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Chapter

Cardio-Oncology: The Role of Echocardiography in Cancer Patients

Theodoros Ntoskas

Abstract

Cardio-oncology is a rapidly emerging medical field that focusses on the improvement of the quality of life of cancer patients by preventing and treating the adverse cardiovascular complications of cancer therapy. Early recognition of cancer therapy-related cardiac dysfunction (CTRCD) provides an opportunity to mitigate cardiac injury and risk of developing late cardiac events. Cardiac imaging, and in particular, transthoracic echocardiography, plays an essential role in the baseline assessment, the detection and the surveillance of CRTCD in patients during and after the cancer therapy. Although the frequency of screening for the cardiotoxicity in patients undergoing active treatments and cancer survivors remains a topic of debate and ongoing research, echocardiography continues to be the leader for continuous monitoring by imaging due to the wide availability, lack of exposure to radiation, ability to recognise the effects on cardiac function and assess haemodynamics and other cardiac structures. The cardiac imaging applied to cardio-oncology includes standard and advanced (speckle tracking and three-dimensional (3D)) echocardiography.

Keywords: cardio-oncology, echocardiography, cancer, cardiotoxicity, heart failure, global longitudinal strain

1. Introduction

Advances in treatment have led to improved survival of patients with cancer but have also increased morbidity and mortality due to treatment side effects [1, 2]. Chemotherapy and radiation therapy can put patients at risk for a variety of cardiovascular complications including heart failure, coronary artery disease, peripheral vascular disease, thromboembolism, pericardial disease and valvular heart disease. Cardiovascular disease is now the second leading cause of morbidity and mortality in cancer survivors [3]. Cancer patients receiving therapy with known cardiac risk require close monitoring during and after treatment. In current cardio-oncology practice, echocardiography is the most widely used technique in the diagnosis, prevention and risk stratification of CTRCD in patients during and after cancer therapy. The utility of the advanced echocardiography is emerging as the three-dimensional echocardiography derived left ventricular ejection fraction (LVEF) has an excellent correlation with cardiac magnetic resonance imaging and can be used to monitor LVEF and the two-dimensional speckle tracking echocardiography

(2D-STE) derived strain and strain rate can detect changes in myocardial mechanics before changes in LVEF occur.

2. Cardiovascular complications of cancer therapy

Cancer treatment can cause various types of cardiovascular (CV) complications. Different cancer therapies have different CV complications. Cancer therapy toxicity is related to the mechanism of action of the drugs, the doses, the manner of administration and the underlying predisposing factors such as cardiac conditions, genetic pattern and age, and it can manifest itself immediately or many years after the treatment. **Table 1** summarises a variety of anti-cancer therapies and their associated complications, including myocardial dysfunction, heart failure, coronary artery disease, valvular heart disease, arrhythmias, hypertension, peripheral vascular disease, stroke and pulmonary hypertension [4].

Echocardiography is a non-invasive method that can perform a comprehensive evaluation in all stages of cancer treatment and detect myocardial, coronary, valve, pulmonary hypertension and pericardial disease complications secondary to the therapeutic regimen used (radiotherapy and/or chemotherapy).

Cardiovascular toxicity	Anti-cancer therapy
Myocardial dysfunction and heart failure	Anthracyclines (doxorubicin, idarubicin and epirubicin), anti-HER2 (trastuzumab), VEGF inhibitors, cyclophosphamide, cisplatin, ifosfamide and taxanes (paclitaxel and docetaxel)
Vasospasm or vasoocclusion resulting in angina or myocardial infarction	Fluoropyrimidines (5-FU, capecitabine and gemcitabine), platinum compounds (cisplatin), VEGF inhibitors (bevacizumab, sorafenib and sunitinib) and radiotherapy
Valvular disease	Radiotherapy
Arrhythmias	Anthracyclines, histone deacetylase inhibitors, tyrosine kinase inhibitors (TKIs) (especially vandetanib high incidence of QT prolongation)
Arterial hypertension	VEGF inhibitors
Peripheral vascular disease and stroke	Nilotinib, ponatinib or BCR-ABL tyrosine kinase inhibitors, radiotherapy. L-asparaginase, cisplatin, methotrexate, 5-FU and paclitaxel can cause Raynaud's phenomenon
Pulmonary hypertension	TKI (dasatinib), the TKI imatinib improved haemodynamics in patients with advanced pulmonary arterial hypertension

Abbreviations: HER2, human epidermal growth factor receptor 2; VEGF, vascular endothelial growth factor.

Table 1.
Cancer drug agents associated with cardiovascular toxicity.

3. Definition of CTRCD

Myocardial dysfunction and heart failure are the most concerning cardiovascular complications of cancer therapies and cause an increase in morbidity and mortality. Different definitions of CTRCD have been used historically [5]. Guidelines from cardiac societies [4, 6] define cardiotoxicity when the left ventricular (LV) ejection fraction (EF) falls to a value below the lower limit of normal (e.g. 53% in American Society of Echocardiography [ASE] guidelines) with more than a 10-percentage point reduction. As per the ESMO guidelines, the cut-off is 50% [7], at which

	Type I	Type II
Anti-cancer characteristic chemotherapy agents	Doxorubicin	Trastuzumab
Clinical manifestation	New onset of heart failure and LV systolic dysfunction	Asymptomatic decrease in LVEF and less often clinical heart failure
Dose effects	Cumulative, dose dependent	Not dose related
Clinical course	May stabilise with heart failure therapy (ACE inhibitors and beta-blockers), but underlying myocyte destruction appears to be permanent and irreversible	Often reversible with treatment discontinuation (to or near baseline cardiac status in 2–4 months)
Effect of rechallenge	High probability of recurrent dysfunction that is progressive	Rechallenge is often tolerated after recovery

Abbreviation: ACE, angiotensin-converting enzyme; LV, left ventricle; EF, ejection fraction.

Table 2.
Characteristics of type I and II cancer therapeutics-related cardiac dysfunction.

point cardio-protection should be considered [8]. ASE/European Association of Cardiovascular Imaging (EACVI) further classifies CRTCD into either those associated with anthracyclines or trastuzumab use. Anthracycline-related CRTCD is cumulative, dose dependent and often progressive and irreversible at cell level. On the other hand, trastuzumab-related CRTCD is dose independent, does not lead to cell death and is often reversible (**Table 2**).

4. Cancer therapy-related cardiac dysfunction (CTRCD) and echocardiography

4.1 LV systolic function

The need for a timely diagnosis of subclinical and clinical heart failure by using cardiac imaging has been addressed by the Expert Consensus of the ASE and EACVI [6] and more recently reinforced by the ESC Position Paper on cancer treatments and cardiovascular toxicity [4]. The quickest and most available imaging tool in detecting cancer therapy-related cardiac dysfunction (CTRCD) is transthoracic echocardiography.

Exposure to potentially cardiotoxic chemotherapeutic agents is a well-recognised indication for baseline and longitudinal evaluation of LV function [9, 10]. The most commonly used parameter for monitoring LV function with echocardiography is LVEF. Traditionally, an echo determination of LVEF is requested by the oncologists in all cancer patients at baseline and in any situation in which the suspicion of heart failure is plausible, during and after completion of the anti-cancer therapy. 2D-derived LVEF is also used to start cardio protection and to establish the interruption from anti-cancer therapies. The calculation of LVEF should be done with the best method available as per the skills and experience of the operators in a given echocardiography department. The same method needs to be maintained for surveillance during and after treatment. Importantly, the digital images obtained should be available for visually comparison with the previous studies and further discussion at multimodality echocardiographic and cardio-oncology team meetings. According to joint recommendations from the ASE/EACVI, the method of choice for LV volume quantification and LVEF calculation is the modified biplane

Simpson's technique by 2D echocardiography, with an LVEF of ≥55% as a normal reference range. Calculation of LVEF should be also combined with assessment of the wall motion score index, which is based on a 16-segment model of the left ventricle [11]. Resting wall motion score index based on a 16-segment model of the left ventricle has been demonstrated to be a more sensitive marker of anthracycline-induced CTRCD than relying on the LVEF alone [12]. When two contiguous LV segments are not well visualised on non-contrast apical images, the use of myocardial contrast agents is recommended [13].

Although LVEF is a commonly accepted measure of cardiac systolic function and an accepted indicator of prognosis in patients with heart failure [14], it has low sensitivity for the detection of small changes in LV function. LVEF measurement using the 2D biplane technique has a temporal coefficient of variation of 7.4% [15], which is important to highlight because the measurement variability is close to the definition of CRTCD (drop in LVEF of 10% or more). This variability is the result of a number of factors including the operator's skills and the geometric assumptions used to estimate three-dimensional (3D) volumes from 2D images. 3D echocardiography has been shown to be more accurate than the 2D echocardiography in the measurement of the LV volumes [16]. However, the feasibility of the 3D technique can be reduced in some cancer patients because of the negative influence of factors such as concomitant radiotherapy (breast cancer and lymphoma) and surgery (mastectomies of left breast cancer, breast expanders or implants), which makes the ultrasound windows under these circumstances suboptimal [17]. The ASE recommends 3D echocardiography as the preferred technique for monitoring LV function and detecting CRTCD. However, it is important to realise that this technology has several limitations as well. It is recommended that calculation of LVEF by 2D biplane Simpson's method also be included in all the oncologic patients echocardiographic report to allow comparison with previous studies if this method was used.

To minimise the risk of irreversible cardiomyopathy, the goal is to identify signs of toxicity as early as possible. Echocardiography-based deformation imaging techniques (strain) have become an essential tool to detect CRTCD. Changes in strain are more sensitive, appear prior to LVEF reduction and before the CRTCD manifests as symptomatic heart failure. Global longitudinal strain (GLS) is of particular interest because it can be incorporated into a clinical echocardiographic examination relatively efficiently with currently available technology [18]. The EACVI and ASE recommend assessing GLS as a routine component of clinical echocardiograms in patients at risk for type 1 or type 2 cardiotoxicity [6]. A relative percentage decrease in GLS > 15% is indicative of subclinical LV dysfunction and could be utilised as the starting point for timely cardio protection therapy.

4.2 LV diastolic function

A comprehensive assessment of LV diastolic function, including grading of diastolic function and providing an estimate of LV filling pressure (by using the E/e′ ratio), should be performed in addition to the assessment of LV systolic function [19]. Although abnormal diastolic function parameters may reflect subclinical LV dysfunction, it has not been found to be prognostic of cardiotoxicity, and its clinical significance remains uncertain.

4.3 Right ventricular (RV) function

The frequency of the RV dysfunction during cancer therapy-related cardiotoxicity has not been accurately examined. As early studies of CRTCD included

RV biopsies, there is a suggestion that the RV is affected by cancer therapies [20]. However, the prognostic value of RV dysfunction at the time of cardiotoxicity warrants further investigation.

5. Coronary artery disease (CAD)

The diagnostic capability of rest echocardiography in CAD is limited to the assessment of the presence and magnitude of regional wall motion abnormalities.

Stress echocardiography, an established technique for the detection and prognostication of stable CAD as recommended by guidelines, may be useful in the evaluation of patients who are undergoing regimens that may be associated with ischemia, as fluoropyrimidines, platinum compounds (cisplatin), vascular endothelial growth factor inhibitors and radiotherapy.

Stress echocardiography is also being used to unmask subclinical abnormalities of the LV function induced by chemotherapeutic agents. Although both exercise [12] and dobutamine stress echocardiography [21–23] have been applied to patients with cancer for the identification of anthracycline-induced CTRCD, the results of these studies appear to be inconclusive and contradictory. Further studies are needed to better understand the prognostic role of stress echocardiography, before can be routinely used into clinical practice.

6. Valvular disease

Patients who have received radiation therapy are at risk of long-term cardiovascular toxicity including radiation-induced heart valve disease, pericardial disease and coronary artery disease.

Transthoracic echocardiography is the main tool to identify valvular damage in these patients. There are distinct echocardiographic characteristics of radiotherapy-induced valvular disease. The main distinguishing features between radiotherapy-induced valvular heart disease and rheumatic heart disease are the presence of commissural fusion after radiotherapy, while the involvement of the mitral leaflet tips is an indication of rheumatic disease.

The EACVI and ASE expert consensus statement recommendations for long-term follow-up after radiation therapy suggest a yearly physical examination to assess for symptoms or signs of radiation-induced heart disease, which if present should prompt further evaluation. In asymptomatic patients, a transthoracic echocardiogram is recommended 5 years after exposure in high-risk individuals and 10 years after exposure in all others [24]. High risk individuals are defined the patients who received anterior or left-side chest irradiation and have at least one additional risk factor (smoking, diabetes mellitus, hypertension, hyperlipidemia and obesity).

7. Pericardial disease

Pericardial disease in cancer patients is relatively common. Pericardial effusion, cardiac tamponade and pericarditis can appear during several types of chemotherapy (anthracyclines [25], cyclophosphamide [26] and cytarabine [27]) but are especially due to radiotherapy. Constrictive pericarditis is more often associated with radiation-induced cardiotoxicity [28]. Additionally, pericardial disease may be secondary to cardiac metastasis.

Echocardiography is the first-line cardiac imaging for the diagnosis of cancer therapy-related pericarditis. It is useful for evaluating the degree of pericardial thickening, the presence of constrictive physiology and the presence and quantification of a pericardial effusion, as guidance of pericardiocentesis and for patient follow-up.

8. Conclusions

CV complications of cancer and its treatment have become increasingly recognised as an important clinical issue, with the potential to cause acute complications during therapy. The field of cardio-oncology is relatively new but developing rapidly. The goal of this emerging subspecialty is to continue anti-cancer therapy without interruption, aiming at cancer cure and remission, or alternatively support the oncologist's choice between different anti-cancer therapies, in order to maintain survival free from cardiovascular morbidity and mortality. In this context, standard and advanced echocardiography plays a pivotal role as the first-line imaging tool.

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Conflict of interest

The author declares that he has no conflict of interest.

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