Cancer and Cardiovascular Health: A Multidisciplinary Approach

Susan Dent, MD, FRCPC, FICOS

Wilmot Cancer Institute, Department of Medicine, University of Rochester, New York

Corresponding author:
Susan Dent, MD
Wilmot Cancer Institute
601 Elmwood Avenue
Rochester, NY 14642
Email: Susan_Dent@urmc.rochester.edu
Tel: (585) 275-5830

Abstract: Early detection and improved cancer therapies have led to increases in cancer survivorship. There were 18.1 million cancer survivors in the United States alone in 2022, and this number will grow to 21.6 million by 2030. Cancer survivors are at increased risk for non–cancer-related morbidity and mortality, including cardiovascular disease. Cardio-oncology has emerged as a new subspecialty of medicine, dedicated to improving the cardiovascular health of patients with cancer and facilitating the administration of the best cancer therapy while optimizing cardiovascular health. Contemporary cancer treatments are associated with multiple types of cancer treatment–related cardiac dysfunction (CTRCD), including heart failure, vascular toxicities, arrhythmias/corrected QT prolongation, hypertension, and myocarditis. In 2022, the European Society of Cardiology published comprehensive guidelines that endorsed the Heart Failure Association/International Cardio-Oncology Society baseline risk stratification tool for assessing all patients with cancer before cancer therapy is started. Primary prevention strategies can be considered for patients at high risk and very high risk for CTRCD, with the goal of facilitating the delivery of cancer therapy while minimizing the risk of cardiovascular toxicity. Dedicated multidisciplinary cardio-oncology clinics have emerged across North America, Europe, South America, Asia, South Africa, and Australia to enhance cancer care while optimizing cardiovascular health.

Keywords
Cancer, cardio-oncology, cardiovascular disease, multidisciplinary care, primary prevention, risk stratification

Introduction

Early detection and improved cancer therapies have led to increases in cancer survivorship. There were 18.1 million cancer survivors in the United States alone in 2022, and this number is expected to grow to 21.6 million by 2030.[1] Although gains in life expectancy are to be applauded, it is important to understand that cancer survivors are at increased risk of non–cancer-related morbidity and mortality, including cardiovascular disease.[2] Traditionally, cancer providers and individuals faced with a cancer diagnosis have focused on treatments that will provide the best chance of "cure" or "optimal control" in the setting of advanced disease. Less attention has been given to the long-term consequences of anticancer treatment and its potential

effect on non–cancer-related morbidity and mortality, including cardiovascular disease. As cancer care providers, however, we have known for decades that cancer therapies can have a negative effect on cardiovascular health. Anthracyclines—the backbone of cancer therapy for both solid and hematologic malignancies—are associated with an increased risk of heart failure, which can manifest clinically years after the completion of treatment.[3] Targeted agents such as trastuzumab have revolutionized the treatment of human epidermal growth factor receptor 2 (HER2)–positive breast cancer but are also associated with heart failure, although it is often reversible.[4] Tyrosine kinase inhibitors such as sunitinib are life-sustaining in advanced renal cell carcinoma but are associated with an increased risk for hypertension.[5] Cardiovascular morbidity and mortality threaten to attenuate the survival gains witnessed with novel cancer treatments and early detection of disease. Starting several years out from their diagnosis, postmenopausal women with early-stage breast cancer are at greater risk of mortality from cardiovascular disease than from a recurrence of their cancer.[6] In a Canadian population-based retrospective cohort study, at a median of 11.8 years, cancer survivors were 33% more likely than individuals without a cancer diagnosis to die of cardiovascular disease.[7] In a large registry study, Wang and colleagues used competing mortality curves to investigate when the cumulative cardiovascular mortality rate began to outweigh the cumulative cancer mortality rate for patients who were at least 10 years out from their cancer diagnosis. At the 15th year, cardiovascular mortality surpassed cancer mortality as the primary cause of death.[8] In the modern era of cancer care, providers must consider both the short- and long-term consequences of cancer treatments, including their effect on cardiovascular health.

Cardio-oncology has emerged as a new subspecialty of medicine, dedicated to improving the cardiovascular health of patients with cancer and facilitating the administration of the best cancer therapy while optimizing cardiovascular health. The effective cardiovascular care of cancer survivors hinges on collaboration between specialists and patients, underscoring the importance of a shared care model in survivorship.

Cardiovascular Toxicity of Modern Cancer Therapies

Chemotherapeutic agents such as anthracyclines continue to play an important role in the treatment of both solid and hematologic cancers.[3] Although cardiotoxicity has historically been defined by left ventricular (LV) dysfunction associated with anthracyclines and HER2-targeted therapies,[3,9] contemporary cancer treatments are associated with multiple types of cancer treatment–related cardiac dysfunction (CTRCD), including heart failure, vascular toxicities, arrhythmias/corrected QT (QTc) prolongation, hypertension, and myocarditis.[10]

LV dysfunction has been reported in clinical trials with HER2-targeted antibody-drug conjugates (ADCs) such as ado-trastuzumab emtansine, also known as T-DM1 (Kadcyla, Genentech), and fam-trastuzumab deruxtecan, also known as T-DXd (Enhertu, Daiichi-Sankyo/AstraZeneca), although the rates have been modest (<1% and 1.6%, respectively).[11] In the landmark DESTINY-Breast studies (01, 03, 04, 06, 12), the incidence of T-DXd–associated decrease in LV ejection fraction (LVEF) was between 1.6% and 11.8% (DB-01, 1.6%; DB-03, 2.3%; DB-04, 4.6%; DB-06, 8.1%; DB-12, 10.8%-11.8%).[12-18]

Vascular toxicities include a heterogeneous group of clinical entities characterized by the injury of arterial and/or venous vessels (eg, vasospasm, acute thrombosis) related to different types of cancer treatment.[10] Hypertension, defined as an increase in blood pressure to more than 130/80 mm Hg, may be the result of the use of targeted therapies; these include tyrosine kinase inhibitors such as sunitinib, proteasome inhibitors such as carfilzomib (Kyprolis, Amgen), and mammalian target of rapamycin (mTOR) inhibitors.[10]

Cancer treatments may also alter the cardiac electrophysiology, leading to alterations in normal rhythm. Arrhythmias can range from benign ectopic beats to life-threatening conditions such as atrial fibrillation and ventricular tachycardia, and they can occur as a direct consequence of heart failure but also independently. Taxanes may cause sinus bradycardia, atrioventricular block, or ventricular tachycardia.[10] In the treatment of breast cancer, particular interest has been shown in therapy-induced prolongation of the QTc interval with CDK4/6 inhibitors, which may predispose to potentially life-threating arrhythmias including torsades de pointes. In a recent meta-analysis of 14 randomized control trials comparing 8576 patients with hormone-positive breast cancer treated with CDK4/6 inhibitors vs controls, QTc prolongation was seen with both palbociclib (Ibrance, Pfizer; relative risk [RR], 1.51; 95% CI, 1.05-2.15; P=.025) and ribociclib (Kisqali, Novartis; RR, 3.12; 95% CI, 2.09-4.65; P<.001), although it was quantitatively much higher with ribociclib.[19]

Phosphatidylinositol 3-kinase alpha (PIK3CA) inhibitors such as alpelisib (Piqray, Novartis) have demonstrated activity in patients with PIK3CA-amplified metastatic breast cancer but are associated with hyperglycemia, which can contribute to metabolic syndrome.[20] Immune checkpoint inhibitors (ICIs) are now approved for several types of cancer but are associated with cardiovascular toxicity, including myocarditis.[21] Although rare (0.04%-1.14%), myocarditis is one of the most serious forms of ICI-induced cardiotoxicity, associated with mortality rates of 25% to 50%.[21]

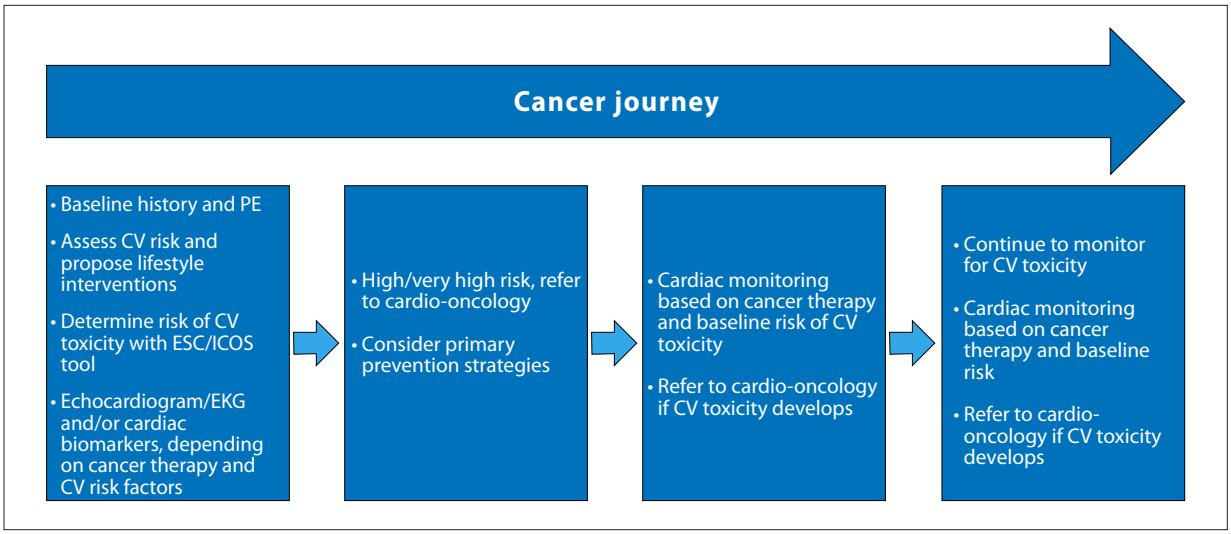

Figure. Cardio-oncology steps in cancer journey. CV, cardiovascular; PE, physical examination.

Risk Stratification

Summary

- *Patients receiving potentially cardiotoxic cancer therapy should be assessed for pre-existing cardiovascular disease, underlying cardiovascular risk factors (eg, hypertension), and previous exposure to cancer therapy (eg, anthracyclines), including radiotherapy (Figure).*
- *The risk of cardiovascular toxicity in patients receiving potentially cardiotoxic cancer therapy can be determined with the comprehensive guidelines published by the European Society of Cardiology (ESC), which endorsed the Heart Failure Association/International Cardio-Oncology Society (HFA/ICOS) baseline risk stratification tool.*
- *Baseline cardiac imaging, including echocardiography and 12-lead electrocardiography, should be performed before cancer therapy is started according to the patient's risk of cardiotoxicity and arrhythmias, respectively.*

The risk of cardiovascular toxicity is a dynamic variable that changes throughout survivorship depending on modifiable and nonmodifiable conditions, as well as the type, duration, and intensity of cancer therapies. Many individuals with a cancer diagnosis are older and more likely to have underlying comorbidities. The presence of comorbidities at the time of cancer diagnosis—such as hypertension, diabetes, and dyslipidemia—can have a significant effect on the ability to deliver effective cancer therapy (eg, anthracyclines in the setting of LV dysfunction) and, importantly, may have a negative effect on cancer outcomes.

In addition, underlying genetics, comorbidities (eg, hypertension, dyslipidemia), and social determinants of health can contribute to the acceleration of insulin resistance, glucose intolerance, and dyslipidemia, contributing to the early development of cardiovascular disease.[22,23]

In 2022, the ESC published comprehensive guidelines on cardio-oncology[24] that endorsed the use of the HFA/ICOS baseline risk stratification tool[25] for all patients with cancer before the initiation of cancer therapy (class I recommendation; level of evidence, B). The development of a risk proforma for 9 different classes of cancer drugs was based on previous risk stratification tools and expert opinion. Unique to this risk stratification tool (https://www.cancercalc.com/hfa-icos_cardio_oncology_risk_assessment.php) is the inclusion not only of the potential cardiotoxic cancer therapy being delivered but also of underlying cardiovascular risk factors (eg, hypertension), pre-existing cardiovascular disease, previous exposure to cardiotoxic drugs, lifestyle risk factors (eg, smoking), previous exposure to radiation therapy, and, when available, cardiac biomarkers (eg, B-type natriuretic peptide) and cardiovascular imaging (eg, echocardiograms to assess LVEF). Patients are categorized as being at low, medium, high, or very high risk of future cardiovascular toxicity (14.0% low, 16.7% medium, 30.3% high/very high; P=.002).[25] Several studies are prospectively evaluating the HFA/ICOS risk score. The CARDIOTOX study applied the HFA/ICOS risk stratification tool to patients undergoing anthracycline-based chemotherapy. At a median follow-up of 54.8 months, the incidence rates of symptomatic or moderately to severely symptomatic CTRCD and all-cause mortality significantly increased with higher HFA/ICOS scores in high-risk patients (HR, 28.74; 95% CI, 9.33-88.5; P<.001) and in very high-risk patients (HR, 7.43; 95% CI, 3.21-17.2; P<.001). The HFA/ICOS score demonstrated good calibration and discrimination for predicating symptomatic or severely/moderately asymptomatic CTRCD at 12 months.[26] Risk stratification can guide further cardiovascular testing, including measurement of cardiac biomarkers such as

cardiac troponin and natriuretic peptides, as well as cardiovascular imaging. Risk stratification can also guide recommendations for follow-up and referral to a cardio-oncologist. Primary prevention strategies can be considered for patients at high and very high risk of CTRCD, with the goal of facilitating the delivery of cancer therapy while minimizing the risk of cardiovascular toxicity.[25]

Prevention Strategies

Summary

- *Oncologists should actively screen and manage/refer patients with cancer who have modifiable cardiovascular risk factors, providing recommendations for smoking cessation, dietary changes, weight management, and exercise.*
- *Patients at high or very high risk for cardiovascular toxicity should be referred to a cardio-oncology clinic to optimize the medical management of their cardiovascular risk/disease.*
- *Cardiac monitoring, including echocardiography, 12-lead electrocardiography, and measurement of cardiac biomarkers during cancer therapy, is based on the class of cancer therapy and an individual's baseline cardiovascular risk (see the ESC's HFA/ICOS guidelines).*[24]

Prevention strategies should be considered for patients with cancer who are exposed to potentially cardiotoxic cancer therapy, particularly those at high and very high risk for CTRCD. All patients should be evaluated for modifiable cardiovascular risk factors, and modifications of cancer treatment and potential cardioprotective interventions should be based on cardiovascular risk at baseline.[24] Clinicians should screen for, and actively manage, modifiable cardiovascular risk factors such as smoking, hypertension, diabetes, dyslipidemia, and obesity. Increasing evidence indicates that aggressive control of cardiac risk factors—including hypertension, hyperlipidemia, and diabetes—along with lifestyle modifications such as dietary changes and exercise may decrease the likelihood of adverse cardiotoxic effects from cancer therapy.[27]

When combined with weight loss, a low-fat diet that is high in fruits, vegetables, and whole grains decreases overall cardiovascular risk.[28] Tobacco smoking is a well-known cardiovascular risk factor; smoking cessation is associated with a 36% reduction in the risk of major adverse cardiac events in cancer survivors.[29] Patients with cancer should be referred to a smoking cessation program that relies on both pharmacologic therapy and psychologic counseling. Obesity and a sedentary lifestyle increase the risk for cardiovascular disease. Exercise and healthful nutrition play a role in preventing cancer, decreasing cancer-related and all-cause mortality, and improving health-related outcomes for cancer survivors.[31] Current guidelines recommend that patients with cancer and survivors of cancer engage in moderate-intensity exercise for at least 150 minutes per week and in 2 to 3 weekly sessions of strength training.[30]

The American Heart Association (AHA) has proposed a comprehensive model of structured exercise training for cardiac rehabilitation in patients with cancer, called cardio-oncology rehabilitation (CORE).[31] CORE can identify patients at high risk for cardiovascular disease and use a multimodality approach to cardiac rehabilitation to prevent or mitigate cardiovascular events. In the ONCORE randomized controlled trial, an exercise-based CORE program was shown to be safe and to help attenuate LVEF decline in patients with breast cancer receiving cardiotoxic therapy.[32] In a prospective study of 55 women with breast cancer and no comorbid cardiovascular disease or risk factors for cardiovascular disease, exercise correlated with a decrease in cardiovascular events.[33] Despite the benefits of exercise in patients with cancer, uptake in clinical practice has been minimal. This omission is likely due to several factors, including lack of infrastructure support and insurance coverage. Rurality is another important cardiovascular risk factor; the incidence of cardiovascular disease is higher in residents of rural areas than in their urban counterparts. A lower socioeconomic status is also considered to be a cardiovascular risk factor.[34]

Pharmacologic Approach

Summary

- *Oncologists should consider alternative, noncardiotoxic therapy (if available) in patients with cancer who are at high or very high risk of CTRCD.*
- *Oncologists may consider dexrazoxane, which has been shown to mitigate the risk of heart failure in patients with cancer who have been exposed to anthracyclines and are at high or very high risk of cardiotoxicity (class IIa recommendation; level of evidence, B).*
- *The use of cardioprotective agents, neurohormonal agents, statins, and sodium-glucose cotransporter 2 (SGLT2) inhibitors should be considered for patients with cancer at high/very high risk in the context of a multidisciplinary approach to cardio-oncology.*

Cardioprotective Agents

Dexrazoxane has been shown to mitigate the risk of heart failure in patients receiving anthracyclines but has not been widely adopted for adult cancer patients owing to concerns of decreased efficacy and myelosuppression in those with metastatic breast cancer. A meta-analysis by Macedo and colleagues showed that dexrazoxane reduced the risk of heart failure in patients with breast cancer undergoing anthracycline chemotherapy without affecting cancer outcomes (ie, progression-free survival and overall survival).[35] Dexrazoxane has been theorized to act as an iron chelator, preventing anthracyclines from generating free radicals that may induce cardiac myocyte apoptosis,

as well as preventing binding between topoisomerase IIβ and anthracyclines to reduce cardiotoxicity.[36] The ESC guidelines currently suggest that dexrazoxane be considered as a cardioprotective agent in patients at high or very high risk of cardiotoxicity (class IIa recommendation; level of evidence, B), such as those for whom a cumulative dose of doxorubicin exceeding at least 250 mg/m^2 or of epirubicin exceeding at least 600 mg/m^2 is anticipated.[24]

Neurohormonal Agents

For patients considered at high or very high risk of CTRCD, the ESC cardio-oncology guidelines recommend that angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and beta blockers be considered for primary prevention (class IIa recommendation; level of evidence, B). The benefits of this approach have been tested in several studies, mainly in patients with breast cancer or lymphoma, with mixed results. The PRADA, MANTICORE, and Guglin studies, which evaluated the benefit of beta blockers with or without ACE inhibitors in patients with early-stage breast cancer treated with anthracyclines with or without trastuzumab, demonstrated small but statistically significant benefits, with fewer patients experiencing a drop (1.5%-3%) in LVEF.[37] In contrast, in a similar patient population, the CECCY and Boekhout trials failed to demonstrate any significant benefit with this approach.[37] These trials have been hampered by small patient numbers, heterogeneous primary endpoints, and the fact that they were conducted in predominantly younger patients who had breast cancer with few comorbidities. The OVERCOME trial compared enalapril and carvedilol (vs placebo) in 90 patients with hematologic malignancies undergoing relatively intense chemotherapy with autologous hematopoietic stem cell transplant.[38] Patients in the intervention arm maintained their baseline LVEF (vs controls) and had a lower incidence of the combined event of death or heart failure (6.7% vs 22%; *P*=.036) and of death, heart failure, or a final LVEF of less than 45% (6.7% vs 24.4%; *P*=.02). The PROACT trial randomized 111 patients with cancer who were at relatively high risk for CTRCD (treated with doxorubicin at >300 mg/m^2) to enalapril or standard of care. Enalapril did not affect myocardial injury or cardiac outcomes as measured by troponin T level, LVEF, and global longitudinal strain.[39] In keeping with the current ESC guidelines, it is reasonable to consider neurohormonal primary prevention strategies in those patients with cancer who are considered to be at high or very high risk of CTRCD. The results of ongoing studies should help clarify the role of primary prevention with neurohormonal agents.[37]

Statins

Statins are thought to reduce cardiotoxicity via their anti-inflammatory and antioxidative effects, inhibiting small Ras homologous GTPases to reduce topoisomerase II inhibitor activity and the generation of reactive oxygen species.[40] The phase 2 PREVENT trial evaluated atorvastatin in patients with early breast cancer or lymphoma undergoing treatment with anthracyclines and showed no difference in LVEF decline.[41] Conversely, in the STOP-CA trial, the use of atorvastatin in patients who had lymphoma treated with an anthracycline was associated with a lower rate of CTRCD and less frequent LVEF reduction.[42] A retrospective study investigated the effect of statin exposure in high-risk patients with early breast cancer treated with an anthracycline and/or trastuzumab. Among the patients treated with anthracyclines, the use of statins was associated with a reduced risk of heart failure.[43] In the absence of a cardiovascular indication, currently no strong evidence is available to recommend statin therapy for patients with cancer as a primary prevention measure.[44] The 2022 ESC guidelines suggest that statins be used only in patients at high or very high risk of CTRCD.[24]

SGLT2 Inhibitors

SGLT2 inhibitors are a class of drugs that reduce cardiovascular events, particularly heart failure, in patients with or without type 2 diabetes; they also may have anticancer effects.[45] These agents have demonstrated not only a reduction in the incidence of hospitalization related to exacerbations of heart failure but also a decrease in mortality.[46,47] Retrospective cohort studies have shown that initiating these agents before anthracycline-based therapy in patients with cancer and type 2 non–insulin-dependent diabetes may lower rates of cardiac events, decrease mortality, and improve outcomes in patients with CTRCD/heart failure.[48] The EMPACT study, a prospective case-control study of 76 patients with breast cancer scheduled to undergo anthracycline-based chemotherapy and considered to be at high or very high risk of cardiotoxicity on the basis of their HFA/ICOS risk score, compared patients who were prescribed empagliflozin (Jardiance, Boehringer Ingelheim) at 10 mg/d 7 days before starting chemotherapy and who continued empagliflozin for 6 months vs a placebo group. No significant differences were noted between the groups in terms of clinical heart failure or mortality/hospitalization due to heart failure.[49] Further prospective studies are needed to clarify the role of SGLT2 inhibitors in patients with cancer treated with potentially cardiotoxic agents.

Multidisciplinary Care

Summary

- *It is important to establish a multidisciplinary team consisting of providers of oncology, cardiology, nursing, pharmacy, exercise physiology, and allied health care.*
- *Ideally, a cardiologist with specific training in cardio-oncology and an oncologist will work together to foster the development of a program.*

- *Multidisciplinary cardio-oncology rounds, journal clubs, and community speaking engagements can help foster a collaborative approach, increase engagement, and promote awareness of the cardio-oncology program.*

International organizations have endorsed cardio-oncology partnerships, including the American Society of Clinical Oncology, the European Society for Medical Oncology, the ESC, the American College of Cardiology, and the American Heart Association, resulting in several position papers and guidelines.[24,50-52] The ICOS (www.ic-os.org), a grassroots, not-for-profit organization, emerged in 2009 owing to the efforts of a small group of dedicated clinicians. This organization, which has a mandate of improving clinical care, educating health care providers and patients, and promoting research, has more than 1500 members from more than 30 countries. Its annual meeting, the Global Cardio-Oncology Summit, hosts more than 500 attendees each year.

Over the past 20 years, we have witnessed dedicated cardio-oncology clinics and programs emerging across North America, Europe, South America, Asia, South Africa, and Australia. When a cardio-oncology clinic is established, it is important to include a multidisciplinary team consisting of oncology, cardiology, nursing, pharmacy, exercise physiology, and allied health care providers. Ideally, both a cardiologist with specific training in cardio-oncology and an oncologist will work together to foster program development. Having an oncologist champion in a leadership role demonstrates commitment to the program and is critical for success. Establishing a dedicated cardio-oncology clinic with a stream-lined and timely referral processes for oncologists is crucial to providing recommendations for a patient's cancer treatment in a timely manner. Multidisciplinary cardio-oncology rounds should be strongly encouraged in cardio-oncology programs. Like a tumor board, this format permits cross-disciplinary discussion of complex cases, leading to shared decision making and ideally better clinical outcomes. The format also provides educational opportunities for all health care providers, including oncology and cardiology trainees. Cardio-oncology talks or journal clubs can provide further engagement and ideally lead to the development of research proposals. Community events or town halls can provide education for patients, their families, and the general public, promoting adherence and enhancing awareness of a cardio-oncology program.

Infrastructure support and strong communication among providers are essential components of a successful program.[53] Despite the value of cardio-oncology clinics, the accessibility gap between urban and rural communities in cardio-oncology contributes to health care disparities and may be an underrecognized determinant of health globally. Accessibility to resources will vary widely depending on the jurisdiction, therefore cardio-oncology services need to adapt to the local environment. Telehealth and artificial intelligence offer opportunities to provide timely care, irrespective of geography.[54] Effective cardio-oncology care hinges on collaboration between specialists and patients, underscoring the significance of models of shared care. A true partnership requires that all parties work together to improve the care of patients.

Conclusion

Traditional cytotoxic anticancer agents as well as newer targeted cancer therapies have led to significant gains in cancer survivorship. However, patients with cancer are at risk of CTRCD, which may lead to premature cardiovascular morbidity and mortality and attenuate the gains made in cancer-specific survival. Risk stratification before the initiation of cancer therapy can identify those patients at high or very high risk of cardiotoxicity and can facilitate referral to cardio-oncology to mitigate cardiovascular risk factors and discuss primary prevention strategies. These should include lifestyle modification (eg, diet and exercise), pharmacotherapy, and enhanced cardiovascular surveillance (in those at high or very high risk). Collaboration among cardiologists, oncologists, pharmacists, primary care providers, and allied health care professionals is needed to ensure that patients with cancer receive optimal cancer therapy while cardiovascular health is promoted.

Disclosures

Dr Dent has received consultant fees from AstraZeneca, Gilead Sciences, Pfizer, Novartis, Eli Lilly, Myocardial Solutions, and Citrus Oncology.

References

1. Tonorezos E, Devasia T, Mariotto AB, et al. Prevalence of cancer survivors in the United States. *J Natl Cancer Inst*. 2024;116(11):1784-1790.
2. Florido R, Daya NR, Ndumele CE, et al. Cardiovascular disease risk among cancer survivors: the atherosclerosis risk in communities (ARIC) study. *J Am Coll Cardiol*. 2022;80(1):22-32.
3. Camilli M, Cipolla CM, Dent S, Minotti G, Cardinale DM. Anthracycline cardiotoxicity in adult cancer patients: JACC: CardioOncology state-of-the-art review. *JACC CardioOncol*. 2024;6(5):655-677.
4. Onitilo AA, Engel JM, Stankowski RV. Cardiovascular toxicity associated with adjuvant trastuzumab therapy: prevalence, patient characteristics, and risk factors. *Ther Adv Drug Saf*. 2014;5(4):154-166.
5. Kappers MH, van Esch JH, Sluiter W, Sleijfer S, Danser AH, van den Meiracker AH. Hypertension induced by the tyrosine kinase inhibitor sunitinib is associated with increased circulating endothelin-1 levels. *Hypertension*. 2010;56(4):675-681.
6. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. *Breast Cancer Res*. 2011;13(3):R64.
7. Paterson DI, Wiebe N, Cheung WY, et al. Incident cardiovascular disease among adults with cancer: a population-based cohort study. *JACC Cardiooncol*. 2022;4(1):85-94.
8. Wang Z, Fan Z, Yang L, et al. Higher risk of cardiovascular mortality than cancer mortality among long-term cancer survivors. *Front Cardiovasc Med*. 2023;10:1014400.
9. Zhang L, Wang Y, Meng W, Zhao W, Tong Z. Cardiac safety analysis of anti-

HER2-targeted therapy in early breast cancer. *Sci Rep*. 2022;12(1):14312.
10. Herrmann J, Lenihan D, Armenian S, et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. *Eur Heart J*. 2022;43(4):280-299.
11. Dent SF, Morse A, Burnette S, Guha A, Moore H. Cardiovascular toxicity of novel HER2-targeted therapies in the treatment of breast cancer. *Curr Oncol Rep*. 2021;23(11):128.
12. Bardia A, Hu X, Dent R, et al; DESTINY-Breast06 Trial Investigators. Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. *N Engl J Med*. 2024;391(22):2110-2122.
13. Bardia A, Jhaveri K, Im SA, et al; TROPION-Breast01 Investigators. Datopotamab deruxtecan versus chemotherapy in previously treated inoperable/metastatic hormone receptor-positive human epidermal growth factor receptor 2-negative breast cancer: primary results from TROPION-Breast01. *J Clin Oncol*. 2025;43(3):285-296.
14. Cortés J, Kim SB, Chung WP, et al; DESTINY-Breast03 Trial Investigators. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *N Engl J Med*. 2022;386(12):1143-1154.
15. Harbeck N, Ciruelos E, Jerusalem G, et al; DESTINY-Breast12 study group. Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: a phase 3b/4 trial. *Nat Med*. 2024;30(12):3717-3727.
16. Modi S, Gambhire D, Cameron D. Trastuzumab deruxtecan in HER2-low breast cancer [reply]. *N Engl J Med*. 2022;387(12):1145-1146.
17. Modi S, Saura C, Yamashita T, et al; DESTINY-Breast01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med*. 2020;382(7):610-621.
18. LeVee A, Deutsh A, Lindgren ES, et al. New drugs, new toxicities: side effects of new and emerging breast cancer therapies. *Am Soc Clin Oncol Educ Book*. 2025;45(3):e473384.
19. Murad B, Reis PCA, Deberaldini Marinho A, et al. QTc prolongation across CDK4/6 inhibitors: a systematic review and meta-analysis of randomized controlled trials. *JNCI Cancer Spectr*. 2024;8(5):pkae078.
20. Tankova T, Senkus E, Beloyartseva M, et al. Management strategies for hyperglycemia associated with the α-selective PI3K inhibitor alpelisib for the treatment of breast cancer. *Cancers (Basel)*. 2022;14(7):1598.
21. Palaskas N, Lopez-Mattei J, Durand JB, Iliescu C, Deswal A. Immune checkpoint inhibitor myocarditis: pathophysiological characteristics, diagnosis, and treatment. *J Am Heart Assoc*. 2020 Jan 21;9(2):e013757.
22. Powell-Wiley TM, Baumer Y, Baah FO, et al. Social determinants of cardiovascular disease. *Circ Res*. 2022;130(5):782-799.
23. Zullig LL, Sung AD, Khouri MG, et al. Cardiometabolic comorbidities in cancer survivors: JACC: CardioOncology state-of-the-art review. *JACC Cardiooncol*. 2022;4(2):149-165.
24. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43(41):4229-4361.
25. Lyon AR, Dent S, Stanway S, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. *Eur J Heart Fail*. 2020;22(11):1945-1960.
26. Rivero-Santana B, Saldaña-García J, Caro-Codón J, et al. Anthracycline-induced cardiovascular toxicity: validation of the Heart Failure Association and International Cardio-Oncology Society risk score. *Eur Heart J*. 2025;46(3):273-284.
27. Dent SF, Kikuchi R, Kondapalli L, et al. Optimizing cardiovascular health in patients with cancer: a practical review of risk assessment, monitoring, and prevention of cancer treatment-related cardiovascular toxicity. *Am Soc Clin Oncol Educ Book*. 2020;40:1-15.
28. Chlebowski RT, Aiello E, McTiernan A. Weight loss in breast cancer patient management. *J Clin Oncol*. 2002;20(4):1128-1143.
29. Lee HH, Lee H, Bhatt DL, et al. Smoking habit change after cancer diagnosis: effect on cardiovascular risk. *Eur Heart J*. 2024;45(2):132-135.
30. Ng AH, Ngo-Huang A, Vidal M, et al. Exercise barriers and adherence to recommendations in patients with cancer. *JCO Oncol Pract*. 2021;17(7):e972-e981.
31. Gilchrist SC, Barac A, Ades PA, et al. Cardio-oncology rehabilitation to manage cardiovascular outcomes in cancer patients and survivors: a scientific statement from the American Heart Association. *Circulation*. 2019;139(21):e997-e1012.
32. Díaz-Balboa E, González-Salvado V, Rodríguez-Romero B, et al. A randomized trial to evaluate the impact of exercise-based cardiac rehabilitation for the prevention of chemotherapy-induced cardiotoxicity in patients with breast cancer: ONCORE study protocol. *BMC Cardiovasc Disord*. 2021;21(1):165.
33. Nagy AC, GulAcsi-BArdos P, CserEp Z, Hangody L, Forster T. Late cardiac effect of anthracycline therapy in physically active breast cancer survivors - a prospective study. *Neoplasma*. 2017;64(1):92-100.
34. Turecamo SE, Xu M, Dixon D, et al. Association of rurality with risk of heart failure. *JAMA Cardiol*. 2023;8(3):231-239.
35. Macedo AVS, Hajjar LA, Lyon AR, et al. Efficacy of dexrazoxane in preventing anthracycline cardiotoxicity in breast cancer. *JACC Cardiooncol*. 2019;1(1):68-79.
36. Ganatra S, Nohria A, Shah S, et al. Upfront dexrazoxane for the reduction of anthracycline-induced cardiotoxicity in adults with preexisting cardiomyopathy and cancer: a consecutive case series. *Cardiooncology*. 2019;5:1.
37. Omland T, Heck SL, Gulati G. The role of cardioprotection in cancer therapy cardiotoxicity: JACC: CardioOncology state-of-the-art review. *JACC CardioOncol*. 2022;4(1):19-37.
38. Bosch X, Rovira M, Sitges M, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). *J Am Coll Cardiol*. 2013;61(23):2355-2362.
39. Austin D, Maier RH, Akhter N, et al. Preventing cardiac damage in patients treated for breast cancer and lymphoma: the PROACT clinical trial. *JACC Cardiooncol*. 2024;6(5):684-696.
40. Obasi M, Abovich A, Vo JB, et al. Statins to mitigate cardiotoxicity in cancer patients treated with anthracyclines and/or trastuzumab: a systematic review and meta-analysis. *Cancer Causes Control*. 2021;32(12):1395-1405.
41. Hundley WG, D'Agostino R Jr, Crotts T, et al. Statins and left ventricular ejection fraction following doxorubicin treatment. *NEJM Evid*. 2022;1(9):10.1056/evidoa2200097.
42. Neilan TG, Quinaglia T, Onoue T, et al. Atorvastatin for anthracycline-associated cardiac dysfunction: the STOP-CA randomized clinical trial. *JAMA*. 2023;330(6):528-536.
43. Seicean S, Seicean A, Plana JC, Budd GT, Marwick TH. Effect of statin therapy on the risk for incident heart failure in patients with breast cancer receiving anthracycline chemotherapy: an observational clinical cohort study. *J Am Coll Cardiol*. 2012;60(23):2384-2390.
44. Thavendiranathan P, Houbois C, Marwick TH, et al. Statins to prevent early cardiac dysfunction in cancer patients at increased cardiotoxicity risk receiving anthracyclines. *Eur Heart J Cardiovasc Pharmacother*. 2023;9(6):515-525.
45. Dabour MS, George MY, Daniel MR, Blaes AH, Zordoky BN. The cardioprotective and anticancer effects of SGLT2 inhibitors: JACC: CardioOncology state-of-the-art review. *JACC CardioOncol*. 2024;6(2):159-182.
46. Hwang H-J, Kim M, Jun JE, Yon DK. Sodium-glucose cotransporter-2 inhibitors improve clinical outcomes in patients with type 2 diabetes mellitus undergoing anthracycline-containing chemotherapy: an emulated target trial using nationwide cohort data in South Korea. *Sci Rep*. 2023;13(1):21756.
47. Avula V, Sharma G, Kosiborod MN, et al. SGLT2 inhibitor use and risk of clinical events in patients with cancer therapy-related cardiac dysfunction. *JACC Heart Fail*. 2024;12(1):67-78.
48. Abdel-Qadir H, Carrasco R, Austin PC, et al. The association of sodium-glucose cotransporter 2 inhibitors with cardiovascular outcomes in anthracycline-treated patients with cancer. *JACC Cardiooncol*. 2023;5(3):318-328.
49. Daniele AJ, Gregorietti V, Costa D, López-Fernández T. Use of EMPAgliflozin in the prevention of CARDiotoxicity: the EMPACARD - PILOT trial. *Cardiooncology*. 2024;10(1):58.
50. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2017;35(8):893-911.
51. Curigliano G, Lenihan D, Fradley M, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol*. 2020;31(2):171-190.
52. Alexandre J, Cautela J, Ederhy S, et al. Cardiovascular toxicity related to cancer treatment: a pragmatic approach to the American and European cardio-oncology guidelines. *J Am Heart Assoc*. 2020;9(18):e018403.
53. Fradley MG, Wilcox N, Frain I, Rao VU, Carver J, Guha A, Dent S. Developing a clinical cardio-oncology program and the building blocks for success: JACC: CardioOncology how to. *JACC CardioOncol*. 2023;5(5):707-710.
54. Kappel C, Rushton-Marovac M, Leong D, Dent S. Pursuing connectivity in cardio-oncology care-the future of telemedicine and artificial intelligence in providing equity and access to rural communities. *Front Cardiovasc Med*. 2022;9:927769.