricular (LV) systolic and diastolic dysfunction, and even heart failure (HF), etc., which seriously affects the quality of life of cancer patients. More importantly, the occurrence of adverse events may lead to the adjustment or the cessation of anti-cancer treatment, which affects the survival rate of patients. Understanding the mechanism of cardiotoxicity (CTX) induced by antineoplastic drugs is the basis of adequate protection of the heart without impairing the efficacy of antineoplastic therapy. Based on current research, a large amount of evidence has shown that oxidative stress (OS) plays an essential role in CTX induced by antineoplastic drugs and participates in its toxic reaction directly and indirectly. Here, we will review the mechanism of action of OS in cardiac toxicity of antineoplastic drugs, to provide new ideas for researchers, and provide further guidance for clinical prevention and treatment of cardiac toxicity of anti-tumor drugs in the future.

## 1. Introduction

Cancer is the leading cause of death, shortening life expectancy, and ranking first or second in most countries, according to statistical data from the World Health Organization (WHO) in 2015 [1]. The World Cancer Report 2014, released in 2015, represents a series of the volume that began in 2003 when it was estimated that 5.3 million men and 4.7 million women had malignant tumors each year, of which 6.2 million died of the disease. In 2014, it was determined that 14.1 million people have cancer each year [2]. With the development of medical research and modern equipment, the methods and techniques of tumor therapy have been greatly improved, and the survival rate of cancer patients has been significantly increased [3]. But at the same time, a variety of treatment methods can also lead to multiple complications. The cardiotoxicity (CTX) is not only the most critical adverse reaction of antineoplastic drugs but also the primary cause of increased mortality of tumor survivors, which directly affects the efficacy of anti-tumor drugs [4]. Currently, the antineoplastic drugs, including anthracyclines (ANTs), alkylating agents, anti-microtubules, antimetabolites, metal platinum drugs, and new molecular targeted drugs all have certain CTX [5,6].

The CTX of antineoplastic drugs has become a “heart disease” for oncologists. Therefore, “cardio-oncology” has attracted a lot of attention of scholars as a hot issue in the field of cancer and cardiovascular disease (CVD). In recent years, the mechanism of CTX induced by antineoplastic drugs is still not completely clear [7], but the relationship between oxidative stress (OS) and CTX has attracted more and more attention of scholars. A large number of data have confirmed that OS is closely related to CTX induced by antineoplastic drugs [8]. Therefore, this paper reviews the role of OS in CTX of antineoplastic drugs.

## 2. Cardiotoxicity of antineoplastic drugs

The CTX of antineoplastic drugs mainly includes myocardial

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damage, hypertension, left ventricular (LV) systolic and diastolic dysfunction, heart failure(HF), thrombosis, pericardial disease, myocardial ischemia, arrhythmia and vasospasm [5,8–10]. The exact definition of CTX of tumor therapy is: (1) cardiomyopathy with reduced left ventricular ejection fraction(LVEF), which is characterized by decreased overall function or decreased ventricular septal motion; (2) symptoms associated with congestive heart failure(CHF); (3) related signs of HF, such as S3 gallop, tachycardia, or both; (4) decline in initial LVEF of at least 5% to < 55% with signs and symptoms of heart failure or asymptomatic decrease in LVEF of at least 10% to < 55% [11]. According to the 2016 Position Paper of the European Society of Cardiology(ESC), the relevant LVEF of CTX was defined as a decrease of higher than10% to a value below the lower limit of normal of < 50% [12].

The CTX is generally manifested as acute or chronic: acute toxicity is characterized by ventricular or supraventricular arrhythmias, which usually occurs within 2 weeks after the end of treatment; chronic toxicity is characterized by asymptomatic LV systolic and diastolic dysfunction [11,13]. The chronic toxicity can be divided into two subtypes based on clinical symptoms, one occurs earlier, within 1 year after termination of chemotherapy; the other occurs later, appears after 1 year of chemotherapy termination. The chronic CTX can develop into severe congestive cardiomyopathy leading to death [11,13]. Traditionally, according to the effects on the myocardial cell, the CTX is classified into type I and II. Type I is associated with irreversible cardiac cell damage, and it is generally caused by ANTs and traditional chemotherapeutic drugs. Type II is usually caused by new biological agents and more targeted medicines, and it is connected with reversible myocardial dysfunction [8,14]. Riccio et al.'s research contradicts traditional views. The cardiomyopathy type I (related to ANTs) was thought to be irreversible while it has been shown that this form of cardiomyopathy can also revert. Moreover, the cardiomyopathy type II (related to trastuzumab and other targeted therapies) would be characterized by reversibility when, on the other hand, it has been demonstrated that in a non-negligible percentage of cases, it does not reverse [15]. Therefore, in the future, we can conduct a more extensive study on the reversibility of CTX induced by various antineoplastic drugs to clarify the correlation.

## 3. Oxidative stress

In cells and tissues, oxidative stress (OS) is caused by the imbalance between the production and accumulation of reactive oxygen species (ROS) and the ability of biological systems to detoxify these products [16]. ROS are normally generated as by-products of oxygen metabolism, or by nicotinamide adenine dinucleotide phosphate (NAPDH) oxidase and xanthine oxidase(XOR), although they could be formed by exogenous stimuli such as UV light, etc. [16–18]. So in other words, OS is a state of imbalance between free radicals (or oxidants) and antioxidants in favor of former, leads to disruption of redox signaling and physiological function [19]. Peroxidation usually denotes a process of oxidation of lipids generating reactive aldehydes and other products known as “second messengers of OS” [20]. In order to resist the excessive production of ROS and limit the peroxidative activity of ROS, the body activates the primary antioxidant defense system composed of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), as well as the secondary antioxidant system composed of glutathione (GSH) [21,22].

When the balance of free radicals (or oxidants) and antioxidants is destroyed, it leads to changes in cell structure, and even damage cell membranes, lipoprotein, and DNA, promote apoptosis or necrosis, etc., resulting in aging, cancer, cardiovascular diseases (CVDs) and inflammatory bowel disease (IBD) and other diseases [16,23–27]. One study has shown that increased oxidant production and decreased antioxidant enzymes mediated by Nrf2/EpRE signaling are involved in aging [23]. In the early stage of atherosclerosis (AS), endothelial cell inflammation leads to the in situ collections of ROS, which oxidizes circulating LDL leading to foam cell formation and lipid accumulation, and induces plaque formation [16]. Another study has shown that excessive accumulation of ROS in myocardial cells damaged by hypoxia and myocardial ischemia/reperfusion (MI/R) produces various toxic effects on cells [28,29]. ROS produced by bone marrow cells drive to epithelial cell mutations, regulate T cell responses, and promote tumor progression [24,30]. Also, ROS can aggravate tumor development by mediating angiogenesis, cell proliferation, and apoptosis-related genes and DNA damage [31]. Thus, OS is involved in the event of tumor and CVDs. The antineoplastic drug doxorubicin (DOX) by cardiomyocyte toxicity is associated with increased ROS production and cell death [32]. Zhao L et al. found that the DOX-induced myocardial oxidative damage toxicity and decreased H9c2 cell viability by regulating intracellular ROS, SOD, GSH, and GPx levels [33]. Another study found that DOX-induced oxidative DNA damage-ATM-p53-apoptosis pathway was mediating its CTX [34]. Besides, the heart progenitor cells (CPC) exposed to ANT showed that the formation of ROS increased and led to increased DNA damage, p53 expression, telomere attrition, and apoptosis, and led to cell cycle arrest during G2/M transition, which resulted in a significant decrease in CPC growth [35]. It can be seen that CTX caused by antineoplastic drugs is closely related to OS [8].

## 4. Antineoplastic drugs cardiotoxicity and oxidative stress

The clinical manifestations of CTX induced by antineoplastic drugs are complex and diverse, and their mechanisms of action are different [36,37]. Clinical manifestations including arrhythmia, myocardial ischemia, coronary artery disease(CAD), abnormal blood pressure, myocardial dysfunction, ECG and myocardial enzyme abnormalities, and even develop into HF [8,38]. Traditionally, there are two main anticancer drugs causing CTX: one is conventional chemotherapy drugs, including ANTs (DOX, epirubicin, daunorubicin, etc.), platinum drugs (cisplatin, carboplatin and oxaliplatin), alkylating agents (CY, isocyclophosphamide, etc.), anti-microtubule agents (vinblastine, paclitaxel), antimetabolic agents (5-FU), another is represented by molecular targeted drugs such as trastuzumab, etc. [8,14,39]. OS plays an important role in the CTX induced by antineoplastic drugs [8,22]. Reduction of myocardial oxygen and energy supply by absolute and relative ischemia and hypoxia is an important factor in OS [40]. OS can also directly alter the structure and function of mitochondria (MT), leading to MT dysfunction, which leads to myocardial damage [41,42].

### 4.1. Anthracyclines

Anthracyclines (ANTs), a kind of anticancer compounds, have been widely used in the treatment of hematological malignancies and solid tumors. They come from Streptomyces [22,43]. The main members of ANTs include DOX, daunorubicin, and epirubicin [39]. They are one of the most effective anticancer drugs, but their clinical application is hindered by the risk of CTX [44]. The CTX induced by ANTs can be classified as acute, subacute, and chronic according to the time of occurrence [38,45]. Acute and subacute CTX can occur within hours of administration. Clinical manifestations include acute HF, pericarditis, myocarditis, supraventricular and ventricular dysrhythmias, or QT interval prolongation seen on the ECG, etc. [38,46,47]. These changes usually resolve spontaneously and do not affect the further use of ANTs [47]. Chronic CTX is the most common cumulative dose-dependent form, which can be divided into early onset and late onset [38]. The early onset occurred within 1 year of the cessation of ANTs, while the late onset occurred after 1 year of the termination of ANTs [38]. Clinically, the most typical feature is LV systolic dysfunction, which further develops into congestive cardiomyopathy, chronic HF and can lead to death in severe cases. Cardiomyopathy and chronic HF are irreversible, and they are life-threatening complications [38,48].

Although the pathogenesis of CTX induced by ANTs is complex, OS

certainly plays a role, which can be proved by the damage caused by ROS, such as lipid peroxidation, and the reduction of endogenous antioxidant defense level [49–51]. Though excessive ROS leads to oxidative modification of cell macromolecules, inhibits protein function, membrane damage, and apoptosis, cell death [41,49,52–54]. ROS is involved in cardiomyocyte death, leading to DOX-induced CTX [55]. Some studies have shown that DOX induces myocardial oxidative damage by regulating intracellular ROS, SOD, GSH, and other levels, significantly reducing the activity of H9c2 cells, inducing apoptosis of H9c2 cells, and eliminating ROS which can reduce apoptosis [33,55,56].ROS is a direct OS primer, including superoxide anion ($O_2\cdot^-$), hydroxyl (HO·), peroxyl ($RO_2\cdot$), alkoxyl (RO·), and hydrogen peroxide ($H_2O_2$) and so on [53]. It is a byproduct of cell metabolism, mainly derived from MT [53]. MT has been identified as an essential target of many drug toxicity, and one of the pathways of ANTs is to induce mitochondrial dysfunction by increasing ROS production [8,14]. As we all know, ANTs produces ROS production through multiple pathways. ANTs loses an electron to form a semiquinone free radical, an unpaired electron that binds to oxygen to form a $O_2\cdot^-$ [22]. $O_2\cdot^-$ forms $H_2O_2$ under the action of SOD disproportionation or spontaneous state [8,21,22]. $H_2O_2$ is a relatively stable and low toxic molecule, which can be scavenged by CAT or GPx under physiological conditions [21,22]. $H_2O_2$ and $O_2\cdot^-$ can produce more active and toxic HO·, but this reaction usually occurs slowly and occurs rapidly only under transition metal catalysis [22,49]. HO· has a very short half-life, high reactivity, and toxicity [22]. It can react with any nearby oxidizable compound, thereby causing damage to large molecules, including lipids, nucleic acids, and proteins [16,22,53]. Besides, compared with other tissues, the myocardium consumes more oxygen and has more MT, and its antioxidant enzymes such as GPx and SOD are relatively inadequate [57,58]. Therefore, the myocardium is more susceptible to ANTs dependent OS.

On the other hand, suitable flavoproteins can be used as catalysts that the semi-quinone radical was induced again to form ANTs through nicotinamide adenine dinucleotide (NADH) or reduced NADPH [22]. NADPH oxidase is another source of ANTs producing ROS [17]. Through this cycle, even a small dose of ANTs can produce more ROS [22]. Studies have shown that ANTs have a very high affinity for iron [59]. In the presence of free iron, ANTs can initiate a cycle of free radical production (redox cycle), and forms an anthracyclic-iron complex with iron [22]. Ichikawa et al. found that in cultured neonatal mice cardiomyocytes, DOX significantly reduced the level of mitochondrial protein ABCB8, which promotes iron output, and increased mitochondrial iron and ROS levels [60]. In addition, nitric oxide synthase (NOS) is also a source of ROS production, and NOS mainly includes endothelial nitric oxide synthase (eNOS), neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS) [49]. ANTs can bind directly to the eNOS reductase domain, grab an electron from NADPH, form a semiquinone structure, and transfer the electron to O2 to form $O_2^{\cdot-}$, resulting in myocardial cell damage [49,61].

### 4.2. Platinum drugs

Since the introduction of cisplatin in 1979, platinum antineoplastic drugs have been widely used in the clinical treatment of various malignant tumors [6,62]. So far, three platinum drugs (cisplatin, carboplatin, and oxaliplatin) have been used worldwide to treat cancer [63]. However, the side effects and drug resistance of platinum drugs also limit their clinical application. There are several reports of cardiotoxic events, especially cisplatin, including arrhythmia [6,63–66], angina, myocarditis, pericarditis, diastolic dysfunction, myocardial ischemia, acute myocardial infarction, thromboembolic events, hypertension, hypotension and HF [6,63–65,67,68]. The acute CTX of cisplatin is characterized by chest pain, palpitation, acute myocardial infarction, elevated cardiac enzymes biomarkers in the short term after administration [65]. At present, it is considered that the CTX of platinum drugs is dose-dependent [69]. Simultaneously, compared with ANTs, the CTX caused by cisplatin is usually silent and may not be detected, so the cardiotoxic effects of cisplatin may be ignored [6]. Therefore, in clinical practice, we should pay attention to the detection of the heart when using platinum drugs and carefully observe the symptoms and signs of the heart and the corresponding examination.

The specific mechanism of CTX represented by cisplatin is still unclear. Existing studies have confirmed that cisplatin-induced CTX is the result of multiple factors, including membrane transporter damage, OS and inflammation, cardiomyocyte apoptosis, and mitochondrial dysfunction [64–66,70]. These factors affect each other, cause and effect each other, and lead to the development of CTX [66,70]. Qian P et al. treated H9c2 cells with cisplatin and found that ROS accumulation increased, promoted membrane potential depolarization of MT, upregulated the expression of apoptosis regulator Bcl-2, and activated caspase 3, caspase 9, indicating that ROS-mediated apoptosis was involved in cisplatin-induced CTX [71]. The results of Zhang P et al. in H9c2 rat myocardial cell in vitro showed that cisplatin indeed promoted the accumulation of intracellular ROS and $O_2\cdot^-$, causing DNA damage in H9c2 cells, leading to apoptosis and significant CTX [72]. Rosic et al. showed that in the isolated hearts of cisplatin-treated rats, $H_2O_2$ increased and lipid peroxidation was observed [73]. Other studies have also demonstrated that GSH level and SOD system activity were debased in myocardial tissue of cisplatin-treated rats, malondialdehyde (MDA) is increased, lipid peroxidation, leading to myocardial cell injury [63,64,74]. A large body of evidence also indicates that cisplatin accumulates in MT, disrupting mitochondrial respiration, leading to excessive ROS production and mitochondrial dysfunction [64,66]. The critical target of platinum drugs is nuclear DNA, which forms adducts with cellular DNA as they enter cells, triggering a series of cell events, further inhibiting DNA synthesis, cell cycle, and replication, leading to MT, nuclear DNA damage and apoptosis [63,64]. It may be caused by the generation of free radicals and other lipid peroxidation, as well as the destruction of mitochondrial DNA, and the direct effect of cisplatin on myocardial protein metabolism, resulting in abnormal cardiac excitability and conduction function [75]. In short, OS is considered to be the primary mechanism of cisplatin-induced CTX [66].

### 4.3. Alkylating agents

Among all kinds of anticancer chemicals, alkylating agents is perhaps the most widely used [76]. Since the use of nitrogen mustard in the treatment of malignant lymphoma, alkylating agents have become the most important class of cancer chemotherapeutic drugs [77,78]. Cyclophosphamide (CY), as a representative of alkylating agents, can interfere with cell division in all rapidly proliferating tissues and has powerful anti-tumor, immunosuppressive, and immunomodulatory effects [77,78]. It is widely used in the treatment of human hematological malignancies and various solid tumors, such as breast cancer, lung cancer, lymphomas, myeloma, acute leukemia, and ovarian cancer as well as immunosuppressive therapy [78,79]. Although CY is widely used in the clinical practice of cancer, it is known to cause a variety of dose-dependent CTX [78]. It has been reported that high doses of CY can cause acute CTX, such as myopericarditis, pericarditis, cardiac tamponade, arrhythmia, myocardial infarction, cardiomyopathy, HF, and even hemorrhagic necrotizing pericarditis, with the risk of sudden death [76,78,80,81]. Also, Ejaz et al. reported that a 65-year-old patient with atrial fibrillation (AF) and rapid ventricular rate (RVR) after receiving a single dose of CY [79]. The morphological features of acute dose-dependent cardiac injury induced by CY are necrosis, hemorrhage, and fibrosis [76]. The CTX induced by CY also can be characterized by abnormal ECG, elevated serum creatine kinase MB (CK-MB), cardiac troponin I(cTnI), cardiac troponin T(cTnT) and lactate dehydrogenase (LDH) [80].

The exact mechanism of CY inducing CTX is not yet clear [80]. At present, a large number of studies have shown that excessive ROS,

increased OS and toxic metabolites (acrolein) that inhibit antioxidant defense mechanisms play vital roles in CY mediated CTX [78,80–83]. CY is metabolized to 4-hydroxycyclophosphamide (HCY) in the liver cytochrome P-450 enzyme system (CYP2B6 and/or CYP2C19), and it enters the cell as the form of aldocyclophosphamide (AldoCY). AldoCY can be converted to phosphamide mustard (PM) and acrolein by β-elimination or may be oxidized by aldehyde dehydrogenase 1 (ALDH1) to the inactive metabolite *o*-carboxyethyl-phosphoramide mustard (CEPM) [82,83]. Kurauchi K et al. found that H9c2 cells were exposed to CY metabolite HCY, acrolein or CEPM and that H9c2 cells did not cause cytotoxicity when exposed to CEPM, while HCY and acrolein inducing increased levels of ROS and myocardium cytotoxicity [82]. The metabolite acrolein interferes with the antioxidant system, producing high ROS radical and $O_2\cdot^-$ and $H_2O_2$ [76]. It was reported that another source of acrolein are these ROS and other free radicals leading to lipid peroxidation and eventually producing active aldehydes including acrolein [81,84]. Therefore, acrolein is considered to be a key substance in the formation and progression of the acrolein-ROS-aldehydes vicious cycle during CY induced CTX [81]. Also, Ogunsanwo et al. indicated significant consumption of antioxidants in the heart after CY treatment, such as GSH, CAT, and SOD, and lipid peroxidation increased [77]. Similarly, another study has also shown that CY treatment significantly reduces the activity of antioxidant enzymes, especially GSH, CAT, GPx and SOD, which may be related to the formation of ROS during the biological activity of CY, and then leads to the creation of $HO^{\bullet}$, lipid peroxidation and CTX [78].

### 4.4. Antimetabolites

Antimetabolites are effective antitumor drugs that interfere with essential biochemical processes [85]. Among them, 5-FU and its prodrug capecitabine are widely used in the treatment of several solid malignancies, including colorectal cancer, breast cancer, and head and neck cancer [85–87]. The most common toxicities of these drugs include gastrointestinal reactions such as abdominal pain, diarrhea, nausea, bone marrow suppression, and skin toxicity, which have been extensively studied clinically [85,87]. Although CTX induced by 5-FU is rare, it poses a potential threat to life, so the CTX caused by antimetabolite is attracting more and more attention [87]. The most common CTX associated with antimetabolites is an acute coronary syndrome, including myocardial infarction [88,89], arrhythmia [86,89,90], hypertension, hypotension, myocarditis, pericarditis, HF, and even death [87,89,91,92]. The most common clinical symptoms were chest pain, palpitations, dyspnea, and hypotension [87]. Among them, chest pain often manifests as atypical chest pain, angina during exercise, or rest [86].

The pathogenesis of this drug-induced CTX has not yet been fully elucidated [87]. Many researchers have shown that there are many mechanisms of CTX, such as the release of vasoconstrictor endothelin-1, neuromodulation of the adrenergic nervous system, injury of cardiac endothelial cells, thrombosis and immune hypersensitivity [87,93]. However, coronary artery spasm is considered to be the primary mechanism [93]. The pathogenesis of coronary artery spasm and secondary myocardial ischemia has been extensively studied, and the theory of endothelial cell injury has attracted full attention [86,87]. Vascular endothelial injury can also lead to CTX, and NOS in the endothelium causes coronary artery spasm and endothelium-dependent vasoconstriction via the protein kinase pathway [14,94]. There is a potential link between ROS and endothelial cells, and ROS is elevated in endothelial response [85]. Lamberti et al. research has shown that 5-FU drugs can also cause OS-induced myocardial cell injury [94]. Other studies have shown that in cardiac myocytes treated with 5-FU, ROS levels such as $O_2\cdot^-$ level increased, while SOD and GSH decreased. However, if the levels of SOD and GSH increased, endothelial cells can be protected from 5-FU inducing free radical mediating lipid peroxidation [86,87]. Depletion of cardiac SOD and GPx directly impair vascular endothelial cells by 5-FU mediated, which leads to thrombosis, the release of vasoactive substances and vasospasm [95].

### 4.5. Anti-microtubule agents

Microtubules are heterodimers formed by the tight junction of two tubulin subunits (α and β subunits). Usually, microtubules are dynamic polymers; that is, there is a dynamic equilibrium between microtubules and tubulin heterodimers, which is involved in mitosis and plays a vital role in many cellular functions [96]. Anti-microtubule drugs can be divided into two categories: one is paclitaxel, which promotes microtubule polymerization, and the other is vincristine and vinorelbine, which promotes microtubule depolymerization [97]. Microtubules are part of mitotic spindles. Anti-microtubule agents not only support cell division arrest but also promote cell apoptosis [96,97]. Paclitaxel and vincristine anti-microtubule drugs have been widely used in various tumor diseases, including breast cancer, non-small cell lung cancer, ovarian cancer, and lymphoma [14,98]. The CTX caused by anti-microtubule agents is relatively rare, but studies have shown that paclitaxel as an anti-microtubule agent can create a series of adverse cardiac reactions, such as asymptomatic reversible bradycardia, atrioventricular block, ventricular tachycardia, blood pressure changes, myocarditis, pericarditis, acute myocardial infarction, chronic HF and so on [14,99,100].

There are few studies on the mechanisms of CTX induced by anti-microtubule agents. According to clinical case reports, vinorelbine can cause acute cardiac ischemic events [101]. Yamada et al. have demonstrated that in many vascular injuries induced by vinorelbine, OS is produced by eliminating intracellular GSH and increasing ROS production in porcine aortic endothelial cells, and OS plays an important role in vinorelbine-induced cell damage [102]. However, the relationship between vinorelbine-induced acute myocardial ischemia events and OS has not been studied. Studies have also shown that injection of vincristine can lead to a decrease in activities of antioxidant enzymes such as SOD, CAT, and GPx [98]. And other results have suggested that myocardial endothelial cells are the main target of vincristine tubulin binding agent CTX, cell cycle arrest is the mechanism of this toxicity [103]. Alexandre et al. have already demonstrated that paclitaxel-induced early accumulation of $H_2O_2$ in A549 cells, which is cytotoxic to cells and induces tumor cell death [104]. Paclitaxel induces up-regulation of atypical G protein Gβ5 in the myocardium, and Gβ5 promotes the transformation of myofibroblasts, and its persistence contributes to pathological remodeling and CTX such as HF, which is related to OS [99]. But another study contradicts that it has argued paclitaxel, which stabilizes microtubules, protects adult mouse cardiomyocytes from $H_2O_2$ induced OS [97]. Simultaneously, short-term pretreatment with vincristine has a significant protective effect on adult mouse myocardial cells cultured under the acute OS. The possible mechanism is that when the microtubules are destroyed, the pro-survival signaling pathway is initiated, leading to increased phosphorylation of Akt, ERK, and GSK-3β and the decreased release of cytochrome C [97]. Therefore, it is necessary to conduct further studies to clarify the relationship between the CTX induced by anti-microtubule agents and OS, to help understand the role of OS in the CTX induced by anti-microtubule agents. Studies have also shown that paclitaxel can induce DOX to affect the heart and cause CTX, which may be associated with decreased drug clearance after combination therapy [105].

### 4.6. Molecular targeted drugs

Molecular targeted drugs are currently the most advanced drugs used to treat cancer. They are based on molecular biology, interfering with specific molecules necessary for tumor growth to prevent cancer cell growth. Trastuzumab is a humanized monoclonal antibody targeting human epidermal growth factor receptor 2 (HER2, also known as ErbB2), mainly used in breast cancer [106]. Although the incidence of

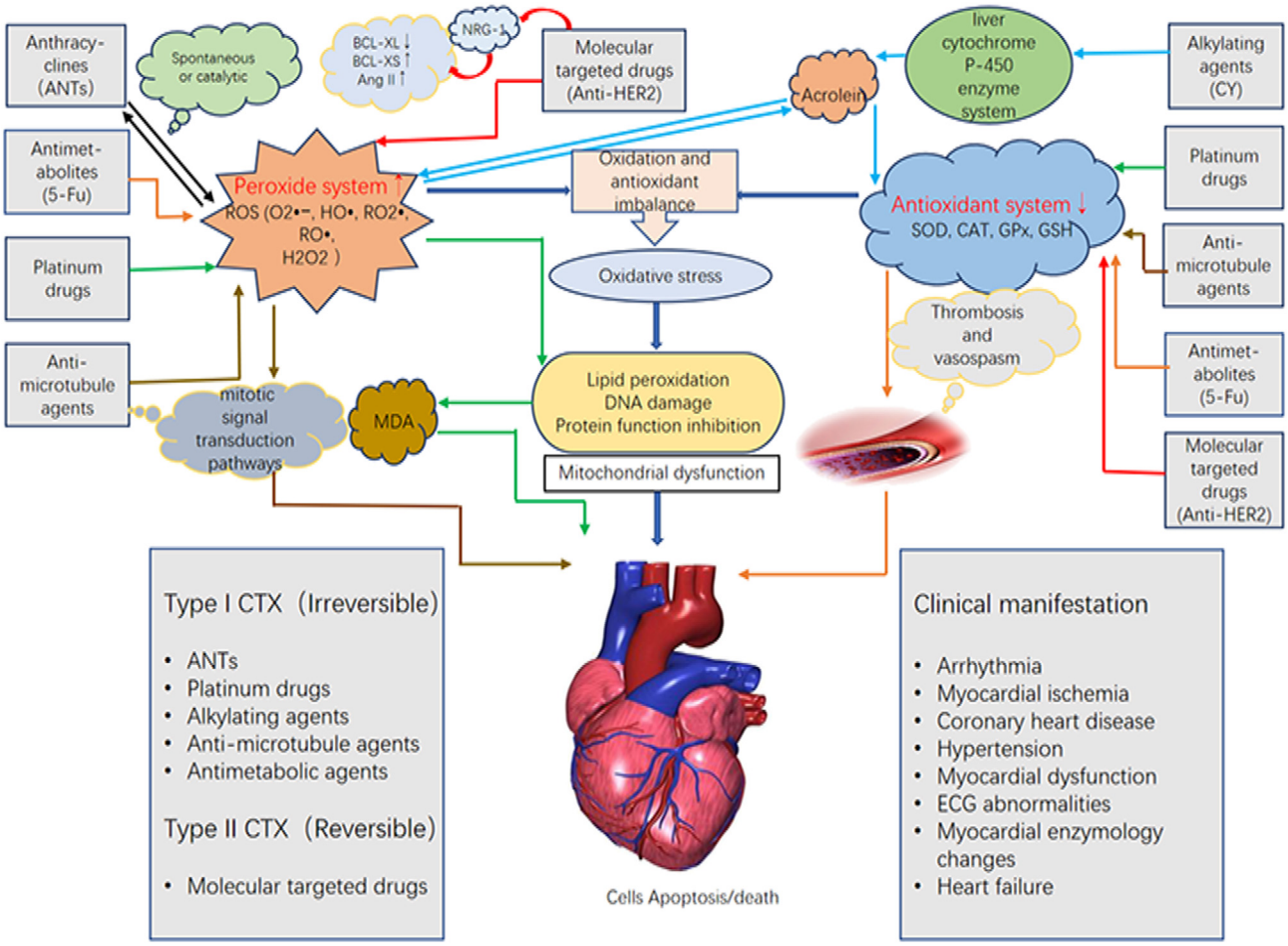


**Fig. 1.** Toxicity mechanism of oxidative stress induced by antineoplastic drugs on the heart. Please refer to each part of the drug for further explanation and acronyms.

adverse reactions of molecular targeted drugs anti-HER2 is lower than that of non-targeted drugs, the cardiovascular adverse reactions have also attracted the attention of oncology [107]. A large-scale clinical trial of adjuvant therapy with trastuzumab and a recent retrospective study in breast cancer patients have indicated that it may cause HF and cardiac dysfunction among many of treated patients [108]. Typically, most CTX caused by trastuzumab is reversible, that is, type II CTX [8,14], and is characterized by a decrease in symptomatic HF and/or subclinical asymptomatic LVEF [106,109–111]. The common ECG abnormalities are sinus tachycardia, sinus bradycardia, and ST-T segment changes [106]. Especially in the combination of trastuzumab and ANTs chemotherapy regimens, the incidence of CTX increased significantly [14,107,109,111,112].

The mechanism of CTX induced by target drug trastuzumab may be related to the inhibition of HER2 [107,113,114]. HER2 presents in cardiomyocytes, and its expression plays an essential role in normal cardiac stress response [115,116]. HER2 can regulate ROS signaling [116]. Preliminary studies have shown that HER2 can inhibit cardiomyocyte apoptosis, reduce ROS release, and up-regulate antioxidant enzymes through HER4, which is essential for maintaining the normal function of cardiomyocytes [115,117]. Without normal HER2 function, it can induce the accumulation of ROS, leading to myocardial dysfunction [115]. It can be seen that anti-HER2 is closely related to ROS [115]. Other studies have shown that trastuzumab related CTX is due to blocking the activation of HER2 mediated by neuroregulatory protein-1(NRG-1), downregulating the anti-apoptotic protein BCL-XL, up-regulating the pro-apoptotic protein BCL-XS which affects mitochondrial function, and up-regulating angiotensin II (Ang II) inducing apoptosis through AT1 receptor [107,117]. When trastuzumab is combined with ANTs, the protective mechanism of HEB2 will be blocked, and the oxidative damage will be more serious [116]. Goyal et al. have suggested that trastuzumab combined with ANTs could decrease cell integrity, increase OS, and increase cardiomyocyte apoptosis in mice [112]. Therefore, trastuzumab, combined with ANTs, is rarely used in clinical practice.

## 5. Conclusions and perspective

Current anti-tumor therapy has dramatically improved the survival of cancer patients, but whether ANTs, alkylating agents, antimetabolites, anti-microtubules, platinum drugs or new molecular targeted medicines have brought CTX [8,14,39]. OS is directly or indirectly involved in CTX induced by different anticancer drugs [8,22]. ANTs produce excessive ROS through various pathways, which leads to oxidative modification of cell macromolecules, induces mitochondrial dysfunction, inhibits protein function, promotes lipid peroxidation, membrane damage, apoptosis and myocardial cell death [22,41,49,52–54]. Cisplatin induces lipid peroxidation through the formation of superoxide radical and HO·, resulting in the elevation of MDA, mitochondrial dysfunction [63,64,74]. At the same time, the decrease of antioxidant GSH content and SOD system activity, and the formation of adducts with DNA after the drug enters the cell, which damages mitochondrial and nuclear DNA and results in cardiomyocyte apoptosis [63,64,66,74]. Acrolein, a toxic metabolite in CY induced CTX, is considered as a key substance in the formation and progression of the acrolein-ROS-aldehyde vicious cycle [81]. Acrolein can induce

excessive ROS production in CY and inhibit the defense mechanisms of antioxidant GSH, CAT, GPx, and SOD, leading to lipid peroxidation [76,78,81,83,84]. On the other hand, ROS and other free radicals undergo lipid peroxidation, and in turn, produce acrolein [81,84]. The two circulates to aggravate myocardial damage. The theory of coronary artery spasm, secondary myocardial ischemia, and endothelial cell injury play essential roles in the antimetabolite induced CTX [86,87]. Multiple factors contribute to myocardial damage. ROS increases in endothelial cell response [85], SOD and GPx activity decrease, which directly damages vascular endothelial cells [95]. NOS in endothelium induces coronary artery spasm and endothelium-dependent vasoconstriction via protein kinase pathway [94]. In the use of anti-microtubule agents, antioxidant enzyme activities decreased, such as SOD, CAT, and GPx, while ROS production increased [98,102]. Studies have suggested that myocardial endothelial cells are the main target of vincristine tubulin binding agents, which induce cell cycle arrest and cause CTX [103]. In targeted therapies such as trastuzumab, the normal function of HER2 is inhibited, resulting in ROS accumulation, down-regulation of antioxidant enzymes, mitochondrial dysfunction, and increased apoptosis of cardiac myocytes [115]. When trastuzumab is combined with ANTs, OS response is enhanced [112,116]. The mechanism of each part of the drug is summarized in Fig. 1.

At present, due to insufficient awareness of CTX of many chemotherapy regimens, the mechanism of action and the degree of CTX reversibility are not well understood, which hinders the possibility of improving the prognosis. The preventive and therapeutic effects of ACE inhibitors, beta blockers, and statins on CTX need to be studied in more extensive clinical trials. The role and pathological mechanism of OS in many tumor drug-induced CVD still have some unsolved problems, such as how to intervene OS and make it transfer to cardiomyocyte, which needs further study. In conclusion, OS plays an important role in the occurrence and development of CTX induced by various antineoplastic drugs, and its pathological mechanism deserves further study to avoid or reduce the cardiac injury to tumor patients, guide clinical rational drug use and improve the prognosis of patients.

## Declaration of Competing Interest

There is no conflict of interest among the authors.

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