Cardio-Oncology at the Beginning of a New Decade

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The improved outcomes with new cancer therapies have led to a substantial increase in the number of cancer survivors over the past decade and to a new subspecialty, cardio-oncology. As the number of cardio-oncology clinics and the interest in the cardiology community are steadily growing, so is the need for scientific evidence to guide our clinical practice. Common problems encountered in cardio-oncology clinics range from surveillance, prevention, and treatment of adverse effects of cardiotoxic cancer therapy and cardiovascular disease in patients with active or treated cancer to issues on long-term cancer survivorship. In light of the sparse direct evidence, our practice is often solely based on extending the principles of general cardiology. Major funding agencies have recognized this unmet need. The American Heart Association recently announced Cardio-Oncology as the topic area for the next round of Strategically Focused Research Networks. Similarly, the National Institutes of Health/National Heart, Lung, and Blood Institute is soliciting grant applications that seek to improve outcomes in cancer treatment–related cardiotoxicity. These initiatives will generate essential data to fill some of the current gaps in our understanding.

With its commitment to providing a platform for publications in areas not covered by other American Heart Association journals, the *Journal of the American Heart Association* (*JAHA*) invited the submission of reviews and original research on the topic of cardio-oncology. This is in line with the recent emergence of *JACC: CardioOncology* and *Cardio-Oncology*, a journal affiliated with the International Cardio-Oncology Society.

The present cluster of articles in this issue includes reviews on highly pertinent issues in the field, such as checkpoint inhibitor–induced myocarditis[1] and multimodality imaging.[2] Articles that complement these reviews provide new evidence for cardiac magnetic resonance imaging[3] or cardiac biomarkers[4] for the prediction of late cardiomyopathy after anthracycline treatment and/or breast cancer. Given the high percentage of patients who develop subclinical impairment of left ventricular (LV) function after anthracycline-based chemotherapy, Brown and colleagues offer their pragmatic views on whether guideline-based heart failure treatment should be deployed as prevention in this cohort and describe how to select patients at greatest risk.[5]

The advent of transcutaneous aortic valve replacement (TAVR) has greatly increased the number of patients deemed eligible for aortic valve replacement, even those with significant comorbidities. Guha and collaborators examine the relative use rate, outcomes, and dispositions in patients with and without cancer who underwent TAVR versus surgical aortic valve replacement (SAVR).[6] Another area that remains widely understudied and poorly understood is radiation-induced coronary disease, attributable in large part to the lag period of decades before disease manifestation. Okwuosa and colleagues provide an exploratory review of the sparse evidence that statins, aspirin, and colchicine reduce the incidence of radiation-induced cardiovascular disease.[7]

Last, this cluster includes a thought-provoking review by Aboumsallem et al, highlighting the communalities between cardiovascular diseases and cancer and their shared molecular mechanisms, including inflammation, clonal hematopoiesis, and hypoxia.[8] In line with the proposed concept of reverse cardio-oncology, Ledard et al provide first experimental evidence that Slug/Snai2, a transcription factor with a well-described role in cancer progression, contributes to inflammation in dedifferentiated smooth muscle cells and, potentially, atherosclerotic plaque formation and instability.[9]

Cardiac biomarkers are promising tools for the early detection and prediction of cancer therapy–related cardiac dysfunction (CTRCD). Prior studies have suggested that elevations in cardiac troponins are common in patients

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treated with anthracyclines, with or without trastuzumab, and that they predict the development of cardiac dysfunction.[10–15] The results with NT-proBNP (N-terminal pro-B-type natriuretic peptide) as a predictor of CTRCD are less consistent.[15,16]

Demissei and colleagues add to this literature with a large prospective cohort study of >300 patients with breast cancer.[4] Repeated cardiovascular phenotyping with established and novel biomarkers, echocardiography, and clinical data attainment were performed during and after therapy with anthracyclines and/or trastuzumab for up to 3.7 years. CTRCD was defined as ≥10% decline in LV ejection fraction to a value <50%. CTRCD occurred in 14.2%, 17.0%, and 39.1% of patients in the doxorubicin, trastuzumab, and doxorubicin+trastuzumab groups, respectively. The authors report 4 main findings. First, high-sensitivity cardiac troponin T (hs-cTnT) elevations were common after anthracycline therapy but only modestly associated with decreases in LV ejection fraction and circumferential strain. Neither baseline values nor repeated assessment was consistently associated with the development of myocardial dysfunction. Thus, a routine serial evaluation of hs-cTnT to predict systolic dysfunction cannot be recommended. Second, elevated hs-cTnT at the time of completion of anthracycline therapy predicted subsequent risk of myocardial dysfunction. Interestingly, an hs-cTnT level <5 ng/L at that time point had 100% sensitivity and negative predictive value for myocardial dysfunction at 1 year. Third, repeated assessments of NT-proBNP over 3.7 years revealed a significant association with changes in LV ejection fraction and risk of myocardial dysfunction, particularly in patients undergoing sequential anthracycline and trastuzumab therapy. On the basis of these findings, the authors propose that routine serial assessment of NT-proBNP has the greatest utility in the surveillance of patients with breast cancer on this regimen. Finally, elevated baseline levels of the oxidative stress marker myeloperoxidase were associated with an increased risk of CTRCD.[17] Thus, a one-time evaluation of hs-cTnT at the end of the chemotherapy regimen may provide important prognostic information, NT-proBNP may be useful as biomarker in select patients, and more exploration of myeloperoxidase as an additional biomarker is warranted.

Similar to serum biomarkers, defining early imaging parameters that predict LV dysfunction at late time points after chemotherapy has remained an area of intense clinical and scientific interest. Several studies have used cardiac magnetic resonance imaging parameters, such as LV volumes, mass, function, and strain, gadolinium enhancement, and T1 and T2 mapping, to identify early parameters of CTRCD.[18] Herein, Suerken and colleagues studied the predictive value of changes in LV end-systolic volume or LV end-diastolic volume by cardiac magnetic resonance imaging at 3 months after initiation of cardiotoxic chemotherapy compared with baseline for deterioration of LV function at 2 years after treatment.[3] Ninety-one patients treated with cardiotoxic chemotherapy were prospectively enrolled, and data from 71 were analyzed. Predominantly patients with breast cancer, lymphoma, or sarcoma were included. The most common cardiotoxic chemotherapy agents were anthracycline and cyclophosphamide. At 2 years after the end of treatment, 42% of patients experienced a >5% decline in LV ejection fraction, independently of cardiovascular disease risk factors. Three predictors of late LV dysfunction were identified: an increase in LV end-systolic volume of ≥3 mL and an increase in global longitudinal strain of ≥10%. More important, the authors took the volume alterations between the measurements at baseline and 3 months into consideration. This is clinically relevant because hypovolemia during chemotherapy attributable to nausea or emesis is not infrequent and an important obstacle to comparing volume-based measurements. In this context, the third predictor identified in this study, a minor change in LV end-systolic volume (increase or decrease of <3 mL) when accompanied by a decrease in LV end-diastolic volume (>10 mL), may be helpful. However, these predictors do not directly translate to the more common evaluation by transthoracic echocardiogram. Moreover, larger studies will be needed to identify combinations of imaging variables that can predict larger declines in LV function that lead to heart failure. In a recent study in a large animal model, T2 mapping, correlating with cardiomyocyte edema, was proposed as the earliest marker of anthracycline-induced cardiotoxicity.[19]

Not long ago, patients with cancer and severe aortic stenosis were commonly deemed ineligible for SAVR. Herein, Guha and collaborators use *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), codes to identify inpatients with a primary diagnosis of aortic stenosis and then examine the effect of the modifier "cancer" on the relative use rate, outcomes, and dispositions associated with propensity-matched cohorts (TAVR versus SAVR).[6] Not surprisingly, over the period from 2012 to 2015, the relative use rates of TAVR in patients with cancer steadily increased and surpassed those of SAVR in this cohort. Compared with patients undergoing SAVR, TAVR was associated with lower risk of acute kidney injury, lower length of stay, and higher likelihood of discharge to home. Because the *ICD-9-CM* codes were used as primary data, several limitations should be acknowledged, including the lack of clinical information, such as aortic stenosis severity, other concomitant diseases, duration of cancer diagnosis, and cancer stage. Moreover, no data on long-term outcomes can be provided with this study design. However, other recent studies have demonstrated that short-term outcomes and midterm survival rates were comparable in patients with and without cancer[20] and that only stage III or IV[21] or active cancer[22] was associated with higher mortality compared with no-cancer patients at 1 year after TAVR. Thus, TAVR provides a

treatment option for patients with cancer who may have previously been offered medical management only.

Ledard and colleagues provide an example of the concept how novel targeted cancer therapies can inform cardiovascular discovery.[23] The process of epithelial-mesenchymal transition is pivotal in dispersing of carcinoma cells from primary epithelial tumors and metastatic dissemination.[24] During epithelial-mesenchymal transition, epithelial cells lose their characteristics, including cell adhesion and polarity, and acquire mesenchymal morphological characteristics and the ability to migrate. Several studies have described a role for the transcription factor Slug/Snai2 in this process (eg, in breast cancer cell lines).[25–27] Ledard and colleagues direct our attention toward the parallels of epithelial-mesenchymal transition and vascular smooth muscle cell dedifferentiation, which prominently contributes to the development of atherosclerotic plaques and neointima formation after balloon injury.[9] In cultured vascular smooth muscle cells, platelet-derived growth factor (PDGF) induced the accumulation of Slug in the nucleus. Mechanistically, Slug promoted a proinflammatory phenotype in vascular smooth muscle cells by expression of cyclooxygenase-2 and related prostaglandin E2 secretion but did not mediate PDGF-dependent smooth muscle cell proliferation or migration. The maintenance of a foam phenotype also results from impaired cholesterol efflux by ATP-binding cassette transporters. Although PDGF-BB suppressed ATP-binding cassette transporters in vascular smooth muscle cells, the knockdown of Slug abolished PDGF-BB–mediated gene inhibition. In human carotid endarterectomy samples, Slug accumulated in smooth muscle cells that surround the prothrombotic lipid core. Thus, inhibition of Slug would be expected to lower plaque vulnerability.

Tyrosine kinase inhibitors (TKIs), such as imatinib, dasatinib, sunatinib, and sorafenib, inhibit the activity of PDGF receptors and are part of treatment regimens for numerous malignancies, including renal cell and hepatocellular carcinoma, gastrointestinal stromal tumors, and chronic myeloid leukemia. The findings by Ledard provide a rationale for testing TKIs with anti-PDGF activity in models of atherosclerotic cardiovascular diseases. However, a complex picture on the cardiovascular effects of TKIs is emerging. In fact, increased rates of myocardial infarction, stroke, and peripheral arterial disease have been reported with some second- and third-generation TKIs.[28] An early study reported that nilotinib blocked endothelial cell proliferation and migration, in contrast to findings of Slug inhibition, but also promoted the expression of proatherogenic molecules, including intercellular adhesion molecule-1 (CD54), vascular cell adhesion molecule-1 (CD106), and E-selectin (CD62E).[29] Recent data suggest that at least in endothelial cells, different TKIs have divergent effects.[30] Thus, a careful dissection of the effects of specific TKIs in endothelial versus smooth muscle cells is needed to fully appreciate their effects as promoters or potentially inhibitors of atherosclerotic vascular disease.

The present cluster of articles demonstrates the breadth of cardio-oncology. Each article includes an extensive discussion of the gaps and opportunities in this new discipline. As cardio-oncology enters a new decade, there is a pressing need for further in-depth studies, ranging from the analysis of molecular mechanisms of novel therapies to well-designed prospective trials and healthcare delivery research. *JAHA* will continue to offer a platform for this exciting and fast-moving field.

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