Review Article

Narrative Literature Review of Cancer Therapy-related Cardiac Dysfunction

CME Credits

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Abstract

Cancer therapy-related cardiac dysfunction (CTRCD) presents a significant challenge for both oncology and cardiology, necessitating a comprehensive understanding of its pathophysiology, risk factors, diagnostic modalities, and pharmacological interventions. The pathophysiology of CTRCD is multifactorial, and various cancer therapies exert cardiotoxic effects through distinct but overlapping mechanisms, highlighting the need for more personalized preventive and therapeutic interventions. In addition to conventional clinical risk factors, baseline echocardiographic evaluation also plays a critical role in the risk stratification of CTRCD, and numerous studies have demonstrated that baseline left ventricular ejection fraction, global longitudinal strain, and diastolic dysfunction are all predictive of the development of cardiotoxicity. Moreover, continuous surveillance of cardiac function throughout the course of cancer therapy is also paramount. A multimodal diagnostic approach, including cardiac biomarkers, echocardiography, cardiac magnetic resonance imaging, and computed tomography, may facilitate early detection of subclinical myocardial injury and enables timely interventions that may mitigate irreversible cardiac damage. Finally, several pharmacologic strategies have demonstrated promising data in reducing cardiotoxic effects and preserving cardiac function. With these advancements, clinicians can now take a more proactive role in integrating cardio-oncology strategies into treatment protocols, thereby optimizing patient outcomes while minimizing unplanned interruptions in oncologic therapy.

Keywords: Cancer therapy-related cardiac dysfunction, diastolic dysfunction, echocardiography, global longitudinal strain , left ventricular ejection fraction

Introduction

Cancer therapy-related cardiac dysfunction (CTRCD) is a serious but often overlooked complication of cancer therapy.[1] With increasing cancer survival rates due to continuous advancements in oncological treatments, the long-term adverse effects of chemotherapy have become a major concern, besides the traditional cancer-related survival.[2] Among them, CTRCD is one of the most important side effects and may have a significant impact on the quality of life of the patients.[3]

While anthracyclines are the most well-recognized therapy associated with CTRCD, other cancer treatments could also cause cardiovascular toxicities. The clinical spectrum of CTRCD ranges from asymptomatic myocardial dysfunction to overt heart failure, myocardial infarction, arrhythmias, and cardiomyopathy.[4] The prevalence of CTRCD varies widely depending on the cancer treatment regimen, patient comorbidities, and genetic predispositions, with the incidence of up to 10% in some cancer-therapy-treated populations.[5]

Therefore, early diagnosis and monitoring are essential to secure the safety and increase the quality of life of the patients under treatment. The diagnosis of CTRCD involves

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Abbreviations

CCT	Cardiac computed tomography
CMR	Cardiac magnetic resonance
CT-FFR	Computed tomography–derived fractional flow reserve
CTRCD	Cancer therapy-related cardiac dysfunction
ECV	Extracellular volume
GLS	Global longitudinal strain
hsTnT	High-sensitivity troponin T
LGE	Late gadolinium enhancement
LVEF	Left ventricular ejection fraction
NT-proBNP	N-terminal pro–brain natriuretic peptide

a combination of clinical evaluation, biomarker analysis, and cardiac imaging. Left ventricular ejection fraction (LVEF) is one of the most important markers in echocardiography and is highly valuable in diagnosing CTRCD.[5] However, a significant decrease in ejection fraction is a late sign for cardiac deformation,[6] making other advanced techniques, such as echocardiography with global longitudinal strain (GLS) and cardiac magnetic resonance imaging (MRI), more critical for the early detection of CTRCD.

Finally, strategies to mitigate CTRCD, including pharmacologic interventions and lifestyle modifications, are crucial for reducing cardiovascular risk in patients undergoing cancer therapy.[7] By implementing comprehensive monitoring programs and early interventions, we can optimize the cardiac function of patients undergoing cancer treatment, improve their long-term outcomes, and ensure timely adjustments to cancer regimens with minimal disruptions to therapy.

Pathophysiology

The mechanisms underlying CTRCD are diverse and multifactorial, involving oxidative stress, mitochondrial dysfunction, immune-mediated myocardial injury, and myocardial fibrosis.[8] Notably, the cardiotoxicity associated with each cancer therapy regimen may arise from distinct but overlapping pathophysiological processes [Figure 1]. Therefore, it is very important to have a comprehensive understanding of these mechanisms to accurately diagnose and treat CTRCD.

Anthracycline

Anthracycline, including doxorubicin and epirubicin, is the most notorious class of cancer therapy regimen, and causes a dose-dependent cardiotoxicity. Several mechanisms have been proposed, and the most widely recognized are anthracycline-induced mitochondrial reactive oxygen species (ROS) production, cardiomyocyte iron-overload and ferroptosis, mitochondrial dysregulation, and inhibition of topoisomerase IIβ.

Anthracyclines stimulate excessive ROS production by interfering with the mitochondrial electron transport chain, which leads to oxidative damage and, eventually, cardiomyocyte apoptosis.[9] Through forming iron-anthracycline complex, iron dysregulation also exacerbates this damage, enhances ROS generation, and lipid peroxidation.[10] Ferroptosis, a type of iron-dependent programmed cell death driven by lipid peroxidation and suppression of protective enzymes such as glutathione peroxidase 4, has been identified as a major contributor to cardiotoxicity.[11] Furthermore, anthracycline also causes mitochondrial dysfunction by disrupting energy production and causing ATP depletion, both of which further exacerbate the cardiotoxic effects.[12] Finally, topoisomerase IIβ inhibition leads to DNA double-strand breaks, mitochondrial dysfunction, and impaired gene expression critical for cell survival.[13]

Human Epidermal Growth Factor Receptor Protein Inhibitors

Human epidermal growth factor receptor 2 (HER2), together with its ligand, neuregulin-1 (NRG1), is closely tied to the maintenance of adult cardiac function and the development of cardiomyocytes. HER2 receptor antagonists, such as trastuzumab, cause cardiotoxicity by interfering with this NRG1 signaling pathway in cardiomyocytes.[14] This disruption impairs phosphatidylinositol 3-kinase and protein kinase B signaling, causes the accumulation of ROS in cardiomyocytes, and finally triggers apoptosis of cardiomyocytes.[15] Moreover, mitochondrial dysfunction and alterations of cardiomyocyte metabolism may also occur with the use of HER2 inhibitors, both of which may partially explain the reversible nature of trastuzumab-induced cardiotoxicity.[15]

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs), such as anti-programmed death-1 (PD-1), anti-programmed death-ligand 1 (PD-L1), and anticytotoxic T-lymphocyte-associated protein 4 (CTLA-4), enhance T-cell-mediated immune responses against cancer cells. However, ICIs may also cause immune-mediated myocarditis since PD-1, PD-L1, and CTLA-4 all play critical roles in maintaining cardiac-immune crosstalk and immune homeostasis.[16] Inflammation and myocardial damage occur as a result of T-cell overactivation and infiltration into the myocardium. Besides myocarditis, ICIs also cause arrhythmias and noninflammatory left ventricular dysfunction, but the underlying mechanism is less well understood.[17]

Other agents

Anti-vascular endothelial growth factor (VEGF) agents, alkylating agents, tyrosine kinase inhibitors (TKIs), and proteasome inhibitors (PIs) can all cause significant cardiotoxic effects through various mechanisms. Anti-VEGF agents impair nitric oxide bioavailability and increase oxidative stress, leading to hypertension, endothelial injury, and potential heart failure or ischemic events.[18,19] Alkylating agents like cyclophosphamide produce acrolein during metabolism, which damages mitochondria, disrupts ATP production, and activates inflammatory and apoptotic pathways in cardiomyocytes.[20-22] TKIs contribute to cardiotoxicity via both on-target effects – such as VEGF

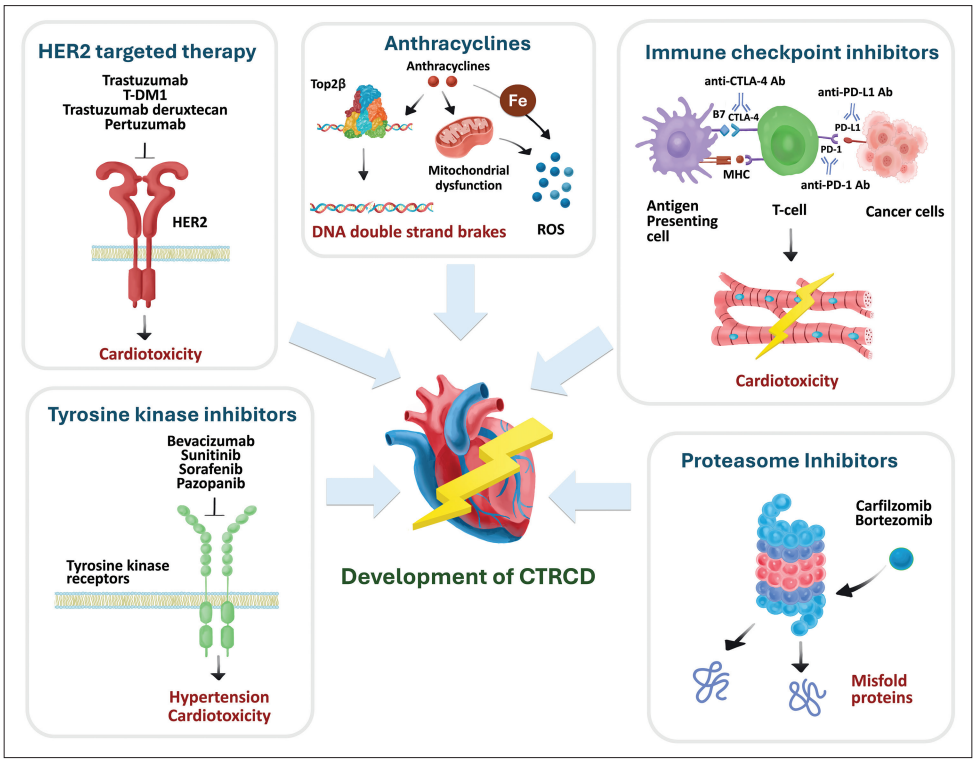

Figure 1: Overview of the pathophysiology of cancer therapy-related cardiac dysfunction. The mechanisms of cardiotoxicity are diverse and multifactorial among different drugs, involving oxidative stress, mitochondrial dysfunction, immune-mediated myocardial injury and myocardial fibrosis. Anti-CTLA-4 Ab: anti-cytotoxic T-lymphocyte-associated protein 4 antibody; anti-PD-1 Ab: Anti-programmed cell death protein 1 antibody; anti-PD-L1 Ab: Anti-programmed death-ligand 1 antibody; B7: B7-1 (CD80)/B7-2 (CD86) costimulatory molecules; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; CTRCD: Cancer therapy-related cardiac dysfunction; Fe: Iron; MHC: Major histocompatibility complex; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; ROS: Reactive oxygen species; T-cell: T lymphocyte; T-DM1: Trastuzumab emtansine; Top2β: Topoisomerase II beta

receptor, platelet-derived growth factor receptor, and BCR-ABL inhibition – and off-target mechanisms like AMPK inhibition, resulting in endothelial dysfunction, mitochondrial damage, and arrhythmias.[23-26] PIs interfere with protein degradation, leading to mitochondrial dysfunction, oxidative stress, and endoplasmic reticulum stress, with carfilzomib showing particularly high rates of cardiovascular events, including heart failure and ischemia.[27,28]

Chest radiotherapy is an essential component in the treatment of several malignancies, including lung, esophageal, breast cancers, and lymphoma, but it may also result in acute and chronic cardiovascular injuries through multiple pathogenic mechanisms. Acutely, radiation can induce microvascular injury and inflammatory responses, leading to pericarditis and pericardial effusions. These are often asymptomatic or may present with self-limiting symptoms; however, they can also predispose to chronic constrictive pericarditis, and rare cases of cardiac tamponade have been reported.[29] Chronically, radiation accelerates atherosclerosis and leads to a 4-to 6-fold increased risk of coronary artery disease – especially in the left anterior descending and right coronary arteries.[30] In addition, radiation-induced myocardial fibrosis impairs both diastolic and systolic function, and heart failure, especially heart failure with reduced ejection fraction, may develop.[31] Finally, progressive valvular dysfunction may occur, characterized by thickening, fibrosis, and calcification of the annulus, basal and mid-leaflets, and subvalvular apparatus without valve tips and commissures involvement.[32]

In conclusion, CTRCD arises from a combination of diverse and overlapping pathophysiology, including oxidative stress, mitochondrial dysfunction, immune-mediated injury, cardiomyocyte apoptosis, and myocardial fibrosis. Understanding these mechanisms is essential to improve the early detection, diagnosis, and management of CTRCD, all of which make cancer treatment strategies safer and more sustainable in clinical practice.

Patient-related Risk Factors

Patient-related risk factors can be classified into three main categories: Clinical risk factors, baseline echocardiographic parameters, and genetic predispositions [Figure 2]. Identifying these risk factors is essential for CTRCD risk stratification and facilitates the implementation of personalized cardiac function monitoring programs.

Clinical Risk Factors

Preexisting cardiovascular conditions, such as hypertension, diabetes, dyslipidemia, coronary artery disease, and heart failure, are among the strongest predictors of CTRCD.[5,33]

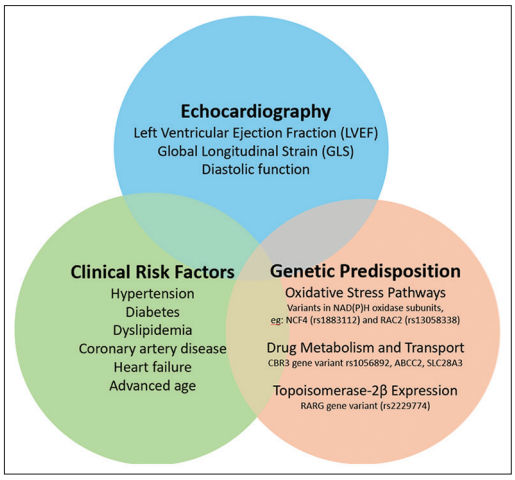

Figure 2: Multimodal risk stratification of cancer therapy-related cardiac dysfunction (CTRCD). CTRCD risk is influenced by the interplay of three major patient-related risk factors, including echocardiographic parameters, clinical risk factors and genetic predisposition. Comprehensive risk stratification prior to the initiation of cardiotoxic agents is very important to guide future monitoring program and intervention strategies. ABCC2: ATP-binding cassette sub-family C member 2; CBR3: Carbonyl reductase 3; CTRCD: Cancer therapy-related cardiac dysfunction; GLS: Global longitudinal strain; LVEF: Left ventricular ejection fraction; NADPH: Nicotinamide adenine dinucleotide phosphate (reduced form); NCF4: Neutrophil cytosolic factor 4; RAC2: Ras-related C3 botulinum toxin substrate 2; RARG: Retinoic acid receptor gamma; SLC28A3: Solute carrier family 28 member 3; Top2β: Topoisomerase II beta

These conditions compromise baseline cardiac function, making cancer patients more vulnerable to CTRCD.

Advanced age is another significant risk factor. With increasing age, myocardial elasticity decreases, and comorbidities such as atherosclerosis become more prevalent, both of which further reduce cardiac reserve.[34] In fact, the increase in cardiovascular risk may be as high as 1.6-to 6.8-fold, according to previous studies.[35] Moreover, with increasing age, patients tend to have a higher likelihood of undertreatment despite better survival outcomes with adherence to guideline-based treatments.[36]

By integrating subclinical and clinical risk factors, many risk scores have been developed for the CTRCD risk stratification. The Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) score is one of such tools.[37] Evidence showed that it has a good correlation with cardiotoxicity and all-cause mortality, and effectively categorizing patients into low, intermediate, and high-risk groups.[38] This scoring system is straightforward to implement and enables comprehensive cardiovascular risk assessment before the initiation of potentially cardiotoxic treatments.

Baseline Echocardiographic Parameters

Echocardiography plays a pivotal role in identifying patients at risk for CTRCD across a wide range of oncologic treatments.

LVEF, a key parameter of global left ventricular systolic function, has been shown to inversely correlate with the likelihood of developing CTRCD.[39] Current guidelines recommend that baseline LVEF assessment should be performed in all patients before the initiation of cardiotoxic agents for CTRCD risk stratification, and preventive strategies should be implemented based on the findings.[40]

Speckle tracking echocardiography (STE) is an advanced technique that provides a detailed evaluation of heart muscle dynamics through tracking natural acoustic markers, or "speckles," within the myocardial tissue. Left ventricular strain and strain rate can be measured by STE and are important parameters to describe myocardial deformation across longitudinal, radial, and circumferential axes.[41] Specifically, strain assesses the percentage change in myocardial length during contraction, while strain rate indicates the rate of deformation.[42]

GLS, by using this technique, has emerged as a sensitive and reproducible marker for the early detection of subclinical myocardial dysfunction, and offers a comprehensive "global" assessment of left ventricular function by integrating strain measurements across all myocardial segments.[41]

A meta-analysis identified baseline GLS <−17.5% as an independent parameter associated with a sixfold increase in subsequent cardiovascular events.[31] Notably, GLS remains a significant prognostic marker for overall mortality even among individuals with preserved LVEF in the range of 50%–59%. These findings highlight the incremental value of GLS beyond conventional LVEF assessment in CTRCD risk stratification.

Baseline diastolic function also serves as a significant predictor of the development of CTRCD, and evidence suggests that the presence of preexisting diastolic dysfunction is associated with an increased risk of subsequent CTRCD.[43] Furthermore, an elevated left atrial volume index >34 mL/m^2, indicative of increased left ventricular filling pressures, has been associated with a higher likelihood of CTRCD.[44]

Therefore, it is very important to perform a comprehensive baseline echocardiogram before the initiation of cardiotoxic agents, and patients with low LVEF, GLS, and diastolic dysfunction are at increased risk for developing CTRCD.

Genetic Predisposition

The ability to identify individuals genetically predisposed to CTRCD is an emerging area of research. Numerous genes have been identified in the pathophysiological mechanisms underlying CTRCD, offering valuable insights into patient susceptibility and guiding future personalized medicine.

Oxidative stress pathways

Genetic polymorphisms in oxidative stress-related genes have been strongly implicated in CTRCD.[45] Variants in NAD(P) H oxidase subunits, such as NCF4 (rs1883112) and RAC2 (rs13058338), increase susceptibility to oxidative damage by modulating ROS production.[46] This is particularly relevant for anthracyclines, which induce cardiotoxicity through ROS generation and lipid peroxidation.[10]

Drug metabolism and transport

Polymorphisms affecting drug metabolism and transport also play a critical role. The CBR3 gene variant rs1056892 leads to increased conversion of doxorubicin to doxorubicinol, a cardiotoxic alcohol metabolite.[47] By exacerbating myocardial injury, CBR3 gene variant may increase the risk of anthracycline-related cardiomyopathy at doses as low as 101–150 mg/m^2. In addition, genes responsible for membrane transporters regulating anthracycline influx and efflux, such as ABCC2 and SLC28A3, have been shown to influence intracellular drug concentrations and cardiotoxicity.[45]

Topoisomerase-2β expression

The interaction of anthracycline with topoisomerase-2β is another mechanism mediating anthracycline-induced cardiotoxicity.[48] A genome-wide association study identified the RARG gene variant (rs2229774) as a significant risk factor for CTRCD, disrupting RARG's regulatory function and increasing topoisomerase-IIβ expression in cardiomyocytes.[49] This variant elevates the risk of CTRCD with an odds ratio of 4.7, highlighting its critical role in anthracycline sensitivity.

Emerging loci and rare variants

Recent meta-analyses and functional studies have identified additional genetic loci associated with CTRCD.[50] The intergenic variant rs28714259 has been identified to influence TP63 gene, a member of the p53 family responsible for cell development, cell cycle regulation, and apoptosis, and, therefore, causes mitochondrial dysfunction, cardiac fibrosis, and structural remodeling.

In summary, multiple genetic variants have been linked to an increased risk of CTRCD, and these findings broaden our understanding about genetic predisposition to CTRCD. However, the cost-effectiveness of genetic testing remains uncertain, and its clinical utility requires further evaluation. Moreover, the current studies mainly focus on anthracycline-induced cardiotoxicity, while the association with other cardiotoxic agents is less investigated.

Diagnostic Tools for Cancer Therapy-related Cardiac Dysfunction

Early detection of CTRCD is crucial to prevent long-term cardiovascular damage and to optimize cancer treatment. Various diagnostic tools, including biomarkers, echocardiography, cardiac computed tomography (CT), and cardiac magnetic resonance imaging (CMR), all play pivotal roles in identifying and monitoring CTRCD [Figures 3 and 4].

Biomarkers in cancer therapy-related cardiac dysfunction diagnosis

High-sensitivity troponin (hsTnT) is a highly specific biomarker of myocardial injury. Elevated hsTnT levels observed 3–6 months after initiating cancer therapies are a robust predictor of CTRCD, with an area under the receiver operating characteristic curve (AUC) of 0.90, as demonstrated in a recent meta-analysis.[51]

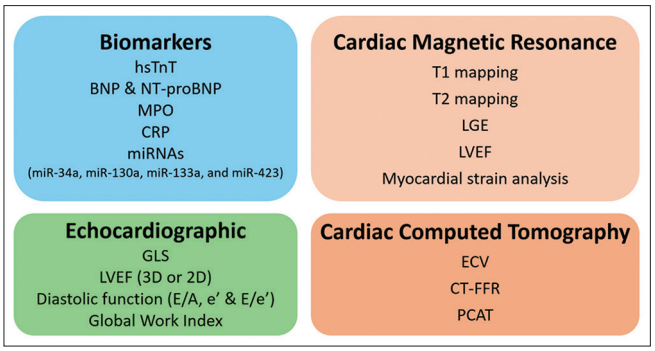

Figure 3: Multimodal approaches for the detection and diagnosis of cancer therapy-related cardiac dysfunction (CTRCD). Various diagnostic tools, including biomarkers, echocardiography, cardiac computed tomography and cardiac magnetic resonance imaging, are crucial for the early detection of CTRCD to prevent long-term cardiovascular damage and optimize cancer treatment. 2D: Two-dimensional; 3D: Three-dimensional; BNP: Brain natriuretic peptide; CMR: Cardiac magnetic resonance; CRP: C-reactive protein; CT-FFR: Computed tomography–derived fractional flow reserve; CTRCD: Cancer therapy-related cardiac dysfunction; e': Early diastolic mitral annular velocity; E/A: Early to late ventricular filling velocity ratio; ECV: Extracellular volume; E/e': Ratio of early mitral inflow velocity to early diastolic mitral annular velocity; GLS: Global longitudinal strain; hsTnT: High-sensitivity troponin T; LGE: Late gadolinium enhancement; LVEF: Left ventricular ejection fraction; miRNA: MicroRNA; MPO: Myeloperoxidase; NT-proBNP: N-terminal pro–brain natriuretic peptide; PCAT: Pericoronary adipose tissue; T1 mapping: Longitudinal relaxation time mapping; T2 mapping: Transverse relaxation time mapping

NT-proBNP is another significant predictor of mortality in cancer patients, and its serum level rises with tumor progression.[52] Furthermore, the risk of CTRCD increases by 56% for every doubling in concentration during follow-up.[53]

Myeloperoxidase (MPO), an enzyme primarily secreted by neutrophils, serves as a biomarker for inflammation and oxidative stress, and is of particular importance for doxorubicin-related cardiotoxicity.[54] Elevated MPO levels correlate with a higher risk of CTRCD, and the risk could be as high as 46.5% in patients with concurrent elevations in hsTnT and MPO levels.[55] In addition, evidence also indicates that both baseline and subsequent increases in MPO levels are significantly lower in patients who maintain stable LVEF than those with substantial LVEF decline.[56]

C-reactive protein, a biomarker for inflammation, demonstrates a high negative predictive value of 94.1% for CTRCD in patients with normal values,[57] effectively identifying high-risk patients who may benefit from closer monitoring. In addition, evidence indicates that serum level of growth differential factor 15 and placental growth factor increases with the use of doxorubicin and trastuzumab and are associated with higher risk of CTRCD.[58]

Finally, MicroRNAs (miRNAs), a class of small, noncoding RNAs, play crucial roles in cardiac pathophysiology

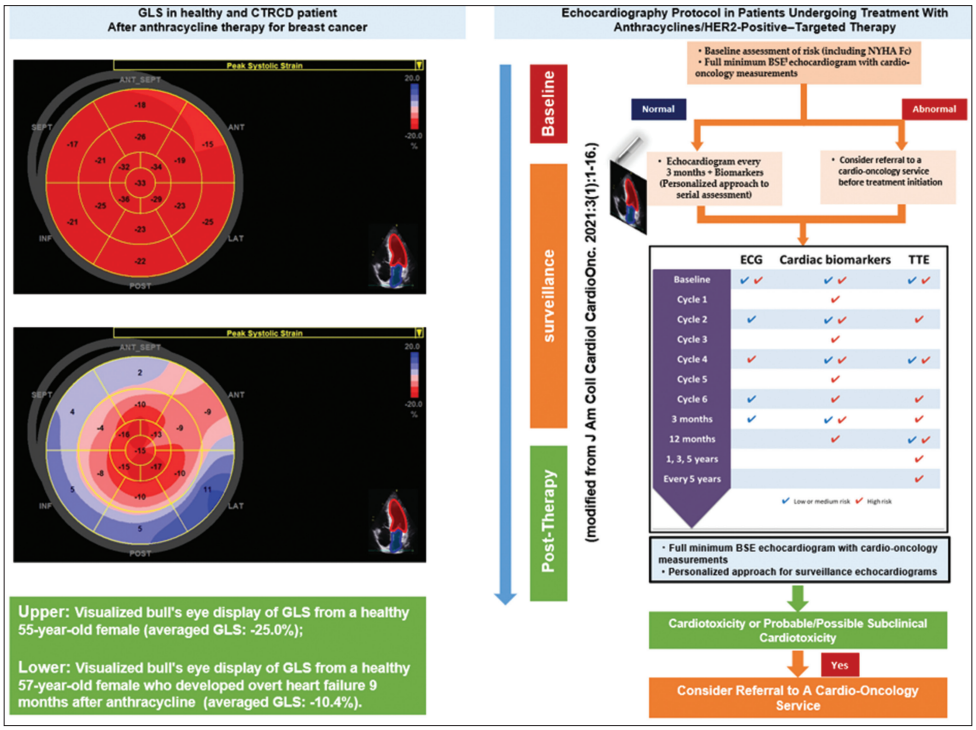

Figure 4: Comprehensive flowchart for cancer therapy-related cardiac dysfunction Risk Stratification, Diagnosis and Surveillance (Left panel) Visualized display of bull's-eye plots of global longitudinal strain obtained from a healthy control and from a patient who developed anthracycline-induced heart failure. (Right panel) Proposed multimodality cardiac-surveillance algorithm comprising (i) comprehensive baseline evaluation, (ii) serial monitoring during therapy, including patients receiving indefinite human epidermal growth factor receptor 2-targeted agents for metastatic disease, and (iii) long-term follow-up after completion of chemotherapy. BSE: British Society of Echocardiography; CTRCD: Cancer therapy-related cardiac dysfunction; ECG: Electrocardiogram; GLS: Global Longitudinal Strain; HER2: Human epidermal growth factor receptor 2; NYHA (FC): New York Heart Association (functional class); TTE: Transthoracic echocardiography

by regulating oxidative stress, inflammation, and apoptosis.[59] Several specific miRNAs, such as miR-34a, miR-130a, miR-133a, and miR-423, have been linked to an increased risk of cardiotoxicity.[60] Notably, recent studies suggest that elevated serum levels of miR-130a during anthracycline plus trastuzumab treatment are an independent predictor of CTRCD and can improve the predictive accuracy of cardiotoxicity with an AUC of 0.94 when combined with other clinical risk factors.[61]

Echocardiographic parameters for diagnosing cancer therapy-related cardiac dysfunction

LVEF reflects global systolic function and is one of the most important indices for CTRCD diagnosis. A decline in LVEF of ≥10% or GLS ≥15% from baseline after the initiation of cardiotoxic cancer therapy is indicative of significant myocardial injury and serves as a key criterion for diagnosing CTRCD.[40] Traditional two-dimensional echocardiography relies on geometric assumptions about the ventricle and carries a higher intra- and interobserver variation, potentially reducing its accuracy.[62] In contrast, three-dimensional echocardiography provides more precise volumetric measurements, facilitating earlier detection of subtle LVEF declines, and is often considered the preferred modality for LVEF assessment.[40]

Nevertheless, LVEF is not sufficiently sensitive to detect early myocardial injury by CTRCD and can sometimes be overlooked when relying solely on LVEF measurements.[63] As a result, the patients may be continuously exposed to cardiotoxic therapies even after subclinical myocardial injury is established. Notably, among individuals whose LVEF falls below 45%, <½ respond favorably to HF therapies.[64] Thus, additional echocardiographic parameters are critical, and there is a growing interest in identifying the earliest markers for CTRCD detection.

Diastolic impairment is another major manifestation of CTRCD, and key echocardiographic parameters include transmitral inflow velocities (E and A waves), tissue Doppler-derived early diastolic mitral annular velocity, and the ratio of early mitral inflow velocity to early diastolic mitral annular velocity.[65] By increasing left ventricular filling pressures and reducing ventricular compliance, diastolic impairment can precede systolic dysfunction in CTRCD and may be correlated with a higher risk of subsequent decrease in LVEF.[66] Consequently, a thorough assessment of diastolic function is essential for detecting early echocardiographic changes of CTRCD.

As previously noted, GLS is a more sensitive modality than conventional LVEF measurement for the early detection

of subclinical myocardial dysfunction. Reduction in GLS often precedes that of LVEF and is predictive of subsequent CTRCD.[67] More specifically, for every 1% relative reduction in GLS, there is a 19% increase in the OR for subsequent CTRCD.[68] The cut-off value for relative GLS reduction remains elusive. Previous study showed that a reduction >15% was more likely to be clinically significant, whereas changes under 8% are likely of limited clinical relevance.[69] Moreover, GLS also provides additional prognostic value for the reversibility of cardiotoxicity caused by anthracycline and trastuzumab. At the time of CTRCD diagnosis, GLS has been identified as the sole independent echocardiographic predictor of subsequent LVEF recovery.[70]

Despite the recognized clinical value of GLS, significant heterogeneity exists between studies regarding the optimal threshold for relative GLS reduction, leaving the ideal cutoff value to distinguish low- and high-risk patients in question.[68] Intervendor variability in strain measurements has been previously documented.[71] Therefore, it is recommended that serial assessments be performed using the same ultrasound vendor machine and analysis software to ensure reproducibility and minimize measurement variability.

Furthermore, GLS is load-dependent, which may present limitations when there are substantial variations in blood pressure between serial examinations. To complement this disadvantage, emerging evidence highlights the utility of myocardial work indices, particularly global work index (GWI), in enhancing diagnostic accuracy in selected clinical scenarios.[72] In patients with a significant reduction in blood pressure after the initiation of cardiotoxic agents, a stable GLS may not adequately rule out ongoing myocardial damage. Notably, a marked decline in GWI under such conditions has been associated with a 24% risk of CTRCD development, highlighting its value as a complementary echocardiographic parameter in this patient subset.

Finally, in addition to LV involvement, the right ventricle (RV) and left atrium (LA) are also susceptible to cardiotoxicity of cancer therapies and may serve as potential predictors of CTRCD. A meta-analysis involving 644 patients with breast cancer demonstrated that treatment with anthracyclines and/or trastuzumab leads to a reduction in RV systolic function, including RV ejection fraction, RV fractional area change and RV free wall longitudinal strain, while tricuspid annular plane systolic excursion values remained less unaffected.[55] In addition, a retrospective study showed that incorporating left atrial reservoir longitudinal strain into LV GLS assessment significantly improves the specificity of CTRCD detection by approximately 20%, with the AUC increasing to 0.90 while remaining similar sensitivity.[73] Despite some heterogeneity among studies, these findings support the value of echocardiography in the early identification of RV and LA dysfunction and highlight the importance of integrating comprehensive biventricular and atrial evaluation into routine cardiac monitoring protocols during cardiotoxic cancer therapy.

Cardiac magnetic resonance for diagnosing cancer therapy-related cardiac dysfunction

CMR is a highly accurate imaging modality for diagnosing CTRCD and provides a comprehensive cardiovascular assessment, including both structural and functional analysis, enabling an earlier detection of subclinical changes caused by cardiotoxic agents.[74]

T1 and T2 mapping techniques provide detailed structural information about the characteristics of myocardium. T1 mapping detects myocardial fibrosis, a later manifestation of CTRCD, and allows for extracellular volume (ECV) quantification to assess the severity of fibrosis.[75,76] In contrast, T2 mapping is highly sensitive to acute inflammation induced by cardiotoxic agents by detecting myocardial edema. It peaks early during therapy and is associated with ventricular remodeling and brain natriuretic peptide (BNP) elevation.[77] A study demonstrated that T2 mapping can predict the reversibility of myocardial injury in CTRCD, potentially enabling earlier intervention before the onset of irreversible fibrosis.[78] Moreover, these parameters are predictive of subsequent LVEF decline and are associated with a significant increased risk of MACE.[75]

Late Gadolinium Enhancement (LGE) is another crucial imaging modality for detecting myocardial fibrosis in CTRCD.[77] By identifying distinct patterns of LGE distribution, it can differentiate between ischemic and nonischemic cardiotoxicity, possibly providing further guidance for risk stratification and treatment planning.[79] A study demonstrated that LGE-positive patients are at significantly higher risk of LVEF decline and MACE.[80] Furthermore, LGE quantification also provides prognostic value, and its value is one of the two independent prognostic factors in multivariable analysis, besides T2 mapping.[75]

Myocardial stain analysis can also be performed using CMR through feature tracking, a technique similar to the speckle tracking method in echocardiography. CMR-deprived myocardial stain analysis offers higher spatial resolution and serves as a reasonable alternative for patients with suboptimal echocardiographic imaging windows.[81] Evidence demonstrated that reduction of GLS precedes that of LVEF and is predictive of subsequent LVEF deterioration and MACE.[82,83]

In conclusion, CMR is a highly valuable imaging modality for CTRCD diagnosis, and advanced techniques, including T1 and T2 mapping, LGE, and myocardial strain analysis, enable earlier detection of subclinical myocardial injury and more timely interventions.

Cardiac computed tomography for diagnosing cancer therapy-related cardiac dysfunction

Although CMR has long been considered the gold standard for diagnosing CTRCD, its use in clinical practice is limited because of its lower accessibility and higher cost. Consequently, other imaging modalities are also being explored, and advancements in CCT technology are reshaping its role as an alternative tool to diagnose CTRCD.[84]

CCT is an effective modality for measuring ECV, a key biomarker for myocardial fibrosis, and the result has an ideal correlation with that measured by CMR, enabling detailed assessment of myocardial changes by CTRCD.[85,86] Evidence also suggests that elevated ECV is inversely correlated with LVEF and is significantly associated with an increased risk of CTRCD. Numerous studies have validated the measurement of ECV volume using CT and MRI, with a high degree of correlation reported between the two methods.[87]

Furthermore, other CCT-derived parameters, such as CT-derived fractional flow reserve (CT-FFR) and pericoronary adipose tissue (PCAT) attenuation, allow simultaneous evaluation of the coronary arteries of the patients both before and after treatment.[85] These parameters provide valuable prognostic information, and high-risk patients are associated with a two-to three-fold increase in CTRCD in multivariable regression analysis.

With greater availability and cost-effectiveness, CCT is the one of the most widely used imaging modality for routine tumor monitoring.[88] Recent studies have demonstrated that measuring ECV during whole-body CT scans conducted for oncological reassessment provides a convenient method for CTRCD screening, and those with elevated ECV values are associated with a more than tenfold increased risk of developing CTRCD.[86]

In conclusion, CCT is a more cost-effective and accessible imaging modality compared to CMR. It has the ability to assess ECV, provide concurrent evaluation of coronary arteries, such as CT-FFR and PCAT attenuation, and can be integrated into routine oncological reassessments, enabling personalized cardio-oncology management strategies. Despite these advantages, the potential risks associated with iodinated contrast agents and radiation exposure must be carefully considered, and further large-scale studies are needed to verify its role and optimize its use in clinical practice.

Pharmacologic interventions for cancer therapy-related cardiac dysfunction

There is a rapidly expanding body of research investigating pharmacologic interventions for CTRCD. Dexrazoxane can be administered concomitantly with anthracyclines to reduce cardiotoxicity, and numerous clinical trials have also examined the efficacy of lipid-lowering therapies and neurohormonal agents commonly used in heart failure management for the treatment and prevention of CTRCD.[40] However, considerable heterogeneity exists among studies, and the results were conflicting. Given these discrepancies, we conducted a comprehensive review of the current evidence and hereby present the important advancements in this evolving field [Table 1].

Dexrazoxane reduces ROS production by inhibiting the interaction between iron and anthracyclines, thereby preventing oxidative myocardial damage.[89] Meta-analysis have shown that dexrazoxane significantly lowers the risk of heart failure and cardiac events despite a neutral impact on overall survival.[90]

Angiotensin-converting enzyme inhibitors (ACEI) can exert cardioprotective effects in CTRCD by reducing oxidative stress, myocardial fibrosis, and adverse cardiac remodeling.[4] A meta-analysis demonstrated that ACEIs significantly preserve LVEF by approximately 4.2% despite an increased risk of hypotension.[91] Angiotensin receptor blockers (ARB), another class of drugs for RAAS inhibition, have demonstrated a significantly lower efficacy in preserving LVEF than ACEIs.[91] In addition, available evidence also suggests that ARBs do not significantly reduce BNP levels or the risk of heart failure in this patient population.[92] Given these findings, it is reasonable to choose ACEIs over ARBs for the prevention and treatment of CTRCD whenever feasible.

Beta-blockers reduce sympathetic nervous system overactivity, myocardial oxygen demand, and improving left ventricular function.[93] Evidence suggests that beta-blockers can attenuate left ventricular dilatation, diastolic dysfunction, and LVEF decline associated with CTRCD,[94] but its effect on reducing BNP levels or the incidence of heart failure remains inconclusive.[92]

Table 1: Summary of pharmacologic interventions for cancer therapy-related cardiac dysfunction

	CTRCD incidence	LVEF decline	CV outcomes
Dexrazoxane	↓	-	-
ACEI	-	↓	BNP, HF↓
ARB	-	-	-
Beta blocker	-	↓	-
MRA	-	↓	BNP↓
ARNI	-	Increase LV-EF	HF functional class↓ NT-proBNP↓, E/e'↓
SGLT2i	↓	↓	All-cause hospitalization and mortality, HF↓
Statin	↓	↓	-

Current evidence about the effectiveness of different class of drugs for the prevention and management for CTRCD. Considerable heterogeneity exists among studies, and the case numbers of the studies are generally insufficient. Future large-scale studies are needed to better consolidate the effects on CTRCD. ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin II receptor blocker, ARNI: Angiotensin receptor–neprilysin inhibitor, BNP: Brain natriuretic peptide, CTRCD: Cancer therapy-related cardiac dysfunction, CV: Cardiovascular; E/e': Ratio of early mitral inflow velocity to early diastolic mitral annular velocity, HF: Heart failure; LVEF: Left ventricular ejection fraction, MRA: Mineralocorticoid receptor antagonist, NT-proBNP: N-terminal pro–brain natriuretic peptide, SGLT2i: Sodium–glucose cotransporter 2 inhibitor

The role of mineralocorticoid receptor antagonists in CTRCD is less well defined, and both preclinical and clinical studies showed conflicting results.[95] In a clinical study, eplerenone did not demonstrate a significant impact on preserving LVEF or diastolic function.[96] Conversely, another randomized controlled trial (RCT) showed that patients receiving spironolactone concomitantly during anthracycline therapy experienced significantly less LVEF decline and diastolic dysfunction.[97]

Sodium glucose co-transport 2 Inhibitors (SGLT2i), initially developed as oral hypoglycemic agents, may also play a promising role in the management of CTRCD.[98,99] Retrospective studies using propensity score matching have indicated that SGLT2is are associated with significant improvements in hard clinical outcomes, including risk of CTRCD development, acute heart failure exacerbation, all-cause hospitalization and mortality, while the most concerning side effects, such as urinary tract infections and lower extremity amputations, are not increased.[100,101] Furthermore, a recent prospective case-control study demonstrated that, in patients at high risk for cardiotoxicity according to HFA-ICOS score, empagliflozin effectively attenuated LVEF decline and development of CTRCD without safety outcomes compromise.[102] Despite these promising findings, larger RCTs are warranted to further support the clinical benefits of SGLT2is for CTRCD.

Angiotensin receptor-neprilysin inhibitor (ARNI) has demonstrated superior cardiovascular benefits beyond traditional ACEIs or ARBs. Meta-analysis showed that ARNI can be beneficial even when the LVEF reduction is already established,[103] and in patients with CTRCD-associated HFrEF, ARNI can significantly improve heart failure functional class, LVEF, diastolic function, GLS, and NT-proBNP. However, the case numbers and follow-up duration in these studies are still relatively small, and larger studies are still needed to better define its role in CTRCD management.

Statins are well-known for anti-inflammatory and anti-oxidative effects, and preclinical studies also showed that statin may attenuate anthracycline induced cardiomyopathy by indirectly inhibiting small Ras homologous GTPases, which play a key role in regulating NAD (P) H oxidase and type II topoisomerase activity.[104] This cardioprotective effect has also been supported by meta-analysis of RCTs, demonstrating a significant reduction in the risk of CTRCD with statin therapy.[105] However, considerable heterogeneity exists among studies, and the impact of statins on LVEF remains inconclusive.

Conclusion

CTRCD arises from complex pathophysiological mechanisms. With its incidence highly influenced by patient-related risk factors, it is very important to perform a baseline risk stratification, and echocardiographic parameters can provide additional benefits on top of conventional clinical risk factors. Biomarkers and cardiac imaging are crucial for early diagnosis, and several pharmacological intervention have shown promising benefits for the prevention and management of CTRCD.

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Conflicts of interest

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