

Review

Chemotherapy-Induced Cardiotoxicity: Detection, Prevention, and Management

Judy Truong,^a Andrew T. Yan, MD,^{b,c,d,*} Gemma Cramarossa, BHSc,^a and
Kelvin K.W. Chan, MD, MSc^{a,d,e,*}

^a Department of Medical Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

^b Division of Cardiology, St Michael's Hospital, Toronto, Ontario, Canada

^c Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario, Canada

^d Department of Medicine, University of Toronto, Toronto, Ontario, Canada

^e Division of Biostatistics, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

ABSTRACT

Chemotherapy-induced cardiotoxicity is a major cause of morbidity and mortality in cancer survivors. It might manifest as arrhythmia, hypertension, myocardial ischemia, thromboembolism, heart failure, systolic dysfunction, or other adverse events. Anthracyclines and trastuzumab are the chemotherapeutic agents with the most documented cardiac side effects; however, the array of novel molecular targeting therapies available is concerning because their side effects are not yet well understood. Nevertheless, there are potential strategies to mitigate the risks of cardiac complications for cancer patients. In this article, the common systemic drugs with cardiotoxic potential and the monitoring and diagnostic tools, including the role of biomarkers for early detection, are reviewed. We will also review the use of cardioprotectant agents as pharmacological interventions in prophylactic and treatment settings. Our aim is to provide a concise and up-to-date summary of the detection, management, and prevention of chemotherapy-induced cardiotoxicity for the busy clinician.

RÉSUMÉ

La cardiotoxicité induite par la chimiothérapie est une cause importante de morbidité et de mortalité chez les survivants du cancer. Elle se manifesterait par l'arythmie, l'hypertension, l'ischémie myocardique, la thromboembolie, l'insuffisance cardiaque, la dysfonction systolique et d'autres événements indésirables. Les anthracyclines et le trastuzumab sont des agents chimiothérapeutiques qui ont les effets secondaires touchant le cœur les plus documentés. Cependant, l'éventail des nouvelles thérapies moléculaires ciblées est préoccupant puisque leurs effets secondaires ne sont pas encore bien compris. Néanmoins, il existe des stratégies pour réduire les risques de complications cardiaques des patients atteints du cancer. Dans cet article, les médicaments à action systémique courants qui présentent un potentiel cardiotoxique et les outils de surveillance et de diagnostic, dont le rôle des biomarqueurs en matière de dépistage précoce, sont passés en revue. Nous passerons également en revue l'utilisation des agents cardioprotecteurs en guise d'interventions pharmacologiques dans le cadre d'une prophylaxie ou d'un traitement. Notre objectif est de fournir aux cliniciens occupés un résumé concis et actualisé sur le dépistage, la prise en charge et la prévention de la cardiotoxicité induite par la chimiothérapie.

Worldwide, the number of cancer survivors has risen because of better treatment options. Some of these effective antineoplastic drugs have been implicated in adverse cardiovascular outcomes in the long-term. In the past, cardiovascular side effects had been less relevant because of the poorer prognosis of malignant neoplasms. However, because cancer patients

now have improved prospects and longer life expectancy, the risks of cardiac adverse events induced by systemic drugs needs to be evaluated. Furthermore, the cardiac injuries sustained by cancer survivors are likely to be further exacerbated by the comorbidities that develop with aging, such as dyslipidemia, hypertension, and coronary artery disease.^{1,2} Although many studies have elucidated the detrimental cardiovascular effects of anthracyclines and some molecular-targeting drugs, cardiovascular complications might not be detected because symptoms might manifest years after cancer treatment.^{2,3} Therefore, rigorous monitoring and a preventative approach to cardiotoxicity are warranted to avoid or minimize the long-lasting and potentially serious cardiac impairments from antineoplastic drugs. The *BRCA1* gene, a tumour

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*These authors contributed equally to this manuscript.

Corresponding author: Dr Kelvin K.W. Chan, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada. Tel.: +1-416-480-4928; Fax: +1-416-480-6002.

E-mail: kelvin.chan@sunnybrook.ca

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suppressor, has been shown to also be essential to normal cardiac function, implicating a common molecular basis for the pathogenesis of certain cancers and adverse cardiac effects.⁴ Recently, the American Heart Association published a comprehensive scientific statement on cardiovascular toxicities in the younger cancer population.⁵ The purpose of this review article is to provide a succinct, up-to-date and practical summary for cardiologists, oncologists, and other health care providers pertaining to the monitoring, detection, management, and prevention of chemotherapy-induced cardiotoxicity.

Chemotherapeutic Agents With Cardiotoxic Potential

Many chemotherapeutic drugs have detrimental effects on cardiovascular health. Several of these agents and their classic cardiac side effects are outlined in Table 1. Although cardiotoxicity is often used to describe left ventricular dysfunction and heart failure (HF), it also encompasses a variety of other complications, including arrhythmias, prolonged QTc interval, hypertension, myocardial ischemia, and thromboembolism.^{13,14} For cardiomyopathy, there are 2 cardiotoxicity prototypes: type I is induced by anthracyclines and causes

Table 1. Summary of common antineoplastic agents and relevant cardiotoxicities^{3,6-12}

Systemic therapy class		Incidence					
Drug Name	Indication(s)*	Arrhythmia	Long QTc	Systolic dysfunction	Hypertension	Myocardial ischemia	Thromboembolism
Anthracycline							
Daunorubicin	Leukemia	++/+++	✓	+	—	—	—
Doxorubicin	Breast, lymphoma	+ / ++	✓	++/+++	—	—	✓
Doxorubicin (liposomal)	Sarcoma	+	✓	—	—	+/++/+++	—
Epirubicin	Breast, gastric	—	✓	+/++	—	—	✓
Idarubicin	Leukemia	++/+++	✓	++/+++	—	—	✓
Mitoxantrone	Leukemia	++/+++	✓	++/+++	++	++	—
Alkylating agent							
Cisplatin	Bladder, HNC, lung, ovarian	✓	✓	✓	✓	✓	++
Cyclophosphamide	Heme cancer	—	—	✓	—	—	+
Ifosfamide	Cervical, sarcoma	✓	—	+++	—	—	+
Antimicrotubule agent							
Docetaxel	Breast, lung	+/++	✓	++	++	++	✓
Nab-paclitaxel	Breast, pancreas	+/++	✓	—	—	—	+
Paclitaxel	Breast, lung	++	✓	+	—	+	—
Antimetabolite							
Capecitabine	Colorectal, breast	✓	✓	✓	—	++	+/++
5-Fluorouracil	Gastrointestinal	✓	✓	+	—	++/+++	✓
Hormone therapy							
Abiraterone acetate	Prostate	++	—	++	++/+++	++	—
Anastrozole	Breast	—	—	—	++/+++	++	++
Exemestane	Breast	—	—	—	++	++	+
Letrozole	Breast	—	—	—	++	++/+++	++
Tamoxifen	Breast	—	✓	—	++/+++	++	++
Monoclonal antibody-based targeted therapy							
Bevacizumab	Colorectal	++	✓	+/++	++/+++	+/++	++/+++
Brentuximab	Lymphoma	—	—	—	—	+	++
Cetuximab	Colorectal, HNC	++	—	✓	++	✓	+/++
Ipilimumab	Melanoma	—	—	—	—	—	—
Panitumumab	Colorectal	✓	—	—	++	++	+
Pertuzumab	Breast	—	—	++	—	—	—
Rituximab	Heme cancer	✓	—	—	++	++	++/+++
Trastuzumab	Breast, gastric	++	—	++/+++	++	—	+/++
Small-molecule targeted therapy							
Bortezomib	Multiple myeloma	+	—	+/++	+	+	+
Dasatinib (TKI)	Leukemia	++/+++	+/++	++	++	++	+/++
Erlotinib (TKI)	Lung	✓	—	—	—	++	++
Gefitinib (TKI)	Lung	✓	✓	—	—	+/++	✓
Imatinib (TKI)	CML	—	—	+/++	—	+++	+
Lapatinib (TKI)	Breast	✓	+++	++	—	—	—
Nilotinib (TKI)	CML	++	++	++	++	✓	+
Pazopanib (TKI)	RCC	—	—	+	+++	+/++	++
Sorafenib (TKI)	RCC, HCC	+	✓	+	+++	++	++
Sunitinib (TKI)	GIST, RCC	+	+	++/+++	+++	++	+/++
Vemurafenib (TKI)	Melanoma	++	✓	+	++	++	++
Miscellaneous							
Everolimus	RCC	—	—	++	++	—	+
Lenalidomide	Myeloma	+/++	+	++	++	++	++/+++
Temsirolimus	RCC	—	✓	—	++	+++	++

+++ Represents > 10%; ++ represents 1%-10%; + represents < 1% or rare; ✓ represents observed but precise incidence not well established; and — represents not well recognized complication with no/minimal data.

CML, chronic myeloid leukemia; GIST, gastrointestinal stromal tumour; HCC, hepatocellular carcinoma; Heme, hematological; HF, heart failure; HNC, head and neck cancer; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.

*Selected examples.

permanent dose-dependent damage; type II is associated with trastuzumab, a molecular-targeting agent, and results in non-dose-related damage, usually reversible on discontinuation.¹⁵⁻¹⁸

Among the systemic drugs with cardiotoxic potential, anthracyclines and trastuzumab have been studied most extensively.^{6,16,19-22} Anthracyclines, such as doxorubicin, have been used to successfully treat a variety of solid tumours and hematological malignancies. However, they are known to cause significant cardiac damage that might lead to severe cardiac dysfunction, failure, and even death.^{20,23} Anthracyclines, tyrosine kinase inhibitors (eg, lapatinib), 5-fluorouracil, cyclophosphamide, tamoxifen, and trastuzumab are known to cause prolonged QT interval.^{7,8} Alkylating agents, like cyclophosphamide, can cause milder forms of cardiac inflammation and arrhythmias.^{24,25} Antimicrotubule agents, such as docetaxel and paclitaxel, are often used to treat breast cancers and are well known for inducing bradycardia, myocardial ischemia, and HF.¹⁸ The antimetabolite drug class, which includes 5-fluorouracil and its prodrug, capecitabine, is associated with HF, coronary vasospasm, arrhythmia, and myocardial ischemia, which ranges from angina to acute myocardial infarction.^{6,26} Hormone therapies (eg, tamoxifen) are associated with thromboembolism.^{18,26} Finally, even though the novel small molecule- (eg, imatinib) and monoclonal antibody-based (eg, bevacizumab) therapies are more target-specific, they are still associated with various cardiovascular problems, particularly with thromboembolism.²⁷⁻³⁰ For example, bevacizumab is known to cause hypertension, thromboembolism, and myocardial ischemia, and imatinib is linked with edema and HF.^{9,31}

Monitoring and Detection

Before starting chemotherapeutic interventions, a complete medical history and physical examination should be obtained to appropriately risk-stratify patients and optimize cardiac surveillance (see Table 2). Patients with a medical history indicating obesity, diabetes, metabolic syndrome, hypertension, family history of cardiomyopathy, and previous or concomitant cancer treatments (eg, radiotherapy) are at higher risk for developing cardiovascular complications and might require interventions, such as cardioprotectant agents (eg, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and β -blockers).^{52,53} Chemotherapy and radiotherapy used in cancer treatments are well recognized causes of future cardiac complications. Radiation exposure might directly cause or indirectly increase susceptibility to cardiac damage, especially in young patients over time, depending on the dose and area radiated.^{5,32} Newer techniques, such as proton and intensity-modulated radiation therapy, can reduce radiation-induced cardiotoxicity.^{5,54}

Patients receiving systemic drugs with cardiotoxic potential should consider having serial assessments to monitor heart function at baseline, during treatment and, in some cases, posttreatment.³² Specific recommendations for surveillance of chemotherapy-induced cardiotoxicity have not been well established. The Canadian Trastuzumab Working Group recommends that left ventricular ejection fraction (LVEF) should be assessed using echocardiography or multigated acquisition scan at least every 3 months until trastuzumab

Table 2. Potential strategies to reduce chemotherapy-induced cardiotoxicity

Strategy	Example(s)
General approach	
Identify and/or treat risk factors	Anthracycline exposure, prior chemotherapy or radiation, young age, female, pre-existing cardiovascular disorders and electrolyte imbalances
Limit cumulative anthracycline dose (mg/m ²) ^{2,11,12,32}	Daunorubicin < 400-900 Doxorubicin < 300-700 Liposomal doxorubicin < 550 Epirubicin < 600-720 Idarubicin < 150 Mitoxantrone < 120
Limit drugs that prolong QTc interval	Antihistamines, 5-hydroxytryptamine antagonists
Limit risk of radiation-induced cardiotoxicity	Minimize dose to heart and heart volume in radiation field. Replace anterior-posterior opposed parallel pair beam radiation with intensity-modulated radiation therapy or proton therapy ⁵
Manage electrolyte imbalances	Hypocalcemia, hyperkalemia, hypokalemia, and hypomagnesium
Treat comorbidities	Coronary artery disease, dyslipidemia, hypertension
Alternative chemotherapy treatment/regimen	
Administration technique	Continuous infusion instead of bolus doxorubicin
Less cardiotoxic drugs	Epirubicin instead of doxorubicin; molecular targeting agents instead of anthracyclines
Liposomal formulation	Liposomal doxorubicin instead of adriamycin
Hold or discontinue chemotherapy	Symptomatic and/or asymptomatic with <40% left ventricular ejection fraction
Cardiovascular drugs	See Tables 3 and 4 for details

therapy is completed, with annual follow-ups only for patients with cardiac symptoms or LVEF decline.¹⁶ Long-term monitoring guidelines from the Children's Oncology Group can be considered for survivors of pediatric malignancies.^{5,55}

Table 5 shows the common diagnostic tools that might be used to evaluate cardiac function. Cardiac dysfunction is typically defined as an LVEF decline of at least 5% from baseline with HF symptoms, or > 10% reduction without symptoms to < 55%.⁵⁶ LVEF is usually assessed using transthoracic echocardiography or radionuclide angiography (multigated acquisition scan), or occasionally using cardiac magnetic resonance imaging (MRI).^{24,57,58} Cardiac MRI is the most accurate and reproducible technique for measuring cardiac function and tissue characterization, but has limited availability and high cost.²⁴ Cardiac MRI might also detect myocardial inflammation or scar tissue related to cardiotoxicity.⁵⁹ Although echocardiography is widely available, relatively inexpensive, and allows assessment of diastolic function, it is subject to greater inter- and intraobserver variability.^{16,24,59-61} Radionuclide angiography is reproducible and widely available, but exposes patients to ionizing radiation (contributing to increased cumulative radiation doses, especially when serial monitoring is required) and provides limited information on diastolic and valve function.^{26,57} Cardiotoxicity might also manifest as arrhythmias, which can be

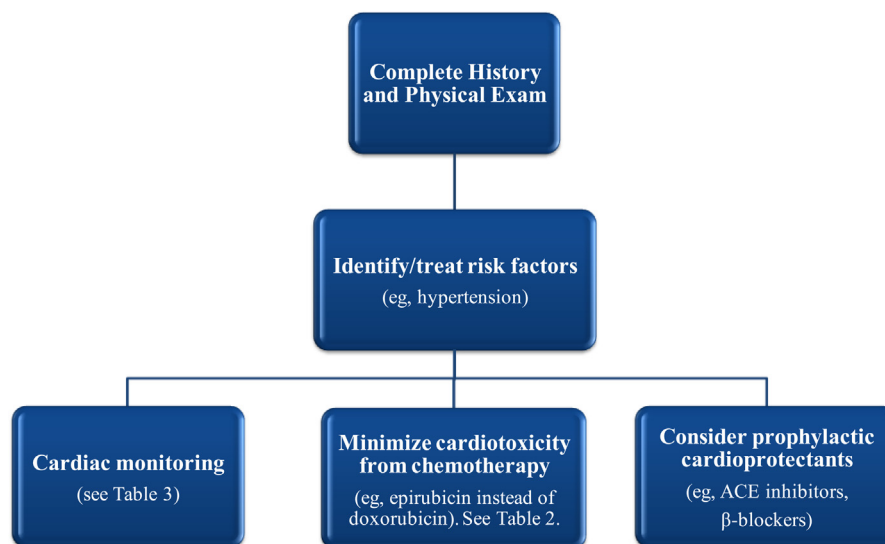


Figure 1. Flow chart for management of chemotherapy-induced cardiotoxicity. ACE, angiotensin-converting enzyme.

routinely monitored using 12-lead electrocardiography. Holter and event loop monitors are useful for workup of patients with syncope presumed to be related to arrhythmia.⁶² QT prolongation is an increasingly recognized side effect.^{7,10,62}

Sensitive diagnostic tools for detecting predictive markers and earlier signs of subclinical cardiotoxicity, before damage becomes overt and permanently irreversible, are of significant interest. Imaging techniques, such as tissue velocity imaging (TVI) and strain rate imaging using echocardiography, might be more accurate predictors of future HF than the conventional LVEF parameter. A few clinical studies assessing TVI and strain rate imaging show that decreases in these indices precede LVEF decline during anthracycline and trastuzumab therapy.^{61,63-65} TVI is particularly useful for evaluating diastolic function of the left ventricle.⁶⁶ Troponins and natriuretic peptides have also shown promising potential to predict cardiac dysfunction before identification using echocardiography.^{24,26,67} Increases in levels of troponins I and T are indicative of cardiomyocyte injury, and brain natriuretic peptides (BNPs) and N-terminal prohormone of BNP might reflect increased myocardial stress.^{24,68,69} These biomarkers have been validated in several studies to be predictive of cardiotoxicity and are especially useful because they are specific to cardiovascular damage and might indicate extent of reversibility.^{58,68,70}

Prevention and Management

Patients who have a moderate to high risk of developing or are suspected to have cardiotoxicities indicated according to their medical history or abnormal imaging and biomarker levels, might warrant treatment of risk factors, alternative cancer treatment options, and administration of cardioprotectants (see Fig. 1).^{16,17} Limiting the cumulative anthracycline dose appears to be the most effective in reducing cardiac risk.²⁶ Substitution with less cardiotoxic drug alternatives, such as epirubicin instead of doxorubicin, or using liposomal formulations (eg, liposomal doxorubicin) for more specific delivery to the target site can further reduce

adverse cardiac effects.^{20,71} In some cases, it might be necessary to withhold or terminate systemic treatment, such as when LVEF declines to < 40%.³² Other strategies involve avoiding or minimizing the use of other drugs that prolong QTc interval (eg, 5-hydroxytryptamine antagonists, a commonly used class of drugs for preventing chemotherapy-induced nausea and vomiting, and antihistamines),^{7,10} minimizing cardiac exposure to radiation,^{2,5,32} managing and treating comorbidities, and correcting electrolyte imbalances.³²

In the past decade, several studies have evaluated the role of standard HF therapies as cardioprotectants in treating and preventing cardiotoxicity induced by systemic drugs. A summary of the studies evaluating ACE inhibitors, ARBs, and β -blockers is shown in Table 3 (used prophylactically) and Table 4 (used for treatment of cardiotoxicity). The data in totality suggest that these standard HF medications are also effective cardioprotectants and can mitigate cardiotoxicity when used prophylactically. A meta-analysis of cardioprotectants by Kalam and Marwick revealed that, when used in a prophylactic setting, ACE inhibitors and β -blockers significantly reduce the occurrence of cardiac events, although it is unclear whether all patients should receive such prophylaxis.⁷² At present, based on the HF treatment guidelines (stage B), these therapies are indicated in patients who exhibit HF symptoms or a decrease in LVEF.^{16,54} Patients receiving cardiotoxic drugs can be regarded as stage A HF, and if they experience an asymptomatic decline in LVEF, they should be treated as per stage B HF guidelines.^{17,73} For example, in the event of decreased LVEF to < 50%, ACE inhibitors may be used (or ARBs) in combination with β -blockers to preserve cardiac function and prevent symptomatic HF.^{16,74} These pharmacological interventions have antioxidant properties and might function by inhibiting free radical formation caused by chemotherapy.^{1,53} The potential for proangiogenic effects using HF therapies to affect cancer prognosis is not well established, but some studies suggest that they might promote tumour inhibition.⁷⁵⁻⁷⁸ Several studies have shown

Table 3. Summary of studies involving prophylactic use of cardioprotectant agents

Study (year)	Study design, follow-up	Cancer type	Chemotherapy	Interventions	Study results*
ARB					
Cadeddu et al. (2010) ³³ ; Dessi et al. (2011) ³⁴ ; Dessi et al. (2013) ³⁵	RCT, 18 months	N = 49 Multiple	Epirubicin	Telmisartan (n = 25) Placebo (n = 24)	LVEF: NS changes throughout follow-up in both arms
Nakamae et al. (2005) ³⁶	RCT, 7 days	N = 40 non-Hodgkin lymphoma	CHOP chemotherapy	Valsartan (n = 20) Control (n = 20)	ARB maintained BNP, but not ANP. Control subjects increased in all, but returned to baseline ($P < 0.05$). LVEF change was NS in both groups
β-Blocker					
El-Shitany et al. (2012) ³⁷	RCT, 7 days	N = 50 pediatric types	Adriamycin	Carvedilol (n = 25) None (n = 25)	Tn I: No intervention arm increased (100%; $P = 0.005$) vs BB arm decreased (62%; $P = 0.0008$)
Kalay et al. (2006) ³⁸	RCT, 6 months	N = 50 multiple	Adriamycin or epirubicin	Carvedilol (n = 25) Placebo (n = 25)	Mean ejection fraction: NS changes in BB group, but lower in the placebo group; $P < 0.05$
Kaya et al. (2012) ³⁹	RCT, 6 months	N = 45 breast cancer	Anthracycline	Nebivolol (n = 27) Placebo (n = 18)	LVEF in the placebo arm decreased more than in the BB arm ($P = 0.01$). NT-proBNP in the placebo arm increased, but was maintained in the BB arm ($P = 0.03$)
Seicean et al. (2013) ⁴⁰	Observational, 3 years	N = 318 breast cancer	Anthracycline or trastuzumab	BBs (n = 106) Control (n = 212)	Continuous BBs had lower risk of new HF events (HR, 0.2; $P = 0.003$)
Multiarm therapy					
Bosch et al. (2013) ⁴¹	RCT, 6 months	N = 90 hematological malignancies	Intensive chemotherapy	Enalapril or carvedilol (n = 45) Control (n = 45)	LVEF: ACEI/BB no change vs control decreased; $P < 0.05$
Georgakopoulos et al. (2010) ⁴²	RCT, 3 years	N = 147 lymphoma	Doxorubicin	Metoprolol (n = 42) Enalapril (n = 43) Control (n = 40)	LVEF: NS changes at 12 months in any arm; $P = 0.06$
Blaes et al. (2010) ¹	Retrospective cohort	N = 142 multiple	Doxorubicin	Cases (n = 22) Control (n = 121)	LVEF: ACEIs are protective, but BBs are not
Farolfi et al. (2013) ⁴³	Retrospective	N = 179 breast cancer	Adjuvant trastuzumab	BB (n = 12) ACEI/ARB (n = 13) ACEI/ARB with BB (n = 17)	Cardiac AE risk greater in BB or ACEI/ARB or both compared with none (OR, 1.46; 95% CI, 0.77-2.76); $P = NS$
Oliva et al. (2012) ⁴⁴	Retrospective	N = 499 breast cancer	Adjuvant trastuzumab	ACEI/ARB (n = 91) BB (n = 59) ACEI/ARB with BB (n = 26) Control (n = 323)	ACEI/ARB with BB had LVEF recovery from 3-12 months; $P = 0.03$
Wilop et al. (2009) ⁴⁵	Retrospective	N = 287 lung cancer	Platinum-based chemotherapy	ACE/ARB (n = 52) BB (n = 54) Other (n = 124)	ACE/ARB group had 3.1 months longer median survival than control (HR, 0.56; $P = 0.03$). BB had NS differences

ACEI, angiotensin-converting enzyme inhibitor; AE, adverse event; ANP, atrial natriuretic peptide; ARB, angiotensin receptor blocker; BB, β-blocker; BNP, brain natriuretic peptide; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; NS, not statistically significant; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OR, odds ratio; RCT, randomized controlled trial; Tn, troponin.

* Select end points and results. See [Supplemental Table S1](#) for more details.

dextrazoxane, an iron chelator, to be promising in preventing doxorubicin-related cardiotoxicity without compromising antineoplastic effects and is recommended by the American Society of Clinical Oncology for certain indications.^{47,72,79-81} It is also unclear whether certain HF therapies are more suitable for specific cancer populations. Drug choice is usually based on clinical presentation and standard HF guidelines. Although there are some discrepancies regarding their effectiveness, these drugs have been recommended for use in at-risk patients undergoing systemic treatment and these patients should be treated as per HF guidelines.^{73,74}

Studies have primarily assessed the following interventions in cancer patients: ACE inhibitors (eg, enalapril); ARBs (eg, telmisartan and valsartan); and β-blockers (eg, carvedilol and metoprolol). Most of these studies (see [Tables 3 and 4](#)) evaluated these interventions in cancer patients who were

exposed to anthracycline and/or trastuzumab. Overall, the full benefits of cardioprotectant agents are somewhat convoluted because these studies evaluated different drug combinations, patient characteristics, end points, and follow-up periods. However, it is evident that in most cases, cardioprotectant usage was associated with better surrogate end points, such as LVEF, and troponin and natriuretic peptide levels, in addition to lower incidence of cardiac adverse events, hospitalization, and deaths. Although selecting the optimal cardioprotectant is important, another study also underscored the importance of the time interval between termination of systemic treatment and initiation of HF therapy, because there was no complete recovery of LVEF after 6 months⁵⁰; hence, the need for active surveillance.

Additionally, exercise has been shown to be a promising intervention to mitigate the risks of chemotherapy-induced

Table 4. Summary of studies involving cardioprotectants in treatment of chemotherapy-induced cardiotoxicity

Study (year)	Study design, follow-up	Cancer type	Chemotherapy	Interventions	Study results*
ACEI					
Cardinale et al. (2006) ⁴⁶	RCT, 12 months	N = 114 multiple	High-dose chemotherapy	Enalapril (n = 56) Control (n = 58)	LVEF decrease: control (43%) vs ACEI (0%); $P < 0.001$
Lipshultz et al. (2002) ⁴⁷	Retrospective, 10 years (median)	N = 18 pediatric cancers	Doxorubicin	Enalapril (n = 18)	In first 6 years, ACEI improved LV function, but deteriorated at 6-10 years
Silber et al. (2004) ⁴⁸	RCT, 5 years	N = 135 pediatric cancers	Anthracycline	Enalapril (n = 69) Placebo (n = 66)	Enalapril reduced LV end-systolic wall stress by 9% by year 5
BB					
Noori et al. (2000) ⁴⁹	Retrospective case-controlled	N = 24 multiple	Adriamycin	Case ACM with BB (n = 8) Control IDC with BB (n = 16)	BB improved overall LVEF by 13% in adriamycin-induced cardiomyopathy arm vs 6% in the IDC arm; $P = 0.23$
Multiarm therapy					
Cardinale et al. (2010) ⁵⁰	Prospective, observational, 36 months (mean)	N = 201 multiple	Anthracycline	Enalapril alone (n = 72) Enalapril with carvedilol (n = 129)	LVEF recovery: 42% responders, 13% partial, 45% nonresponders. No complete LVEF recovery after 6 months; cardiac events: responders, 5%; partial, 31%; and nonresponders, 29%; $P < 0.001$
Tallaj et al. (2005) ⁵¹	Prospective, observational, 71 ± 58 months (mean)	N = 25 Multiple	Doxorubicin	ACEI (n = 23) ARB (n = 2) ACEI/ARB (n = 15)	LVEF: improved by ACEI with BB ($P = 0.028$), not seen in ACEI ($P = 0.054$)

ACEI, angiotensin-converting enzyme inhibitor; ACM, adriamycin-induced cardiomyopathy; ARB, angiotensin receptor blocker; BB, β -blocker; IDC, idiopathic dilated cardiomyopathy; LV, left ventricular; LVEF, LV ejection fraction; NS, not statistically significant; RCT, randomized controlled trial.

*Select end points and results. See [Supplemental Table S2](#) for more details.

cardiotoxicity in breast cancer survivors.⁸²⁻⁸⁵ Although specific exercise regimens and intensities vary across studies, a meta-analysis has confirmed the role exercise plays in improving overall cardiorespiratory function.⁸⁶ In particular, in a review, the authors concluded that exercise before or during doxorubicin treatment can attenuate injury to left ventricular systolic and diastolic function, but data are largely limited to animal models.⁸⁷ In contrast, a small study (n = 17) showed that exercise was unable to maintain LVEF during adjuvant trastuzumab treatment.⁸⁸

Future Directions

The present review is limited by the paucity of specific evidence-based recommendations for prevention and treatment of chemotherapy-induced cardiotoxicity. The recommendations for detecting, monitoring, and managing chemotherapy-induced cardiotoxicity are largely extrapolated from HF guidelines from the general population to cancer survivors. Further research into the evolving role of tertiary care centres in cardio-oncology is warranted. Results of recent studies have suggested the importance of centralized care by

Table 5. Screening/diagnostic tests for chemotherapy-induced cardiotoxicity

Diagnostic tool	Assessment	Advantages	Disadvantages
Cardiac MRI	LVEF; cardiac structure; systolic and diastolic function	<ul style="list-style-type: none"> • Most accurate and reproducible • Tissue characterization (edema/scar) • Versatile 	<ul style="list-style-type: none"> • Contraindication to MRI • Expensive • Gadolinium contrast contraindicated in severe CKD • Less available • Time-consuming
12-Lead ECG	Arrhythmia, prolonged QT	<ul style="list-style-type: none"> • Easy to perform • Inexpensive • Wide availability 	<ul style="list-style-type: none"> • Limited information on cardiac structure, and systolic and diastolic function
ECG	LVEF; cardiac structure; systolic and diastolic function	<ul style="list-style-type: none"> • Inexpensive • Widely available • Versatile 	<ul style="list-style-type: none"> • Inter/intraobserver variability
Holter	Arrhythmia	<ul style="list-style-type: none"> • Easy to perform • Inexpensive • Wide availability 	<ul style="list-style-type: none"> • Limited information on cardiac structure, systolic and diastolic function
Radionuclide angiography (MUGA scan)	LVEF; systolic function	<ul style="list-style-type: none"> • Reproducible • Widely available 	<ul style="list-style-type: none"> • Limited information on diastolic and valve functions • Low temporal and spatial resolution • Radiation exposure

CKD, chronic kidney disease; ECG, electrocardiography; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multi-gated acquisition.

experienced clinicians in high-volume centres for adequate cardiac monitoring during adjuvant trastuzumab treatment, which might be associated with better use of cancer therapies and better cardiac outcomes.^{89,90} More studies are needed to provide optimal cardiovascular monitoring and management of cancer survivors.

At present, studies are ongoing to evaluate cardioprotectant agents in larger prospective randomized controlled trials (see [Supplemental Table S3](#)). NCT01009918, the largest randomized controlled trial to date, is currently being conducted and will involve 468 patients undergoing trastuzumab chemotherapy to study the cardioprotective effects of lisinopril. The International Cardioncology Society (ICOS)-ONE trial is the only study that is designed to determine whether cardioprotectant usage is the most optimal in a prophylactic setting or after cardiotoxicity is indicated (NCT01968200). Enalapril will be administered concomitantly with chemotherapy in one arm and after anthracycline-induced cardiac injury in another arm (NCT01968200). Finally, in NCT01708798, the potential ability of the aldosterone antagonist, eplerenone, to prevent doxorubicin-induced cardiotoxicity, will be explored in a randomized controlled trial of breast cancer patients. Most of these studies have already or are expecting to complete accrual by 2014, except for NCT01724450 and NCT01009918 (expected for 2016). Clearly, there is much interest in using cardioprotectant agents for mitigating the harmful cardiac effects of antineoplastic drugs, and this appears to be a promising alternative to changing or even withdrawing treatment. Further research should evaluate the effect of cardioprotectant agents for other systemic drugs aside from anthracyclines and trastuzumab, and whether their effects can be optimized in a prophylactic or treatment setting.

Conclusions

Cardiovascular complications from chemotherapeutic agents might potentially limit the survival and quality of life of cancer survivors. Fortunately, premature cardiac-related morbidity and mortality might be alleviated using preventative strategies that include frequent monitoring and administration of cardioprotectant agents. Surveillance and earlier detection using biomarkers will be essential to mitigate cardiac risk from newer drugs, because their pathophysiological mechanisms and degree of reversibility remain to be elucidated. Further investigations into the usage of ACE inhibitors, ARBs, and β -blockers in larger randomized trials and in different chemotherapy settings would be helpful to guide patient management. As newer systemic drugs are developed and used in clinical practice, there will be a greater need for collaboration among health care providers in the growing field of cardio-oncology to provide optimal contemporary treatment for cancer without compromising cardiac health in the long-term.

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Supplementary Material

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