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Society Guidelines

Canadian Cardiovascular Society Guidelines for Evaluation and Management of Cardiovascular Complications of Cancer Therapy

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This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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ABSTRACT

Modern treatment strategies have led to improvements in cancer survival, however, these gains might be offset by the potential negative effect of cancer therapy on cardiovascular health. Cardiotoxicity is now recognized as a leading cause of long-term morbidity and mortality among cancer survivors. This guideline, authored by a pan-Canadian expert group of health care providers and commissioned by the Canadian Cardiovascular Society, is intended to guide the care of cancer patients with established cardiovascular disease or those at risk of experiencing toxicities related to cancer treatment. It includes recommendations and important management considerations with a focus on 4 main areas: identification of the high-risk population for cardiotoxicity, detection and prevention of cardiotoxicity, treatment of cardiotoxicity, and a multidisciplinary approach to cardio-oncology. All recommendations align with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. Key recommendations for which the panel provides a strong level of evidence include: (1) that routine evaluation of traditional cardiovascular risk factors and optimal treatment of preexisting cardiovascular disease be performed in all patients before, during, and after receiving cancer therapy; (2) that initiation, maintenance, and/or augmentation of antihypertensive therapy be instituted per the Canadian Hypertension Educational Program guidelines for patients with preexisting hypertension or for those who experience hypertension related to cancer therapy; and (3) that investigation and management follow current Canadian Cardiovascular Society heart failure guidelines for cancer patients who develop clinical heart failure or an asymptomatic decline in left ventricular ejection fraction during or after cancer treatment. This guideline provides guidance to clinicians on contemporary best practices for the cardiovascular care of cancer patients.

RÉSUMÉ

Les stratégies modernes de traitement du cancer ont permis d'améliorer le taux de survie, mais ce gain pourrait être contrecarré par les possibles effets négatifs du traitement anticancéreux sur la santé cardiovasculaire. En effet, il est maintenant reconnu que la cardiotoxicité liée au traitement anticancéreux constitue la principale cause de morbidité et de mortalité à long terme chez les survivants du cancer. Ces lignes directrices, dont l'élaboration par un groupe pancanadien d'experts en soins de santé a été mandatée par la Société canadienne de cardiologie, ont pour but d'orienter le traitement des patients cancéreux atteints d'une maladie cardiovasculaire établie ou à risque de subir des effets toxiques liés au traitement anticancéreux. On y trouve des recommandations et d'importantes considérations pour la prise en charge des patients qui ont été réparties en quatre volets distincts, soit la reconnaissance de la population à risque élevé de cardiotoxicité, le dépistage et la prévention de la cardiotoxicité, le traitement de la cardiotoxicité et l'approche multidisciplinaire de la cardio-oncologie. Toutes les recommandations contenues dans les lignes directrices sont conformes aux critères du système GRADE (*Grading of Recommendations Assessment, Development, and Evaluation system*). Les principales recommandations auxquelles le groupe d'experts a accordé un niveau de preuve élevé sont les suivantes : 1) l'évaluation systématique des facteurs de risque cardiovasculaire traditionnels de même que le traitement optimal d'une cardiopathie préexistante doivent être effectués chez tous les patients avant, pendant et après le traitement anticancéreux; 2) le traitement antihypertenseur doit être instauré, poursuivi et/ou ajusté conformément aux lignes directrices du Programme éducatif canadien sur l'hypertension, chez les patients souffrant déjà d'hypertension ou chez ceux qui développent ce problème au cours du traitement anticancéreux; et 3) les patients cancéreux qui présentent une insuffisance cardiaque clinique ou un déclin asymptomatique de leur fraction d'éjection ventriculaire gauche au cours du traitement anticancéreux ou après ce dernier doivent être évalués et pris en charge conformément aux lignes directrices actuelles sur le traitement de l'insuffisance cardiaque de la Société canadienne de cardiologie. Ces lignes directrices ont pour objectif de faire connaître aux professionnels de la santé les meilleures pratiques actuelles en matière de soins cardiovasculaires destinés aux patients atteints de cancer.

Approximately 40% of Canadians will be diagnosed with cancer in their lifetime. In the past 2 decades significant gains have been made in cancer detection and treatment. Between 2001 and 2010, age-standardized mortality rates in women with cancer have declined by 1.2% per year and in men with cancer by 1.8% per year (Canadian Cancer Society; www.cancer.ca). Improvement in survivorship, however, can come at a cost. Although the number of cancer survivors is increasing at twice the rate of new cancer diagnoses,[1] extended follow-up from registry data, in selected populations, has shown that death from cardiovascular causes is more frequent than death from cancer.[2,3] Cardiotoxicity is now recognized as a leading cause of long-term morbidity and mortality among cancer survivors.[4]

Cardio-oncology is a new discipline, which has developed in response to the need for optimal strategies to manage this at-risk population. This guideline, commissioned by the Canadian Cardiovascular Society (CCS), and endorsed by the Canadian Cardiac Oncology Network is intended to optimize the care of cancer patients with established cardiovascular disease or those at risk of experiencing toxicities related to their cancer treatment.

The methodology and processes for development of this guideline are well described on the CCS Web site (www.ccs.ca). Recommendations are aligned with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system,[5] which has been adopted by the CCS Guidelines Committee to promote quality and rigour in guideline development.

The objectives of this guideline are to provide recommendations on 4 key topics within cardio-oncology, specifically: (1) the patient population at highest risk for cardiovascular toxicity related to cancer therapy; (2) strategies for detection and prevention of cardiotoxicity; (3) treatment of cardiotoxicity; and (4) the need for a multidisciplinary approach in the management of individuals who experience cardiotoxicity related to their cancer therapy.

Identifying the High-Risk Population

Cancer and cardiovascular disease: The multiple hit hypothesis

The multiple hit hypothesis is a framework for understanding cancer therapy-induced cardiac dysfunction. This framework suggests that traditional atherosclerotic risk factors and cardiac disease, in combination with cardiotoxic cancer therapy, can overwhelm cardiac reserve and lead to cardiac dysfunction (Fig. 1).[6,7] The childhood cancer survivorship study reported that when hypertension and other cardiac risk factors operate on a cardiovascular system exposed to cancer therapy, survivors have a high risk of cardiac disease (Table 1).[8-10] Such observations appear to validate this hypothesis as a suitable framework to understand, evaluate, prevent, and treat cancer therapy-induced cardiac dysfunction in adults.

Patient- and treatment-related risk factors for cardiotoxicity from cancer therapy

Risk factors for cancer therapy-induced cardiac dysfunction are well established for chemotherapy (eg, anthracyclines), several targeted therapies (eg, trastuzumab), and radiation therapy (Supplemental Tables S1-S6). Limited experience, variable definitions, and inconsistent monitoring of cardiac function have hindered evaluation of risk factors for cardiotoxicity associated with newer cancer therapies. In general, patients with preexisting cardiovascular disease, multiple, or poorly controlled cardiovascular risk factors, advanced age, and exposure to multiple cardiotoxic agents are at highest risk for cancer therapy-induced cardiotoxicity. These toxicities, which might include left ventricular (LV) dysfunction, hypertension, myocardial ischemia, arterial thrombosis, and arrhythmias are discussed in greater detail in the following sections.

LV dysfunction. Risk factors for anthracycline-induced heart failure (HF) and asymptomatic LV dysfunction are well established (Supplemental Tables S1-S6). High-risk patients include those at the extremes of age, non-Caucasian individuals, women, and those with preexisting cardiac disease and established cardiovascular risk factors. Anthracycline-induced cardiotoxicity is largely irreversible, such that cumulative lifetime dose is one of the most important risk factors for LV dysfunction[11]; as such, contemporary chemotherapy regimens have evolved to minimize anthracycline exposure, particularly in the adjuvant setting. LV dysfunction associated with targeted therapies has been most extensively evaluated in the breast cancer population treated with trastuzumab; in the adjuvant setting, cardiotoxicity associated with these agents appears to be largely reversible.[12,13] At highest risk of LV dysfunction are those aged older than 50 years, with underlying heart disease or hypertension, baseline ejection fraction between 50% and 55%, and those who have received anthracycline therapy.[14,15] There is less information available on the short- and long-term effect of novel targeted therapies (eg, regorafenib) on cardiovascular health (Supplemental Tables S1-S6).

Baseline assessment of LV function, before treatment, with agents associated with the development of LV dysfunction, is a necessary component of established monitoring protocols for treatment-related cardiotoxicity.[16-18]

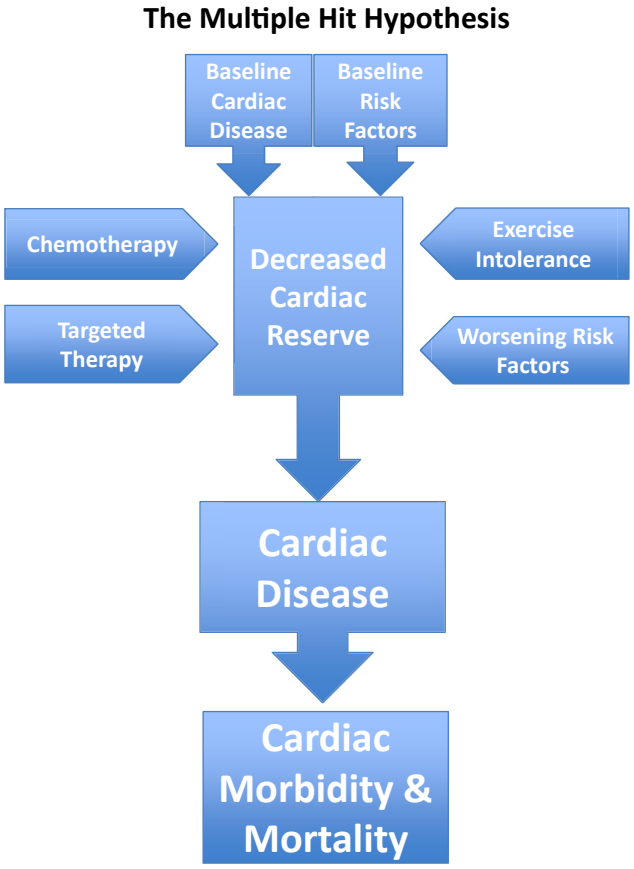

Figure 1. Preexisting cardiovascular disease and cardiac risk factors combine with chemotherapy and targeted therapy to produce subclinical and clinical cardiovascular disease, during and long after cancer therapy. This model for cancer therapy-induced cardiotoxicity emphasizes multiple risk factors, each of which is a potential target for intervention. Whether such intervention translates into clinical benefit requires further study. Modified from Jones et al.[6] and Cardinale et al.[7] with permission from Elsevier.

Hypertension. A number of novel targeted cancer therapies are associated with hypertension (Supplemental Tables S1-S6). Therapy-associated hypertension was first described for the antiangiogenic agent sunitinib and might relate to reduced function of nitric oxide synthase, endothelial dysfunction, and disruption of normal capillary function in nontumour tissue.[19,20] Other antiangiogenic agents that might contribute to or worsen hypertension include: bevacizumab[21] and regorafenib[22] in colorectal cancer, and sorafenib[23] and axitinib[24] in renal cell carcinoma.

Myocardial ischemia/arterial thrombosis. Fluoropyrimidines, including 5-flurouracil and capecitabine, are the most well established cause of coronary arterial spasm leading to acute myocardial ischemia during cancer therapy. Patients with preexisting coronary artery disease (CAD) and those receiving concomitant cisplatin therapy or previous mediastinal irradiation are at highest risk (Supplemental Tables S1-S6). Chest radiation is an important cause of

Table 1. Risk of cardiac disease and cardiac risk factors in long-term survivors of childhood cancer vs healthy siblings (Childhood Cancer Survivor Study)

	CAD[9]	Heart failure[9]	Hypertension[10]	Diabetes[10]	Dyslipidemia[10]
RR (95% CI)	10.4 (4.1-25.9)	15.1 (4.8-47.9)	1.9 (1.6-2.2)	1.7 (1.2-2.3)	1.6 (1.3-2.0)
n	10,397	10,397	8599	8599	8599

CAD, coronary artery disease; CI, confidence interval; RR, relative risk.

accelerated CAD leading to increased long-term coronary events. However, with modern delivery techniques, the mean radiation cardiac volume exposure dose has decreased with a lifetime risk of major coronary events of 0.05%-3.5%. Risk factors for major coronary events among breast cancer survivors include exposure at a young age, combination with other cardiotoxic agents, and presence of traditional cardiovascular risk factors (Supplemental Tables S1-S6). There are early and late effects of chest radiation that lead to radiation-induced heart disease (RIHD), including pericardial disease, myocardial fibrosis, cardiomyopathy, CAD, valvular disease, and arrhythmias in the setting of myocardial fibrosis.[25] RIHD morbidity and mortality can be attenuated through careful control of cardiovascular risk factors, lifestyle modification, and avoiding cardiotoxic cancer treatment.[26] Antiangiogenic agents (eg, bevacizumab) have been associated with an increased incidence of arterial thromboembolism, especially in patients older than the age of 65 years with vascular disease.[27] As with LV dysfunction, the rate of arterial thrombotic events with this group of agents is less well established.

Arrhythmias. Fluoropyrimidine therapy can cause ventricular arrhythmias as a consequence of myocardial ischemia. Novel cancer therapies, such as tyrosine kinase inhibitors, can prolong the QT interval leading to ventricular arrhythmias. High-risk patients include those with congenital long QT syndrome, history of torsades de points, or baseline corrected QT (QTc) interval $>$ 450 ms. The use of supportive medications for cancer therapy (eg, antiemetics, antidepressants) in combination with cancer treatments can lead to QT prolongation, and careful review of drug interactions should be considered standard of care for all patients who receive cancer treatment.

RECOMMENDATION

1. We recommend evaluation of traditional cardiovascular risk factors and optimal treatment of cardiovascular disease, as per current CCS guidelines, be part of routine care for all patients before, during, and after receiving cancer therapy (Strong Recommendation, Moderate-Quality Evidence).
2. We recommend that patients who receive potentially cardiotoxic cancer therapy undergo evaluation of LV ejection fraction (LVEF) before initiation of cancer treatments known to cause impairment in LV function (Weak Recommendation, Moderate-Quality Evidence).

Detection and Prevention of Cardiotoxicity

The most widely applied modality used to detect chemotherapy-induced cardiotoxicity is serial determination of LV function measured before and during cancer therapy.[28] The frequency of imaging varies according to the goals of cancer therapy (eg, curative vs palliative) and the type of therapeutic regimen used. The most commonly used marker of LV function is LVEF, regardless of which imaging modality is used. Although the imaging modality chosen should adapt to local institutional expertise, transthoracic echocardiography is the method of choice in view of its wide availability, reproducibility, and versatility. Moreover, transthoracic echocardiography does not expose the patient to radiation and provides additional information on abnormalities of the right ventricle, pericardium, and heart valves.[29]

There are currently no consistent recommendations on the frequency and modality with which cardiac imaging should be performed in patients at risk of LV dysfunction related to cancer therapy. Existing surveillance protocols are on the basis of methodology from clinical trials and expert opinion.[18] In the case of trastuzumab however, there appears to be consensus in the adjuvant setting to assess LV function at baseline and every 3 months during therapy.[30]

Echocardiographic evaluation

Although 2-dimensional (2-D) measurement of LVEF has been widely used, its reproducibility is limited with the ability to reliably detect differences only $>$ 10% in LVEF. Because this is the same magnitude of change that is used to adjudicate cardiotoxicity, the sensitivity of 2-D echocardiography for the diagnosis of chemotherapy-induced cardiotoxicity has been questioned.[31-33]

Three-dimensional (3-D) echocardiography has emerged as the preferred technique for monitoring cardiac function and for the detection of cardiotoxicity.[28] Specifically in cancer patients, it has been shown to be more accurate for the detection of chemotherapy-induced cardiotoxicity[34] and has the best reproducibility.[28]

For patients with suboptimal image quality using 2-D echocardiography, the use of myocardial contrast agents might be useful.[35] Contrast agents should be used when 2 contiguous LV segments from any apical view are not visualized on noncontrast images.[36]

Complementary imaging modalities for LVEF assessment

There is extensive experience on the efficacy of radionuclide angiography scans (mulitigated acquisition scan [MUGA]) for the identification of asymptomatic declines in LVEF among cancer patients. MUGA scans have consistently

been shown to be more reproducible and accurate than standard 2-D echocardiography and have better correlations with 3-D imaging methods such as cardiac magnetic resonance (CMR) imaging and 3-D echocardiography.[37-39] The inability to assess other cardiac structures, and the required radiation exposure, limit the widespread use of this technique.

In addition to echocardiography and MUGA scans, CMR imaging might be useful for the noninvasive assessment of LV volumes and LVEF in the cancer setting.[39-41] CMR imaging is considered the gold standard for the noninvasive assessment of LV systolic function.[42] In addition to accurate and highly reproducible determination of LV volumes and systolic function.[43,44] CMR imaging is also useful for the detection of myocardial edema, perfusion abnormalities, and cardiac fibrosis. The role of these advanced CMR imaging techniques in the assessment of cardiotoxicity is currently evolving.

Because LV volumes and LVEF values differ significantly across techniques, the imaging modality and method used to determine LVEF should be maintained during treatment and for surveillance after treatment. Importantly, the digital images obtained to calculate LVEF regardless of imaging modality used should be compared with previous ones to minimize interobserver variability.

Subclinical LV dysfunction evaluation using novel echocardiographic techniques

Although LVEF remains the best surrogate for systolic function, it is a late marker of cardiotoxicity and one that is highly dependent on preload and afterload conditions. Detecting a decreased LVEF after cancer therapy might be a late finding; therefore, earlier markers of myocardial dysfunction are needed. Echocardiographic myocardial strain analysis, using 2-D speckle tracking imaging, has shown promise in this regard. Global longitudinal strain is a useful early marker predictive of a further decrease in LVEF.[45-47] For patients with available baseline strain measurements, a relative percentage reduction in global longitudinal strain of $< 8\%$ from baseline is not meaningful whereas those with $> 15\%$ reduction from baseline are very likely to be abnormal.[46]

Utility of cardiac biomarkers for the early detection of chemotherapy-mediated cardiotoxicity

Although not routinely used in clinical practice, cardiac biomarkers are a reliable diagnostic tool for the early identification, and monitoring of cardiotoxicity. In the breast cancer setting, troponin is a sensitive and specific marker for myocardial injury in chemotherapy-treated patients, and is an early predictor of LV systolic dysfunction.[48,49] Several studies have confirmed that the administration of anticancer drugs, specifically anthracyclines, induce subclinical myocardial injury, which can be associated with increasing levels of B-type natriuretic peptide (BNP).[50] Conversely, in a recent study on human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients treated with combined doxorubicin and trastuzumab, troponin T, C-reactive protein, and BNP were not able to predict early LV systolic dysfunction, which ultimately developed in 25% of the study population.[46] Further prospective studies are warranted to evaluate the potential use of cardiac biomarkers, including troponin and C-reactive protein, to identify a subset of patients at highest risk of developing cardiac dysfunction during and after chemotherapy.[51,52]

RECOMMENDATION

3. We recommend the same imaging modality and method be used to determine LVEF before, during, and after completion of cancer therapy (Suggestion, Low-Quality Evidence).
4. We suggest that myocardial strain imaging be considered a method for early detection of subclinical LV dysfunction in patients treated with potentially cardiotoxic cancer therapy (Suggestion, Low-Quality Evidence).
5. We suggest that serial use of cardiac biomarkers (eg, BNP, troponin) be considered for early detection of cardiotoxicity in cancer patients who receive cardiotoxic therapies implicated in the development of LV dysfunction (Weak Recommendation, Moderate-Quality Evidence).

Values and preferences. We prefer the use of 3-D echocardiography, whenever feasible and technically satisfactory, for LVEF determination because of its enhanced reproducibility and accuracy.

Drug therapy in primary prevention

Primary prevention strategies can be considered for HF, ischemia, arrhythmia, hypertension, or arterial thromboembolism. Primary prevention might include universal treatment of all patients who receive potentially cardiotoxic cancer therapy[53] or early detection of subclinical cardiac injury with targeted treatment.[54] The former is attractive because it has the potential to prevent any myocardial injury from occurring and does not rely on repeated surveillance. The corollary however, is that primary prophylaxis might unnecessarily expose patients to treatment-related side effects in the absence of any clear benefit.

Much of the literature on prevention of HF has been generated in subsets of patients treated with anthracyclines.[55] This has included predominantly breast cancer, but also sarcoma, lymphoma, and leukemia patients. Drugs that have been tested for primary prevention include: β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and dexrazoxane. Overall, the evidence in support of primary prevention is quite limited because of small study size, variable follow-up, and variable end points; in some studies patients already had HF at the time of medication initiation. However, an important strength of the limited data is that they predominantly come from randomized controlled trials.[56] On the basis of a recent meta-analysis, in which trials with similar characteristics were combined, the relative risk reduction for LV dysfunction and/or HF with dexrazoxane ranged from 55% to 73% ($n = 1163$), β-blockers 37%-84% ($n = 458$), statins 23%-87% ($n = 241$), and angiotensin antagonists 71%-96% ($n = 244$) compared with placebo.[55] Although these data are promising, it is unclear whether they are sufficient to support universal adoption of cardioprotection. Some studies have shown significant intolerance to cardiac medications necessitating discontinuation in

approximately one-third of the patients.[54] This is a particular concern for patients who are at low risk for cardiotoxicity. Unfortunately, there are currently no robust methods for pretreatment risk stratification that would allow for selective treatment of patients who are at high risk for cardiotoxicity. There are currently several ongoing studies such as **M**ultidisciplinary **A**pproach to **N**ovel **T**herapies **i**n **C**ardiology **O**ncology **Re**search (MANTICORE) 101,[57] **Pr**evention of C**a**rdiac **D**ysfunction During **A**djuvant Breast Cancer Therapy (PRADA),[58] **S**train S**u**rveillance During **C**hemotherapy for Improving **C**ardiovascular **Ou**tcomes (SUCCOUR) (http://www.anzctr.org.au/TrialSearch.aspx?searchTxt=SUCCOUR&isBasic=True), and ELEVATE (https://clinicaltrials.gov/ct2/show/NCT01708798), which should provide further guidance on the optimal primary prevention approach.

Currently, there are no data on primary prevention strategies for myocardial ischemia, hypertension, arrhythmias, or arterial thromboembolism in patients who receive cancer therapies. The most significant challenge in articulating a primary prevention strategy is the relative paucity of tools to identify patients at high risk of adverse cardiovascular outcomes. However, general principles should apply until more robust data become available. This includes guideline- and evidence-based treatment of underlying ischemia before initiation of cancer therapy, use of radiation treatment strategies to minimize cardiac injury, treatment of preexisting hypertension, and management of underlying cardiac arrhythmias and conduction system disease.

RECOMMENDATION

6. We suggest that in patients deemed to be at high risk for cancer treatment-related LV dysfunction, an ACE inhibitor or angiotensin receptor blocker, and/or β-blocker, and/or statin be considered to reduce the risk of cardiotoxicity (Weak Recommendation, Moderate-Quality Evidence).

Prevention related to RIHD

The underlying mechanisms of RIHD are related to micro- and macrovascular damage, which leads to clinical manifestations such as pericarditis, CAD, acute myocardial infarction, valvular heart disease, and cardiomyopathy.[59] Darby et al. reported that the risk of major coronary events increased linearly with the mean radiation dose to the heart. This increased risk was observed as early as 5 years after radiotherapy and continued for 3 decades.[60] The most important factors influencing RIHD are dose to the heart and the target volume.

Several modern radiation techniques have been introduced with the aim of reducing the radiation dose to the heart. Modern 3-D conformal radiotherapy planning and intensity-modulated radiotherapy have been reported to reduce radiation dose to the heart, especially in patients with unfavourable cardiac anatomy.[61] Active breathing control helps patients to reproducibly perform breath-holding during radiotherapy with the aim of reducing the dose to the whole heart and the proximal portion of the left anterior descending coronary artery.[61,62]

It is important to explore the risk:benefit ratio and individualize treatment decisions, taking into consideration other factors, such as smoking, diabetes, or history of ischemic heart disease.[60,63]

RECOMMENDATION

7. We suggest that modern radiotherapy techniques (eg, 3-D conformal radiotherapy, intensity-modulated radiotherapy) be used during planning mediastinal and chest radiation to reduce the risk of short- and long-term cardiotoxicity (Weak Recommendation, Moderate-Quality Evidence).

Treatment of Cardiotoxicity

Despite the beneficial effects of many anticancer drugs, cardiotoxic complications of these treatments might require specific interventions. Herein, we broadly categorize the most common complications of anticancer treatment, including hypertension arrhythmias, ischemia, and LV dysfunction, and describe an approach to management.

Hypertension. The treatment of hypertension in the setting of malignancy will vary depending on the underlying cause and the overall goals of care.

Before considering treatment with an anticancer agent known to cause hypertension (eg, anti-vascular endothelial growth factor inhibitors or multitargeted tyrosine kinase inhibitors), assessment and treatment of baseline cardiovascular risk factors, per established guidelines,[64] is recommended. Baseline blood pressure (BP) measurements should be measured at ≥ 2 initial clinic visits to account for, and rule out, transient hypertension. When diagnosed, treatment of hypertension should follow established Canadian Hypertension Education Program guidelines.[64]

With respect to choice of antihypertensive agent, there are currently no studies to suggest the superiority of any given drug in the cardio-oncology setting. Treatment for cancer patients can be started with a diuretic, β-blocker, ACE inhibitor, angiotensin receptor blocker, or calcium channel blocker accordingly.[64] The choice of agent should be tailored to the individual clinical situation including consideration for potential drug-drug interactions. Careful attention to volume status and renal function, at baseline and through the course of therapy are warranted, because this will affect the choice of an antihypertensive agent and the need for dose adjustments. After initiation of treatment with an antihypertensive agent, weekly monitoring of BP is recommended during the first cycle of therapy, and then every 2-3 weeks for the duration of cancer therapy.

Arrhythmia. Arrhythmias represent a less common effect of cancer drugs. Although there might be direct effects of chemotherapy and radiation therapy, there are also many other preexisting patient factors that independently predispose to arrhythmia. Importantly, cancer itself creates an arrhythmogenic milieu. It can be difficult to determine whether one anticancer agent is responsible for an arrhythmia, when multidrug regimens are used. In addition, arrhythmias might coexist in the

setting of other cardiotoxic effects (ie, LV systolic dysfunction, ischemia, hypertension), rather than directly related to the administration of the chemotherapeutic agent itself.

Evaluation and management of new-onset atrial fibrillation should follow CCS guidelines.[65] If the atrial fibrillation is considered to be secondary to the chemotherapy agent, or it complicates the successful delivery of appropriate cancer therapy, it might be reasonable to consider restoration and maintenance of sinus rhythm with elective cardioversion and/or antiarrhythmic therapy, especially if the patient remains symptomatic despite adequate rate control. Decisions to continue with the presumed offending anticancer agent will depend on the clinical situation; however, the existence of atrial fibrillation alone does not warrant discontinuation of cancer therapy.

Use of warfarin and the novel oral anticoagulants in the setting of chemotherapy poses a unique challenge. It might be more appropriate to anticoagulate at-risk patients with alternative agents, such as low molecular weight heparin; particularly in those who might require multiple procedures or whose cancer treatments can affect the metabolic pathway of oral anticoagulants, making anticoagulant effects unpredictable.

Drugs associated with asymptomatic bradycardias require no specific monitoring, and no specific intervention is required if identified. The elective concomitant use of heart rate-controlling drugs (ie, β-blockers or nondihydropyridine calcium channel blockers) should be avoided if bradycardia is detected.

Initial evaluation of patients receiving QT-prolonging drugs should include a baseline electrocardiogram examination and periodic monitoring of the QTc interval should be performed during treatment with these agents. Treatment interruption and dose reduction is advised if no other reversible cause is identified. Permanent discontinuation is indicated if significant QTc prolongation recurs or is accompanied by an arrhythmia, HF, hypotension, shock, syncope, or torsade de pointes.[66-68]

Ischemia. Proposed mechanisms for the spectrum of ischemic complications attributable to anticancer treatments have been inconsistent (coronary vasospasm, thrombosis, and vascular dysfunction), making management challenging. Importantly, these pathologies have not been reliably associated with underlying CAD risk.[69]

In the case of antimetabolites (5-fluorouracil [5-FU] and derivatives), it is important to establish the temporal relationship between drug administration and chest pain onset. If symptoms occur during 5-FU administration, the 5-FU should be stopped and an electrocardiogram, cardiac troponin levels, and cardiac monitoring should be performed until cardiac symptoms resolve.

Acute symptoms should be treated with sublingual nitroglycerin and opioids.[70] If cardiac enzyme levels are found to be elevated, management per American College of Cardiology/American Heart Association acute coronary syndrome (ACS) guidelines should be initiated.[71] Treating physicians should be mindful of issues such as thrombocytopenia and need for future cancer surgery when choosing a revascularization strategy, if needed. In the non-ACS setting, elective assessment for the presence of underlying CAD might be warranted.

When a diagnosis of myocardial ischemia due to cancer therapy is made (eg, 5-FU), an alternate antineoplastic treatment should be considered. Rechallenge of the offending agent might be considered if no alternate treatment is available. However, this is not routinely recommended, and must be approached with caution because of the frequent recurrence of symptoms[72,73] and should be performed in a controlled setting with close cardiac monitoring and with safer administration regimens (ie, bolus 5-FU instead of infusion, dose reduction).[73] Prophylactic therapy with nitrates and calcium channel blockers does not appear to be universally effective, but are the only available options.[73]

For other classes of chemotherapy drugs associated with myocardial ischemia, there are insufficient data to propose management strategies. If ischemia is confirmed, the cancer therapy should be stopped and alternate options should be considered.

RIHD is an important cause of ischemia in patients treated with radiation to the chest.[61] It is important to manage cardiac risk factors before, during, and after radiation therapy. Coronary manifestations of RIHD are typically seen several years after completion of treatment and present similarly to other causes of ischemic heart disease.[74] Patients with stable angina should be assessed and managed in the same manner as patients with stable angina from atherosclerotic CAD,[75] and those with unstable symptoms managed as per existing ACS guidelines.[71,76] Patients with RIHD might also have mediastinal fibrosis, aortic calcification, valvular heart disease, pericardial disease, and cardiomyopathy.[77] Careful review of cardiac imaging is necessary to assess these concomitant lesions, because they have an important effect on the choice of coronary intervention, if needed.

HF and LV dysfunction. We now recognize the dose dependency of LV systolic dysfunction with anthracyclines and the potential reversible decline in LVEF seen with trastuzumab, but evidence-based guidelines for management of HF before, during, and after chemotherapy are still elusive in the literature. In cancer patients who develop clinical HF or an asymptomatic decline in LVEF during or after treatment, investigations and management should follow current CCS HF guidelines.[78] Other causes of LV dysfunction should be excluded.

Cardiac function should be optimized with standard guideline-driven pharmacotherapy for HF. Treatment interruption and avoidance of agents known to cause LV dysfunction (particularly anthracyclines) is appropriate and alternative agents should be used where possible. Daily exercise should be encouraged among all patients before, during, and after chemotherapy as evidence mounts regarding the beneficial effects of exercise in attenuating the risk of cardiotoxicity.[79,80]

Trastuzumab presents a unique challenge to the clinician in that LV dysfunction is generally assumed to be transient. Management of patients who experience a reduction in LVEF during trastuzumab therapy have largely followed protocols from large clinical trials in the adjuvant breast cancer setting. It should be noted, however, that the schedule of cardiac assessment and criteria for withholding therapy vary across different trastuzumab studies. In general, patients in these trials with $>$ 10 % reduction in LVEF or to below institutional lower limit of normal using similar imaging modalities of LV function, had therapy held for one cycle, cardiac

assessment repeated, and therapy restarted if cardiac function normalized. If not, further therapy was held. There is emerging evidence that early initiation of ACE inhibitor therapy and/or β-blockers can reverse the effects of trastuzumab on LV dysfunction.[81,82]

Aside from trastuzumab adjuvant trials, there are very few studies on the effect of holding or rechallenging patients with these agents. In general, if the risk of LV dysfunction or HF during treatment with the agent exceeds the risk of cancer recurrence without the agent, the agent should be discontinued. This prioritization might shift in the metastatic setting or other scenarios where there might be significant benefit in continuing cancer treatment. Initiating evidence-based LV enhancement therapies, continuing cancer treatment, and close clinical monitoring might be appropriate strategies in this setting.

RECOMMENDATION

8. We recommend that for patients with preexisting hypertension or for those who experience hypertension related to their cancer therapy, it is important to start, maintain, or augment antihypertensive therapy as per the Canadian Hypertension Education Program guidelines. A target BP of < 140/90 mm Hg should be established for all patients except those with diabetes in whom the goal should be adjusted to < 130/80 mm Hg (Strong Recommendation, High-Quality Evidence).
9. We suggest in patients who receive QTc-prolonging agents, a baseline electrocardiogram examination before cancer treatment and periodic monitoring of the QTc during treatment. If the QTc interval exceeds 500 ms during treatment, metabolic and electrolyte disturbances should be identified and corrected, and the use of concomitant QT-prolonging drugs be minimized where possible (Weak Recommendation, Moderate-Quality Evidence).
10. We recommend that in cancer patients who develop clinical HF or an asymptomatic decline in LVEF (eg, > 10% decrease in LVEF from baseline or LVEF < 53%) during or after treatment, investigations, and management follow current CCS guidelines. Other causes of LV dysfunction should be excluded (Strong Recommendation, High-Quality Evidence).
11. We suggest that alternate antineoplastic treatments be considered if patients experience myocardial ischemia due to their cancer therapy (Suggestion, Low-Quality Evidence).

Values and Preferences.

i. Treatment targets (eg, hypertension) should be tailored on the basis of goals of care (eg, curative vs palliative) and by assessing the overall risks and benefits of cancer therapies within this context.
ii. We suggest cautious use of drugs metabolized by the cytochrome P450 system (eg, diltiazem or verapamil) for hypertension management in patients who receive tyrosine kinase inhibitors because of potential drug-drug interactions.
iii. Although the CCS guidelines recommend institution of ACE inhibitors/angiotensin receptor blockers, and β-blockers in patients with an LVEF < 40%, in clinical practice, the combination of LV enhancement therapy might be considered in patients with an asymptomatic decline in LVEF (eg, > 10% decrease in LVEF from baseline or LVEF < 53%) during cancer therapy.
iv. In the setting of trastuzumab-related LV dysfunction, we recommend following the algorithm proposed by Jones et al.,[30] recognizing there might be clinical scenarios in which continuing trastuzumab alongside initiation of evidence-based HF therapies might be considered.

Recommendations for a Multidisciplinary Approach to Cardio-oncology

Cardio-oncology is a collaborative medical discipline with focused expertise in the prevention, diagnosis, and treatment of cardiovascular disease in cancer patients.[83] Historically, cancer patients at high risk of treatment-related cardiotoxicity were referred to cardiology services outside of a formalized program resulting in variability in cardiac assessment, delays in diagnosis, and treatment of cardiac disease, as well as the risk of stopping a potential life-saving cancer treatment. Improved collaboration between oncology and cardiology is needed to address the clinical care gaps experienced by this at-risk patient population, thus leading to the evolution of cardio-oncology as a distinct, inter- and multidisciplinary patient-centred clinical specialty.

There are currently no established benchmarks to guide clinicians with regard to timely access and assessment of patients who experience cancer-related cardiotoxicity. For cancer patients, wait times to be assessed in a cardio-oncology clinic need to be balanced with the urgency of impending cancer treatments. The CCS HF Companion[84] provides wait-time benchmarks for HF patients to be seen in a specialty clinic. The patient receiving active treatment will generally require more urgent access (1-2 weeks), and it might be appropriate for patients not receiving active therapy (eg, surveillance) to be seen in a less timely fashion (weeks to months). We believe this framework might also be applicable in the cardio-oncology setting.

It is important to acknowledge the potential for late cardiac complications in long-term cancer survivors. Although beyond the scope of this document, health care providers caring for adult survivors of pediatric cancer should refer to the Children's Oncology Group long-term follow-up guidelines at: http://www.survivorshipguidelines.org/pdf/LTFUGuidelines_40.pdf.

A Call to Action

In clinical practice, the cardiovascular surveillance of cancer patients is inconsistent and there is a lack of evidence to guide therapies. The European Society of Medical Oncology have published guidelines for the cardiovascular surveillance of cancer patients who receive anthracyclines (with or without trastuzumab) and have recommended assessment of heart function (LVEF) with serial echocardiograms, and troponin levels (with each cycle of anthracycline-based therapy).[18] However, the feasibility and cost effectiveness of this

multimodality approach is not defined and has not yet been evaluated in the cancer community at large. Furthermore, it is unclear if early detection strategies decrease the burden of cardiovascular disease and ultimately improve the outcome of cancer survivors. Further complicating the clinical management of cardiotoxicity is the lack of high-quality evidence for effective primary and secondary prevention strategies.

Thus, we believe that there is an urgent need for collaborative studies to help guide patient management. Large prospective registries will enable the development of risk models for predicting cardiovascular events among cancer survivors as well as evaluate the downstream effect of surveillance strategies for cardiac toxicity prevention. Multicentre randomized controlled trials are also needed to test traditional and novel pharmacotherapy as primary and secondary interventions. Effective knowledge translation strategies as well as education of trainees will be required to increase awareness and provide guidance on the management of these patients. Organizations such as the CCS, Canadian Cardiac Oncology Network (www.cardiaconcology.ca) and the International CardiOncology Society (www.icosna.org) will continue to play an important role in promoting the development of clinical care models, development of educational structures, and promotion of evidence-based research.

RECOMMENDATION

12. We suggest that patients at high risk of cancer therapy-related cardiovascular disease or patients who develop cardiovascular complications during cancer therapy (eg, > 10% decrease in LVEF from baseline or LVEF < 53%) be referred to a cardio-oncology clinic or practitioner skilled in the management of this patient population, for optimization of cardiac function and consideration of primary or secondary prevention strategies (Suggestion, Low-Quality Evidence).

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Supplementary Material

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