

PRIMERS IN CARDIO-ONCOLOGY



Permissive Cardiotoxicity

The Clinical Crucible of Cardio-Oncology

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ABSTRACT

The field of cardio-oncology was born from the necessity for recognition and management of cardiovascular diseases among patients with cancer. This need for this specialty continues to grow as patients with cancer live longer as a result of lifesaving targeted and immunologic cancer therapies beyond the usual chemotherapy and/or radiation therapy. Often, potentially cardiotoxic anticancer treatment is necessary in patients with baseline cardiovascular disease. Moreover, patients may need to continue therapy in the setting of incident cancer therapy-associated cardiotoxicity. Herein, we present and discuss the concept of *permissive cardiotoxicity* as a novel term that represents an essential concept in the field of cardio-oncology and among practicing cardio-oncology specialists. It emphasizes a proactive rather than reactive approach to continuation of lifesaving cancer therapies in order to achieve the best oncologic outcome while mitigating associated and potentially off-target cardiotoxicities. (J Am Coll Cardiol CardioOnc 2022;4:302-312)

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The fundamental tension in the clinical practice of cardio-oncology is the balance between effective cancer-directed therapy and the risk for developing irreversible cardiovascular (CV) complications. We propose the term *permissive cardiotoxicity* to represent the concept that balances the benefits of effective cancer treatment with acceptance of its associated and often off-target cardiotoxicity, while providing the best possible surveillance and attenuation of the toxicity. *Cardiotoxicity* in this case loosely refers to the overall toxicity to the CV system sometimes associated with cancer therapy.

Permissive cardiotoxicity is a balance of clinical determinants in which optimal cancer therapy may have negative impact on the CV system, but the overall goal is to allow the best outcome from cancer treatment. Although the detection, surveillance, and management of cardiotoxicity associated with anti-neoplastic therapies have taken the center stage in the field of cardio-oncology, it is crucial to recognize that these therapies are providing lifesaving or sustaining benefits.

The concept of permissive cardiotoxicity emphasizes that rather than calling for cessation of the

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HIGHLIGHTS

- Permissive cardiotoxicity is a terminology that represents a vital concept in cardio-oncology
- It emphasizes continued cancer therapy if appropriate, while mitigating cardiotoxicities.
- Its application is guided by understanding the cancer treatment, alternatives, and prognosis.

cardiotoxic treatment, the managing cardio-oncology specialist acknowledges the potential toxicity to the patient and the cancer treating team while using the most favorable CV management strategy that yields an optimal CV prognosis and enables the patient to remain on designated cancer therapy. This strategy applies principally to treatments delivered over time, with manifestations of cardiotoxicity that demand decisions regarding if and how treatment should be continued. The permissive cardiotoxicity strategy is a dynamic compromise that recognizes that not all CV complications are irreversible and that some degree of manageable cardiotoxicity can be an acceptable trade-off for highly effective cancer-directed therapies. In the subset of patients with cancer with pre-existing CV conditions, permissive cardiotoxicity may have a narrower therapeutic window but still may be achievable to attain the best oncologic outcome without lethal or debilitating major adverse CV events (Figure 1).

THE NECESSITY FOR PERMISSIVE CARDIOTOXICITY

Cancer and CV disease (CVD) are the 2 most common diseases worldwide. With an aging population and improvement in therapeutics and overall survival, greater overlap between both disease entities is observed and will continue to expand. The concept of permissive cardiotoxicity begins even prior to initiation of cancer therapies. Although newly diagnosed cancer most commonly does not present as a medical emergency, there is a sense of urgency, both from the provider and patient perspective, regarding the initiation of antineoplastic therapy to positively influence prognosis. Many of these patients may have significant underlying CV risk factors or CVD, which may increase the risk for subsequent development of cardiotoxicity. The starting point for permissive

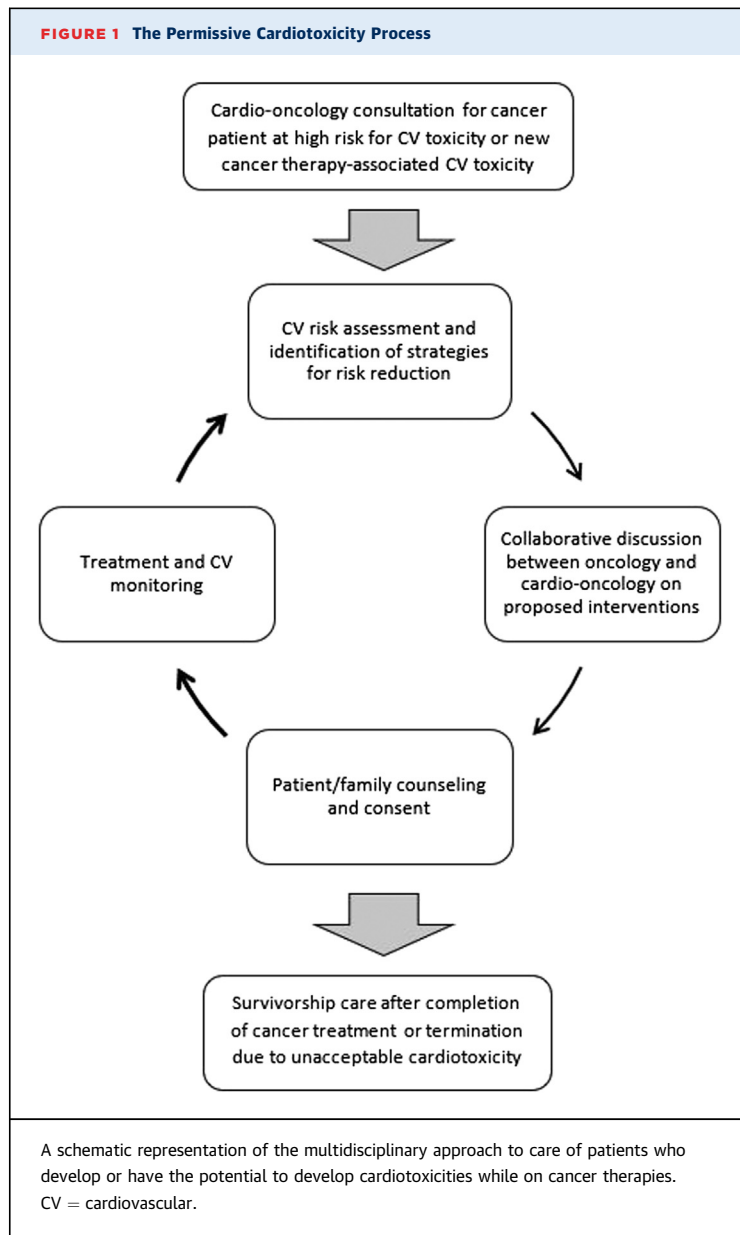
cardiotoxicity-based treatment strategies is often the recognition of this urgency to commence anticancer therapy in the setting of a new diagnosis of a hematological or solid tumor malignancy. This results in the need for urgent cardiology evaluation of CV risk status so that cancer treatment can begin without delay. Such patients may require a cardioprotective strategy implemented without the luxury of a few weeks of guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction, or the scheduling of several diagnostic studies over a period of days or weeks, which may unnecessarily delay important cancer treatment, before the patient is deemed ready for cancer therapy. In such high-need patients, a permissive cardiotoxicity management plan may need to begin concurrently with cancer treatment, or during cancer treatment, among those who develop cardiotoxicity in the process of cancer therapy.

CV complications of cancer-directed therapies are common with such agents as anthracyclines,¹ anti-human epidermal growth factor receptor 2 (HER2) targeted therapy,^{2,3} anti-vascular endothelial growth factor (VEGF) agents,^{4,5} tyrosine kinase inhibitors,⁶⁻⁸ proteasome inhibitors, immune checkpoint inhibitors (ICIs), and antimetabolites,⁹ among others. This list continues to grow with newer immune therapies (particularly ICIs)¹⁰ and adoptive cell therapies¹¹ and other targeted therapies. In pediatrics, compared with age- and sex-matched control subjects, childhood cancer survivors are 15 times more likely to develop heart failure and 8 to 10 times more likely to die of CV complications.¹² The co-occurrence of cancer and CVD is usually a reflection not only of exposure to the toxicities of the individual anticancer therapies but of individual risk factors and common underlying pathways for both CVD and cancer.¹³ Furthermore, interruption of anticancer treatment because of cardiotoxicity is associated with worse outcomes in patients with HER2⁺ breast cancer.^{14,15} It may be reasonable to extrapolate these findings to other anticancer agents, though data are limited.

This review is not intended to provide detailed management recommendations in the situations being discussed. Our aim is to articulate a management strategy that provides a foundation of principles and examples related to continuation of cancer therapy when the risk for recurrent

ABBREVIATIONS AND ACRONYMS

- 5-FU** = 5-fluorouracil
- CAD** = coronary artery disease
- CV** = cardiovascular
- CVD** = cardiovascular disease
- GDMT** = guideline-directed medical therapy
- HER2** = human epidermal growth factor receptor 2
- ICI** = immune checkpoint inhibitor
- GLS** = global longitudinal strain
- HSCT** = hematopoietic stem cell transplantation
- LVEF** = left ventricular ejection fraction
- VEGF** = vascular endothelial growth factor



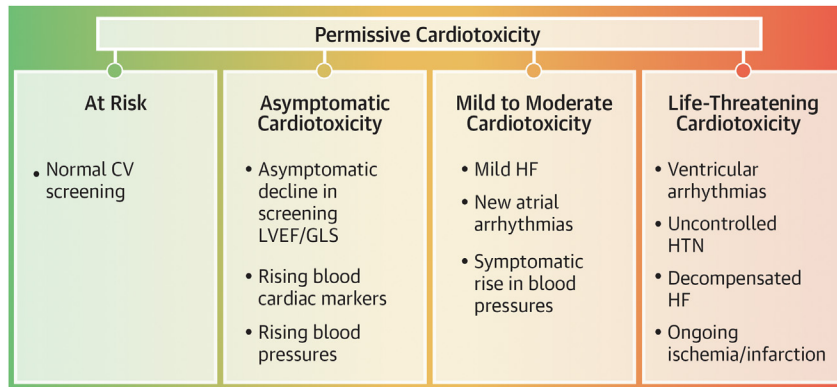
cardiotoxicity may be sufficiently reduced to allow this. In such situations, cancer treatment benefits outweigh the residual CV risks during intensively monitored therapy using best available cardioprotective techniques.

PERMISSIVE CARDIOTOXICITY: IMPLICATIONS FOR CANCER TREATMENT INTERRUPTIONS

Interruptions in cancer therapy can lead to suboptimal survival outcomes from dose reductions, temporary delays, or even permanent discontinuation of anticancer therapy. Most often, these

interruptions are due to either symptoms associated with the cancer or side effects secondary to anti-cancer treatment. The detrimental impact on survival is likely more pronounced when interruptions in cancer treatment occur in patients being treated with curative intent. Several of the systemic therapy options for cancer treatment can be cardiotoxic and cause interruptions in potentially life-prolonging medications. Trastuzumab is a monoclonal antibody that targets the HER2 receptor expressed in 15% to 20% of breast cancers diagnosed in the United States. One study investigated the impact of interruptions in adjuvant trastuzumab therapy in operable HER2-positive breast cancer and revealed 29% temporary delays and 11% permanent discontinuations. Cardiotoxicity was the most common reason for the interruptions (62%). Multivariable analyses demonstrated worse disease-free (adjusted HR: 4.4; 95% CI: 1.8-10.5; $P = 0.001$) and overall survival (adjusted HR: 4.8; 95% CI: 2.5-9.2; $P < 0.001$) after adjusting for age, stage, grade, estrogen receptor status, node status, and trastuzumab-associated cardiotoxicity.¹⁴ Furthermore, chemotherapeutic agents such as anthracyclines have well-known cardiotoxicities, with a maximum lifetime cumulative dose to which a patient can be exposed. In a retrospective study, anthracycline dose reductions and delays were associated with a 3-fold increased mortality risk (HR: 3.17; 95% CI: 1.7-5.9; $P < 0.001$) in patients with localized breast cancer.¹⁶ Similarly, the importance of the permissive cardiotoxicity strategy when managing severe hypertension in patients receiving VEGF inhibitors cannot be over-emphasized, as hypertension caused or exacerbated by these agents is associated with improved cancer outcomes in some tumors sensitive to VEGF inhibitors.¹⁷ Although uncommon, CV adverse effects associated with ICIs, such as myocarditis, pericarditis, arrhythmias, and impaired ventricular function with heart failure, have been reported.¹⁸ Current American Society of Clinical Oncology guidelines recommend permanent discontinuation of ICI therapy for any cardiac adverse effect worse than grade 1.¹⁹ Interestingly, small studies have demonstrated improved disease-free and overall survival in patients who develop any immune-related side effects. Further prospective studies are needed to investigate these reported outcomes.²⁰⁻²⁴ In situations in which ICI therapy has caused significant cardiotoxicity or in the case of solid organ transplant recipients, rechallenge with different types of ICIs or with modified doses may

CENTRAL ILLUSTRATION The Spectrum of Permissive Cardiotoxicity: From “At Risk” Through Life-Threatening Cardiotoxicity



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A schematic representation of examples of the spectrum of cardiotoxic manifestations of cancer therapies. CV = cardiovascular; GLS = global longitudinal strain; HF = heart failure; HTN = hypertension; LVEF = left ventricular ejection fraction.

be a reasonable consideration, although long-term outcomes may not be modifiable.

THE SPECTRUM OF PERMISSIVE CARDIOTOXICITY

Despite the significance and frequency of cardiotoxic events, there is a growing body of evidence that continuation of potentially cardiotoxic cancer therapy in patients with mild to moderate cardiotoxicity and initiation in patients with prior cardiac disease can be safely accomplished among some patients treated with trastuzumab and anthracyclines.^{25,26} There are case reports and reports of experiences of successful treatment rechallenges with other agents, including 5-fluorouracil (5-FU)²⁷ and ICIs,²⁸ after the development of cardiotoxicity.

In essence, the question traditionally asked when a patient developed cardiotoxicity from cancer-directed therapies was “Should this therapy be discontinued?” We suggest a shift in mind-set to “How can this therapy be continued?” This may include suggesting the initiation of cardioprotective agents, interventional cardiac procedures, management of comorbid disease, or a temporary cessation in therapy (Central Illustration, Figure 1). For example, dexrazoxane has attained an expanded role as a currently off-label cardioprotective

strategy for the management of patients with pre-existing left ventricular dysfunction at increased risk for further cardiotoxicity with anthracycline therapy. A useful analogy is the concept of permissive hypercapnia used in critical care, in which higher blood carbon dioxide is seen as an acceptable trade-off for improved oxygenation with a lung-protective ventilation strategy.²⁹ In contrast, in the pediatric population, it is especially difficult to find the right balance for permissive cardiotoxicity, as one must account for the child’s age and long-term consequences of cardiotoxicity. This decision is usually jointly made with the cardio-oncology specialist, the primary oncologist, and the child and parents through shared decision making. The risk and benefits must be weighed as to continuing the cancer-directed therapies and the potential for lifelong CV consequences. As such, many centers will elect to use dexrazoxane up front, for both solid tumor and hematologic malignancies, if a child’s treatment plan calls for a significant dose of anthracycline, usually >250 mg/m² doxorubicin or equivalent.

Central to the concept of permissive cardiotoxicity is screening for cardiotoxicity. If the stated goal is to intervene prior to irreversible, symptomatic effects, then screening needs to be instituted to diagnose subclinical disease. The most widely studied and accepted imaging tool for CV risk assessment among

patients with cancer is echocardiography, in which left ventricular ejection fraction (LVEF) and right ventricular ejection fraction and global longitudinal strain (GLS) are the primary imaging tools used to assess cardiotoxicity risk.³⁰⁻³² It is crucial to recognize and factor in the variabilities in systolic function and GLS on the basis of the loading conditions (fluid status, blood pressure, etc.), type of imaging modality, as well as interobserver and intervender variability (particularly for GLS assessment). Performing surveillance imaging in the optimal physiological conditions with the same modality on the same or a similar machine and software may help alleviate some of the variation. This would reduce the chances of misinterpretation of differences in the findings as cardiotoxicity.³³ Similarly, blood biomarkers such as brain natriuretic peptide and troponin also have prognostic value.^{34,35} With these available tools, several cutoff values have been suggested, but none are in widespread use. More recently, standard definitions for cardiotoxicity have been created that will hopefully allow standardization in practice and evaluation of patient outcomes.³⁶ CV surveillance, as outlined in the 2016 American Society of Clinical Oncology practice guideline and endorsed by the American College of Cardiology and American Heart Association,³⁷ is underused during cancer treatment and survivorship.^{38,39} These pitfalls are compounded in pediatric cardio-oncology, as there is a paucity of published research or guidelines that are pediatric specific.

PERMISSIVE CARDIOTOXICITY CASES

Herein, we present a series of hypothetical patient cases on the basis of our clinical experience, for which the concept of permissive cardiotoxicity can be used to provide optimal patient care in a multidisciplinary fashion (Figure 1). Furthermore, a list of potentially cardiotoxic anticancer agents, manifestations of cardiotoxicity, screening suggestions, and management concepts is presented in Table 1.

CASE 1: TRASTUZUMAB. A 37-year-old woman with history of hypertension and early-stage HER2-positive lymph node-negative breast cancer received neoadjuvant systemic treatment with docetaxel, carboplatin, trastuzumab, and pertuzumab, followed by a mastectomy and sentinel lymph node biopsy. Her treatment plan included completion of 1-year of HER2-targeted therapy with trastuzumab. Prior to treatment initiation, echocardiography demonstrated an LVEF of 55% to 60% and GLS of -19% . After 3 months of treatment, repeat echocardiography demonstrated an LVEF of 45% to 50% with GLS of -15% . Her blood

pressure had been controlled with amlodipine throughout her treatment, and she remained asymptomatic. She was referred for an expedited cardio-oncology consultation, and after discussion with the patient and primary oncologist, the decision was made to change amlodipine to carvedilol as a cardioprotective strategy and to hold trastuzumab for 1 or 2 cycles. Repeat echocardiography following these interventions demonstrated an improved LVEF to 55% to 60% and GLS to -17% . Trastuzumab was reinitiated, with repeat echocardiography the following 2 cycles and then every 3 months per the current U.S. Food and Drug Administration recommendations. Her cardiac function remained stable. She completed therapy without further complications.

KEY POINTS.

- Early recognition of subclinical cardiotoxicity
- Rapid access to cardio-oncology specialist
- Shared decision making
- Treatment of hypertension known to be a significant risk factor for cancer therapy-related cardiac dysfunction
- Clear monitoring plan

Note that trastuzumab and HER2-targeted therapies can sometimes be continued along with GDMT and close monitoring in settings of LVEF lower than 50% (usually 40%-50%).^{26,40}

CASE 2: ANTHRACYCLINES. A 68-year-old man was diagnosed with diffuse large B-cell lymphoma. He had known coronary artery disease (CAD) and an ischemic cardiomyopathy with an LVEF of 40% to 45% on echocardiography. While planning for treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy, he was evaluated by a cardio-oncology specialist at the request of his hematologist. His current heart failure regimen was already optimized, and the cardio-oncology specialist and hematologist discussed the use of dexrazoxane in this patient. The potential benefits of dexrazoxane for mitigating progressive heart failure and the potential risks of reduced treatment efficacy were presented to the patient. After joint discussions, the patient was treated with up-front dexrazoxane with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. He successfully completed treatment and continued to follow his survivorship care plan.

KEY POINTS.

- Rapid access to cardio-oncology specialist
- Optimization of existing therapies

TABLE 1 Examples of Cardiotoxic Agents, Clinical Presentations, and Management Considerations

Therapy	Representative Cardiotoxicity Manifestations	Monitoring	When to Intervene	Intervention	Discontinuation Criteria
HER2-targeted therapy ^a	Asymptomatic LV dysfunction and heart failure	Baseline <ul style="list-style-type: none"> Echocardiography BNP or NT-proBNP Troponin Recommended monitoring every 3 mo <ul style="list-style-type: none"> Echocardiography Consider alternative monitoring strategy in non-high-risk patients every 3 mo <ul style="list-style-type: none"> BNP or NT-proBNP Troponin Echocardiography if increasing BNP/troponin and/or heart failure symptoms 	Decrease in LVEF $\geq 10\%$ to absolute LVEF $< 50\%$ GLS decrease $> 15\%$ from baseline Rise in BNP/troponin from baseline Symptomatic heart failure	ACE inhibitors/angiotensin receptor blockers, beta-blocker (carvedilol or nebivolol preferred) Increase frequency of echocardiography to every 4 wk until stable Decision to pause trastuzumab made jointly with patient and oncologist	Heart failure refractory to medical management, refractory or worsening LV function despite management
Anthracyclines	Declines in LVEF and symptomatic heart failure, arrhythmias	Baseline <ul style="list-style-type: none"> Echocardiography BNP or NT-proBNP Troponin ECG Monitoring on the basis of doxorubicin dose equivalent $\geq 250\text{-}300$ mg/m ² and/or if heart failure symptoms/concerns or if high-risk patient <ul style="list-style-type: none"> Echocardiography BNP or NT-proBNP Troponin 	Symptomatic heart failure Decrease in LVEF $\geq 10\%$ to absolute LVEF $< 50\%$ or symptomatic heart failure Rise in BNP/troponin from baseline	ACE inhibitors/angiotensin receptor blockers, beta-blocker, spironolactone, SGLT-2 inhibitor ^b ICD/CRT as indicated per standard guidelines and prognosis Frequency of imaging/biomarkers dependent on LVEF and/or symptoms Upfront dexrazoxane in patients with preexisting LV dysfunction and in those receiving high doses as in sarcoma regimens can be considered	Heart failure refractory to medical management, refractory or worsening LV function despite management Overall prognosis and availability of alternative regimen should be considered
Antimetabolites (5-FU, capecitabine) ^{35,42}	Coronary vasospasm and subsequent ventricular arrhythmias and cardiomyopathies	Baseline <ul style="list-style-type: none"> ECG Echocardiography Troponin Monitoring <ul style="list-style-type: none"> None if asymptomatic 	Chest pain/acute coronary syndrome	Nitrates and calcium-channel blockade, angiography to rule out vasospastic acute coronary syndrome Ranolazine can be considered given less impact on blood pressure and heart rate, though experience is limited In select patients with chest pain, rechallenge can be considered with prophylactic calcium-channel blockers and nitrates, after risk-benefit discussion among cardio-oncology specialist, oncologist, and patient	Malignant ventricular arrhythmia Continued chest pain/acute coronary syndrome during rechallenge with prophylactic calcium-channel blockers and nitrates
VEGF inhibitors ⁴³	Hypertension and heart failure	Baseline <ul style="list-style-type: none"> Blood pressure Echocardiography ECG Monitoring <ul style="list-style-type: none"> Blood pressure Echocardiography every 3 mo 	New or worsening hypertension, asymptomatic or symptomatic decrease in LV systolic function	Aggressive management of hypertension using specific drugs (ACE inhibitors/angiotensin receptor blockers preferred upfront) Cardioprotective drugs for management of heart failure	Refractory hypertension, refractory heart failure, other end-organ dysfunction related to VEGF inhibitors such as renal failure

Continued on the next page

- Discussion related to dexrazoxane as it relates to cardioprotection vs potentially decreased cancer therapy efficacy⁴¹
- Patient-oriented decision making

CASE 3: 5-FU. A 53-year-old woman was diagnosed with stage IV squamous cell carcinoma of the head and neck. She was initiated on therapy with docetaxel, cisplatin, and 5-FU. She developed substernal chest pain during her first cycle and was found to

have T-wave inversions on electrocardiography and an elevated troponin level. She was taken emergently for coronary angiography by cardiac catheterization, and no angiographic CAD was found. She was subsequently diagnosed with 5-FU-induced coronary vasospasm and was treated with intravenous diltiazem and nitrates, with resolution of her symptoms. She was seen prior to discharge by a cardio-oncology specialist and transitioned to oral amlodipine and long-acting nitrates per a collaboratively developed

TABLE 1 Continued

Therapy	Representative Cardiotoxicity Manifestations	Monitoring	When to Intervene	Intervention	Discontinuation Criteria
ICIs ⁵⁰	Myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis	Baseline <ul style="list-style-type: none"> • ECG • Troponin • BNP • Echocardiography Monitoring <ul style="list-style-type: none"> • Troponin and BNP at each follow up or with symptomatic changes 	Any abnormal screening test result and/or symptoms warrant further workup and intervention; additional tests include as indicated BNP, echocardiography, CXR, stress test, cardiac catheterization with possible endomyocardial biopsy, cardiac MRI	Hold ICI High-dose corticosteroids (methylprednisol 1 mg/kg daily for 3 d, followed by 1 mg/kg prednisone) Cardiology consult and management of cardiac symptoms according to ACC/AHA guidelines For initial steroid refractoriness, consider the addition of either mycophenolate, infliximab, or antithymocyte globulin Discuss abatacept	Greater than CTCAE grade 1 toxicity; rare cases of rechallenge with ICI if no other options for cancer treatment
Ibrutinib ^{44,45}	Atrial fibrillation and increased bleeding risk	Baseline <ul style="list-style-type: none"> • ECG • Echocardiography • Blood pressure Monitoring <ul style="list-style-type: none"> • Cardiac examination • ECG at each follow up • Cardiac monitor if atrial fibrillation is suspected 	New atrial arrhythmias	DOAC for stroke risk reduction, rate/rhythm control as warranted	Refractory, symptomatic arrhythmias not controlled with conventional therapy, arrhythmias in conjunction with recurrent bleeding events, malignant ventricular arrhythmias

This table does not include all cardiotoxic agents but rather a selection of commonly encountered agents with expected cardiotoxicities. Other agents, such as androgen deprivation therapy (risk for coronary artery disease), proteasome inhibitors (risk for cardiomyopathy), aromatase inhibitors (risk for dyslipidemia and metabolic syndrome), and many more, are not addressed here. ^aTrastuzumab and anti-HER2 agents can sometimes be continued along with guideline-directed medical therapy and close monitoring in settings of LVEF lower than 50% (usually 40%-50%). ²⁶ ^bSome data exist for benefit of SGLT-2 inhibitors in patients with cancer, though no randomized trials have been conducted.⁵¹

5-FU = 5-fluorouracil; ACC = American College of Cardiology; ACE = angiotensin-converting enzyme; AHA = American Heart Association; BNP = B-type natriuretic peptides; CRT = cardiac resynchronization therapy; CTCAE = Common Terminology Criteria for Adverse Events; CXR = chest radiography; DOAC = direct oral anticoagulant agent; ECG = electrocardiography; GLS = global longitudinal strain; HER2 = human epidermal growth factor receptor 2; ICD = implantable cardioverter-defibrillator; ICI = immune checkpoint inhibitor; LV = left ventricular; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SGLT-2 = sodium-glucose cotransporter-2; VEGF = vascular endothelial growth factor.

predefined protocol. Following discussion with the patient and primary oncologist, the patient was readmitted for the next cycle of treatment, and the 5-FU-based chemotherapy was reinitiated with caution; she tolerated it without complications. In a recent study, 5-FU rechallenge after pretreatment with calcium-channel blockers and nitrates, under the guidance of a cardio-oncology service, was safe and permitted continued 5-FU therapy.⁴²

KEY POINTS.

- Rapid recognition of cardiotoxicity and exclusion of severe obstructive CAD
- Rapid access to cardio-oncology specialist
- Multiagent protocol to suppress coronary vasospasm (and associated ischemia) that can include nitrates and calcium-channel blockers
- Patient-oriented decision making
- Discussions leading to therapy change

CASE 4: IBRUTINIB. A 71-year-old man was diagnosed with chronic lymphocytic leukemia. He was initiated on the Bruton’s tyrosine kinase inhibitor ibrutinib. Three months following therapy initiation, he developed symptomatic atrial fibrillation. He was

subsequently initiated on metoprolol for rate control, as well as apixaban 5 mg twice daily for anticoagulation. Four months later, he developed symptomatic gastrointestinal bleeding requiring endoscopic therapies. He was seen by a cardio-oncology specialist, and a discussion was held with the referring hematologist and the patient. Given the need for anticoagulation for atrial fibrillation and concomitant concern for increased bleeding risk associated with ibrutinib, anticoagulation was reinitiated at a lower dose of apixaban 2.5 mg twice daily, and his Bruton’s tyrosine kinase inhibitor cancer therapy was switched to acalabrutinib without further complications.

KEY POINTS.

- Patient-oriented decision making
- Longitudinal multidisciplinary care
- Use of strategies to minimize the complications associated with cardiotoxicity

CASE 5: BEVACIZUMAB. A 77-year-old woman was diagnosed with colorectal cancer. Given her poor performance status due to several comorbid conditions, she was initiated on therapy with capecitabine

and bevacizumab. She developed new systolic hypertension, with a rise in systolic blood pressure to 170 mm Hg during regular screening after 2 weeks of therapy. She remained asymptomatic and was initiated on amlodipine 5 mg/d, which was subsequently titrated up to 10 mg/d with adequate control of her blood pressure.

KEY POINTS.

- Regular screening for common side effects
- Prompt recognition and management of cardiotoxic effect

Of note, angiotensin-converting enzyme inhibitors are recommended as first-line agents for management of anti-VEGF-induced hypertension, mostly for their potential renoprotective effects given higher risk for proteinuria on VEGF inhibition therapy.^{43,44}

CASE 6: PEDIATRICS. A 7-year-old girl was diagnosed with acute myeloid leukemia when she was 3 years of age. Her treatment included a daunorubicin-containing regimen, with a total dose of 150 mg/m², and hematopoietic stem cell transplantation (HSCT). Four years later, she was diagnosed with relapsed acute myeloid leukemia. She was noted to have an LVEF of 50% to 55% at this time, with GLS of -18%, and subsequently began therapy with venetoclax with curative plans for further HSCT in the coming weeks. Routine echocardiography 1 year prior to relapse had shown an LVEF of 55% to 60% and GLS of -20%. However, pre-HSCT screening echocardiography 2 months after relapse showed an LVEF of 40% to 45%, with GLS of -14%. Her parents reported that she has seemed more tired than usual but thought it was related to the relapsed leukemia and current chemotherapy. Given the decline in her left ventricular systolic function, she was deemed not a candidate for HSCT and was quickly referred to a pediatric cardio-oncology specialist, who initiated therapy with enalapril and carvedilol. Follow-up echocardiography 1 month later demonstrated improvement in her LVEF to 50% and GLS of -17%. In discussion with her cardio-oncology specialist, primary oncologist, primary HSCT oncologist, and parents, it was decided that she was now a reasonable candidate for repeat HSCT and would continue her CV medications at least through treatment with close follow-up, including frequent echocardiography.

KEY POINTS.

- Prompt referral and access to a cardio-oncology specialist
- Patient- and family-oriented decision making

- Multidisciplinary management in limiting toxicity and continuing with cancer-directed therapies

LIMITATIONS OF THE PERMISSIVE CARDIOTOXICITY STRATEGY

It should be noted that permissive cardiotoxicity management strategies cannot be applied to every type of cardiotoxicity that develops during a course of cancer treatment. Permissive cardiotoxicity-based strategies can be advocated only for toxicities whose natural history during ongoing cancer treatment creates a reasonably large “safe harbor” zone in which a graduated degree of cardiotoxicity can be effectively monitored and managed in a manner that protects the patient from development of severe irreversible cardiotoxicity that will not respond to GDMT. For example, the development of severe pulmonary hypertension with dasatinib is poorly responsive to treatment and can lead to a fatal outcome if no mitigation strategy seems available. The mitigation strategy mentioned here could potentially allow a patient who had mild pulmonary hypertension to receive protective treatment that would predictably allow resumption of dasatinib. Similarly, retreatment of patients who have had ICI-related myocarditis or suggestions of other off-target effects can be selectively considered when limited options exist and could include trial of a different ICI agent. The risk for accelerated atherosclerosis is increasingly recognized as an off-target effect of ICI therapy that is not as distinctive as myocarditis. Such possibilities merit consideration in the risk-benefit assessment of resumption of ICI therapy in patients with prior cardiotoxicity. Oversight by a cardio-oncology team with advanced experience and strong collaborative relationship with oncology partners are likely prerequisites for managing such cases. The diversity of malignancies and their respective therapies mean that a “best fit” model is unlikely to be successful. Furthermore, cardiotoxicities can range from cardiomyopathies seen classically with anthracyclines,^{45,46} to coronary vasospasm with 5-FU,⁴⁷ to dyslipidemia, metabolic syndrome, and hypertension among hormone-specific agents in breast and prostate cancer,^{2,48} to myocarditis with ICIs,¹⁰ and many more (Table 1, Figure 1). This results in a landscape that can be very complex given heterogeneous patient populations, therapies, and outcomes. As such, clinical care is ideally delivered in a multidisciplinary fashion involving the patient, oncologist, pharmacist, and cardio-oncology specialist

in close communication. Collaborative cardio-oncology registries can provide further insight and can harness more patients and outcomes than any individual cardio-oncology specialist or institution.

CONCLUSIONS

Early detection and treatment of cancer have led to a 27% decline in death rates in the United States from 2001 to 2020.⁴⁹ This progress has been driven by improved therapies but at the cost of increased CV toxicities. Both cardiologists and oncologists have a role in the detection and management of these toxicities, and there is significant benefit to regular dialogue between the cardio-oncology specialist and the oncologist. Furthermore, increasing data suggest that it may be safe to continue these potentially cardiotoxic anticancer agents with close monitoring and aggressive management, in the setting of cardiotoxicity. Overall, clinicians should be vigilant for the adverse CV effects of certain cancer therapies, such as dyslipidemia and metabolic syndrome with endocrine and androgen deprivation therapy, and hypertension with anti-VEGF and multiple receptor tyrosine kinases. Blood pressure, diabetes, and lipid screening should be a routine part of long-term surveillance in patients with cancer. Optimization of modifiable risk factors, such as poor diet, sedentary lifestyle, tobacco use, and alcohol use, often in a multidisciplinary approach, remains the foundation for minimizing cardiotoxicity during treatment and survivorship.^{13,37}

The concept of permissive cardiotoxicity is to encourage physicians to provide optimal cancer therapy while limiting long-term, symptomatic cardiotoxicities. To do so necessarily involves assessment of the patient's comorbidities at baseline, as well as frequent CV assessment tailored to the anticancer agents being used. It also requires the ability of health care systems to provide patients with rapid access to cardio-oncology specialists when cardiotoxicity is anticipated or noted to be present. This also necessitates greater understanding of cardio-

oncology in the general cardiology and oncology practices. These challenges, although complex, are surmountable at both the institution and system levels with appropriate allocation of resources, administrative support, and education.

It is our hope that the paradigm of permissive cardiotoxicity shifts the mind-set of cancer care providers from "Should this therapy be discontinued?" to "How can we safely continue this therapy?"

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED

PRACTICE: Permissive cardiotoxicity is a balance of clinical determinants in which optimal cancer therapy may have negative impact on the cardiovascular system, but the overall goal is to allow the best outcome from cancer treatment. We introduce for the first time, this vital concept in cardio-oncology that emphasizes a proactive rather than reactive approach to continuation of lifesaving cancer therapies in order to achieve the best oncologic outcome; while at the same time managing the patient to mitigate associated and potentially off-target cardiotoxicities.

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