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Multi-Modality Imaging in the Assessment of Cardiovascular Toxicity in the Cancer Patient

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ABSTRACT

Cancer therapy can be associated with both cardiac and vascular toxicity. Advanced multi-modality imaging can be used to stratify patient risk, identify cardiovascular injury during and after therapy, and forecast recovery. Echocardiography continues to be the mainstay in the evaluation of cardiac toxicity. Particularly, echocardiography-based strain imaging is useful for risk stratification of patients at baseline, and detection of subclinical left ventricle (LV) dysfunction during therapy. Cardiac magnetic resonance (CMR) serves a complementary role in the patient with poor echocardiographic or equilibrium radionuclide angiographic image quality or in situations where a more accurate and precise LV ejection fraction measurement is needed to inform decisions regarding discontinuation of chemotherapy. New CMR techniques like T1 and T2 mapping and positron emission tomography (PET) imaging will help us better understand the structural, pathological, and metabolic myocardial changes associated with ventricular dysfunction or release of serum biomarkers. CMR may also be helpful in the evaluation of vascular complications of cancer therapy. Stress echocardiography, stress CMR, computed tomography, and PET are excellent imaging options in the evaluation of ischemia in patients receiving therapies that could potentially cause vasospasm or accelerated atherosclerosis. (J Am Coll Cardiol Img 2018;11:1173–86)

The field of oncology has advanced remarkably. In some instances, cancer is either cured or converted to a chronic disease. Nevertheless, some of the old and new emerging cancer therapies are associated with development of cardiovascular toxicities (1,2), which may have the potential to offset the gains in survival obtained with these cancer treatment advances (3). Much of the focus on cardiovascular toxicities has been in the early detection of myocardial damage and prediction of cancer therapeutics-related cardiac dysfunction (CTRCD). However, because the toxicities associated with cancer therapies are much broader (**Table 1**) (4), this report discusses advanced multi-modality imaging and how it can be used to stratify patients' risk before cancer therapy is started, identify early cardiovascular injury during therapy, predict recovery from injury, and detect cardiovascular injury in long-term cancer survivors (**Central Illustration**).

CLINICAL CASE

A 51-year-old female with left-sided, high-risk, early stage human epidermal growth factor receptor 2-positive (HER2+) breast cancer was referred to the

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CMR = cardiac magnetic resonance

CTRCD = cancer therapeutics-related cardiac dysfunction

EDV = end-diastolic volume

ERNA = equilibrium radionuclide angiocardiography

ESV = end-systolic volume

GLS = global longitudinal strain

GCS = global circumferential strain

HER2+ = human epidermal growth factor receptor 2-positive

cardio-oncology clinic. Her treatment plan included mastectomy, epirubicin, 300 mg/m^2, 17 cycles of trastuzumab, radiation therapy (50 Gy), and hormone therapy. She had no known cardiovascular risk factors, was not receiving medications, and had excellent functional capacity. Imaging and biomarker assessments were performed prior to cancer therapy, throughout her treatment, and 1 year later (Table 2). Her baseline blood pressure was 138/80 mm Hg, cardiac examination was unremarkable; her left ventricular ejection fraction (LVEF) by 3-dimensional (3D) echocardiography was 61%; global longitudinal strain (GLS) was −21.3%; and global circumferential strain (GCS) was −20.3%. Several questions were raised during her initial consultation and follow-up: How does cardiac imaging play a role in identifying cardiovascular toxicity risk in this patient? What is the best method to detect early cardiac injury from treatment? What are the predictors of ventricular function recovery after cardiotoxicity?

ASSESSMENT OF BASELINE RISK OF CARDIOVASCULAR COMPLICATIONS IN PATIENTS RECEIVING CANCER THERAPY

ASSESSING RISK OF CTRCD AND HEART FAILURE. American Society of Clinical Oncology guidelines recommend risk stratification for cardiac dysfunction prior to initiation of potentially cardiotoxic cancer treatment. We refer the readers to their discussion of which patients with cancer are at increased risk of developing cardiac dysfunction (5). From an imaging standpoint, patients with borderline cardiac function (LVEF of 50% to 55%, a history of myocardial infarction, and presence of other cardiac comorbidities, e.g., ≥moderate valvular heart disease) before the start of anthracycline or trastuzumab therapy are at a 3.6- to 11.8-fold increased risk for developing cardiac dysfunction (5). The expert consensus for multi-modality imaging evaluation of the adult patient during and after cancer therapy recommends a baseline echocardiogram, with the calculation of LVEF, ideally using 3D echocardiography and GLS if the technology is available and the operators are comfortable with their performance and interpretation (6). The latter is a reflection of the superior reproducibility of 3D LVEF and GLS measurements (7,8). In addition to LVEF, pre-treatment measurements of GLS appear to identify patients at elevated risk of major adverse cardiac events in the context of anthracycline therapy (9,10). Similarly, every 1% difference in baseline circumferential strain has been associated with 31% increased odds of cardiotoxicity in women receiving breast cancer therapy (11).

Cardiac magnetic resonance (CMR) is usually not used as a first-line tool for risk stratification because of its cost and lack of wide availability. However, in patients with a nondiagnostic echocardiogram, unexplained dilation of the left or right ventricles, or morphological abnormalities raising concern for infiltrative cardiomyopathy, CMR can complement the echocardiographic evaluation to assess for a potential cause. To date, however, there are no data to determine whether pre-treatment CMR parameters identify patients at risk for cardiotoxicity.

CORONARY ARTERY DISEASE RISK. Stress echocardiography may be useful in the evaluation of patients with intermediate or high probability of coronary artery disease (CAD) who are undergoing regimens that may be associated with ischemia (e.g., 5-fluoracil, capecitabine, bevacizumab, sorafenib, and sunitinib) (6). Cardiac computed tomography (CCT) has changed the landscape of coronary assessment in the field of cardiology. Its role in cardio-oncology is primarily restricted to assessment of coronary calcium and obstructive CAD (12). Both nuclear and positron emission tomography stress testing represent alternatives for the evaluation of CAD in these patients. Stress CMR can detect the presence and extent of inducible myocardial ischemia with high diagnostic accuracy (13). The attraction of stress echocardiography and stress CMR is the lack of radiation exposure. However, stress echocardiography may be challenging in patients who have had mastectomies, breast expanders, or implants. In those situations, the use of ultrasonic enhancing agents may improve visualization of the myocardial segments and accuracy of interpretation (14). CMR may not be feasible in the presence of certain breast tissue expanders because of their ferromagnetic components (6).

VASCULAR TOXICITY. Many agents used in cancer treatment such as tyrosine kinase inhibitors, vascular endothelial growth factor inhibitors, antimetabolites, and radiation therapy are associated with direct vascular toxicity, whereas hormone therapy can increase the risk of atherosclerotic vascular events (15,16). Potential vascular toxicities include hypertension, CAD, peripheral arterial disease, pulmonary hypertension, and venous thrombosis (16). Although certain clinical risk factors for these toxicities have been described (e.g., pre-existing hypertension), unlike cardiomyopathy,