

## Cancer Therapy–Related Cardiac Dysfunction and Heart Failure

### Part 2: Prevention, Treatment, Guidelines, and Future Directions

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**Abstract**—Success with oncologic treatment has allowed cancer patients to experience longer cancer-free survival gains. Unfortunately, this success has been tempered by unintended and often devastating cardiac complications affecting overall patient outcomes. Cardiac toxicity, specifically the association of several cancer therapy agents with the development of left ventricular dysfunction and cardiomyopathy, is an issue of growing concern. Although the pathophysiologic mechanisms behind cardiac toxicity have been characterized, there is currently no evidence-based approach for monitoring and management of these patients. In the 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 this second part, we discuss the prevention and treatment aspects in these patients and conclude with highlighting the evidence gaps and future directions for research in this area. (*Circ Heart Fail.* 2016;9:e002843. DOI: 10.1161/CIRCHEARTFAILURE.115.002843.)

**Key Words:** cardiomyopathies ■ cardiotoxicity ■ heart failure ■ heart ■ trastuzumab

Mortality from cancer has decreased tremendously over the past few decades, in part, through earlier diagnosis and novel treatments. Unfortunately, although cancer-free survival has increased, complications from cancer therapy, particularly effects of cardiac function have limited patient outcomes, impacting the overall morbidity and mortality adversely.<sup>1</sup> Heart failure (HF) as a result of cancer therapy has been linked to a 3.5-fold increased mortality risk compared with idiopathic cardiomyopathy.<sup>2</sup> An integrative approach between the oncologist and cardiologist can aid in minimizing these detrimental effects. In the second part of this 2-part review, we discuss evaluation, surveillance, prevention, and treatment in this patient population. We highlight a proposed algorithm for approaching these patients before, during, and following cancer therapy. We conclude highlight challenges within the field and areas that need further research.

### Prevention Strategies

#### β-Blockers

There is growing evidence suggesting a cardioprotective role of β-blockers in prevention of anthracycline-induced

cardiotoxicity. Carvedilol, which is also an antioxidant and has the ability to chelate iron, prevented cardiac histopathology caused by doxorubicin.<sup>3</sup> Carvedilol may prevent strain abnormalities after anthracycline use.<sup>4</sup> In studies with carvedilol<sup>5</sup> and nebivolol<sup>6</sup> at initiation of anthracycline use, both agents resulted in higher degree of left ventricular ejection fraction (LVEF) preservation. The use of β-blockers during treatment with trastuzumab and anthracyclines was associated with a lower incidence of HF over a 5-year period.<sup>7</sup> Although carvedilol and nebivolol are beneficial, nonselective β-blockers, such as propranolol, may in fact be cardiotoxic,<sup>8</sup> and the effect of metoprolol is neutral.<sup>9</sup>

#### Renin–Angiotensin Inhibitors

Animal studies suggest that angiotensin-converting enzyme inhibitors (ACEI) may be cardioprotective in anthracycline toxicity.<sup>10</sup> Enalapril treatment 1 week before doxorubicin and continued for 3 weeks after the last dose preserved mitochondrial function and downregulated free-radical generation.<sup>11</sup> Beneficial mechanisms include attenuation of fibrosis and oxidative stress and decreased angiotensin-induced blockade of the neuregulin/ERb system.<sup>12</sup> Some data on ACEI benefit

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in reducing chemotherapy-related HF have been disappointing,<sup>9,13</sup> although criticism of these trials included delay in initiation and broad enrollment of patients on multiple chemotherapy regimens. The benefit of a prophylactic ACEI strategy may be enhanced with risk stratification. Treatment with enalapril using troponin I elevation to identify and stratify high-risk anthracycline patients prevented reduction in LVEF and the development of cardiotoxicity.<sup>14</sup> The role of ACEI in trastuzumab or radiation-treated patients has not yet been extensively studied. Telmisartan, when administered immediately before epirubicin, may reduce the formation of reactive oxygen species and attenuate the development of myocardial dysfunction in patients receiving higher doses of epirubicin.<sup>15</sup>

### Aldosterone Antagonist Therapy and Other HF Therapies

Aldosterone antagonists have been speculated to attenuate trastuzumab-induced myocardial dysfunction through inhibition of the EGFR receptor, though further study is warranted.<sup>16</sup> Spironolactone, used simultaneously with anthracyclines in breast cancer patients with preserved left ventricular (LV) function, may attenuate left ventricular dysfunction (LVD) suggesting a role in prevention of both systolic and diastolic dysfunctions.<sup>17</sup> The role of other agents used in HF management, such as hydralazine/nitrates and digoxin, has not been studied in the cancer cardiotoxicity population; however, guideline derived medical treatment in general should be employed in all patients with LVD.

### Combination Therapy

The OVERCOME trial (Prevention of Left Ventricular Dysfunction with Enalapril and Carvedilol in Patients Submitted to Intensive Chemotherapy for the Treatment of Malignant Hemopathies) used a combination of carvedilol and enalapril in patients with leukemia or those planned for stem cell transplantation. In patients who received combination therapy, there was no reduction in LVEF compared with those who received placebo. In addition, patients on combination therapy had a lower incidence of death or HF.<sup>18</sup> Preliminary results of the Prevention of Cardiac Dysfunction during Adjuvant Breast Cancer Therapy (PRADA) trial revealed that candesartan, but not metoprolol tartrate, prevented a modest short-term decline in LVEF during anthracycline inclusive breast cancer therapy as measured by cardiac magnetic resonance imaging. Longer term follow-up will further establish a preventative role of angiotensin receptor blockade.<sup>19,20</sup> MANTICORE-101 (Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research) is examining the use of perindopril versus bisoprolol in patients with human epidermal growth factor receptor (HER2+) breast cancer undergoing treatment with trastuzumab in the prevention of LVD as assessed by cardiac magnetic resonance imaging.<sup>21</sup>

### Dexrazoxane

Dexrazoxane, a derivative of the metal-chelating agent EDTA, is thought to attenuate anthracycline cardiac toxicity through iron chelation and decrease in production of free radicals.<sup>22</sup> In addition, dexrazoxane binds to topoisomerase 2, preventing the formation of anthracycline-mediated DNA-Top2 complexes.<sup>23</sup> In patients treated with anthracyclines, dexrazoxane decreased

HF risk and increased cardiac event-free survival.<sup>24</sup> However, the mechanism by which dexrazoxane provides cardioprotection has raised concerns that this agent may attenuate doxorubicin antitumor activity, through binding to both Top2- $\alpha$  and Top2- $\beta$ .<sup>25</sup> Clinical trial data are inconclusive, but a Cochrane review demonstrated no difference in efficacy of anthracyclines against the primary malignancy with the addition of dexrazoxane.<sup>23</sup> The American Society of Clinical Oncology recommends that use of dexrazoxane should be limited to adult patients in the metastatic breast cancer setting and other malignancies who have received >300 mg/m<sup>2</sup> and who may benefit from use of additional anthracyclines.<sup>26</sup> Recent data demonstrated long-term efficacy in reducing HF in cancer survivors from the pediatric cohort,<sup>27</sup> and therefore, new studies are required to determine safety and efficacy in adult cancer populations. A meta-analysis on the prophylactic use of dexrazoxane in patients receiving anthracyclines revealed a decrease in cardiac events.<sup>28</sup>

### Statins

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, in addition to their lipid lowering, exert cardioprotective effects through pleiotropic mechanisms. Studies suggest the benefit of statins in reducing anthracycline-mediated cardiomyocyte death.<sup>29</sup> In a retrospective cohort study of >600 cancer patients, uninterrupted statin use resulted in reduced HF.<sup>30</sup> In patients without preexisting cardiovascular abnormalities, prophylactic atorvastatin led to higher preservation of LVEF.<sup>31</sup> To date, no prospective trials have addressed the role of statins in the prevention of cancer therapy-related cardiotoxicity (Table 1).

### Primordial Versus Primary Versus Secondary Prevention

Prevention may be primary, extended to all patients already treated with potentially cardiotoxic therapies, or secondary in selected high-risk patients showing preclinical signs of cardiotoxicity as in the form of biomarker increase, strain decrease, etc. More recently, the concept of primordial prevention with cardioprotective therapies has been described to address the population of patients immediately after initial cancer diagnosis but preceding cancer therapy.<sup>33</sup> A tailored prevention strategy based on the cardiac risk stratification according to patient-related (including genetic predisposition) and to therapy-related risk factors bears further investigation.

### Treatment of LVD and HF

Conventional therapy with  $\beta$ -blockers and ACEI in LVD and HF is extrapolated to patients with chemotherapy-induced cardiotoxicity, although randomized trial data are lacking. Enalapril and carvedilol given 1 to 2 months after anthracycline therapy in patients with LVD led to LVEF recovery in most cases; however, when treatment was delayed, recovery was partial or absent.<sup>34</sup> In another study, patients with LVD, regardless of the presence of symptoms, were given either enalapril (before 1999) or enalapril and  $\beta$ -blocker (carvedilol or bisoprolol after 1999) and showed recovery of LVEF with greater improvement with combined therapy.<sup>35</sup> The role of HF treatment in trastuzumab-induced LVD has not been established (Table 2).

**Table 1. Prevention of Left Ventricular Dysfunction in Patients with Cardiotoxic Chemotherapy**

Reference	Type of Study	Patient Population and Cancer Therapy	N	Cardiac Treatment Modality	Timing of Initiation of Treatment	Mean Follow-Up	Results
<b>β-Blockers</b>							
Kalay et al <sup>5</sup>	RCT	Patients planned to receive anthracyclines, planned (breast, lymphoma, other) adriamycin or epirubicin	50	Carvedilol 12.5 mg once daily vs placebo	Initiated before chemo	6 mo	Mean EF 68.9 vs 52.3 ( $P<0.001$ ) at 6 mo follow-up Both systolic and diastolic diameters were significantly increased in control, and diastolic parameters (E and E/A ratios significantly reduced in control group) Lower mortality (but not statistically significant) in carvedilol group
Seicean et al <sup>7</sup>	Propensity matched control; Competing risk framework	Breast cancer patients with normal EF before between 2005 and 2010; Anthracyclines or anthracyclines followed by trastuzumab with or without radiotherapy	920 (318 used)	Continuous BB (n=106) vs not on continuous BB (n=212)	BB initiated before cancer rx	3.2 y	Coincidental continuous use of BB associated with lower incidence of new HF in breast cancer patients with normal EF during median follow-up of 5.2 y (hazard ratio, 0.2; CI, 0.1–0.5, $P=0.003$ ) HF events 5 vs 27 ( $P=0.008$ ) in continuous BB vs no BB group
Kaya et al <sup>6</sup>	RCT	Breast cancer and planned chemotherapy	45	Nebivolol 5 mg daily vs placebo		Echocardiogram and NT pro-BNP at baseline and 6 mo of chemo	At 6 mo, LVESD and LVEDD increased in placebo group but remained unchanged in nebivolol group ( $P=0.01$ for both) Placebo group had lower LVEF than nebivolol at 6 mo NT BNP increased in placebo group
Elitok et al <sup>4</sup>	RCT	Patients with breast cancer planned for anthracyclines	80	Carvedilol vs placebo	Carvedilol 12.5 mg daily for 6 mo	Echo with strain at baseline and 6 mo post anthracycline	Significant decrease in strain parameters in control group at 6 mo
<b>RAAS inhibitors</b>							
Nakamae et al <sup>32</sup>	RCT	Patients scheduled to undergo standard chemo with CHOP	40	Valsartan 80 mg daily vs none	ARB simultaneous on day 1 of CHOP	Neurohormonal, echo, and ECG parameters measured before, days 3,5,7 and after initiation of CHOP 7 d	Valsartan significantly prevented transient increases in LVEDD, QTc dispersion and BNP elevation ( $P<0.05$ ) with no significant change in BP or HR Ang II may play a role in acute chemo-induced cardiotoxicity and ARB may prevent acute CHOP toxicity
Cardinale et al <sup>14</sup>	RCT	High-risk, high-dose chemo patients (defined by early increased troponin I level) from 2002 to 2004 Included primary resistant BC, AML, relapsed, or refractory Hodgkins lymphoma, Ewing's sarcoma	114	Enalapril 20 mg daily vs none	1 month after last high-dose chemo, continued for 1 y	Cardiac evaluation including: late Tnl (at randomization, before enalapril, 2,3,6,12 mo later) At baseline, 1,2,6, and 12 mo after high-dose chemo	Absolute decrease in LVEF >10% to decline below normal value (LVEF, 50%) (43% vs 0%) and increase in end-diastolic and end-systolic volumes only in untreated patients ( $P<0.001$ )
Cadeddu et al <sup>15</sup>	RCT, placebo cont.	Patients planned to undergo chemo with epirubicin (cumulative dose 400 mg/m <sup>2</sup> ) based chemo with baseline EF >55% and no history of heart disease, HTN, DM	49	Telmisartan 40 mg daily vs placebo	1 week before chemo	Echo, TD, strain/strain rate (SR) and plasma levels of inflammatory and oxidative stress markers at baseline and at 7 d after every new epirubicin dose of 100 mg/m <sup>2</sup> 3 mo	Impairment in strain rate peak at epi dose of 200 mg/m <sup>2</sup> (no significant difference between groups) but at 300 and 400 mg/m <sup>2</sup> SR normalized only in telmisartan group ( $P<0.001$ ) Significant increase in ROS and interleukin-6 in placebo

(Continued)

Table 1. Continued

Reference	Type of Study	Patient Population and Cancer Therapy	N	Cardiac Treatment Modality	Timing of Initiation of Treatment	Mean Follow-Up	Results
Combination neurohormonal blockade							
Bosch et al <sup>18</sup>	RCT	Acute leukemia or malignancies planned for HSCT Without LVSD	90	Enalapril 10 mg BID and carvedilol 25 mg BID vs control	Started simultaneously at least 24 h before first chemo cycle	Echo and CMR before and at 6 mo after randomization, troponin I and BNP at baseline and 12 h after each cycle 6 mo	LVEF significantly decreased in controls Compared with controls, patients in treatment group had lower incidence of combined end point of death or HF (6.7% vs 22%, $P=0.036$ ) and of death, HF, or LVEF <45% (6.7% vs 24.4%, $P=0.02$ ) Marked differences in the acute leukemia group
Georgakopoulos et al <sup>9</sup>	RCT	Lymphoma patients (HL and NHL)	125	Metoprolol vs enalapril vs placebo		Echo at baseline and 12 mo 1 y follow-up	Nonsignificant reduction in HF, primarily in metoprolol group 16% early cardiotoxicity 7.3% late cardiotoxicity (more in elderly) Overall negative study: Metoprolol and enalapril do not reduce risk of cardiotoxicity in patients with doxorubicin
Statins							
Acar et al <sup>31</sup>	RCT placebo control	Patients undergoing anthracycline chemotherapy without previous cardiac history and regardless of lipid levels; adriamycin or idarubicin	40	Atorvastatin 40 mg qd vs placebo	Before chemotherapy	Echo at baseline and 6 mo after chemotherapy 6 mo	Statin vs control at 6 mo: LVEF: +1.3% vs -7.9% in statin vs control ( $P<0.001$ ) LVEDD (mm): 0.15 vs +2.0 ( $P=0.021$ ) LVESD -1.35 vs 2.1 ( $P<0.001$ ) Note: primary endpoint of LVEF <50% did not reach statistical significance
Seicean et al <sup>30</sup>	Observational clinical cohort study	628 women with newly diagnosed breast cancer; anthracyclines± trastuzumab	628 (201 matched)	Uninterrupted statin therapy	Statin therapy initiated incidentally before cancer therapy		New onset HF in 67 of 201 matched patients. HR significantly lower 0.3 ( $P=0.02$ ) for statin patients. Cardiotoxicity RFs: baseline EF, <55%; Trastuzumab use

ARB indicates angiotensin receptor blocker; CHOP, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone; CI, confidence interval; E, early diastolic mitral inflow velocity; E/A, early diastolic mitral inflow velocity/late diastolic mitral inflow velocity; EF, ejection fraction; HF, heart failure; HL, Hodgkin's lymphoma; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVSD, left ventricular systolic dysfunction; NHL, non-Hodgkin's lymphoma; NT-proBNP, n-terminal pro-brain natriuretic peptide; RAAS, renin-angiotensin-aldosterone system; RCT, randomized controlled trial; RF, risk factor; Rx, treatment; and TD, tissue doppler.

### Surveillance: Before, During, and After Cancer Treatment

Surveillance strategies are currently based on expert consensus. One approach includes screening for high-risk cardiac and oncologic factors to stratify patients. Optimization of pre-existing conditions before cancer therapy should be attempted. Baseline detailed echocardiogram, including strain imaging when available, should be performed.<sup>36,37</sup> The presence of high-risk features should prompt cardio-oncology consultation. Incorporation of biomarkers is recommended, although their role in routine monitoring is not fully established.<sup>37,38</sup> The frequency and intervals with which to image patients vary with risk factors, type of chemotherapy, and planned dosing,<sup>38</sup> and are currently center-dependent. Radiation therapy requires a different surveillance algorithm<sup>38,39</sup> because of the potential for delayed cardiac dysfunction (Figure).

Not all asymptomatic left ventricular dysfunction and HF that develop during or after cancer therapy can be assumed to be the direct result of treatment, and thus, all new or worsening

cardiac dysfunction should be evaluated according to guideline recommendations. This should include evaluation for other reversible causes of myocardial dysfunction and ischemic evaluation in those patients in whom suspicion is high.<sup>40</sup> Higher suspicion for alternate causes is especially important in both older individuals and those with multiple comorbidities.<sup>38</sup>

### Alterations in Cancer Therapy in Patients With Ventricular Dysfunction and HF

The Food and Drug Administration recommends withholding trastuzumab for at least 4 weeks if LVEF drops  $\geq 16\%$  from pretreatment values or if it falls below normal and  $\geq 10\%$  absolute decrease in LVEF from pretreatment values. The agent can be resumed if the LVEF returns to normal and the absolute decrease from baseline is  $\leq 15\%$  within 4–8 weeks.<sup>41</sup> It is also recommended to discontinue doxorubicin in patients who develop HF.<sup>42</sup> The indications for withdrawal or withholding of therapy in patients with asymptomatic LVEF decline are not as clear. The Canadian Trastuzumab working group

**Table 2. Treatment of ASLVD in Adult Patients with Cardiotoxic Chemotherapy**

Reference	Type of Study	Patient Population an Cancer Therapy	N	Cardiac Treatment Modality	Timing of Initiation of Treatment	Mean Follow-Up	Results
Cardinale et al <sup>34</sup>	Prospective	201 patients with LVEF $\leq$ 45% due to anthracyclines	201	Enalapril up to 20 mg/d and coreg up to 50 mg /d; of note: mean dose enalapril 11 mg/d and coreg 14 mg/d	Rx initiated immediately after detection of ASLVD	Echo at baseline, every month for 3 mo, and every 3 mo during following 3 y, every 6 m thereafter Mean follow-up 36 mo	Primary EP: LVEF response to therapy Responders,* 42%; partial responders, 13%; nonresponders, 45% Responders showed lower rate of cum cardiac events than partial and nonresponders (5%, 31%, 29%, $P<0.001$ )
Cardinale et al <sup>35</sup>	Prospective	Mix of cancer, non-Hodgkin's lymphoma Chemotherapy naive patients scheduled for anthracyclines (note excluded high-dose anthracycline or trastuzumab)	2625	Enalapril alone (before 1999) enalapril and $\beta$ -blockers carvedilol or bisoprolol (after 1999)	Therapy promptly administered and uptitrated to maximal tolerated doses	Echo at baseline, every 3 mo during chemotherapy, at end of treatment (within 1 mo, every 3 mo during first year following chemotherapy, every 6 mo during the following 40 y, yearly afterward) Median follow-up 5.2 y	Anthracycline-induced cardiotoxicity occurred in 9% of adult treated patients (dose dependent; highest incidence in first year after completion of chemotherapy) Median time between last dose of anthracycline and development of cardiotoxicity was 3.5 mo, 98% of cases within the first-year follow-up 82% of patients recovered from cardiotoxicity (11% full recovery; 71% partial recovery)

ASLVD indicates asymptomatic left ventricular dysfunction; EP, end point; LVEF, and left ventricular ejection fraction.

\*Responders had a significantly shorter time to initiation of therapy.

recommendations for stopping/restarting directly reflect those used in the largest adjuvant trastuzumab trials, based on baseline systolic function and degree of LVEF % decline.<sup>43</sup> Decisions on alteration in dosing or discontinuation of cancer treatment need to be weighed against oncologic risk and require collaboration between cardiologists and oncologists, personalizing the strategy to the individual patient and their prognosis. Predictors of LV recovery are poorly understood. Retrospective data have suggested that LV recovery can be expected in roughly 50% of patients who develop cancer therapy–related cardiotoxicity, and that younger age, smaller left atrial volume, and lower brain natriuretic peptide (BNP) levels may be multivariate predictors of LV recovery.<sup>44</sup>

### Advanced HF Therapies in the Cancer Population

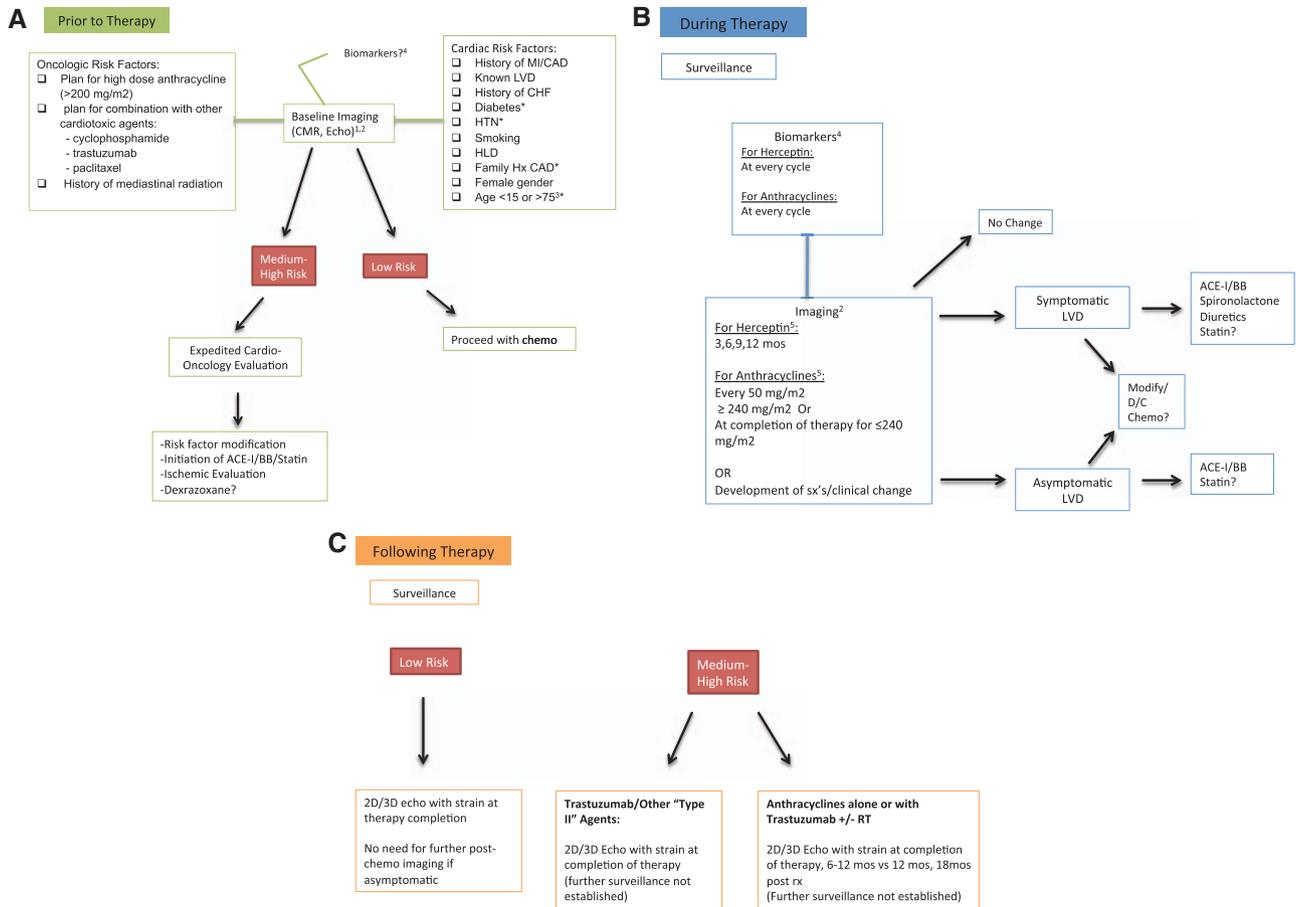
Similar to the non-cancer HF population, option for therapies in the chemotherapy-induced cardiomyopathy population includes implantable cardioverter defibrillator and chronic resynchronization therapy, LV assist devices, and orthotopic heart transplantation. In a recent study, patients with adriamycin–induced cardiomyopathy derived a similar echocardiographic and clinical benefit with chronic resynchronization therapy compared with other nonischemic patients.<sup>45</sup> About 2.5% of nonischemic cardiomyopathy patients undergoing transplantation have chemotherapy-related cardiotoxicity, and survival is comparable with that of other nonischemic etiologies.<sup>46</sup> Not surprisingly, cancer patients with cardiac toxicity are more likely to undergo mechanical circulatory support as destination therapy rather than as bridge to transplant, given the obligatory 5-year cancer-free survival as a requisite for transplant candidacy. Overall survival after mechanical

circulatory support in these patients is 73% at 1 year and 63% at 5 years, also similar to the general population.<sup>47</sup> Importantly, chemotherapy-related cardiomyopathy patients have higher rates of right ventricular dysfunction and, thus, are more likely to require right ventricular mechanical support. Nevertheless, cancer patients requiring mechanical circulatory support and orthotopic heart transplantation should be evaluated and considered appropriately for these advanced therapies.

### Current Guidelines

Several groups have published recommendations and consensus statements in the adult cancer population,<sup>36–38,48</sup> but formal guidelines for prevention, surveillance, and treatment of cancer therapy–related cardiac toxicity are not yet available. Currently, the American College of Cardiology/American Heart Association HF guidelines report that agents, such as anthracyclines, trastuzumab, cyclophosphamide, taxanes, 5-fluorouracil, and interferons, may cause cardiotoxicity, and dexrazoxane is cardioprotective against anthracycline-induced cardiotoxicity.<sup>49</sup> However, there are no specific monitoring recommendations. The European Society of Cardiology HF guidelines are similar and also recommend pre- and posttherapy LVEF evaluation and discontinuation of chemotherapy along with initiation of standard HF therapy once LVD ensues.<sup>50</sup> The Canadian Trastuzumab Working group recommends baseline and 3-month interval imaging assessment for all patients under trastuzumab treatment, advocating for more frequent/stringent assessments in those patients at higher risk.<sup>51</sup>

The American Society of Echocardiography suggests echocardiography for baseline and follow-up monitoring, but there are no specific recommendations regarding frequency or duration of follow-up.<sup>52</sup> American Society of Clinical Oncology



**Figure.** Proposed algorithm for the surveillance and treatment of cardiotoxicity in patients receiving potentially cardiotoxic chemotherapy before (A), during (B), and following (C) therapy. \* continuous variables of risk; <sup>1</sup>MUGA may be considered if echocardiography or CMR not available; <sup>2</sup>for high-risk patients or when available, strain imaging, use of Echo contrast when indicated; <sup>3</sup>65–74 may represent an intermediate risk group; <sup>4</sup>Troponin, BNP; and <sup>5</sup>Consider earlier imaging if higher baseline risk. ACE-I, indicates angiotensin-converting enzyme inhibitors; BB, beta-blocker; CAD, coronary artery disease; CHF, congestive heart failure; CMR, cardiac magnetic resonance; D/C, discontinue; HTN, hypertension; Hx, history; LVD, left ventricular dysfunction; MI, myocardial infarction; MUGA, multigated acquisition scan; RT, radiation therapy; and Sx, symptoms.

recommends dexrazoxane only in metastatic patients who have received >300 mg/m<sup>2</sup> doxorubicin and would benefit from additional anthracycline administration.<sup>26</sup> American Society of Clinical Oncology reports that there is currently no standard strategy for long-term monitoring through biomarkers or imaging and no direct evidence regarding the treatment of LVD in asymptomatic patients<sup>1</sup> (Table 3).

### Knowledge Gaps and Future Directions

The specialty of cardio-oncology has gained significant momentum, with increasing awareness and interest in advancing the field. This parallels the larger armamentarium of therapies now available to patients with cancer, many of which have redefined life expectancy. There are, however, multiple gaps in the field, which bear addressing (Table 4). At present, there are no internationally published guidelines to address this specific patient population, and no standardized classification system to define cancer-related cardiac toxicity, LVD, and HF. Cardio-oncology guidelines will need to account for different subpopulations, such as those with metastatic and nonmetastatic disease. Furthermore, defining cardiac dysfunction through LVEF alone is insufficient. LVEF estimation may

predict development of later cardiotoxicity but may not be sensitive enough to assess early preclinical changes, which might impact on management decisions. Currently, incidence of cancer therapy–related LVD and HF are likely underestimated, representing the typically younger and healthier population in largest cancer trials. Standardization of cardiac toxicity definitions will allow for prospective study of epidemiology.

There are various limitations in our understanding of optimal clinical management of cardiac disease in the cancer population. At present, the largest focus has centered on HF reduced ejection fraction, but the incidence and management of HF preserved ejection fraction is largely unknown. Clinical trials addressing prevention, prophylactic medical therapy, length and types of therapy once cardiotoxicity develops, and the safety of rechallenging with cancer therapy, all remain critical unaddressed issues. Furthermore, prospectively validated risk predictive models would help clinicians to individualize care, tailor biomarker and imaging surveillance strategies, and initiate early or prophylactic medical therapy for those patients in highest risk categories. Another issue is cardioprotection during reinitiation of the culprit chemotherapy in the context of optimizing cancer

**Table 3. Guideline Recommendations for Cardiac Monitoring**

Guideline	Year	Recommendation	Level of Evidence
<b>Cardiology</b>			
American College of Cardiology/ American Heart Association Management of Heart Failure <sup>49</sup>	2013	The incidence and reversibility of chemotherapy-related cardiotoxicity are not well documented, and meaningful interventions to prevent injury have not yet been elucidated	Not stated
European Society of Cardiology <sup>50</sup>	2012	Pre- and postevaluation of EF is essential in patients receiving cardiotoxic chemotherapy Patients developing LVSD should not receive further chemotherapy and should receive standard treatment for HFrEF	Not stated
American Society of Echocardiography <sup>52</sup>	2003	Baseline and re-evaluation examinations in patients receiving cardiotoxic chemotherapeutic agents	Class I
<b>Oncology</b>			
Canadian Trastuzumab Working Group <sup>43</sup>	2008	Cardiac imaging (echo or MUGA) at baseline and 3-mo intervals until completion of therapy at minimum with more frequent/stringent monitoring for higher risk patients	Not stated
American Society of Clinical Oncology: Cardiac and Pulmonary Late Effects <sup>1</sup>	2007	The optimal duration, frequency, and method of cardiac monitoring during trastuzumab and anthracycline treatment remains unknown	Not stated
<b>Position statements</b>			
American Society of Echocardiography/European Association of Cardiovascular Imaging: Multimodality Imaging Evaluation <sup>36</sup>	2014	Treatment with anthracycline→baseline LVEF assessment with 3D or 2D Echo, GLS, and troponin I measurement. If abnormal, cardiology consultation. Follow-up at completion of therapy and 6 mo later for doses <240 mg/m <sup>2</sup> -Treatment with trastuzumab→baseline LVEF assessment with 3D or 2D Echo, GLS, and TROPONIN I measurement. If abnormal, cardiology consultation. Follow-up every 3 and 6 mo later.	Not stated
ESMO Clinical Practice Guidelines <sup>37</sup>	2012	In patients receiving anthracyclines±trastuzumab→serial monitoring of cardiac function at baseline, 3, 6, and 9 mo during treatment, 12 and 18 mo after start of treatment	Level I, Grade A
		In patients with metastatic disease→monitor EF at baseline and infrequently in absence of symptoms	Level II, Grade A
		Measurement of troponin, BNP at baseline, and periodically during therapy	Level III, Grade B
		Cardiac function assessment 4–10 y after anthracycline in patients treated at <15 yoa or >15 with cumulative dose doxorubicin >240 mg/m <sup>2</sup>	Level II, Grade B
		LVEF drop <50% during anthracycline-containing →reassess in 3 wk. If confirmed, hold chemotherapy and consider therapy for LVSD	Level II, Grade B
LVEF drop <50% during trastuzumab therapy→reassess in 3 wk. If confirmed, continue trastuzumab and consider therapy for LVSD	Level II, Grade B		
Heart Failure Association of the European Society of Cardiology: Cardiovascular Side Effects of Cancer Therapies <sup>48</sup>	2011	Regular cardiovascular evaluation should be part of routine care in patients receiving treatment regimens known to be associated with cardiotoxicity Follow-up beyond completion of therapy should be considered, particularly in those receiving high doses of anthracyclines Use of troponin and BNP should be strongly considered	Not stated

EF indicates ejection fraction; GLS, global longitudinal strain; HFrEF, heart failure reduced ejection fraction; LVSD, left ventricular systolic dysfunction; and yoa, years of age.

outcomes for patients with previous cancer therapy–related cardiotoxicity.

There is a lack of universal agreement on prospective cardiovascular screening, especially for newer chemotherapeutic agents and for treatment strategies that require dual or additive therapy. Further understanding of drug mechanisms would allow for more targeted prevention and treatment. Echocardiographic imaging remains critical to surveillance. The addition of strain/speckle tracking shows promise, but the additive role of this technique in routine practice requires further definition.

There is limited understanding on the long-term effect of modest LVEF declines during therapy, the implications of dose interruptions and treatment delays in cancer therapy, and how cardiac interventions impact on long-term

cardiac and cancer survival. Altering cancer treatment without strong supportive data may put patients at risk of undertreatment or decreased efficacy of therapy. Although all patients receiving anthracyclines should be considered to have some degree of cardiac toxicity, choosing which patients command dose alterations or treatment discontinuation remains arbitrary, with potentially far reaching implications on survival. The term actionable cardiotoxicity has been put forth to address the when and if of treatment alterations.<sup>53</sup>

Cardiac progenitor cells may play a role in the treatment and prevention of anthracycline-induced cardiotoxicity and may be considered as a potential translational therapy in the future, helping to promote cardiac repair. Autologous cardiac progenitor cells can be obtained before antineoplastic drugs are

**Table 4. Future Directions in the Field of Cardio-Oncology**

Domain	Problem	Potential Solution
Definition	Lack of universally accepted definition of cardiac toxicity Definition of cardiac dysfunction through LVEF alone is insufficient	Consensus-driven definition for use in prospective clinical trials and practice
Disease entity	Limited understanding of the pathophysiologic mechanisms of various chemotherapy agents	More basic science research to better define pathophysiology of cancer therapeutics
Guidelines	No internationally published guidelines to account for different subsets of patient populations	More large prospective clinical trials to influence evidence-based guideline development
Epidemiology	Probable underestimation of incidence as most trials include younger, healthier population Focus on systolic dysfunction	Inclusion of older and/or higher risk populations in clinical trials Study HF with both reduced and preserved LVEF
Risk stratification	No universal validated risk prediction mod	Development of validated model based on different clinical profiles
Screening and surveillance	Lack of universal agreement on best practice for screening and surveillance interval	Development of prospective monitoring paradigm
Prevention	Lack of data to support prevention of cardiotoxicity and the role for prophylactic medical therapy	More trials for prevention of cardiotoxicity with attention to primary vs secondary prevention strategies
Surrogate markers	Focus on primarily troponin and natriuretic peptide	Further studies on novel biomarker approaches
Treatment	No established treatment in this population; lack of data on safety and feasibility of rechallenging with chemotherapy once LVD ensues	More clinical trials to address role of single agent vs combination therapy
Novel approaches	Limited data on novel approaches for management, eg, the role of cardiac progenitor cells in treatment or the role of genetic polymorphisms in cardiotoxicity	Expansion of data from animal studies to human subjects Better definition of the role for genetic testing

HF indicates heart failure; LVEF, left ventricular ejection fraction; and LVD, left ventricular dysfunction.

given to cancer patients and subsequently administered to individuals who are particularly predisposed to cardiotoxicity.<sup>54</sup>

Significant individual variability in tolerance to cumulative anthracycline dose has suggested a role for genetic susceptibility. The clinical significance of this remains unknown but with further study may allow for more personalized oncologic therapy.

### Conclusion

With survival gains in cancer therapy, attention and recognition of cardiac toxicities in cancer patients has become increasingly critical. Patients with cancer, either with preexisting cardiac disease or increased cardiac risk, require individualized risk stratification strategies. Patients who develop myocardial dysfunction during therapy often require modifications or withdrawal of life-saving cancer therapies, with profound implications on clinical outcome. Preclinical identification of cardiac toxicities may allow oncologists to continue cancer therapy without interruption. An evidence-based approach would allow enhanced delivery of care to this patient population. This can only be accomplished by further investigation and through a partnership between cardiologist and oncologist, increasingly delivered via formal cardio-oncology services with access to a multidisciplinary team effort to ensure optimal patient outcomes.

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AstraZeneca, Bayer Schering Pharma AG, Cardiorentis Ltd, CorThera, Cytokinetics, CytoPhex Inc, DebioPharm SA, Errekappa Terapeutici, GlaxoSmithKline, Ikaria, Intersection Medical Inc, Johnson & Johnson, Medtronic, Merck, Novartis Pharma AG, Ono Pharmaceuticals USA, Otsuka Pharmaceuticals, Palatin Technologies, Pericor Therapeutics, Protein Design Laboratories, sanofi-aventis, Sigma Tau, Solvay Pharmaceuticals, Sticcare InterACT, Takeda Pharmaceuticals North America Inc, and Trevena Therapeutics. Dr Butler reports receiving research support from the National Institutes of Health and European Union and serve as a consultant to Amgen, Bayer, Cardiocell, Celladon, Novartis, Trevena, Relypsa, Z Pharma, and Zensun. The other authors report no conflict of interest.

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### **Cancer Therapy–Related Cardiac Dysfunction and Heart Failure: Part 2: Prevention, Treatment, Guidelines, and Future Directions**

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