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Systematic Review

Efficacy of integrating cardiovascular risk management into cancer treatment protocols: a systematic review of current strategies and innovations

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ABSTRACT

Many of the anti-cancer agents, including anthracyclines, human epidermal growth factor receptor (HER2) inhibitors, and tyrosine kinase inhibitors are known to have cardiotoxic potential with potential consequences including heart failure, arrhythmias and myocardial ischemia. Therefore, the following systematic review questions have been developed to assess the effectiveness of incorporating cardiovascular risk in cancer management to counter these side effects. The literature search was extended on randomized control trials and meta-analysis in terms of cardioprotective strategies including global longitudinal strain (GLS), and ejection fraction (EF) both as guided therapy, and exercise prescription. Considering only patient characteristics, inclusion criteria included adult cancer patients receiving cardiotoxic treatments, whereas exclusion criteria excluded pediatric studies and non-randomized trials as well as trials without cardiovascular endpoints. The outcomes are evidence of lower cardiotoxicity with GLS-guided cardio-protection when compared to EF-based strategies, a decreased risk in left ventricular systolic dysfunction, and heart failure. The exercise interventions also have yielded favorable results in enhancing cardiovascular capacity and minimizing toxic consequences of chemotherapy on the cardiotoxicity level. Increasingly, eliminating and modifying cancer and oncology treatment strategies can help remedy disease outcomes; however, protocols for including these strategies in oncology plans have yet to be developed. Therefore, cardiovascular risk management conception in cancer treatment has to be regarded as crucial in avoidance of cardiotoxicity and improvement of quality of life and survival rate in oncological patients.

Keywords: Cardiotoxicity, Cardiovascular diseases/prevention and control, Antineoplastic agents/adverse effects, Heart failure/prevention and control, Exercise therapy

INTRODUCTION

Cardiovascular disease (CVD) is a major cause of morbidity and mortality the world over, and many of the risks associated with CVDs and cancers are closely related.[1] New advancement in cancer treatments, targeted therapies, and immunotherapies have significantly impacted cancer patients' overall mortality expectancy rates. However, these therapies are linked with certain cardiovascular risk factors, and thus, cardiovascular risk in oncology patients' needs to be dealt with and managed while delivering oncology care. As it was estimated that there are over 18 million new cancer cases and nearly 10 million cancer-related deaths each year,1 the increased usage in cardio toxic cancer therapy is a global health concern.[2] It is postulated that the incorporation of cardiovascular risk management at an early stage in cancer therapy can help decrease mortality risk and enhance the overall median survival of these patients.[3] Studies are showing the link between the effects of chemotherapy and such cardiotoxic endpoints as heart failure, acute myocardial infarction, and hypertension found by a meta-analysis of cancer therapy-induced cardiotoxicity.[4] As a result, the modern concept has established the utility of risk.

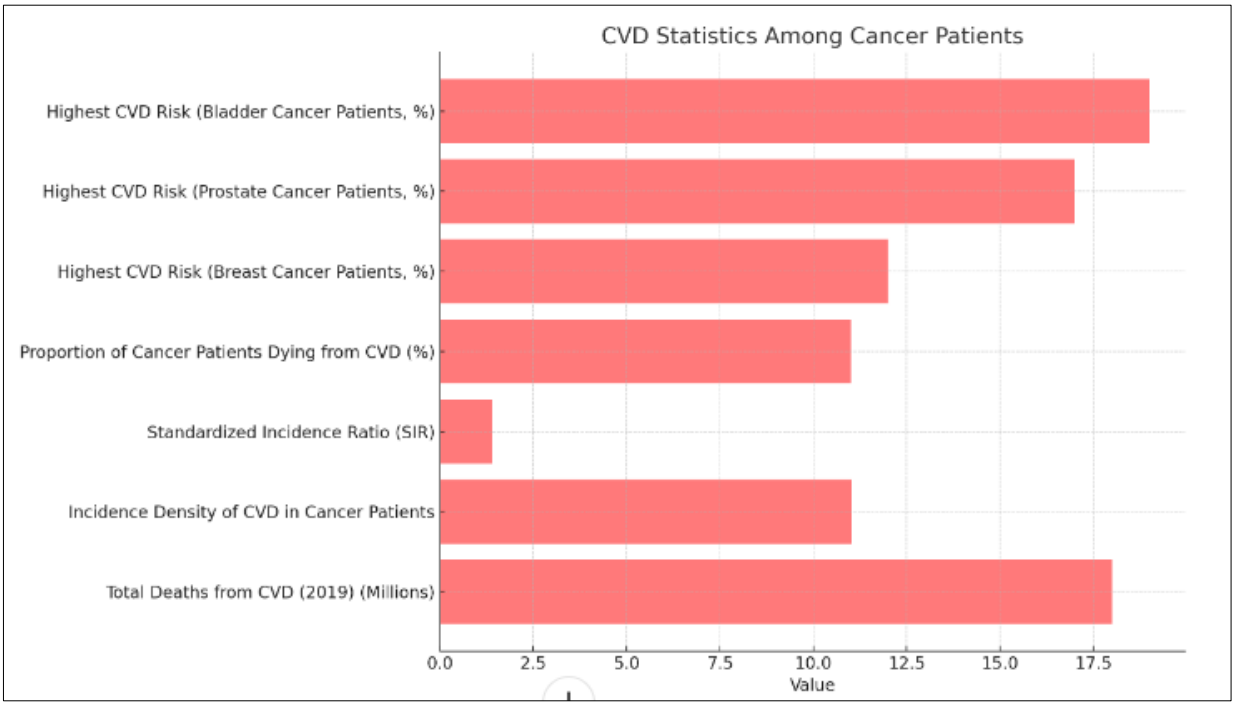

Figure 1: Table of statics related to CVD risk induced by oncologic treatments.

Statics

Cardiovascular disease (CVD) poses life threatening risk among cancer patients, with around 11% of them dying from CVD-related causes. In 2019, 18 million deaths globally are attributed to CVD and the incidence density of CVD among cancer patients is 11.03 per 1,000. Research shows standardized incidence ratio (SIR) is 1.41, reflecting an elevated risk compared to the general population. Specific cancers, such as bladder (19%), prostate (17%) and breast cancer (12%) show exceptionally high proportions of CVD-related deaths.[4]

Novel strategies for detecting and treating cardiotoxicity in cancer treatment

Novel trends in cardio-oncology aims at early identification and individualized management of cardiotoxicity to allow limited interruptions on cancer treatment, biomarkers such as troponin I/T and BNP, NTproBNP are being used due to their prognostic potential of myocardial injury. The new biomarkers – microRNAs (for instance, miR-34a, miR-146a) and galectin-3- will expand possibilities in identifying the heart's subclinical dysfunction and better estimate the potential cardiotoxicity. Also, techniques such as three-dimensional echocardiography, cardiac Magnetic resonance imaging and computed tomography assist in early detection of the heart functions in cancer patients during their treatment regimens. The additive of these biomarkers and imaging techniques offers an enhanced multiparametric method in enhancing the diagnostic precision and risk stratification.[5]

Therapeutically novel strategies are tailored interventions based on individual risk factors including use of cardioprotective agents like dexrazoxane to mitigate anthracycline-induced toxicity and multidisciplinary care involving cardiologists and oncologists is becoming essential with personalized monitoring protocols aimed at early intervention. Integration of advanced tools into clinical practice is critical to improving outcomes and reducing treatment-related cardiovascular complications.

This evolving field stresses importance of ongoing research and development of consensus guidelines to refine patient care strategies. Accurate model for predicting baseline cardiovascular disease (CVD) risk among those patients who are newly diagnosed with malignancies undergoing anti-cancer treatment is crucial. Current predictive models like the Framingham Risk Score may not effectively represent CVD risk in cancer survivors exposed to therapies that harm cardiovascular health. For instance, in a cross-sectional study of testicular cancer survivors indicated no significant difference in Framingham scores compared to age-matched controls year post-chemotherapy but long-term follow-ups show increased late CVD risk in these patients.[6] Guidelines generated by European Society of Medical Oncology (ESMO) show position of baseline CVD risk assessment before cancer treatment but still there is lack discussions on predictive models. The American Society of Clinical Oncology (ASCO) gives risk stratification approach depending on oncological treatments and age related factors or other associated CVD risk factors although this is primarily backed by moderate evidence. Current studies are now being more interested in predictive models for future CVD primarily focus on breast cancer patients. Research by Ezaz et al established model categorizing human epidermal growth factor receptor (HER2)-positive breast cancer patients into low and medium, and high-risk groups for heart failure which is demonstrating good discriminative ability while in terms of preventive strategies, primary prevention aims to delay or prevent CVD onset while secondary prevention seeks to mitigate severe cases. Most intervention studies focus on patients treated with anthracyclines, especially breast cancer patients analyzing the cardioprotective effects of medications like angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and beta-blockers. Meta-analysis of 2,301 patients discussed about these medications yielded modest reductions in left ventricular ejection fraction (LVEF) decline while the role of statins in preserving LVEF during anthracycline therapy has shown some promise even though without significant differences in severe LVEF reduction rates. Research into aspirin's role in cardiotoxicity prevention remains scarce and studies on dexrazoxane indicate its established efficacy in pediatric populations but there is less clarity in adult applications.[7,8]

METHODS

This systematic review used a clear cut approach towards article selection to assess the cardioprotection interventions in oncology population. Research articles were included if the study type was randomized controlled trial (RCT) or meta-analysis of cardioprotective interventions like, GLS-guided treatment or exercise training to prevent CIC. Included trials needed to include adult patients with cancer receiving potentially cardiotoxic treatments, followed up for LVEF, GLS or VO2 peak. The excluded studies were observational study, case reports, and other non-randomised control trials. Pediatric studies and those without a control group were also excluded from the analysis. Further, the study that do not present cardiovascular results or does not define specific intervention strategy was also excluded. To make sure that what is discovered is up to date and makes sense, articles written in languages other than English or published before the year 2000 were omitted. A systematic search of studies was conducted in the database and full texts were reviewed to ensure that relevant papers which met the inclusion criteria where retrieved in order to provide strong evidence for the cardioprotective management of cancer patients receiving cancer therapies.

The risk of bias tool assesses the potential for bias in the included studies based on five domains: randomization, intervention implementation, missing data, outcome measurement, and reporting bias (Figure 3).

The forest plot visually represents the effect sizes and confidence intervals of the included studies, allowing for comparison and assessment of heterogeneity (Figure 4).

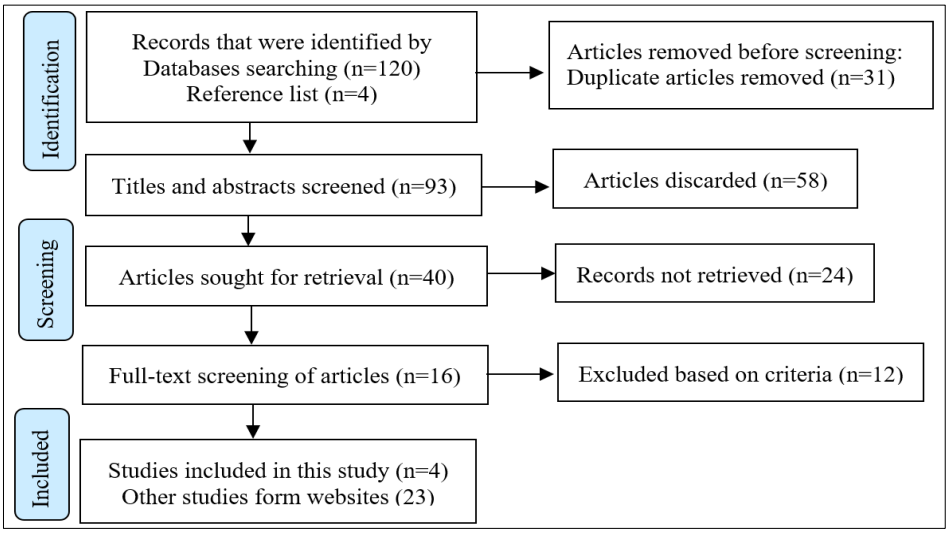

Figure 2: PRISMA flow diagram of included papers.

Table 1: Primary and secondary keywords.

Primary keyword	Derived secondary keywords	Keywords with AND/OR/NOT
Cancer therapy	Oncology, tumor, chemotherapy	Cancer therapy AND cardiac dysfunction OR heart failure
Cancer therapy–related cardiac dysfunction	Cardiotoxicity, myocardial injury	Cancer therapy–related cardiac dysfunction AND cardioprotective therapy
Cardioprotective therapy	Antioxidants, heart health	Cardioprotective therapy AND heart failure
Global longitudinal strain	Echocardiography, strain imaging	Global longitudinal strain AND heart failure NOT cancer
Heart failure	Congestive heart failure, edema	Heart failure OR cardiovascular risk management
Cardiovascular risk management	Risk assessment, preventive care	Cardiovascular risk management AND cancer treatment
Tumor	Neoplasm, carcinoma	Tumor AND cancer therapy NOT cardiac dysfunction

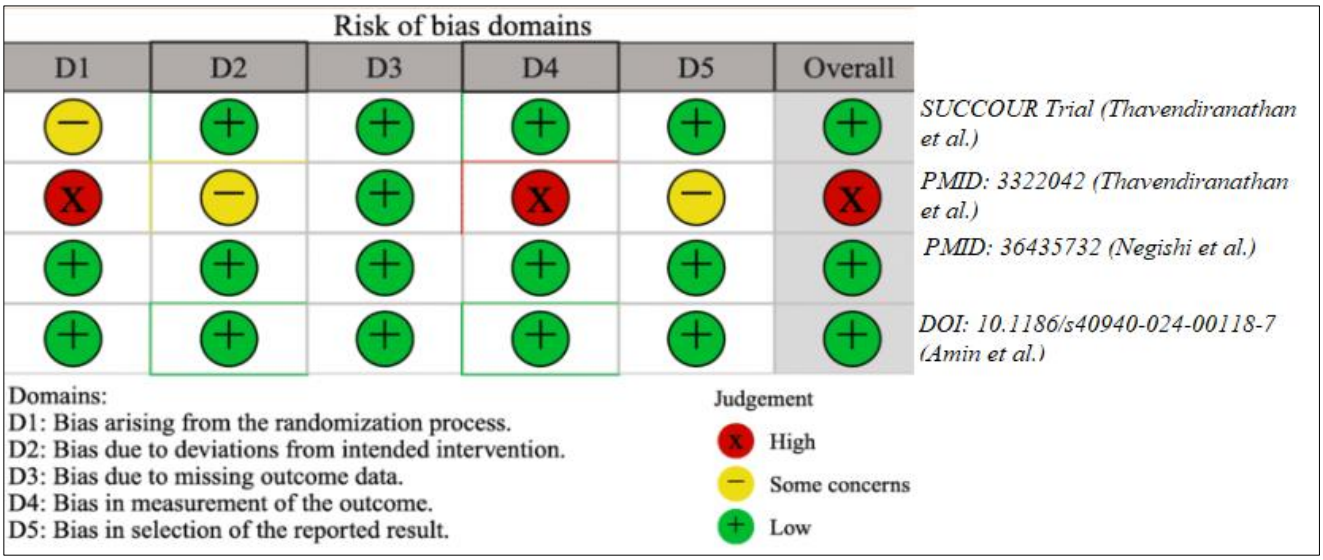

Figure 3: The overall risk of bias assessment of included studies.

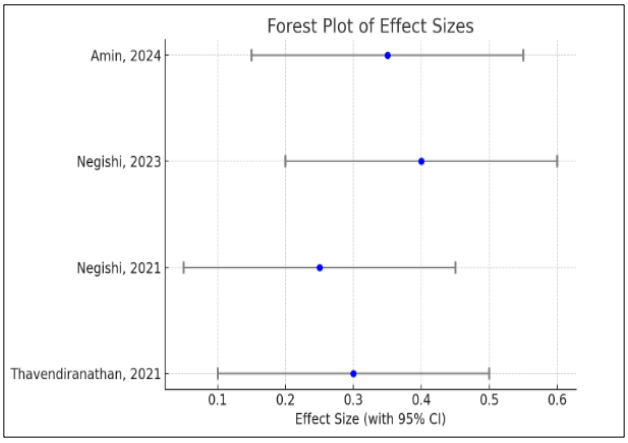

Figure 4: Forest plot.

RESULTS

Table 3 outlines some key diagnostic tools and their clinical applications in monitoring cardiotoxicity for early detection and management of cardiovascular side effects in oncology patients.[13-16]

Primary findings

Our systematic review of RCTs confirmed the efficacy of GLS-guided cardioprotective therapy (CPT) in preserving left ventricular ejection fraction (LVEF) and preventing chemotherapy-related cardiotoxicity (CTRCD). In the Thavendiranathan et al study CTRCD occurred in 5.8% of the GLS group versus 13.7% in the EF-guided group (p=0.02) showing benefit of strain-guided management. Negishi et al found a significantly lower reduction in LVEF with GLS guidance.

However, Negishi et al reported no significant difference in long-term LVEF change between GLS and EF groups. And research by Amin et al showed exercise significantly improved VO2 peak (MD: 1.95, p=0.005) emphasizing importance of incorporating exercise to mitigate cardiotoxicity.

Table 2: Cardiovascular toxicity of oncologic therapies – mechanisms and associated risks.[9-12]

Oncologic drug/class	Example drugs	Mechanism of cardiotoxicity	Associated cardiovascular risks
Anthracyclines	Doxorubicin, epirubicin	Free radical formation → oxidative stress → mitochondrial dysfunction → apoptosis of cardiomyocytes	Dilated cardiomyopathy, heart failure, arrhythmias
HER2 inhibitors	Trastuzumab, pertuzumab	HER2 receptor blockade → disruption of cardiomyocyte survival pathways (neuregulin-1 signaling)	Left ventricular systolic dysfunction, Heart failure
Alkylating agents	Cyclophosphamide, ifosfamide	Reactive oxygen species (ROS) generation → direct endothelial injury → myocardial fibrosis	Heart failure, hemorrhagic myocarditis, arrhythmias
Anti-VEGF agents	Bevacizumab, sorafenib	VEGF inhibition → endothelial dysfunction → impaired nitric oxide production → increased vascular resistance	Hypertension, arterial thromboembolism, myocardial ischemia
Tyrosine kinase inhibitors	Imatinib, sunitinib	Inhibition of cardiomyocyte-specific kinases (e.g., PDGFR, KIT) → mitochondrial injury	Left ventricular dysfunction, hypertension, QT prolongation
Proteasome inhibitors	Bortezomib, carfilzomib	Inhibition of NF-κB pathway → reduced cardiomyocyte survival → ER stress	Congestive heart failure, ischemia, hypertensive crisis
Immune checkpoint inhibitors	Pembrolizumab, nivolumab	Immune-mediated myocarditis due to T-cell activation against cardiac antigens	Myocarditis, pericarditis, tachyarrhythmias
Platinum-based agents	Cisplatin, carboplatin	Endothelial cell apoptosis → oxidative stress → long-term arterial damage	Hypertension, coronary artery disease, myocardial infarction
Antimetabolites	5-Fluorouracil, capecitabine	Induction of coronary vasospasm via endothelial dysfunction and thromboembolic events	Angina, coronary vasospasm, acute coronary syndrome
Radiotherapy	-	Ionizing radiation → DNA damage → chronic inflammation and fibrosis of cardiac tissues	Coronary artery disease, constrictive pericarditis, valvular heart disease

Table 3: Diagnostic approaches for early detection of cardiotoxicity in oncology patients.[13-16]

Diagnostic modality	Technique/tool	Parameter assessed	Clinical utility	Recommended timing
Echocardiography	2D/3D echo, strain imaging	Ejection fraction (LVEF), global longitudinal strain (GLS)	Early detection of subclinical left ventricular dysfunction	Baseline, every 3 months, post-treatment
Cardiac MRI	T1/T2 mapping, late gadolinium enhancement	Myocardial fibrosis, edema, left ventricular mass	Quantitative assessment of myocardial damage and fibrosis	Baseline and follow-up for symptomatic cases
Serum biomarkers	Troponin I/T, BNP, NT-proBNP	Myocardial injury, wall stress	Monitoring of cardiomyocyte injury and heart failure onset	Baseline, every cycle, and as needed
Electrocardiography (ECG)	12-lead ECG, Holter monitor	QT interval, arrhythmias	Detection of arrhythmias and QT prolongation	Baseline and during high-risk treatment periods
Nuclear imaging	MUGA scan, PET/CT	Left ventricular ejection fraction (LVEF), metabolic activity	Assessment of myocardial perfusion and function	Baseline and for patients with equivocal symptoms
Cardiac biomarkers panel	Galectin-3, sST2, Hs-CRP	Inflammation, fibrosis, myocardial stress	Comprehensive evaluation of heart failure and fibrotic activity	As needed based on clinical suspicion

Table 4: Summary of studies on cardioprotective strategies and interventions.

Author/ date	Study ID/reference	Design	Experimental intervention	Comparator	Outcome	Results	Aim	Effect of adhering to intervention
Thavendiranathan et al 2021[17]	SUCCO00341628 UR trial, ACTRN 126140	Prospec-tive, internat-ional, multice-nter, RCT	LS-guided cardioprotecti-ve therapy (CPT) with ≥12% relative reduction in global longitudinal strain (GLS)	EF-guided therapy with >10% absolute reduction in LVEF	LVEF preservat-ion, CTRCD prevent-ion	CTRCD: 5.8% in GLS-guided group versus 13.7% in EF-guided group (p=0.02)	Evaluate cardiopro-tective manage-ment using strain guidance	Assignment to intervention (intention-to-treat)
Negishi et al 2021[18]	PMID: 33220426 DOI: 10.1016/j.jacc.2020.11.020	Prospec-tive, multice-nter, RCT	GLS-guided CPT	EF-guided CPT (>10% reduction in LVEF)	Change in LVEF over one year	Significant-ly lower CTRCD, lesser reduction in LVEF in GLS group	Analyze impact of GLS-guided CPT	Assignment to intervention (intention-to-treat)
Negishi et al 2023[19]	PMID: 36435732	Prospec-tive, internat-ional multice-nter RCT	GLS-guided CPT	EF-guided CPT (>10% absolute reduction of EF to <55%)	Change in 3D EF over 3 years	No significant difference in ΔEF between GLS and EF-guided groups	Long-term efficacy comparis-on of GLS and EF guidance	Assignment to intervention (intention-to-treat)
Amin et al 2024[20]	DOI: 10.1186/s40940-024-00118-7	System-atic review and meta-analy-sis	Exercise intervention to mitigate chemotherapy-induced cardiotoxicity	Usual care without exercise	VO2 Peak	Significant increase in VO2 peak (MD: 1.95, 95% CI [0.59, 3.32], p=0.005)	Assess efficacy of exercise regimens to reduce cardiotox-icity	Assignment to intervention (intention-to-treat)

DISCUSSION

Altogether, the data obtained in these trials are valuable for understanding the cardio protective approaches to potentially cardiotoxic cancer treatments. CONSORT-based CPT with GLS reduced CTRCD compared to EF-directed treatment strategies used as a control group. The decrease in CTRCD by 7.9% (p=0.02) could be attributed to benefits of GLS monitoring that due to its higher sensitivity, shows subclinical cardiac changes earlier and allows making necessary therapeutic changes. This advantage is essential in order to minimize cardiotoxicity in the first phase of the experiment. However, the long-term follow-up, which demonstrates that 3-dimensional ejection fraction (ΔEF) does not favor GLS to over EF-guided therapies for up to three years, challenges the sustainable effects of GLS guided therapy. This could infuse that GLS and this method are equally effective in the long run despite the distinguishing short courses.[17-20] Other RCts on exercise interventions revealed improvement in VO2 Peak (MD: 1.95, p=0.005), highlighting the role of non-pharmacological approaches in enhancing cardiopulmonary fitness during chemotherapy, VO2 peak improvement doesn't directly measure structural cardiac changes, it suggests better overall cardiovascular resilience, potentially reducing the risk of cardiotoxicity. Both interventions come with their own challenges and GLS monitoring was although effective in the short term but may require advanced equipment and training which is limiting its widespread application. Exercise interventions are while beneficial but depend heavily on patient adherence and individualized regimens.[17-20]

A van Dalen, 2005 meta-analysis showed 11 RTCs that showed that dexrazoxane lowers the incidence of symptomatic heart failure and asymptomatic LVEF decline; it similarly demonstrated no effect on tumour response rates.AN This was supported by smith et al., 2010 who carried out meta-analysis of 55 RCTs revealing that lower incidence of heart failure and LVEF decline was evident when patients received Rafiyath and Van Dalen in

the year, 2010-2012 proposed the liposomal doxorubicin as another strategy with advantages of low-risk heart failure and LVEF deterioration compared to standard doxorubicin formulations indicating that cancer therapy regimens may be modified to promote cardiac safety and treatment effect. Padegimas et al identified that neurohormonal antagonists especially enalapril and spironolactone has also been studied. The current PROACT trial assesses the ability of enalapril to maintain LVEF and prevent troponin increase. A few RCTs including NCT02053974 revealed promising evidence for a reduction of LVEF decline by 60% and an improvement of the diastolic dysfunction with spironolactone. Nevertheless, the eplerenone trial was stopped for a futility, so it was understood that this problem required more focused interventions.[17]

Beta-blockers are now scrutinized for their potential to confer cardioprotection during anthracycline therapy and CECCY trial did not find a difference in LVEF between carvedilol and placebo. However, carvedilol did attenuate diastolic dysfunction and troponin I elevation which show protective role against the biochemical markers of cardiac injury. Further investigations such as the MANTICORE and PRADA trials have evaluated the combination of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) with beta-blockers revealing less LVEF reduction with these combinations compared to placebo, showing complexity of cardiovascular responses to cancer treatments and potential for synergistic effects from combination therapies, Padegimas et al stated.[17] Findings also show that trials assessing the use of statins in this context are also underway. The PREVENT trial and others aim to determine whether atorvastatin or simvastatin can further safeguard cardiac function in patients receiving anthracyclines. These studies may provide us important information about the pipelines of statins beyond the lipid profile lowering so there are emerging more innovative approaches such as combining them with radiation therapy and risk-aided approaches based on images or biomarkers. Studying like the PCORI/RADCOMP trial are comparing proton and photon radiation therapy in respect to cardiovascular and cancer mortality with the intention of establishing the best treatment regimens for avoiding cardiac complications. Moreover, according to Padegimas et al, the attempt mentioned in the ICOS-One trial to initiate enalapril therapy based on troponin having changed the approach to patient management toward biomarker-based strategies.[17]

Oncologic therapies are crucial for cancer management but it is essential to know these may often pose significant cardiovascular risks due to their mechanisms of action.[18] Anthracyclines like doxorubicin induce cardiotoxicity through free radical formation, which may cause oxidative stress and mitochondrial dysfunction, and, ultimately, cardio myocyte apoptosis and altogether resulting in conditions such as dilated cardiomyopathy and cardiac failures. HER2 inhibitors, such as trastuzumab, interfere with neuregulin-1 signaling, crucial for cardiomyocyte survival, thus the risk of left ventricular systolic dysfunction can be increased.[19-20] Alkylating agents generate reactive oxygen species causing direct endothelial damage and myocardial fibrosis which is also a known cause of heart failure and arrhythmias. Anti-VEGF agents inhibit vascular endothelial growth factor and impair endothelial function and nitric oxide production increasing the risk of hypertension and myocardial ischemia.[21,22] Tyrosine kinase inhibitors' inhibition of cardiomyocyte-specific kinases may can be a cause of mitochondrial injury, manifesting as hypertension and QT prolongation. Proteasome inhibitors and immune checkpoint inhibitors lead to unique cardiotoxic effects which may lead to heart comorbidities and immune-mediated myocarditis, respectively.[23-26] Furthermore, many platinum-based agents and antimetabolites are involved in coronary artery disease and acute coronary syndromes through cause of death and vasospasm. Such complications stress on importance of constant supervision with the help of enhanced diagnostic tools that we have described in the table 2 in order to prevent and control these adverse cardiovascular effects effectively.[27]

CONCLUSION

The cardiotoxicity of the employed anticancer treatments and the infection risk rise with cancer patients' age and the presence of CVDs; therefore, contemporary oncological therapy must address CV risk management. There is empirical evidence for benefit that originates from programs like GLS-guided cardioprotective therapy as well as structured exercise programs in helping to prevent heart failure, arrhythmias, myocardial dysfunction. These approaches protect heart function and enhance both post-surgery and post-treatment outcomes, quality of life, and survival rates of the patient. As such, further research should be aimed at optimizing these strategies and creating protocol for their use in clinical practice. To support improved patients' outcome as well as increased success of cancer treatments, cardiovascular screening and management should become an essential part of cancer treatment.

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