Early Detection of Chemotherapy Induced Cardiomyopathy

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Abstract

Cancer is an issue that have faced health care globally for many years, more than before, it requires a multidisciplinary approach to find and treat the underlying causes and malignancy, also managing comorbidities that are often associated with cancer treatment.

Over past three decades, cancer survival rates have increased as a consequence of improved early detection techniques, pharmaceutical therapies, and surgical techniques that have significantly increased cancer-related chances of survival [1,2]. By 2022, there will be an estimated 18 million protracted cancer survivors in the USA alone, a growth of around 30percent over the following ten years [3]. Due to their extended survival, cancer victims are now more vulnerable to the adverse effects of ageing and the emergence of new risk factors that influence their likelihood of developing cardiovascular disease (CVD) in the future [5]. In this situation, CVD, which has always been the leading cause of death in breast cancer persons over the age of Fifty [4, 6] and a more frequent cause of death than cancer amongst older survivors, may restrict the survival advantages of oncology.

Key Words: Heart Failure, Coronary Artery Disease, Left Ventricular Ejection Fraction.

DOI Number: 10.14704/nq.2022.20.6.NQ22655 **NeuroQuantology 2022; 20(6):6523-6528**

Introduction

Groups made up of experts in clinical cardiology, oncology, and radiology are necessary to address the complicated issue of CVD caused by prior cancer therapy. The creation of cardio-oncology teams is mostly driven by a shared desire to offer the best treatment possible for cancer patients and cancer survivors. The level of care as well as how the various specialties will interact with one another have not yet been established. The development of a program outlining the information and abilities required to provide the best treatment possible as well as the hospital context where these specialists would be engaged is vital due to the intricacy of the clinical concerns that cardio-oncologists must address. These cardio-oncology teams ought to be engaged with in long-term monitoring of cancer survivors who may experience late-onset cardiovascular events and also the development of potential new treatments that could have cardiotoxic side effects and the assessment of cardiac events associated with such medications.

- The 9 major categories of cardiovascular side effects associated with cancer treatment are: myocardial dysfunction and heart failure (HF), coronary artery disease (CAD), valve disease, arrhythmias, particularly those brought on by QT-prolonging medications, arterial hypertension, thromboembolic disease, peripheral vascular disease and stroke, pulmonary hypertension, and pericardial complications.

Cardiotoxicity is better managed in people with cancer with earlier identification. The cardiovascular effects of chemotherapies will become the main topic of our discussion, along with the advantages and drawbacks of each imaging modality and the patient identification recommendations that are accessible.

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An growing percentage of individuals may experience treatment-related heart illness, often known as cardiotoxicity, even though cancer survival rates rise. The left ventricular ejection fraction (LVEF), the measure so when decreased is just a late manifestation in the cardiotoxic paradigm and then when the opportunity for reversibility falls, is serially measured as part of current standard procedures for detecting cardiotoxicity. Since clinical results can indeed be improved with the early administration of cardioprotective medicines, early diagnosis of cardiotoxicity may be crucial. Imaging techniques including echocardiography and cardiac magnetic resonance (CMR) have made significant strides in the last ten years.

Whilst key benefits of CMR are enhanced spatial resolution as well as complementary tissue characterization, breakthroughs across both echo and CMR allow for the early diagnosis of myocardial changes that occur, including such global longitudinal strain, that take place before the onset of left ventricular (LV) dysfunction.

Cardiotoxicity following chemotherapy is strictly defined as a drop in LVEF of between 5% and 55% in the context of Heart Failure (HF) symptoms or a reduction in LVEF of between 5% and 10% in the absence of HF symptoms. The concept of toxicities goes above basic and cardiac and takes into account a variety of conditions that might contribute to the development of cardiotoxicity.

Current Imaging Guidelines

The most latest American Society of Clinical Oncology (ASCO) recommendations advise using echocardiography to evaluate the LVEF prior to the beginning of cardiotoxic chemotherapy and, for several patients, following. In the event that echocardiography is neither accessible or logistically viable, CMR imaging and mitigated acquisition (MUGA) scans are indeed the alternate modalities of choices, with CMR being preferred [8]. Depending on the chemotherapy dose and baseline cardiovascular risk factors, it is advised to undergo a follow-up imaging examination and assess the LVEF. For example, LVEF measurements should be performed after receiving greater doxorubicin doses (250 mg/m2 or more) as opposed to lower risk patients who get lower doses [7, 9, 10]. Trastuzumab's producers advise doing a baseline assessment of LVEF before repeating the assessment. In contrast to decrease risk patients who get a lower dosage, greater doses of doxorubicin (250 mg/m2 or more) justify further evaluation of the LVEF [7, 9, 10]. Regarding trastuzumab, the makers advise measuring LVEF at baseline, then every 3 months (4 cycles) while receiving treatment, every 6 months during the first two years after finishing the regimen, and then every 3 weeks if there is a substantial reduction in LVEF with medication discontinued. [11]

Imaging Modalities for Cardiotoxicity Screening

Echocardiography

A most popular imaging technique for assessing patients before, during, and then after potentially cardiotoxic medication is two-dimensional (2D) echocardiography [8]. Its widespread accessibility, repeatability, adaptability, absence of radiation exposure, and safety for individuals with concurrent renal illness all contribute to this.

In order to measure radioactive material cardiotoxicity, it is crucial to evaluate the size, volume, the functioning of the left and right ventricles as well as any pericardial, valvular, or major vascular pathology [12, 13]. The temporal variability in LVEF, which then in 2D echocardiography is close to 8% to 10%, is one of the key constraints of echocardiography [14]. Contrasting can be used to reduce this unpredictability, particularly in individuals with insufficient acoustic windows [15]. Additionally, three-dimensional (3D) echocardiography increases precision and repeatability [16], although it may not be easily accessible in all labs.

Notwithstanding known toxicity, many anthracycline-treated individuals may see a reduction in systolic function and still have a normal level of LVEF. The introduction of additive echocardiographic markers for the identification of subclinical myocardial dysfunction has thus received substantial scientific attention. The usefulness of echocardiographic measurements of diastolic function has been investigated following chemotherapy, but the findings are conflicting, thus diastolic tests really aren't usually advised for this indication [19, 20]. Diastolic dysfunction frequently occurs before systolic failure.

Myocardial Strain Imaging

Strain imaging may be used to identify myocardial injury earlier [21,22]. Cardiac stress is a method that accurately measures the mechanical function of the myocardium and more effectively identifies cardiac systolic function than EF [22,23]. Through the measurement of the time shift between nearby

reflections, myocardial displacement or strain may be estimated in all three dimensions (longitudinal, radial, and circumferential).

Radionuclide Imaging

Its 2016 ASCO recommendations advise using multiple gated acquisition (MUGA) to estimate LVEF if this cannot be done with echocardiography or CMR. Due to its accessibility, precision, and repeatability, MUGA has historically been the most popular imaging technique for assessing LVEF. Technetium-99 m (99MTc) tagged red blood cells are used by MUGA to evaluate heart function. In comparison to 2D echocardiography, this modality is more accurate, repeatable, and linked to decreased inter- and based on inter variance [24]. Additionally, MUGA and other 3D imaging technologies like CMR have strong correlations. A single approach may well be the optimum choice for serial LVEF monitoring, albeit individual left ventricular volumes and LVEF values still range considerably between the techniques [25]. Given the rising worry about radiation exposure, limitations include a radiation dose of around 5 to 10 millisieverts and its inability to evaluate heart anatomy [26].

SPECT: Prior to the publication of the most recent ASCO recommendations, single-photon electron computed tomography (SPECT) was one of the main modalities for cardiotoxicity screening. The prior recommendations, which were in place for over three decades, were based on the single biggest research, which followed approximately 1500 patients for seven years while they were on anthracyclines and examined their hearts using serial SPECT. By using this screening technique, it was shown that 19% of patients had a high risk of cardiotoxicity (defined as LVEF 50%, a decline in LVEF of 10%, and cumulative doxorubicin dosage 450 mg/m2). Research results that were confirmed in a more study conducted of a comparable cohort revealed that a similar percentage (16%) of patients receiving doxorubicin have been deemed at threat at some point all through their therapy (characterised as individuals with normal LVEF at benchmark 50% who had a 10% fall in LVEF to a stage 50% during therapy) [27]. In comparison to those who did not acquire clinical heart failure, those who did saw a larger absolute decline in LVEF (mean decline in LVEF, 23 percent to 14 percent vs. 12 percent to 10 percent) [28]. Even while SPECT monitoring of resting LVEF aids in the early detection of anthracycline cardiotoxicity, it still has a poor sensitivity (53 percent) in comparison to myocardial tissue biopsy and involves extra radiation.

Due to its superior high temporal resolution, high diagnostic responsiveness, and accuracy, positron emission tomography (PET) is indeed the de facto method for evaluating myocardial metabolism and perfusion. Cardiovascular PET has only been used in a few clinical investigations to check potential anthracycline cardiotoxicity.

Computed Tomography

After radiotherapy, computed tomography (CT) evaluation of the heart for cardiotoxicity is mostly helpful. Although CT may be used to check the function of the heart, it is most effective for assessing pericardial or coronary artery dysfunction brought on by cancer, chemotherapy, or radiation treatment [29]. If there are CMR contraindications, it might also be an appealing option or complement to CMR in the evaluation of cardiac masses. Whenever intravenous contrast is employed, cardiac CT can provide a precise delineation of the heart chambers and veins from surrounding tissues [30]. Cardiac CT can also provide comprehensive cross-sectional anatomical imaging of the chest. Motion-free and phase-consistent pictures of a heart may be produced by synchronising the acquisition or reconstruction of the images to the ECG. These images are crucial for the accurate representation of the coronary arteries and analytical model. High spatial resolution, quick exam times, and high sensitivity for calcified tissues are benefits of cardiac CT as compared to other imaging modalities. Particularly, CT is indeed a trustworthy noninvasive method for seeing coronary arteries [30]. Coronary calcium scoring as well as coronary CT angiography are the two primary forms of cardiac CT (CCTA). Coronary calcium scoring is primarily used to evaluate asymptomatic patients with poor or moderate risk of CAD for the identification of calcifying plaque. Which does not use x-ray contrast and instead, images of the heart are chosen to take to look for the presence of calcium reserves in the coronary arteries [30]. The load of complete and non-calcifying coronary plaque as well as the degree of stenosis may be further quantified by CCTA [31].

Additionally, pericardial effusions and thickening related to pericarditis that may be brought on by cancer or its treatments can be detected with CT scans of the pericardial area.

Cardiovascular Magnetic Resonance (CMR) Imaging

In addition, CT can evaluate the pericardial area for pericardial effusions and thickening linked to pericarditis that may develop as a result of the malignancy or associated therapy.[32]. Anthracycline chemotherapies are known to induce cardiotoxicity that can lead to non-focal, irreversible cardiac injury. Safe, noninvasive methods for accurately detecting early evidence of cardiac injury are critically needed to prevent irreversible cardiotoxicity. An early detection methodology could confirm the absence of myocardial injury and thereby enable a patient to receive the maximum benefit of their chemotherapy [33].

Magnetic resonance imaging achieves a range of contrasts by varying the inversion time, repetition time, and echo time in the pulse sequence to create qualitative T1-weighted and T2-weighted images. T1-weighted and T2-weighted CMR techniques have been successful in identifying myocardial infarction through observation of voxel statistics and may provide valuable information for the early detection of cardiotoxicity since many pathophysiological changes are shared by MI and cardiotoxicity. For example, T1-weighted and T2-weighted images have shown vascular dysfunction and edema in addition to changes in quantitative measures of tissue dysfunction in patients with MI [34]. In one preliminary study using contrast-enhanced CMR in an anthracycline cardiotoxicity model, myocardial voxels showed an increase in relative signal enhancement of T1-weighted images, and an enhancement of more than 5 times predicted a decrease of left ventricular ejection fraction, or LVEF. Delayed enhancement CMR imaging is rapid and standard in clinical practice but may yield variable results due to T2 effects. Comparison of signal intensities from qualitative images cannot be compared with signal intensities from another scan due to the dependence of the contrast-to-noise ratio on the inversion time and amount of gadolinium used. Quantifying the myocardial voxel statistics of delayed enhancement T1weighted images would provide a more accurate method than relative signal enhancement of precontrast and postcontrast images.

Recent advances in CMR techniques have enabled quantitative mapping of magnetic relaxation values (T1 and T2), which overcome many of the disadvantages of qualitative techniques. T1 mapping may be acquired with a series of inversion recovery T1-weighted images of varying inversion times and long repetition times to measure the relaxation recovery curve on a voxel-by-voxel basis. Although there is an increased scan time associated with quantitative mapping of tissue, T1/T2 readings may be immediately examined on several scanners and on various pictures without the need to provide a contrast agent [35]. Prior mouse investigations of T1 and T2 increases in cardiotoxicity have employed spectroscopy and nuclear magnetic resonance to demonstrate an increase in myocardial T1 of mice with histological evidence of cardiotoxicity. These studies, however, show conflicting results in changes of T2 relaxation, warranting further investigation in a longitudinal human study. A quantitative method is presented that can identify longitudinal changes, avoid some of the error of weighted images, and result in direct measurements of intrinsic properties of myocardial tissue.

Another manifestation of cardiotoxicity, impaired myocardial strain, can be identified on tagged CMR images. Patients with MI, dilated cardiomyopathy, and hypertrophic cardiomyopathy showed reduced circumferential strain and poorer contractility as signs of left ventricular (LV) failure. Furthermore, strain analysis is more sensitive and specific than wall thickening analysis in detecting myocardial infarct areas. When dilated cardiomyopathy sufferers, decreased contractility and increased torsion occur before irreversible tissue damage [36]. Therefore, the incorporation of strain as a measurement of regional LV function may be of value in monitoring anthracycline cardiotoxicity.

An early detection methodology has been developed that can quantify LV functional (strain) and structural (T1 and T2) properties of the myocardial tissue. It is hypothesized that this new method will be able to acquire longitudinal, quantitative data that will predict a decrement in LVEF in patients receiving chemotherapy, either individually or together in combination. To address this hypothesis, the following translational specific aims are proposed:

Specific Aim 1: Determine the association between postcontrast CMR voxel intensity measures and LVEF in patients receiving anthracycline chemotherapy using delayed enhancement CMR.

Specific Aim 2: Determine the association between CMR T1 and T2 measures and LVEF in patients receiving anthracycline chemotherapy. CMR T1 and T2 measures will be determined from:

Aim 2a: MOLLI T1 mappings, or Modified Look-Locker Inversion Recovery

Aim 2b: True FISP T1 and T2 mapping

Specific Aim 3: Determine the association of

quantitative measures of CMR strain measures (peak mid-wall LV circumferential strain) and LVEF in patients receiving anthracycline chemotherapy.
Specific Aim 4: Determine if combined measures of CMR structural/tissue measures (voxel intensity measures, T1, T2) and LV function (strain) are superior to the functional measures used in isolation in determining LVEF after receipt of anthracyclines.

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