Review

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Cardioprotective strategies in the management of chemotherapy-induced cardiotoxicity: current approaches and future directions

Zeineb Al-Hasnawi, MBChB[a], Hawraa Mohammed Hasan, MBChB[b], Jaafar Mohammed Abdul Azeez, MBChB[c], Naam Kadhim, MBChB[d], Aya Ahmed Shimal, MBChB[d], Maryam Hussein Sadeq, MBChB[d], Noor Al-Huda Ali Motashar Mahood, MBChB[e], Abdulmelik A. N. Al-Qara Ghuli, MBChB[f], Ahmed Safaa Hussein, MBBS[g], Priyadarshi Prajjwal, MBBS[h], Hritvik Jain, MBBS[i], Aman Goyal, MBBS[j], Omniat Amir, MBBS[k,*]

Background: Chemotherapy-induced cardiotoxicity (CIC) is a significant challenge in cancer treatment, leading to heart failure and myocardial infarction. With rising cancer survival rates, the long-term cardiovascular health of survivors has gained importance. While several cardioprotective medications have been studied to mitigate chemotherapy's harmful effects on the heart, more research is needed to confirm their effectiveness and optimal use.

Methodology: This review synthesizes evidence on cardioprotective drugs in managing CIC. The authors conducted a comprehensive literature search of peer-reviewed articles, clinical trials, and meta-analyses published between January 2000 and May 2024. Studies were selected based on relevance, quality, and focus on mechanisms, efficacy, and clinical outcomes of cardioprotective agents such as beta-blockers, ACE inhibitors, ARBs, statins, and dexrazoxane.

Results and discussion: Cardioprotective medications show potential in alleviating the impact of chemotherapy on heart function. Beta-blockers and ACE inhibitors effectively reduce heart failure incidence and improve cardiac outcomes. Statins, with their anti-inflammatory and antioxidative properties, and dexrazoxane, which reduces anthracycline-induced cardiotoxicity, also show promise. However, variability in study designs, patient groups, and chemotherapy treatments complicates the establishment of standardized treatment protocols.

Conclusion: Cardioprotective drugs hold significant promise in managing CIC and improving cardiac outcomes for cancer patients. Current evidence supports the efficacy of beta-blockers, ACE inhibitors, statins, and dexrazoxane. Further research is needed to establish standardized protocols, evaluate long-term safety, and optimize treatment timing. Integrating cardioprotective strategies into oncological care can enhance the quality of life and prognosis for cancer survivors.

Keywords: ACE inhibitors, beta-blockers, cancer treatment, cardioprotective drugs, chemotherapy-induced cardiotoxicity, statins

Introduction

Chemotherapy, a fundamental component in the management of many types of cancer, has greatly enhanced the chances of survival for patients with malignancies in recent years[1]. Nevertheless, its use is frequently restricted due to the presence of cardiotoxicity, which presents a significant risk to the cardiovascular well-being of patients[1,2]. Chemotherapy-induced cardi otoxicity (CIC) can cause significant and perhaps permanent damage to the heart, resulting in impaired cardiac function that can have a negative impact on the long-term prospects and well-being of those who have survived cancer[3]. The prevalence of CIC varies according to the specific chemotherapy agents used, its dosage, duration of treatment, age of patients, and the type of cancer they have, in addition to many other factors. The overall prevalence of CIC in cancer patients is estimated to be 37.5%[4].

Chemotherapy-induced cardiotoxicity is categorized into two primary types: type 1 and type 2. Type 1 cardiotoxicity, associated with early onset, results from irreversible cardiomyocyte

[a]College of Medicine, University of Kufa, Najaf, Iraq, [b]Al Kadhimiyah Teaching Hospital, Baghdad, Iraq, [c]Babylon College of Medicine, University of Babylon, Babil, Iraq, [d]College of Medicine, University of Baghdad, Baghdad, Iraq, [e]Al-Kindy College of Medicine, University of Baghdad, Baghdad, Iraq, [f]College of Medicine, University of Diyala, Diyala, Iraq, [g]Ulyanovsk State University, Ulyanovsk State Medical University, Ulyanovsk, Russia, [h]Bharati Vidyapeeth Deemed University, Pune, India, [i]All India Institute of Medical Sciences, Jodhpur, India, [j]Department of Internal Medicine, Seth GS Medical College and KEM Hospital, Mumbai, India and [k]Almanhal Academy for Science, Khartoum, Sudan

N.K., A.A.S. contributed equally.

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*Corresponding author. Address: Manhal University, Almanhal academy for science, Khartoum, Sudan. Tel.: +249 099 263 3363. E-mail: omniatamir123@gmail.com (O. Amir).

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necrosis and apoptosis, often linked to anthracyclines like doxorubicin[2–4]. Type 2 cardiotoxicity, characterized by a delayed onset, involves reversible cardiomyocyte dysfunction and is commonly associated with drugs such as trastuzumab.

The underlying mechanisms of CIC are complex and involve several factors, including oxidative stress, inflammation, mitochondrial malfunction, and direct damage to the heart muscle[1]. Anthracyclines, such as doxorubicin, produce reactive oxygen species (ROS) that induce DNA damage and death in cardiac myocytes[3]. Trastuzumab, however, interferes with the HER2 signaling pathway, which is essential for the survival and function of cardiac cells. The cardiotoxic consequences might occur either during or immediately after chemotherapy, or they may appear years after, requiring ongoing care and management.

Additional chemotherapeutic drugs, such as antimetabolites, alkylating agents, and tyrosine kinase inhibitors (TKIs), also have a role in causing CIC through different mechanisms[5,6]. For example, the drug 5-fluorouracil (5-FU) causes the narrowing of coronary blood vessels and the accumulation of harmful molecules, resulting in reduced blood flow to the heart muscle and cell death. Cyclophosphamide and cisplatin, which are alkylating drugs, induce oxidative damage and enhance the expression of pro-apoptotic genes. On the other hand, TKIs such as trastuzumab interfere with mitochondrial activity and promote the generation of ROS.

Given the prevalence and severity of CIC, there is an urgent need for effective cardioprotective interventions. Current strategies include the use of cardioprotective drugs, lifestyle modifications, and early detection methods to mitigate the risk of CIC. The aim of this study is to provide a comprehensive review of current and emerging cardioprotective drugs used in the management of chemotherapy-induced cardiotoxicity (CIC). By evaluating the mechanisms, efficacy, and clinical outcomes associated with cardioprotective agents, the review seeks to identify promising treatment strategies and address the variability in existing evidence. Additionally, our study aims to highlight future research directions for developing standardized protocols and optimizing the integration of cardioprotective strategies into oncological care.

HIGHLIGHTS

- Chemotherapy-induced cardiotoxicity is a significant issue in cancer treatment, leading to adverse cardiovascular events like heart failure and myocardial infarction.
- Cardioprotective medications including Beta-blockers, ACE inhibitors, ARBs, statins, and dexrazoxane show promise in mitigating the cardiotoxic effects of chemotherapy.
- Beta-blockers and ACE inhibitors significantly reduce heart failure incidence and improve cardiac outcomes, while statins offer anti-inflammatory benefits and dexrazoxane lessens anthracycline-induced cardiotoxicity.
- However, variability in study designs, patient populations, and chemotherapy regimens complicates the development of standardized treatment protocols despite positive outcomes.
- Additional research is necessary to establish uniform guidelines, assess long-term safety, and optimize the timing of cardioprotective treatments to enhance the quality of life and prognosis for cancer survivors.

Methodology

Study design

This is a narrative review that summarizes current studies on the use of cardioprotective drugs in the management of chemotherapy-induced cardiotoxicity. We focused on the mechanisms, efficacy, and clinical outcomes associated with these agents.

Literature search strategy

A principal investigator performed the literature search using electronic databases such as PubMed, MEDLINE, and Cochrane Library. The search covered publications from January 2000 to May 2024 to ensure the inclusion of recent and relevant studies. Search terms included “chemotherapy-induced cardiotoxicity,” “cardioprotective drugs,” “anthracyclines,” “trastuzumab,” “oxidative stress,” “inflammation,” and “cardiac dysfunction.”

Inclusion and exclusion criteria

We focused on (1) Original and review studies published in peer-reviewed journals. (2) Articles with the main language as English, (3) Studies evaluating the efficacy of cardioprotective drugs in preventing or treating chemotherapy-induced cardiotoxicity, (4) Clinical trials, cohort studies, case-control studies, and systematic reviews. Studies were excluded from our review if (1) Studies were not related to cardioprotective drugs, (2) Animal studies and in vitro studies, (3) Articles lacking sufficient data on clinical outcomes or mechanisms of cardioprotection.

Results and discussion

Mechanisms of chemotherapy-induced cardiotoxicity

Chemotherapy-induced cardiotoxicity is the main limiting factor for a good prognosis. As we mentioned earlier, it is categorized into two types. These cardiomyocyte injuries result from inflammation and oxidative stress, the main two phenomena underlying chemotherapy-induced cardiotoxicity mechanisms through direct and indirect pathways.

Anthracyclines are a group of potent cytotoxic antibiotics used in many cancers. They work by interfering with redox cycling and producing reactive oxygen and nitrogen species (ROS and RNS) causing DNA damage (Fig. 1). Anthracyclines accumulate in the mitochondria by their favorable binding to cardiolipin, a type of phospholipid present in the inner mitochondrial membrane. This accumulation inhibits complexes I and II of the electron transport chain (ETC) resulting in increased mitochondrial ROS and RNS production[1]. This stressful oxidative environment is linked to cellular and macromolecular damage including myofibrillar proteins such as troponin and actin impairing cardiac contractility and function[2]. Additionally, anthracyclines bind to Top2B, an isoenzyme present in quiescent cells and constantly expressed through the cell cycle, forming the Top2B—anthracycline-DNA complex. This complex triggers a sequence of events that culminate with cardiac cell apoptosis. Top 2—anthracycline-DNA complex breaks the double stands of DNA and inhibits the peroxisome proliferator-activated receptors that result in the initiation of p53 signaling, disruption of intracellular Ca+2 balance, impairing mitochondrial function, and ultimately cardiac cell apoptosis[3].

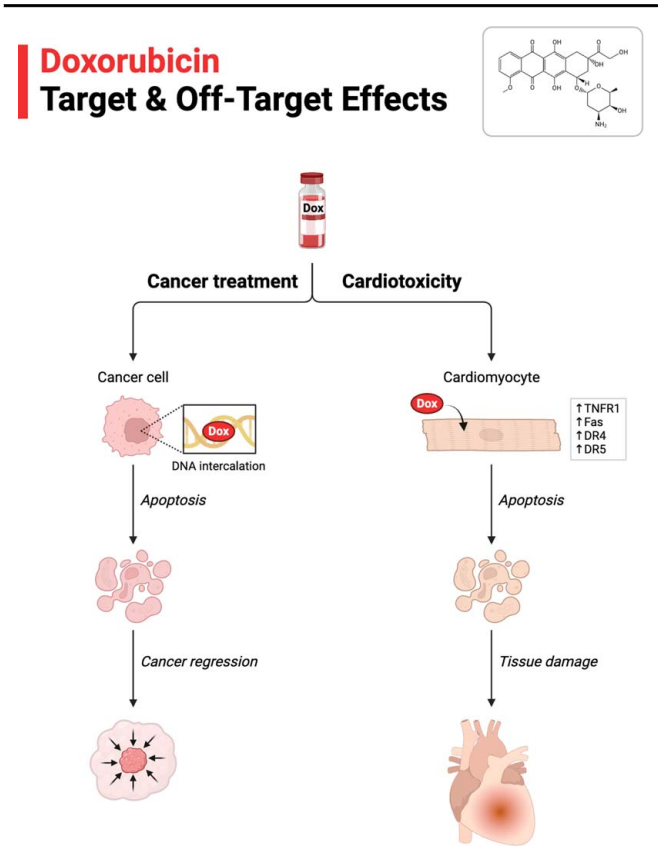

Figure 1. Doxorubicin causes heart damage by increasing the expression of death receptors, which leads to programmed cell death in heart muscle cells.

Antimetabolites are among the most common chemotherapeutics for blood and solid tumors that work by interfering with DNA synthesis. The most notable in terms of cardiotoxicity is 5-fluorouracil (5-FU), a pyrimidine analog. Although the exact mechanism is uncertain, it is suggested to involve endothelial and primary smooth muscle dysfunction, decreased nitric oxide (NO) release, and increased endothelin-1 level. These factors induce coronary vasospasm reducing oxygen delivery to the heart and resulting in ischemia[4]. Additionally, 5-FU increases ROS and decreases antioxidants, resulting in an oxidative environment that ultimately leads to inflammation and cardiomyocyte apoptosis[5]. Antifolate antimetabolites, such as methotrexate, incite their cardia damage by lowering antioxidant levels and interfering with DNA and RNA synthesis[6,7].

Alkylating agents, such as cisplatin and cyclophosphamide, exert their cytotoxic effect through their intermediate metabolites that damage both nuclear and mitochondrial DNAs. Cyclophosphamide causes oxidative damage, apoptosis, and cardiomyopathy by activating p53 and upregulating the expression of COX2, TNF-a, and IL-1B[8]. Cisplatin raises ROS and lipid peroxidation while lowering glutathione antioxidant levels. These effects depolarize the mitochondrial membrane, modify structural components, and upregulate the pro-apoptotic gene transcription[9].

TKIs are a class of chemotherapeutics used in many metastatic cancers and HER2-positive breast cancer. This class includes small molecule TKIs (smTKIs) and monoclonal antibodies. Trastuzumab, a monoclonal antibody, binds to HER2 and prevents HER2-HER4 heterodimerization and subsequently inhibits the activation of cascades that activate MAPK (essential for mitochondrial membrane stabilization) and P13K/Akt (modulate the mitochondrial respiration to produce less ROS) metabolic pathways (Fig. 2). The resulting ROS accumulation destabilizes cardiac muscle by disrupting sarcomeres, resulting in cardiotoxicity[10]. Regarding microtubule inhibitors, the risk of cardiotoxicity is high when combined with anthracyclines, monoclonal antibodies, or alkylating agents[11]. The exact underlying mechanism is not fully known, but many studies suggest the association with oxidative stress and inflammatory response[12].

Risk factors associated with chemotherapy-induced cardiotoxicity

Many factors contribute to chemotherapy-induced cardiotoxicity, high cumulative dose, patient characteristics such as age and weight, cardiovascular risk, comorbid diseases such as diabetes and hypertension, and concomitant chemotherapy and radiation, in addition to different pathological and genetic factors[13]. Many studies reported the relation between the pathophysiologic effects of hypertension on cardiomyocyte injury in patients with anthracycline-induced cardiotoxicity (AIC) and the role of oxidative stress and inflammation in cardiac fibrosis[13]. Further evi dence is provided by a meta-analysis of 16 retrospective studies that exclude any study with prior use of antihypertensive drugs, particularly beta-blockers (which reduce AIC), thereby enhan cing study quality[14]. Diabetes mellitus is another risk factor; continuous exposure to high blood sugars, fatty acids, and tri glycerides increases fat droplets in myocardial cells, mediating cardiotoxicity[14,15]. A recent study confirmed that obese breast cancer patients who undergo anthracycline treatment have increased cardiotoxicity risk. This is related to elevated oxidative damage in the heart and hormonal changes, including increased leptin levels and decreased adiponectin levels[16].

In addition, studies show that there are genetic variations in 40 genes involved in increased AIC risk[17]. ATP-binding cassette (ABC) genes encode trans-membrane proteins responsible for transporting chemotherapeutic drugs out of cardiomyocytes. Genetic variations in these specific genes alter the rate of ABC gene expression, leading to drug-exporting defects and anthracycline buildup in the cardiomyocytes[18]. The carbonyl reductase (CBR) gene family encodes cardiomyocyte enzymes that meta bolize many compounds, including anthracyclines, into C-13 hydroxy metabolites, which are toxic alcohol metabolites that cause cardiotoxicity[17]. In patients with breast cancer, HFE gene variations were associated with increased cardiac iron deposition and a higher risk of AIC[19].

Cardiotoxicity manifests as arrhythmia, decreased systolic function, and myocarditis, and they differ by treatment options, cumulative dose, and the patient's clinical condition. Patients may experience these symptoms immediately after treatment, or they may develop months or years later[20]. More than 50% of anthracycline-exposed patients develop symptoms 10-20 years later, including arrhythmia and CHF, characterized by features of dilated cardiomyopathy in the asymptomatic stage[21,22]. In trastuzumab-treated patients, the adverse effects are an asymptomatic drop in the LVEF, chronic cardiopulmonary function damage, and a high risk of mortality[20,23,24]. While the incidence of immune-related cardiac adverse effects from immune checkpoint inhibitors (ICIs) is very low, life-threatening myocarditis can manifest within 30 days from the beginning of treatment[25,26].

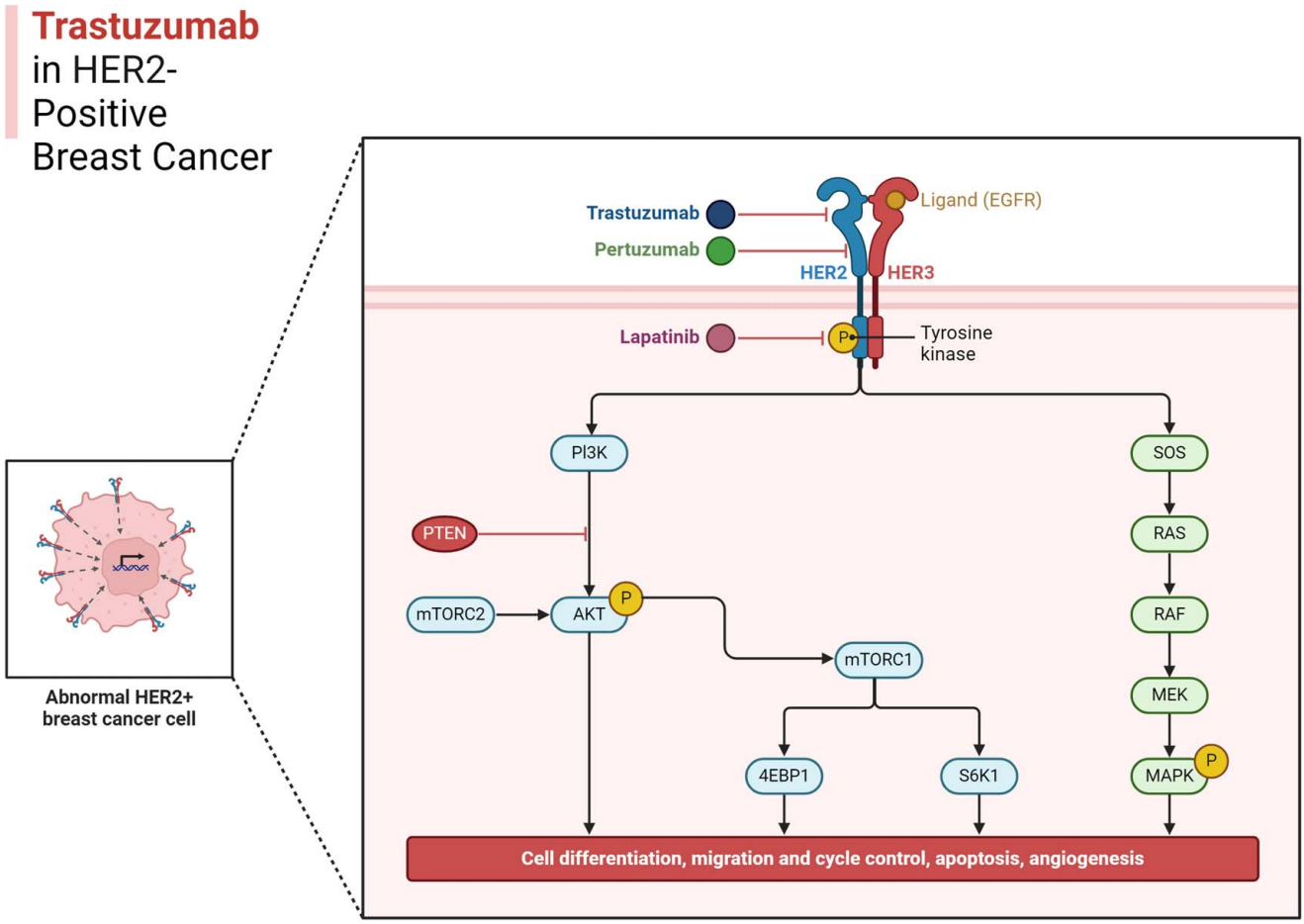

Figure 2. The treatment and cardiotoxicity mechanism for trastuzumab in breast cancer. Tyrosine kinase inhibitors (TKIs), specifically those with multiple kinase activities affect the signal transduction. One of these signal transduction pathways is the cardiotrophin and its receptor gp130, EGFR, ErbB2, HER2, PI3K, AMPK. In addition, the VEGF which is involved in angiogenesis and myocardial perfusion are often implicated in the development of the cardiovascular damage induced by TKIs. Finally, the accumulation of these drug metabolites causes the development of reactive oxygen species disrupting the structure and function of the sarcomeres. 4EBP1, eukaryotic translation initiation factor 4E-binding protein 1; EGFR, epidermal growth factor receptor; gp130: Glycoprotein 130; HER2, human epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; MEK: mitogen-activated protein kinase; mTORC1, mammalian target of rapamycin complex 1; P, phosphorous; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; RAS, A family of related proteins involved in transmitting signals within cells; S6K1, ribosomal protein s6 kinase beta-1; SOS, son of sevenless (a guanine nucleotide exchange factor).

Diagnosis of cardiac damage caused by chemotherapeutic drugs

ECG is a routine method used before, during, and after chemotherapy. Different chemotherapeutics produce different ECG changes, and the most important are QT prolongation and premature ventricular beats. Among patients receiving anthracycline treatment, premature ventricular beats are the most prevalent form of arrhythmia[27,28]. Echocardiography is used to measure cardiac global longitudinal strain (GLS), a measure of longitudinal cardiac deformation. This can detect early cardiac changes. However, it is limited by factors such as patient age and sex as well as image acquisition[29,30]. For better results, it could be used with native T1 mapping.

Cardiovascular magnetic resonance (CMR) measures native myocardial T1 mapping. This provides a quantitative measure for detecting early asymptomatic cardiac changes, particularly inflammation and fibrosis. This appears as an increase in T1 mapping from the baseline in patients who have normal left ventricular ejection fraction (LVEF)[31]. In addition, serum cardiac troponin (cTn) is an early biomarker of cardiotoxicity. In the setting of cardiotoxicity, the rise from baseline is more reflective of both cardiomyocyte apoptosis and myofibril degeneration than necrosis and predicts LVEF reduction and cardiovascular complications[32]. Many clinical trials have reported the high specificity and sensitivity of cTns in predicting LVD[33,34]. A study by Cardinale and colleagues of patients who underwent high doses of chemotherapy reported the association between max imal Troponin I (cTnI) levels and LVEF reduction[35,36]. A meta-analysis by Michel *et al.*[34] indicated that both cTnI and troponin T (cTnT) are equal in detecting LVD in anthracycline and anti-HER2 therapy; high cTns also predict myocarditis with immune checkpoint inhibitors (ICIs). BNP and NT-proBNP are markers for physical and electrochemical cardiac changes that predict subsequent congestive heart failure and mortality in che motherapy patients[37]. Various factors affect the BNP level, lim iting its specificity, including multiple medications, patient age, and BMI, and it is increased in the presence of metastasis[38,39].

Oxidative stress and inflammatory biomarkers like ROS and IL-6 both correlate with reduced strain peak and systolic dysfunction[40,41]. Many studies have reported significant elevations in C-reactive protein and high-sensitivity C-reactive protein (CRP and hs-CRP) levels after anthracycline-based chemotherapy (ANT). However, only one study has reported their association with echocardiographic changes[42].

Finally, microRNAs (miRNAs), especially miRNA-1, have been demonstrated as an early biomarker for chemotherapy-induced cardiotoxicity. The miRNA-1 levels are more sensitive than the total serum miRNA, particularly in patients with high levels of cardiac troponin I (cTnI). However, patient factors and the type and stage of the disease influence its levels[43].

Comprehensive approaches to reduce cancer therapy-related cardiac dysfunction

Various studies researched the possible strategies to lower cardiotoxicity associated with chemotherapeutics. Most studies have concluded that the initial step is improving cardiovascular risk by addressing hyperlipidemia, smoking, hypertension, obesity, diabetes, and any other modifiable risk factors. Addressing these risk factors allows for higher cumulative doses to cure cancer and improves post-chemotherapy outcomes. Behavioral and pharmacological interventions to reduce these factors are the key to reducing the toxicity associated with cancer therapy[44,45].

Non-pharmacological strategies

Physical activity is essential to the overall well-being of cancer survivors because it improves the quality of life, reduces weight, and lowers the risk of cardiovascular events. Exercise guidelines for cancer survivors released by the International Multidisciplinary Roundtable suggest 90 minutes of moderate-intensity exercise per week, focusing on strength training and targeting every muscle in the body[44].

Foulkes and colleagues found in a 2022 RCT that the complete cancer treatment regimen should include exercise. Functional disability was 68% less likely in exercise participants at four months, but not at 12 months. However, participants who adhered to exercise showed complete attenuation of functional disability at 12 months. Exercise also improved VO2peak and biventricular ejection fraction[46]. Similarly, a review by Varghese *et al.*[44] found that aerobic exercise improves cardiac dysfunction and cardiorespiratory fitness (VO2peak), which is impacted in patients receiving anthracycline and cardi ovascular mortality.

Anthracyclines-based preventions

Research indicates that anthracycline-induced cardiotoxicity is more likely to occur in patients who receive higher cumulative doses over shorter periods. In 2017, the American Society of Clinical Oncology recommended multiple ways to reduce cardiotoxicity, including the use of dexrazoxane, continuous infusions of anthracycline instead of bolus doses, and liposomal formulations[47].

Continuous infusions, which can last from 6 to 96 h, show 4.13 times less cardiotoxicity than bolus applications. Prolonged weekly administration of treatment has also been associated with lower cardiotoxicity (0.8 vs. 2.9)[48]. A meta-analysis of RCTs comparing bolus and continuous infusions of anthracycline established that continuous infusions have a lower incidence of cardiotoxicity[47].

Liposomal coating modifies the pharmacokinetic properties of anthracycline. The larger molecular size alters the tissue distribution, relatively sparing the heart from damage by restricting drug passage through cardiac capillary junctions while still allowing distribution in areas of tumor angiogenesis, reducing cardiotoxicity by 80%[47,48].

Dexrazoxane

The only FDA-approved drug for chemotherapy-induced cardiotoxicity is dexrazoxane (since August 2014). It is a chemoprotectant and iron-chelating agent that enters the cell easily due to its hydrophilic and enclosed ring nature. It binds to iron in its metabolized form that is similar to ethylenediaminetetraacetic acid (EDTA), reducing the iron-anthracycline complex formation and thus inhibiting free radicals that cause harm to the myocardial cell by peroxiding the lipid membrane, offering lower cardiotoxicity in anthracycline use[48,49]. It also decreases DNA damage by antagonizing the anthracycline molecular target, prompting topoisomerase IIb selective degeneration by binding to topoisomerase II[49,50].

Initially, there were concerns that dexrazoxane may disrupt the activity of anthracyclines or may cause secondary malignancies[51]. These causes were unfounded, yet dexrazoxane is only recommended for patients who received doses of doxorubicin greater than 300 mg/m^2 or doses of epirubicin greater than 550 mg/m^2, and for patients with advanced anthracycline-sensitive cancers scheduled to receive further doses[52]. It is given as an infusion over 15 min immediately before starting anthracyclines at a ratio of 10:1 to doxorubicin[49].

Reichardt and colleagues reviewed a group of randomized clinical trials led by the Cochrane Group. They found that the risk of heart failure was significantly lower in patients who took dexrazoxane and anthracycline (11 out of 769, 1.4%) compared to patients who took anthracycline alone (69 out of 792, 10%), with a relative risk (RR) of 0.18, 95% CI[53]. In another study, dexrazoxane showed only a slight improvement in survival (71.9–75.4%), which encouraged early screening and primary prevention to reduce mortality from cardiotoxic effects[50].

The role of cardioprotective agents in heart failure and chemotherapy

Cardioprotective medications are medications used routinely in the treatment of heart failure with reduced ejection fraction (HFrEF). They function by minimizing the negative remodeling caused by adrenergic and neuroendocrine imbalances. They include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), aldosterone antagonists, beta-blockers (BB), and statins[47].

Angiotensin-converting enzyme inhibitors (ACEIs)

Experimental models have demonstrated that the cardiac renin-angiotensin system catalyzes anthracycline-induced cardiotoxicity, a process that ACEIs can either delay or prevent[54]. They are considered the best initial intervention for the prevention of anthracycline-induced cardiotoxicity because they inhibit

angiotensin II formation, leading to a decline in vascular resistance and myocardial afterload, reducing bradykinin degradation, increasing NO synthesis, preserving sarcoplasmic reticulum Ca2+ homeostasis, and, in turn, the contractility of the myocardium. In some animal models, pre- or co-treatment of ACEI with concurrent cancer therapy resulted in a reduction in heart failure, hypertrophy, serum markers of myocardial damage, and a general increase in hemodynamic function[55,56].

The majority of ACEIs have almost identical actions, yet they differ due to variations in their chemical structures. Enalapril is the most widely utilized and extensively studied. It is recommended to include enalapril early in the treatment to minimize late cardiotoxicity. In a randomized, double-blind, controlled clinical trial, Gupta *et al.* divided patients receiving anthracyclines into two groups: group A received enalapril at a dosage of 0.1 mg/kg/d from the first day of chemotherapy for 6 months, while group B received a placebo. After 6 months, LVEF declined greater than 20% in 3 patients in group B, while none were seen in group A (62.25 ± 5.49 compared to 56.15 ± 4.79, $P < 0.001$). Cardiac biomarkers also increased for group B, especially proBNP (49.60 ± 35.97 compared to 98.60 ± 54.24, $P < 0.001$). Overall, this study established enalapril as cardioprotective against AIC[57]. In a randomized study, Valsartan (ARB) demonstrated significant efficacy in preventing doxorubicin-induced cardiotoxicity, reducing plasma brain natriuretic peptides, reducing left ventricular end-diastolic diameter in echocardiography, and reducing Qtc interval in electrocardiography[55].

Beta-blockers (BBs)

Beta-blockers (BBs), such as nebivolol and carvedilol, block beta-1, 2, and 1-adrenoreceptors. They have antioxidant and anti-apoptotic properties that could neutralize the ROS generated by anthracycline and other chemotherapeutics, protecting left ventricular systolic and diastolic function[47,55]. Doxorubicin downregulates sarcoplasmic reticulum Ca2+-ATPase (SERCA2) gene expression. Carvedilol blocks the downregulation of SERCA2 gene expression, thus restoring its activity[58].

Carvedilol is the most widely used and researched drug in this group. In an early randomized clinical trial by Avila and colleagues in 2018, carvedilol did not protect against the reduction in LVEF. However, it did stabilize troponin levels and diastolic function, demonstrating myocardial protection[59]. Contrasting these results, a meta-analysis in 2019 by Huang *et al.*[60] con cluded that carvedilol provides significant protection against cardiotoxicity in chemotherapy patients. In an updated meta-a nalysis by Attar *et al.*[61] in 2022, BBs were associated with lower systolic and diastolic dysfunction but showed no significant reduction in chemotherapy-induced cardiotoxicity.

In contrast, multiple studies have shown that metoprolol has no protective or preventive effects on cardiotoxicity[60,62]. Alizadehasl and colleagues conducted a randomized clinical trial to study nebivolol, a β1-selective adrenergic receptor antagonist, in breast cancer patients undergoing chemotherapy. Researchers randomly assigned the patients to receive either nebivolol (5 mg/d) or a placebo. The results recommend the prophylactic use of nebivolol to prevent chemotherapy-induced cardiotoxicity[54,62]. Enalapril and carvedilol are the most effective drugs for achieving normalization of anthracycline-caused decreases in LVEF. However, these effects are less marked than in dexrazox ane-based prevention[63].

Aldosterone antagonists

Spironolactone is the first and most commonly used drug in this class. It blocks the last step of the renin-angiotensin-aldosterone system, which has a vital role in myocardial remodeling. Spironolactone has a well-known beneficial role in cardiac fibrosis and remodeling in patients with heart failure and myocardial infarction[64].

Akpek and colleagues published a randomized, double-blinded, placebo-controlled clinical trial that established the effectiveness of spironolactone in preventing anthracycline-induced cardiotoxicity. The study divided 83 female breast cancer patients receiving anthracycline into two groups: one group received a placebo, while the other group received 25 mg/d of spironolactone. LVEF was reduced from 67.0 ± 6.1 to 65.7 ± 7.4 ($P = 0.094$) in the spironolactone group, while the control group showed a reduction from 67.7 ± 6.3 to 53.6 ± 6.8 ($P < 0.001$)[64]. Supporting these results, a systematic review by Alizadehasl *et al.*[62] in 2020 concluded that LVEF reduction was the lowest in breast cancer and lymphoma patients receiving spironolactone, nebivolol, rosuvastatin, carve dilol, and enalapril while on concurrent anthracycline therapy.

Statins

Statins are common medications used in patients with high cardiovascular risk factors. They inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme-A reductase (HMG-CoA reductase), lowering low-density lipoprotein (LDL) levels. They also inhibit proatherogenic Rho-kinase, leading to a reduction in NFkB signaling. Eventually, this raises the activity of endothelial nitric oxide synthase, which leads to more nitric oxide (NO) being available in the body. This, in turn, causes troponin-1 to be phosphorylated and heart muscle to relax[65].

An article by Heiston and colleagues published in 2022 on statins for cardiac and vascular protection reviewed a randomized control trial for patients on cancer therapy and statins. The trial randomly assigned forty patients to receive either anthracycline and 40 mg/d atorvastatin or anthracycline alone. The results revealed a significant decrease in LVEF, a decline in high-sensitivity C-reactive protein (hs-CRP), preservation of ejection fraction, and lower inclines in left ventricular end-diastolic and left ventricular end-systolic diameters. Rosuvastatin showed comparable results to atorvastatin[65]. However, LVEF shows less deterioration at higher statin doses (40–80 mg/d) compared to lower doses or no statin at all[62,66].

These results mirror data from an article by Henninger and colleagues published in 2017 on statins and their cardioprotection, entailing a clinical cohort study that resulted in a reduced risk of heart failure in breast cancer patients receiving concurrent cancer therapy and statins. In addition, a meta-study found that statins are equally effective in the prevention of anthracycline-induced cardiotoxicity as dexrazoxane, BB, or ACEI[63]. Although these studies prove significant protection, the pooled results of a meta-analysis on two randomized controlled trials revealed no significant reduction in the cardiotoxicity risk (RR: 0.49; 95% CI: 0.17–1.45; $P = 0.20$)[45].

Risk-guided strategies to mitigate chemotherapy-induced cardiotoxicity

A fundamental question remains in chemotherapy-induced cardiotoxicity prevention, which is: do all patients undergoing cancer

therapy receive cardioprotective agents, or only selected groups at higher risk? A few trials presented cardioprotective agents depending on the patient's risk factors that are assessed at baseline and while receiving cancer therapy using biochemical markers such as cardiac troponin or imaging markers like echocardiographic GLS. These interventions demonstrated promising effects[45].

The ICOS-ONE (international cardiooncology society-one) trial

This is a randomized, controlled, open-label, multicenter study held by 21 centers in Italy, aiming to describe the time course of the cardiac biomarkers (troponin, BNP, PTX3) and LVEF over 36 months. It included 273 first-in-life breast cancer patients with low cardiovascular risk who were indicated for anthracyclines. One arm of the trial received prophylactic enalapril, and the second arm was initiated on enalapril based on abnormal troponin levels. Regarding the primary outcome of elevation in cardiac troponin levels, there was no reported between-group difference, with 23% in the early prevention group compared to 26% in the troponin-triggered group. At the same time, the BNP remained within the normal range, and PTX3 peaked and then returned to normal levels. In this study, cardiotoxicity was defined as an LVEF reduction of 10% or an LVEF drop below 50%. The occurrence was very low, with just 2 cases in the preventive group and 1 case in the troponin-triggered group. Over the 3-year follow-up period, there were no new cases of cardiotoxicity or troponin level elevation reported[45,67].

The SUCCOUR (strain surveillance of chemotherapy for improving cardiovascular outcomes)

LVEF has been the main marker for cardiotoxicity for the past three decades despite challenges related to image quality, LV geometry presumption, and the inability to detect minor changes due to broad confidence intervals. Two-dimensional (2D) strain is an automated method for measuring global long-axis function using grayscale images, providing a quantitative measure. Due to its ability to detect minor changes in cardiac function in response to chemotherapy, 2D global longitudinal strain (GLS) has become a standard approach in assessing cardiac function. Particularly when LVEF is borderline (50–59%), early detection and intervention with cardioprotective agents can lead to a less significant change in LVEF within three years[68,69].

The SUCCOUR trial was a multicenter, prospective, randomized, open-blinded endpoint study that involved 28 centers worldwide from 2014 to December 2019. They randomly assigned 331 anthracycline-receiving patients to either LVEF or GLS monitoring in a 1:1 ratio. Once an abnormality was detected in either arm, participants were introduced to the same regimen of BB or ACEI. The cut-off points were a reduction of greater than 10% or 5% associated with symptoms or less than 55% in LVEF and a reduction of greater than 12% in GLS. The primary outcome showed no significant between-group differences (–3.0% vs. –2.7%; $P = 0.69$) after 1 year. The GLS-guided group used more cardioprotective agents and experienced a lower incidence of cardiotoxicity (5.8% vs. 13.7%; $P = 0.02$) as a secondary endpoint. After 3 years, the ejection fraction of both the LVEF- and GLS-guided groups got better (–0.03% ± 7.9% LVEF compared to –0.02% ± 6.5% GLS) ($P = 0.99$), but there was no difference in the ejection fraction of the two groups (58% ± 6% LVEF compared to 59% ± 5% GLS) ($P = 0.06$)[45,68].

Cardiac CARE trial

It is a multicenter, prospective, open-label, endpoint-blinded controlled trial with 175 participants that aims to determine the ability of cardiac troponin levels to identify patients at risk of developing left ventricular dysfunction. It also compares the efficacy of the randomized initiation of candesartan plus carvedilol plus standard care versus standard care in participants with elevated troponin levels (high-risk patients), testing their cardioprotection after six months. These results are compared with those of nonrandomized patients with low troponin levels at the end of therapy (low-risk patients), evaluating troponin ability[45,70].

The study concluded after six months that the low-risk nonrandomized participants exhibited a decline in their LVEF (from 69.3 ± 5.7% to 66.4 ± 6.3%), similar to the randomized group (from 69.4 ± 7.4% to 65.7 ± 6.6% for combination regime and from 69.1 ± 6.1% to 64.9 ± 5.9% for standard care), throwing doubt on the ability of troponin screening to predict cardiotoxicity in order to prevent it. In this trial, the effectiveness of cardioprotection with the combination of neurohormonal blockage drugs (candesartan plus carvedilol) in participants receiving anthracycline with high troponin levels showed similar results to the standard care[70].

Limitations

The majority of the studies included in this review were observational in nature, with a limited number of randomized controlled trials (RCTs). This could lead to confounding factors that were not adequately controlled for, thereby impacting the strength of the evidence. Furthermore, many studies did not account for the potential interactions between different cardioprotective drugs, nor did they consistently assess long-term cardiovascular outcomes, which are critical in understanding the full impact of these interventions. In addition, while this review focuses on the most commonly studied cardioprotective agents, it does not comprehensively cover all possible interventions or emerging therapies that may be relevant in the future. Additionally, the review did not include studies published in languages other than English, which may have led to the exclusion of relevant international research.

Conclusion

Various drugs have been found to be effective in reducing the harmful effects of chemotherapy on the heart. These include beta-blockers, ACE inhibitors, statins, and dexrazoxane. There is significant evidence supporting their use as cardioprotective agents. These agents provide valuable advantages in maintaining cardiac function and decreasing the occurrence of heart failure in individuals with cancer. Nevertheless, the variation in current studies emphasizes the importance of establishing uniform treatment protocols and conducting additional research on the safety and ideal timing of administration. By integrating cardioprotective strategies into standard oncological care, healthcare providers have the potential to greatly improve the cardiovascular health and overall outlook for individuals who have survived cancer.

Ethical approval

Ethics approval was not required for this review.

Consent

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Author contribution

Z.A.-H.: resources, investigation, visualization, validation, writing—original draft. H.M.H.: resources, investigation, visualization, validation, writing—original draft. J.M.A.A.: resources, investigation, validation, writing—original draft, writing—review and editing. N.K.: investigation, validation, resources, writing—original draft, writing—review and editing. A.A.S.: investigation, data, curation, validation, writing—original draft. M.H.S.: resources, investigation, data curation, validation, writing—review and editing. N.A.-H.A.M.M.: data curation, formal analysis, validation, writing—original draft. A.A.-Q.: resources, investigation, validation writing—original draft. A.S.H.: resources, investigation, validation, writing—review and editing. P.P.: conceptualization, investigation, validation writing—original draft, writing—review and editing. H.J.: investigation, validation writing—original draft, writing—review and editing. A.G.: validation, writing—review and editing. O.A.: supervision, validation, writing—review and editing.

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