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Cardio-Oncology: A Focused Review of Anthracycline-, Human Epidermal Growth Factor Receptor 2 Inhibitor–, and Radiation-Induced Cardiotoxicity and Management

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Background: Cardio-oncology is a collaborative approach between cardiologists and oncologists in the treatment of patients with cancer and heart disease. Radiation and chemotherapy have played a major role in the decreased cancer-related mortality achieved in the past 2 decades. However, anthracycline-, tyrosine kinase-, and radiation-based therapies are each associated with independent cardiovascular (CV) risks, and these risks are cumulative when these therapies are used in combination.

Methods: We analyzed several published articles, studies, and guidelines to provide a focused review of cardiotoxicity associated with anthracyclines, human epidermal growth factor receptor 2 inhibitors, and radiation therapy and its management.

Results: The focus on CV risk among individuals being treated with cardiotoxic agents is important because once the cancer is cured, CV disease becomes the number 1 cause of death among cancer survivors. Cardio-oncology focuses on assessing CV risk prior to starting therapy, optimizing modifiable risk factors, and providing surveillance and treatment for any early signs of cardiotoxicity in patients undergoing radiation and chemotherapy. A collaborative approach between oncologists and cardiologists is integral to the optimal care of patients with cancer. Although radiation and chemotherapy treatments have evolved with the aim of targeting cancer cells while having minimal effect on the heart, the increased risk of cardiomyopathy in patients receiving these treatments remains significant.

Conclusion: Proper screening and treatment of cardiotoxicity are essential for patients with cancer. As cardiac diseases and cancer remain the first and second causes of mortality in developed nations, respectively, cardio-oncology is the answer to this group of individuals who are especially vulnerable to both causes of mortality.

Keywords: *Anthracyclines, cardiotoxicity, heart failure, radiation, trastuzumab*

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INTRODUCTION

Cardio-oncology is an integrative medical approach that involves close interaction between cardiologists and oncologists with the goal of mitigating cardiac risk and providing optimal care to patients who will be receiving cardiotoxic agents. This collaborative approach aims to address 3 general emerging factors that affect cancer survivors. First, virtually all antineoplastic drugs and radiation therapies are potentially cardiotoxic.[1] Second, patients with preexisting cardiac abnormalities are especially susceptible to chemotherapy and radiation-induced cardiotoxicity. Third, even when antineoplastic therapy is not the main culprit of cardiomyopathy (CMY), the decreased cancer-related mortality achieved in the past 25 years has inadvertently increased the prevalence of cardiovascular (CV) diseases among cancer survivors.

Chemotherapy-induced cardiotoxicity is often categorized in 5 major groups: (1) cardiac systolic and diastolic dysfunction, (2) arrhythmias, (3) pericardial disease, (4) repolarization abnormalities (QT prolongation), and (5) ischemia.[1] Radiation therapy is associated with coronary artery disease, as well as fibrotic changes to cardiac valves, the myocardium, and the pericardium.[1] As is the case for neoplastic cells, rapidly dividing normal cells are targeted by antineoplastic treatments. Abdominal discomfort, for instance, is a recognized side effect of chemotherapy linked to the speed of cell turnover in the gastrointestinal tract. Unlike the gastrointestinal system, however, some CV cells have limited regenerative capabilities. Consequently, the CV system is susceptible to long-term damage from antineoplastic agents.[2]

To address the relatively new problem of cardiotoxicity in patients with cancer, several institutions have created cardio-oncology departments focused on managing the cardiac risk factors and diseases among cancer patients and survivors. As of 2015, there were at least 49 cardio-oncology departments in the United States, with our clinic at Ochsner Medical Center being the first in Louisiana. This combined approach allows for additional screening of CV disease prior to initiating radiation or chemotherapy, prompt evaluation and treatment once cardiotoxicity is observed, and adequate monitoring for late symptoms. The International CardiOncology Society and the online journal *Cardio-Oncology* have been formed to increase awareness and information regarding cardio-oncology.

We discuss anthracycline, human epidermal growth factor receptor 2 (HER2) inhibitor, and radiation therapy cardiotoxicity and its management to provide a basic understanding for other institutions planning to form a cardio-oncology clinic.

ANTHRACYCLINES

Anthracyclines are antibiotics that promote DNA damage. This group, which includes doxorubicin, is found in the soil of *Streptomyces* bacteria. Anthracyclines were introduced in the 1960s and remain a major component of many chemotherapy regimens, including those for lymphomas, breast cancer, and small cell lung cancer. Anthracycline-induced CMY can occur at any time during treatment. Acutely, most patients present with arrhythmias, whereas congestive heart failure appears to be the most common chronic presentation.[3] While acute cardiotoxicity has been a known reversible side effect for decades, chronic cardiotoxicity of anthracyclines is a relatively new challenge. Moreover, acute symptoms are relatively rare compared to chronic complications. For example, in a trial that included 1,697 individuals, only 3.2% of trial participants developed acute symptoms that included atrial fibrillation, acute heart failure, myocarditis, and myocardial infarction,[3] whereas, in the now-famous study by Lipshultz et al published in 2013, two-thirds of asymptomatic patients with a history of childhood chemotherapy were found to have progressive CMY.[2] Therefore, while monitoring in the peritreatment period is important, chronic monitoring, particularly of childhood cancer survivors during adulthood, is important.

The strongest risk factor for anthracycline-induced CMY is the cumulative dose (Table 1). The risk of doxorubicin-induced CMY increases significantly with doses >550 mg/m^2.[4] Weaker risk factors, such as age, hypertension, diabetes, previous heart disease, concurrent treatment with other chemotherapy agents, hematopoietic cell transplantation, host susceptibility, and previous radiation therapy, are, however, clinically relevant.[5,6] For example, the probability of developing heart failure at a cumulative dose of 550 mg/m^2 was 0.07% in one study, while in patients >64 years, a 29% increased risk of congestive heart failure occurred with any doxorubicin dose.[4,7] Finally, hypertension has been reported as the only synergistic risk factor with doxorubicin for the development of congestive heart failure.[7]

The mechanism of injury of doxorubicin has long been thought to be secondary to formation of doxorubicin-iron complexes that catalyze the generation of free radicals. Free radicals, in return, interfere with mitochondrial function inside the myocardium, resulting in decreased contractility of the heart.[8] Additionally, the oxidative stress causes lipid peroxidation, vacuolation, and myocyte death.[9,10] Doubt about this hypothesis has, however, been raised by at least 2 studies that failed to prevent doxorubicin-induced cardiotoxicity with the use of reactive oxygen species scavengers.[11,12]

Table 1. Risk of Cardiotoxicity Associated With Chemotherapy

Risk Factor	Anthracycline	Trastuzumab
Cumulative dose >550 mg/m^2	Yes	
Age	Yes ($\geq$64 years)	Yes ($\geq$50 years)
Hypertension	Yes	Yes
Previous heart disease	Yes	
Previous radiation therapy	Yes	
Concurrent chemotherapy	Yes	Yes[a]
Hematopoietic cell transplantation	Yes	
Host susceptibility[5]	Yes	
Obesity (BMI $\geq$30)		Yes
Diabetes	Yes	No[b]

Blank cells in the table denote characteristics that are not risk factors or are inconclusive.
BMI, body mass index.
[a]Especially with concurrent anthracycline use.
[b]Small study suggests association in elderly women with diabetes.[6]

An alternative hypothesis suggests the involvement of the enzyme topoisomerase-II.[13,14] Topoisomerase-II-alpha (α) is a known marker of rapid cellular proliferation that is overexpressed in tumor cells,[15] while topoisomerase-II-beta (β) is prevalent among all cells.[16] The mechanism of action of doxorubicin has been described as the binding of the drug to DNA and topoisomerase-II (doxorubicin has affinity to both the α and β types) to form a cleavage complex that promotes cell death.[17] Adult mammalian cardiomyocytes only express topoisomerase-II-β.[18] As previously stated, however, doxorubicin interacts with both types of topoisomerase-II. In the case of topoisomerase-II-β, the resulting topoisomerase-doxorubicin-DNA complex breaks DNA strands and thereby causes cardiac cell death in a fashion similar to tumor cell death. This alternative hypothesis has been supported by animal studies that show the deletion of the gene that encodes topoisomerase-II-β is protective against doxorubicin-induced DNA damage and, consequently, prevents progressive heart failure.[15] Interestingly, dexrazoxane, a drug that chelates iron and prevents hydroxyl radical formation in the presence of anthracyclines, has been shown to be cardioprotective, thus lending support to the classic mechanism of action.[19] However, some studies suggest dexrazoxane may be involved in topoisomerase-II-α–dependent cell death while depleting topoisomerase-II-β.[17,20] Therefore, an alternative explanation of the cardio-

protective effect of dexrazoxane is the prevention of doxorubicin binding to topoisomerase-II-β.[16]

TRASTUZUMAB

Trastuzumab (Herceptin) is a monoclonal antibody that targets the HER2. HER2 normally helps in growth, proliferation, repair, and control of abnormal cells.[21] HER2s are found in up to 30% of breast cancers and are associated with an increased risk of brain metastases, a decreased response to hormonal therapy, an increased risk of recurrence, and death.[21-23] Treatment with trastuzumab for 1 year after standard chemotherapy has been shown to improve outcomes in patients with HER2-positive breast cancer.[24]

Asymptomatic decreased left ventricular ejection fraction (EF) is the most common trastuzumab-associated cardiotoxicity. In contrast to anthracycline-induced cardiotoxicity, trastuzumab cardiotoxicity is not dose dependent, is often reversible, and does not show typical anthracycline-induced myocyte cell death on biopsy.[25-27] Concurrent or previous use of anthracyclines and age >50 years have been reported as the main risk factors in multiple studies (Table 1).[28-32] Risk factors such as radiation, diabetes, valvular heart disease, or coronary artery disease do not appear to be associated with an increased risk of trastuzumab-induced cardiotoxicity.[31,33-35] Trastuzumab binds to the extracellular domain of HER2 and inhibits the activation of intracellular tyrosine kinase.[36] Several mechanisms of action have been proposed for trastuzumab. For instance, several studies report that trastuzumab cleaves the extracellular domain in targeted cells and promotes cell death via antibody- and complement-dependent pathways.[37-39] Trastuzumab's mechanism of injury is not clear, but several studies suggest involvement of HER2. One hypothesis is that myocytes depend on HER2 activation to induce a repair mechanism when responding to stress.[40] Consequently, the blockage of this repair mechanism in the presence of anthracyclines leads to cardiotoxicity.[23] This hypothesis may explain the increased risk of cardiotoxicity associated with the concurrent use of trastuzumab and anthracyclines. Other studies suggest a direct cardiac effect from HER2 downregulation, a hypothesis that is supported by elevated HER2 levels in patients with chronic heart failure.[23,41]

RADIATION

The impact of radiation therapy can be appreciated from the mortality rate of patients with breast cancer. Mortality has decreased yearly for the past 30 years, and as of 2012, there were an estimated 3 million breast cancer survivors in the United States.[42,43] Breast cancer management has evolved from radical surgeries, diffuse chest radiation, and high-dose chemotherapy to targeted therapies and smaller surgeries. Radiation therapy is now a major component of the treatment of breast cancer in patients undergoing breast conservation surgery or patients with a high risk of recurrence after mastectomy.[42,44] Early radiation therapy techniques involved the whole chest and were associated with cardiac complications. The newer approach to radiation therapy aims to target the breast with the least amount of exposure to the heart.[42]

However, a 2013 population-based case-control study of patients who underwent radiation therapy using the localized radiation approach found an increase in subsequent ischemic heart disease.[45] The risk of ischemic heart disease was present even at a minimum dose of radiation. The risk appeared to increase after 5 years and continued for at least 2 decades after radiation therapy. Finally, this study found an even greater absolute risk in patients with preexisting cardiac risk factors or ischemic heart disease. Therefore, novel chemotherapy approaches do not completely remove the risk of cardiac complications.

The most common mechanism of injury is thought to be secondary to direct blood vessel damage resulting from DNA damage by reactive oxygen species.[46] Histologically, radiation therapy is associated with diffuse interstitial fibrosis and narrowing of the arterial lumen and capillaries.[47] The injury to the capillaries results in decreased vascular access and subsequent myocyte death. Pericardial fibrosis, on the other hand, is thought to be due to replacement of cardiac outer adipose tissue with dense collagen and fibrin.[46]

TREATMENT AND PREVENTION

The management of chemotherapy- or radiation-induced cardiotoxicity has a 4-pronged approach: (1) pretreatment assessment, (2) risk reduction, (3) surveillance and early treatment of cardiotoxicity during therapy, and (4) posttreatment surveillance. Although no clear guidelines are available, noninvasive cardiac evaluation prior to anthracycline treatment has been endorsed by the American Heart Association/American College of Cardiology.[48] The American Society of Clinical Oncology, in addition to providing recommendations for cardioprotective therapies, has set guidelines for treatment alteration based on cardiac function.[49] Multiple noninvasive imaging modalities exist today to assess left ventricular function, although 2-dimensional (2-D) echocardiography remains the most widely used tool for cardiac assessment because of its cost, availability, and lack of radiation. Left ventricular EF is a common parameter used to screen patients at risk of cardiotoxicity. For instance, an EF <30% on 2-D echocardiography is generally used as a contraindication for anthracycline-based chemotherapy.[50]

The 2 major chemotherapy/radiation CMY preventive measures are treatment modification and cardiac risk reduction. For instance, to decrease the risk of cardiotoxicity, anthracycline lifetime cumulative dose is often limited to <550 mg/m^2 (Table 2). Moreover, an infusion delivered during a period of 6 hours or more is favored over bolus therapy, based on data from multiple studies.[51-54] Additional approaches to reduce the cardiotoxicity of anthracyclines include encapsulation and the use of cardioprotective agents such as dexrazoxane. Despite concerns that dexrazoxane may blunt the effect of chemotherapy, a Cochrane metaanalysis review found it to be cardioprotective without having an effect on mortality from interference with chemotherapies.[54] Finally, agents such as doxorubicin have been modified to reduce cardiotoxicity. Epirubicin and mitoxantrone are 2 analogs of doxorubicin that are associated with less cardiotoxicity compared to doxorubicin.[55-58]

Table 2. Prevention of Anthracycline-Induced Cardiomyopathy

Treatment Modification	Comments
Anthracycline dose limitation	Dose limited to <550 mg/m^2
Infusion timing	Slow infusion during a 6-hour or more period preferred over boluses
Encapsulation	
Dexrazoxane	
Structural modification	Less cardiotoxic alternatives: epirubicin, mitoxantrone
Risk Factors Reduction	**Comments**
Screening for cardiomyopathy	Echocardiography most common modality
Hypertension	ACEI/ARB and/or β-blockers
Diabetes	ACEI, glucose control
Advanced age	ACEI/ARB and/or β-blockers

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; β, beta.

CV risk reduction includes treatment of modifiable risk factors such as hypertension and diabetes. Although data are lacking and no clear guidelines are available, patients with nonmodifiable risk factors such as advanced age are sometimes treated with β-blockers and/or angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) prophylactically. This practice is supported by multiple small trials that show some possible benefits of these drugs. Enalapril has been shown to possibly prevent late cardiotoxicity in patients with elevated troponin after treatment with high-dose chemotherapy.[59] The PRADA (PRevention of cArdiac Dysfunction during Adjuvant breast cancer therapy) trial results suggest that prophylactic ACEIs/ARBs may be beneficial, whereas no statistically significant results were observed with β-blockers.[60] This study is significant for being a randomized controlled trial, but its power was limited by a small sample size (n=120), and the long-term benefit of therapy was limited by its short follow-up time (about 3 years). Furthermore, the findings for β-blockers in the PRADA study differ from several previous trials that showed possible benefits.[61-63] The OVERCOME (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies) trial findings further suggest that combined enalapril and carvedilol may have additive protective effect against chemotherapy-induced CMY.[63] Thus, although β-blockers and ACEIs/ARBs are main components of guideline-directed medical therapy for heart failure, their role in chemotherapy-induced heart failure is less clear because of small study populations.

Once signs of cardiotoxicity are observed, the risks and benefits of proceeding with the current treatment strategy vs using an alternate therapy are reevaluated. This risk-benefit evaluation highlights the importance of cardiac surveillance during treatment. For example, discontinuation of anthracycline is recommended once EF reaches $\leq$30% or decreases by at least 10%.[50] Routine posttreatment surveillance with echocardiography for children who received anthracycline therapy is recommended.[64] The role and timing of surveillance in asymptomatic adults after treatment are, however, less clear. A study that included 201 patients reported that the amount of recovery in left ventricular EF was associated with early initiation of treatment after chemotherapy. Complete recovery was only achieved when therapy (enalapril and carvedilol) was initiated 6 months after chemotherapy.[65] This trial supports early evaluation and treatment of chemotherapy-induced CMY. Left ventricular EF is often assessed at the completion of chemotherapy in asymptomatic patients with normal EF. The benefits of posttreatment surveillance are perhaps warranted in symptomatic patients or patients with elevated cardiac risks; however, apart from small trials such as the aforementioned,[65] significant data and guidelines are lacking.

While the treatment of heart failure is common among clinical cardiologists, the treatment of cancer survivors with cardiac complications is a recent and growing phenomenon. While the arsenal of therapies provided to the cardio-oncologist includes commonly prescribed medications such β-blockers and ACEIs/ARBs, the understanding of the various side effects of chemotherapeutic agents and the significance of altering treatment regimens requires expertise in cardio-oncology. By building a collaborative clinic among cardiologists and oncologists, individuals undergoing cancer treatment can be assured they are being provided pretreatment CV risk assessment, appropriate monitoring for symptomatic and asymptomatic cardiotoxicity with CV treatment initiation if needed, and appropriate follow-up once the cancer has been cured. At the Ochsner Medical Center, we have seen more than 300 individuals during the last 3 years and have received positive feedback from both patients and oncologists regarding this collaborative approach. Patients appreciate the connection with a cardiologist prior to any problems developing, providing reassurance in an already stressful situation.

CONCLUSION

A collaborative approach between oncologists and cardiologists is integral to the optimal care of patients with cancer. Chemotherapy and radiation have played a major role in the survival of patients with cancer but are associated with CMY. Although radiation and chemotherapy treatments have evolved with the aim of targeting cancer cells while having minimal effect on the heart, the increased risk of CMY remains significant. Therefore, proper screening and treatment of cardiotoxicity remain essential for these patients. As cardiac diseases and cancer remain the first and second causes of mortality in developed nations, cardio-oncology is the answer to this group of individuals who are especially vulnerable to both causes of mortality.

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