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REVIEW

Cardiotoxicity of Anticancer Drugs: Molecular Mechanisms, Clinical Management and Innovative Treatment

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Abstract: With the continuous refinement of therapeutic measures, the survival rate of tumor patients has been improving year by year, while cardiovascular complications related to cancer therapy have become increasingly prominent. Exploring the mechanism and prevention strategy of cancer therapy-related cardiovascular toxicity (CTR-CVT) remains one of the research hotspots in the field of Cardio-Oncology in recent years. Cardiotoxicity of anticancer drugs involves heart failure, myocarditis, hypertension, arrhythmias and vascular toxicity, mechanistically related to vascular endothelial dysfunction, ferroptosis, mitochondrial dysfunction and oxidative stress. To address the cardiotoxicity induced by different anticancer drugs, various therapeutic measures have been put in place, such as reducing the accumulation of anticancer drugs, shifting to drugs with less cardiotoxicity, using cardioprotective drugs, and early detection. Due to the very limited treatments available to ameliorate anticancer drugs-induced cardiotoxicity, a few innovations are being shifted from animal studies to human studies. Examples include mitochondrial transplantation. Mitochondrial transplantation has been proven to be effective in in vivo and in vitro experiments. Several recent studies have demonstrated that intercellular mitochondrial transfer can ameliorate doxorubicin(DOX)-induced cardiotoxicity, laying the foundation for innovative therapies in anticancer drugs-induced cardiotoxicity. In this review, we will discuss the current status of anticancer drugs-induced cardiotoxicity in terms of the pathogenesis and treatment, with a focus on mitochondrial transplantation, and we hope that this review will bring some inspiration to you.

Keywords: cancer therapy-related cardiovascular toxicity, CTR-CVT, mitochondrial dysfunction, oxidative stress, ferroptosis, mitochondrial transplantation

Introduction

Continuously updated therapeutic measures have improved the prognosis of patients with malignant tumors. However, many anticancer drugs exhibit interactions with cardiovascular signals that produce serious side effects, and proper management may be crucial to ultimately improve the longevity and quality of life of cancer patients. The potential for cardiovascular adverse effects during cancer therapy has led to the emergence of the discipline of Cardio-Oncology. This discipline focuses on preventing and treating cardiac problems that may occur during cancer therapy, thereby reducing the incidence of related complications and mortality. For patients suffering from cardiovascular diseases, the Cardio-Oncology specialty provides a one-stop comprehensive management program to improve the patient's outcome and quality of life. With the continuous development of Cardio-Oncology, more and more doctors have begun to recognize the association between cancer and heart disease, which has contributed to the popularity and development of this discipline. Public awareness of the discipline of Cardio-Oncology is also gradually increasing.

Cancer treatment-related cardiotoxicity was first defined in the 2022 European Society of Cardiology Guidelines for Cardiac Oncology, which explicitly define cancer therapy-related cardiac dysfunction/heart failure(CTRCD), Immune checkpoint inhibitors(ICIs) myocarditis, hypertension, arrhythmias and vascular toxicity.[1]

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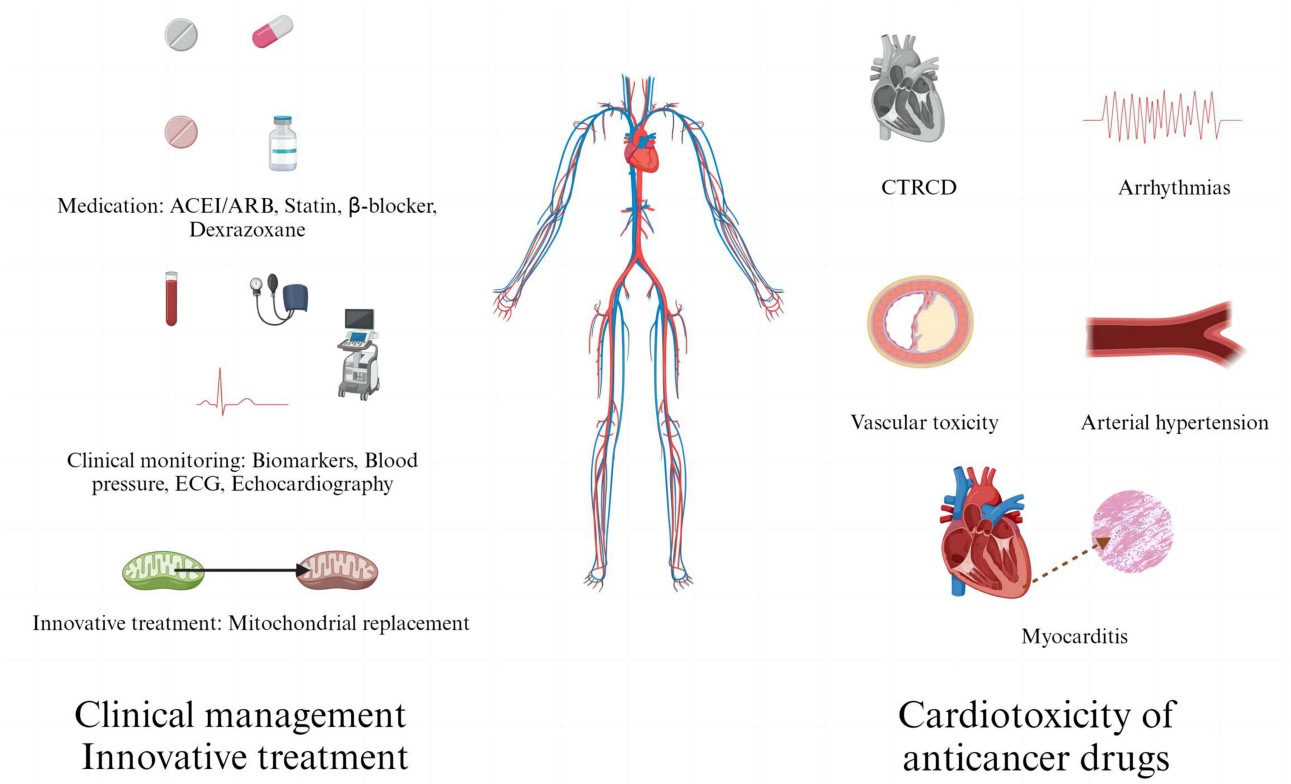
Graphical Abstract



Anthracyclines such as doxorubicin and drugs targeting the human epidermal growth factor receptor 2 (HER/ErbB2), which are representative drugs for the treatment of breast cancer, have cardiotoxicity that manifests mainly as CTRCD.[2,3] ICIs are mainly cytotoxic T lymphocyte-associated protein 4 (CTLA-4) inhibitors and proteins programmed cell death 1 (PD-1) inhibitors, whose main cardiotoxicity is myocarditis.[4] The vascular endothelial growth factor (VEGF)-targeted drugs include mainly monoclonal antibodies and tyrosine kinase inhibitors (TKIs), which often lead to hypertension.[5] Other common anticancer drugs such as paclitaxel, fluorouracil and proteasome inhibitors often lead to arrhythmias and vascular toxicity.[6–8]Anticancer drugs-induced cardiotoxicity is categorized as Type I or Type II, depending on whether the resulting cardiotoxicity is reversible or not. Type I refers to the irreversible cardiotoxicity, such as anthracyclines commonly used in clinical practice. Type II refers to reversible cardiotoxicity, which can be effectively alleviated by timely intervention.[9] However, the serious cardiotoxicity associated with trastuzumab belonging to type II is irreversible; therefore, the reliability of this typology remains to be considered.[9]

In response to cardiotoxicity, there are no superior measures to improve the prognosis of cardiotoxicity, which is currently treated symptomatically. Once the patient is monitored for abnormal LVEF and biomarkers, cardioprotection such as ACEI/ARB needs to be administered immediately.[1] The side effects of the ACEI/ARB itself may slow the heart rate and lower blood pressure in cancer patients. Cancer patients may already have an abnormal heart rate or abnormal blood pressure due to cancer or anti-cancer treatments, and an ACEI/ARB may worsen these symptoms. Similarly, there is a paucity of research on the safety and efficacy of β-blocker and statins in cancer patients, and the inherent side effects of both drugs make it impossible to determine the ultimate degree of benefit to patients[10–12] (Table 1). Dexrazoxane is a promising cardioprotective agent for anthracycline-induced cardiotoxicity, but its side effects limit its use.[13] Dexrazoxane interferes with anthracycline binding to topoisomerase 2β, which prevents cardiac damage without disturbing the antitumour efficacy of anthracyclines.[14] However, a report from the International Late Effects of Childhood Cancer Guideline Harmonisation Group states that in 13 randomised trials of dexrazoxane (in five paediatric and eight adult studies), dexrazoxane was able to prevent or reduce cardiac damage in adult patients treated with

Table 1 Summary of Anticancer Drugs-Induced Cardiotoxicity

Drugs	Cardiotoxicity	Prevention	Reference
Anthracyclines	LV dysfunction/HF	Liposomal anthracycline Dexrazoxane	[1,16]
HER2 Inhibitors	LV dysfunction	ACEI/ARB β-blockers	[17–19]
Immune checkpoint inhibitors	Immune myocarditis	Haemodynamically unstable:1000 mg of methylprednisolone daily.	[1,20–24]
VEGF Inhibitors and Multi-Targeted Kinase Inhibitors	Hypertension LV dysfunction Vascular toxicity	Daily home blood pressure monitoring during the first treatment cycle, and every 2–3 weeks thereafter for patients treated with VEGFi. BP ≥140/90 mmHg:receive antihypertensive therapy.	[1,25–28]
TKIs and Anti-BCR-ABL Agents	Cardiac dysfunction QTc prolongation	Discontinuation of chemotherapy Aspirin and statin	[1,29]
Taxanes	Bradycardia LV dysfunction Ischemia	Cortisol Antihistamines	[30–35]
Fluorouracil	Coronary spasms/ischemia	Discontinuation of chemotherapy Calcium channel blockers or nitrates	[36–40]
Proteasome inhibitors	LV dysfunction	ACEI/ARB β-blockers	[1,41,42]

Abbreviations: LV, left ventricle; HF, heart failure; HER2, human epidermal growth factor receptor 2;VEGF, vascular endothelial growth factor; TKIs, tyrosine kinase inhibitors.

anthracyclines; whereas, in children, there was only one difference in cardiac outcome between treatment groups (clinical heart failure and subclinical myocardial dysfunction) to support the role of dexrazoxane. It is worth noting that children treated with dexrazoxane may be at higher risk of developing subsequent malignant neoplasms. This outcome was not evaluated in adults.[15] Therefore, we will discuss the main molecular mechanisms and clinical features of cardiotoxicity produced by representative drugs in this review, providing selected guidelines for the clinical management of anticancer drugs-induced cardiotoxicity.

Among anticancer drugs, studies on anthracycline-induced cardiotoxicity are more comprehensive. Doxorubicin-induced cardiotoxicity is a hot topic of current research. Considering the application value, economic effect and social burden of anthracyclines, we will focus on the cardiotoxicity of doxorubicin and raise the alarm of cardiotoxicity of anticancer drugs through this review. Also mitochondrial transplantation as a novel treatment modality for doxorubicin-induced cardiotoxicity will be focused here.

Although there is some interest in anticancer drugs-induced cardiotoxicity, there are not many reviews on this topic, and innovative therapeutic approaches need to be explored. We expect that a review of the molecular mechanisms of anticancer drugs-induced cardiotoxicity and its clinical management will be emphasized by various disciplines.

Anthracyclines

Anthracyclines-Induced Cardiotoxicity

In 1950, anthracyclines were named by scientist H. Brockmann, and then a series of anthracyclines such as daunorubicin and doxorubicin were gradually developed and used in the treatment of various malignancies.[43] With the widespread use of anthracyclines, serious cardiac side effects have gradually attracted the attention of clinicians. The CTRCD of Anthracycline is divided into early cardiotoxicity and late cardiotoxicity. Early cardiotoxicity is divided into early acute cardiotoxicity and early chronic cardiotoxicity. Early acute cardiotoxicity occurs mostly during or a few days to weeks after anthracycline treatment and is mostly manifested as arrhythmias, while early chronic cardiotoxicity occurs mostly within 1 year after anthracycline treatment and

is mostly manifested as heart failure or cardiomyopathy. Late cardiotoxicity occurs mostly after 1 year at the end of anthracycline treatment, it is mostly manifested as insidious cardiac dysfunction.[44] In a prospective study of 630 patients (including breast and small-cell lung cancer), researchers found that cumulatively 26% of patients developed doxorubicin-induced congestive heart failure at a cumulative doxorubicin dose of 550 mg/m^2, and age was an important risk factor for doxorubicin-induced congestive heart failure at a cumulative dose of 400 mg/m^2.[16] Here, we review doxorubicin as a representative.

Mechanisms of Doxorubicin-Induced Cardiotoxicity

Multiple studies have shown that doxorubicin-induced cardiotoxicity is the result of the interaction of multiple factors. Doxorubicin enters cardiomyocytes and accumulates in mitochondrial DNA(mtDNA) to produce large amounts of reactive oxygen species(ROS), triggering lipid peroxidation and leading to the development of ferroptosis. Doxorubicin disrupts the structure of mitochondria, interferes with mitochondrial dynamics and mitochondrial autophagy, and generates ROS that further aggravates mitochondrial dysfunction and induces cardiomyocyte apoptosis. Doxorubicin inhibits the function of the mitochondrial respiratory chain and reduces the level of ATP in cardiomyocytes. Doxorubicin disturbs intracellular Ca^{2+} homeostasis and opens the mitochondrial permeability transition pore(mPTP), leading to mitochondrial membrane depolarization, matrix swelling, outer membrane rupture, and release of apoptotic signaling molecules such as cytochrome c(Cyt C), resulting in cardiomyocyte apoptosis. Doxorubicin binding to topoisomerase 2β disrupts the DNA double-strand, resulting in apoptosis of cardiomyocytes.[45] Among the numerous mechanisms, mitochondrial dysfunction, as well as oxidative stress and ferroptosis, which are tightly linked to mitochondria, are the crucial components (Figure 1).

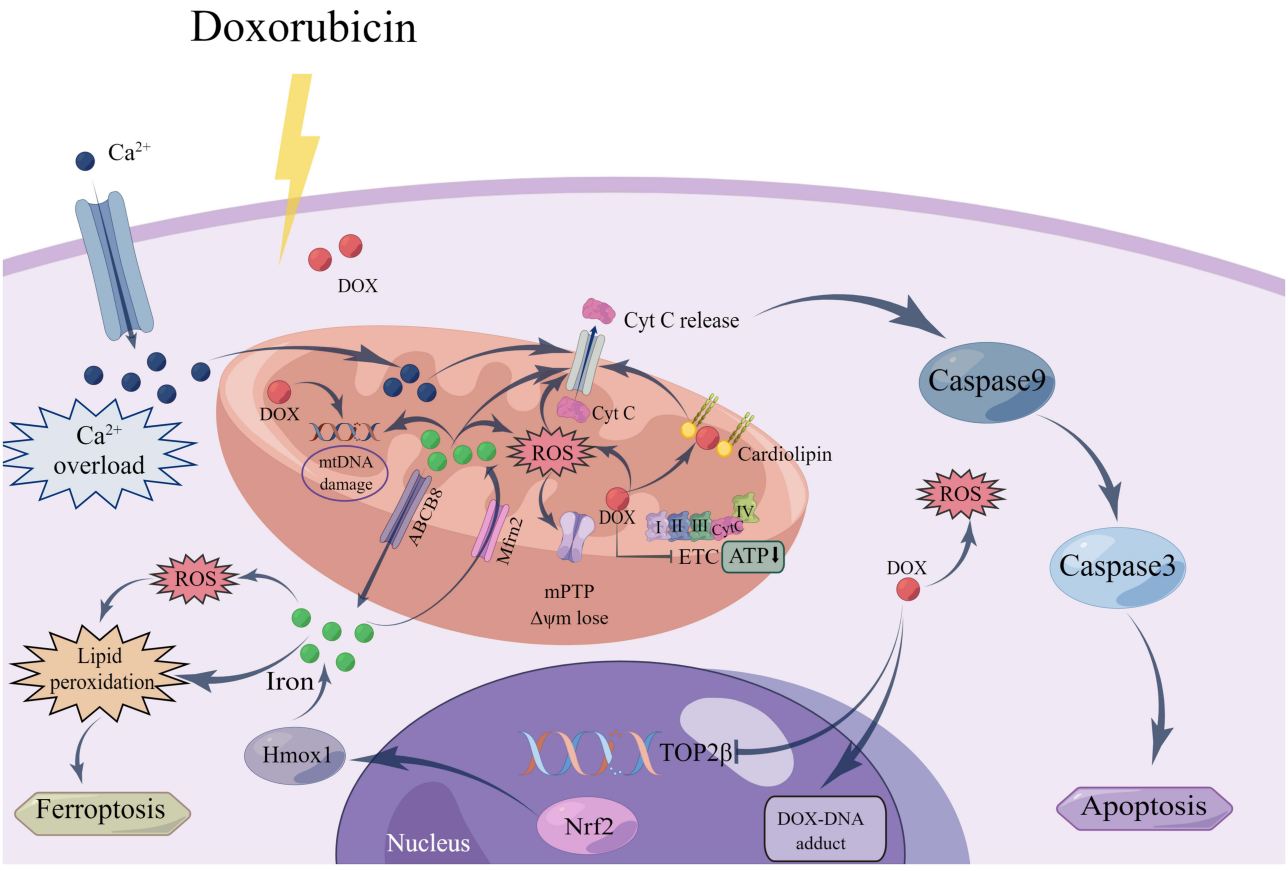


Figure 1 Pathogenesis of doxorubicin-induced cardiotoxicity. DOX can disrupt intracellular Ca^{2+} homeostasis, open the mPTP and release apoptotic signalling molecules such as CytC. DOX can disrupt the structure of mitochondria, producing ROS that exacerbates mitochondrial dysfunction. Doxorubicin can inhibit the function of the mitochondrial ETC and reduce the level of ATP in cardiomyocytes. DOX can accumulate in mtDNA,leading to the development of ferroptosis. DOX can bind to topoisomerase 2β and disrupt the DNA double strand, leading to apoptosis of cardiomyocytes. By Figdraw.

Abbreviations: DOX, Doxorubicin; mPTP, mitochondrial permeability transition pore; Δψm, mitochondrial membrane potential; TOP2β, topoisomerase 2β; Mfrn2, mitoferrin-2; ABCB8, ABC protein B8; ETC, electron transport chain, including the NADH dehydrogenase (complex **I**), succinate dehydrogenase (complex II), cytochrome bc1 complex (complex III), and cytochrome c oxidase (complex IV); Cyt C, cytochrome c.

Mitochondrial Dysfunction of Doxorubicin-Induced Cardiotoxicity

Mitochondrial quality control maintains mitochondrial integrity and function primarily through mitochondrial proteostatic, mitochondrial biosynthesis, mitochondrial dynamics, and mitochondrial autophagy. Here we describe the mitochondrial proteostatic system and the mechanism of doxorubicin-induced mitochondrial energy imbalance, doxorubicin interference with mitochondrial division and fusion and mitochondrial autophagy.[46]

The mitochondrial proteostatic system removes damaged proteins by proteases that catalyse protein folding of chaperone proteins.[47] When the capacity of proteases and chaperones is overwhelmed by an excess of unfolded or misfolded proteins, the mitochondrial unfolded protein response (UPR^{mt}) is activated and the mitochondria release signals that enhance protein folding to prevent the aggregation of deleterious proteins within the mitochondria.[46] Impairment of cellular protein degradation pathways at the lysosomal level can lead directly to perturbation of endoplasmic reticulum and mitochondrial function, and a recent study has shown that the adverse effects of DOX on cardiomyocytes include disruption of lysosomal function. In the latest study, DOX inhibited the expression of transcription factor EB, induced lysosomal dysfunction, impaired autophagy to induce cardiotoxicity.[48]

Doxorubicin accumulated initially in the mitochondria after entering the cardiomyocytes and destroyed the structure of mitochondria. As the main supplier of ATP to myocardial tissue, mitochondria are responsible for about 90% of energy supply. Under physiological conditions, the mitochondrial creatine kinase (MtCK) is associated with the adenine nucleotide translocator (ANT) in the inner mitochondrial membrane and the voltage-dependent anion channel (VDAC) in the outer mitochondrial membrane. VDAC on the outer mitochondrial membrane and ATP synthase are responsible for transporting ATP to the cytoplasm. After doxorubicin enters cardiomyocytes, it first accumulates in the mitochondria, disrupting the homeostasis of MtCK and affecting the activity of MtCK, resulting in an impaired creatine/phosphocreatine energy system and an imbalance in the supply of ATP, which leads to apoptosis of cardiomyocytes.[49] Cardiolipin located on the inner mitochondrial membrane is an essential component for the maintenance of the activity of mitochondrial respiratory chain complex III (cytochrome bc1 complex) and respiratory chain complex IV (cytochrome c oxidase). Under normal conditions, about 15% of cytochrome c is bound to cardiolipin. Doxorubicin enters cardiomyocytes and binds to cardiolipin on the inner mitochondrial membrane, leading to the release of cytochrome c, which enters the cytoplasm, activating caspase-3 and inducing apoptosis.[50] In vivo studies confirmed that apoptosis of cardiomyocytes due to the release of cytochrome c as well as the apoptotic factor caspase-3 was observed in mice treated with doxorubicin.[51] In vitro studies showed that doxorubicin inhibited the activity of mitochondrial respiratory chain complexes I–IV in rats and bovine cardiomyocytes, mechanistically mediated by the binding of doxorubicin to cardiolipin.[52,53] Further studies have demonstrated that doxorubicin inhibits mitochondrial respiratory chain complex activity by affecting respiratory chain complex components. Cytochrome c oxidase subunit 5A (COX5A) is the nuclear-encoding subunit of the terminal oxidase involved in the mitochondrial respiratory chain. It has been shown that the expression of COX5A was downregulated in doxorubicin-treated H9c2 cells, while overexpression of COX5A attenuated doxorubicin-induced mitochondrial dysfunction.[54] Meanwhile, DOX promotes mitochondrial DNA damage, causes p53 activation, promotes p53 binding to the promoters of Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) and peroxisome proliferator-activated receptor γ coactivator-1β(PGC-1β), and inhibits the expression of PGC-1α and PGC-1β, thereby inhibiting mitochondrial biogenesis and affecting mitochondrial energy production.[46]

In addition, doxorubicin contributes to the development of cardiotoxicity by interfering with mitochondrial fission, mitochondrial fusion and mitochondrial autophagy. By sensing changes in the in vivo environment, the mitochondrial quality control system regulates mitochondrial fusion protein 2(Mfn2) to promote the fusion of damaged mitochondria with healthy mitochondria, and mitochondrial dynamin-related protein 1(Drp1) to bind to the outer mitochondrial membrane to split damaged mitochondria. At the same time, the mitochondrial quality control system stimulates PTEN-induced putative kinase 1(PINK1)-mediated mitochondrial autophagy to remove damaged mitochondria. Mitochondrial fission and fusion are essential in maintaining normal mitochondrial morphology, distribution and function. Abnormal mitochondrial fission results in mitochondrial fragmentation, whereas abnormal mitochondrial fusion results in abnormal mitochondrial morphology, both of which can lead to mitochondrial dysfunction. Ding et al's study found that doxorubicin inhibited mitochondrial fusion mediated by Mfn2, and overexpression of Mfn2 ameliorated doxorubicin-

induced cardiac dysfunction in mice.[55] Zhuang et al showed that increased expression of Drp1, which is associated with mitochondrial fission, was observed in both C57BL/6 mice and H9c2 cells treated with doxorubicin, and the use of the Drp1 inhibitor Mdivi-1 significantly reduced the doxorubicin-induced Drp1 phosphorylation at the ser616 site, thereby attenuating doxorubicin-induced cardiotoxicity.[56] Qin et al demonstrated in their study that the use of Oseltamivir downregulated Drp1 expression in doxorubicin-treated rats and H9c2 cells and attenuated doxorubicin-produced cardiotoxicity.[57] Mitochondrial autophagy is the process by which mitochondria are wrapped in autophagosomes and fused with lysosomes to maintain the homeostasis of the intracellular environment when mitochondrial damage occurs. Pink1 is a serine/threonine kinase that is continuously transferred to the inner mitochondrial membrane under physiological conditions and cleaved by the inner mitochondrial membrane protein presenilin-associated rhomboid-like protein (PARL).[58] When mitochondria are damaged, Pink1 accumulates in the outer mitochondrial membrane and recruits the cytoplasmic E3 ubiquitin ligase. E3 ubiquitin-protein ligase-Parkin, which induces ubiquitination of mitochondrial outer membrane proteins and promotes mitochondrial autophagy.[58] Yin et al used doxorubicin to treat adult ventricular myocytes to observe the occurrence of cardiotoxicity and found that the content of autophagosomes in mitochondria increased with exposure to doxorubicin concentration, while the expression of Pink1 and Parkin proteins were upregulated.[59] Gharanei et al used the rat Langendorff heart model to demonstrate that doxorubicin increased mitochondrial autophagy and that the use of the mitochondrial autophagy inhibitor Mdivi-1 had a protective effect against doxorubicin-induced cardiotoxicity.[60]

Therefore, approaches involved in regulating mitochondrial homeostasis and mitochondrial autophagy, inhibiting mitochondrial division, promoting mitochondrial fusion, and stimulating mitochondrial biosynthesis are expected to provide the opening of new ideas for the treatment of DOX-induced cardiotoxicity.

Oxidative Stress of Doxorubicin-Induced Cardiotoxicity

Oxidative stress is caused by an imbalance in the production and scavenging of ROS. Doxorubicin is reduced to semiquinone by reduced coenzyme II (NADPH) and cytochrome P450 upon entry into cardiomyocytes, generating oxygen radicals that inhibit sodium pump activity on cardiac myocyte membranes, aggravating calcium overload, damaging mitochondrial structure and exacerbating mitochondrial dysfunction, inhibiting nitric oxide leading to nitric stress, and inducing apoptosis in cardiomyocytes.[45]

Numerous studies have confirmed that oxidative stress mediates doxorubicin-induced cardiotoxicity and that the antioxidant protein nuclear factor erythroid-2 related factor (Nrf2) plays an important role in counteracting doxorubicin-induced oxidative stress. Under physiological conditions, Nrf2 is tightly bound to Kelch like ECH associated protein 1 (Keap1) in the cytoplasm and is continuously degraded by ubiquitination. In the presence of oxidative stress, Nrf2 is transferred from the cytoplasm to the nucleus and forms a heterodimer with Maf protein, allowing Nrf2 to bind to the antioxidant response element(ARE) to induce transcription of downstream antioxidant factors and exert antioxidant effects.[61,62] Decreased keap1 expression and increased expression of Nrf2 and its downstream genes were observed in adriamycin-treated rat H9c2 cells.[63] Using microRNA microarray to screen 18 differentially expressed microRNAs in doxorubicin treated myocardial tissues, miR-140-5p was found to be significantly increased in myocardial tissues treated with doxorubicin and confirmed that miR-140-5p exacerbated doxorubicin-induced cardiotoxicity by targeting Nrf2.[64] In the next study, the team verified that the natural diosgenin could reverse the onset of doxorubicin-induced oxidative stress by promoting Nrf2 nuclear translocation.[65]

Epigenetic modulators can improve the redox state and ROS levels. Firstly, Sirtuin proteins act as deacetylases and play an important role in doxorubicin-induced cardiotoxicity.[66] PGC-1α is deacetylated by Sirt1 to activate genes involved in mitochondrial biogenesis. Increased Sirt1 expression and Sirt1-dependent Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) activation increase Nrf2 expression and promote transcription of downstream antioxidant genes.[67,68] SIRT2 reduces DOX-induced Forkhead box O3 (Foxo3a) inhibition and oxidative stress by activating Foxo3a and up-regulating MnSOD levels.[69,70] Sirt3-mediated deacetylation of MnSOD, SOD2 and isocitrate dehydrogenase 2 (IDH2) regulates ROS production and Sirt3 repairs DOX-induced mtDNA damage by deacetylating and increasing the activity of oxoguanine-DNA glycosylase-1 (OGG1).[66] Other epigenetic modifications also play an

important role in doxorubicin-induced cardiotoxicity.DOX induces p300 upregulation, and increased p300 protects against oxidative stress via acetylating and activating STAT3.

It was shown that after doxorubicin damaged the structure of mitochondria, the increase in mitochondrial membrane permeability increased the inflow of Ca^{2+}, leading to the generation of oxygen radicals, while the sharply elevated Ca^{2+} reduced the activity of mitochondrial respiratory chain and impaired mitochondrial oxidative phosphorylation, thus forming a malignant cycle between oxidative stress and mitochondria.[71,72]

Ferroptosis of Doxorubicin-Induced Cardiotoxicity

Iron is one of the essential trace elements involved in many physiological activities, but iron overload can be toxic.[73] The concept of "ferroptosis" was first introduced in 2012 as a novel iron-dependent non-apoptotic and non-necrotic cell death,[74] and subsequent studies confirmed that ferroptosis is a critical step in the pathogenesis of doxorubicin-induced cardiotoxicity.[75]

Primarily, under physiological conditions iron-regulatory proteins (IRPs) bind to iron-responsive element(IRE) at the 3' end of the transferrin receptor 1 (TfR1) and promote iron uptake. Entry of doxorubicin into cardiomyocytes inactivates IRPs thus leading to intracellular iron overload.[76] Upon iron overload, mitoferrin on the inner mitochondrial membrane transports iron from the cytoplasm to the mitochondria, while the ATP-binding cassette b10 on the inner mitochondrial membrane interacts with mitoferrin to further enhance the action of mitoferrin, leading to iron accumulation in mitochondria, which disrupts mitochondrial function and induces ferroptosis.[77]

Secondly, doxorubicin enters the mitochondria and forms a complex with Fe^{3+}, which is reduced to DOX-Fe^{2+} complex in an oxygen concentration-dependent manner and generates a large amount of ROS, which intensifies oxidative stress and leads to lipid peroxide accumulation, resulting in the development of ferroptosis.[78] Recent studies have shown that the mitochondrial outer membrane protein FUNDC2 is closely associated with the occurrence of ferroptosis in doxorubicin-induced cardiotoxicity and that glutathione peroxidase 4 (GPX4) localized in mitochondria can scavenge lipid peroxides, protect the structural and functional integrity of cell membranes, and inhibit the occurrence of ferroptosis.[79,80] GPX4 is regulated by Nrf2, and PRMT4 inhibits the Nrf2/GPX4 signaling pathway, promotes the occurrence of ferroptosis and exacerbates doxorubicin-induced cardiotoxicity.[81] This suggests that therapeutic approaches targeting ferroptosis, oxidative stress and mitochondria may be a new direction to ameliorate doxorubicin-induced cardiotoxicity.

Alternative Mechanisms of Doxorubicin-Induced Cardiotoxicity

Autophagy degrades dysfunctional cellular components via lysosomes inside the cell. The process of autophagy involves initiation/isolation, fusion with lysosomes, and degradation. It was shown that autophagy is involved in doxorubicin-induced cardiotoxicity, but whether doxorubicin inhibits or promotes autophagy could not be determined.[82] AMPK can control autophagosome formation by recruiting downstream autophagy-associated proteins to autophagosome formation sites, and thus activation of AMPK is considered to be the initiation of autophagy. In doxorubicin-induced cardiotoxicity, there is an increase in AMPK expression and a decrease in AMPK expression.[83] Recent studies have shown that doxorubicin increases LC3-II, p62 and Beclin1 protein levels and induces autophagy but then blocks lysosomal proteolysis resulting in accumulation of autophagosomes and autolysosomes and ROS, thereby aggravating cardiomyocyte injury and leading to cardiomyocyte death.[84]

Necroptosis is cell death due to external stimuli such as toxins, chemosynthetic drugs. Dox increases mitochondrial ROS and lipid peroxidation and is the main cause of myocardial necroptosis.[85] Studies have shown that DOX induces mitochondrial dysfunction leading to upregulation of Poly (ADP-ribose) polymerase(PARP), resulting in increased intracellular NAD+ and ATP consumption, slowing down glycolysis and mitochondrial respiration rates, leading to cell necroptosis.[86] Doxorubicin has been demonstrated to upregulate tumour necrosis factor-α (TNF-α) and to activate TNFR-associated death domain (TRADD) and Fas-associated via death domain (FADD). Furthermore, it has been shown to inhibit caspase-8 and to activate phosphorylates receptor-interacting serine/threonine-protein kinase 1 (RIPK1), RIPK3 and mixed lineage kinase domain-like protein (MLKL), thereby inducing necroptosis. Doxorubicin can also activate

necroptosis through the RIPK1-independent pathway, where RIPK3 activates phosphorylates calmodulin kinase II(CAMKII) and the mitochondrial permeability transition pore, resulting in loss of membrane potential and integrity.[87]

Many studies have shown that pyroptosis is one of the mechanisms of DOX-induced prolapse cardiotoxicity. Amentoflavone is a naturally occurring biflavone with antipyroptotic and anti-inflammatory properties.[88] Honokiol inhibition of focal prolapse in H9c2 cells attenuates DOX-induced cardiotoxicity, and this effect is mediated by activation of AMPK to regulate Nrf2 signalling.[89] DOX activated caspase-3 and triggered gasdermin E(GSDME)-dependent pyroptosis, whereas silencing or inhibitors of caspase-3 reduced pyroptosis. Knockdown of GSDME inhibited DOX-induced pyroptosis in cardiomyocytes. DOX increased Bnip3 expression, whereas Bnip3 silencing attenuated DOX-induced pyroptosis in cardiomyocytes through caspase-3 activation and GSDME cleavage.[90]

Clinical Management and Innovative Treatment

Primarily, cardiac function is assessed by biomarkers and transthoracic echocardiography or cardiac magnetic resonance prior to the initiation of chemotherapy.

Temporarily interrupt anthracycline chemotherapy in patients presenting with moderately symptomatic CTRCD and in patients presenting with severe symptomatic CTRCD. Secondly, for patients presenting with mildly symptomatic CTRCD, Multidisciplinary team(MDT) is recommended for the option of interrupting or continuing anthracycline chemotherapy. If anthracycline chemotherapy is continued, the dose of anthracycline chemotherapy can be reduced, liposomal anthracycline preparations can be switched, and dexrazoxane can be used for pretreatment to avoid aggravation of cardiotoxicity.[1] However, in clinical practice, due to the significant side effects of dexrazoxane and the poor prognosis of most patients once cardiotoxicity occurs, there is the continuation of the exploration of treatment for doxorubicin-induced cardiotoxicity.

Doxorubicin-induced cardiotoxicity is strongly associated with Nrf2, therefore therapeutic modalities targeting Nrf2 may be effective against doxorubicin-induced cardiotoxicity. Several studies have shown that betaine, a modulator of oxidative stress and inflammation, is protective against doxorubicin-induced cardiotoxicity. In an animal study, betaine significantly reduced Nrf2 expression and oxidative stress in cardiomyocytes, thereby restoring oxidative homeostasis, while up-regulating AMPK expression and decreasing the levels of inflammatory and fibrotic factors such as NLRP3, suggesting that betaine prevents doxorubicin-induced cardiotoxicity through anti-inflammatory and anti-fibrotic properties.[91] A protective role of betaine by reducing Nrf2 expression was also observed in doxorubicin-induced nephrotoxicity.[92] In a study of acetaminophen overdose-induced acute hepatotoxicity, betaine played a protective role by reducing Nrf2 expression.[93] The above studies suggest that betaine may provide an important role in various oxidative stress-related injuries by modulating the expression of Nrf2. It may provide new ideas for exploring therapeutic measures to ameliorate antitumour drug-induced cardiotoxicity.

While focusing on doxorubicin, we found that a novel mitochondrial replacement therapy has recently become a hot research topic to improve the cardiotoxicity of doxorubicin, so we characterize this section as an additional focus, which will be specifically addressed in Part 8. It has been found that doxorubicin-induced cardiotoxicity is firmly associated with mitochondrial dysfunction, and improvement of mitochondrial function can ameliorate doxorubicin-induced cardiotoxicity, such as the use of mitochondria-targeted antioxidants(MitoQ) and mitochondrial fission inhibitors (Liensinine).[94,95] In contrast to these therapeutic measures, mitochondrial transplantation is achieved by intercellular transfer of mitochondria through tunneling nanotubes, extracellular vesicles, and partial or complete cell fusion, so that the damaged mitochondria in the original cell or organ are replaced by healthy mitochondria, thus restoring mitochondrial function from the mitochondrial gene level. The role of mitochondrial transplantation in the restoration of mitochondrial function and renewal of mitochondrial DNA has been demonstrated in in vivo and in vitro trials in myocardial ischemia-reperfusion injury, doxorubicin-induced kidney injury, acute respiratory distress syndrome, and depression.[96–99] Therefore the use of mitochondrial transplantation as a novel strategy to modify doxorubicin-induced cardiotoxicity may etiologically address doxorubicin-induced cardiotoxicity.

Since there are few applications of mitochondrial transplantation in doxorubicin-induced cardiotoxicity and there is still a gap in research on the mechanism of mitochondrial transplantation action, we emphasize the prospect of mitochondrial transplantation as a new technique in doxorubicin-induced cardiotoxicity and hypothesize its possible

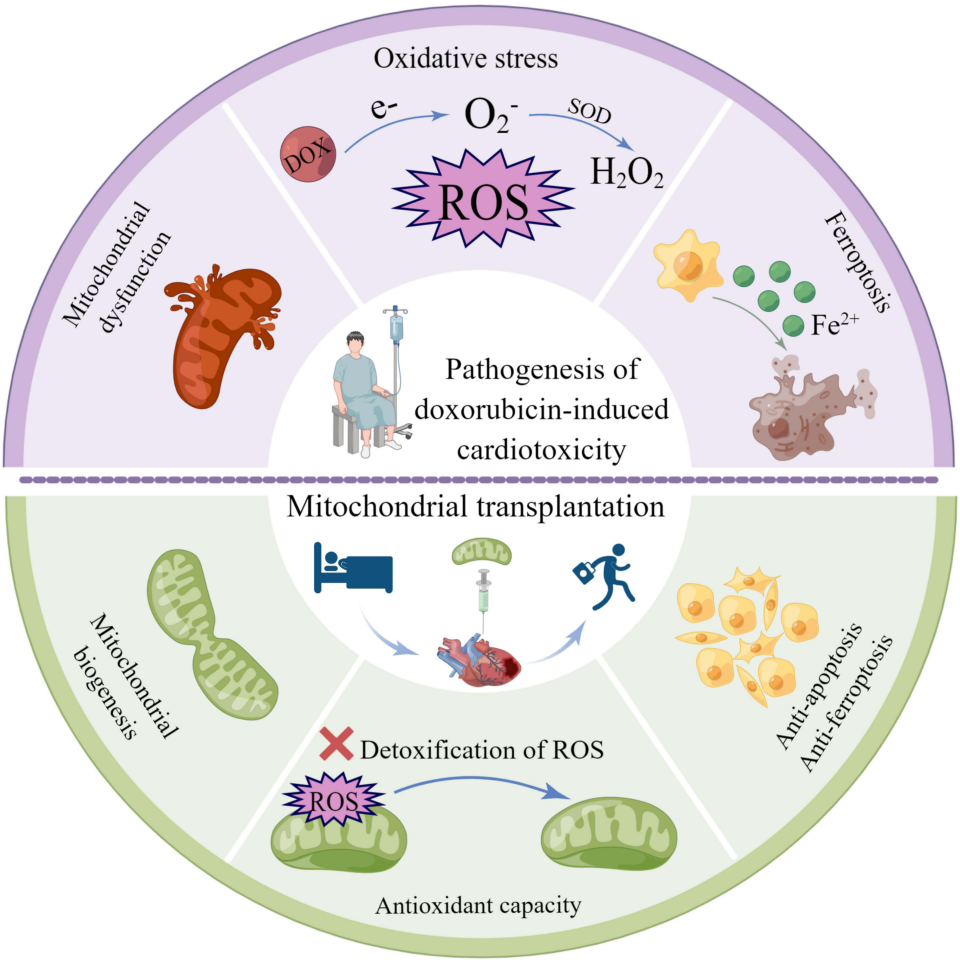


Figure 2 Mitochondrial transplantation and doxorubicin-induced cardiotoxicity. Doxorubicin–induced cardiotoxicity is closely related to mitochondrial dysfunction, oxidative stress,ferroptosis. Mitochondrial transplantation can alleviate ferroptosis by enhancing mitochondrial function, reducing reactive oxygen species production. By Figdraw.

role from previous applications of mitochondrial transplantation in other diseases to provide some ideas for future research on mitochondrial transplantation in doxorubicin-induced cardiotoxicity (Figure 2).

HER2 Inhibitors

HER2 Inhibitors-Induced Cardiotoxicity

HER2 Inhibitors are a type of therapeutic drugs that specifically target HER2-positive breast cancer. The following are several common HER2-targeted drugs: 1. Trastuzumab: it is a monoclonal antibody that binds specifically to HER2 and inhibits the growth of HER2-positive breast cancer through inhibition of its downstream signaling and activation of antibody-dependent cell-mediated cytotoxicity effects. 2. Lapatinib: this is a tyrosine kinase inhibitor that competes with intracellular ATP to block HER2 signaling, which in turn prevents phosphorylation and downstream molecular pathway alterations, exerting anti-tumor effects. 3. Neratinib: this is also a TKI with a similar mechanism of action as lapatinib, which can be used as adjuvant therapy for breast cancer. 4. Ado-trastuzumab emtansine (T-DM1): Antibody-drug conjugates (ADC) consist of a monoclonal antibody directed against a target antigen, a linker, and a cytotoxic drug (payload), which can be used for the treatment of breast cancer with the help of the affinity of the antibody. With the affinity of the antibody, the small molecule drug is targeted and delivered to HER2-positive cells. 5. DS-8201 (T-Dxd): it is a novel ADC that received accelerated approval from the Food and Drug Administration (FDA) in December 2019 for use in inoperable HER2-positive patients who have been previously treated with at least two anti-HER2 drugs.[100]

In clinical trials, cardiac dysfunction was seen in 3%-7% of patients receiving trastuzumab monotherapy.[101] The incidence of cardiac dysfunction increased to 28% when trastuzumab was concomitantly treated with anthracyclines.[102] In addition, a race-based study showed an increased risk of cardiotoxicity in black women during HER2-targeted therapy for unknown reasons.[103]

Mechanisms of HER2 Inhibitors-Induced Cardiotoxicity

ErbB2 (also known as HER2) is a member of the human epidermal growth factor receptor (HER) family, which also includes ErbB1(EGFR), ErbB3, and ErbB4. HER2 cannot form ligand-dependent dimers by itself to activate downstream signals, and needs to form heterodimers with other HER family proteins to perform its functions, with the EGFR/HER2 and HER2/HER3 complexes being the most important for physiological functions and most relevant to tumourigenesis.[104] Different degrees of cardiac abnormalities were observed in ErbB1, ErbB2, ErbB3, and ErbB4 knockout mice, such as semilunar valve defects, lack of ventricular trabeculation, underdeveloped cushions, and disrupted endocardial cushion formation.[105] HER2 inhibitors contribute to the development of cardiotoxicity by interfering with multiple pathways such as neuregulin 1(NRG1), oxidative stress, and ferroptosis, and studies on the mechanisms are still limited and require more attention. Activation of the NRG1-ERbB4 signaling pathway has been shown to stimulate mature cardiomyocyte division.[106–108] HER2-targeted drugs such as trastuzumab block the function of NRG1, which is secreted by endothelial cells and is essential for the heart to maintain its physiological function, interfering with the NRG1-ErbB4-ErbB2 axis in the myocardium and inhibiting the mitogen-activated protein kinases-(MAPK) and phosphatidylinositol-3-kinase(PI3K) pathways, leading to myocardial injury.[109–111] CRONE et al showed that ErbB2 signaling itself plays an important role in heart failure, which may be key to the cardiotoxicity caused by HER2-targeted drugs.[112] Belmonte et al showed that ErbB2 overexpression could attenuate adriamycin-induced cardiotoxicity by upregulating antioxidant enzymes and reducing basal levels of reactive oxygen species. This study suggests that drugs targeting HER2 may cause cardiotoxicity by disrupting the intracellular antioxidant system, resulting in increased mitochondrial reactive oxygen species production.[113] The novel study found that trastuzumab decreased H9c2 cell viability, increased intracellular and mitochondrial ROS levels, decreased mitochondrial membrane potential and ATP content, and decreased GPX expression and GSH/GSSG ratio in H9c2 cells. These alterations were reversed using Ferrostatin-1, a ferroptosis inhibitor, and this study demonstrated that ferroptosis is strongly associated with HER2 inhibitor-induced cardiotoxicity.[114]

EGFR is the first member of the HER family, which is essential for cardiac growth and development, but it has a dual role in cardiovascular disease. Upon ligand binding, EGFR is converted from an inactive monomer to an active homodimer or heterodimer with other ErbB family members (ErbB2/HER2/neu, ErbB3 and ErbB4) to activate downstream signalling.[105] Studies have shown that activation of EGFR can regulate vasoconstriction or diastole, resulting in either hypertensive or antihypertensive effects. This largely depends on whether EGFR has a greater effect on the content of substances that dilate endothelial vessels or on smooth muscle contraction.[115–117] Several studies have shown that EGFR activation promotes angiogenesis, and in hindlimb ischemia models, activation of EGFR promotes collateral vessel formation exerting a beneficial effect, whereas in diabetic mice, EGFR increases vascular leakage, leading to a poor outcome due to retinal edema; and in restenosis animal models, inhibition of EGFR-blocking antibodies reduced the number of vascular smooth muscle cells proliferation and endothelial hyperplasia after balloon injury.[118,119] Studies have shown that EGF activates EGFR tyrosine kinase activity to increase myocyte cAMP levels and increase myocardial contractility; however, EGFR leads to vascular remodelling and thus mediates cardiac remodelling, and aldosterone increases EGFR expression leading to myocardial fibrosis and vascular remodelling. The detrimental effects of activation of EGFR on the heart may be due to activation of AKT signalling, which leads to oxidative stress and endoplasmic reticulum.[120,121] Ali et al showed that gefitinib modulated the expression and function of the cardiac PTEN/AKT/Foxo3a pathway, triggering mitochondrial dysfunction and inducing cardiotoxicity.[122] Interestingly egfr is strongly associated with doxorubicin resistance.

Activation of HER2 inhibits rapid endocytosis and degradation of EGFR, prolongs downstream phosphorylation signalling, and promotes cell growth and proliferation leading to tumourigenesis. As a dual inhibitor of EGFR and Her2, lapatinib blocks doxorubicin efflux by inhibiting ATP-dependent ABC-type efflux transporter proteins, increasing

intracellular doxorubicin concentration and exacerbating myocyte injury.[123] However, a new mechanism of trastuzumab cardiotoxicity was identified by Xu et al. This study found that HER2 is still abundantly expressed in adult mouse cardiac capillary vascular endothelial cells (VECs) and that treatment of cardiomyocytes with trastuzumab-treated VECs medium leads to impaired cardiomyocyte contraction. Since PTX3 is the only protein that can be released by VECs, it plays a key role in endothelial dysfunction and cardiomyocyte injury. Trastuzumab treatment led to an increase in PTX3 levels in a time- and dose-dependent manner and resulted in a decrease in intracellular calcium levels, leading to impaired cardiomyocyte contraction. Inhibition of PTX3 increased intracellular calcium levels and improved cardiomyocyte contractile dysfunction. Further studies have shown that inhibition of HER2 by trastuzumab activates EGFR, and activated EGFR contributes to increased PTX3 transcription and secretion, whereas the dual EGFR/HER2 inhibitor lapatinib decreases PTX3 levels. Further studies showed that trastuzumab increased phosphorylated STAT3 levels, and lapatinib reversed this result. It was shown that trastuzumab activates EGFR/STAT3 signaling in vascular endothelial cells to promote PTX3 excretion, which inhibits cellular calcium signaling ultimately leading to impaired cardiomyocyte contractility. Meanwhile, they confirmed that lapatinib may be a feasible drug to prevent trastuzumab-induced cardiac complications.[124]

Doxorubicin is widely used clinically for the treatment of breast cancer, but resistance occurs within a short period of time. Breast cancer drug resistance features are mainly associated with the P-glycoprotein (P-gp) encoded by the ABCB1 gene, which uses the energy generated by ATP hydrolysis to pump chemotherapeutic drugs out of the cell, thus reducing the concentration of effective intracellular drugs and mediating chemotherapy resistance, and whose expression and function are mainly regulated by signalling pathways, such as PI3K/AKT/mTOR, MAPK, NF-κB, and so on. Both breviscapine and ivermectin can alleviate doxorubicin resistance by inhibiting EGFR, probably due to their competitive binding to the P-gp substrate binding site, reducing P-gp-mediated doxorubicin efflux and enhancing the efficacy of chemotherapy.[125,126]

Clinical Management and Innovative Treatment

If cardiotoxicity with clinical symptoms occurs during the use of HER2 Inhibitors, or if the patient is asymptomatic but has a left ventricular ejection fraction of <40% or a decrease from baseline of >15%, the drug should be discontinued. MDT is recommended for such patients in order to guide clinical decisions and prevent worsening of heart failure.[1]

For patients with asymptomatic moderate CTRCD (LVEF 40%-49%), HER2-targeted therapy should be continued with administration of ACEI/ARB and β-blockers along with frequent cardiac monitoring. In patients with asymptomatic mild CTRCD (LVEF≥50%), continue HER2-targeted therapy and administer ACEI/ARB and/or β-blockers according to 2022 ESC Oncology Cardiology Guidelines.[17–19] With the elevated incidence of cardiotoxicity, regular long-term follow-up becomes critical.

Considering that the mechanisms of HER inhibitors-associated cardiotoxicity are multiple and complex, it is particularly important to continue original research for innovative therapeutic approaches.

Immune Checkpoint Inhibitors

ICI-Induced Cardiotoxicity

CTLA-4 and PD-1, as important co-inhibitory elements on the surface of T-cells, negatively regulate the immune response by decreasing the activity of T-cells and sparing tumor cells from immunologic surveillance. Monoclonal antibodies against CTLA-4, PD-1, and programmed death receptor ligand-1 (PD-L1) are called immune checkpoint inhibitors. Ipilimumab and tremelimumab are anti-CTLA-4 monoclonal antibodies currently in clinical use, while pembrolizumab and nivolumab are monoclonal antibodies targeting PD-1/PD-L1.[127]

ICI-associated cardiotoxicity includes myocarditis, pericarditis, arrhythmias, heart failure, acute coronary syndromes, thromboembolism, vasculitis, the most common of which is myocarditis and myocarditis occurs in less than 1% of patients with the drug, but the lethality rate is 40%.[20–24] The incidence of ICI-related cardiotoxicity depends on a variety of factors. In a retrospective study including 1047 participants, the incidence of ICI-induced cardiotoxicity was 7.0%.[128] A meta-analysis summarized the incidence and characteristics of ICI-associated cardiotoxicity. Of the 4751 study patients, 1.3% developed cardiotoxicity, with myocarditis being the most common (50.8%); 15 patients (24.6%) died

from ICI-induced cardiotoxicity. Patients treated with anti-PD-1 antibodies experienced more adverse cardiac events than those treated with anti-CTLA-4.[129] ICI-associated cardiotoxicity requires vigilance because of its low incidence but high mortality.

Mechanisms of ICI-Induced Cardiotoxicity

The mechanism of ICI-induced myocarditis is complex and is currently thought to be related to the activation of T-cells, which under normal physiological conditions maintain the stability of the immune system through co-stimulatory molecules, such as B7/CD28 and B7/CTLA-4.[130,131] However, immune checkpoint inhibitors block the negative regulatory effects of these co-stimulatory molecules on T cells and activate anti-tumor immune responses, while making healthy tissues in the body more vulnerable to attack, leading to autoimmune complications such as cardiotoxicity.

In addition, PD-1 is also an important co-inhibitory molecule on the surface of T-cells, which negatively regulates the immune response and down-regulates the activity of specific T-cells, avoiding the possibility of autoimmune diseases in physiological states and damage to normal tissues by the immune system in pathological states. However, immune checkpoint inhibitors also block the negative effects of PD-1 on T cells, further activating the anti-tumor immune response while increasing the risk of autoimmune complications such as cardiotoxicity.

Numerous studies have confirmed that immune checkpoint inhibitors-induced toxicity can accumulate in multiple organs of the body and is also seen in the cardiovascular system.[132,133] Wei et al demonstrated a functional interaction between CTLA4 and PD-1 in the development of myocarditis and that intervention with CTLA-4 agonist (abatacept) attenuates myocarditis, clarifying the mechanisms underlying the development of ICI-associated myocarditis.[134] Its occurrence may be related to individual differences, drug dosage, timing of administration, and other factors. Rubio et al evaluated the cardiotoxicity of ICI in a mouse model (C57BL/6) and showed a significantly higher incidence of myocarditis in mice with hypertension-induced pathological remodeling compared with controls.[135]

Clinical Management and Innovative Treatment

Before starting ICI therapy, electrocardiography and biochemical parameters such as Natriuretic peptides(NP) and Cardiac troponin(cTn) are necessary in all patients. Transthoracic echocardiography and cardiac magnetic resonance are recommended for all patients with suspected ICI associated myocarditis.[1]

For cardiotoxicity caused by immune checkpoint inhibitors, the choice of treatment needs to be based on the type and severity of the toxic reaction. All patients with suspected ICI-associated myocarditis were immediately interrupted from ICI therapy, and a MDT was conducted after symptoms resolved to determine the pros and cons of continuing ICI therapy. For haemodynamically unstable patients 500–1000 mg of methylprednisolone is administered intravenously daily. If clinical improvement is observed, switch to oral prednisone and taper according to changes in condition.[1]

It should be noted that cardiotoxicity-induced by immune checkpoint inhibitors is a complex issue that requires comprehensive consideration of the patient's specific condition, the mechanism of action of the drug, and the type of toxic reaction to formulate a treatment plan. Therefore, when using immune checkpoint inhibitors for treatment, the cardiac function of patients should be closely monitored, and cardiotoxic reactions should be detected and treated in a timely manner to ensure the safety of patients and the effectiveness of treatment.[136–138]

The guidelines suggest that intravenous mycophenolate mofetil, anti-thymocyte globulin, immunoglobulin, plasma exchange, tocilizumab, abatacept, alemtuzumab, and tofacitinib and have shown significant efficacy in a number of cases and may become valuable therapies for ICI-associated cardiomyopathy in the future. Abatacept has been shown to significantly improve ICI-related myocarditis in basic research.[134]

VEGF Inhibitors and Multi-Targeted Kinase Inhibitors

VEGF Inhibitors and Multi-Targeted Kinase Inhibitors-Induced Cardiotoxicity

VEGF is an important growth factor, which plays a key role in tumour angiogenesis.[139] Targeting VEGF signaling pathway (VSP) has become one of the major tools used to treat tumours. Among them, monoclonal antibodies such as bevacizumab, which can inhibit the activity of VEGF have been widely used in the clinic.[140,141] TKIs, such as sorafenib, Cediranib and sunitinib, inhibit the activity of the Vascular endothelial growth factor receptor-1 (VEGFR-1), VEGFR-2,

VEGFR-3 and plate-derived growth factor receptor (PDGFR), which further blocks the VSP and inhibits the proliferation of tumour cells. Although these drugs have achieved some efficacy in the clinic, there are some side effects and drug resistance problems that need to be further studied and addressed.[142–145]

Cardiomyocyte growth, coronary and systemic vascular integrity and diastolic function can be affected by VEGF and multi-target kinase inhibitors. By interfering with the VEGF signalling cascade, they contribute to the development of hypertension, thromboembolism, left ventricular dysfunction and heart failure. About 80% of patients have a sharp rise in blood pressure, either as a result of new-onset hypertension or a worsening of pre-existing hypertension.[5,25,26] A meta-analysis that included participation in 72 randomised controlled trials (including 30,013 patients) showed that the overall incidence of VEGFR-TKI-associated high-grade and all-grade hypertensive events was 23.0% and 4.4%.[27]

Mechanisms of VEGF Inhibitors-Induced Cardiotoxicity

Cardiotoxicity caused by VEGF inhibitors and multi-target kinase inhibitors is the result of multiple factors. Firstly, in cancer patients, eukaryotic initiation factor 4E overexpression is associated with higher VEGF levels and microvessel density (MVD) counts. VEGF inhibitors block the action of VEGF, resulting in a decrease in MVD.[146–148] Secondly, VEGF antagonists reduce the bioavailability of nitric oxide NO, causing vasoconstriction and increased peripheral vascular resistance. At the same time, VEGF inhibitors inhibit the production of endothelin-1, which can cause vasoconstriction.[149–151] Recent studies have also shown that oxidative stress is also one of the mechanisms leading to VEGFR-TKI-induced vascular dysfunction in hypertension, and is closely related to the down-regulation of Nrf2 and its regulated antioxidant gene expression.[152]

Clinical Management and Innovative Treatment

Treatment strategies for cardiotoxicity induced by VEGF antagonists and multi-target kinase inhibitors are multifaceted. A combination of medication, drug discontinuation or switching, lifestyle changes, and psychological support can be effective in protecting heart health and alleviating symptoms of toxicity.[28]

In 2016, the ESC made recommendations for home blood pressure monitoring during treatment, weekly during the first cycle and every 2 to 3 weeks thereafter.[153] The 2022 ESC guidelines propose daily home blood pressure monitoring during the first treatment cycle, and every 2–3 weeks thereafter for patients treated with VEGFi. Patients with blood pressure ≥140/90 mmHg should receive antihypertensive therapy according to the guidelines for the treatment of hypertension. ACEIs or ARBs are the first-line antihypertensive drugs suggested for use in cancer patients, and combined therapy with ACEI or ARBs and dihydropyridine CCBs is recommended for cancer patients with systolic blood pressure ≥160 mmHg and diastolic blood pressure ≥100 mmHg. Patients should actively cooperate with their physician's treatment recommendations to obtain the best possible outcome.[1]

TKIs and Anti-BCR-ABL Agents

TKIs and Anti-BCR-ABL Agents-Induced Cardiotoxicity

TKIs targeting BCR-ABL1 are the mainstay of treatment for chronic myeloid leukemia (CML). With the emergence and popularization of TKIs targeting BCR-ABL1, the therapeutic efficacy of CML has been significantly improved.[154,155] Imatinib became the first FDA-approved TKI for the treatment of CML in 2003.[156] Nilotinib, dasatinib and bosutinib are second-generation TKIs.[157–159] Ponatinib is a third-generation BCR-ABL TKI that is effective in imatinib-, dasatinib-, and nilotinib-resistant CML.[160] Olverembatinib, recently approved for marketing, is a novel third-generation orally active BCR-ABL1 TKI, the first third-generation BCR-ABL inhibitor in China.[161]

A prospective study analyzed the incidence of cardiovascular toxicity in 531 patients treated with first-line TKIs (imatinib 400 mg (n=71) and 800 mg (n=203), nilotinib (n=108), dasatinib (n=106), and ponatinib (n=43)). The results showed that 237 patients (45%) experienced cardiovascular adverse events and 46 patients (9%) experienced atherothrombotic adverse events. 175 patients experienced hypertension (33%). Among the TKIs, ponatinib had the highest rates of cardiovascular and atherothrombotic events.[29]

Mechanisms of TKIs and Anti-BCR-ABL Agents-Induced Cardiotoxicity

A variety of TKI-associated adverse events, such as cardiovascular adverse events, rash, pleural effusion have been reported, and at the same time, these adverse events have become a key impediment to the long-term use of TKI drugs.[162–164] This section describes the mechanisms involved in the occurrence of cardiotoxicity associated with each representative drug generation.

Studies have shown that imatinib treatment has a favorable safety record for cardiovascular events, and a 5-year follow-up study of patients with newly diagnosed CML showed a low detection rate of cardiotoxicity.[165] However, Kerkelä et al reported 10 patients who developed severe congestive heart failure while taking imatinib and found left ventricular systolic dysfunction in imatinib-treated mice. It causes endoplasmic reticulum (ER) stress through activation of the IRE1 kinase arm. IRE1 activates c-Jun N-terminal kinase (JNK) and single-regulating kinase 1 (ASK1), which inhibit the release of Bcl-2 and mitochondrial cytochrome c, leading to mitochondrial dysfunction and cell death.[166–168]

The main side effects of dasatinib are pleural effusion and pulmonary hypertension.[169,170] However,In a study of dasatinib, patients underwent electrocardiograms on days 1 and 8 and at the end of treatment, which showed a statistically significant 3–6 ms prolongation of QTc, but the mechanism was not clear.[171] There is evidence of prolongation of the QT interval with nilotinib.[172] FDA adverse event reports and meta-analyses have shown that patients treated with nilotinib have an increased risk of cardiovascular events, particularly those associated with peripheral arterial disease, primarily related to its effects on platelets and coagulation.[173–175] However, it does not cause cardiac dysfunction.[176] Bosutinib has a very low rate of cardiovascular events compared to other TKIs.[177] No original study of ECG abnormalities in second-generation TKIs is available.

Ponatinib is the most cardiotoxic TKI approved by the FDA. In Phase 2 trials, ponatinib had significant antileukemic activity in the mutant state, but it resulted in serious cardiovascular events.[178] In a Phase 3 trial conducted from August 14, 2012, to October 9, 2013, 307 patients were randomly assigned to receive either ponatinib (n=155) or imatinib (n=152), which demonstrated more arterial occlusive events with ponatinib than imatinib.[179] Sharma et al showed that ponatinib produces cardiotoxicity by inhibiting growth signaling, and that upregulation of cardioprotective signaling with exogenous insulin or insulin-like growth factor-1 (IGF1) improves the viability of human induced pluripotent stem cell-derived cardiomyocytes generated from patients treated for cancer.[180] Singh et al demonstrated that ponatinib inhibits extracellular signal-regulated kinase (ERK) and the cardiac prosurvival signalling pathways AKT to induce cardiomyocyte apoptosis.[181] Tousif et al demonstrated that imatinib mediated cardiotoxicity through the S100 A8/A9-NLRP3-IL-1β inflammatory signaling pathway.[182] Yan et al demonstrated that imatinib-induced mitochondrial dysfunction triggered an integrated stress response (ISR) inducing the onset of imatinib-related cardiotoxicity.[183] Olverembatinib has demonstrated efficacy in several studies and no cardiovascular adverse events have been reported.[184]

Clinical Management and Innovative Treatment

The 2022 ESC guidelines recommend baseline electrocardiography in all patients and QTc monitoring in patients treated with second-generation BCR-ABL TKIs, discontinuation of chemotherapy in patients with confirmed pulmonary hypertension, and consideration of the administration of aspirin and statin therapy in patients presenting with peripheral arterial disease.[1]

More original research is urgently needed to elucidate the mechanisms of cardiotoxicity in the search for innovative therapeutic modalities to improve patient prognosis.

Other Anticancer Drugs

Taxanes-Induced Cardiotoxicity

Taxanes (Taxanes and Vincristine) are cardiotoxic, primarily in the form of arrhythmias, which often manifest as sinus bradycardia, ventricular tachycardia, and atrioventricular block. However, bradycardia due to taxanes is generally asymptomatic and self-limiting.[30–32] The mechanism of cardiotoxicity of taxanes involves several aspects, including abnormal calcium ion concentration, abnormal energy metabolism, cardiomyocyte damage and apoptosis. In order to mitigate cardiotoxicity, strict control of drug dosage and frequency of use, as well as close monitoring of patients' cardiac function, are required in clinical practice. Previous studies have shown that paclitaxel affects histamine release leading to

the development of bradyarrhythmias, and Khaled et al showed that the development of paclitaxel cardiotoxicity is closely related to oxidative stress, and that it induced cardiotoxicity can be ameliorated with the use of Naringin and Naringenin.[32] The use of cortisol and antihistamines may ameliorate paclitaxel-induced cardiotoxicity to some extent.[33–35]

Fluorouracil-Induced Cardiotoxicity

Fluorouracil is a commonly used chemotherapeutic agent for the treatment of many types of cancer. Cardiovascular events including angina pectoris, ischemia-related electrocardiographic abnormalities, and myocardial infarction occur in approximately 10% of patients when fluorouracil is administered and are usually closely related to the dose administered, the timing of administration, and the mode of administration.[36,185–187] A population-based study of 5-fluorouracil use in Romania showed a strong correlation between plasma concentration and 5-fluorouracil cardiotoxicity.[36] In a prospective study 30.6% of patients developed cardiotoxicity. 20.9% developed arrhythmias, 19.9% developed ischemic changes, 3.8% developed heart failure, and 1.1% developed myocardial infarction.[37]

The mechanism of fluorouracil cardiotoxicity may involve several aspects. First, fluorouracil activates protein kinase C, leading to vasospasm of coronary arteries and branch arteries. Second, fluorouracil directly damages vascular endothelial cells, leading to microthrombosis. During continuous fluorouracil infusion, up to 50% of patients develop nonspecific electrocardiographic changes with clinical manifestations of angina pectoris and abnormal cardiac rhythm, which may lead to acute myocardial infarction and cardiogenic shock.[188–190] An important role of ferroptosis in fluorouracil cardiotoxicity was confirmed in the study by Li et al.[191] Muhammad et al reported that 5-FUinduced the development of cardiotoxicity in rats by increasing serum NT-pro-BNP levels, ET-1 and thromboxane A2 levels, and Nox, cyclooxygenase-2, malondialdehyde(MDA), phosphorylation of Akt (p-Akt), phosphorylation protein expression of extracellular signal-regulated kinase (p-ERK)1/2 and rho kinase and caspase-3.[192] The study by Refaie et al demonstrated 5-fluorouracil-induced cardiotoxicity, which may be associated with peroxisome proliferator-activated receptor α (PPAR-α), IL-6 (interleukin-6)/signal transducer and activator of transcription(STAT) signaling pathway, was attenuated by the use of fenofibrate.[193]

Patients with a history of symptomatic cardiovascular disease undergo baseline electrocardiography and transthoracic echocardiography. Chemotherapy should be stopped as soon as symptoms develop during chemotherapy and then calcium channel blockers or nitrates should be used empirically, which have been shown to significantly improve coronary artery spasm in patients. When angina occurs, patients with cardiovascular risk factors can undergo coronary angiography, and patients without cardiovascular risk factors can be screened for coronary artery disease using noninvasive tests such as CT coronary angiography and managed accordingly.[38–40]

Proteasome Inhibitors-Induced Cardiotoxicity

Proteases play an important role in tumor cell invasion and metastasis, and the application of proteasome inhibitors can reduce tumor cell invasion and metastasis-induced by protease hydrolysis, thus slowing down the process of malignant tumor development. Bortezomib was the first proteasome inhibitor approved for the treatment of cancer; Isazomib, Marizomib, Delanzomib, Carfilzomib and Orozomib are second-generation drugs.[194–199]

Proteasome inhibitors may cause heart failure, atherosclerosis, myocardial infarction and cardiac arrest.[41] A meta-analysis of bortezomib-associated cardiotoxicity showed that the incidence of all grades and high-grade cardiotoxicity was 3.8% (95% CI:2.6%-5.6%) and 2.3% (1.6%-3.5%), respectively, with a mortality rate of 3.0% (1.4%-6.5%). The incidence of cardiotoxicity depended on tumor type, treatment regimen, and stage of trial.[42]

The pathogenesis of proteasome inhibitor-associated cardiotoxicity is primarily related to dysregulation of calcium-ion homeostasis and abnormal energy metabolism in cardiomyocytes. Nowis et al demonstrated that bortezomib leads to ultrastructural abnormalities within the mitochondria, a decrease in ATP synthesis, and a decrease in cardiomyocyte contractility.[200] Of the proteasome inhibitors used in clinical practice, carfilzomib has the strongest correlation with cardiotoxicity. Carfilzomib decreases left ventricular function by increasing PP2A activity and inhibiting AMPKα and its downstream autophagic targets.[201]

Patients treated with proteasome inhibitors should be assessed for their baseline risk of adverse cardiovascular events. Monitor patients at higher risk or with abnormal baseline function. NP every cycle during the first 6 cycles under carfilzomib or bortezomib. Administer ACEI/ARB and β-blocker therapy in the presence of heart failure.[1]

Mitochondrial Transplantation in Cardiovascular Disease and Doxorubicin-Induced Cardiotoxicity

Introduction of Mitochondrial Transplantation

"Mitochondrial transplantation" is a therapeutic strategy that involves the transfer of isolated mitochondria to damaged areas of cells or organs.[202,203] It was first proposed in 2009 by the McCully group at Boston Children's Hospital, Harvard Medical School, who improved cardiac dysfunction after myocardial ischemia by injecting mitochondria isolated from normal tissue of New Zealand white rabbits directly into the site of myocardial ischemia, and reported the method of mitochondrial isolation in this study.[204] Since then, there has been a rapid development of research on mitochondrial transplantation.

Research on the source and isolation of mitochondria, the mechanism of mitochondria entry into cells, the mode of mitochondrial transplantation and the mitochondrial dose have been hot topics in recent years.

Mitochondrial transplantation is divided into autologous mitochondrial transplantation and allogeneic mitochondrial transplantation. Since the technology of vitro mitochondrial proliferation has not yet been mastered, the source of mitochondria is mainly isolated from tissues or cells, and the current sources of mitochondria are pectoralis major muscle, gastrocnemius muscle, liver, and also from H9c2 cells, mesenchymal stem cells, and fibroblast cell lines.[205–207] Commonly used extraction methods include differential centrifugation and density gradient centrifugation. Frezza et al described in detail the extraction of mitochondria from mouse liver, skeletal muscle, and fibroblasts and stated that the process of mitochondrial isolation needs to be rapid and at 4°C to ensure maximum mitochondrial activity.[208]

The widely recognized mechanisms of internalization include caveolae-dependent/clathrin- dependent endocytosis, actin-mediated endocytosis and macropinocytosis.[209–211] Kesner et al demonstrated that mitochondria maintain an intact bilayer membrane structure after internalization into cells and fuse with endogenous mitochondria, and that the integrity of the outer mitochondrial membrane is essential for mitochondrial transplantation.[212] Shi et al injected fluorescently labeled mitochondria from the tail vein of mice and found that mitochondria were distributed in the brain, heart, liver, kidney, and muscle tissues of mice, indicating that mitochondria could permeate blood vessels to reach tissues. The study found that mitochondria did not penetrate the red blood cell membrane and did not affect the oxygen-carrying capacity of red blood cells.[213] This provides a new transplantation modality for mitochondrial transplantation to treat mitochondrial diseases.

Currently, the main methods of mitochondrial transplantation are direct injection, co-incubation, centrifugation, magnetomitotransfer, cell-penetrating peptide, biocompatible polymer, photothermal nanoblade and fluidic force microscope (FluidFM).[214–216] These methods are widely used in animal experiments and cellular experiments.

Regarding the dose of mitochondrial transplantation, different doses are available for different animal and cellular models. When mitochondrial transplantation was applied to treat myocardial ischemia-reperfusion injury, McCully et al used $7.7\times10^6 \pm 1.5\times10^6$ of mitochondria perfused into the ischemic region of rabbit myocardium,[204] while 5×10^4 of mitochondria were injected into the ischemic region of mouse myocardium in the experiments of Jia et al.[217] The animals' cardiac function was improved in both experiments. There is insufficient information to determine the optimal dose of mitochondrial transplantation to ameliorate doxorubicin-induced cardiotoxicity. There is yet a long way to go in the study of mitochondrial transplantation doses.

Existing Studies on Mitochondrial Transplantation in Cardiovascular Disease and Doxorubicin-Induced Cardiotoxicity

Existing Research on Mitochondrial Transplantation in Cardiovascular Disease

Research on mitochondrial transplantation in cardiovascular disease has focused on animal models of ischemia-reperfusion and heart failure. Cowan et al demonstrated that mitochondrial transplantation could reduce infarct size and improve cardiac function after myocardial ischemia by coronary delivery of mitochondria derived from adult cardiac

fibroblasts at the onset of reperfusion in the rabbit Langendorff ischemia-reperfusion model.[218] This opens up the possibility of future clinical applications of mitochondrial transplantation.Weixler et al established a porcine right heart failure model in which transplantation of mitochondria isolated from porcine gastrocnemius muscle into the heart attenuated cardiomyocyte apoptosis and preserved contractility.[219] Ali Pour et al transplanted mitochondria isolated from rat skeletal muscle cells of the L6 cell line into normal rat heart H9c2 cells and human retinal ARPE-19 cells, demonstrating for the first time the feasibility of mitochondrial transplantation in different cell lines of the same genus as well as in cells of different species. This experiment also demonstrated that mitochondrial transplantation into normal cardiomyocytes transiently improved the bioenergetics of normal cardiomyocytes.[220]

In 2016, Emani et al performed the first mitochondrial transplantation in humans in voluntary subjects of five pediatric patients with myocardial ischemia-reperfusion injury requiring reliance on ECMO, and the team improved cardiac systolic function in five patients by transplanting mitochondria extracted from the rectus abdominis muscle into the myocardium via epicardial injection, enabling four of the patients to be removed from ECMO support on the second day of mitochondrial transplantation and without mitochondrial transplantation-related arrhythmias, myocardial hematomas, or scarring, which confirmed the potential of mitochondrial transplantation for use in human myocardial ischemia-reperfusion injury.[221]

Existing Studies of Mitochondrial Transplantation in Doxorubicin-Induced Cardiotoxicity

A recent study has validated the protective effect of mitochondrial transplantation in doxorubicin-induced cardiac injury. Yip et al showed that rats receiving mitochondria extracted from rat liver injected into the anterior left ventricular wall immediately after doxorubicin-induced dilated cardiomyopathy had preserved cardiac function with increased levels of the Nrf2, and decreased levels of NOX1 and NOX2, major members of the NADPH oxidase family, decreased levels of Drp1, increased levels of Mfn2, decreased levels of Caspase-3 and Bax.[222] Liu et al ameliorated doxorubicin-induced heart failure by M2-like macrophage transplantation and demonstrated that this protective effect was achieved by intercellular mitochondrial transfer.[223] Maleki et al first used mitochondrial transplantation in a study of doxorubicin-induced cardiotoxicity and restored the activity of rat primary cardiomyocytes after receiving mitochondrial transplantation[224] (Table 2).

Mechanism of Mitochondrial Transplantation

Although studies have confirmed the effectiveness of mitochondrial transplantation in myocardial infarction, heart failure, and doxorubicin-induced cardiotoxicity, the mechanisms by which mitochondrial transplantation improves cardiac function are not clear.

The currently recognized mechanisms by which mitochondrial transplantation exerts a protective effect are the following: (1) increased myocardial ATP content; (2) replacement of damaged mitochondrial DNA; (3) upregulation of protein pathways of mitochondrial function (Figure 3).[225,226] Zhang et al utilized differences between humans and mice to find that the accumulation of human mitochondrial DNA in the mouse heart drove the increase in endogenous mouse mitochondrial DNA, suggesting that the mechanism by which mitochondrial transplantation acts may be related to the renewal of mitochondrial DNA.[227]

Shin et al showed that mitochondria isolated from porcine pectoralis major muscle were transported into the myocardium through the coronary arteries, increasing myocardial ATP content, increasing coronary blood flow, and improving cardiac function after ischemia.[228] Jia et al verified the role of Nrf2 in mitochondrial transplantation for ischemia-reperfusion injury, and both wild-type mice and Nrf2 knockout mice received autologous mitochondrial transplantation after ischemia-reperfusion. The results showed that Nrf2 was essential in mitochondrial transplantation for ischemia-reperfusion injury, and the expression of mitochondrial Drp1 decreased after mitochondrial transplantation, while the expression of Mfn1 and Mfn2 increased, and the apoptotic factors Caspase-3 and Bax decreased, while the content of anti-apoptotic protein Bcl-2 increased, indicating that Nrf2 plays an important role in mitochondrial transplantation. Meanwhile, healthy intact mitochondria extracted from H9c2 cells were transplanted into H9c2 cells treated with doxorubicin, and it was found that the content of mitochondrial DNA in H9c2 cells increased after receiving

Table 2 Summary of Mitochondrial Transplantation in Cardiovascular Disease and Doxorubicin-Induced Cardiotoxicity

Model	Source of mitochondria	Isolation method	Transplantation method	Transplantation dose	Result	Reference
Rabbit Ischemia	Heart	Differential centrifugation	Direct injection	$7.7\times10^6\pm1.5\times10^6$/mL mitochondria	Enhance postischemic functional recovery and cellular viability	[204]
Mice Ischaemia-reperfusion injury	Pectoralis major muscle	Differential centrifugation	Direct injection	5×10^4 mitochondria	Alleviate cardiomyocyte Injury, improved cardiac function, and reduced apoptosis	[217]
Rabbit Ischaemia-reperfusion injury	Human adult cardiac fibroblasts	Differential filtration centrifugation	Intracoronary Delivery	1×10^8 mitochondria	Enhance myocardial function and salvage the ischemic myocardium	[218]
Porcine Heart failure	Gastrocnemius muscle	Differential filtration centrifugation	Direct injection	10×10^6/mL mitochondria	Preserve contractility and reduce apoptotic cardiomyocyte loss	[219]
H9c2 cells; ARPE-19 cells	L6 cells	Commercial isolation kit	Co-incubation	Mitochondria from L6 skeletal cells were isolated (from 100 cells per 1 recipient cell)	Lead to short-term improvement of bioenergetics	[220]
Pediatric patients Ischaemia-reperfusion	Abdominis muscle	Not mentioned	Direct injection	$1\times10^8\pm1\times10^5$particles/mL	Improvement in ventricular function and separate from ECMO support	[221]
Rat Dilated cardiomyopathy	Liver	Differential centrifugation	Direct injection	750 or 1500ug mitochondria	Preserve LVEF and myocardium integrity	[222]
Mice Doxorubicin-induced heart failure	M2-like Macrophages	Commercial Isolation kit	Systemic Injection	Mitochondria from 1×10^6cells	Attenuate cardiac fibrosis and cardiomyocyte apop tosis, as well as increased the level of circulating IL-4 and Th2 response	[223]
Neonatal rat cardiomyocytes Doxorubicin-induced cardiotoxicity	Liver	Different filters centrifugation	Co-incubation	15.77×10^6 mitochondria	Increase cell viability	[224]

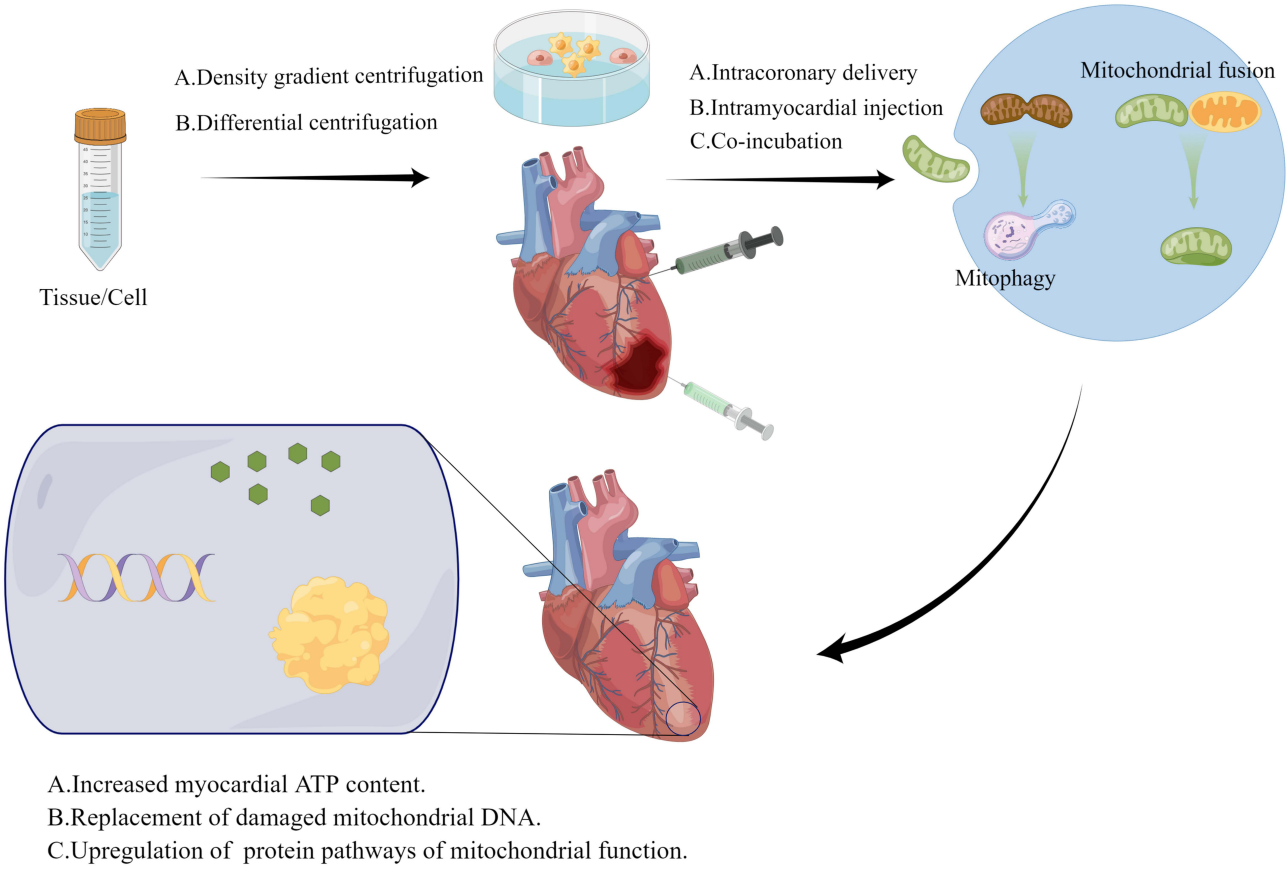


Figure 3 The process of mitochondrial transplantation and the protective mechanisms of mitochondrial transplantation. Mitochondria from different tissues or cells are transferred in different ways to dysfunctional tissues or cells to improve their function. By Figdraw.

mitochondrial transplantation, indicating that the transplanted mitochondria entered the cells and renewed the intracellular mitochondria thus regulating apoptosis, mitochondrial fusion and autophagy in cardiomyocytes.[217]

Prospects and Limitations

First for anticancer drugs, limiting the cumulative dose is an important measure to prevent cardiotoxicity. For patients with underlying cardiac disease, other drugs with less cardiotoxicity can be substituted. For example, the new generation of anticancer drugs such as epirubicin, and desmethylxorubicin are considered to be relatively less cardiotoxic and can be used as an alternative to doxorubicin. In addition changing the mode of administration to intravenous injection of liposomes, taking advantage of the difference in distribution of liposomes in different tissues to reduce their concentration in sensitive organs such as the heart and gastrointestinal tract, thus reducing cardiotoxicity. Use cardioprotective agents such as free radical scavengers to reduce the incidence of cardiac events. Despite the above treatments, there are still limitations in the treatment of anticancer drugs-induced cardiotoxicity. Current preventive and therapeutic measures do not completely eliminate cardiotoxicity because of the complexity of the mechanism of action of anticancer drugs on cardiotoxicity. Due to individual patient differences and the complexity of drug reactions, it is difficult for physicians to accurately predict which patients may develop cardiotoxicity. Therefore, all patients should undergo a comprehensive cardiac evaluation, focus on prevention, and try to achieve early detection, early diagnosis and early treatment. The current research on anticancer drugs-induced cardiotoxicity is not deep enough, and further understanding of its mechanism of action and influencing factors is needed for better prevention and treatment of cardiotoxicity. More clinical studies are also needed to verify the efficacy and safety of existing treatments and to explore new treatments.

Secondly, for mitochondrial transplantation, the present study showed no significant rejection after transplantation of mitochondria of either autologous or allogeneic origin, which could contribute to the promotion of donor origins of

mitochondria and provide the possibility of promoting allogeneic mitochondrial transplantation. The development of doxorubicin-induced cardiotoxicity is closely associated with mitochondrial dysfunction, and contrary to other mitochondrial diseases, patients often do not have a combination of systemic mitochondrial dysfunction, making it easier to obtain mitochondria from autologous sources. These make the use of mitochondrial transplantation in doxorubicin-induced cardiotoxicity easier to pass ethical review. However, there are still some problems in the application of mitochondrial transplantation in humans, for example, whether mitochondria by direct injection will lead to hematoma and scar formation at the injection site which will further affect the organ function, and whether mitochondrial transplantation by systemic injection will cause vascular blockage and immune rejection, which are important factors limiting the development of mitochondrial transplantation at present. Improvements in transplantation methods may be an important factor in the development of mitochondrial transplantation. In addition, research on mitochondrial transplantation to improve doxorubicin-induced cardiotoxicity is extremely limited and is currently limited to cellular studies and the mechanism by which mitochondrial transplantation works is unknown. For example, whether the interaction between normal and abnormal mitochondria occurs after mitochondrial transplantation and whether this interaction is affected by certain intracellular proteins, and whether mitochondrial transplantation exerts its protective effect by more significantly damaging the DNA of mitochondria. The feasibility of mitochondrial transplantation still needs to be verified by further research and clinical trials. Currently, there are many unknowns about the efficacy and safety of mitochondrial transplantation, such as the source of mitochondria, the optimal infusion method, and the cellular response after transplantation. Therefore, at this stage, mitochondrial transplantation cannot be widely used in clinical treatment. Overall, although mitochondrial transplantation is a promising therapeutic method, its feasibility needs further research and verification. In the future, with the deepening of scientific research and the development of technology, we are expected to see more breakthroughs and applications of mitochondrial transplantation. The exploration of mitochondrial transplantation modalities and the mechanisms by which mitochondrial transplantation works will facilitate the development of mitochondrial transplantation.

Summary

In the course of cancer treatment, we should fully recognize the possible cardiotoxicity caused by anticancer drugs. Understanding the characteristics of various anticancer drugs, paying attention to patients' heart health, and conducting regular checkups are the keys to preventing and treating cardiotoxicity. Adequate discussion with multidisciplinary doctors to choose the appropriate treatment plan for patients and minimize the risk of cardiotoxicity is a right that every cancer patient should enjoy. With individualized therapy, doctors can better understand a patient's risk factors and develop a treatment plan that is more appropriate for the patient, thereby reducing cardiotoxicity.

With a better understanding of the pathogenesis of cancer and heart disease, more precise anticancer drugs may be developed in the future to reduce the adverse effects on the heart. Novel treatment strategies may be developed in the future to reduce the cardiotoxicity of anticancer drugs. With the continuous progress of medical technology and improvement of treatment methods, it is believed that there will be more effective treatments to reduce the adverse effects of anticancer drugs on the heart in the future.

Targeting mitochondria to treat doxorubicin-induced cardiotoxicity is currently a promising research point. Many studies have shown that the therapeutic effect of mitochondrial transplantation is maintained longer than some drugs, and no significant adverse effects have been found with autologous mitochondrial transplantation. Healthy mitochondria are essential for maintaining cellular integrity and function, and thus the source, isolation approach, delivery, transplantation dose, immunogenicity and ethical issues still need to be thoroughly explored. Therefore, studies to ameliorate doxorubicin-induced cardiotoxicity by mitochondrial transplantation remain compelling and promising.

Through this review, we hope to provide readers with a basic understanding of anticancer drugs-induced cardiotoxicity and a preliminary understanding of the current status of the application and development possibilities of the novel technique of mitochondrial transplantation, and we look forward to more scientific researchers committing themselves to the study of anticancer drugs-induced cardiotoxicity, so as to bring benefits to oncology patients.

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Disclosure

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