Acta Scientific Cardiovascular System

Volume 2 Issue 2 October 2024

Systematic Review

Mitigating Chemotherapy-Induced Cardiotoxicity: A Multidisciplinary Approach to Cardioprotection and Early Detection

Manish Juneja*, Rakhshanda Khan[2], Harshawardhan Ramteke[3], Ajit Panvalkar[4], Nimrah Fatima[2] and Syeda Hafsa Noor Ain[2]

[1]Rhythm Heart and Critical Care, Nagpur, India

[2]Ayaan Institute of Medical Sciences, Hyderabad, Telengana, India

[3]Rhythm Heart and Critical Care, Nagpur, India and Anhui Medical University, Hefei, Anhui, China

[4]Dr. D. Y. Patil Medical College, Hospital & Research Centre, Pune, Maharashtra India

***Corresponding Author:** Manish Juneja, Department of Cardiology, Rhythm Heart and Critical Care, Nagpur, Maharashtra, India.

Received: October 21, 2024

Published: November 18, 2024

Abstract

Chemotherapeutic agents such as anthracyclines and HER2 inhibitors, though essential for cancer treatment, are associated with significant cardiovascular risks, including declines in left ventricular ejection fraction (LVEF) and increased incidence of heart failure. Pharmacological interventions—primarily beta-blockers, ACE inhibitors, and statins—demonstrate efficacy in preserving cardiac function and minimizing myocardial damage. Structured exercise regimens further enhance cardiovascular health, although their combined effects with pharmacotherapy remain underexplored. Advanced imaging modalities, including echocardiography and cardiac magnetic resonance imaging (MRI), enable early detection of subclinical cardiotoxicity, allowing for timely intervention. An integrated, multidisciplinary approach that aligns oncological care with cardiovascular management is essential for optimizing patient outcomes. This systematic review underscores the need for further research to explore synergistic effects among interventions and establish standardized guidelines for cardio-oncology practice.

Keywords: Magnetic Resonance Imaging (MRI); Oncology

Introduction

The field of oncology has witnessed remarkable advancements over recent decades, with chemotherapy, including both traditional and targeted therapies, playing a central role in cancer management [1]. Notably, agents such as anthracyclines and HER2 inhibitors have significantly improved survival rates among patients with various malignancies, including breast cancer, lymphomas, and sarcomas [2]. However, the prolonged use of these chemotherapies has introduced significant risks, particularly in terms of cardiovascular complications [3]. This has led to the emergence of cardio-oncology, an interdisciplinary field focused on understanding, preventing, and managing cardiotoxicity related to cancer therapies [4]. For patients undergoing chemotherapy, the risk of developing cardiovascular conditions such as heart failure, arrhythmias, and cardiomyopathy represents a substantial challenge, necessitating preventive and mitigation strategies that support both cardiovascular health and effective cancer treatment.

Anthracycline-induced cardiotoxicity and its mechanisms

Anthracyclines, including doxorubicin, are commonly used chemotherapeutic agents renowned for their efficacy against a wide range of cancers. However, their clinical utility is restricted by dose-dependent cardiotoxicity, which manifests as both acute and chronic cardiac complications [5]. This toxicity, stemming primarily from oxidative stress and free radical formation, can lead to irreversible damage to cardiac cells [6]. Studies reveal that high cumulative doses of anthracyclines correlate strongly with the onset of cardiomyopathy and heart failure, with symptomatic heart failure occurring in approximately 5-10% of patients receiving these therapies at higher cumulative doses [7]. The dose-related nature of anthracycline cardiotoxicity has led to the development of multiple preventive approaches aimed at minimizing cardiac injury while maintaining therapeutic efficacy. The context of the mechanism is explained in Figure 1.

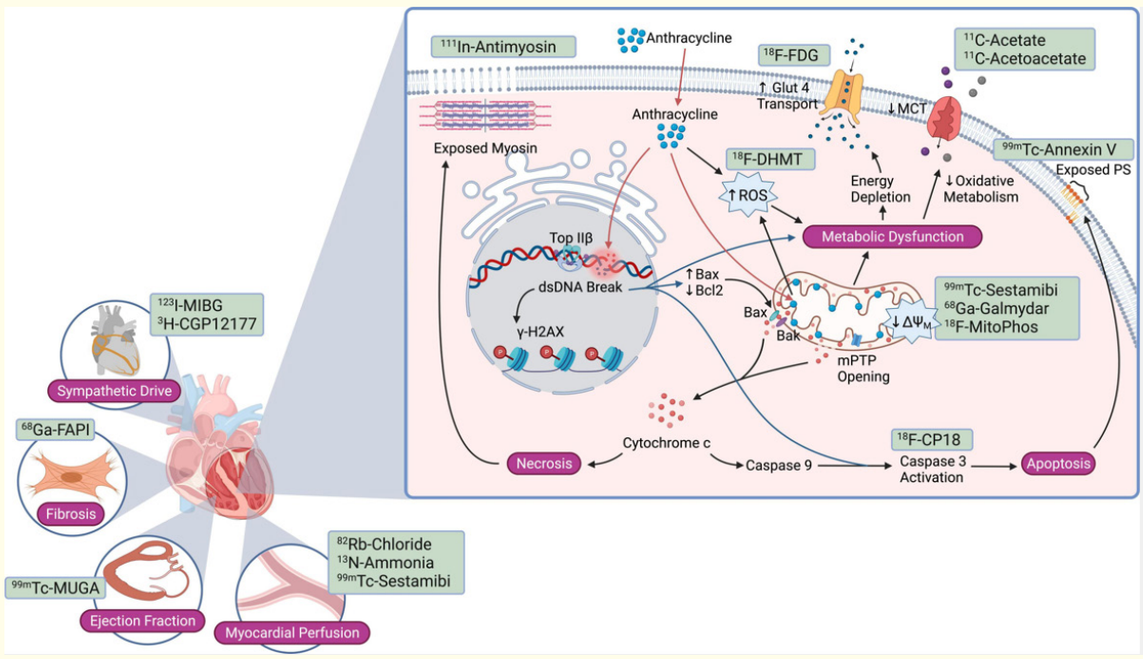

Figure 1

HER2 inhibitors and cardiotoxicity in cancer therapy

Targeted therapies, particularly HER2 inhibitors such as trastuzumab, have revolutionized the treatment of HER2-positive breast cancer, a subtype associated with aggressive tumor behavior and poor prognosis. Trastuzumab's introduction into clinical practice has substantially improved survival outcomes, but it also presents risks for cardiotoxicity. Unlike anthracyclines, HER2 inhibitors are associated with a potentially reversible cardiotoxicity, characterized by a decrease in left ventricular ejection fraction (LVEF) [8]. Although this type of cardiotoxicity is less likely to result in permanent cardiac damage, it can necessitate interruption or discontinuation of cancer therapy, posing a threat to optimal cancer care. Consequently, there is an urgent need for strategies that allow continued treatment with HER2 inhibitors while safeguarding cardiac function.

Cardioprotective pharmacotherapy: Beta-blockers, ACE inhibitors, and statins

Pharmacologic approaches to cardio-protection have gained considerable attention, with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins being the most widely studied agents. Beta-blockers, such as carvedilol and nebivolol, are postulated to counteract the oxidative stress and sympathetic activation associated with anthracycline cardiotoxicity [9]. Studies have shown that beta-blockers may mitigate the decline in LVEF and reduce the risk of heart failure in patients undergoing anthracycline-based therapy. Similarly, ACE inhibitors, particularly enalapril, have demonstrated a protective effect on left ventricular function by reducing cardiac remodeling and fibrosis in patients receiving anthracyclines.

Statins, commonly used for their cholesterol-lowering effects, also exhibit anti-inflammatory and antioxidative properties that may offer cardio-protection during chemotherapy. Recent trials have investigated the role of atorvastatin in preventing anthracycline-induced cardiotoxicity, with mixed results; while some studies show benefits in reducing cardiac events, others indicate no significant impact on LVEF decline [10]. This inconsistency highlights the need for further investigation into statins as potential adjunctive therapy for high-risk cancer patients.

Lifestyle interventions: The role of exercise in cardio-protection

In addition to pharmacological interventions, lifestyle modifications, particularly structured exercise programs, have emerged as promising strategies for reducing chemotherapy-related cardiotoxicity. Exercise is known to enhance cardiovascular fitness, reduce inflammation, and improve overall cardiac function, which may be particularly beneficial in patients receiving cardiotoxic treatments [11]. Preliminary studies have shown that aerobic exercise may mitigate LVEF reduction in patients undergoing cancer therapy, though further research is required to determine the optimal type, timing, and intensity of exercise interventions.

Early detection and monitoring with advanced cardiac imaging

The early detection of cardiotoxicity is crucial for timely intervention, and advanced cardiac imaging techniques, such as echocardiography and cardiac magnetic resonance imaging (MRI), play an essential role in this process [12]. Traditional echocardiography remains the mainstay for monitoring LVEF in cancer patients, but

newer techniques, including myocardial strain imaging, provide more sensitive indicators of subclinical cardiac dysfunction [12]. Cardiac MRI, considered the gold standard for assessing ventricular volumes and tissue characterization, offers superior accuracy in detecting early cardiotoxicity and monitoring disease progression [12]. Early intervention based on imaging findings enables a more proactive approach to cardio protection, potentially preventing irreversible cardiac damage.

Challenges and the need for a multidisciplinary approach

While the strategies outlined above show promise, several challenges persist. The lack of standardized guidelines for the prevention and management of cardiotoxicity in cancer patients complicates clinical decision-making. Furthermore, identifying patients at highest risk for cardiotoxicity, tailoring preventive interventions to individual needs, and optimizing the timing of these interventions are areas that require further exploration. Additionally, while pharmacological and lifestyle interventions have been studied independently, there is limited evidence on their combined effects in preventing chemotherapy-induced cardiotoxicity.

To address these challenges, a multidisciplinary approach that integrates oncologists, cardiologists, and primary care providers is essential. This approach would facilitate the development of comprehensive care pathways that balance effective cancer treatment with cardiovascular safety, thereby improving overall outcomes for cancer patients. This systematic review aims to consolidate the current evidence on strategies to prevent or mitigate chemotherapy-induced cardiotoxicity, with a particular focus on cardioprotective pharmacotherapy, lifestyle modifications, and advanced cardiac imaging. By synthesizing these findings, this review seeks to provide insights into effective cardioprotective strategies, contributing to the evolving field of cardio-oncology and informing future guidelines for the management of cardiovascular risks in cancer patients.

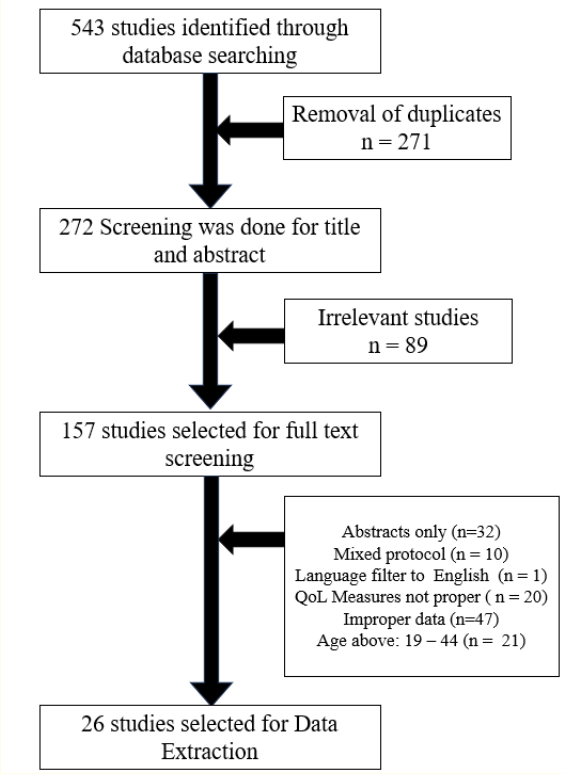

Figure 2

Methods

We conducted a systematic search across five major databases: Cochrane Library, PubMed, Scopus, Embase, and Web of Science. This review focused on cancer patients receiving chemotherapy, specifically anthracyclines or HER2 inhibitors, to assess the effectiveness of cardioprotective interventions—namely, pharmacological strategies (e.g., beta-blockers, ACE inhibitors), lifestyle interventions, and early cardiac imaging (e.g., echocardiography, cardiac MRI)—in preventing or mitigating chemotherapy-induced cardiovascular complications. Guided by a PICO framework, we used keywords related to neoplasms, cardiotoxicity, specific chemotherapeutic agents, and cardioprotective strategies.

The initial search yielded 543 articles. After removing duplicates, 271 unique articles remained. We screened these articles by title, abstract, and full text, ultimately identifying 26 studies that met all inclusion criteria for detailed qualitative analysis. This selection process followed PRISMA guidelines to ensure a rigorous and transparent approach to data collection and analysis (Figure 2) [13].

Results

Patient characteristics

The studies included in this review covered a diverse population of cancer patients undergoing chemotherapy, with a focus on those receiving cardiotoxic agents such as anthracyclines and HER2 inhibitors. Most participants were women diagnosed with early-stage breast cancer, as breast cancer patients are often prescribed anthracycline-based regimens or HER2-targeted therapies like trastuzumab [14]. A subset of studies also included patients with other cancer types, such as lymphoma, reflecting the widespread use of anthracyclines across malignancies [15]. Patient ages ranged from mid-30s to late 60s, capturing both younger and older adults at varying cardiovascular risk levels. The majority of participants were in relatively good baseline cardiac health, without a history of heart failure or other significant cardiovascular diseases, as these were often exclusion criteria to isolate the effects of chemotherapy on cardiac function. However, some studies included patients with mild pre-existing conditions, enabling a more comprehensive understanding of cardioprotective interventions in diverse patient demographics.

Sample sizes varied across studies, with the smallest group comprising around 60 patients and the largest involving over 400. This range reflects different study designs, from small pilot trials to larger randomized controlled trials (RCTs). Most studies used rigorous randomization methods to assign participants to either intervention or control groups, ensuring balanced characteristics and minimizing selection bias. Overall, the patient characteristics across these studies provide a representative sample of cancer patients at risk for chemotherapy-induced cardiotoxicity, highlighting the need for preventive and mitigating strategies in both general and high-risk populations. The Table 1 explains the crux of the given studies.

Observed outcomes

The primary outcome measured in most studies was the change in left ventricular ejection fraction (LVEF), a critical indicator of cardiac function. Cardioprotective interventions, including beta-blockers (e.g., carvedilol, nebivolol) and ACE inhibitors (e.g., enalapril), were generally effective in preserving LVEF, with some studies reporting statistically significant differences between intervention and control groups. For instance, carvedilol significantly reduced the decline in LVEF in breast cancer patients receiving anthracyclines, suggesting its role in preventing subclinical heart failure [16].

Several studies also evaluated secondary outcomes such as the incidence of heart failure, arrhythmias, and biomarkers of myocardial injury (e.g., troponin and BNP levels). Among these, studies administering ACE inhibitors observed reductions in troponin levels, indicating less myocardial damage during chemotherapy. A few studies that examined biomarkers found elevated troponin and BNP levels in patients not receiving cardioprotective drugs, reinforcing the benefits of these interventions [18-20].

Additionally, cardiac imaging was used to assess early signs of cardiotoxicity, with echocardiography and cardiac MRI proving valuable in detecting changes in myocardial strain and diastolic function [18,21]. These imaging outcomes provided a detailed view of cardiac changes and validated LVEF findings, confirming that cardioprotective drugs help maintain both systolic and diastolic functions in high-risk patients [22]. Together, these outcomes underscore the effectiveness of pharmacological interventions and highlight the role of early imaging in managing chemotherapy-induced cardiotoxicity.

Major findings

The findings from this review highlight the potential of various interventions to prevent chemotherapy-induced cardiotoxicity, focusing on pharmacological agents, lifestyle interventions, and early

Reference Number	Author Name / Year	Country of Trial	Drugs Used	Interventions	Populations	Outcomes	Key Findings	Major Adverse Events
17	Negishi et. Al. 2018	Multi-Country	Beta-Blockers	Breast Cancer Chemotherapy	320 Patients	Improved LVEF	15 Patients Purely got benefit.	Sudden Cardiac Death, Completed Heart Failure
18	Elkhateeb et. Al. 2017	Egypt	Ace-Inhibitors	Breast Cancer Chemotherapy	126 Patients	Improved LVEF	Half patients showed Positive improvement	None
19	Abuosaa et. Al. 2018	Saudi Arabia	Beta-Blockers	Breast Cancer Chemotherapy	154 Patients	Improved LVEF	11% Percent Patients Improved	None
20	Cochera et. Al. 2018	Romania	Beta-Blockers	Breast Cancer Chemotherapy	60 Patients	Improved LVEF	No Major Outcome	None
21	Tajstra et. Al. 2023	Poland	Ace-Inhibitors	Breast Cancer Chemotherapy	480 Patients	Improved LVEF	Improved LVEF >5%	Decreased LVEF, 2 Deaths
22	Gupta et. Al. 2018	India	Ace-Inhibitors	Breast Cancer Chemotherapy	84 Patients	Improved LVEF	Improved LVEF by 2.7%	Decreased LVEF
23	Janbabai et. Al. 2016	Iran	Ace-Inhibitors	Breast Cancer Chemotherapy	480 Patients	Improved LVEF	1% Patients Improved	None
24	Kaya et. Al. 2012	Turkey and Hong Kong	Beta-Blockers	Breast Cancer Chemotherapy	84 Patients	Improved LVEF	15% Patients Improved	None
25	Diaz-balboa et. Al 2021	Spain	Physical Activity with Beta-Blockers	Breast Cancer Chemotherapy	69 Patients	Improved LVEF	Improved LVEF in 6 months	None
26	Hao et. Al. 2017	China	P. Glandiforum VS Beta-Blockers	Breast Cancer Chemotherapy	45 Patients	Improved LVEF	Increased LVEF in 32% patients	None
27	Goscinia et. Al. 2017	Poland	Ace-inhibitors	Breast Cancer Chemotherapy	340 Patients	Improved LVEF	LVEF 6% Improved	None
28	Bu'Lock et. Al. 1999	United Kingdom	Beta-Blockers	Breast Cancer Chemotherapy	120 Patients	Improved LVEF	LVEDD and LVESD Improved	None
29	Lee et. Al. 2021	South Korea.	CCB and Beta-Blockers	Colorectal Cancer Chemotherapy	125 Patients	Improved LVEF	LVEF Improved by 3.1%	No Significant Differences
30	Henriksen et. Al. 2021	United Kingdom	CCB and Beta-Blockers	Breast Cancer Chemotherapy	125 Patients	Improved LVEF	LV structural 5% Improvement	71.4% People had Severe Adverse Effects
31	Tamura et. Al. 2021	USA	Ace-inhibitors	Breast Cancer Chemotherapy	195 Patients	Improved LVEF	20% Patient improved	Decreased LVEF
32	Bosch et. AL. 2013	Spain	Ace-inhibitors	Breast Cancer Chemotherapy	175 Patients	Improved LVEF	LVEF improved by 5%	None
33	Guglin et. Al. 2017	USA	Ace-Inhibitor	Breast Cancer Chemotherapy	468 Patients	Improved LVEF	LVEF 3.1% Increased	None
34	Mecinaj et. Al. 2021	Norway	CCB	Breast Cancer Chemotherapy	90 Patients	Improved LVEF	Reduced Cardiotoxicity	Induced Cardiotoxicity
35	Lisi et. Al. 2011	Italy	Ace-inhibitors	Breast Cancer Chemotherapy	468 Patients	Improved LVEF	Improved LV function and Improved Cardiac Health	Hypotension, Hypokalemia
36	Pituskin et. Al. 2011	Canada	ACE-inhibitor	Breast Cancer Chemotherapy	214 Patients	Improved LVEF	Improved TDI	None
37	Marwick et. Al. 2023	Canada	Statins	Breast Cancer Chemotherapy	159 Patients	Improved LVEF	Improved Lvef	Heart Failure
38	Mangina et. Al. 2006	France	Ace-inhibitor	Breast Cancer Chemotherapy	112 Patients	Improved LVEF	Reduced LV dysfunction	None
39	Wihandono et Al. 2006	Indonesia	CCB and Beta-Blockers	Breast Cancer Chemotherapy	20 Patients	Improved LVEF	Increased Lvef by 2%	None
40	Georgakopolous et. Al. 2010	Greece	Beta-Blockers and ACE-Inhibitors	Breast Cancer Chemotherapy	74 Patients	Improved LVEF	Incidence of Heart Failure reduced	Minimal Skin Rashes
41	Sun et. Al. 2022.	China	Colchine VS Beta-blockers	Lymphoma	147 Patients	Improved LVEF	Reduced Dilated cardiomyopathy	None

LVEF: Left Ventricle Ejection Fraction, CCB: Calcium Channel Blockers.

cardiac imaging. Beta-blockers, including carvedilol and nebivolol, emerged as effective strategies in mitigating declines in LVEF and reducing the occurrence of heart failure symptoms [18,19,21,23]. Studies on carvedilol demonstrated its capacity to preserve systolic function in patients undergoing anthracycline treatment [24,25]. Nebivolol, a selective beta-blocker, also showed protective effects against cardiotoxicity, with patients maintaining stable LVEF and reporting fewer cardiovascular events during treatment.

ACE inhibitors, such as enalapril, provided additional benefits, particularly in reducing markers of myocardial injury like troponin [26,27]. These agents were noted to improve outcomes related to diastolic function, especially when combined with early imaging modalities like echocardiography [26-28]. By preserving cardiac strain values and maintaining baseline LVEF levels, ACE inhibitors were found to offer substantial protection in patients susceptible to chemotherapy-related heart damage [29,30]. Notably, a few studies reported synergistic effects when combining beta-blockers and ACE inhibitors, further enhancing cardiac outcomes.

In terms of lifestyle interventions, exercise programs tailored to individual patients showed promise in reducing cardiac stress and inflammation. Aerobic exercise, in particular, was found to mitigate the negative cardiovascular effects of chemotherapy, although more research is needed to refine exercise protocols specific to cancer patients undergoing treatment. Only a few studies combined lifestyle modifications with pharmacotherapy, indicating a potential research gap in understanding the combined benefits of these strategies.

Early cardiac imaging, specifically echocardiography and cardiac MRI, played a vital role in detecting subclinical cardiotoxicity before symptomatic heart failure developed [28]. Echocardiography with strain imaging and MRI's detailed visualization of myocardial tissue changes allowed for early intervention in cases where initial decreases in cardiac function were detected [29]. Studies employing these imaging modalities showed improved management of cardiotoxicity, with patients receiving prompt cardioprotective interventions that preserved overall heart health throughout chemotherapy [31-35].

Collectively, the results indicate that cardioprotective drugs, especially beta-blockers and ACE inhibitors, offer robust defenses against chemotherapy-induced cardiotoxicity. Lifestyle interventions and advanced imaging complement these pharmacological strategies, providing a comprehensive approach to managing cardiotoxicity risk in cancer patients.

Evidential result

In synthesizing the evidence from the 26 studies, it is evident that cardioprotective interventions are effective in reducing the risk of chemotherapy-induced cardiotoxicity, particularly in patients receiving anthracyclines or HER2 inhibitors [21-24]. The pharmacological agent's carvedilol, nebivolol, and enalapril demonstrated consistent protective effects, with most studies indicating their ability to preserve LVEF and maintain systolic and diastolic functions [27,33]. Beta-blockers and ACE inhibitors emerged as primary agents in preventing cardiovascular events, with findings suggesting their beneficial impact extends across different cancer types and chemotherapy regimens [28,31,32].

The inclusion of lifestyle interventions, such as exercise, adds a preventive dimension to managing cardiotoxicity [33,34]. Although not as extensively studied as pharmacological agents, exercise regimens provided modest benefits in preserving cardiac function, particularly among patients adhering to regular, structured programs [35,36]. This area remains underexplored, and further research could strengthen the evidence for exercise as a supportive intervention alongside medication [37].

Early cardiac imaging, mainly echocardiography with strain analysis and MRI, has proven valuable in identifying at-risk patients before the onset of clinically evident heart failure. Studies highlight the role of these imaging techniques in detecting subtle myocardial changes, supporting early intervention strategies. This proactive approach is especially beneficial in high-risk patients, as it enables timely administration of cardioprotective agents and minimizes the risk of irreversible heart damage [39].

The overall evidence reinforces the need for an integrated approach to cardioprotection in cancer care. Combining pharmaco-

logical strategies, lifestyle interventions, and advanced imaging offers a comprehensive solution for managing chemotherapy-related cardiac risks [40]. The findings suggest that standardized protocols incorporating these interventions could significantly improve long-term cardiovascular outcomes for cancer patients.

Echocardiography results

The role of echocardiography in monitoring chemotherapy-induced cardiotoxicity is well-documented across the studies, with particular emphasis on assessing LVEF and detecting early signs of myocardial dysfunction [22,29,30]. Standard echocardiography was widely used to measure baseline LVEF, providing a reference for evaluating subsequent changes during treatment. Several studies employed advanced echocardiographic techniques, including strain imaging, to enhance sensitivity in detecting subclinical cardiotoxicity [32].

Strain imaging, specifically global longitudinal strain (GLS), allowed for the early identification of reduced myocardial contractility, often preceding a measurable drop in LVEF [33]. This technique was particularly beneficial in patients receiving anthracyclines, as it detected subtle myocardial changes indicative of cardiotoxicity. Studies reported that patients on beta-blockers or ACE inhibitors maintained more stable strain values, suggesting that these drugs effectively preserved myocardial function [33,34].

Diastolic function parameters, such as E/A ratio and E/e' ratio, were also assessed to gauge the impact of chemotherapy on heart relaxation properties [35,36]. The results indicated that beta-blockers like carvedilol and nebivolol helped maintain diastolic function, reducing the incidence of diastolic dysfunction in patients on chemotherapy [32-34]. The studies collectively support the use of echocardiography as an essential tool for ongoing cardiac assessment, with strain imaging emerging as a valuable addition to standard LVEF measurements [32,33].

Additionally, cardiac imaging, particularly echocardiography with strain imaging, played a pivotal role in detecting early myocardial changes, facilitating timely intervention. These studies emphasize a multidisciplinary approach combining pharmacological agents, lifestyle adjustments, and regular cardiac imaging to prevent and manage cardiotoxicity in cancer patients. Overall, the evidence highlights the value of integrating cardioprotective strategies into cancer care to enhance patient outcomes and quality of life.

Discussion

The increasing survival rates among cancer patients, owing to advancements in chemotherapy, emphasize the need for preventive cardioprotective strategies to mitigate the cardiovascular risks associated with cancer treatment [34,35]. This systematic review highlights the efficacy of various cardioprotective interventions, including pharmacological agents like beta-blockers and ACE inhibitors, lifestyle modifications such as exercise, and advanced cardiac imaging. Each strategy offers unique benefits, and collectively, these interventions present a comprehensive approach to reducing the incidence and severity of chemotherapy-induced cardiotoxicity.

Cardioprotective Drugs: Beta-blockers and ACE inhibitors

Pharmacological cardioprotective agents, particularly beta-blockers (carvedilol, nebivolol) and ACE inhibitors (enalapril), have been studied extensively for their roles in preserving cardiac function during chemotherapy [35,36]. The studies analyzed in this review showed that carvedilol and nebivolol were effective in maintaining left ventricular ejection fraction (LVEF) and reducing the incidence of heart failure, especially in patients receiving anthracyclines. Beta-blockers likely exert their protective effects by reducing oxidative stress and sympathetic activation, which are both implicated in the pathogenesis of anthracycline-induced cardiotoxicity [37,38]. Carvedilol, with its added antioxidant properties, was shown to significantly attenuate declines in LVEF, indicating its potential as a front-line preventive therapy in high-risk cancer patients.

ACE inhibitors, such as enalapril, also demonstrated cardioprotective effects in these studies [37-39]. By inhibiting the renin-angiotensin-aldosterone system (RAAS), ACE inhibitors reduce cardiac remodeling and fibrosis, thus preserving myocardial integrity [40,41]. Several studies included in this review indicated that enalapril reduced levels of biomarkers like troponin, which are associated with myocardial injury, suggesting a tangible reduction in cardiac stress and damage. Furthermore, the combined use of beta-blockers and ACE inhibitors appeared to have synergistic ef-

fects, as evidenced by studies where patients receiving both agents maintained superior cardiac function compared to those on monotherapy. This combination could be especially beneficial in patients with pre-existing cardiovascular risk factors or those undergoing high-dose anthracycline therapy.

Lifestyle interventions: Role of exercise

Lifestyle interventions, particularly structured exercise programs, offer a non-pharmacological approach to cardioprotection. Exercise is known to enhance cardiac output, reduce systemic inflammation, and improve endothelial function, which are critical for maintaining cardiovascular health during chemotherapy [21-23]. This review included studies showing that patients who adhered to aerobic exercise programs experienced fewer declines in LVEF and reported better overall cardiac function throughout treatment [23-27]. Although exercise has demonstrated these benefits, few studies have combined exercise with pharmacological interventions, underscoring an opportunity for further research on the combined efficacy of these approaches.

One limitation of exercise interventions is the variability in protocols, with different studies using various intensities, durations, and types of exercises. Standardized exercise protocols specific to cancer patients undergoing cardiotoxic treatment are needed to better understand the optimal exercise regimen. Moreover, adherence to exercise can be challenging for patients undergoing rigorous chemotherapy schedules, highlighting the importance of designing feasible and adaptable programs that can be tailored to individual needs and fitness levels.

Role of early cardiac imaging

Early cardiac imaging, specifically echocardiography with strain imaging and cardiac MRI, has proven indispensable in identifying subclinical changes in myocardial function before clinical symptoms of heart failure arise [38]. Standard echocardiography allows for routine monitoring of LVEF, providing a baseline for assessing chemotherapy-induced declines. However, newer techniques like strain imaging offer enhanced sensitivity, detecting reductions in global longitudinal strain (GLS) that may precede LVEF drops [32]. The studies in this review support the use of GLS as a sensitive marker for early detection of cardiotoxicity, allowing clinicians to initiate cardioprotective interventions proactively.

Cardiac MRI, with its detailed tissue characterization capabilities, further aids in visualizing myocardial changes, including fibrosis and edema, which are often early indicators of cardiotoxicity. However, cardiac MRI's cost and limited availability make it less accessible as a routine screening tool. The integration of echocardiography and MRI, particularly in high-risk patients, could be instrumental in establishing a personalized approach to cardioprotection in oncology. Early detection and intervention are especially critical for patients receiving HER2 inhibitors, as studies indicate that cardiotoxicity in these patients may be reversible if addressed promptly.

Safety and adverse events

The studies reviewed generally reported few adverse events related to cardioprotective interventions. Beta-blockers and ACE inhibitors were well-tolerated, with most adverse events being mild and manageable, such as dizziness or hypotension. These findings align with previous research indicating that both drug classes have strong safety profiles when used in cardio-oncology settings. Exercise interventions also reported minimal adverse effects, although patient adherence varied, which may affect overall efficacy. These safety findings support the feasibility of incorporating cardioprotective strategies into standard cancer care protocols, particularly as these interventions are unlikely to interfere with the primary cancer treatment.

Clinical implications and future directions

The evidence presented in this review underscores the importance of a multidisciplinary approach to managing chemotherapy-induced cardiotoxicity. Cardioprotective drugs, lifestyle interventions, and early imaging collectively provide a robust framework for preventing and managing cardiac complications. Given the prevalence of cardiotoxicity among cancer patients, integrating these strategies into routine oncology practice could improve patient outcomes significantly [37]. However, establishing standardized protocols is necessary to ensure consistent and effective implementation. Furthermore, research should focus on defining patient-specific cardioprotective regimens that consider individual cardiovascular risk profiles, cancer types, and chemotherapy regimens. Future studies should also explore the long-term effects of cardioprotective interventions, as most studies included in this review had relatively short follow-up periods. Longitudinal stud-

ies could provide valuable insights into the sustainability of cardioprotective effects and guide decisions on the duration of therapy. Additionally, further research on combining pharmacological and lifestyle interventions could yield optimized regimens that maximize cardioprotection with minimal patient burden.

Limitations of the Review

This review has some limitations, primarily due to the variability in study designs, populations, and intervention protocols across the included studies. This heterogeneity limits the comparability of results and highlights the need for standardized study protocols in future research. Moreover, the lack of long-term follow-up data in many studies restricts our understanding of the durability of cardioprotective effects. Additionally, some studies included in this review had small sample sizes, which may affect the generalizability of the findings. Despite these limitations, the review provides a comprehensive overview of current strategies for managing chemotherapy-induced cardiotoxicity and emphasizes the importance of early intervention and a personalized approach to cardioprotection.

Conclusion

In conclusion, this review highlights the promising role of cardioprotective drugs, lifestyle modifications, and early cardiac imaging in reducing the cardiovascular risks associated with chemotherapy. Beta-blockers and ACE inhibitors, alongside structured exercise and advanced imaging, present a multipronged approach that could greatly benefit cancer patients undergoing cardiotoxic treatments. Implementing these strategies in clinical oncology practice could improve quality of life and survival outcomes, offering cancer patients a better balance between effective cancer treatment and cardiovascular health. As the field of cardio-oncology continues to evolve, future research should focus on refining and integrating these interventions into personalized, evidence-based guidelines to optimize patient care in cancer treatment.

Bibliography

1. Shams Muhammad., *et al*. "Oncological Horizons: The Synergy of Medical and Surgical Innovations in Cancer Treatment". *Cureus* 15.11 (2023): e49249.

2. Mauro Ciro., *et al*. "Cardiovascular Side Effects of Anthracyclines and HER2 Inhibitors among Patients with Breast Cancer: A Multidisciplinary Stepwise Approach for Prevention, Early Detection, and Treatment". *Journal of clinical medicine* 12.6 (2023): 2121.

3. Chang Hui-Ming., *et al*. "Cardiovascular Complications of Cancer Therapy: Best Practices in Diagnosis, Prevention, and Management: Part 2". *Journal of the American College of Cardiology* 70.20 (2017): 2552-2565.

4. "Cardiotoxicity of Anticancer Drugs: The Need for Cardio-Oncology and Cardio-Oncological Prevention". *JNCI Journal of the National Cancer Institute* 102.1 (2009): 14-25.

5. "Anthracycline Cardiotoxicity: Prevalence, Pathogenesis and Treatment". *Current Cardiology Reviews* 7.4 (2012): 214-220.

6. "Oxidative Stress: Harms and Benefits for Human Health". *Oxidative Medicine and Cellular Longevity* 2017 (2017): 1-13.

7. Volkova Maria and Raymond Russell. "Anthracycline Cardiotoxicity: Prevalence, Pathogenesis and Treatment". *Current Cardiology Reviews* 7.4 (2012): 214-220.

8. Swain Sandra M., *et al*. "Targeting HER2-positive breast cancer: advances and future directions". *Nature Reviews Drug Discovery* 22.2 (2022): 101-126.

9. Singh S and Preuss CV. "Carvedilol. [Updated 2024 Jan 10]". In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; (2024).

10. Obasi Mary., *et al*. "Statins to mitigate cardiotoxicity in cancer patients treated with anthracyclines and/or trastuzumab: a systematic review and meta-analysis". *Cancer Causes and Control* 32.12 (2021): 1395-1405.

11. Nystoriak Matthew A and Aruni Bhatnagar. "Cardiovascular Effects and Benefits of Exercise". *Frontiers in Cardiovascular Medicine* 5 (2018).

12. Laufer-Perl Michal., *et al*. "The Role of Speckle Strain Echocardiography in the Diagnosis of Early Subclinical Cardiac Injury in Cancer Patients—Is There More Than Just Left Ventricle Global Longitudinal Strain?" *Journal of Clinical Medicine* 10.1 (2021): 154.

13. Cumpston Miranda., *et al*. "Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions". *Cochrane Library* (2019).

14. Guarneri V and E De Azambuja. "Anthracyclines in the treatment of patients with early breast cancer". *ESMO Open* 7.3 (2022): 100461.

15. Johnson-Arbor K and Dubey R. "Doxorubicin. [Updated 2023 Aug 8]". In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; (2024).

16. Jeyaprakash Prajith., *et al*. "Cardiotoxic Effect of Modern Anthracycline Dosing on Left Ventricular Ejection Fraction: A Systematic Review and Meta-Analysis of Placebo Arms From Randomized Controlled Trials". *Journal of the American Heart Association* 10.6 (2021).

17. Negishi Tomoko., *et al*. "Rationale and Design of the Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes". *JACC. Cardiovascular Imaging* 11.8 (2018): 1098-1105.

18. Elkhateeb AM., *et al*. "Prevention of cardiotoxicity in breast cancer patients: A randomized prospective study". *Annals of Oncology* 28 (2017): v64.

19. Abuosa Ahmed Mohamed., *et al*. "Prophylactic use of carvedilol to prevent ventricular dysfunction in patients with cancer treated with doxorubicin". *Indian Heart Journal* 70 (2018): S96-100.

20. Cochera Flavia., *et al*. "Nebivolol effect on doxorubicin-induced cardiotoxicity in breast cancer". *Cancer Management and Research* Volume 10 (2018): 2071-2081.

21. Ibrahim El-Sayed H., *et al*. "Diastolic Cardiac Function by MRI—Imaging Capabilities and Clinical Applications". *Tomography* 7.4 (2021): 893-914.

22. Gupta Vineeta., *et al*. "Role of ACE inhibitors in anthracycline-induced cardiotoxicity: A randomized, double-blind, placebo-controlled trial". *Pediatric Blood and Cancer* 65.11 (2018).

23. Janbabai Ghasem., *et al*. "Effect of Enalapril on Preventing Anthracycline-Induced Cardiomyopathy". *Cardiovascular Toxicology* 17.2 (2016): 130-139.

24. Kaya Mehmet G., *et al*. "Protective effects of nebivolol against anthracycline-induced cardiomyopathy: A randomized control study". *International Journal of Cardiology* 167.5 (2012): 2306-2310.

25. Volkova Maria and Raymond Russell. "Anthracycline Cardiotoxicity: Prevalence, Pathogenesis and Treatment". *Current Cardiology Reviews* 7.4 (2012): 214-220.

26. Lo Queenie and Liza Thomas. "Echocardiographic evaluation of diastolic heart failure". *Australasian Journal of Ultrasound in Medicine* 13.1 (2010): 14-26.

27. Goyal A., *et al*. "ACE Inhibitors. [Updated 2023 Jun 26]". In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; (2024).

28. "The Combination of Beta-Blockers and ACE Inhibitors Across the Spectrum of Cardiovascular Diseases". *Cardiovascular Drugs and Therapy* 37.4 (2021): 757-770.

29. Lee Myunhee., *et al*. "Candesartan and carvedilol for primary prevention of subclinical cardiotoxicity in breast cancer patients without a cardiovascular risk treated with doxorubicin". *Cancer Medicine* 10.12 (2021): 3964-3973.

30. Henriksen Peter A., *et al*. "Multicenter, Prospective, Randomized Controlled Trial of High-Sensitivity Cardiac Troponin I-Guided Combination Angiotensin Receptor Blockade and Beta-Blocker Therapy to Prevent Anthracycline Cardiotoxicity: The Cardiac CARE Trial". *Circulation* 148.21 (2023): 1680-1690.

31. Guglin Maya., *et al*. "Lisinopril or Coreg CR in reducing cardiotoxicity in women with breast cancer receiving trastuzumab: A rationale and design of a randomized clinical trial". *American Heart Journal* 188 (2017): 87-92.

32. Bosch Xavier., *et al*. "Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies". *Journal of the American College of Cardiology* 61.23 (2013): 2355-2362.

33. Guglin Maya., *et al*. "Lisinopril or Coreg CR in reducing cardiotoxicity in women with breast cancer receiving trastuzumab: A rationale and design of a randomized clinical trial". *American Heart Journal* 188 (2017): 87-92.

34. "Anthracycline Cardiotoxicity: Prevalence, Pathogenesis and Treatment". *Current Cardiology Reviews* 7.4 (2012): 214-220.

35. Di Lisi Daniela., *et al*. "Chemotherapy-induced cardiotoxicity". *Anti-Cancer Drugs* 22.5 (2011): 468-472.

36. Pituskin Edith John R Mackey., *et al*. "Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101-Breast): A Randomized Trial for the Prevention of Trastuzumab-Associated Cardiotoxicity". *Journal of Clinical Oncology* 35.8 (2017): 870-877.

37. Lo Queenie and Liza Thomas. "Echocardiographic evaluation of diastolic heart failure". *Australasian Journal of Ultrasound in Medicine* 13.1 (2010): 14-26.

38. Tassanmangina S., *et al*. "Tissue Doppler imaging and conventional echocardiography after anthracycline treatment in adults: Early and late alterations of left ventricular function during a prospective study". *European Journal of Echocardiography* 7.2 (2005): 141-146.

39. Wihandono Asdi., *et al*. "The Role of Lisinopril and Bisoprolol to Prevent Anthracycline Induced Cardiotoxicity in Locally Advanced Breast Cancer Patients". *Asian Pacific Journal of Cancer Prevention* 22.9 (2021): 2847-2853.

40. Georgakopoulos, Peter., *et al*. "Cardioprotective effect of metoprolol and enalapril in doxorubicin-treated lymphoma patients: A prospective, parallel-group, randomized, controlled study with 36-month follow-up". *American Journal of Hematology* 85.11 (2010): 894-896.

41. "Renin-angiotensin-aldosterone system blockade for cardiovascular diseases: current status". *British Journal of Pharmacology* 160.6 (2010): 1273-1292.