COMMENTARY

Mitigating Cardiovascular Dysfunction Across the Cancer Continuum

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The mechanisms and outcomes of cancer treatment–related cardiovascular dysfunction are complex and influenced by cardiotoxic treatment exposure, preexisting heart disease, and lifestyle factors. Establishing and implementing evidence to prevent, detect, and manage cancer treatment–related cardiotoxicity requires engagement by the nursing science community.

The article "Heart Failure and Long-Term Survival Among Older Women With Breast Cancer" highlights the well-established challenge of multiple chronic conditions in older adults (Harrison et al., 2018). Older adults who have been diagnosed with cancer often have preexisting cardiovascular disease, including heart failure. Although chemotherapies with cardiotoxic side effects are sometimes the best treatment to eradicate the cancer (Levis, Binkley, & Shapiro, 2017), they may exacerbate preexisting heart disease. Patients without preexisting heart disease may incur heart failure from these cardiotoxic treatments through direct effects on cardiomyocytes (Levis et al., 2017). Other contributors, such as the lifestyle factors noted in the study by Harrison et al. (2018), can increase the risk for heart failure among patients with a history of cancer. Each of these diseases is often thought of separately and evaluated in terms of one being diagnosed prior to the other; however, common mechanisms predispose individuals to these and other chronic conditions. Evaluating and targeting these underlying mechanisms for prevention and management strategies may lead to improved cardiovascular and cancer outcomes.

Chronic inflammation is a major contributor to many of these diseases, which are often associated with chronic risk behaviors (e.g., diets high in fat and sugar, smoking, sedentary lifestyle) coupled with environmental and, for some, genetic factors. In fact, 30%–45% of cancer-related deaths are associated with risky lifestyle behaviors alone (Islami et al., 2017; World Health Organization, 2017). Chronic inflammation, in turn, promotes the process of immunosenescence (immune cell aging) (Nikolich-Žugich & Davies, 2017). The integrity of the immune system is critical for the detection and elimination of foreign microorganisms, the arresting of aberrant cell growth, and tissue repair. Cancer formation and progression, particularly among older adults, can be a consequence of chronic inflammation (Oishi & Manabe, 2016). Similarly, chronic inflammation is implicated in cardiovascular disease (Fougère, Boulanger, Nourhashémi, Guyonnet, & Cesari, 2016). With chronic inflammation as an underlying mechanism for cancer, cardiovascular disease, and other conditions (e.g., diabetes, some neurodegenerative diseases), particularly among older adults, the concept of "inflammaging" has emerged (Fougère et al., 2016; Oishi & Manabe, 2016). Inflammaging is the process of chronic inflammation interfering with immune function that, ultimately, leads to increased risk for these chronic conditions. In addition, chronic inflammation can contribute to adverse outcomes among patients undergoing treatment for one or more chronic diseases.

Taken together, the known common co-occurrence of high blood pressure/cardiovascular disease, lifestyle risk factors, and associated chronic inflammation among patients with cancer renders the findings of the Harrison et al. (2018) study unsurprising. About 2% of the U.S. population has heart failure; this figure increases to 12% among individuals aged 80 years or older (Vigen, Maddox, & Allen, 2012). In the analysis by Vigen et al. (2012), among women aged 65 years and older with invasive breast cancer, the rate of heart

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failure was about 6%. Among the patients who were aged 85 years or older, 12% had heart failure. The rate of heart failure in the population of the Harrison et al. (2018) study paralleled the rate of heart failure in the general older adult population. The challenge is in the management of these comorbid conditions.

In the Harrison et al. (2018) study, having heart failure as a comorbidity was associated with an increased risk of death among women with early-stage breast cancer. In addition, other comorbidities (e.g., diabetes, stroke, chronic lung disease) and smoking increased the risk of death. The lack of difference in risk of death among those with and without heart failure with late-stage cancer may be attributable to cancer progression, more so than to the contribution of heart disease and/or other comorbid conditions. Regardless of cancer stage, comorbidities can contribute to numerous adverse events and diminished quality of life among patients undergoing treatment for cancer. The evidence for increased risk of adverse events and poor outcomes among patients with cancer with heart failure and other chronic conditions is well established. Interventions to comanage these conditions by targeting the underlying mechanisms (e.g., chronic inflammation) are essential and understudied.

Although the Harrison et al. (2018) study highlights heart failure, which is the most frequent type of cardiovascular disease, preexisting acute coronary syndromes, hypertension, arrhythmias, and thromboembolic events can also be complicated by cardiotoxic cancer treatment through alterations in hemodynamic flow and damage to vascular endothelium. Identification of preexisting cardiovascular risk factors has significant clinical relevance in establishing cancer regimens and follow-up care; however, established guidelines continue to lack evidence that supports specific risk assessment, prevention, screening, and management approaches.

As was demonstrated in the Harrison et al. (2018) study, cardiovascular risk factors present at cancer diagnosis strongly affect morbidity and mortality. This calls for standardized risk assessment approaches that accurately characterize an individual's cardiovascular health. Clinical trials document the cardiotoxic potential of new drugs and drug combinations, but study eligibility criteria exclude those with known cardiovascular comorbidities (de Azambuja et al., 2014), resulting in a nonrepresentative sample of patients with cancer. Observational studies include patients with cardiovascular comorbidities, but, to date, have focused on cardiotoxicity risk in women with breast cancer receiving adjuvant therapy. Evidence supporting cardiotoxicity guidelines is limited to cardiomyopathy risk secondary to chest irradiation including the heart field (30 Gy or greater), with or without anthracyclines and with anthracyclines independent of radiation therapy (Armenian et al., 2017; Curigliano et al., 2012; Yancy et al., 2013). Existing guidelines provide cardiovascular risk factors (e.g., smoking, hypertension, diabetes, dyslipidemia, obesity, age, cardiac dysfunction) that should be assessed prior to treatment, but they lack evidence to support validated cardiovascular risk tools for treatment decision making. This dearth of evidence limits the applicability of current guidelines.

Little translation of cardiotoxicity prevention, screening, and management strategies into practice exists. Evidence-based interventions to prevent and minimize cardiotoxic effects encourage the selection of less cardiotoxic treatment when possible, management of modifiable risk factors (e.g., smoking, hypertension, diabetes, dyslipidemia, obesity), and consultation with specialists in cardiology (Armenian et al., 2017; Curigliano et al., 2012; Yancy et al., 2013). Research focused on the use of pharmacologic (e.g., angiotensin-converting enzyme inhibitor) and nonpharmacologic (e.g., exercise, nutrition) interventions need to be explored across cancer types and treatments, with a focus on translation into practice. The application of heart imaging results (e.g., left ventricular ejection fraction), blood pressure readings, and biomarkers (e.g., B-type natriuretic peptide, troponin) in detecting and monitoring cardiac outcomes in patients remains unclear in directing when cancer treatment should be modified or stopped (Cardinale, Biasillo, & Cipolla, 2016).

To fill the large research gap at the intersection of cardiovascular disease and cancer, the National Cancer Institute and National Heart, Lung, and Blood Institute have collaborated with the interprofessional field of cardio-oncology to study strategies for mitigating cardiovascular dysfunction while optimizing cancer outcomes. Funding opportunity announcements (FOAs) PA-18-003 (R01) and PA-18-013 (R21), titled Improving Outcomes in Cancer-Treatment Related Cardiotoxicity, encourage the submission of grant applications on risk prediction, prevention, detection, management, and coordination of care across all cancer treatment–related cardiac-specific adverse events. These funding announcements can be found on the National Institutes of Health website (http://bit.ly/2zCqstq, http://bit.ly/2js1J4x). The translation of research findings into measurable risk

assessments with validated interventions to prevent, detect, and manage cardiotoxicities in patients receiving cancer treatment is of serious importance. Imagine an evidence-based cardio-oncology plan of care that incorporates the following:

- A heart-healthy lifestyle for those with or at risk for developing cardiotoxicity
- Biomarker and imaging techniques that detect asymptomatic cardiovascular compromise before the onset of disease
- Evidence-based management strategies that decrease long-term cardiovascular complications into cancer survivorship

The engagement of nursing science across cardiology and oncology is needed to fill these research gaps and to translate findings into clinical practice.

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