Journal of Cardiac Failure 31 (2025) 415–455

JCF
Journal of Cardiac Failure

Review Article

Cardio-Oncology and Heart Failure: a Scientific Statement From the Heart Failure Society of America

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List of Acronyms: ACEi, Angiotensin Converting Enzyme inhibitor; ACS, Acute Coronary Syndrome; ARB, Angiotensin Receptor Blocker; ASCO, American Society of Clinical Oncology; BNP, brain [B-type] natriuretic peptide; BP, Blood Pressure; BRAF, proto-oncogene B-Raf; BTK, Bruton tyrosine kinase; CAD, Coronary Artery Disease; CAR-T, Chimeric antigen receptor T cell; CHIP, Clonal Hematopoiesis of Indeterminate Potential; CM, Cardiomyopathy; CMR, Cardiac Magnetic Resonance imaging; CRS, Cytokine Release Syndrome; CTCAE, Common Terminology Criteria for Adverse Events; cTn, cardiac Troponin; CTRCD, Cancer Therapy-Related Cardiac Dysfunction; CV, Cardiovascular; CVD, Cardiovascular Disease; DM, Diabetes; EGFR, Epidermal Growth Factor; ESC, European Society of Cardiology; FDA, Food and Drug Administration; GDMT, Guideline Directed Medical Therapy; GLS, Global longitudinal strain; GVHD, Graft-Versus-Host Disease; HER2, Human Epidermal growth factor 2; HF, Heart Failure; HFpEF, Heart Failure with Preserved Ejection Fraction; HPrEF, Heart Failure with Reduced Ejection Fraction; HR, Hazard Ratio; HSCT, Hematopoietic Stem Cell Transplantation; HTN, Hypertension; ICI, Immune checkpoint inhibitor; ICOS, International Cardio-Oncology Society; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; irAEs, immune-related Adverse Events; ISHLT, International Heart and Lung Transplantation; LV, Left Ventricular; LVAD, Left Ventricular Assist Device; LVEF, Left Ventricular Ejection Fraction; MEK, Mitogen-activated Extracellular signal-regulated Kinase (MEK) inhibitors; MI, Myocardial Infarctions; MUGA, Multi-gated acquisition; NCCN, National Comprehensive Cancer Network; NT-proBNP, N-terminal prohormone of BNP; OR, Odds Ratio; PH, Pulmonary Hypertension; PREVEND, Prevention of Renal and Vascular End-Stage Disease; RAASi, Renin Angiotensin AldoSterone inhibitors; RR, Relative Risk; RT, Radiation Therapy; RV, Right Ventricular; T-DM1, Trastuzumab emtansine; TKI, Tyrosine Kinase Inhibitors; TTE, TransThoracic Echocardiography; VEGF, Vascular Endothelial Growth Factor; VTE, Venous ThromboEmbolism

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Manuscript received April 16, 2024; revised manuscript received August 27, 2024; revised manuscript accepted August 28, 2024.

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See page 447 for disclosure information.

1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2024.08.045

ABSTRACT

Heart failure and cancer remain 2 of the leading causes of morbidity and mortality, and the 2 disease entities are linked in a complex manner. Patients with cancer are at increased risk of cardiovascular complications related to the cancer therapies. The presence of cardiomyopathy or heart failure in a patient with new cancer diagnosis portends a high risk for adverse oncology and cardiovascular outcomes. With the rapid growth of cancer therapies, many of which interfere with cardiovascular homeostasis, heart failure practitioners need to be familiar with prevention, risk stratification, diagnosis, and management strategies in cardio-oncology.

This Heart Failure Society of America statement addresses the complexities of heart failure care among patients with active cancer diagnoses and cancer survivors. Risk stratification, monitoring and management of cardiotoxicity are presented across stages A through D heart failure, with focused discussion on heart failure with preserved ejection fraction and special populations, such as survivors of childhood and young-adulthood cancers. We provide an overview of the shared risk factors between cancer and heart failure, highlighting heart failure as a form of cardiotoxicity associated with many different cancer therapeutics. Finally, we discuss disparities in the care of patients with cancer and cardiac disease and present a framework for a multidisciplinary-team approach and critical collaboration among heart failure, oncology, palliative care, pharmacy, and nursing teams in the management of these complex patients. (*J Cardiac Fail 2025;31:415–455*)

Key Words: Heart failure, cancer, cardiotoxicity, cardio-oncology, cancer treatment-related cardiac dysfunction, cardiomyopathy, heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, bone marrow/stem cell transplant, pulmonary hypertension, mechanical circulatory support, myocarditis, stress cardiomyopathy, cancer survivorship, pregnancy, palliative care, multidisciplinary care, health disparities, and social determinants.

Heart Failure in Patients with Cancer: Shared Pathophysiology and Risk Factors

The Intersection of Cancer and Heart Failure

The intersection between cancer and heart failure (HF) is intricate and complex. What were historically characterized as 2 independent disease states have more recently been recognized as having shared epidemiology and biology. Inflammation, cell death and proliferation, neurohormonal or genomic alterations, and angiogenesis are mechanisms common to both cancer and cardiovascular disease (CVD).[1] The presence of HF itself may predispose an individual to tumor development, with perturbations in cardiac and inflammatory biomarkers as independent predictors of new-onset cancer. In failing heart murine models, the degree of fibrosis and left ventricular (LV) dysfunction was correlated with tumor growth.[2] Clonal hematopoiesis of indeterminate potential (CHIP) has long been recognized as a predictor of malignant transformation potential but more recently as a marker for CVD. In a retrospective cohort of 623 patients with acute myelogenous leukemia, there was a significant association between CHIP-related pathogenic mutations and increased risk of cardiovascular (CV) events.[3] Specific somatic mutations in certain CHIP genes were correlated with progression and worsened prognosis in HF.[4]

Shared Risk Factors Between Cancer, Cardiovascular Disease and Heart Failure

Many CV risk factors are common in both HF and cancer and are often undertreated and undermanaged, increasing the risk of HF.[5,6] There is a high prevalence and burden of hypertension (HTN) in patients with cancer.[5] HTN is a well-established risk factor for CVD; however, it is less known that it may portend adverse cancer risk.[7] In an observational study of 7 international cohorts including nearly 600,000 patients, elevated blood pressure (BP) (defined as $>$ 140/90 mm Hg) was associated with a small increase in incident cancer among men and with an increased cancer mortality rate among men and women.[7] The relationship between diabetes mellitus (DM) and HF has been long recognized; however, DM is also associated with increased risk of cancer, possibly driven by inflammation, oxidative stress, and/or alteration in insulin/glucose signaling pathways.[8] Obesity and smoking are established risk factors for both HF and cancer, and systemic inflammation has been proposed as a possible mechanistic link.[9] In the Framingham Heart Study and PREVEND (Prevention of Renal and Vascular End-Stage Disease) study, investigators reported obesity and abdominal adiposity to be associated with higher risks of certain cancers.[10] Further research is needed to address many of the open questions, including differences in mechanisms and strength of the associations between specific cancer types and distinct CV pathologies and, importantly, causality and the role of shared risk factors.

Heart Failure Incidence in Patients with Cancer

The risk of HF as an adverse effect of certain cancer therapies is well established (Table 1); however, beyond treatment-related toxicities, cancer itself can play a role in the development of HF through indirect mechanisms, such as metabolic derangements, oxidative stress,

Table 1 Cancer therapies associated with cardiomyopathy and heart failure: incidence, mechanism and clinical presentation

Drug or Therapeutic Class	Direct Myocardial Toxicity		Incidence of Cardiomyopathy and HF*		Mechanism of Cardiotoxicity†	Onset of Symptoms/ Clinical presentation	HF Phenotype
	Yes	No	Asymptomatic	Symptomatic			
Anthracyclines[376]	+		Dose-dependent: 7% @150mg/m^2, 18% @ 350 mg/m^2, 65% @ 550 mg/m^2	Dose-dependent: 0.2-5.4% for the same dose ranges	Generation of reactive oxygen species Inhibition of topoisomerase 2β Mitochondrial damage with decreased energy production	Acute: During treatment Subacute: Within 1 year of treatment Delayed: Many years after treatment	HFrEF with dilated phenotype in adult survivors HFrEF with dilated or restrictive phenotype in childhood survivors
Anti-HER2 targeted therapy[378]	+		No dose dependency 4%–30% Risk higher if there is exposure to anthracyclines	No dose dependency 0.6%–3.8% Risk higher if there is exposure to anthracyclines	Inhibition of HER2 receptors interferes with neureglin-induced cardioprotective pathways needed for myocardial recovery after injury	Usually occurs during trastuzumab therapy. Cardiomyopathy often reversible with discontinuation of therapy	HFrEF with dilated phenotype
Cyclophosphamide[36]	+		Dose-dependent 8-20% @ 120–150 mg/kg in adults 5% @ 120–150 mg/kg in childhood survivors	Dose-dependent Wide variations, depending on the setting and combination regimens: from <5%–10%–29%	Metabolite, acrolein, increases oxidative stress and inflammation Activation of p53 and p38 kinase pathways Myocardial calcium dysregulation Decreased myocardial energy production	Usually acute, within days to weeks after cyclophosphamide treatment	HFrEF with dilated phenotype most common Can cause hemorrhagic myocarditis with restrictive phenotype as well as pericarditis
Trabectedin[377]	?		6% in adults	4% in adults Risk higher if there is exposure to anthracyclines	Alkylating agent that affects DNA transcription and repair mechanisms	Median 5.3 months after treatment initiation Usually reversible with withdrawal of trabectedin or anthracyclines	HFrEF most common
MEK inhibitors and BRAF inhibitors[45,374]	+		6%–8.1% in adults 9% in childhood survivors		Inhibition of MAP kinase mediated cardioprotective pathways Increased inflammation with IL-6-mediated activation of pathways involved in hypertrophy, cell survival, mitochondrial dysbiogenesis, mitophagy and oxidative stress	Usually occurs within 6–12 months after treatment initiation	HFrEF with dilated phenotype
5-FU, capecitabine[40]	+		No dose dependency Rare		Vasospasm (the most common clinical presentation) Inflammatory infiltrate and vacuolization of cardiomyocytes; global reversible endothelial injury	Usually occurs during or after initial exposure to agent Usually reversible	Takotsubo cardiomyopathy
Osimertinib[47]	+		No dose dependency 3.9%	No dose dependency 0.7%	Weak inhibitor of HER-2	Median 5.5 months after treatment initiation Usually reversible after stopping the agent	HFrEF w/ dilated phenotype
VEGF inhibitors[375]	+	+	Risk of HF varies across different agents: overall range 3%–15%	Risk of HF varies across different agents; overall, up to 10%	Hypertension Impaired nitric oxide bioavailability and endothelial signaling Mitochondrial dysfunction	Occurs during treatment Usually reversible after stopping the agent	HFpEF or HFrEF
Bruton tyrosine kinase inhibitors[49–51]		+		3.7%–7.7% w/ ibrutinib 2.1% w/ acalabrutinib	Hypertension Atrial fibrillation		HFpEF or HFrEF
Bcr-Abl inhibitors[371–373]		+		0.8% w/ imatinib 1.9% w/ bosutinib 1.6% w/dasatinib 1.1%–7% w/ponatinib	Hypertension Acute ischemic events (w/bosutinib, nilotinib and ponatinib) Pulmonary hypertension (w/dasatinib)		HFpEF or HFrEF
Proteasome inhibitors[53,54]	+	+		5.6%–10.8% w/carfilzomib 4.1% w/bortezomib	Hypertension Proteasome impairment and apoptosis Mitochondrial dysfunction	Occurs during treatment Usually reversible after stopping the agent	HFpEF or HFrEF

(*Continued*)

Table 1. *(Continued)*

Drug or Therapeutic Class	Direct Myocardial Toxicity		Incidence of Cardiomyopathy and HF*		Mechanism of Cardiotoxicity†	Onset of Symptoms/ Clinical presentation	HF Phenotype
	Yes	No	Asymptomatic	Symptomatic			
Immune checkpoint inhibitors (ICI)[62,229]	+	+		HF reported with and without myocarditis: overall incidence 0.6%–2.5% Risk increased w/ dual ICI therapy and in combination with targeted therapies	Increased inflammation Cross-reactivity to antigens on myocytes	Median 34 (IQR 21–75) days after initial exposure to agent	Acute myocarditis; HF w/preserved or reduced EF may also be present Myositis and myasthenia gravis often present with myocarditis
Chimeric antigen receptor (CAR) T-cell therapy[379]		+	10.3%	5%	Cytokine release syndrome with IL-6 mediated cardiac dysfunction	Median 12.5 (range, 2–24) days from CAR T-cell infusion	Acute HFrEF
Chest Radiation Therapy (RT)[27,151]	+	+		Dose-dependent At 25 years:4.4% for 0-15 Gy, 6.2% 16-20 Gy, 13.3% ≥ 21 Gy Risk higher if there is exposure to anthracyclines	Oxidative stress and endothelial dysfunction increase pro-inflammatory and pro-fibrotic mediators leading to myocardial fibrosis HF due to radiation-associated coronary artery disease and valvular heart disease Acceleration of traditional atherosclerosis and fibrosis	Median 20.6 (IQR 13.7–25.2) years after radiation therapy	HFpEF or HFrEF with restrictive or constrictive phenotype

BRAF, v-raf murine sarcoma viral oncogene homolog B1; HER-2, human epidermal growth factor receptor-2; 5FU, 5-fluorouracil; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; MAPK, Mitogen-activated Extracellular signal-regulated Kinase (MEK) inhibitors; MEK, mitogen activated protein kinase kinase; VEGF, vascular endothelial growth factor;

*This table is designed to provide estimates of cardiotoxicity with each class of drugs based on varied sources, including package inserts, primary literature and review articles.

†These represent the major known mechanisms underlying cardiotoxicity and are not meant to be comprehensive.

neurohormonal dysregulation, and inflammation.[11] In a study comparing patients with new diagnoses of cancer vs those without cancer, patients with cancer had an increased risk of HF, and a new cancer diagnosis was an independent predictor of CV death.[12] In a retrospective analysis of data from the Women's Health Initiative, patients with breast cancer had a cumulative incidence of hospitalization for HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) of 6.68% and 3.96%, respectively, over a median of 7.2 years, and the presence of HF was associated with higher mortality risk.[13] In another report from the Women's Health Initiative, among women with incident breast cancer, prevalent HF was associated with increased mortality risk over a median follow-up time of 15 years.[14] In the same study, among women with incident hospitalized HF, prevalent breast cancer also increased mortality risk.[14]

Cancer Incidence in Patients with Heart Failure

Patients with HF have an increased risk of incident cancer,[15] yet the connection between HF and cancer is poorly understood. Putative mechanistic links include a pro-inflammatory state, neurohormonal activation, oxidative stress, and/or a dysregulated immune system[15]; however, other factors, such as more frequent contact with health care and increased testing and imaging may contribute to the observed associations.[16] In an analysis of claims data of > 27 million individuals without cancer, those with CVD were 13% more likely to develop cancer compared with those without CVD, and this association was most pronounced in those with atherosclerotic heart disease, even after controlling for other risk factors.[17] In a study of patients with HF compared with matched controls, those with HF had a 68% higher risk of developing cancer after adjustment for comorbidities, and those with incident cancer had higher rates of death.[18] Among patients > 50 years old, the incidence of cancer in those with HF was higher than in controls, and cancer mortality rates were higher in those with HF, especially in those patients < 70 years old.[19] In a prospective cohort study of 1081 patients with incident myocardial infarction (MI), patients with new-onset HF within a month after MI had a higher likelihood of future cancer than non-HF controls.[20] Although mortality in patients with HF is most commonly HF or CV-related, patients with HF commonly die of cancer.[15] In 3 large HF clinical trials (I-Preserve[21] [Irbesartan in Heart Failure with Preserved Ejection Fraction Study], TOPCAT[22] [Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist], and PARADIGM-HF[23] [Prospective comparison of Angiotensin Receptor-neprilysin inhibitor (ARNI) with Angiotensin converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and morbidity in Heart Failure]), death from cancer accounted for 35%–40% of non-CV mortalities.[15] In a meta-analysis evaluating cancer, CV, and all-cause mortality in phase III HFrEF trials, cancer mortality

accounted for 6%−14% of all deaths and 17%−67% of non-CV deaths. Importantly, HF treatment did not influence cancer deaths (OR = 1.08, 95% CI = 0.92−1.28) but reduced the risk of CVD (OR = 0.88, 95% CI = 0.79−0.98) and all-cause mortality (OR = 0.91, 95% CI = 0.84−0.99).[24]

Cancer Therapeutic Agents and Modalities Associated with Heart Failure Risk

Incidence, mechanisms, and clinical presentations of HF associated with various cancer-treatment modalities are summarized in Table 1, while details of pharmacokinetic and pharmacodynamic profiles of specific cancer therapeutics can be found Table 2.

Anthracyclines

Anthracyclines are among the oldest cancer therapeutic agents known to cause cardiac toxicity. This class of agents can lead to a dose-dependent toxicity, classically presenting with LV systolic function decline and/or symptomatic HFrEF. Anthracycline dosing conversions for adult and pediatric treatment are presented in Table 3. Risk factors for cardiac toxicity with anthracyclines include higher cumulative doxorubicin-equivalent doses exceeding 250 mg/m^2, older age (medium-risk age 65−79, high-risk age > 80 years old),[25] pre-existing CV risk factors or disease, concomitant use of other cardiotoxic agents (such as chest Radiation therapy (RT), anti-HER2 targeted agents, cyclophosphamide), and the presence of certain genetic polymorphisms.[26] Patients may present acutely during treatment, sub-acutely within the first year or many years after completion of treatment, at times making it difficult to attribute HF presentation specifically to cancer treatment.[27] Reported incidence of HF varies significantly across studies, depending on the definitions used, the study design and the presence and type of LV function monitoring. Recent data support that most events occur during the first year post treatment and that early detection and intervention resulted in significant cardiac function recovery,[28] contrary to the prior belief suggesting that anthracyclines cause irreversible cardiac damage and cardiomyopathy (CM).

Anti-HER2 Targeted Agents

The use of anti-human epidermal growth factor 2 (HER2)-targeted therapy has revolutionized the treatment of HER2-positive breast cancer, and multiple trials demonstrated improvement in survival rates (in patients with metastatic disease) and recurrence-free survival (in patients with localized breast cancer).[29] Trastuzumab, a HER2 receptor antagonist used in the treatment of HER2-positive breast cancer, has been associated with asymptomatic LV dysfunction and less frequently with symptomatic HF.[30] Anthracycline use and preexistence of CV risk factors (eg, HTN, coronary artery disease (CAD)), CM can perpetuate risk for trastuzumab-related cardiac toxicity.[31,32] Since the approval of trastuzumab, multiple anti-HER2 targeted agents, including antibody-drug conjugates ado-trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan, have received Food and Drug Administration (FDA) approval (Table 2). Compared to initial trastuzumab trials, no additional cardiac toxicity has been reported.[33,34] Importantly, clinical trials of the newer anti-HER2 targeted agents excluded patients with abnormal baseline cardiac function and incorporated holding/discontinuation criteria in patients with evidence of cardiotoxicity. LV dysfunction associated with anti-HER2-targeted agents is largely reversible with interruption of the therapy and initiation of neurohormonal blockade.[35]

Alkylating Agents

Alkylating agents, particularly cyclophosphamide, are associated with CM and HF. Risk factors for cardiac toxicity include high cyclophosphamide dosage (> 1.5 gm/m^2), older age, underlying ischemic heart disease, exposure to other cardiotoxic agents, and the type of cancer being treated.[36] Cardiac toxicity may manifest acutely within 48 hours of drug exposure but can be observed up to 10 days after treatment initiation. With early detection and supportive care, systolic function can improve in some cases, but in other cases, dysfunction may persist or be associated with cardiogenic shock and death.[37] Rarely, cyclophosphamide can lead to a fatal hemorrhagic myocarditis.[36] Early toxicity post hematopoietic stem cell transplantation is associated with the use of regimens that include cyclophosphamide and should be used with caution in elderly and other high-risk patients.[38] Trabectedin is another alkylating agent commonly used to treat sarcoma, and it may cause systolic dysfunction and HF.[39] Patients who previously received anthracycline-based chemotherapy are at increased risk for trabectedin-related cardiotoxicity, yet data regarding its reversibility remain limited.[39]

Antimetabolites

The antimetabolite 5-fluorouracil and its oral pro-drug, capecitabine, are associated with a spectrum of both direct and indirect CV toxicities, including rare reports of stress-induced CM that usually improve with supportive management and withdrawal of the drug.[40] Risk factors for the development of cardiac toxicity include pre-existing CAD, prior chest RT, renal insufficiency, and dihydropyridine dehydrogenase deficiency.[41−43]

Tyrosine Kinase Inhibitors

In the class of tyrosine kinase inhibitors (TKI), vascular endothelial growth factor (VEGF) inhibitors such as sunitinib, sorafenib and bevacizumab,[44] proto-oncogene B-Raf (BRAF) and Mitogen-activated Extracellular signal-regulated Kinase (MEK) inhibitors (MEK) inhibitors[45,46] and the epidermal growth factor (EGFR) inhibitor osimertinib[47] have all been linked to reversible CM that often improves

Table 2 Cancer therapies associated with cardiomyopathy and heart failure: pharmacokinetics, pharmacodynamic and clinical pearls relevant for the HF clinician

Therapeutic Class	Selected Drug/Class Specific Properties*			
Anthracyclines Daunorubicin (IV), Doxorubicin (IV), Epirubicin (IV), Idarubicin (IV), Mitoxantrone (IV), Liposomal daunorubicin/Cytarabine (IV), Liposomal Doxorubicin (IV)				
PK Interactions	**CYP3A4 SUB:** Doxorubicin, Liposomal Doxorubicin	**P-gp SUB:** Daunorubicin, Doxorubicin, Idarubicin, Mitoxantrone, Liposomal Daunorubicin/Cytarabine, Liposomal Doxorubicin; **P-gp IND:** Daunorubicin, Doxorubicin, Liposomal Daunorubicin/Cytarabine, Liposomal Doxorubicin		
PD Interactions	• Additive risk of CTRCD with HER-2 agents and other therapies known to cause CTRCD • Additive risk of thrombosis with Doxorubicin and IMiDs/steroids, Ponatinib, or Pegaspargase • Additive risk of QTP/TdP with Doxorubicin and other QTP therapies			
Clinical Pearls	• Doxorubicin may decrease digoxin by 50% (potential lesser interaction with liposomal doxorubicin or digoxin elixir), monitor SDC • Select CYP3A4 and P-gp INHs (eg, select AADs/CCBs, Atorvastatin, Ticagrelor) may increase select anthracyclines • Doxorubicin and liposomal doxorubicin may decrease digoxin via P-gp induction • Liposomal anthracyclines may be associated with less P-gp induction compared to conventional formulations, but data are limited			
HER-2 antagonists HER-2 only: Ado-Trastuzumab Emtansine (IV), Fam-Trastuzumab Deruxtecan (IV), Margetuximab (IV), Pertuzumab (IV), Trastuzumab (IV), Trastuzumab and Hyaluronidase (SC), and Pertuzumab, Trastuzumab, and Hyaluronidase (SC); HER-2/EGFR TKI: Lapatinib (PO), Neratinib (PO), Tucatinib (PO)				
PK Interactions	**CYP3A4 SUB:** Ado-Trastuzumab Emtansine, Fam-Trastuzumab Deruxtecan, Lapatinib, Neratinib, Tucatinib; **CYP3A4 INH:** Lapatinib, Tucatinib	**P-gp SUB:** Ado-Trastuzumab Emtansine, Fam-Trastuzumab Deruxtecan, Lapatinib, Neratinib; **P-gp INH:** Lapatinib, Neratinib, Tucatinib		
PD Interactions	• Additive risk of CTRCD with anthracyclines and other therapies known to cause CTRCD • Additive risk of QTP/TdP with select HER-2/EGFR TKIs therapies and other QTP therapies			
Clinical Pearls	• Select CYP3A4 and P-gp INHs (eg, select AADs/CCBs, Atorvastatin, Ticagrelor) may increase select HER-2 antagonists • Carvedilol may increase select HER-2 antagonists • Select oral HER-2 antagonists may interact with select DOACs, select CCBs, select AADs			
Selected Alkylating Agents Cyclophosphamide (IV, PO); Trabectedin (IV)				
PK Interactions	**CYP3A4 SUB:** Cyclophosphamide, Trabectedin	**CYP2C19 SUB:** Cyclophosphamide	**CYP2C9 SUB:** Cyclophosphamide	**P-gp SUB:** Trabectedin
PD Interactions	Additive risk of CTRCD with Anthracyclines and other therapies known to cause CTRCD			
Clinical Pearls	• Select CYP3A4 INHs (eg, select AADs/CCBs, Atorvastatin, Ticagrelor) may increase Cyclophosphamide, trabectedin			
BCR-ABL Tyrosine Kinase Inhibitors Asciminib (PO), Bosutinib (PO), Dasatinib (PO), Imatinib (PO), Nilotinib (PO), Ponatinib (PO)				
PK Interactions	**CYP3A4 SUB:** Asciminib, Bosutinib, Dasatinib, Imatinib, Nilotinib, Ponatinib; **CYP3A4 INH:** Asciminib, Dasatinib[a,*], Imatinib, Nilotinib	**CYP2C9 SUB:** Imatinib; **CYP2C9 INH:** Asciminib, Imatinib	**CYP2D6 SUB:** Imatinib, Ponatinib; **CYP2D6 INH:** Imatinib	**P-gp SUB:** Asciminib, Dasatinib, Imatinib, Nilotinib, Ponatinib
PD Interactions	• Additive risk of HTN with Ponatinib, Imatinib (less), and other therapies associated with HTN • Additive risk of pulmonary HTN with Dasatinib, Imatinib (less), and other therapies known to cause pulmonary HTN • Additive risk of thrombosis with Ponatinib with steroids and/or Doxorubicin			
Clinical Pearls	• Select CYP3A4 and P-gp INHs (eg, select AADs/CCBs, Atorvastatin, Ticagrelor) may increase select BCR-ABL TKIs • Carvedilol may increase select BCR-ABL TKIs • Select BCR-ABL TKIs may increase select Statins/DOACs/AADs/CCBs/PDE5Is, Ticagrelor, Eplerenone and VPAs • Asciminib and Imatinib may increase select ARBs and Statins, Warfarin, Bosentan and Torsemide • Imatinib may increase select beta-blockers, Flecainide and Propafenone • Caution with vitamin E, fish oil and other CAM products that can increase bleed risk, like garlic and ginseng			

(*Continued*)

Table 2. (*Continued*)

Therapeutic Class	Selected Drug/Class Specific Properties*			
BRAF/MEK inhibitors Dabrafenib (PO), Encorafenib (PO), Vemurafenib (PO), Binimetinib (PO), Cobimetinib (PO), Trametinib (PO), Selumetinib (PO)				
PK Interactions	**CYP3A4 SUB:** Dabrafenib, Encorafenib, Vemurafenib, Cobimetinib, Selumetinib; **CYP3A4 IND:** Dabrafenib, Vemurafenib, Encorafenib[a,*]; **CYP3A4 INH:** Encorafenib[a,*]	**CYP2C9 INH:** Vemurafenib; **CYP2C9 IND:** Dabrafenib	**CYP2D6 SUB:** Encorafenib; **CYP2D6 INH:** Vemurafenib	**P-gp SUB:** Dabrafenib, Encorafenib, Vemurafenib, Binimetinib, Cobimetinib, Selumetinib; **P-gp INH:** Vemurafenib, Encorafenib
PD Interactions	• Additive risk of myocarditis with BRAF INHs and ICIs • Additive risk of HTN with vemurafenib and other therapies known to cause HTN • Additive risk of QTP/TdP with select BRAF/MEKIs and other QTP therapies			
Clinical Pearls	• Select CYP3A4 and P-gp INHs (eg, select AADs/CCBs, Atorvastatin, Ticagrelor) may increase select MEK/BRAF inhibitors • Carvedilol may increase select MEK/BRAF inhibitors • Select MEK/BRAF inhibitors may increase or decrease select Statins/DOACs/AADs/CCBs/PDE5Is, Ticagrelor, Eplerenone and VPAs • Dabrafenib, Encorafenib and Vemurafenib may increase or decrease DOACs • Vemurafenib and Dabrafenib may increase or decrease select ARBs and Statins, Warfarin, Bosentan and Torsemide • Vemurafenib may increase select Beta blockers, Flecainide and Propafenone • Vitamin E can increase bleeding risk of selumetinib			
Select Antimetabolites Fluorouracil (IV), Capecitabine (PO)				
PK Interactions	**CYP2C9 INH:** Fluorouracil, Capecitabine			
PD Interactions	• Additive risk of bleeding with other cancer therapies known to cause bleeding or thrombocytopenia			
Clinical Pearls	• Fluorouracil and Capecitabine may increase select ARBs and Statins, Warfarin, Bosentan and Torsemide			
Selected EGFR inhibitors Afatinib (PO), Erlotinib (PO), Mobocertinib (PO), Osimertinib (PO)				
PK Interactions	**CYP3A4 SUB:** Erlotinib, Mobocertinib, Osimertinib; **CYP3A4 INH:** Erlotinib, **CYP3A4 IND:** Mobocertinib		**P-gp SUB:** Afatinib, Osimertinib, Mobocertinib; **P-gp INH:** Afatinib[b], Erlotinib[c], Osimertinib	
PD Interactions	• Additive risk of QTP/TdP with select EGFRis and other QTP therapies			
Clinical Pearls	• Select CYP3A4 and P-gp INHs (eg, select AADs/CCBs, Atorvastatin, Ticagrelor) may increase select MEK/BRAF inhibitors • Carvedilol may increase select EGFR inhibitors • Select EGFR inhibitors may increase select Statins/DOACs/AADs/CCBs/PDE5Is, Ticagrelor, Eplerenone and VPAs			
VEGF inhibitors (VEGFIs) Monoclonal Antibodies: Ziv-Aflibercept (IV), Bevacizumab (IV), Ramucirumab (IV), Tyrosine Kinase Inhibitors: Axitinib (PO), Cabozantinib (PO), Lenvatinib (PO), Pazopanib (PO), Regorafenib (PO), Sorafenib (PO), Sunitinib (PO)				
PK Interactions	**CYP3A4 SUB:** Axitinib, Cabozantinib, Lenvatinib, Pazopanib, Regorafenib, Sorafenib, Sunitinib, Tivozanib, Vandetanib; **CYP3A4 INH:** Pazopanib	**CYP2C9 SUB:** Cabozantinib; **CYP2C9 INH:** Cabozantinib, Regorafenib	**CYP2C19 INH:** Cabozantinib	**P-gp SUB:** Lenvatinib, Pazopanib, Sorafenib; **P-gp INH:** Cabozantinib, Sorafenib, Sunitinib, Vandetanib
PD Interactions	• Additive risk of HTN with dual VEGFIs • Additive risk of bleeding with select VEGFIs and other therapies known to cause bleeding or thrombocytopenia • Additive risk of QTP/TdP with select VEGFs and other QTP therapies			
Clinical Pearls	• Select CYP3A4 and P-gp INHs (eg, select AADs/CCBs, Atorvastatin, Ticagrelor) may increase select VEGFIs • Carvedilol may increase select VEGFIs • Select VEGIs may increase select Statins/DOACs/AADs/CCBs/PDE5Is, Ticagrelor, Eplerenone and VPAs • Cabozantinib, Regorafenib may increase select ARBs and Statins, Warfarin, Bosentan and Torsemide • Caution with vitamin E, fish oil, and other CAM products that can increase bleed risk, like garlic and ginseng			

(*Continued*)

Table 2. (*Continued*)

Therapeutic Class	Selected Drug/Class Specific Properties*			
Bruton Tyrosine Kinase Inhibitors (BTKIs) Acalabrutinib (PO), Ibrutinib (PO), Pirtobrutinib (PO), Zanubrutinib (PO)				
PK Interactions	**CYP3A4 SUB:** Acalabrutinib, Ibrutinib, Pirtobrutinib, Zanubrutinib; **CYP3A4 INH:** Pirtobrutinib, **CYP3A4 IND:** Zanubrutinib	**CYP2D6 SUB:** Ibrutinib	**CYP2C19 INH:** Pirtobrutinib; **CYP2C19 IND:** Zanubrutinib	**P-gp SUB:** Acalabrutinib, Pirtobrutinib; **P-gp INH:** Pirtobrutinib
PD Interactions	• Additive risk of bleeding with other cancer therapies known to cause bleeding or thrombocytopenia			
Clinical Pearls	• Select CYP3A4 and P-gp INHs (eg, select AADs/CCBs, Atorvastatin, Ticagrelor) may increase select BTKIs • Carvedilol may increase select BTKIs • Acalabrutinib, Pirtobrutinib and Zanubrutinib may increase select DOACs • Pirtobrutinib and Zanubrutinib may increase or decrease select AADs/Statins/CCBs/PDE5Is, Ticagrelor, Eplerenone and VPAs • Caution with vitamin E, fish oil, and other CAM products that can increase bleed risk like garlic and ginseng			
Proteasome Inhibitors Bortezomib (IV/SC), Carfilzomib (IV), Ixazomib (PO)				
PK Interactions	**CYP3A4 SUB:** Bortezomib, Ixazomib	**CYP2C9 SUB:** Bortezomib	**CYP2D6 SUB:** Bortezomib	**P-gp SUB:** Carfilzomib, Ixazomib
PD Interactions	• Additive risk of with other cancer therapies or agents known to cause hypertension			
Clinical Pearls	• Select CYP3A4 and P-gp INHs (eg, select AADs/CCBs, Atorvastatin, Ticagrelor) may increase Bortezomib or Ixazomib • Amiodarone may increase Bortezomib, Ixazomib, or Carfilzomib • Carvedilol may increase Carfilzomib or Ixazomib			
Select Immune checkpoint inhibitors(ICIs) PD1-inhibitors: Cemiplimab (IV), Dostarlimab (IV), Nivolumab (IV), Pembrolizumab (IV), PD-L1 inhibitors: Atezolizumab (IV), Avelumab (IV), Durvalumab (IV), Pembrolizumab (IV), CTLA-4 inhibitors: Ipilimumab (IV), Tremelimumab (IV), LAG-3 inhibitor: Relatlimab (IV)[d]				
PK Interactions/ Clinical Pearls	Not applicable			
PD Interactions	• Additive risk of CTRCD (eg, anthracyclines), HTN (eg VEGFIs), myocarditis with dual ICIs			
Chimeric antigen receptor (CAR) T-cell therapy Axicabtagene ciloleucel, Brexucabtagene autoleucel, Ciltacabtagene autoleucel, Idecabtagene vicleucel, Lisocabtagene maraleucel, Tisagenlecleucel				
PK/PD Interactions/ Clinical Pearls	Not applicable			
Selected Cancer Therapies Indirectly Associated with CTRCD Through Hypertension				
VEGF inhibitors, EGFR inhibitors, Bruton TKIs, Proteasome inhibitors, Platinum-based compounds (Cisplatin, Carboplatin, Oxaliplatin), Alkylating agents (Cyclophosphamide), Busulfan, Ifosfamide, carmustine, +/ -melphalan, Calcineurin inhibitors (Tacrolimus, Cyclosporine), BRAF/MEK Inhibitors, RET kinase inhibitors (Selpercatinib, Pralsetinib), Poly (ADP-ribose) polymerase inhibitors (Niraparib), Androgen receptor blockers (Enzalutamide), Androgen synthesis inhibitors (Abiraterone, Leuprolide), Aromatase inhibitors (Anastrozole, Letrozole), mTOR inhibitors (Everolimus, Sirolimus)				

AAD, antiarrhythmic drugs; CAM,complementary and alternative medicine; CCB, calcium channel blockers; CTRCD, cancer therapy-related cardiac dysfunction; HTN, hypertension; ImiDs, immunomodulators; IND, inducer; INH, inhibitor; mTOR, mammalian target of rapamycin; PD, pharmacodynamic; PDE5Is, phosphodiesterase inhibitors; PK pharmacokinetics; SDC serum digoxin concentration; SUB substrate; TKIs tyrosine kinase inhibitors; VPAs, vasopressin antagonists; IV intravenous; PO oral; SC subcutaneous.

*This table was prepared to provide examples of index substrates, inhibitors and inducers and is not intended to be an exhaustive list. For example, not all enzymes are represented (eg, CYP2C8, UGT, OAT, BCRP), and not all interactions with a given enzyme (eg, CYP2D6, CYP2C19) are represented. Summaries of relevant enzymes vary depending on resource (eg, package insert, primary literature, tertiary references). Strengths of interaction (mild, moderate, strong) are not represented.

[a]Time dependent. For encorafenib, clinical relevance of encorafenib *in vitro* metabolism and elimination studies are not well elucidated.

[b]Interaction may be minimized/avoided by spacing timing of inhibitor and substrate.

[c]Clinical relevance of drug interaction unclear.

[d]In combination with nivolumab.

Table 3 Anthracycline dose conversion

Anthracycline	Adult Conversion Factor (mg/m^2) for Doxorubicin Equivalent	Pediatric Conversion Factor (mg/m^2) for Doxorubicin Equivalent	Maximum Cumulative Lifetime Dose (mg/m^2)
Doxorubicin	1	1	450-550*
Epirubicin	0.611	0.67-0.8	900
Daunorubicin	1	0.5-0.6	450-550*
Idarubicin	3.667	5	150
Mitoxantrone	3.929	4-10.5	140

*A maximum lifetime exposure of 450 mg/m^2 for those exposed to chest radiation therapy or in elderly patients.

with dosage reduction and/or withdrawal of the offending agent. Many TKIs, particularly those with VEGF inhibitor pathway-targeting properties, are associated with HTN. If inadequately treated, HTN in these patients can result in diastolic dysfunction and symptomatic HF.[44,48] Bruton tyrosine kinase (BTK) inhibitors can increase the risk of HTN and atrial fibrillation, potentially leading to diastolic and systolic dysfunction and/or HF.[49–51] Adequate blood pressure (BP) management and restoration of sinus rhythm might reverse cardiac dysfunction in these cases.[52]

Proteasome Inhibitors

Proteasome inhibitors, such as bortezomib and, more commonly, carfilzomib, may lead to HTN, diastolic dysfunction and symptomatic HF, with systolic dysfunction occurring in some cases.[53,54] In many instances, dosage reduction or drug withdrawal improves systolic function.[48,55] Risk factors for cardiac toxicity with these agents include prior history of CVD risk factors and established CVD, prior anthracycline or chest RT exposure. Patients with preexisting CM are at particularly high risk.[55]

Immune Checkpoint Inhibitor Therapies

Immune checkpoint inhibitor (ICI) therapies leverage the premise that tumors evade the immune system through the activation of checkpoint receptors that inhibit T cells from attacking the tumor.[56] FDA-approved ICIs include inhibitors of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein-1 (PD-1),[57] programmed cell death protein ligand-1 (PDL1), [58] and lymphocyte activation gene-3 (LAG-3),[59] with more immune-targeted approaches expected in the pipeline.[56] ICIs have been associated with a new class of toxicities termed immune-related adverse events (irAEs), which can affect almost any organ.[60] HF clinicians should be aware of the rare (ranging from 0.5%–1.% incidence) but potentially fatal complication of ICI-related myocarditis that can carry an associated mortality rate of 25%–50% in fulminant cases.[60] Patients with ICI myocarditis often present with normal LVEF and a spectrum of clinical HF severity.[61,62] Progressive atherosclerosis in patients on ICI treatment is of particular interest and deserves further investigation.[63] In any patient with the appropriate clinical context, including even mild troponin on ICI therapy, ischemia and/CAD should be excluded.[64]

Cardiovascular Complications with Chimeric Antigen Receptor T-cell Therapy: Cytokine Release Syndrome

Chimeric antigen receptor T cell (CAR-T) therapy is a form of cellular immunotherapy that involves the engineering of a patient's T cells to express the chimeric antigen receptor of interest and then infusing those cells back to the patient to attack the tumor. Since 2017, there have been 7 approved CAR-T cell therapies for the treatment of liquid tumors, including lymphoma, leukemia and multiple myeloma.[65] The most common toxicity associated with CAR-T cell therapy is cytokine release syndrome (CRS), a systemic inflammatory response driven by cytokines released from the infused engineered T cells, such as interleukin 6, interferon γ, tumor necrosis factor α, and interleukin 10.[66] Patients commonly develop systemic signs and symptoms of palpitations, dizziness, sweating, fever, tachycardia, hypotension and, occasionally, hypoxia.[67] The incidence of CRS ranges from 35%–93%, with severe cases of CRS occurring in 1%–47% of patients receiving CAR-T.[67] Several grading criteria for CRS have been proposed, including a combination of vital-sign parameters (heart rate, temperature, blood pressure, and oxygen saturation).[68] Typical treatment of CRS includes supportive care, tocilizumab (IL-6) and dexamethasone.[69] In addition to CRS, major adverse cardiac events have been reported in up to 16% of patients following CAR-T.[70] The majority of CV events include arrhythmias, but MI and acute HF (most often due to stress CM) have been described.[70] Management of CAR-T-associated cardiac toxicity should include a multidisciplinary team including intensive care specialists.[71]

Radiation Therapy

RT to the mediastinum or thoracic region is associated with an increased risk of CVD, including CAD, valvular heart disease, pericardial disease, conduction abnormalities, and CM/HF.[72] The pathophysiology of RT-associated heart disease relates to acceleration of traditional

atherosclerosis and fibrosis.[73–76] The risk of CV disease increases with mean heart dosage of RT[74,77,78] and is accentuated by younger age at time of RT exposure, exposure to other cardiotoxic therapies, pre-existing CV risk factors, and time from RT. RT-associated valvular heart disease is a long-term complication with a median time to occurrence of 22 years after treatment. The most affected valves include the aortic valve, followed by the mitral and tricuspid valves.[74,77,79,80] RT-related HF can be a consequence of ischemic heart disease, valvular heart disease, constrictive pericarditis, restrictive cardiomyopathy, or direct myocardial injury. CAD is the most common manifestation of radiation-associated CV disease that can occur as early as 2–4 years after RT or as late as 30 years after treatment completion and can lead to ischemic CM.[78,81]

Definitions of Cancer Treatment-Related Cardiac Dysfunction and Heart Failure Used in the Cardio-Oncology Literature

The definitions of cancer therapy-related cardiac dysfunction (CTRCD) have varied over time and across studies and have commonly included a new reduction in left ventricular ejection fraction (LVEF), with or without clinical HF. The origins of CTRCD definitions were informed largely by the oncology clinical trials and the Common Terminology Criteria for Adverse Events (CTCAE) definitions. In the United States, the CTCAE criteria, developed by the National Cancer Institute, represent a standard for adverse events grading and regulatory reporting of oncology trials, thus informing the FDA label.[82] However, the CTCAE definitions had not been harmonized with contemporary definitions of HF proposed by cardiology societal guidelines.[83,84] The LVEF cutoffs within oncology trials vary, and correlation with clinical outcomes are ill defined. An LVEF-based definition for CTCRD that has gained wider acceptance is that of a reduction in LVEF by $\geq$ 10% to a value $<$ 50%, with or without symptoms of HF. Of note, clinical trials have used both LVEF of 50% as well as 55% as lower limits of normal.[85] LVEF-based definitions do not account for variability in measurements, changes in diastolic function, or increase in LV volumes that all might predate decline in LVEF or the development of clinical HF.[86] None of the current definitions specifically recognize HFpEF.[87]

In an attempt to standardize the reporting of CTRCD in the HF, cardiology, and oncology literature, the International Cardio-Oncology Society (IC-OS) published a consensus statement defining cancer therapy-related CV toxicities including cardiac dysfunction and HF, reconciling with CTCAE definitions from oncology clinical trials.[85] In the IC-OS statement, cardiac dysfunction and/or HF are defined as cardiac dysfunction or structural injury associated with cancer therapy, that can remain asymptomatic, or present as clinical HF, ranging from mild to severe. Fig. 1 depicts the integration of IC-OS definitions within the framework of HF stages.[83,84] The attribution of cancer treatment to cardiac toxicity is based on the temporal association and/or expected cardiotoxic effect of a therapy. In clinical practice, a change in symptoms and/or LVEF decline requires comprehensive evaluation and exclusion of other etiologies potentially contributing to the clinical presentation (eg, ischemia, stress-CM) as well as consideration of the potential contribution of non-treatment-related risk factors (eg, HTN, genetic susceptibility).

Risk Stratification and Cardiac Safety Monitoring in Oncology Patients

Risk Algorithms and Prediction Models in Heart Failure and Cancer

Multiple prediction models have been developed within cardio-oncology populations, albeit with limited external validation.[88–93] Receipt of high dosages of anthracyclines and chest RT have been recognized as 1 of the 2 of the key treatment-related contributors to HF risk, based largely on the studies of survivors of childhood, adolescent and young-adult cancers.[94] The risk-stratification model recommended by the 2023 International Late Effects of Childhood Cancer Guideline Harmonization Group is included in Table 4.

In patients with adult cancers treated with anthracyclines, the 2023 National Comprehensive Cancer Network (NCCN) Survivorship Guidelines define *high risk* as a cumulative doxorubicin equivalent dosage of $\geq$ 250 mg/m^2 or lower doxorubicin dosages in patients with CV comorbidities or risk factors.[95] Similarly, the American Society of Clinical Oncology (ASCO) guidelines on cardiac dysfunction in survivors of adult cancers use the cumulative doxorubicin dosage of $\geq$ 250 mg/m^2 as high risk and also recognize the role of chest RT and CV risk factors.[96] The 2022 European Society of Cardiology (ESC) Guidelines on Cardio-Oncology recommend the use of cancer therapy-specific risk stratification schemas or proformas that account for patient- and therapy-related risk factors. The proposed criteria categorize patients as being at very high risk, high risk, moderate risk, or low risk prior to initiation of cancer therapy, with specific algorithms for anthracyclines, anti-HER2 targeted therapies, VEGF inhibitors, BCR-ABL inhibitors, multiple myeloma therapies, and BRAF or MEK inhibitors inhibitors.[32] At this time, these risk stratification schemas are based on expert consensus and remain to be prospectively validated.

Role of Imaging in Risk Stratification

Baseline assessment of cardiac function, most commonly with transthoracic echocardiography (TTE), is recommended for patients who are expected to receive cancer

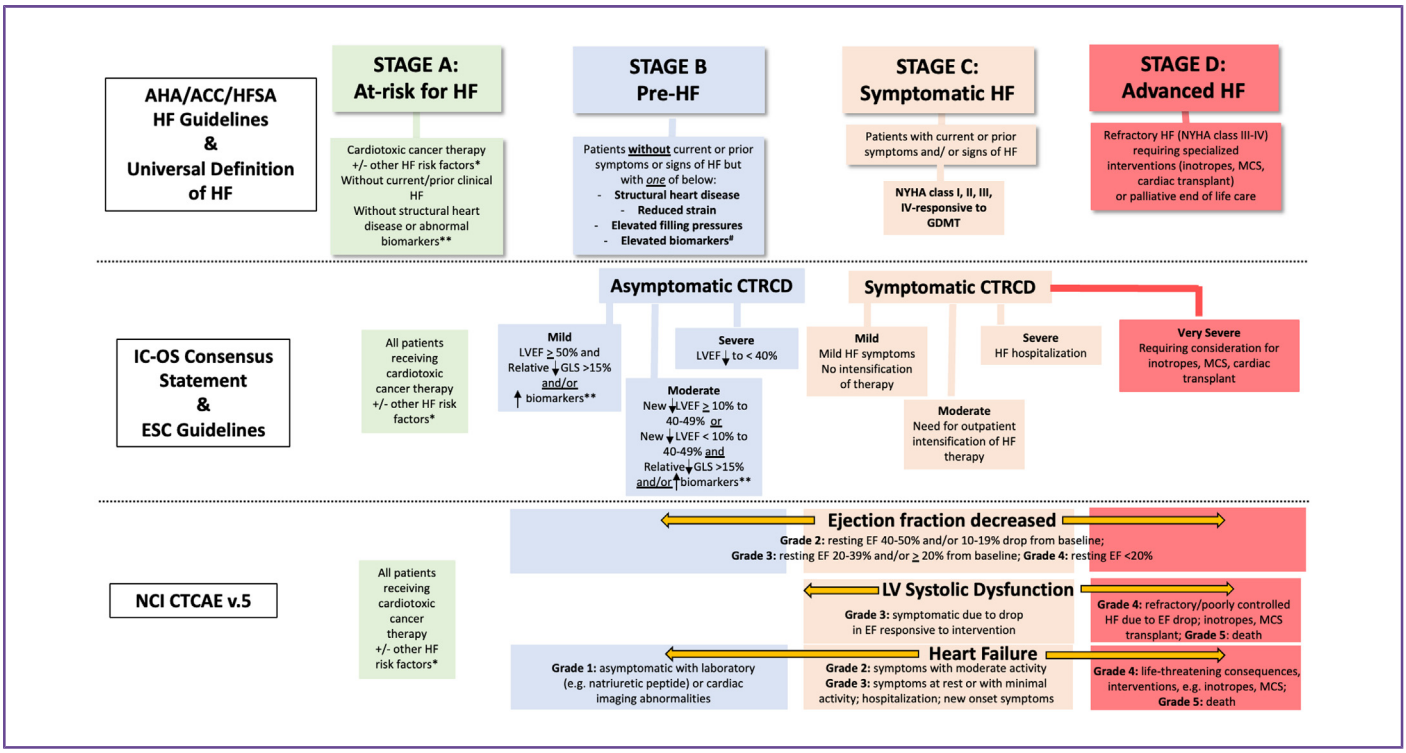

Fig. 1. Definitions of heart failure and cancer treatment-related cardiac dysfunction (CTRCD) in select professional society statements and oncology clinical trials. AHA American Heart Association; ACC, American College of Cardiology; HFSA, Heart Failure Society of America; HF, Heart Failure; IC-OS, International Cardio-Oncology Society; ESC, European Society of Cardiology; NCI, National Cancer Institute; CTCAE v5, Common Terminology Criteria for Adverse Events, version 5. Adapted from 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure,[83] Universal Definition and Classification of Heart Failure,[84] IC-OS Consensus Statement on Definitions of Cardiovascular Toxicities,[85] 2022 ESC Guidelines on Cardio-Oncology,[32] and CTCAEv5.[82]

treatment associated with direct cardiotoxicity (eg, anthracyclines, anti-HER2-targeted therapies) (Table 5). In these patients, findings of abnormal LVEF (most often defined as LVEF < 50%) require multidisciplinary discussion regarding the safety of oncology therapy, further cardiac evaluation and joint cardiology and oncology management during cancer treatment.

TTE remains the most widely used and available modality for the assessment of cardiac function in patients with cancer at baseline during and post cancer treatment. Global longitudinal strain (GLS), a marker of myocardial contractility, can be measured by speckle tracking echocardiography, and is a predictor of LVEF decline in patients receiving anthracyclines and/or anti-HER2-targeted therapies.[97] The ESC guidelines[32] and contemporary cardiac imaging statements[98,99] recommend TTE with GLS measurement as part of the comprehensive assessment of cardiac function in patients receiving cancer therapies. In patients receiving anthracycline therapy GLS- vs LVEF-guided cardioprotection did not show differences in LVEF;[100] however, in a more recent trial that selectively randomized patients with GLS-decline the use of cardioprotective therapy was associated with benefit.[380] Together, these results suggest that GLS could be used to identify patients who will benefit form cardioprotection during or after treatment with anthracyclines.[381]

Table 4 Risk stratification and monitoring in adult survivors of childhood, adolescent, and young adulthood cancer

Guideline	Risk	Anthracycline Dose (mg/m^2) based on doxorubicin equivalent	Chest Radiation Therapy (Gy)	Anthracycline (mg/m^2) + Chest Radiation (Gy)	Is Screening Recommended?	Interval
IGHG	Low	0-99	0-14	N/A	No	No Screening
COG	Low	none	0−14	N/A	No	No Screening
IGHG	Moderate	100−<250	15−29	N/A	Maybe	Every 5 years
COG	Moderate	>0−<250	15−34	<250 + <15 Gy	Yes	Every 5 Years
IGHG	High	≥250	≥30	≥ 100 + ≥15Gy	Yes	Every 2 years
COG	High	≥250 mg/m^2	≥35	< 250 + ≥15	Yes	Every 2 years

COG, National Cancer Institute and Children's Oncology Group; IGHG, International Late Effects of Childhood Cancer Guideline Harmonization Group.

Table 5 Heart failure risk stratification and monitoring strategies for cancer therapies

	HF Risk Modifiers		Monitoring Strategies to Consider[a]	
Drug or Therapeutic Class	Patient Factors	Cancer Therapy Factors	Stage A HF[b]	Stage B HF[c]
Anthracyclines (ANT)	Older age, LVEF <55%, CAD, mod/severe valve disease, HTN, DM, obesity	Lifetime cumulative ANT dose, Sequential anti-HER2 therapy, RT	Baseline TTE in all patients Adults: TTE 6-12 months post ANT chemo CAYA: Lifelong TTE every 2−5 years in mod or high risk	Baseline TTE in all patients TTE during and post ANT-chemo NP and cTn screening before and during ANT-chemo
Anti HER-2 therapy (infusional including monoclonal antibodies)	Older age, LVEF <55%, CAD, mod/severe valve disease, HTN, DM	Sequential anthracycline followed by anti- HER2 therapy	Baseline TTE and every 3 months during therapy[d]	Baseline TTE and every 3 months during therapy More frequent TTE monitoring if LVEF declines[e] NP at baseline and during therapy
Cyclophosphamide	Older age	Dose >120−200 mg/kg, timing post-allogeneic stem cell transplant	Insufficient evidence	Insufficient evidence
BRAF/MEK inhibitors	Insufficient evidence	Combination BRAF/MEK inhibitor	Baseline TTE in all patients TTE every 3−6 months while on treatment	Baseline TTE in all patients Surveillance TTE every 3-6 months during treatment
5-Fluorouracil, capecitabine	Insufficient evidence	Insufficient evidence	Insufficient evidence	Baseline TTE in patients with CAD or CM Baseline ischemia evaluation in patients with CAD or unexplained CM, if it may guide treatment
Osimertinib	Insufficient evidence	Insufficient evidence	Baseline and surveillance TTE in patients with HF risk factors	Baseline and surveillance TTE in all patients
Vascular endothelial growth factor inhibitors	HTN, CAD	Insufficient evidence	Insufficient evidence	Baseline TTE in high-risk patients
Proteosome inhibitors	Elevated NP	Insufficient evidence	Baseline TTE and NP	Baseline TTE and NP Surveillance TTE and NP during therapy
Immune checkpoint inhibitors	Insufficient evidence	Combination therapy with CTLA-4 and PD-1/PD-L1	Baseline ECG, cTn and NP in high-risk patients	Baseline ECG, cTn and NP in all patients Baseline TTE in high risk patients
Chimeric antigen receptor (CAR) T-cell therapy	Insufficient evidence	Insufficient evidence	Insufficient evidence	Baseline TTE, NP and cTn
Chest radiation therapy (RT)	HTN	Mean heart dose Combination ANT and chest RT	TTE every 5 years post RT Consider Ischemia Evaluation	TTE 1,3 and 5 years and every 5 years post RT, depending on mean heart dose

[a]Monitoring strategies refer to screening in asymptomatic patients and largely reflect recommendations included in recent European Society of Cardiology (ESC) cardio-oncology guidelines.[32] Patients with signs or symptoms of HF should have an echocardiogram, cardiac biomarkers and timely evaluation by a clinician

[b]Exposure to cardiotoxic therapies classifies individuals as Stage A heart failure (HF).

[c]Evidence of structural heart disease, elevated filling pressures or cardiac risk factors with biomarker evidence of neurohormonal or cardiac injury are classified as Stage B HF.

[d]Reduced frequency of LVEF assessments can be considered in asymptomatic patients with low cardiovascular risk, in particular patients receiving long-term anti-HER2 targeted therapies (eg, for metastatic HER2+ breast cancer).

[e]Recommendations for stage B HF are based on small studies and expert opinion.

ANT, anthracyclines; CAD, coronary artery disease; CAYA, childhood and young adulthood cancer survivors; CM, cardiomyopathy; cTn, cardiac troponin; DM, diabetes mllitus; 5-FU, 5-Fluorouracil; HTN, hypertension; LVEF, left ventricular ejection fraction; Mod, moderate; NP, natriuretic peptide; RT, radiation therapy; TTE, transthoracic echocardiogram.

Cardiac magnetic resonance (CMR) imaging has higher accuracy for LV volume and LVEF assessment compared with TTE. Use of CMR is recommended in several clinical scenarios, including when TTE images are suboptimal, when serial TTE images yield variable LVEF results, when management decisions will be impacted in cases of borderline or mildly abnormal LVEF, and when more accurate assessment of LV volumes or further characterization of myocardial structural abnormalities or tissue characterization (eg, fibrosis, infiltrative disease) is sought.[98] Multigated acquisition scan (MUGA) was historically used for the quantification of LVEF in patients with cancer but is no longer recommended for serial LVEF assessment due to the associated radiation exposure and inability to provide data on cardiac structural and functional abnormalities other than LVEF.[101] In circumstances when TTE images are suboptimal and CMR is not available, MUGA can still be considered for LVEF assessment.[98] Variability in LVEF estimation across different imaging techniques is well described, and using the same imaging modality for serial imaging in an individual patient is recommended.[98] To this end, when a different modality is used for LVEF assessment in an individual patient, caution and tailored decision making should account for potential discrepancies in imaging type.

Table 5 summarizes imaging strategies for monitoring patients with cancer at risk for HF.[83,95,96] It is important to recognize that professional society guidelines differ in the terminology they use to define CV and HF risk and provide varying level of detail in recommendations for cardiac function assessment. Beyond anthracyclines and anti-

HER2-targeted monoclonal antibodies, very few cancer therapeutics have cardiac imaging surveillance included in the drug-label recommendations, resulting in significant variations in clinical practices.

Role for Biomarkers in Risk Stratification

The role of biomarkers in risk stratification in patients receiving cancer therapies is an area of ongoing research. In a meta-analysis investigating cardiac troponin (cTn) and natriuretic peptides (brain [B-type] natriuretic peptide [BNP]) and N-terminal prohormone of BNP (NT-proBNP) in patients receiving cancer therapy, elevation in cTn was associated with LV dysfuncyion, and negative cTn had a 93% negative predictive value.[102] In this analysis, patients with anthracycline-induced LV dysfunction had elevated BNP/NT-proBNP levels compared to controls; however, the predictive value of natriuretic peptide elevations could not be calculated due to the limited number of studies that used BNP/NT-proBNP during treatment.[102]

In patients with multiple myeloma treated with proteasome inhibitors, elevated baseline BNP or NT-proBNP values were associated with increased risk of cardiac events and HF,[103] indicating the need for further research into the role of biomarkers in specific cancer and cancer-treatment scenarios. ESC guidelines[32] recommend cTn and BNP or NT-proBNP at baseline and with each cycle of chemotherapy in anthracycline-treated patients considered to be at high or very high risk for HF. Similarly, in patients with high cardiac risk, biomarker surveillance at baseline and during therapy has been recommended by the ESC guidelines for other types of cancer therapy (Table 5), although the value of routine longitudinal screening remains to be validated.[32]

Stage A Heart Failure: Prevention of Heart Failure and Cardiomyopathy in Adults With Cancer and in Childhood Survivors of Cancer

General Preventive Strategies

Like general HF practice, preventive strategies for stage A patients throughout the course of cancer therapy are used with the overall goal of minimizing cardiac toxicity, including CM and HF. Given the overlapping risk factors between cancer and CVD, lifestyle modifications are recommended for overall prevention in the population with cancer, irrespective of the type of cancer or type of therapy.[32] Prior to the initiation of potentially cardiotoxic cancer treatment, professional society guidelines recommend a comprehensive examination, including screening for modifiable CV risk factors and a baseline TTE to detect prevalent CM.[32,96,104] CV therapy tailored to an individual patient is part of a general preventive strategy throughout the continuum of cancer care, from diagnosis through survivorship.[32,96,104,105] With respect to modification of oncology treatment, avoidance or minimization of potentially cardiotoxic therapy is recommended when the alternative cancer treatment plan would not compromise cancer-specific outcomes, highlighting the importance of open communication between cardiology and oncology specialists.[32,96] In patients in whom chest RT is planned, modern RT techniques with CT planning allow the use of more precise radiation fields, thus reducing the exposure to the heart (eg, deep inspiration breath holding, proton-beam therapy, prone imaging).[96,106–110]

Pharmacologic Approaches to Prevent Cancer Treatment-Related Cardiac Dysfunction

To minimize the risk of cardiac toxicity, several pharmacological strategies have been investigated, primarily for patients receiving anthracyclines and/or trastuzumab. These strategies can be largely categorized as cancer- or cardiac-centered therapies.

Liposomal Anthracycline Preparations

Liposomal anthracyclines remain within the vascular space and are more likely to enter damaged tissue with decreased capillary integrity such as in a cancer environment.[111] Due to this decreased volume of distribution and enhanced permeability and retention in tumor cells, liposomal formulations may offer improved cardiotoxicity profiles compared to conventional formulations. Liposomal formulations are not interchangeable with conventional agents and have been studied in limited disease states and patient populations. Pegylated liposomal doxorubicin preparations, for example, are FDA-approved for patients with ovarian cancer, multiple myeloma and Kaposi sarcoma.[112] Non-pegylated liposomal doxorubicin formulations are approved in Europe and Canada for metastatic breast cancer.[113] In a meta-analysis of 19 trials (6 of which included liposomal doxorubicin), there was a nonsignificant trend toward lower cardiac toxicity with liposomal preparations (odds ratio [OR] = 0.6, 95% CI = 0.34–1.07).[114] Additionally, individual assessments have demonstrated low incidences of LVEF reductions in patients receiving cumulative doses exceeding 1000 mg/m^2 of liposomal doxorubicin.[115–117] Recently, the FDA approved a combination liposomal agent consisting of cytarabine and daunorubicin (CPX-351) formulated in a 5:1 ratio for patients with treatment-related acute myeloid leukemia or acute myeloid leukemia with myelodysplasia-related changes, based on a phase-3 study in older adults that demonstrated improved treatment-response rates and a more favorable safety profile compared to the standard 7+3 regimen.[118,119] Preliminary data from a small post hoc analysis demonstrated a lower incidence of LVEF decline in patients who received CPX-351.[120] This early signal will have to be further evaluated. Current ESC and ASCO guidelines suggest consideration of liposomal preparations in patients at high or very high risk of cardiotoxicity when there is no reasonable alternative to anthracyclines, and efficacy data exist.[32,96] Importantly, more randomized controlled studies need to be

conducted to assess the efficacy of liposomal anthracyclines in treating underlying malignancies as well as to evaluate their cardiac safety in more varied diseases and patient populations, including in the nonmetastatic setting and in younger patients.

Dexrazoxane

Dexrazoxane is an infusional iron chelator that has been FDA-approved as "a cytoprotective agent to reduce the incidence and severity of CM associated with doxorubicin in patients with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m^2 and continue to receive doxorubicin therapy to maintain tumor control."[121] In a meta-analysis that included randomized and nonrandomized clinical trials in patients with breast cancer treated with anthracyclines with or without trastuzumab, dexrazoxane reduced the risk of clinical HF (relative risk [RR] = 0.19; 95% CI = 0.09−0.40) and cardiac events (RR = 0.36; 95% CI = 0.27−0.49), regardless of prior anthracycline exposure, with no effect on oncologic therapy response or overall and progression-free cancer survival.[122] In contemporary practice, the use of dexrazoxane with breast cancer treatments remains uncommon, in part due to a decline in the use of high dosages of anthracycline (standard cumulative doxorubicin dosage for early breast cancer treatment is 240 mg/m^2) and also due to the increasing use of liposomal doxorubicin in metastatic breast cancer.[123] In childhood and pediatric malignancies, the use of dexrazoxane was investigated in prospective randomized trials, and investigators in recent analyses reported a long-term cardioprotective effect[124] without adverse cancer outcomes.[125] Dexrazoxane remains the agent with the largest evidence base for cardiac protection against anthracycline-related CM and HF in patients receiving high-dose anthracyclines. It is administered as an 15-minute infusion with a dosage ratio of 10:1 dexrazoxane:doxorubicin (eg, 500 mg/m^2 dexrazoxane: 50 mg/m^2 doxorubicin) given at least 30 minutes prior to each anthracycline dose.[121] In clinical practice, dexrazoxane is often considered in adult patients at high or very high CV risk (eg, preexisting HF or CM or low−normal LVEF)[32] and in those who have received ≥ 250 mg/m^2 of doxorubicin equivalents per ASCO guidelines[96] when there is no reasonable alternative to anthracyclines (eg, patients with sarcoma or lymphoma).

Neurohormonal Antagonist and Statin Therapies

Table 6 summarizes the design, cancer-treatment setting, cardiac imaging modalities, and outcomes of several key randomized controlled trials that used neurohormonal antagonists or statins for primary prevention of cardiac dysfunction in patients receiving anthracyclines and/or anti-HER2 targeted therapies. Together, these studies have demonstrated safety and feasibility, with the most consistent signal being that of modest benefit among high-risk patients.[126] There are also a number of ongoing trials exploring the role of other cardioprotective strategies in patients with cancer,[127] including the use of sacubitril/valsartan in patients with breast cancer,[128] as well as recent data suggesting the potential benefit of the use of sodium glucose transport inhibitor therapy in patients with cancer.[129−131]

Risk-guided Prevention Strategies

One of the challenges of primary prevention studies in cardio-oncology has been the low overall risk of cardiac events, which led to the notion that cardioprotective strategies would be best used in patients at higher risk. There is a growing interest in risk-guided approaches to cardioprotective therapies. In the ICOS-ONE trial, investigators compared enalapril during cancer therapy in all patients, vs enalapril only in patients with elevated troponin levels.[132] In that study, there was no difference in the primary outcome of troponin rise using a risk-guided intervention strategy at 1 year[132] or 3 years,[133] noting overall low rates of cardiac toxicity. The SUCCOUR (Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes) study compared GLS-guided vs LVEF-guided initiation of neurohormonal antagonist during cancer treatment.[100] At the end of 1 year, the primary outcome (defined as an absolute change in 3-dimensional LVEF from baseline to 1 year) was not statistically different between GLS- and EF-guided strategy, although fewer patients in the GLS-guided group met criteria for cardiac toxicity.[100] The SUCCOUR-MRI trial randomized only patients who experienced GLS decline (without significant LVEF decline) during or after anthracycline therapy to cardioprevention vs. standard care (no treatment) and demonstrated attenuation of LVEF decline at one year measured by magnetic resonance.[380] Individual patient factors (such as HTN, DM) and cancer therapy-related factors (eg, drug type and dosage, early vs late stage of disease, options for alternative therapies) should weigh in heavily on decisions about when/if and how to use specific cardioprotective agents. Patients and their oncology teams should both be involved in the decision making.

Prevention and Treatment of Cancer Therapy-Related Hypertension

Systemic HTN is a known side effect of several cancer therapy agents,[48,134] including VEGF and TKI therapies, with incidence and degree of HTN varying across differing agents[135] (Table 1) (Table 2). Prior to the initiation of such agents, it is essential to evaluate patients for symptoms consistent with HF, to evaluate volume status and to identify baseline renal function. Patients should have not only assessment of blood pressure (BP) in office, but they should also be instructed about home monitoring, noting that patients with cancer have higher likelihoods of white-coat HTN.[134] If BP increases while on cancer therapy, pharmacological therapy is usually necessary, with close monitoring and rapid uptitration.[136] In the absence of guidelines specific to patients with cancer, treatment of cancer therapy-related HTN should emulate current

Table 6 Summary of randomized controlled trials of cardioprotective strategies in cardio-oncology

Study Authors/ Acronym/ Year	Cancer population Studied/ Number of Patients (N)	Cancer Therapy	Cardiac Prevention Strategy	Primary Outcome Definition	Imaging Modality	Primary Outcome Results	Other Relevant Findings
Cardinale, et al[382] 2006	BC, lymphoma, sarcoma with high CV risk (defined by elevated cTn) n = 473	High-dose chemo (not all ANT)	enalapril 20 mg vs placebo ACEi started 1 month post chemo x 1 year	LVEF > 10% decline to below normal value	TTE	24% developed cTn increase and were included LVEF decline 43% control vs.0% in enalapril ($P < 0.001$)	Overall 31 cardiac events with higher incidence in control vs ACEi group (p<0.001) No cardiac events in pts with negative cTn
Kalay et al.[383] 2006	BC and lymphoma n = 25	ANT (adriamycin or epi)	carvedilol 12.5 mg once daily vs. placebo x 6 months	Change in LVEF, systolic and diastolic parameters	TTE	Mean LVEF in carvedilol 68.9% vs 52.3% placebo at 6 months ($P = 0.001$).	Diastolic parameters significantly reduced in placebo
Gulati, et al. PRADA 2016[384,385]	Early BC no prior CV disease n = 130	5-FU, epi, cyclophosphamide (FEC) (23.6% had trastuzumab)	candesartan 32 mg vs. metoprolol sucinate 100 mg vs both vs. placebo (2 × 2 factorial design)	Absolute LVEF decline at 10 and 64 weeks after cancer treatment	CMR and 2D TTE/strain	LVEF decline candesartan 0.8% vs. 2.6% placebo ($P = 0.026$) no effect in metoprolol vs placebo	Small decline in LVEF but no significant differences noted in extened 23 month follow up
Boekhoet, et al 2016[386]	HER-2+ BC n = 210	Dox/Epi/ Taxanes/RT + anti-HER2 therapy	candesartan 32 mg/d vs placebo x 78 weeks	Decline in LVEF >15% or to <45%	TTE or MUGA	LVEF decline 19% candesartan vs. 16% placebo (p=0.58) 2-yr incidence of CV events 0.28 vs 0.13 ($P = 0.56$)	Ala1170Pro homozygous ERBB2 genotype was associated with a lower likelihood of the occurrence of a cardiac event compared with Pro/ Pro + Ala/Pro genotypes in multivariate analysis ($P = .003$).
Pituskin et al.[387] MANTICORE 2017	HER-2+ BC n = 94	anti-HER2 therapy ± ANT (epi or dox)	perindopril 8 mg vs bisoprolol 10 mg vs. placebo (1:1:1) for duration of trastuzumab rx	Change in LVEDVi and LVEF	CMR	No mean change in LVEDi	Absolute LVEF decline lower in bisoprolol (1% [5%]) vs perindopril (3% [4%]) or placebo (5% [5%]; $P = 0.001$)
Guglin, et al[388] 2019	HER-2+ BC n = 468	anti-HER2 therapy (± ANT)	lisinopril 10 mg vs carvedilol (CR) 10 mg vs placebo	LVEF decline >10% or >5% to below 50%	TTE and MUGA	No change in cardiac toxicity rates in 3 arms (32% vs 29% vs 30% For pts receiving ANT, event rates higher in placebo (47%) vs lisinopril (37%) and carvedilol (31%)	Cardiotoxicity-free survival longer on both carvedilol p = 0.009) and lisinopril P = 0.015) vs placebo. Patients on active therapy with either ACEi or BB fewer interruptions in trastuzumab vs placebo
Avila et al.[389] CECCY 2018	HER-2 neg BC receiving ANT n = 200		carvedilol (max 25 mg twice daily) vs placebo	Prevention of 10% decline in LVEF at 6 mo		LVEF decline 14.5% carvedilol vs 13.5% placebo (NS)	

(*Continued*)

Table 6. (*Continued*)

Study Authors/ Acronym/ Year	Cancer population Studied/ Number of Patients (N)	Cancer Therapy	Cardiac Prevention Strategy	Primary Outcome Definition	Imaging Modality	Primary Outcome Results	Other Relevant Findings
Livi et al.[390] SAFE 2021	Non-metastatic BC ANT based chemo ± trastuzumab n = 174n		bisoprolol 5 mg qd vs ramipril 5 mg qd vs both vs placebo X 1 yr after chemo or until end of trastuzumab	: >10% decline in 3D EF, 2D LVEF or GLS	2D/ 3D TTE GLS	3D-LVEF worsened by 4.4% in placebo arm and 3.0%, 1.9%, 1.3% in the ramipril, bisoprolol, ramipril plus bisoprolol arms, respectively (P = .01). GLS worsened by 6.0% in placebo arm and 1.5% and 0.6% in the ramipril and bisoprolol arms, respectively	
Hundley et al.[391] PREVENT 2022	BC and lymphoma without CV indication for statin N= 279	Dox low (<250 mg/m^2) or high dose (>250 mg/m^2)	atorvastatin 40 mg vs placebo	difference in 24 month LVEF	CMR	No change in LVEF decline, GLS, LV mass, cognition, or inflammatory biomarkers at 2 years post anthracycine Rx	
Thavendiranathan, et al[392] SPARE-HF 2022	**BC, lymphoma,leukemia, sarcoma, thymoma high risk for cardiac toxicity** n = 112	>200 mg/m^2 or >250 mg/m^2 dox equivalent based on risk	atorvastatin 40 mg vs placebo	post-anthracycline LVEF, adjusted for baseline (CTRCD was defined as a fall in LVEF by > 10% to < 53%)	CMR and biomarkers	No difference in post ANT LVEF	
Neilan, et al.[393] STOP-CA 2023	Lymphoma	high dose (>300 mg/m^2) dox	atorvastatin 40 mg vs placebo	>10% decline in LVEFto <55% at 1 year		Atorvastatin 9% vs placebo 22% (*P* = 0.002)	

ACEi, Angiotensin Converting Enzyme inhibitors; ARB, Angiotensin II receptor blocker; ANT, anthracyclines; BC, breast cancer; cTn, Chemo, chemotherapy; cardiac troponin; CV, cardiovascular; Dox, Doxorubicin; Epi, Epirubicin; 5-FU, 5-Fluorouricil; GLS, global longitudinal strain; LV, left ventricular; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; Pts, patients; 3D, 3-dimensional; 2D, 2-dimensional.

guidelines.[48,137] Angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and dihydropyridine calcium channel blockers are commonly first-line therapy for treatment, given their efficacy, and some observational studies even demonstrate improvement in outcomes with ACEi in patients with renal cancer.[138,139] Certain unique issues specific to patients with cancer might be relevant to the management of BP. For example, thiazide diuretics might be avoided in volume-depleted patients and nondihydropyridine calcium channel blockers are often contraindicated due to drug-drug interactions related to the induction of CYP3A4[48] (Table 2). If BP increases to > 180 mm Hg systolic or > 110 mm Hg diastolic, the responsible cancer therapy may need to be temporarily held and reintroduced at the same or lower dosage when systolic pressure is < 160/110 mm Hg. Ideally, antihypertensive therapy should be optimized before the initiation of cancer treatment,[48] and patients should be advised that a cancer treatment resulting in hypertension might require rapid titration of antihypertensive treatment. Close follow-up and rapid escalation of antihypertensive therapy may be necessary not only to prevent adverse CV effects, such as HF, stroke, and renal dysfunction, but also to allow for uninterrupted cancer therapy. Standard CV risk-management methods (pharmacotherapy and lifestyle modifications) should parallel those of the general population,[82,140] considering that cancer therapy may increase overall CV risk.[141,142]

Stage B Heart Failure: Management of Asymptomatic Cardiac Dysfunction in Patients with Cancer

In patients receiving potentially cardiotoxic cancer therapies, stage B HF might be present at baseline or might represent cardiotoxicity diagnosed via cardiac monitoring during or following cancer therapy.[143] Contemporary cardiology and oncology guidelines agree that decisions about changes in oncology treatment should not be based solely on asymptomatic changes in GLS, biomarkers, or declines in LVEF and they recommend multidisciplinary discussion between cardiology and oncology teams.[32,96]

Initiation of HF therapy is recommended following ACC/AHA/HFSA Guidelines,[83] with the overall goal of continuing optimal cancer therapy without interruption.

The notion of *permissive cardiotoxicity* is a more recently developed paradigm that acknowledges the need to accept and balance some increased HF risk to ensure optimal cancer treatment.[144] The safety of this approach is supported by 2 small prospective studies, both of which included patients with stage B HF receiving anti-HER2 targeted therapies. The SAFE-HEaRt (Cardiac Safety Study in Patients With HER2 + Breast Cancer) study was the first prospective trial to investigate starting or continuing anti-HER2 agents (trastuzumab, trastuzumab + pertuzumab, or ado-trastuzumab [T-DM1]) in women with HER2-positive breast cancer and stage B HF (defined as asymptomatic LVEF 40%−49% at baseline).[126] All patients underwent cardiac monitoring and received cardioprotective therapies, including carvedilol and/or renin angiotensin aldosterone inhibitors (RAASi).[126] Of 30 enrolled patients, 27 (90%) were able to complete the planned cancer treatment; 2 experiencd HF and 1 experienced further LVEF decline to < 40% (both prospectively defined safety endpoints).[126] Although larger studies are needed to further validate these findings and investigate implementation practices, the long-term follow-up of the SAFE-HEaRT study suggests the absence of long-term HF risk with this strategy.[145] The SCHOLAR (Safety of Continuing Chemotherapy in Overt Left Ventricular Dysfunction Using Antibodies to Human Epidermal Growth Factor Receptor-2) trial was a phase 1 study that included 20 patients with HER2-positive, nonmetastatic breast cancer who developed an asymptomatic decline in LVEF to 40%−54% during trastuzumab treatment.[146] All women received carvedilol and/or RAASi, and 18 (90%) were able to continue intended adjuvant trastuzumab treatment, with only 2 (10%) meeting the criteria for cardiac toxicity and requiring cancer-treatment discontinuation.[146] Both studies highlight the impact of collaboration between cardiology and oncology toward improved outcomes in patients with cancer, and they highlight the concept of permissive toxicity as strategy for cancer-therapy continuation in selected patients with stage B HF. Moving forward, the management of stage B cardio-oncology patients will need to account for the differing cancer types, oncologic treatment targets, comorbid CV conditions, intensity of multimodality and multiagent oncology regimens, and the differing mechanisms of cardiac injury resulting from cancer therapeutics.[147]

Stage C Heart Failure: Diagnosis and Management of Symptomatic Heart Failure Across the Spectrum of Left Ventricular Ejection Fraction

New signs or symptoms of a cardiac nature in a patient on or post cancer therapy should prompt an expedited evaluation, including history and physical examination, electrocardiogram, TTE, and laboratory studies, including natriuretic peptides (ie, BNP, NT-proBNP). Even in patients undergoing cancer therapy, alternate etiologies of HF must be considered, in alignment with professional-society guidelines for the general population.[32,83,95,96] History of chest RT or allogenic stem cell transplant may put the patient at higher risk for CAD and ischemic heart disease. A comprehensive and detailed history of current and prior cancer treatment (eg, type of chemotherapy, dosages, timing) is crucial to the evaluation.[78,148−151] Although TTE is the standard first-line imaging modality, CMR imaging with myocardial tissue characterization is recommended in patients with new CM to assess etiology as well as for higher accuracy of cardiac structure and function assessment when cardiac ultrasound imaging is suboptimal.[98]

Noncardiac Causes to Consider in Patients With Cancer and Heart Failure Symptoms

In patients with cancer and new signs or symptoms that raise concern for HF, it is important to consider noncardiac etiologies concomitant with cardiac evaluation. Dyspnea, fatigue, and edema may occur due to cancer itself (eg, tumor burden) or, alternatively, due to noncardiac issues, such as venous thromboembolism, lymphatic obstruction, concomitant pulmonary, renal or hepatic disease, anemia, malnutrition with low serum protein, or cancer cachexia. Some chemotherapy agents, such as docetaxel[152] and gemcitabine,[153] may cause peripheral edema by direct vascular toxicity. High-dose corticosteroid treatment, used in many cancer therapy regimens, may also contribute to noncardiac edema due to fluid retention. Assessment of intravascular volume by the examination of jugular venous pressure, TTE and invasive hemodynamics should be considered when diagnosis remains in question. BNP or NT-proBNP can aid in the diagnosis of HF in patients with cancer who present with dyspnea or edema; however, cardiac biomarkers are nonspecific and may also be elevated with advanced age, anemia, renal failure, pulmonary embolism, or critical illness.[154]

Management of Patients with Cancer and Pre-existing Heart Failure

Patients with pre-existing stage C HF are largely excluded from cancer clinical trials,[155] leaving HF clinicians with a limited evidence base for management decisions in these patients with complex illnesses. In patients with prior histories of HF and newly diagnosed cancer, optimization of guideline-directed medical therapy and close monitoring for hypervolemia, arrhythmia, fatigue, or other signs and symptoms of worsening HF should be practiced in close collaboration with oncology. Even cancer-treatment regimens that are not known to cause direct cardiotoxicity may contribute to the development of acute decompensated HF via indirect mechanisms, including prophylactic prehydration with chemotherapy (eg, high-dose methotrexate) or corticosteroid pretreatment to avoid hypersensitivity reactions (eg, taxanes[156] or daratumumab[157]). Noncardiac complications, such as infection or acute kidney

injury, are common and can exacerbate HF in these patients as well. Close monitoring of fluid status and possible adjustment of loop diuretics and other cardiac medications (ie, sodium-glucose cotransporter-2 inhibitors) should be planned for during and following cancer therapy. Additionally, patients should be educated about signs and symptoms of volume overload or other cardiac complications that might be expected during treatment.

The safety and management of cardiotoxic cancer therapies in patients with preexisting HF has not been well studied prospectively. In a small case series study, investigators described expanded off-label use of the cardioprotective agent dexrazoxane in patients with pre-existing CM.[158] Importantly, in this case series, patients did not receive anthracyclines in the presence of symptomatic HF. As discussed, the safety of *permissive cardiotoxicity* in patients with anti-HER2-targeted therapies has been extrapolated largely from patients with stage B HF, and patients with moderate or severe LV dysfunction or with New York Heart Association (NYHA) class III or IV HF prior to enrollment were excluded. This highlights the importance of caution in extrapolating these results to patients with stage C or greater HF.[159] Patients with preexisting HF were also largely excluded from trials of targeted therapies (eg, BRAF and MEK inhibitors, EGFR inhibitors, and BTK inhibitors), limiting the data concerning safety and risk-benefit trade-offs with these agents in patients wih HF.

Special consideration should be given to patients with preexisting HF and implantable cardioverter-defibrillators or pacemakers who require radiation therapy (RT). Such patients should undergo risk stratification for potential RT-induced device malfunction. This should include assessment of pacemaker dependence, location of the device within the field of planned RT, and the potential toxicity of the planned dosage and neutron emission with respect to the device. In rare cases, consideration of device removal or replacement to an alternative location might be necessary.[160,161]

In patients with pre-existing stage C HF, determining the risk of further cardiac toxicity vs the oncological benefit of a particular cancer agent can be particularly challenging. For example, in patients with aggressive lymphomas such as diffuse large B-cell lymphoma, anthracycline-containing regimens are the standard of care as front-line therapy. In an analysis of older patients with diffuse large B-cell lymphoma, preexisting HF was present in 13.9% of the cohort, and those patients were less likely to receive an anthracycline-based regimen. Authors reported higher lymphoma mortality at 1 year among patients with preexisting HF (HR = 1.24, 95% CI = 1.18−1.31).[162]

In cases where initiation or continuation of potentially cardiotoxic chemotherapy is being considered for patients with stage C HF, multidisciplinary risk-benefit discussions including oncology, HF cardiology and the patient are necessary to weigh the risks of worsening HF against the benefit of improved cancer outcomes compared with less cardiotoxic alternatives.

Heart Failure With Preserved Ejection Fraction in Patients With Cancer

Although HFrEF has been the focus of cancer therapy-related cardiac toxicity discussions, HFpEF in patients with cancer has received much less attention, and HFpEF is currently not included in the CTRCD definition.[85] However, both HFpEF as a comorbid condition at the time of cancer diagnosis and the development of HFpEF during or following cancer therapy are highly relevant. In the general population, HFpEF has been reported to account for more than 50% of HF cases,[163] with outcomes comparable to those in HFrEF,[164] but much less is known about its prevalence and outcomes in patients with cancer. Although patients with cancer have been largely excluded from HF trials, a recent report suggested that the presence of cancer in patients with HFpEF was not associated with worse outcomes.[165] This raises the question of whether patients with cancer, especially if localized or under control, should be broadly excluded from HF trials. Version 5 of the CTCAE criteria, the "gold standard" of oncology trials, defines cardiotoxicity categorized by decreased ejection fraction, LV systolic dysfunction, right ventricular (RV) dysfunction, and HF in general, without a specific category for HFpEF (Fig. 1).[82] Many patients with cancer may be at risk for HFpEF based on other comorbidities at the time of cancer diagnosis, such as HTN, DM, obesity, and chronic kidney disease, and many cancer therapies are becoming increasingly recognized as predisposing to HFpEF through vascular, metabolic and myocardial mechanisms (Fig. 2).[166]

Epidemiological data indicate that concomitant cancer is more common in patients with HFpEF than in those with HFrEF, even after accounting for age, and cancer increases mortality rates, irrespective of ejection fraction.[167] Among patients with HFpEF, cancer was an independent predictor of both mortality and HF hospitalizations.[168] Furthermore, the incidence of hospitalizations for HFpEF was higher than that for HFrEF among a racially diverse cohort of patients with histories of breast cancer.[13] It is well established that older females have a higher prevalence and incidence of HFpEF in the general population,[169] and these findings were recently recapitulated in patients with HF and breast cancer.[170] Similar to patients with the pathophysiology of HFpEF, among females with breast cancer, impaired cardiac, peripheral vascular and skeletal muscle function were proposed as the mechanisms limiting peak oxygen uptake.[171,172] Atrial fibrillation, well recognized as a risk factor for HFpEF, is prevalent in patients with cancer.[173] Proposed mechanisms include shared pathophysiology and risk factors. At a population level, HTN has the largest attributable risk for the development of HFpEF and is highly prevalent in patients with cancer.[174] Beyond traditional CV risk factors, social determinants of health might

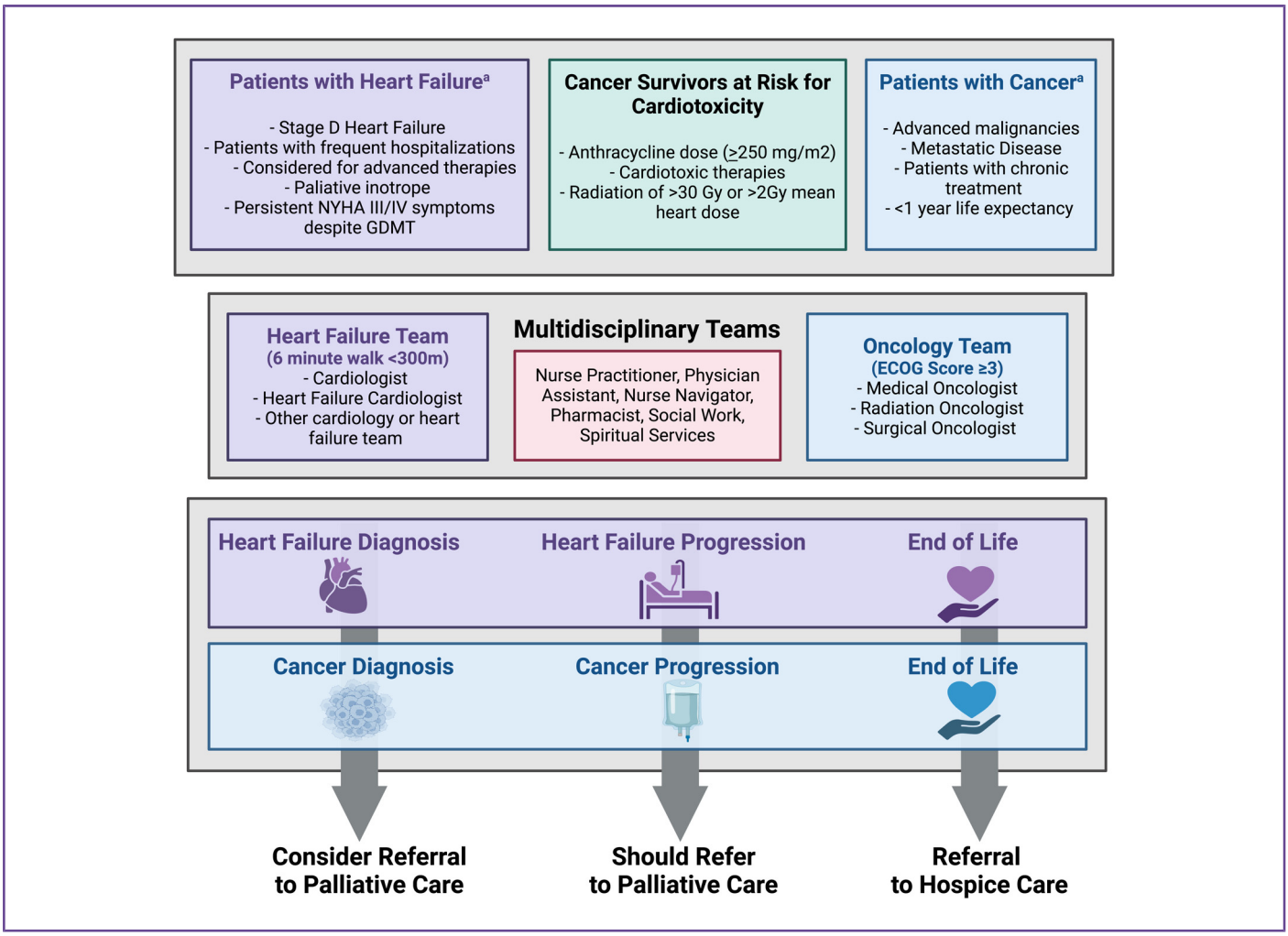

Fig. 2. Role of palliative care across the spectrum of disease in patients with heart failure and patients with cancer. The figure depicts existing recommendations for patient populations most likely to benefit from palliative care referral and highlight the intersection of disease processes and opportunity for palliative care involvement in cardio-oncology. [a]Suggested populations are not comprehensive.

contribute to the development of HFpEF in patients with cancer.[175]

Cancer Therapies Contributing to Risk of Heart Failure With Preserved Ejection Fraction

Cancer therapies, including cytotoxic chemotherapy, molecular-targeted therapies and chest RT have been linked to myocyte damage, myocardial fibrosis, LV dysfunction, thrombogenesis, pericardial pathology, HTN, ischemia, conduction and rhythm disturbances, and vasospasm.[87,176] Several of these abnormalities can contribute to HFpEF with or without other inciting factors. Higher dosages of anthracyclines may cause systolic dysfunction, but lower dosages were linked to diastolic dysfunction that might precede systolic abnormalities.[177] A prior study demonstrated incident diastolic dysfunction by TTE as early as 1 week after completion of anthracycline-based regimens, even in the absence of underlying CV risk factors.[178] Increased arterial stiffness was associated with anthracycline - and nonanthracycline-based chemotherapy regimens.[179] Cancer agents such as BTK inhibitors are well known to increase the risk of atrial fibrillation through off-target effects, and they might lead to or exacerbate HFpEF[173] Other cancer-treatment modalities, including CAR-T therapies, hematopoietic stem cell transplantation (HSCT) and thoracic cancer surgery were described as precipitants of atrial fibrillation and, thus, HFpEF,[180,181] further demonstrating the close relationship between these 2 entitles in patients with cancer.

RT is a widely used treatment modality in patients with cancer and can contribute to the development of HFpEF. In a population-based case-control study of incident HF in females with breast cancer who received RT, higher odds of HFpEF were reported in older females with breast cancer, even after contemporary RT.[78] Of interest, only 18.6% of patients in that study experienced ischemic events between radiotherapy and HFpEF diagnosis, suggesting that radiation may contribute to HFpEF via multiple pathways beyond ischemia.[78] In another study of females with breast cancer treated with chemotherapy or left-sided RT,

the overall cumulative incidence of HFpEF at 10 years was higher than that of HFrEF.[170] RT-induced HFpEF is likely to be underreported and recognized as a consequence of RT for many different cancer types, including breast, lung, esophageal, and lymphoma.[175,182]

Cancer Therapies and Hypertension as Contributors to Heart Failure With Preserved Ejection Fraction

Although pre-existing HTN increases the CV toxicity of cancer therapeutics, several of the cancer therapies themselves can induce new onset of HTN or worsen pre-existing HTN (Table 1) (Table 2), often with rapid onset and aggressive progression, and can, therefore, contribute to the risk of HFpEF.[183] Cancer-therapy agents known to induce treatment-associated HTN include the antimicrotubule agents (paclitaxel, docetaxel, cabazitaxel),[184–186] alkylating agents (cisplatin, cyclophosphamide and ifosfamide derivatives),[187] vinca alkaloids (vincristine), mammalian target of rapamycin mTOR inhibitors, androgen receptor antagonists (abiraterone), and interferon-alpha.[185] More recently, targeted cancer therapies, such as TKIs, vascular endothelial growth factor inhibitors (VEGFi), and proteasome inhibitors, specifically carfilzomib,[55] have been recognized as triggers of HTN.[188] Among TKIs, multitargeted kinase inhibitors are of particular interest, with HTN reported in as many as 30%–80% of patients,[189] reflecting individual agents' inhibitory activities, often against multiple kinases in the VEGFi signaling pathway. The mechanisms of BP elevations with VEGFi are not fully understood but are proposed to include vasoconstriction related to reduced nitric oxide synthase activity, increased endothelin production, capillary rarefaction, and alteration in endothelin-1 levels.[190] Increases in incident BP with various cancer agents have been typically well captured in clinical trials, but the data on HF, and particularly HFpEF, are lacking. At the present time, given the close relationship between HFpEF and HTN,[191] aggressive BP control remains the most important target for prevention of HFpEF in patients with cancer who are receiving offending agents.[137,192]

Diagnosis and Management of Heart Failure With Preserved Ejection Fraction in Patients With Cancer and Survivors

The diagnosis of HFpEF may be particularly challenging in patients with cancer, given the nonspecific symptoms, such as dyspnea, reduced exercise capacity, and edema, that are common and of multifactorial etiologies in this population. A high index of suspicion is necessary to avoid attributing symptoms of HFpEF to other causes. Although HFpEF scoring systems, such as the H2FPEF score[191] and the HFA-PEFF algorithm[193] have not been validated in patients with cancer, they can provide guidance when interpreted with caution and with awareness of the oncology setting. Normal values of BNP and NT-proBNP, in the absence of obesity, have high negative predictive value in the general population,[191,194,195] and it is plausible to hypothesize that these low BNP or NT-proBNP values would perform similarly in patients with cancer.[196] In contrast, BNP or NT-proBNP levels have been suggested to be more often elevated in patients with cancer, even in the absence of HF,[197] potentially due to the systemic inflammatory state. Invasive hemodynamic testing with or without exercise may be needed in patients with nonspecific or exertional symptoms of unclear etiology to establish or negate the diagnosis of HFpEF.[195] Similar to the general population, when HFpEF is suspected in patients with cancer, HFpEF "mimickers," such as HF due to valvular heart disease, constrictive pericarditis, restrictive cardiopathy, or volume overload not directly related to the heart (eg, advanced kidney disease or anemia), should be ruled out.[198] Further, when a cardiac etiology is suspected, specific diagnoses, such as hypertrophic CM or cardiac amyloidosis, should be considered in the appropriate clinical setting.

In the absence of specific guidance for the management of HFpEF in patients with cancer, general management should follow those recommended by the HF guidelines.[83] Management of HFpEF should focus on risk stratification and management of comorbidities, decongestion when appropriate, and implementation of GDMT to improve symptoms and functional capacity and to reduce the morbidity and mortality associated with HF.[83] Exercise and weight loss in appropriate patients can improve functional status and HF-related morbidity.[199,200] Initiation of GDMT is safe and effective in both acute and chronic-care settings in HFpEF,[201,202] though closer attention to diuretic dosage adjustment may be necessary in patients with cancer. Compared with the general population, patients with cancer might experience more frequent changes in volume status, given the need for intravenous fluid with cancer therapies, hypovolemia related to poor oral intake after chemotherapy or procedures, or medications such as corticosteroids in cancer regimens that may cause fluid retention. Interruption of SGLT2is might be necessary several days before procedures that require fasting or that may predispose to poor oral intake to avoid the uncommon occurrence of euglycemic ketoacidosis as is now recommended in the general population.[203]

Stage D Heart Failure: Advanced Heart Failure in Patients With Cancer

Cardiogenic Shock in Cardio-oncology

Cardiogenic shock in patients with cancer requires accurate identification of the underlying etiology, because presentations and trajectories vary. Common etiologies include LV dysfunction secondary to cancer agents, acute coronary syndrome (ACS), stress-induced CM, and ICI-associated myocarditis.

Cardiogenic shock with associated LV dysfunction may occur after therapy with almost any cancer drug class, but it is most common with anthracyclines, anti-HER2-targeted therapies and TKIs.[83] Consideration of ACS is

important, because patients with cancer and ACS are less likely to undergo revascularization and have worse clinical outcomes.[204] Stress-induced CM should be considered in patients with cancer in cardiogenic shock, because this presentation is common,[205] may result in hemodynamic instability, and is often reversible with conservative management. Immediate recognition of ICI-associated myocarditis is critical, as these patients may have a fulminant clinical course[206] and require rapid initiation of immunosuppression to prevent progressive shock.

Mechanical Circulatory Support in patients With Cancer

There are unique considerations regarding the use of temporary mechanical circulatory support devices in patients with cancer in cardiogenic shock, as they are at increased risk for both bleeding and thrombosis. Although there is a lack of data specific to cancer patients, the competing risk of cancer for survival, the potential for reversibility of cardiogenic shock and overall prognosis should factor into decision making. Due to the complexity of these cases, multidisciplinary collaborative care with involvement of HF cardiology, interventional cardiology, critical care, and oncology is crucial.

Durable left ventricular assist devices (LVADs) may be an option for patients with end-stage HF from progressive chemotherapy-induced CM. Although prior data from 2006−2011 using the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) have reported a higher risk for RV failure,[207] more contemporary data suggest that this is no longer the case. Among patients undergoing continuous-flow LVAD from the INTERMACS registry from 2008−2017, no differences were observed in 1-year survival rates between those with anthracycline-induced CM as compared to idiopathic dilated CM or ischemic CM, and only 1.6% of patients with anthracycline-induced CM required RV support, similar to other etiologies of HF.[208] Further, patients with cancer had slightly higher risks of mortality, lower rates of heart transplantation and higher risks for bleeding but showed no difference in other adverse events, including RV failure, compared to patients without cancer.[209] Thus, current data support that LVAD support a viable strategy for patients with history of cancer when using judicious patient selection.

There are limited data concerning the use of LVADs in patients with active cancer or undergoing cancer treatment. In a prior study, patients with active cancer at the time of LVAD insertion and in those who developed cancer after LVAD implantation, the median survival was 3.5 years from time of implant, with no differences in complication rates (stroke, infection or thrombosis).[210] In a systematic review of patients with LVADs and cancer, patients treated with surgery had higher probability of survival for 3 years as compared to those who underwent nonsurgical treatment.[211] However, this could reflect the cancer type or stage at the time of treatment. Retrospective studies could be biased toward the use of LVADs in a relatively less sick cohort of patients with cancer. The International Heart and Lung Transplantation (ISHLT) 2013 guidelines for mechanical circulatory support recommend that carefully selected patients with treated or active cancer and with life expectancies of 2 or more years can be considered for LVAD implantation as destination therapy.[212] A multidisciplinary approach is critical for balancing the competing risks of HF and cancer mortality when evaluating patients with LVAD and active cancer.

Malignancy in Heart Transplant Recipients

Malignancy after heart transplantation remains a significant cause of morbidity and mortality.[213] A growing number of heart transplant recipients from the ISHLT Registry developed de novo malignancy 1−5 years post-transplantation, with rates that have increased from 10% when patients had undergone transplantation between 2000 and 2006 to 12.4% for those transplanted between 2006 and 2011. This increasing trend was attributed to an increase in skin cancer, a small increase in solid-organ malignancy, and essentially no change in post-transplantation lymphoproliferative disease (with a low incidence of approximately 1%).[214]

Heart transplant recipients are 65−250 times more likely to develop skin cancer compared to the general population, with pre-transplantation skin cancer serving as a major risk factor for the development of skin cancer post-transplantation.[215] More than 90% of cases are due to squamous and basal cell carcinomas. Unlike the general population, in whom the incidence of basal cell carcinoma exceeds that of squamous cell cancer, the reverse is true in recipients of organ transplants. Compared with basal cell carcinoma, squamous cell cancer among transplant recipients tends to be more aggressive, to present with more local recurrences, and to have greater metastatic potential than in the general population.[216,217] Factors that increase risk of skin cancer after transplantation include environmental exposure, oncogenic viral infections and genetic predisposition, aggravated by chronic immunosuppression. It is not clear whether alteration of immunosuppression regimens would mitigate the risk of skin cancer or whether induction therapy prior to heart transplantation increases the risk of post-transplant malignancy.[214,217,218] The most promising data concerning the decrease of cancer risk in the long term propose the use of sirolimus or everolimus, which inhibit the mammalian target of rapamycin pathway, which is known to regulate cell growth. After heart transplantation, patients treated with mammalian target of rapamycin inhibitors might have lower risks for cancer than those on alternative immunosuppressive regimens, likely related to their antiproliferative effects.[219,220]

The presence of pre-transplant malignancy impacts the overall risk of post-transplant malignancy. Data from the 2000−2020 United Network of Organ Sharing network

reports an increasing prevalence of pre-transplant malignancy from 3.2%−8.2%. Rates of malignancy at 5 years post-transplant were higher in the group with pre-transplant malignancy (20.4% vs 13.1%). Further, pre-transplant malignancy was associated with higher rates of 1-year mortality after heart transplantation (11.9% vs 9.2%), driven by a 2-fold increased mortality rate among patients with histories of hematologic malignancy.[221]

The trajectory of outcomes in heart transplant recipients with doxorubicin-induced CM have improved over time, with increasing 5-year survival rates (72% between 1987 and 2011 and 81% betwen 2008 and 2018), despite a higher proportion of patients' being bridged to transplant with durable LVADs (13% −76%).[222,223] Thus, while patients in the contemporary era may be at higher risk of mortality due to an increase in LVAD use,[213] outcomes have improved, and they highlighting the importance of careful and individualized patient selection and care.

Cancer Screening Strategies for Malignancy in Pre- and Post-transplant Candidates

All heart transplant candidates should be screened for solid-organ tumors based on recommendations from relevant expert societies targeted to the general population, as there are few data to support specific screening recommendations before and after heart transplant in patients with prior cancer.[224] In addition to traditional screening for colon, breast and prostate cancer, as well as lung cancer screening in current and former smokers in the general population,[225] skin cancer screening with full-body skin examination by a dermatologist is recommended in heart transplant candidates and recipients.[226]

In heart transplant candidates with prior histories of cancer, collaboration with hematology/oncology specialists is recommended for individualized risk stratification of malignancy-related survival and risk of recurrence in the context of immunosuppression. Pre-existing neoplasms are diverse, and many are treatable with excision, radiotherapy, chemotherapy, or immunotherapy to achieve cure or remission. Heart transplantation is typically considered when malignancy-related survival will not meaningfully impact post-transplant survival and the risk of cancer recurrence is low based on tumor type, response to therapy and negative metastatic evaluation. These candidates may include certain early-stage cancers after full resection and/or treatment (eg, prostate adenocarcinoma, renal cell carcinoma, cervical cancer, and bladder cancer), though careful consideration is warranted on a case-by-case basis.[227] A period of observation prior to transplant listing may be recommended, but the timing will be individualized and dictated by the specific cancer history. A personalized approach with multidisciplinary collaboration is essential to prevent unnecessary delays in transplant listing. Further guidance is available in consensus statements from the American Society of Transplantation with granular recommendations based on tumor type, grade and stage.[227,228]

Diagnosis and Management of Myocarditis Related to Immuno-oncology Therapies

HF clinicians should be aware of several cardiac-related iRAEs, including pericarditis, accelerated coronary atherosclerosis and myocarditis; the latter carries an associated mortality rate of 25%−50%.[60] Patients with ICI-related myocarditis often present with normal LVEF and a spectrum of clinical HF severity.[61] Importantly, the differential diagnosis of acute HF in these patients also includes stress CM and non-inflmmatory CM.[229,230] Progressive atherosclerosis among patients on ICI treatment warrants further investigation.[63] In any patient with the appropriate clinical context including mild troponin on ICI therapy, ischemia and coronary artery disease should be excluded.[64]

The diagnosis of ICI myocarditis is dependent on a combination of clinical presentation, laboratory findings, cardiac imaging, and/or invasive cardiac testing and varies based on source[32,231,232] (Table 7). Patients with ICI myocarditis might present with a range of non-specific symptoms, ranging from fatigue and dyspnea to overt clinical syndromes, such as chest pain (mimicking ACS), HF (dyspnea, orthopnea, lower-extremity edema), and symptomatic arrhythmias, such as ventricular tachycardia and/or advanced atrioventricular block (lightheadedness and hypotension).[61] Myocarditis can occur at any time during or following ICI therapy, with most occurring early (median onset of 2 months; the majority occur within 3 months).[46] The presence of immune-related adverse events in other organs, including ocular, pulmonary (pneumonitis), gastrointestinal (colitis), endocrine, renal (nephritis), and dermatologic, should raise suspicion and prompt evaluation for cardiac involvement.[233] Striated muscle involvement (muscle weakness, diplopia, ptosis) raises suspicion for myositis and/or myasthenia gravis, and should tigger evaluation for myocarditis. A comprehensive assessment should include particular attention to neuromuscular symptoms, because clustered presentation (eg, myasthenia gravis and myositis occurring with myocarditis) has been well recognized and is associated with worse mortality rates.[231]

Noninvasive Diagnostic Strategies: Laboratory Evaluation Including Cardiac Biomarkers

The initial laboratory evaluation should include troponin and natriuretic peptides (BNP or NT-pro BNP) levels. Higher elevations in troponin have prognostic value and are associated with more severe cases,

Table 7 Comparing diagnosis and treatment recommendations for immune checkpoint inhibitors-related myocarditis

DIAGNOSIS

International Cardio-Oncology Society (IC-OS)[85] and European Society of Cardiology Guidelines[32]		Bonaca et al. certainty adjudication criteria[232]		Society for Immunotherapy of Cancer Clinical Practice Guidelines[231]	
Histologic	Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy of cardiac tissue samples	Definite	- Pathology consistent with myocarditis. - Diagnostic CMR, clinical syndrome of myocarditis, and positive biomarker or ECG. - Echocardiography with wall motion abnormality, clinical syndrome of myocarditis, positive biomarker, positive ECG, and negative angiography for CAD.	Diagnosis	New cardiac symptoms, new cardiac arrhythmias, new heart block, or cardiac lab findings (eg, asymptomatic troponin elevation) in a patient who has received an ICI therapy in the past 12 weeks.
Clinical	A troponin elevation (new, or significant change from baseline) with 1 major criterion or a troponin elevation (new, or significant change from baseline) with 2 minor criteria after exclusion of acute coronary syndrome or acute infectious myocarditis based on clinical suspicion Major Criteria - CMR diagnostic for acute myocarditis (modified Lake Louise criteria) Minor Criteria: - Clinical syndrome (including any one of the following: fatigue, muscle weakness, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnea, lower extremity edema, palpitations, lightheadedness/dizziness, syncope, cardiogenic shock) - Ventricular arrhythmia and/or new conduction system disease - Decline in cardiac (systolic) function, with or without regional WMA in a non-Takotsubo pattern - Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis - Suggestive CMR (meeting some but not all of the modified Lake Louise criteria)	Probable	- Diagnostic CMR without clinical syndrome of myocarditis, positive ECG, or positive biomarker - Suggestive CMR with one of the following: a. Clinical syndrome of myocarditis. b. Positive ECG. c. Positive biomarker - Echocardiography with wall motion abnormality and clinical syndrome of myocarditis with either positive ECG or biomarker - Clinical syndrome of myocarditis with positron emission tomography scan evidence and no alternative diagnosis.	Cardiac Testing	Patients with suspected ICI-induced myocarditis should undergo cardiac MRI if available (with or without right heart catheterization and myocardial biopsy), EKG, and testing for serum troponin levels.
		Possible	- Suggestive CMR without clinical syndrome of myocarditis, positive ECG, or positive biomarker - Echocardiography with wall motion abnormality and clinical syndrome of myocarditis or positive ECG - Elevated biomarker with clinical syndrome of myocarditis or positive ECG and no alternative diagnosis.		

Table 7 (Continued)

TREATMENT					
European Society of Cardiology (ESC) Guidelines on cardio-oncology[32]		American Society of Clinical Oncology Immune-Related Adverse Event Guidelines[394]		Society for Immunotherapy of Cancer Clinical Practice Guidelines[231]	
First-line treatment	- Discontinue ICI - Admit to hospital with ECG monitoring - 500—1000 mg IV methyl-prednisolone for at least 3 days	First-line Treatment	Grade 1*** - Hold ICI and recheck troponin in 6 hours- may resume ICI if normalized or not believed to be myocarditis Grade ≥2**** - Discontinue ICI - Early (<24 hours) steroid initiation - Steroid dose 1-2mg/kg/day - Admit to hospital and cardiology consultation	First-line treatment	- High-dose steroids - Early (<24 hours from presentation) initiation of steroids
If recovering*	- Switch to oral prednisolone (1 mg/kg/day) - Taper prednisone by 10 mg/week - Troponin monitoring	Without immediate response to steroids	- Increase steroid dose to transplant rejection dose (1000 mg IV methylprednisolone/day) - Initiate either mycophenolate mofetil, infliximab, or antithymocyte globulin	Steroid refractory	- Initiation of second-line agents such as: - Antithymocyte globulin - Mycophenolate mofetil - Abatacept - Alemtuzumab
If steroid refractory**	- Add second-line immunosuppression with one of the following: - Intravenous Immunoglobulin - Plasmapheresis - Antithymocyte globulin - Mycophenolate mofetil - Alemtuzumab - Abatacept - Tofacitinib	Life-threatening cases	In addition to the above add abatacept or alemtuzumab		
Hemodynamically Unstable/ Fulminant Myocarditis	- Admission to intensive care unit - Consider mechanical circulatory support - Second-line immunosuppression as above				

including fulminant myocarditis[62,234]; however, the role of serial troponin assessment for surveillance in asymptomatic patients receiving ICI therapies is of unclear clinical utility,[235,236] requiring consideration of noncardiac causes of troponin elevation.[63,231] Elevations of high-sensitivity cardiac troponin T are associated with major cardiac events and increased risk of respiratory failure and may indicate the presence of an inflammatory myopathy.[63,237] Natriuretic peptides are commonly elevated in patients with ICI myocarditis; the most significantly elevations are reported in patients with concomitant HF.[61] Additional laboratory evaluations should be informed by the clinical symptoms that may raise suspicion of concomitant immune-related adverse events and may include creatine kinase, creatine kinase myocardial band, aspartate transaminase, alanine transaminase, and lactate dehydrogenase levels among others.[233]

Noninvasive Diagnostic Strategies: Electrocardiogram

An ECG should be obtained in any patient in whom there is clinical suspicion or cardiac biomarker elevation that raises concern for ICI myocarditis; ECG abnormalities include prolonged PR interval and advanced atrioventricular block.[234] Most guidelines recommend obtaining a baseline ECG prior to ICI initiation, to serve as comparison if ICI myocarditis is suspected during or following therapy. The presence of new conduction abnormalities can occur in the presence or absence of concomitant HF. However, due to the lack of specificity of ECG changes for ICI myocarditis, alternative cardiac etiologies (eg, myocardial ischemia/infarction, electrolyte abnormalities) should be ruled out.

Imaging: Transthoracic Echocardiogram and Cardiac Magnetic Resonance Imaging

The presence of pericardial effusion, depressed ejection fraction and/or wall-motion abnormalities on TTE raise suspicion for ICI myocarditis, although these findings are not specific for myocarditis. More than half of ICI myocarditis cases present with preserved ejection fraction, although these patients have prognoses similar to those with reduced ejection fraction. Global longitudinal strain (GLS) predicts worsened outcomes irrespective of LVEF. With respect to major adverse cardiac events, every 1% decline in global longitudinal strain is associated with a 1.5-fold increase in depressed ejection fraction (HR = 1.5, 95% CI = 1.2,1.8) and a 4.4-fold increase in preserved ejection fraction (HR = 4.4, 95% CI = 2.4,7.8).[237] CMR is the preferred method for noninvasive imaging diagnosis of acute ICI myocarditis, with abnormalities in T1- and T2-weighted imaging sequences using the updated Lake-Louise Criteria.[238] Both a diagnostic CMR and a new troponin elevation are sufficient to make a clinical diagnosis of ICI-myocarditis.[32] However, the sensitivity of CMR was low in the international cohort registry, demonstrating elevated T2-weighted signal/edema in only 28% of patients with diagnosed ICI myocarditis, which may be due to the time from the initial presentation to CMR, lack of consistent parametric imaging and initiation of treatment with high dosages of corticosteroids prior to imaging.[239]

Invasive Diagnostic Strategies

Endomyocardial biopsy is considered the gold standard for diagnosis of ICI myocarditis. Histologic diagnosis is based on the Dallas Criteria and requires both an inflammatory infiltrate and myocyte loss,[240] with dense inflammatory infiltrate and myocyte loss that resembles acute cellular transplant rejection.[61] Classically, the inflammatory infiltrate in ICI myocarditis has a patchy myocardial infiltration. The immunohistochemical staining will show a predominantly CD8 T cell infiltrate in a 2:1 ratio with CD4 T cells.[61,241] Additionally, there is often a monocyte/macrophage lineage infiltrate with CD68+ immunohistochemical staining and positive PD-L1 staining of cardiomyocytes.[61] In order to limit sampling error leading to false-negative pathologic diagnosis, a minimum of 5 endomyocardial biopsy samples should be obtained.[61,242] Endomyocardial biopsy should be performed at high-volume centers with pathologists experienced in ICI myocarditis and/or heart-transplant rejection. Advanced HF specialists are often involved in the management of patients who have suspicion for ICI myocarditis, when there is consideration for endomyocardial biopsy, such as in patients with cardiogenic shock. Endomyocardial biopsy in lieu of CMR might be warranted in clinical situations, including hemodynamic instability or inability of a patient to breath hold safely. Left- and right-heart catheterizations with coronary angiography are often performed concomitant with biopsy to rule out other cardiac diagnoses and to better define cardiac hemodynamics. The presence of CAD on coronary angiogram can occur concomitantly with ICI myocarditis and should not rule out myocarditis or obviate the need for endomyocardial biopsy.[243,306] Using a combination of the above testing, a diagnosis of ICI myocarditis can be made based on certaintly adjudication criteria,[232] and growing data incorporating severity grading will be important in further refining management. Table 7 shows key elements of proposed diagnostic criteria and management of ICI myocarditis.

Heart Failure Diagnosis and Management of Special Populations

Radiation Therapy-Induced Heart Failure and Cardiomyopathy

Therapeutic radiation to the mediastinum or thoracic region increases the risk for development of CM and HF

by direct toxicity and indirectly due to CAD, valvular heart disease, pericardial disease, and conduction disease.[72,182] Pericardial disease is a recognized complication of chest RT of particular importance to the HF clinician. The exact incidence is hard to estimate, in part, due to heterogeneity and often long delay between exposure to clinical presentation, as well as due to limited understanding of contributing factors.[244] Acute pericarditis and radiation-induced pericardial effusion may occur early after chest RT, but pericardial effusions have also been reported months to years afterward,[245,246] in which case it may be difficult to ascribe the etiology to chest RT. Delayed effects, in particular, of high-dose RT, can include pericardial thickening and clinical constrictive pericarditis, manifesting many years after treatment.[247,248] Pericardial stripping for RT-associated constrictive pericarditis should be approached cautiously, because it is associated with adverse outcomes,[249] often due to the presence of concomitant myocardial restriction. Although RT typically causes restrictive CM, dilated CM may be observed when RT is administered with anthracyclines. Importantly, high-dose radiation can present as myocardial (eg, restrictive CM) and pericardial (eg, constrictive pericarditis) abnormalities in the same patient; thus, careful evaluation with consideration of myocardial/pericardial/vascular mechanisms is warranted in patients with histories of chest RT presenting with HF.[250]

There is a dosage relationship for CVD and RT dosages; for example, among female patients with breast cancer in Denmark and Sweden, major cardiac events increased by 7.4% per radiation Gray unit of mean heart dose, irrespective of preexisting CV risk factors.[251] Long-term studies of CV morbidity and mortality have largely analyzed older RT techniques and dosages, and significant alterations have been made to RT delivery with contemporary cancer management to reduce radiation exposure. For patients with breast cancer, these include the use of a breast board to improve angling of RT delivery, prone positioning to reduced dose to the heart, and gating and breath alterations.[252,253] During the past few decades, advances in RT practices, such as intensity-modulated RT, prone positioning, deep inspiratory breath hold, and proton therapy, have significantly lowered the risk of RT-induced CV disease.[254] These changes have likely contributed to the declining trends in CV mortality after RT treatment among female patients with breast cancer observed from 1975−2017[255]; however, given the latency of RT-induced heart disease, epidemiological studies with sufficient follow-up will be necessary to quantify accurately the CV risk associated with modern radiation techniques.

Management of RT-induced CM and HF follows the guidelines developed for the general population.[80,256] In general, cardiac surgery in patients who have received RT is associated with worse outcomes than those in nonradiated patients,[257,258] and individualized approaches are needed that weigh the benefits and risks of percutaneous coronary revascularization[259] and/or transcatheter aortic valve replacement.[260] In patients with advanced HF secondary to RT-associated restrictive CM, transplantation remains the treatment of choice, but it is associated with increased early post-operative mortality rates compared to other restrictive cardiomyopathies.[261]

Pulmonary Hypertension Related to Cancer Treatment

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure $\geq$ 20 mmHg at rest[262] and can be classified by the 6th World Symposium on PH groups 1−5.[263] Cancer therapy-related PH has been associated with all PH groups and can be related to cancer itself and cancer therapies, including venous thromboembolism (VTE), direct tumor invasion or extrinsic compression of pulmonary vasculature.[264,265] Although cancer therapy-related PH is rare and generally reversible, it can potentially be fatal.[265] Cancer treatment-related causes of PH can be categorized based on World Health Symposium groups.

Group 1 PH: TKI therapies have been associated with group 1 PH. In clinical trials for chronic myelogenous leukemia, incident PH was reported in 2.4% of patients treated with dasatinib, a second-generation BCR-ABL inhibitor.[266] In a report from the French PH Registry, the majority of patients who developed PH after taking dasatinib presented with NYHA class III/IV symptoms that improved after dasatinib discontinuation and initiation of PH-directed pharmacotherapy.[268] Most patients showed normalization of pulmonary arterial pressures; however, a third of patients had persistent PH. Dasatinib targets the Src family of TKIs, and it is hypothesized that Src-mediated vasoconstriction, rather than vascular remodeling, leads to the reversible PH seen with dasatinib.[268] Although isolated cases have been reported with other TKIs,[265] the most consistent evidence has been with dasatinib, and PH has not been considered a class effect. Proteosome inhibitors, bortezomib and carfilzomib, used in multiple `myeloma, have also been reported to cause group 1 PH, although the incidence of PAH with these agents is rare.[55] Pulmonary veno-occlusive disease is a rare and severe complication observed in patients undergoing HSCT and is associated with a particularly poor prognosis. Pulmonary veno-occlusive disease is characterized by remodeling and obliteration of small pulmonary veins and is believed to be mediated by alkylating chemotherapeutic agents and radiation used during HSCT conditioning regimens. Cyclophosphamide and mitomycin have been associated with pulmonary veno-occlusive disease in both animal models and humans.[266,269]

Group 2: Several cancer agents, including anthracyclines and certain targeted therapies, can cause LVD and HF

and, in turn, lead to the development group 2 PH.[262] These agents are discussed elsewhere, including in Table 1 and Table 2.

Group 3: Bleomycin, busulfan and thoracic radiation may cause lung parenchymal disease, including acute lung injury and interstitial pulmonary fibrosis/hypoxia, leading to group 3 PH.[265]

Group 4: Chronic thromboembolic PH can be associated with both malignancy itself and cancer therapies. Cancer is a hypercoagulable state that is associated with an increased risk of VTE.[270] This risk is higher in certain malignancies (hematologic cancers, gastrointestinal tumors, brain tumors, and lung cancer) and in patients with distant metastases.[270,271] Treatment factors, such as hospitalization, surgery, central venous catheters, and certain anticancer agents, also increase the risk of VTE and, consequently, group 4 PH.[271] Cancer therapies associated with an increased risk of VTE include platinum-based agents (cisplatin and carboplatin),[272] tamoxifen,[273] immunomodulatory agents, such as thalidomide, lenalidomide and pomalidomide,[274] epidermal growth factor-targeted antibodies (cetuximab, panitumumab, necitumumab),[275] second- and third-generation BCR-ABL inhibitors (dasatinib, nilotinib and ponatinib),[276,277] and cyclin-dependent kinase inhibitors (especially abemaciclib).[271]

Group 5: Group 5 PH in patients with cancer comprise a group of multifactorial and poorly understood conditions.[32] Tumoral PH includes a group of tumor-related disorders, including pulmonary micro emboli and thrombotic microangiopathy that can be difficult to diagnose and treat and are associated with poor prognosis.[278]

Diagnosis and Management of PH in Patients with Cancer

To diagnose PH in patients with symptoms or signs of right-sided HF, TTE is recommended to assess pulmonary arterial pressures and RV function. Confirmation of PH typically requires right-heart catheterization, and treatment should follow established guidelines.[262] In cases of dasatinib-associated PH, discontinuation of dasatinib is recommended in all patients with suspected PH, and alternative BCR-ABL inhibitors should be considered for confirmed cases.[32]

Patients Undergoing Bone Marrow/Stem Cell Transplantation

Hemopoietic stem cell transplantation (HSCT) is a potential curative treatment for various malignant and nonmalignant hematopoietic disorders, but it has been associated with both early and late CM and HF. Autologous HSCT recipients have a 4.5-fold higher risk of symptomatic HF compared to the general population during their lifetimes.[279] In a contemporary multicenter trial of adult patients with autologous or allogeneic HSCT, investigators reported HF incidence at 1.1% at 100 days and 5.4% at 5 years.[280] Among the common factors influencing the development of HF are conditioning regimens that include anthracyclines, cyclophosphamide or alkylating agents, chest RT, the presence of CV risk factors before or after HSCT, and the development of graft vs host disease.[279,281] Conditioning regimens, typically involving high-dose alkylating agents (eg, cyclophosphamide) sometimes in combination with total body irradiation are administered prior to HSCT to achieve adequate immunoablation, prevent graft rejection and reduce tumor burden. Cyclophosphamide has also been increasingly used post-allogeneic HSCT as a preventive strategy for graft vs host disease. A retrospective study comparing patients treated with and without post-transplant cyclophosphamide found that its use was associated with an increased incidence of CM within the first 100 days after HSCT.[38] Further, both pre- and post-transplant cyclophosphamide was predictive of adverse CV events.[38] In contrast, another study found that post-, but not pre-transplant, cyclophosphamide was associated with an increased risk of early adverse CV events after allogeneic HSCT.[282] Other risk factors for early post-transplant CM include pre-existing CV disease, total body irradiation, severe acute Graft-versus-host disease (GVHD), and sepsis.[282–284] These adverse events have been associated with increased post-HSCT mortality rates.[38,282,283]

Induction chemotherapy, which is administered before HSCT to achieve disease control, often includes anthracyclines (eg, 7+3 regimen containing cytarabine for 7 days and daunorubicin or idarubicin for the first 3 days), which are known to increase risk of CM and HF. In a case-control study of patients after HSCT who survived for at least 1 year, cumulative anthracycline dosage $\geq$ 250 mg/m^2, a greater number of pre-HSCT chemotherapy cycles, and $\geq$ 2 comorbidities after HSCT were independently associated with late HF.[285] To reduce the risk of cardiotoxicity in patients with high baseline risk, alternative induction regimens that do not include anthracyclines or use of liposomal anthracycline formulations such as CPX-351 are being investigated.[120]

Risk models for long-term cardiotoxicity among HSCT recipients often assign points to various risk factors, such as age, HTN, DM, smoking history, anthracycline dose, and chest radiation (including total body irradiation of $>$ 2 Gy).[286] Patients with higher risk scores are more likely to develop HF.[286] The Cardiovascular Registry in Bone Marrow Transplantation (CARE-BMT) risk score is a present-day risk calculator that can be used to predict 5-year CV outcomes, including HF, in high-risk patients.[280] The NCCN guidelines recommend a baseline ECG and TTE before HSCT for all patients and cardiology consultation for those with compromised LVEFs.[287] The presence of

CM with moderate to severely reduced LV systolic function has traditionally been considered a contraindication to HSCT. Although there is no specific guidance, and LVEF cutoffs are center-dependent, patients with moderate−severe symptomatic systolic dysfunction may not be suitable candidates for HSCT but, conversely, patients with asymptomatic systolic dysfunction might not necessarily need to be disqualified. In single-center studies, authors suggested that patients with borderline or mild cardiac dysfunction or with histories of ischemic heart disease require increased awareness and monitoring.[288,289] A comprehensive approach of primary CV risk stratification and secondary cardio-oncology monitoring is proposed to foster early implementation of preventive and treatment strategies.[290] The 2022 ESC Cardio-Oncology Guidelines additionally recommend CV risk-factor assessment and modification, ECG and TTE 3 and 12 months after HSCT in high-risk recipients.[32] Long-term surveillance involves annual CV risk-factor assessment and modification, combined with a detailed CV history and examination to guide further testing as needed.

Pregnancy, Cancer Therapy and Heart Failure

Approximately 60% of childhood and adolescent cancer survivors are treated with anthracyclines or chest radiation, and 1 in 640 young adults between 20 and 39 years of age is a cancer survivor.[291] The physiological changes in pregnancy can lead to decompensated HF and arrhythmias in patients with established HF or CM and, thus, pre-pregnancy cardiac risk assessment is recommended for patients with prior cardiotoxic cancer therapy who are considering pregnancy.[32,94] Risk factors for HF during pregnancy include a history of prior cancer therapy-associated cardiotoxicity, LV systolic dysfunction on antenatal TEE, cumulative anthracycline dosage, age at cancer diagnosis, and time from cancer treatment to pregnancy.[292−294] Current data are limited to several single-center cohorts, which indicate that cancer survivors without histories of cancer therapy-associated cardiotoxicity and with normal LVEFs prior to conception have low rates of HF or other cardiac events during pregnancy (< 1%).[292,293] In a meta-analysis of 6 single-center cohort studies, overall risk of HF or LVEF decline was 1.7% among cancer survivors with prior cardiotoxic cancer therapy, and there were no maternal mortalities.[292] However, in a single-center study of 94 pregnant cancer survivors with prior exposure to cardiotoxic cancer therapy (with LVEF declines or abnormal LVEF on antenatal TEE), the risk of HF during pregnancy was 31%.[293]

Although data for cancer survivors are limited, the CARPREG II (Cardiac Disease in Pregnancy Risk Index) and the World Health Organization tool can be used to provide risk stratification for shared decision making in females with cardiac disease who are contemplating pregnancy.[295−297] Cancer survivors with prior chest RT are at risk for valvular heart disease and CAD in addition to HF. All patients with prior histories of anthracycline or chest RT exposure should have a TTE prior to or in the first trimester of pregnancy in addition to history, physical examination and assessment of functional capacity. Patients with prior or current CM should receive multidisciplinary preconception counseling about the potential maternal and fetal risks of pregnancy and, if pregnancy is pursued, they should be monitored closely by a multidisciplinary team with experience in the management of HF during pregnancy.[32,94,296,297] Risk stratification and management of these conditions during pregnancy are reviewed in recent guidelines and scientific statements.[296,298] In certain very high-risk conditions, such as LVEF < 30%, NYHA class III/IV symptoms, severe mitral or aortic stenosis, LVAD in place or heart transplant with reduced allograft function, avoidance of pregnancy or termination are typically recommended. Shared decision making is critical, given the very high risk of maternal mortality and morbidity in observational studies.[296,297] If conception is not desired, females with established CM or HF should receive information about the risks and benefits of various contraception options. Intrauterine devices are typically preferred over combination oral contraceptives in patients with severely reduced LVEF, given concerns about thrombotic risk and worsening HF with estrogen-containing contraceptives.[296]

Stress Cardiomyopathy in Patients With Cancer

The occurrence of stress CM in patients with cancer has been increasingly recognized in recent years,[299] and the onset of stress CM is variable, ranging from the initial administration to subsequent therapy cycles several weeks beyond initiation. Prior research has demonstrated that stress CM is associated with 5-fluorouracil and its derivatives[300] and other chemotherapeutic and targeted therapies (eg, cytarabine, capecitabine, TKIs).[301] Among patients with clinical presentations of stress CM while on ICIs, it is critical to rule out checkpoint inhibitor-associated myocarditis, because the treatment of the 2 conditions is very different.[302]

Limited data are available concerning stress CM among cancer patients, and 1 case series study over a 12-year period documented 373 patients who presented with ACS, met the modified Mayo criteria for stress CM,[303] and underwent coronary angiography.[299] Of the patients, 22% met criteria for stress CM; 70% were female, 29%. had undergone chemotherapy, 9% had immunomodulatory therapy, 5% had RT-associated stress CM, 27% had physical medical conditions as the cause; 22% of the cases were related to procedures, and only 9% were associated with emotional triggers. In general, poor clinical outcomes were related to the underlying cancer rather than the stress CM, with recovery of cardiac function highest in those with emotional triggers and lowest in chemotherapy-associated triggers.[299] It is estimated that chemotherapy treatment accounted for overall 1%−2% of stress CM

triggers, and that females comprised a slightly lower percentage of patients with cancer (60%–70%) compared to those in the general population with stress CM (90%).[301] However, it is difficult to disentangle direct myocardial toxicity related to the chemotherapy vs true stress CM as the sole etiology of LV dysfunction, as well as separating pure emotional stress from the psychological and physical stress that parallels the diagnosis, treatment and follow-up of cancer.

General principles in the management of stress CM in patients with cancer are the same as those recommended in patients without cancer.[304] However, having a stress CM event in the setting of chemotherapy is associated with substantial mortality rates,[305] requiring cessation of chemotherapy until the acute episode of stress CM is addressed. There are limited data concerning the safety of reinitiation of the offending chemotherapy after recovery from the stress CM. Management should include shared decision making with the patient and a careful risk-benefit assessment consideration for alternative cancer therapies when feasible. Close monitoring is necessary if chemotherapy is reinitiated. Similar to the care of stress CM in the general population, there are limited data to support a cardioprotective medication strategy to improve outcomes and reduce reoccurrence, as prior studies suggest that beta-blockers did not reduce the risk of recurrence. whereas ACE inhibitors or ARB therapies were associated with lower risks of recurrence.[306,307] In more recent data, beta-blockers led to mitigation of reoccurrence.[308] Whether routine use of neurohormonal blockade is beneficial in the long-term care of patients with cancer and stress CM in the absence of persistent LV systolic dysfunction is unknown.

Cancer Survivorship and Heart Failure

Despite advances in cancer care and survivorship, cancer survivors do not have the same life expectancy as individuals without cancer, even when cured of their cancer.[309–311] Depending on their age at cancer diagnosis and the types of treatment received, cancer survivors are at an elevated risk for CVD and secondary cancers, as well as other late effects that can affect quality of life and functioning, such as loss of muscle and bone mass, infertility and premature menopause. For the HF specialist managing a cancer survivor, understanding a patient's cancer-treatment history, including age at diagnosis, type and dosages of chemotherapy, radiation field and mean heart dosage, is essential to providing comprehensive CV care. Appreciation of these key components in a patient's cancer history will aid in understanding their overall cardiac risk as well as their risk of second cancers, which are the 2 of the leading causes of death in this population of patients. A cancer-treatment summary or survivorship care plan has been proposed by the Institute of Medicine and by the Commission on Cancer,[312] although implementation is limited due to lack of time and resources. It is important for HF specialists to be aware that many cancer survivors lack details about their cancer histories. Obtaining records detailing prior cancer treatments is essential to providing risk-stratified screening and treatment recommendations unique to each cancer survivor. Innovative solutions to providing patients with their own cancer-therapy records for any future use are much needed.

The spectrum of CVD affecting cancer survivors can vary depending on the types of cancer therapy received, and in many situations the CV mortality rate surpasses the cancer mortality rate.[313] For example, childhood cancer survivors who have received anthracyclines and chest radiation are at substantially elevated risk for HF, ischemic heart disease, and valvular heart disease.[314,315] Survivors of testicular cancer receiving platinum- based chemotherapies are at elevated risk for endothelial dysfunction and ischemic heart disease.[316] Survivors of breast cancer who have received trastuzumab-based chemotherapy without anthracyclines or radiation are still at elevated risk for HF, but the risk is substantially higher in those who also received anthracyclines and/or radiation.[317] Cardiac-risk factors such as HTN substantially amplify the risk of these CV complications in cancer survivors but are often not managed optimally.[318] In addition, antihypertensives are frequently discontinued during treatment and not restarted.[315,319]

For survivors of childhood, adolescent and young-adult cancers (CAYA), consultation with a survivorship clinic can help to provide recommendations for risk stratification, secondary cancer screening and cardiac surveillance monitoring. Although there are small differences in recommendations, surveillance TTE is recommended every 2 years for childhood and young-adult survivors of cancer at highest risk for HF by both the Children's Oncology Group survivorship guidelines[104] and the International Late Effects of Childhood Cancer Guideline Harmonization Group,[94] with the elimination of surveillance screening for those at the lowest risk (Table 4). Ischemic evaluation is recommended in patients who have received high dosages of chest RT, although prospective data are lacking to support routine screening, particularly with modern RT techniques.[320] Importantly, many CV risk calculators underestimate individual cancer survivors' actual CV risk, because they do not account for these treatment effects.[321,322] Risk calculators, such as those put forth by the Childhood Cancer Survivor Study[323] and resources for providers and patients,[324] are available to help estimate risk.

For adult survivors of cancer, guidelines recommend CV risk-factor modification with aggressive optimization of BP, lipids, maintenance of ideal body weight and, for all high-risk survivors who received cardiotoxic cancer therapy, to have a TTE post-cancer treatment and during other high-risk situations (ie, pregnancy after

anthracyclines), although timing and frequency depend on source and individual patient.[32,96] Additionally, cancer rehabilitation and exercise are essential in minimizing CV risk and associated accelerating aging in the cancer survivor.[325] Finally, primary care providers (PCPs) play a vital role in cancer survivorship, addressing not only late and long-term side effects, but also with identification and management of new and pre-existing comorbidities. Transitioning from active disease to survivorship poses many challenges.[326,327] This, along with the diversity of patients, contributes to the importance of including PCPs in overall care teams to ensure implementation of management strategies to minimize CV risk.

Although pathways for referral of cancer survivors to an HF clinician are not well defined, expected clinical scenarios for referral to a HF clinic might include patients along the spectrum of stage A through stage D HF, including those with HFpEF, concerns for constrictive/restrictive CM, autonomic dysfunction, accelerated and complex valvular or atherosclerotic disease, or other complex cases that might be better served by a subspecialty cardiology service.

Role of Palliative Care in Cardio-oncology

The overarching goal of palliative care in patients with cancer and HF is to enhance the patients' care experience by focusing on quality of life for patients and families and is an integral component of comprehensive care.[328] Multiple issues confronting these patients present challenges to decision making, especially surrounding the decision about the appropriate timing of palliative care. Informed and collaborative decision making between patients and their families and with cardiology and oncology teams is challenging but essential. For example, cancer and HF can become a chronic disease that requires longitudinal symptom management and, for other patients, cancer remission and relapse might lead to additional cardiotoxic treatment exposure and can compound risk. Patients with cancer and HF require attention to the complex balance between the 2 disease states, at times with the need to harmonize aggressive cancer treatment with the risk of cardiotoxicity and quality or quantity of life. These difficult conversations should address the complex questions of whether more invasive therapies are feasible, which patients will derive benefit, and at what cost these therapies will come.

Given the complexity of management in patients with cancer and HF, the involvement of palliative care should be considered early, with the goal of overall improvement in quality of life, symptom management, psychological stress mitigation, and spiritual well-being and as a tool for shared decision making and coordination of resources and medical care among patients, caregivers and the medical team.[329] There is growing interest in leveraging the existing experience of palliative care in oncology and HF, respectively, and merging this understanding with a more integrated model that best serves the cardio-oncology population. This initiative is supported by growing clinical research and organizations such as the World Health Organization[330] and the National Academy of Sciences.[331] Professional societies, such as the American College of Cardiology,[83] ASCO,[96] and the NCCN[332] recommend improving access to palliative care. The Palliative Care and Hospice Education Training Act, advocating expanded training for all levels of health care professionals, was submitted to the U.S. Senate in July 2023.[333] Both the adoption of existing recommendations and the merging of palliative care experience in oncology and HF populations will propel the implementation of palliative services in cardio-oncology.[334] As the field evolves, cardio-oncology training should include formal palliative training (Fig. 3).

Multidisciplinary Approach and Coordination of Care With Oncology

The field of cardio-oncology is a multidisciplinary, collaborative specialty involving a network of dedicated professionals whose collective goal is to provide coordinated and cost-effective, specialized CV diagnosis and management in patients with cancer at all stages of the cancer journey. A dedicated cardio-oncology service can facilitate optimal CV treatment that enables completion of cancer therapy to achieve an optimal cancer outcome.[335,336]

The objectives of an effective cardio-oncology team include management of cardiotoxicity across the cancer treatment continuum: (1) prior to initiating cancer therapy, comprehensive risk stratification through the identification of CV risk factors and cancer therapy-related factors and timely and aggressive management of risk factors; (2) during cancer treatment, early detection of CTRCD using biomarkers and advanced imaging when appropriate and prompt management of cardiotoxicity and related symptoms to minimize alteration, interruption or discontinuation of cancer treatment; and (3) post cancer treatment, optimization of preventive strategies, screening for late-onset CV effects of cancer therapies and continuous reassessment of emerging CV risk. The objectives and goals of the cardio-oncology team are summarized in Fig. 3.

The multidisciplinary nature of cardio-oncology necessitates a team-based approach to care, devoid of "silos" of practice. The cardio-oncology team typically includes *core* members (medical, radiation and surgical oncologists, hematologists, cardiologists, clinical pharmacists, and specialized nurses) and *support* members (patients' internists and/or family care practitioners or general practitioners, cardiac surgeons, cardiologists specialized in other domains, pathologists, radiologists, palliative care team, clinical laboratory specialists, psychologists, social

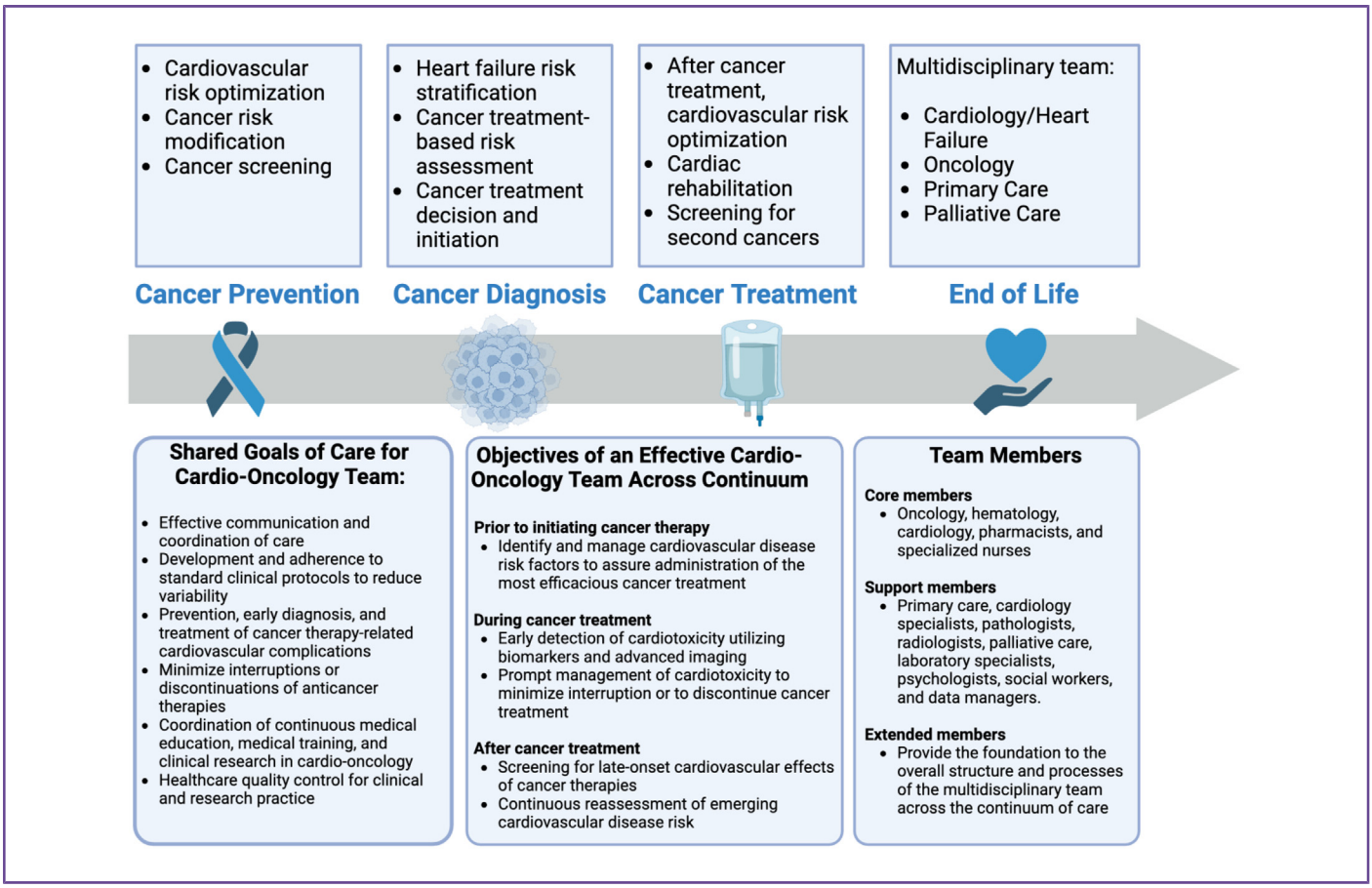

Fig. 3. Multidisciplinary team approach to cardio-oncology and heart failure. Multidisciplinary team approach spans from the time of cancer diagnosis, during treatment and after cancer treatment completion. Goals and objectives of the cardio-oncology team aid with coordinated and optimized care.

workers, research and clinical team support staff). In addition, *extended* members such as HF specialists add to the overall structure and processes of the multidisciplinary team across the continuum of care. The composition of the cardio-oncology team and models of care may vary based upon hospital size and organization (eg, structures of the local health service, hospitals and their specializations) as does the scope of cardio-oncology services offered. [32,335,336]

The roles of the nurse navigator, clinical pharmacist and clinical researcher/clinician scientist in ensuring optimal delivery of care and high-quality outcomes cannot be overstated. Serving as an advocate for the patient at all care intersections, nurse navigators work to eliminate administrative barriers to the numerous health care entities in addition to providing continuous education to patients and providers to facilitate informed decision making.[206,337] Clinical pharmacists play a critical role in streamlining access to cancer and CV therapies (eg, prior authorization), providing guidance on optimal dosing of cancer and CV therapies, avoidance of drug-drug interactions and addressing therapy intolerability.[338] Cardio-oncology researchers and clinician scientists contribute to the availability of investigational therapies for patients intolerant of standard cancer options due to cardiotoxicity, and they contribute to the incorporation of translational research findings into clinical practice.

The key to the success of a cardio-oncology program within the context of a HF center is the implementation of established criteria for appropriate patient referral to cardio-oncology and HF clinics. Other aspects of cardio-oncology care should also be streamlined for patients with cancer, including protocols for cardiac imaging and reporting, pretreatment CV risk assessment during and post treatment surveillance, and management. Multidisciplinary development and implementation of standards help to facilitate clear diagnostic testing, early interventions in cases of clinical and subclinical toxicity, and clinical decision making regarding continuation, modification, interruption, and reinitiation of cancer therapy.

Coordinated multidisciplinary care requires institutional support to build an effective cardio-oncology infrastructure, allowing for collaborative development and innovative solutions to overcome the challenges of everyday practice, ensuring more seamless coordination of care and timeliness of cardiac expertise for patients with cancer. Regular multidisciplinary cardio-oncology team meetings including HF clinicians, as well as organized software

with automated tools, may further optimize care (eg, data tracking to guide multidisciplinary decision making and coordination of care).

Health Disparities and Social Determinants of Health Across the Spectrum of HF in Patients with Cancer

Despite declines in cancer-incidence rates in the U.S., individuals from racial and ethnic minoritized populations continue to experience disproportionately higher rates of mortality due to cancer.[339] Additionally, there is a greater CVD burden among racial and ethnic minorities and within lower socioeconomic communities.[340–342] Inequities in cancer screening, care, and treatment, combined with the increased risk of heart disease after cancer, in part due to cancer therapies, likely contribute to inequities in HF incidence and mortality rates among patients with cancer, particularly by race and ethnicity, neighborhood environments, socioeconomic status, sex and gender, and cultural factors. These disparities are also related to the downstream effects of systemic and structural racism, which are embedded into whole systems and their structural components (eg, laws, policies, practices).[343]

Non-Hispanic Black patients with cancer are more likely to die of CVD than their non-Hispanic white counterparts,[344–347] especially among patients with breast cancer who are living longer and often receive cardiotoxic cancer treatments. These racial disparities are nearly 2 times greater among non-Hispanic Black patients diagnosed at younger ages (< 55 years).[346] When compared to the race- and ethnic-matched general populations, non-Hispanic Black, non-Hispanic Asian American, Native Hawaiian and other Pacific Islanders (NHPI), and Latinas, breast cancer survivors have elevated rates of mortality due to heart disease, persisting with advanced stage or chemotherapy. In contrast, non-Hispanic breast cancer survivors had a lower CV mortality rate compared to the general population.[348] A prior study reported lower CVD mortality rates among Asian American and NHPI individuals as an aggregate[349]; however, Asian American individuals are a distinctly different racial group from NHPI individuals, and aggregating data can often mask disparities for NHPI populations, who often have higher cancer mortality rates compared to those of other racial and ethnic groups.[350] Non-Hispanic Black patients with breast cancer are more likely to experience declines in LVEF after treatment with trastuzumab,[351,352] and non-Hispanic Black and Hispanic patients are less likely to receive clinical guideline-recommended cardiac surveillance (eg, TTE) compared to non-Hispanic white counterparts.[353] Survivors of breast cancer and adolescent and young-adult cancers living in lower socioeconomic status and more rural areas were more likely to die of CVD compared to those living in higher socioeconomic status and more urban areas.[354–356] There is a paucity of studies assessing agender, asexual, bisexual, gay, gender diverse, genderqueer, genderfluid, intersex, lesbian, nonbinary, pansexual, queer, and transgender (LGBTQI+) populations in cardio-oncology. Importantly, LGBTQI+ populations have worse health outcomes than their non-LGBTQI+ counterparts, yet insufficient evidence exists for the relationship between hormone therapy and cancer or CVD risk.[357]

Mechanisms resulting in health-care inequities for CV care of patients with cancer are likely related to various factors. These include delayed screening, resulting in later cancer stages and more aggressive or cardiotoxic cancer treatment[358–360], less access to high-quality health care, cardio-oncology specialists or cardioprotective strategies and established cardiac treatments,[361–366], environmental barriers to care, such as transportation or proximity to high-quality health care,[367,368], implicit bias among health care providers, and lack of inclusion of minorities in clinical trials.[369,370] Proposed strategies to mitigate health care inequities and reduce barriers include the use of community-based programs and/or community-outreach activities to identify problems and solutions, inclusion of community and cultural partners/stakeholders in research, collection of detailed racial and ethnic data, inclusion of diverse clinical trial participants, and conducting studies of disparities in HF care among patients with cancer.

Future Directions and Gaps in Knowledge

At present, there are several major gaps in the field of cardio-oncology as it intersects with HF. There is paucity of clinical trials with longer term follow-up to inform risk-stratification and HF management specific to patients with cancer, particularly in patients with symptomatic HF at the time of cancer diagnosis. New approaches, including innovative trial design, are required to meet the needs of the growing population of high-risk oncology and HF patients. Rapid developments in cancer therapeutics exponentially increase the complexity of our understanding of the mechanisms of CV toxicity and present a challenge in the paradigm of HF risk vs oncology benefit. Cancer therapy-related CV toxicity definitions need to align with contemporary cardiology and HF standards more seamlessly, and both need to be incorporated into oncology clinical trials' adverse outcome reporting. The understanding of individual susceptibility and risk of cancer treatment-related toxicity is an area ripe for further research. Critical to the field are the applications of HF genetics and basic and translational research into shared pathophysiology mechanisms between cancer and HF. Validation of the proposed risk-prediction models of cancer-treatment-related toxicity is needed in large cohorts of

patients with specific malignancies and should include long-term follow-up. The HF community remains a critical partner with oncology to address the growing needs in this complicated population of patients in a multidisciplinary and patient-centric collaboration that integrates all aspects of the care of the cardio-oncology patient.

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Disclosures

MWB reports compensation for serving as faculty or as a speaker for a medical education program and consulting fees for Astra Zeneca. AN receives research support from Bristol Myers Squibb and consulting fees from AstraZeneca and Takeda Oncology. AD reports being a consultant for Bayer. NP reports support from the Cancer Prevention & Research Institute of 23 Texas (CPRIT) RP200670, NIH/NCI 1P01CA261669-01, Andrew Sabin Family Foundation, Replimmune, and Kiniksa. Pharmaceuticals. BK reports consulting for Astra Zeneca, Roche, BMS, IIS, and Pfizer. DL reports consultant fees from Myocardial Solutions, Clementia, OncXerna, AstraZeneca, Roche, SecuraBio, Intellia and Novo-Nordisk. MSM reports grant support from NIH R01HL139671, 1R01AG081582-01 and grants and personal fees from Attralus, Alnylam, Pfizer, Eidos, and Ionis, and personal fees from Astra Zeneca and Intellia. AB reports consulting fees for Astra Zeneca. All other authors report no disclosures.

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