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REVIEW ARTICLE

Late Cardiac Effects of Cancer Treatment

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ABSTRACT

Cardiac toxicities from cancer therapy can become evident many years after treatment, and these late cardiac effects can have a profound impact on cancer survivors. There are a myriad of potential cardiovascular complications from cancer therapy, but these can be grouped into three main categories. First, vascular conditions including atherosclerosis, thrombosis, and hypertension predominate. Second, cardiac structural problems, especially valvular degeneration, can have a dramatic impact long term. Lastly, and most importantly, cardiac dysfunction and heart failure are potentially common late cardiac effects and can certainly be prevented or detected early during active cancer therapy to result in optimal outcomes. Future research on late cardiac effects in cancer survivors needs to include advanced cardiac imaging techniques, novel cardiac biomarkers, and genetic determinants of response to cancer treatment.

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INTRODUCTION

There is a growing need to characterize long-term health issues in patients who have undergone treatment for cancer. This burgeoning issue is largely the result of of the success of cancer therapy and the enhanced long-term survival after contemporary treatment. Overall, this has to be considered a great development; however, cardiac toxicities related to cancer or its treatment can affect not only how patients may feel but also their longevity and general capacity.[1-4] For this reason, consideration of how to prevent cardiac toxicity, determination of necessary measures for early detection and cardiac-specific treatment, and anticipation of long-term cardiac limitations years after cancer treatment have become of paramount importance.

There are potentially many aspects of the cardiovascular (CV) system that are affected by cancer therapy and can be important to cancer survivors.[5-11] For the purposes of clarity, this review will group these conditions into three main categories (Table 1). First, vascular conditions are common in cancer survivors and can range from severe ischemia (resulting from atherosclerosis) or thrombosis in any vascular bed to long-standing or acutely severe hypertension (HTN) with resultant vascular compromise in organs sensitive to marked changes in blood pressure, such as brain, renal, or cardiac tissue.[12-17] Second, cardiac structural problems may develop as a result of cancer or cancer treatment, and these include a wide range of complications, such as valvular heart disease, pericardial disease, or even rhythm disturbances resulting from conduction system damage.[18] The third general category includes myocardial dysfunction and heart failure (HF) resulting predominately from chemotherapy, although other cancer treatments, such as radiation, may have synergistic impact on cardiac function.[19-21] By condensing a variety of cardiac conditions into three definable groups, the intent of this review is to focus on the practical manifestations of cardiac disease in cancer survivors. In particular, understanding how these CV conditions can be detected, treated, and ideally prevented will undoubtedly have a great impact on the CV complications and overall outcomes of cancer survivors. Additionally, an assessment of current research knowledge will be outlined, with proposed areas in which clinical research gaps can be narrowed.

VASCULAR COMPROMISE

The CV effects of cancer therapy can be quite profound when one considers the full extent of cancer treatment on the vasculature. It can only be anticipated that vascular effects will continue to be prominent among the concerns of cancer survivors, especially because a high percentage of newer cancer therapies have antiangiogenic properties.[22,23] No doubt the potential for a myriad of long-term vascular issues is a legitimate concern, but it also seems these issues can be prevented or managed quite effectively. Our collective understanding of vascular complications resulting from cancer therapy has improved significantly over the years, but continued effort is needed.

Table 1. Causes of Selected Common Late Cardiovascular Conditions in Cancer Survivors

Condition and Causes
Vascular
Atherosclerosis
Hypertension
Arterial thrombosis
Deep venous thrombosis/pulmonary embolus
Structural
Valvular heart disease
Pericardial effusion
Pericardial constriction
Conduction system disease
Myocardial dysfunction and heart failure
Anthracyclines
Trastuzumab
Antiangiogenic therapy
Radiation therapy
Restrictive cardiomyopathy

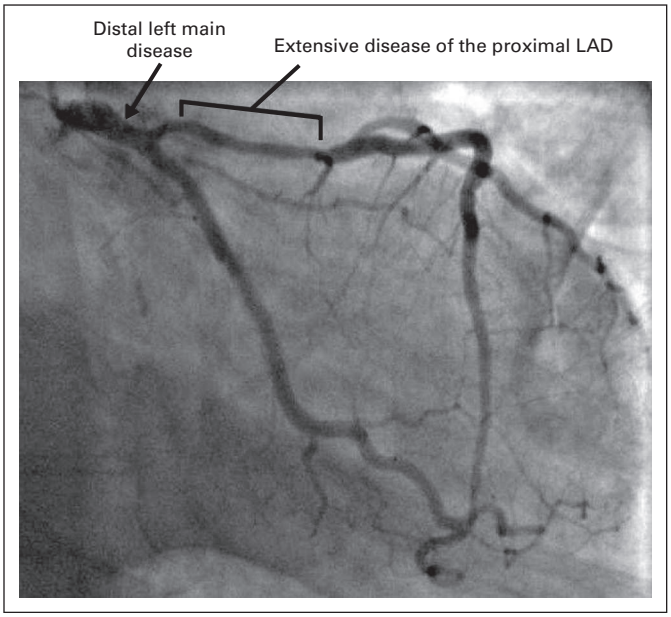

Fig 1. This young patient had distal left main coronary disease and diffuse proximal left anterior descending (LAD) disease localized to areas subject to radiation. The more distal vessels were normal, and it is notable that the more distal coronaries are larger than more proximal areas, indicating circumferential atherosclerosis.

Predominant Vascular Problems: Atherosclerosis and Thrombosis, Arterial or Venous

Patient case 1. A 26-year-old woman presents with an anterior myocardial infarction (MI) and profound hypotension requiring mechanical blood pressure support. She ultimately survives her hospitalization but has severe left ventricular dysfunction, with a left ventricular ejection fraction (LVEF) of less than 20%. Her cancer history is notable for a Wilms tumor at age 6 years, treated with nephrectomy, resection of a solitary lung nodule, and whole-lung irradiation (52.4 Gy). Additionally, she was administered anthracycline-based chemotherapy at that time (total dose, 250 mg/m^2). She did well for many years. However, at age 25 years (1 year before MI), she was diagnosed with HTN; she was not very active but not obese, and she did have normal LVEF on echocardiography. No stress testing or lipid profile was performed then, and at the time of her MI presentation 1 year later, her total cholesterol is 255 mg/dL. She dies within 1 year of MI as a result of refractory HF.

In terms of atherosclerosis, the effects of radiation therapy are most profound. Any vascular location that is in the radiation field is at high risk for early and complex atherosclerosis.[24] Mediastinal irradiation is a major risk factor for the development of coronary artery disease (CAD), which is typically proximal and usually complex in nature (Fig 1).[25] As a result, appropriate screening for asymptomatic CAD with stress testing must be considered in patients with a history of mediastinal or left-sided irradiation.[26-28] As illustrated in the patient case 1 presentation, our young patient had multiple risk factors for CAD, and no screening was performed. Furthermore, angiography of the internal mammary branches should strongly be considered whenever angiography is being performed for cardiac diagnostic reasons because of the proclivity of radiation to affect the internal mammary arterial bed.[24] Additionally, neck irradiation is a major risk factor for significant carotid disease (Fig 2).[29,30] Frequently, there are no symptoms attributable to either CAD or carotid disease, and screening is appropriate in selected cancer survivors with multiple CV risk factors who received radiation as part of their treatment. In the case of carotid disease, ultrasound is the safest and most effective tool. Another consideration is that any vascular bed in which radiation is used to control cancer is subject to early atherosclerosis.[31] Therefore, a high degree of suspicion is needed to truly detect important silent diseases. Peripheral vascular disease is thus a consideration and should be included in a symptom complex that is relevant to a particular vascular supply (eg, claudication in a patient with radiation administered to an extremity

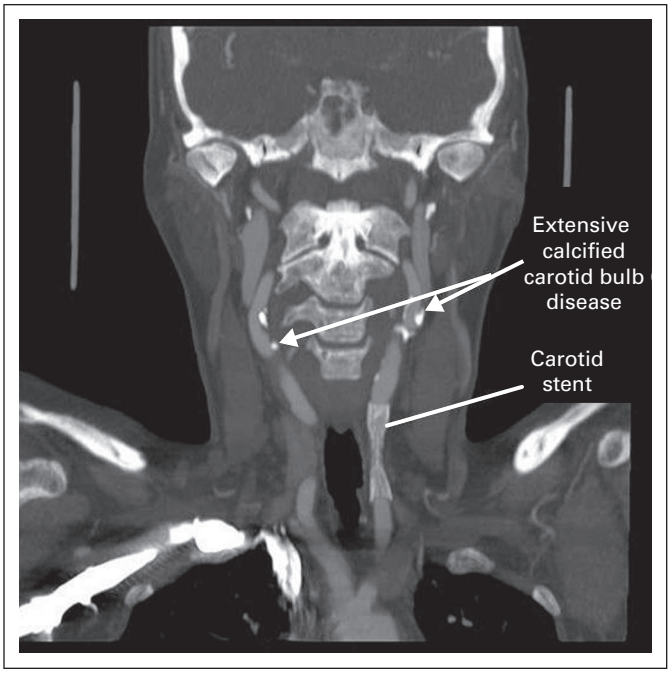

Fig 2. Extensive and complex carotid atherosclerosis in a 50-year-old patient with neck irradiation for sarcoma. This patient already has a left carotid stent and persistent stenosis in both carotid bulbs.

or intestinal ischemia for those who have undergone abdominal irradiation).[32,33] To a large degree, aggressive risk-factor management is the best prevention or early-management principle for atherosclerosis in cancer survivors. Optimal management of atherosclerosis in general includes aspirin (at least 81 mg); statin-based lipid therapy, if possible; and, in selected patients, additional antiplatelet therapy with clopidogrel (Plavix; Bristol-Myers Squibb/Sanofi Partnership, Bridgewater, NJ) or other anticoagulants depending on severity and location. Frequently, regular exercise is also a major component, because this stimulates the development of collaterals in both CAD and peripheral vascular disease and extends life expectancy in all patients, including those treated for cancer.[34-36]

Other vascular events faced by survivors of cancer therapy include HTN, a common manifestation, and thrombosis, either arterial or venous.[16] HTN is a long-term consequence of many cancer therapies, including *cis*-platinum, but recently, antiangiogenic therapy, both concurrent or previous treatment, has resulted in substantial elevation of blood pressure in up to half of those patients treated with these agents.[37] US Food and Drug Administration–approved antiangiogenic-based therapies include bevacizumab, sunitinib, sorafenib, pazopanib, and vandetanib, but there are several in the later stages of clinical trials.[22,38] Because HTN is an easily recognized and treated condition, education is the key to early detection and prevention of complications. Home monitoring is crucial, and general parameters for patient medication adjustment are typically needed. Unrecognized or poorly treated HTN is a major cause of stroke, HF, or even sudden death, especially in patients with cancer treated with long-term antiangiogenic therapy.[39] In general, medications commonly used to treat HTN are used, but recommended therapies would be those that are effective at preventing HF (eg, angiotension-converting enzyme inhibitors [ACE-Is], beta-blockers [BBs], or angiotension receptor blockers). Diuretics might not be an optimal choice given their propensity to result in electrolyte disturbances.

Thrombosis, either arterial or venous, is a major concern in cancer survivors. The causes of thrombosis can be myriad and may be related to the disease itself or the treatment. Arterial thrombi typically occur in areas where atherosclerosis is a defined condition but also may occur in vascular areas remote from the source. The development of atrial fibrillation and a resultant left atrial clot is a classic example and is occurring with increasing frequency among cancer survivors.[40] Venous thrombosis, either deep venous thrombosis or pulmonary embolus, is an extremely common condition related to cancer diagnosis, but it especially affects those patients with chronic intravenous access for chemotherapy or blood transfusions.[41] Striking a balance between how aggressively to anticoagulate while managing the risk of bleeding is constantly a challenge in cancer survivors who may be at higher risk for bleeding complications. Certainly, removal of any permanent intravenous lines when not required is prudent, and prevention of thrombosis through long-term anticoagulation either with aspirin, warfarin, or newer thrombin or factor Xa inhibitors is an important consideration in cancer survivors.[42-44]

Practical Recommendations

- Radiation therapy should be considered a major risk factor for the development of atherosclerosis in any vascular bed in the field of therapy.
- Optimal treatment for CV risk factors is of paramount importance among cancer survivors.
- Screening for asymptomatic carotid or CAD is necessary to prevent major CV complications in cancer survivors treated with radiation therapy.
- Thromboses, with attendant complications, are preventable in cancer survivors but, if not properly treated, are associated with significant morbidity.

CARDIAC STRUCTURAL COMPLICATIONS

The late cardiac effects of cancer therapy can potentially damage any component of the cardiac structure; thus, all combinations of pathology must be considered in cancer survivors. Because many cardiac structural disorders typically have long asymptomatic periods, these structural issues may not be commonly considered. However, the timing of surgical or medical treatment can be critical for optimal outcomes in cardiac structural disorders, and monitoring is essential.

Most Common Important Cardiac Structural Problem: Valvular Dysfunction

Patient case 2. A 51-year-old woman, initially treated for Hodgkin lymphoma at age 15 years with mantle radiation (40 Gy) and lymph node removal/splenectomy, presents for routine follow-up in survivorship clinic. She was also diagnosed with left-sided breast cancer (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 [HER2] negative) at age 46 years and treated with partial mastectomy, 50.4 Gy left-sided irradiation, and hormonal therapy. She is asymptomatic on presentation, but her examination is remarkable for a blood pressure of 142/70 and 3/6 systolic murmur at the right upper sternal border without a third heart sound. Her lipid profile is notable for low-density lipoprotein (LDL) of 135 mg/dL and total cholesterol of 217 mg/dL. Screening echocardiogram reveals moderate to severe aortic insufficiency with moderate aortic stenosis (Fig 3) and normal LVEF. Her B-type natriuretic peptide level (BNP), obtained to monitor for asymptomatic cardiac dysfunction and volume overload, is elevated at 247 pg/mL (normal, $<$ 100 pg/mL). She is placed on baby aspirin, a statin, and carvedilol (BB) for control of

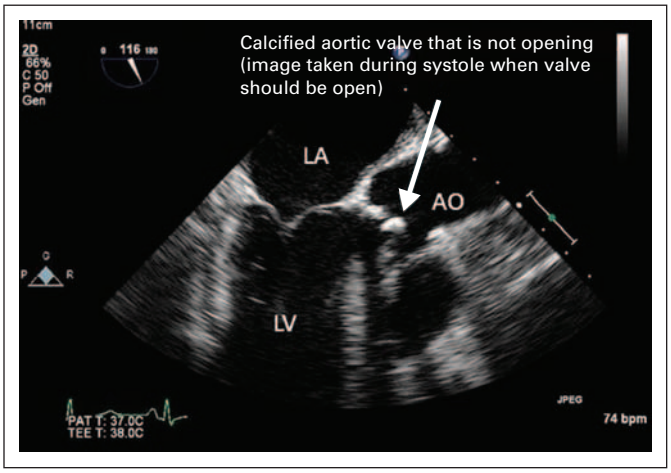

Fig 3. Extensive calcification with resultant stenosis and/or regurgitation of any valve can occur as a late cardiac effect of radiation therapy. These problems can be silent for many years; then patients can present clinically decompensated. AO, aorta; LA, left atrium; LV, left ventricle.

HTN and cardioprotection. Return visits over the next year reveal no progression of aortic valve disease and normalization of the BNP value as well as LDL level.

Valvular degeneration with calcification is a long-term consequence of mediastinal irradiation and this is exacerbated by hyperlipidemia and HTN.[12,14] Long-term survivors, much like the patient in case 2, are typically unaware of these conditions, and providers do not consistently monitor for such issues. Even though this patient was asymptomatic, she was not active and may have adjusted her activity over the years to compensate. Sudden progression of aortic stenosis and/or regurgitation may result in sudden death or HF that can preclude valve surgery.[45] Periodic assessment, involving at least physical examination, is essential to monitor for valvular disease progression so as not miss the proper clinical timing of intervention.

Pericardial disease, either pericardial effusion, with or without tamponade, or pericardial constriction, may be a particularly difficult clinical condition encountered among cancer survivors.[46] Pericardial effusions are typically seen in the active-treatment phase of breast and lung cancers and may become manifest early in the course of treatment; however, this condition can be an uncommon later-occurring consequence of chest irradiation that requires coordinated management even in patients who have no evidence of cancer and are long-term survivors. In many instances, pericardial effusion or constriction can be observed for an extended period of time, even if initially related to malignancy, until symptoms of HF result. Selected experienced researchers use pericardioscopy with success in assisting in the diagnosis of pericardial disease. Pericardiectomy, if undertaken, is a challenging treatment, and surgical outcomes are not optimal, but in selected cases, it can be critically important.[47,48] Monitoring for pericardial disease is best done by echocardiography and periodic clinical assessment.

Conduction disease, an indication of electrical structural damage, is a substantial concern as a late cardiac effect in cancer survivors. Atrial fibrillation, bradycardia and heart block are all occurring with increased frequency in selected subsets of cancer survivors such as those receiving thalidomide as maintenance therapy or those treated for Hodgkin lymphoma.[49]

Practical Recommendations

- Valvular degeneration is a common late consequence of mediastinal irradiation.
- Periodic screening with physical examination and potentially echocardiography is needed to uncover significant valve dysfunction or pericardial disease.
- Pericardial disease can occur as a late cardiac event in cancer survivors and requires careful coordination between cardiologists and oncologists.

MYOCARDIAL DYSFUNCTION AND HF

The development of myocardial dysfunction and HF as late effects of cancer therapy is a devastating consequence, leading to increase mortality and significant morbidity.[50] The outcomes of cancer survivors who develop cardiomyopathy, either chemotherapy or radiation related, are generally poor, and efforts to detect cardiac dysfunction at its earliest time and provide cardiac-specific therapy to prevent progression are of paramount importance.[51]

Most Serious Late Cardiac Adverse Effect: Myocardial Damage Resulting in Cardiomyopathy or HF

Patient case 3. A 61-year-old woman, initially treated for estrogen receptor–positive (HER status unknown), left-sided breast cancer at age 44 years with six cycles of anthracycline-based chemotherapy (total dose, 250 mg/m^2), presents for treatment of symptomatic HF that developed over a 2-month period. Her breast cancer was first treated with partial mastectomy, chemotherapy, and left-sided irradiation. She had a local recurrence 2 years later and underwent modified radical mastectomy. She had been cancer free for nearly 20 years until she developed HF. Her initial cardiac evaluation reveals severe LV dysfunction, with LVEF of 25%, elevated lipid profile (total cholesterol, 208 mg/dL; LDL, 137 mg/dL; high-density lipoprotein, 26 mg/dL), HTN (168/106), and markedly elevated BNP (576 pg/mL), indicating significant volume overload. She is started on carvedilol (BB), lisinopril (ACE-I), a statin for hyperlipidemia, and furosemide as needed for edema. Her HTN is easily controlled, and over the next 4 months, her laboratory abnormalities normalize, as do her symptoms and LV function (LVEF, 55%).

Cardiotoxicity, typically related to certain chemotherapy agents, is a major concern as a late effect of cancer treatment. It is important to note that historically, cardiotoxicity, as it has been defined, has generally meant LV dysfunction detected by echocardiogram or multigated analysis (Figs 4A and 4B).[52] Currently, cardiac dysfunction is defined in Common Terminology Criteria (version 4) as LV dysfunction or HF, and this represents cardiotoxicity in the current lexicon.[53] Incorporating this more inclusive definition of cardiac dysfunction is necessary, because a patient can commonly develop HF with normal LVEF.[54] In fact, HF resulting from poorly controlled HTN is a typical clinical scenario in which a cancer survivor might develop cardiac dysfunction with normal LVEF.[55,56]

The classical offending agents with regard to cardiotoxicity as a late effect for cancer survivors are any anthracycline analogs (doxorubin, epirubicin, liposomal doxorubicin, or mitoxantrone as well as others). The typical belief is that it takes a large dose ($>$ 450 mg/m^2) to develop cardiotoxicity, although a person can be susceptible at much lower doses, as was evident in patient case 3. Additionally, there is historical evidence that this cardiotoxicity related to anthracyclines is irreversible.[20] However, what is clear is that if subclinical cardiac dysfunction is not detected or treated, it is certainly irreversible and likely progressive, as in the patient in case 3. There is now convincing

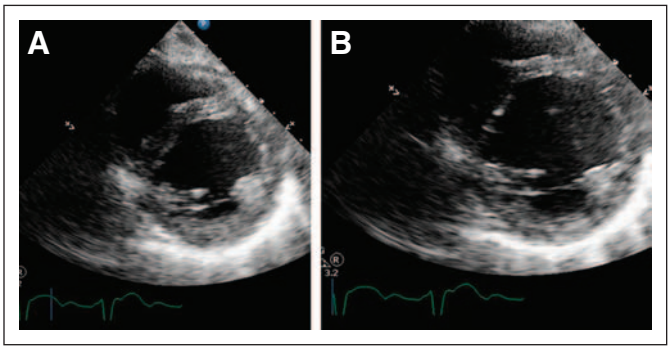

Fig 4. Severe systolic dysfunction in a global fashion with left ventricular dilation in a patient with anthracycline-related cardiomyopathy. Images are similar, although one is (A) systole, whereas the other is (B) diastole. This indicates severe cardiomyopathy.

evidence that early identification of cardiotoxicity and prompt therapy for HF can lead to substantial improvement in LVEF to even normal levels.[57,58] Most importantly, if subclinical LV dysfunction is left untreated for periods longer than 6 months, the likelihood of recovery is low. With this principle in mind, cardiac biomarkers, such as troponin I and BNP, have shown utility in early detection of cardiotoxicity and optimization of cardiac protective medications to prevent or ameliorate damage that may occur during cancer treatment.[56,59] This proactive process can virtually eliminate cardiotoxicity as a substantial late cardiac effect for cancer survivors.

Other crucial chemotherapeutic agents are known to be associated with cardiotoxicity and may have late effects important for cancer survivors. Trastuzumab, an HER2-receptor blocker, is a major treatment option in selected patients with breast cancer overexpressing the *HER2* gene.[60,61] This treatment has become a cornerstone therapy that reduces mortality in HER2-positive patients, but there is clearly an increase in cardiac dysfunction in treated patients, especially when used in combination with anthracyclines. In many instances, cardiac dysfunction related to this therapy can be reversible when treated optimally with appropriate HF medications[62]; unfortunately, it is not always reversible, especially if typical HF medications are not used.[63] Additionally, there is not a wealth of data describing the long-term outcomes of patients with transient LV dysfunction during chemotherapy with trastuzumab or how long these patients should be treated with HF-appropriate medications like ACE-I or BB. It does seem prudent to be reluctant to withdraw ACE-I or BB in patients with transient HF and LV dysfunction until a long period of stability exists, and the patients are no longer being actively treated for cancer.

Antiangiogenic-based chemotherapy has become a mainstay of standard treatment for selected cancers, and the multiple specific targeted therapies have HTN as a common cardiac adverse event.[37] The frequency and severity of HTN as an adverse event depend on the population being treated, length of therapy, and dosage used. It is also apparent that HF and acute coronary syndrome are potential complications resulting at least in part from vasoconstriction with antiangiogenic therapy.[64-66] Therefore, appropriate cardiac risk factor management is imperative for optimal outcomes in these patients. This includes making use of not only antihypertensive therapy that prevents the development of HF (eg, ACE-I or BB), but also other important management principles including aspirin, statin therapy, dietary sodium restriction, regular exercise, and weight control, if possible.

Less common cofactors leading to late cardiac dysfunction in cancer survivors include irradiation of myocardial tissues and restrictive cardiomyopathy. Mediastinal irradiation certainly sensitizes the myocardial tissue to the toxic effects of chemotherapy and would result in a patient being highly susceptible to this complication. A careful history of the exact timing of cancer treatments is necessary. Regarding restrictive cardiomyopathy, radiation therapy is also implicated in this condition, but transition of multiple myeloma to amyloidosis and subsequent cardiac involvement is also a consideration.[67,68] Usually, a myocardial biopsy is necessary to clarify these concerns, although magnetic resonance imaging can provide important information.

Practical Recommendations

- Several classes of chemotherapy agents commonly used are known to have myocardial dysfunction and HF as important consequences (anthracyclines, HER2-receptor antagonists, and antiangiogenic-based treatment).
- Cardiac biomarkers, particularly troponin I and BNP, are becoming useful in stratifying and identifying those patients undergoing cancer therapy at risk for cardiac dysfunction.
- Antihypertensive therapy is crucial to managing HTN during certain types of chemotherapy, and those agents known to prevent HF are preferred.
- Once a patient develops cardiac dysfunction related to chemotherapy, appropriate therapy for HF should be used.
- Early discontinuation of cardioprotective HF therapy is not recommended.

FUTURE RESEARCH DIRECTIONS

Early detection, monitoring, and prevention of CV toxicity resulting from cancer treatment are the keystones for the continued improvement of long-term outcomes for patients with cancer. Therefore, emphasizing these areas of research is the overall goal (Table 2).

Early Detection and Monitoring for Patients at Risk for Myocardial Dysfunction

Novel imaging techniques. The current recommendation of monitoring cardiac function by periodic assessment of LVEF, mainly using two-dimensional echocardiography, has limited clinical utility.

Table 2. Practical Screening Tools for Cardiovascular Disease in Cancer Survivors

Test	Timing Interval
Fasting lipid profile	Yearly, if abnormal
TSH (especially with neck irradiation)	Every several years, unless symptoms occur
Self-measurement of blood pressure	Several times per week in high-risk patients
Careful history and physical examination	At least yearly
Echocardiography (especially with any mediastinal irradiation or previous cardiotoxic chemotherapy)	Every 1-2 years in high-risk patients
Carotid ultrasound (particularly with mantle or neck irradiation)	Every 2 years in high-risk patients
Cardiac biomarkers (troponin, BNP)	Every 1-2 years in high-risk patients, unless symptoms occur
ECG	At least once every 2-3 years

Abbreviations: BNP, B-type natriuretic peptide level; TSH, thyroid-stimulating hormone.

Largely, this is because of the relative insensitivity to detect myocardial dysfunction at the early stages of the disease, precluding reliable early intervention.[69] Recognition of this limitation has prompted investigators to develop new sophisticated echocardiographic techniques, such as tissue Doppler imaging and strain-rate echocardiography. These new techniques seem to be more sensitive than standard echocardiography in detecting subclinical changes in cardiac performance, which usually precede a decrease in conventional LVEF. Long-term data in large populations confirming the clinical relevance of such promising results are needed.[70-75]

Cardiac biomarkers. A novel approach based on the use of cardiac biomarkers, including troponins and BNP, has emerged as clinically relevant in the last decade. This strategy can result in a cost-effective diagnostic tool for early, real-time identification, assessment, and monitoring of anticancer drug–induced cardiotoxicity.[76] Overall, this approach has proven to be more sensitive and specific, cheaper, and repeatable without risk to patients; readily available even in small hospitals; and without interobserver variability. Today, strong evidence exists that troponin detects anticancer drug–induced cardiotoxicity in its earliest phase, long before any reduction in LVEF has occurred.[76] Early identification of patients at risk of developing cardiac dysfunction, the stratification of risk for cardiac events after chemotherapy, and the opportunity for a preventive targeted therapy in selected high-risk patients are all achieved by troponin measurement during chemotherapy.[59] However, standardization of routine troponin use in the clinical setting, particularly when to measure and the verification of the sensitivity of the assay, is an issue that needs to be clarified to maximize single–time point assay sensitivity and specificity. This is desperately needed and should be an important focus of future research.

New potential biomarkers of cardiotoxicity. Because many newer cancer therapies have markedly different mechanisms of action, underlying cardiotoxic effects may not be associated with release of troponin by myocardial cells. Thus, new potential biomarkers should be considered for the early detection of myocardial cell injury and for the better elucidation of other possible cardiotoxic mechanisms. An example is cytochrome C, a proapoptotic protein typically released by dysfunctioning cardiac mitochondria. This protein is not detectable in the blood of healthy humans, but an increase has been recently observed in the early stage of MI treated with primary angioplasty. In this clinical setting, it has been suggested to be a potential marker of ischemic and reperfusion injury.[77] In the oncologic setting, it is well established that mitochondrial function is rapidly affected by doxorubicin.[78] However, it is not clear whether novel drugs can have a direct impact on mitochondrial membrane permeability and whether the assessment of markers of mitochondrial damage, like cytochrome C, may be useful in early identification of toxicity.

Other biomarker possibilities include microRNA, short RNA molecules that regulate gene expression, which are typically found in the normal systemic circulation of both animals and humans. Certain microRNA levels can change in the presence of several cancers, including breast cancer, lymphoma, and lung cancer.[79] Because levels can change after cardiac stress, circulating microRNAs have been proposed as diagnostic biomarkers for cardiac diseases such as HF and MI[80] and, in animal models, anthracycline-induced cardiotoxicity.[81] Mobilization of microRNAs occurs in the first phase by active secretory mechanisms through exosomes and microvesicles and later in a second phase by passive secretion associated with cell necrosis.[82] It is possible, therefore, to speculate that the active release of specific circulating microRNA may reveal anthracycline-related myocardial cell injury that precedes cardiac cell necrosis and troponin release. To meaningfully investigate these theories, multicenter translational studies are warranted.

Genetic investigations. Pharmacogenomics are increasingly being investigated in general cardiology in the search for genetic variations that contribute to the development of CV disease. Significant interindividual variability in tolerance to cumulative anthracycline exposure has indicated a role for genetic susceptibility.[83,84] Genome-wide screening has identified several single nucleotide polymorphisms associated with genetic predisposition, indicating increased sensitivity to chemotherapy. The clinical significance of these findings is still under evaluation, but it has been hypothesized that genetic variation might modulate the risk of CV toxicity after cancer treatment. It is believed this information may allow for more personalized oncologic therapy.[85]

Early Detection and Monitoring for Patients at Risk for Vascular Complications

Anticancer treatment should be considered a specific CV risk factor, because it may induce endothelial dysfunction and accelerate atherosclerosis processes, leading to an increased risk for future CV events.[83,86] Several clinical studies have investigated endothelial damage in patients with cancer. Increased levels of markers of endothelial dysfunction, like endogenous inhibitors of nitric oxide and asymmetric and symmetric dimethylarginines, were detected many years after chemotherapy in long-term cancer survivors.[76] Therefore, monitoring markers of endothelial function after chemotherapy may aid in future prediction of CV events, including brachial artery flow-mediated dilation.[87] Adequate prospective studies should be conducted to determine if these markers are useful in prediction of risk or management of cancer survivors.

Prevention of HF and Myocardial Dysfunction

The cardioprotective effects of many pharmacologic agents have been demonstrated during cancer therapy. However, most of the previous studies have been conducted in animal models. In the clinical arena, only dexraxosane (iron-chelating agent),[88] carvedilol (BB),[89] valsartan (angiotension receptor blocker),[90] and enalapril (ACE-I),[59] have been effective in preventing myocardial dysfunction in patients treated with anthracyclines. Adequate prospective investigations should be conducted to address whether these or other strategies could be effective in patients treated with anthracyclines or antiangiogenic therapies. At present, two large trials are ongoing: the OVERCOME (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies) study,[91] testing whether ACE-Is and/or BBs are protective during chemotherapy, and the MANTICOR (Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research) trial,[92] evaluating a different ACE-I, perindopril, and bisoprolol (BB) in the prevention of trastuzumab-mediated cardiotoxicity. It is hoped that the findings of these trials will provide important insight into the prevention of HF and myocardial dysfunction.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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