Cancer Therapy–Related Cardiac Dysfunction and Heart Failure

Part 1: Definitions, Pathophysiology, Risk Factors, and Imaging

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Abstract—Advances in cancer therapy have resulted in significant improvement in long-term survival for many types of cancer but have also resulted in untoward side effects associated with treatment. One such complication that has become increasingly recognized is the development of cardiomyopathy and heart failure. Whether a previously healthy person from a cardiovascular perspective develops cancer therapy–related cardiac dysfunction or a high-risk cardiovascular patient requires cancer therapy, the team of oncologists and cardiologists must be better equipped with an evidence-based approach to care for these patients across the spectrum. Although the toxicities associated with various cancer therapies are well recognized, limitations to our understanding of the appropriate course of action remain. In this first of a 2-part review, we discuss the epidemiologic, pathophysiologic, risk factors, and imaging aspects of cancer therapy–related cardiac dysfunction and heart failure. In a subsequent second part, we discuss the prevention and treatment aspects, concluding with a section on evidence gap and future directions. We focus on adult patients in all stages of cancer therapy from pretreatment surveillance, to ongoing therapy, and long-term follow-up. (***Circ Heart Fail*****. 2016;9:e002661. DOI: 10.1161/CIRCHEARTFAILURE.115.002661.)**

Key Words: anthracyclines ■ cardiomyopathies ■ cardiotoxicity ■ chemotherapy ■ heart failure ■ trastuzumab ■ ventricular dysfunction, left

Early detection and treatment has transformed cancer from a uniformly fatal disease to one that in many cases is a chronic condition. Improved survival, however, is often accompanied by treatment-related complications, including adverse effects of cancer therapies on the heart. In the long term, the risk of death from cardiovascular causes exceeds that of tumor recurrence for many forms of cancer.[1,2] Patnaik et al[3] found that cardiovascular disease (CVD) was the leading cause of death among older female breast cancer survivors without an initial diagnosis of CVD. Risk of toxicity was increased in patients with advanced age, multiple comorbid conditions, and in those requiring prolonged or intensive treatment. Cancer therapies including cytotoxic chemotherapy, molecular targeted therapies, and mediastinal irradiation have been linked to myocyte damage, left ventricular dysfunction (LVD), heart failure (HF), thrombogenesis, pericardial pathology, hypertension, ischemia, conduction and rhythm disturbances, and vasospasm.[4,5] HF as a result of cancer therapy has been linked to a 3.5-fold increased mortality risk compared with idiopathic cardiomyopathy[6] In part 1 of this 2-part review, we describe the definitions, pathophysiology, risk factors, and imaging aspects relevant to cancer therapy–related cardiac dysfunction.

Definitions

Several definitions of cancer therapy–related cardiac dysfunction have been proposed, making development of uniformly accepted recommendations for diagnosis, surveillance, and treatment challenging. The National Cancer Institute broadly defines cardiotoxicity as toxicity that affects the heart[7] and proposes the Common Terminology Criteria for Adverse Events that defines LVD and HF based on severity into grades

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1 to 5. Grade 1 is defined as asymptomatic elevations in biomarkers or abnormalities on imaging. Grades 2 and 3 consist of symptoms with mild and moderate exertions. Grade 4 includes severe, life threatening symptoms requiring hemodynamic support, and grade 5 involves death.[8] The Food and Drug Administration defines anthracycline cardiotoxicity as >20% decrease in left ventricular ejection fraction (LVEF) when baseline LVEF is normal, or >10% decrease when baseline LVEF is not normal.[9]

The Cardiac Review and Evaluation Committee supervising trastuzumab trials defines cardiotoxicity as a decrease in LVEF that is either global or more severe in the septum and decline in LVEF of at least 5% to <55% with accompanying signs or symptoms of HF, or a decline of at least 10% to <55% without HF signs or symptoms.[10] Several trials have specified toxicity with different parameters making estimation of the prevalence of cardiac toxicity difficult. In the Herceptin Adjuvant (HERA) trial, definitions of asymptomatic LVEF reductions were different and included decrease by ≥10% from baseline to an LVEF <50%, and HF as above accompanied by symptoms.[11] The Breast Cancer International Research Group (BCIRG) used >10% reduction from baseline LVEF assessment to define asymptomatic LVD.[12] An expert consensus published by the American Society of Echocardiography and European Association of Cardiovascular Imaging, comprised several well-respected cardiologists and oncologists within the field of cardio-oncology, defines cancer therapeutics–related cardiac dysfunction as a decrease in the LVEF of >10%, to a value <53% confirmed by repeat imaging. Further characterization is based on the presence or absence of symptoms.[13] These definitions include arbitrary cutoffs without taking into account baseline risk and are not guided by clinical outcomes. In addition, LVEF-based definition has limitations including variable reproducibility, and the fact that many patients with HF have preserved LVEF. A more comprehensive definition for diagnosis of cancer therapy–related cardiotoxicity should take into account other imaging and biomarker based abnormalities as well.

Classification

Several attempts have been made to classify cardiotoxicity. Ewer and Lippman[14] proposed cardiotoxicity based on the type and extent of structural abnormalities and degree of reversibility. Type I is irreversible and dose related with myocyte injury, whereas type II includes reversibility with cessation of treatment, lack of dose-relationship, and absence of ultrastructural abnormalities. Although intuitive, with anthracyclines as an example of type I and trastuzumab of type II cardiotoxicity, subsequent studies have raised concerns. This classification does not reflect the reality that anthracyclines and trastuzumab are rarely administered as sole agents and are usually shortly preceded or followed with drugs belonging to other classes. Hence, it is likely that the final cardiotoxic effect results from a synergic/combined action. Although anthracyclines and trastuzumab are different in their mechanisms of cardiotoxicity, early recognition and initiation of neurohormonal antagonists may reverse LVD in both cases.[15,16] Trastuzumab cardiotoxicity may be associated with troponin elevation and is not always reversible.[15] Therefore, it is more appropriate to understand the biological mechanisms of cardiotoxicity and the clinical features at different stages of presentation.

Pathophysiology and Epidemiology

Anthracyclines

Anthracyclines (eg, doxorubicin, daunorubicin, epirubicin, and idarubicin) are a class of highly effective chemotherapy agents used for the treatment of many solid and hematologic cancers.[17] In breast cancer, doxorubicin and epirubicin are used in both the neoadjuvant (before definitive surgery) and adjuvant (following definitive surgery) setting, as well as in metastatic patients. The mechanisms of action of anthracyclines include intercalation into nuclear DNA to impair protein synthesis, production of reactive oxygen species, and inhibition of topoisomerase II to inhibit DNA repair. Topoisomerase, an enzyme involved in DNA transcription and replication, is a known target of anthracyclines.[18] There are 2 isozymes of topoisomerase, Top 2-α, expressed in rapidly dividing cells, and Top 2-β, expressed in quiescent cells such as cardiac myocytes.[19] The cardiac toxicity of anthracyclines is thought to be mediated through the binding of these agents to DNA and Top 2-β in cardiac myocytes, resulting in a complex formation that ultimately culminates in cell death (Figure).[20] Older studies suggest an association between cumulative dosing and cardiotoxicity, with diastolic dysfunction reported at doses of 200 mg/m^2 of doxorubicin and systolic dysfunction at 400 to 600 mg/m^2.[21] This has been challenged in recent literature suggests that LVD can occur at any dose as evidenced in 18.9% of patients receiving a doxorubicin dose of 240 mg/m^2 in combination with cyclophosphamide.[22] Factors increasing the risk of anthracycline toxicity include the presence of other CVD risk factors, associated therapies like mediastinal irradiation, and concomitant therapy with agents such as cyclophosphamide, paclitaxel, and trastuzumab.[23] Anthracycline toxicity may be acute, sub-acute, or chronic. Acute toxicity is uncommon (≈1%) and generally reversible, whereas early-onset chronic progressive toxicity (1.6–2.1%) developing during treatment and late-onset chronic progressive types (1.6–5%) are more likely to be irreversible.[24] This classification has been challenged as possible evolution of one phenomenon being clinically identified at various stages.[16]

Alkylating Agents

Alkylating agents (eg, cyclophosphamide, ifosphamide, and melphalan) inhibit DNA transcription, thereby affecting protein synthesis.[25] Agents such as cyclophosphamide have been associated with development of LVD in 7% to 28% of patients and may be dose related (≥150 mg/kg and 1.5 g/m^2 per day), occurring shortly after initial administration.[26] LVD has also been observed with ifosfamide at doses that exceed 12.5 g/m^2.[27]

Microtubular Polymerization Inhibitors

Taxanes (eg, paclitaxel and docetaxel) bind to and inhibit disassembly of microtubules, interrupting cell division.[28] Taxanes interfere with the metabolism and excretion of anthracyclines and may potentiate LVD risk, particularly with high-dose anthracycline use. HF incidence with these agents is relatively low, with a reported 1.6% versus 0.7% incidence in patients

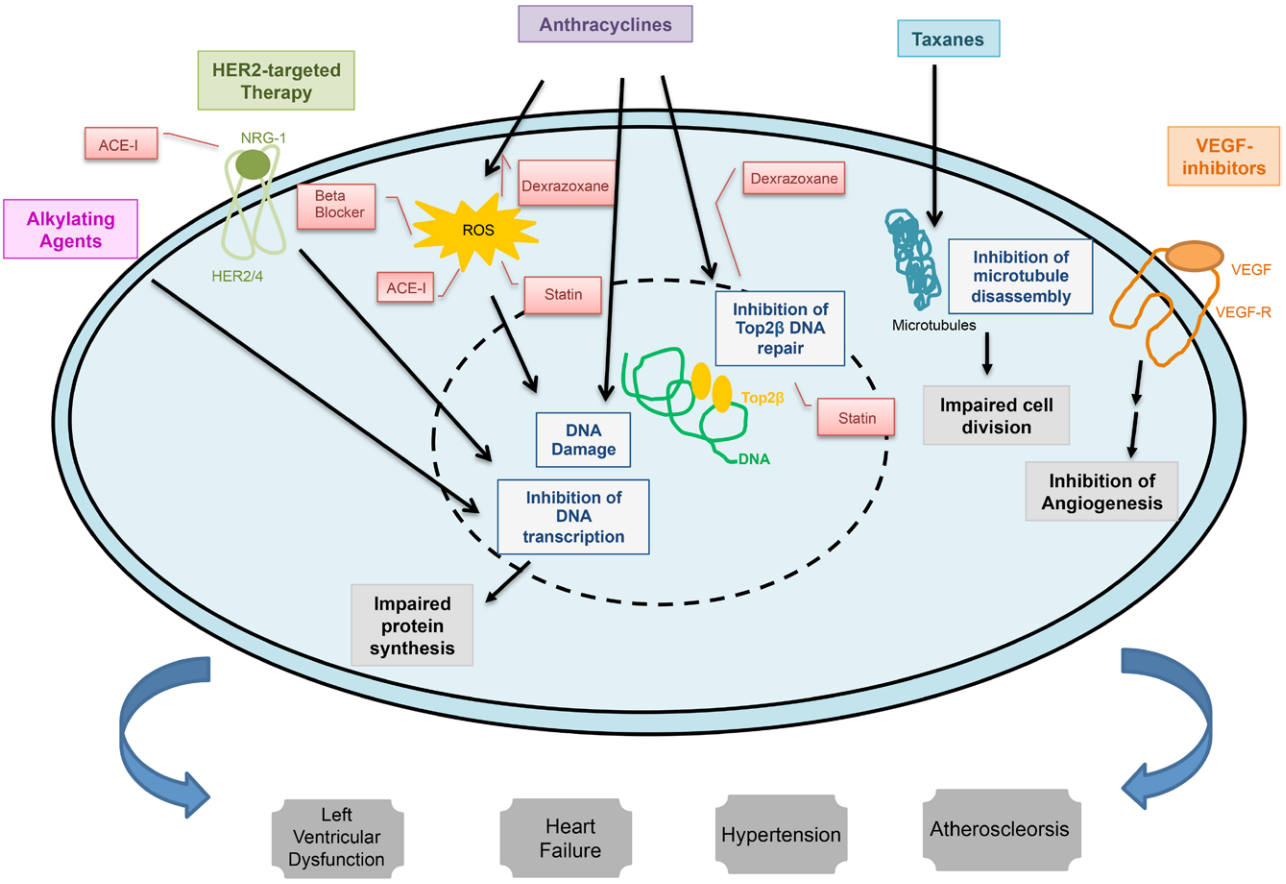

Figure. Pathophysiology of cardiac toxicity from various chemotherapeutics and role of preventative therapies. Alkylating agents inhibit DNA transcription, impairing protein synthesis. Human epidermal receptor 2 (HER2/ErbB)-targeted therapy inhibits the activation of HER2 resulting in the inhibition of a signal transduction pathway that ultimately impairs DNA transcription. Anthracyclines intercalate into DNA, impairing protein synthesis, generate reactive oxygen species (ROS) resulting in DNA damage as well as inhibit topoisomerase II-beta (Top2B), impairing DNA repair. Taxanes impair microtubule function needed for cell division. Vascular endothelial growth factor (VEGF)-inhibitors blocks the activation of kinases resulting in the downstream inhibition of angiogenesis. Dexrazoxane, an iron-chelating agent, may decrease the formation of ROS through prevention of anthracycline–iron complex formation as well as inhibit the formation of Top2B-DNA cleavage complexes, which impair DNA repair. β-Blockers, statins, and angiotensin converting enzyme inhibitors (ACE-I), through antioxidant properties, may inhibit the production of ROS. ACE-Is may decrease angiotensin-induced blockade of the neuregulin-1 (NRG-1)/ErbB pathway. Statins have also been shown to inhibit Top2B-mediated DNA damage. The various cellular effects of these chemotherapy agents may ultimate result in cardiovascular manifestations in the form of left ventricular dysfunction, heart failure, hypertension, and atherosclerosis.

with anthracycline-containing versus anthracycline-sparing regimens.[12] Slower infusion or increasing intervals between paclitaxel and doxorubicin may attenuate toxicity.[29] Newer adjuvant protocols and formulations might decrease the likelihood of toxicity.[30]

HER2-Targeted Cancer Therapies

Overexpression of human epidermal growth factor receptor 2 (HER2/ERbB2) in breast cancer is a poor prognostic indicator, as these tumors tend to be more aggressive and associated with higher reoccurrence rates.[31] Trastuzumab, a humanized anti-HER2 monoclonal antibody targeting the extracellular domain of this oncoprotein, has been shown in both the metastatic[32] and the adjuvant[33] setting to dramatically change the survival in HER2 positive breast cancer. HER2/ERbB2 is expressed on myocytes and plays a protective role against myocardial stress.[21] The binding of cancer drugs to HER2 receptor may disrupt this cardioprotective pathway and result in cardiotoxicity. Trials with trastuzumab observed increased incidence of LVD and its use with anthracyclines potentiate cardiotoxicty risk.[10] Previous trials in the adjuvant setting reported HF in 1.7% to 4.1% and LVD in 7.1% to 18.6% of patients receiving trastuzumab, although in practice, incidence may be higher.[34] Lapatanib, an oral tyrosine kinase inhibitor of HER2 and epidermal growth factor receptor, is approved in the metastatic setting and pertuzumab, a monoclonal antibody that blocks the dimerization of HER2 with other HER2 receptors, is approved in both the neoadjuvant and metastatic setting in combination with trastuzumab and docetaxel.[35] Combination treatment using 2 anti-HER2 agents improves rates of pathologic complete responses in the neoadjuvant setting and survival in the metastatic settings, with comparable cardiotoxicity.[36] Trastuzumab emtansine is a HER2-targeted antibody drug conjugate combining trastuzumab with a cytotoxic agent DM1, reported a 2.7% incidence of LVD.[37] As the available treatments expand, new questions arise with respect to the development of cardiotoxicity.

VEGF Inhibitors (Monoclonal Antibodies and Small Molecules, Eg, Tyrosine Kinase Inhibitors)

Vascular endothelial growth factor (VEGF) inhibitors exert their action by inhibiting VEGF-mediated angiogenesis through various mechanisms.[38] Small molecule tyrosine kinase inhibitors (sunitinib and sorafenib) are nonselective inhibitors of VEGF receptors, inhibiting up to 50 different kinases in addition to their intended target, thus, producing unwanted effects.[39] These agents have been linked to hypertension, ischemia, LVD, and HF.[40] Initial reports of sunitinib showed a 10% incidence of LVD but with recovery upon completion of therapy,[41] and a 1.5% to 4.1% incident of HF.[42] The real world experience is in fact worse, with ≈14% of patients experiencing a >10% decline in ejection fraction.[43] Bevacizumab is a monoclonal antibody that targets VEGF and is associated with a 5-fold increase in HF risk.[44]

Radiotherapy

Radiation-induced heart disease is well recognized and may manifest years after exposure. Radiotherapy is associated with macrovascular, microvascular, and endothelial injury; valvular dysfunction; atherosclerosis; fibrosis; and pericardial disease. LVD and HF can occur as acute radiation myocarditis[45] but more commonly develops as a long-term consequence of fibrosis leading to ventricular dysfunction or restrictive cardiomyopathy.[45] The presence of other CVD risk factors, concomitant anthracycline use, and anterior or left chest irradiation all increase risk. Mediastinal irradiation increases CVD and HF risk even 40 years after initial exposure.[46] In a recent study of patients receiving radiation, there was a linear increase in coronary events with radiation dose. Events occurred 5 years after initial exposure and continued through the third decade following exposure.[47]

Risk Factors

Identification of patients at risk is difficult though important. Patient-related risk factors include those with preexisting cardiac risk factors such as hypertension, diabetes mellitus, smoking, previous LVD or HF, coronary disease, increasing age, female gender, and postmenopausal status.[48] Genetic polymorphisms may predispose to cardiotoxicity at lower anthracycline dose,[49] suggesting that genetic variation might modulate the risk of cardiovascular toxicity after cancer treatment. In an unselected group of cancer patients, even before chemotherapy, the presences of N-terminal pro-brain natriuretic peptide, mid-regional pro-atrial natriuretic peptide, mid-regional pro-adrenomedullin, high-sensitivity troponin T, and copeptin were associated with all-cause mortality.[50] Therapy-related risk factors include use of combination cancer therapy, particularly if administered simultaneously, or as bolus, addition of mediastinal irradiation, and higher doses. Certain agents, such as anthracycline, trastuzumab, and cyclophosphamide, carry higher risk while others, such as bevacizumab, etoposide, and lapatinib, carry lower risk.[51] Prior treatment with anthracyclines increases the risk if a patient presents with recurrent disease or a new malignancy requiring further anthracycline therapy.[52]

Risk Prediction

Several risk scores have been published, although there is no consensus model. Herrmann et al[53] proposed a risk model including both cancer therapy and patient factors. Romond et al[54] used a model including age and baseline LVEF to estimate HF risk, also reporting LVEF recovery. Dranitsaris et al[55] developed and tested a cycle-based risk-prediction tool in metastatic breast cancer patients receiving doxorubicin or its pegylated liposomal form. This score included age, weight, anthracycline exposure, and performance status, adding points for each additional chemotherapy cycle. Ezaz et al[56] developed a 7-point risk score for 3-year HF risk after trastuzumab therapy in older females. Risk factors such as coronary disease, atrial fibrillation, hypertension, diabetes mellitus, and renal failure all portended higher risk. HF incidence was higher than previously reported, with the oldest patients approaching 45% incidence (Table 1).

Biomarkers

A biomarker approach for early identification, risk stratification, and monitoring of chemotherapy-related cardiotoxicity holds promise, although challenges exist with respect to timing of measurement, optimal assays, and whether this strategy is best used alone or in conjunction with imaging.

Biomarker of Injury (Eg, Troponin)

Troponin levels can be monitored before and after each therapy cycle and serve as a predictor of future cardiac dysfunction. A

Table 1. Overview of Validated Risk-Prediction Models

Reference	Population	Risk Factors	n	Definition of Cardiotoxicity	Discrimination	Calibration	Validation
Ezaz et al[56]	Women with early-stage breast cancer who underwent surgery and adjuvant trastuzumab therapy	Adjuvant therapy type, Age, CAD, AF, DM, HTN, renal failure	1664	ICD-9CM code for HF or CM that seems in at least 1 inpatient claim or 2 outpatient claims at least 30 d apart	NR	NR	NR
Romond et al[54]	Women with HER2+ breast cancer	Age, baseline LVEF	1830	LVEF drop >10% from baseline to <55% or drop >5% to level below lower limit of normal	0.72 (0.70 after bootstrapping)	NR	Bootstrapping
Dranitsaris et al[55]	Women with metastatic breast cancer receiving anthracycline-based chemotherapy	Age, weight, baseline anthracycline exposure, performance status, no. of cycles	509	(1) LVEF drop 20% but still normal range, (2) LVEF drop 10% if abnormal, (3) signs/symptoms HF	0.84	NR	Bootstrapping

AF indicates atrial fibrillation; CAD, coronary artery disease; CM, cardiomyopathy; DM, diabetes mellitus, HF, heart failure; HTN, hypertension; LVEF, left ventricular ejection fraction NR, not reported.

high negative predictive value with absence of troponin elevation has been reported in patients receiving high-dose anthracyclines.[57] Early increase in troponin I after anthracycline use predicted diastolic dysfunction in 34% of patients.[58] Increased troponin I in patients receiving trastuzumab had a decreased likelihood of LVEF recovery and a higher incidence of cardiac events.[15] Troponin I levels at completion of anthracycline treatment were predictive of subsequent reduction in LVEF and cardiac events.[59] Smaller studies have looked at troponin use for identification of at-risk patients with newer agents, such as anti-VEGF monoclonal antibodies, anti-VEGFR tyrosine kinase inhibitors, and a kinesin inhibitor.[60]

Biomarker of Load (Eg, Natriuretic Peptide)

Natriuretic peptides have been studied in chemotherapy-treated patients with variable results. In one study, brain natriuretic peptide was predictive of LVD at 3-, 6-, and 12-month follow-up.[61] In patients undergoing doxorubicin therapy, an increase in natriuretic peptides during the first 90 days was predictive of LVD at 4 years.[62] Several studies, however, have failed to show an association between these biomarkers and cardiac dysfunction,[59,63] and they may be more useful for their negative predictive value as part of a surveillance strategy. Further studies are needed to understand the role of natriuretic peptide use in this population and to understand the differences in the various types of natriuretic peptides.

Other Biomarkers

High-sensitivity C-reactive protein predicts cardiotoxicity in patients treated with trastuzumab.[64] Other studies of patients receiving anthracycline-containing regimen followed by taxanes and trastuzumab showed no association between C-reactive protein, galectin-3, ST-2 or growth differentiation factor 15, and cardiotoxicity but 1 study reported that changes in myeloperoxidase levels were associated with cardiotoxicity.[59,65] In a recent study of multiple biomarkers, myeloperoxidase levels rose early, persisted throughout the course of therapy, and were associated with cardiotoxicity[66] (Table 2).

Imaging

Echocardiography

Two-Dimensional Echocardiography

Because of its widespread availability and safety, 2-dimensional echocardiography (2DE) is increasingly used in monitoring patients with cancer; 2DE allows for characterization of systolic and diastolic function, pulmonary pressures, valvular function, right ventricular (RV) function, and the pericardium. Assessment of LVEF is based on assumptions of cardiac geometry, depends on image quality, cannot detect small regional alterations in myocardial function, and may vary based on loading conditions.[74] The American Society of Echocardiography suggests the addition of contrast to 2DE for better definition of endocardial borders in patients with breast implants or mastectomy.[75] One of the drawbacks of 2DE is in its inability to detect small (<10%) changes in LVEF, a limitation in patients with cancer in whom subtle differences in cardiac function may have important implications on treatment dose adjustment or cessation.[13,76]

Three-Dimensional Echocardiography

Three-dimensional echocardiography increases the accuracy of detecting more subtle changes in LVEF, with a higher reproducibilty.[77] Thavendiranathan et al[78] demonstrated that non-contrast three-dimensional echocardiography had the highest inter- and intraobsever reproducibility for LVEF and LV volume detection in sequential 1 year follow-up of patients receiving cancer therapy. Unlike with 2DE, the study of use of contrast in three-dimensional echocardiography has not been firmly established.[78,79]

Diastolic Function

Diastolic dysfunction often precedes systolic dysfunction in patients receiving chemotherapy.[80] Although findings have been inconsistent, changes in diastolic parameters, such as isovolumetric relaxation and deceleration time, have been shown in patients as early as 3 months following doxorubicin and were predictive of systolic dysfunction at 6 months, with a sensitivity similar to strain imaging.[81] Early reductions in early diastolic mitral inflow velocity and early diastolic mitral inflow velocity/late diastolic mitral inflow velocity ratio, or increase in early diastolic mitral inflow velocity/early diastolic mitral annular velocity, predict future decrement in systolic function years after chemotherapy.[82] Still, the use of diastolic parameters to predict subsequent cancer-related cardiotoxicity remains unclear, given the variability based on loading conditions in patients with cancer.[79]

Strain and Speckle Tracking

More recent techniques, including strain and speckle tracking may allow for earlier detection of more subtle changes in myocardial function. Strain imaging assesses myocardial function based on measurements of myocardial velocities in adjacent areas as they relate to distance between those areas during the cardiac cycle. Speckle tracking has largely replaced tissue Doppler imaging for analysis of myocardial deformation and holds promise in early prediction of chemotherapy cardiotoxicity. Global longitudinal strain reduction precedes LVD in patients who later develop HF.[59] Strain abnormalities can be seen early despite preserved LVEF. Persistent abnormalities were found in patients receiving high-dose anthracyclines.[83] In patients receiving trastuzumab alone or with anthracyclines, a change in global longitudinal strain of >11% was the strongest predictor of cardiotoxicity.[84] This technique is limited by availability, image quality, variability of quantification between vendors, and lack of universal definitions. In addition to measuring linear deformation, speckle tracking can assess torsion, a newer parameter requiring further study in patients receiving anthracyclines.[85]

Right Ventricular Function

Subclinical changes in RV systolic and diastolic parameters have been described early after anthracycline therapy and correlated with elevations in N-terminal pro-brain natriuretic peptide levels.[86] RV involvement after chemotherapy has been noted in earlier studies involving RV myocardial biopsies, but frequency is not known.[87] In patients receiving isolated left ventricular mechanical support in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), markers of RV dysfunction were more common and more

Table 2. Role of Cardiac Biomarkers in Chemotherapy-Induced Cardiotoxicity

Reference	Patient Population	N	Chemotherapy	Biomarker	Value Cutoff	Timing of Measurement	Results
Ky et al[65]	HER2+ breast cancer	78	Doxorubicin, cyclophosphamide, paclitaxel, trastuzumab	TnI, CRP NT-proBNP GDF-15, MPO PIGF, sFlt-1 gal-3		Biomarkers measured at baseline, 3, and 6 mo LVEF measured at baseline, 3, 6, 9, 12, and 15 mo	TnI and MPO rise at 3 mo was associated with subsequent cardiotoxicity
Skovgaard et al[67]	Breast cancer, hematologic malignancies, uterine/ovarian cancer	333	Anthracycline	BNP	100 pg/mL	No standard interval of measurements	BNP and LVEF independently predicted CHF Only BNP was associated with overall mortality
Sawaya et al[59]	HER2+ breast cancer	81	Anthracycline, paclitaxel, trastuzumab	Troponin NT-proBNP ST-2	≥30 pg/mL >125 pg/mL >35 pg/mL	Baseline, 3,6,9,12, and 15 mo	Elevated TnI at 3 mo was predictive of subsequent cardiotoxicity No change in NT-proBNP and ST-2
Lipshultz et al[62]	Children with high-risk ALL	156	Doxorubicin	TnT NT-proBNP hs-CRP	Any detectable amount ≥150 pm/mL, age<1; ≥100 pm/mL, age>1 ≥1.9 mg/L	Biomarkers measured at baseline, days 1–7 of doxorubicin induction, 7 days after a doxorubicin dose, and at end of doxorubicin therapy LVEF measured at baseline, after therapy, and every 2 y thereafter	Increase in TnT and NT-proBNP during first 90 days predicted cardiac dysfunction at 4 y
Onitilo et al[63]	HER2+ breast cancer	54	Trastuzumab adjuvant	BNP hs-CRP TnI	≥200 pg/mL ≥3 mg/L ≥0.01 ng/mL	Biomarkers measured at baseline, every 3 wk up to 1 y LVEF measured every 3–4 mo	Only hs-CRP was associated with increased risk for clinically significant decline in LVEF
Morris et al[68]	HER2+ breast cancer	95	Doxorubicin, cyclophosphamide, paclitaxel, trastuzumab, lapatinib	TnI CRP	>0.04 n g/mL (DF/HCC); >0.06 ng/mL (MSKCC) ≥0.8 mg/dL (MSKCC) ≥0.3 mg/dL (DF/HCC)	Biomarker measured every 2 wk during chemo, 6,9, and 18 mo LVEF measured at months 0,6,9, and 18	TnI rise (peaking at ≈14 wk) preceded maximal decline in LVEF but no relation to max LVEF decline CRP did not correlate with LVEF decline
Romano et al[61]	Breast cancer	92	Anthracycline, taxane, 5-fluorouracil, cyclophosphamide	NT-proBNP TnI	>153 pg/mL, age ≤50; 222 pg/mL, age >50 5 ng/mL, age ≤50; 0.08 ng/mL, age >50	Biomarkers measured at baseline, before, and 24 h after each drug administration LVEF measured at baseline, every 2 cycles, end of chemo, 3, 6, and 12 mo follow-up	NT-proBNP was predictive of LV impairment at 3,6, and 12 mo follow-up
Cardinale et al[15]	Breast cancer	251	Trastuzumab, anthracycline, cyclophosphamide, paclitaxel	TnI	>0.08 ng/mL	Biomarker measured before and after each cycle LVEF measured at baseline, every 3 mo during therapy and every 6 mo after	TnI was an independent predictor of cardiotoxicity and LVEF recovery
Mavinkurve-Groothuis et al[69]	Various pediatric cancers	122	Anthracycline-containing regimen	NT-proBNP TnT	>10 pmol/L, male; >18 pmol/L, female >0.01 ng/mL	Measured once	Elevated NT-proBNP was associated with cumulative anthracycline dose
Dodos et al[70]	Solid or hematological malignancy	100	Anthracycline-containing regimen	TnT NT-proBNP	>0.010 ng/mL <153 pg/mL, female, age < 50; <334 pg/mL, female, age, 50–70; <88 pg/mL, male, age < 50; <227 pg/mL, male, age, 50–70	Measured 24–72 h, 1, 6, and 12 mo after last course of chemo	TnT and proBNP did not predict cardiac dysfunction
Jingu et al[71]	Esophageal cancer	197	Radiotherapy	BNP		Measured before, <1 mo, 1–2, 3–8, 9–24, >24 h after radiotherapy	BNP higher in patients who had high FDG accumulation
Sandri et al[72]	Various	179	Various regimens including epirubicin, cyclophosphamide, taxotere, carboplatin	TnI	>0.08 ng/mL	Biomarkers measured at baseline, at end of infusion, 12, 24, 36, 72 h after each cycle LVEF measured at baseline, 1, 2, 3, 4, 7, and 12 mo after end of treatment	Increase in TnI as early as first cycle predicted subsequent LVEF decline
Cardinale et al[73]	Breast cancer, ovarian cancer, small-cell lung cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma	204	Various regimens including epirubicin, cyclophosphamide, taxotere, carboplatin, etoposide	TnI CK CK-MB	>0.5 ng/mL >190 U/L >5 ng/mL	Before, immediately after, and then 12, 24, 36, and 72 h after every cycle of chemo	TnI elevation predicted future LVEF decline

Studies ordered by date with sample size >50 patients. ALL indicates acute lymphoblastic leukemia; CHF, congestive heart failure; CK, creatinine kinase; CK-MB, creatinine kinase, MB fraction; CRP, C-reactive protein; DF/HCC, Dana Farber/Harvard Cancer Center; FDG, fludeoxyglucose; gal-3, galactin 3; GDF-15, growth differentiation factor 15; HER2+, human epidermal growth factor receptor 2; LVEF, left ventricular ejection fraction; MPO, myeloperoxidase; MSKCC, Memorial Sloan-Kettering Cancer Center; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PIGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase receptor 1; ST-2, interleukin family member; TnI, troponin Ic.

severe in chemotherapy-induced cardiotoxicity compared with ischemic or nonischemic cardiomyopathy. These included higher levels of transaminases, lower systolic pulmonary pressures, moderate tricuspid regurgitation, and higher ratios of central venous to pulmonary capillary wedge pressures. Echocardiographic assessment of the RV should involve careful attention to chamber size, tricuspid annular plane systolic excursion, estimation of pulmonary artery systolic pressure, and RV diastolic parameters.[88] Areas of future interest include usage of speckle tracking for more in depth understanding of chemotherapy-related RV involvement.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) is the gold standard for detection of ventricular volumes and function. CMR has a greater intra- and interobserver reproducibility than echocardiography and may identify a higher prevalence of cardiomyopathy compared with echocardiography in patients with cancer.[89] CMR affords the opportunity for noninvasive tissue characterization including myocardial edema, inflammation, and fibrosis, thus, playing an important role in identification of early and late cardiotoxicity in patients with cancer.[90] Early increases in pre- and postcontrast signal intensity may predict reductions in LVEF at 28 days and 6 months. Subepicardial delayed enhancement with gadolinium has been noted in the lateral wall of trastuzumab-treated patients who developed cardiomyopathy[91]; however, studies on delayed enhancement have demonstrated mixed results.[90] CMR may also have prognostic value in detection of late cardiotoxicity. LV mass index has been shown to be an independent predictor of major adverse cardiac events in cancer patients with cardiomyopathy following treatment with anthracyclines.[92] Larger patient cohorts require study to further define the role of CMR in the prediction of cardiotoxicity. As with use of CMR in the general cardiac population, higher cost, lack of universal availability, and patient-related factors, such as pacemakers and claustrophobia, limit its widespread use, though it plays an important role particularly in patients with technical limitations to echocardiography.

Radionuclide Imaging

Multiple-gated acquisition used to be the mainstay for cardiac functional assessment in patients with cancer because of high reproducibility and availability[93]; however, these advantages are now limited because of changes in equipment and technique.[79] Other limitations include the inability to obtain other structural and functional information, which can be obtained by echocardiogram. Multiple-gated acquisition relies on ejection fraction being the most appropriate parameter to measure, at a higher cost compared with echocardiography. The largest disadvantage of multiple-gated acquisition is radiation exposure, which must be weighed against necessity on an individual basis when other options are available.

Positron Emission Tomography/Magnetic Resonance

Positron emission tomography/magnetic resonance is an emerging modality, though currently largely limited to research algorithms. In the assessment of cardiomyopathy, positron emission tomography allows for the determination of myocardial perfusion and glucose metabolism. Furthermore, positron emission tomography allows for the evaluation of myocardial viability.[94,95] The combined use of positron emission tomography /magnetic resonance allows not only for the acquisition of complimentary data on cardiac structure and function[96] but also limits exposure to radiation.[97] This is an important advantage when imaging patients with cancer, who may have already been exposed to large amounts of radiation.

Conclusion

Cancer therapy–related cardiotoxicity has become a topic of growing concern. Early toxicity can limit a patient's ability to complete effective cancer therapy. Late-onset toxicity impacts cardiac mortality among cancer survivors. This complex population of patients presents unique challenges to clinical care. Overlaps in clinical symptomatology can make the delineation between symptoms of cardiac dysfunction and expected side effects of chemotherapy difficult. Additional barriers include a lack of a universal definition of cardiotoxicity as well as the absence of established guidelines for monitoring and surveillance. Certain biomarkers and novel imaging techniques have been investigated, but further study is necessary to clarify and optimize their role in routine clinical practice. Enhanced recognition and awareness of this unique patient population, and more universally accepted definitions of cancer-related cardiac toxicities, will allow advancement in the field of cardio-oncology.

Disclosures

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Circulation
Heart Failure

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