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Assessing the Cardiac Toxicity of Chemotherapeutic Agents: Role of Echocardiography

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Abstract

Advancements in cancer treatment have resulted in sufficient survival length for patients to experience treatment-related cardiac complications. In particular, chemotherapy-induced cardiac dysfunction significantly impacts morbidity and mortality rates in cancer patients. The presence of cardiotoxicity from chemotherapy has been traditionally assessed using clinical symptoms and decreases in left ventricular ejection fraction (LVEF). However, in this indication, LVEF lacks accuracy as a measure of subclinical cardiotoxicity and its prognostic value is controversial. There is an emphasis to identify subclinical and left ventricular dysfunction early, in order to allow cancer patients and their physicians to make informed decisions about therapeutic options. Echocardiography is a readily available noninvasive tool to measure cardiac function and plays a major role in the diagnosis of cardiotoxicity. This review focuses on the role of echocardiography in detecting cardiotoxicity, and will discuss conventional and more recent echocardiographic approaches for assessing subclinical cardiotoxicity.

Keywords

Echocardiography; Chemotherapy; Cardiotoxicity; Anthracyclines

Introduction

Cancer therapy has evolved markedly over the last decades. Classically, chemotherapy agents used in the treatment of cancer predominantly comprised chemical agents such as anthracyclines, antimetabolites, alkylating and antimicrotubule agents. However, the recent discovery of new classes of treatments such as monoclonal antibodies and tyrosine kinase inhibitors, has expanded the arsenal of cancer treatments currently available for use in the clinical setting. These novel therapies in combination with more intensive treatment regimens and better supportive care have increased overall survival in cancer patients [1]. This increase in survival rate, however, is also paralleled by a concurrent augmentation of the rate of cardiovascular complications particularly from the use of chemotherapeutic agents [2–4] A number of factors may contribute to this increase including: 1) an increase in the number of cancer survivors who are older (therefore more susceptible to cardiovascular diseases and have more cardiovascular risk factors) [1], 2) the rise in the incidence of more aggressive cancers requiring more aggressive agents and treatment regimens [4], and 3) the

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recent influx in the number of new classes of treatment agents, many of which have cardiotoxic effects [2, 5•, 6]. The impact of chemotherapy-induced cardiotoxicity on the morbidity and mortality of cancer patients has grown to a level significant enough that it is now recognized as a health concern and has spurred the emergence of much needed cardio-oncology programs and support groups.

Cardiac Toxicity of Chemotherapy Agents

The cardiovascular complications arising from cancer treatment include cardiac dysfunction (heart failure), myocardial ischemia or infarction, hypertension, thromboembolism and arrhythmias [5•]; the present review will mainly focus on cardiac dysfunction. Anthracycline induced cardiac dysfunction has been recognized since the 1970s, and is the topic of the vast majority of research on cardiotoxicity. More recently, cardiac dysfunction has been detected in patients treated with tyrosine kinase inhibitors (in particular trastuzumab). Although these treatments are not strictly chemotherapies, they will briefly be discussed in this review.

The cardiotoxic effects of anthracyclines can be categorized into acute/subacute or chronic (early or late/delayed) cardiotoxicity based on the time of onset and the duration of symptoms (for full review see [5•]). Acute cardiotoxicity events are relatively rare (<1 % of patients), can arise anytime from the initiation of the therapeutic agent to two weeks after termination of chemotherapy, and with few exceptions, generally resolve within one to two weeks [7]. These include abnormalities in ventricular repolarization and QT-interval, conduction abnormalities, acute coronary syndromes and pericarditis/myocarditis syndromes. Chronic cardiotoxicity secondary to anthracyclines is more prevalent (1.6–5 % of symptomatic heart failure during long term follow-up and up to 40 % of asymptomatic LVEF decreases in some studies), and is most frequently characterized by a persistent cardiac dysfunction which occurs either within the first year of completing treatment (early – 1.6 % to 2.1 %) or several years beyond the first year of treatment (late/delayed – 1.6 % to 5 %) [5•, 7].

Tyrosine kinase inhibitors such as trastuzumab (Herceptin) or sunitinib may also induce cardiac dysfunction. While anthracycline cardiotoxicity is generally believed to be the result of cardiomyocyte injury from oxidative stress, tyrosine kinases inhibitors are thought to cause cardiotoxicity by inhibition of normal growth, repair and survival of cardiomyocytes [6]. When used in combination with anthracyclines, tyrosine kinases inhibitors potentiate anthracyclines-induced injury. Cardiotoxicity of tyrosine kinase inhibitors is particularly important to characterize since more than 600 agents of this class are currently in development.

The early detection of chemotherapy-induced cardiotoxicity is of great interest as cancer therapy drug combinations may be modified to reduce cardiotoxicity [8•]. Furthermore, it has been suggested that interventions may slow the progression of left ventricular dysfunction or prevent the development of late cardiotoxicity. Recently, Cardinale et al. demonstrated that of 201 cancer patients with anthracycline-induced cardiomyopathy, 42 % classified as responders showed LVEF recovery and a reduction in cardiac events due to the early initiation of enalapril, an angiotensin converting enzyme II inhibitor [9•]. Hence early detection of cardiotoxicity may potentially enable chemotherapeutic treatment combinations regimens to be modified or prophylactic treatment instituted.

There are currently guidelines for monitoring for chemotherapy-induced cardiotoxicity in children treated with anthracyclines but no clearly defined guidelines for the adult population. The American Heart Association only recommends close monitoring of cardiac function in adults during anthracycline therapy but does not specify any recommendations

for the methods that should be used to assess for cardiotoxicity, follow up duration, the frequency of testing, or the thresholds that should be used [10, 11].

Evaluating Cardiac Dysfunction

LVEF as a Measure of Chemotherapy-Induced Cardiotoxicity

The gold standard for the evaluation of anthracycline-induced cardiomyopathy is endomyocardial biopsy [12]. However this technique is limited by its invasive nature, the quality of the sample biopsied and the success of obtaining a biopsy containing damaged myocardium. Thus, endomyocardial biopsy is unsuitable as a first-line method for cardiotoxicity detection or monitoring. While nuclear angiography and MRI can also be used for the detection of cardiac toxicity, echocardiography, a widely available, noninvasive, and non-radioactive technique, is presently the test of choice for the repeated evaluation of cardiotoxicity.

Left ventricular ejection fraction (LVEF) is a commonly accepted measure of cardiac systolic function and an accepted indicator of prognosis [13]. A study of 4257 individuals revealed that individuals with asymptomatic left ventricular dysfunction in the community were at high risk of congestive cardiac failure and death, even when only mild impairment of EF was present [14]. In the setting of chemotherapy, cardiotoxicity is routinely defined as a decline in LVEF but there has been considerable confusion so far as to what decline in LVEF constitutes cardiotoxicity; studies have defined cardiotoxicity as LVEF decreases from normal baseline to values below 50 %, LVEF decreases of more than 20 % from baseline but remaining above the lower limits of normal, LVEF decreases below 45 %, a reduction of LVEF >5 % to LVEF <55 % with symptoms of heart failure or an asymptomatic reduction of LVEF of >10 % to a LVEF <55 % [15, 16].

LVEF is routinely measured using echocardiography or multi gated acquisition (MUGA) [17]. Standard 2-dimensional echocardiographic assessment of LVEF has slightly higher inter-observer and intra-observer variability than MUGA scan (8.8 % vs 6.8 % respectively) [18] but provides additional information on valvular and diastolic function and does not expose the patient to radiation.

It is generally admitted that pre-treatment LVEF is predictive of subsequent cardiotoxicity, at least in the adult population. For example, a study involving 1664 patients with breast cancer treated with anthracyclines or anthracyclines and trastuzumab demonstrated that the absolute value of pre-treatment LVEF was associated with the later occurrence of heart failure, even though patients with LVEF <50 % were excluded from the study [16]. The predictive value of pre-treatment LVEF may be lower in children, as underlined by a recent retrospective review of all echocardiograms and related clinical decisions for 356 children who were followed for anthracycline cardiotoxicity [19]. In this study, the routine use of echocardiograms to screen for anthracycline-induced cardiac damage before and during chemotherapy rarely identified significant cardiac damage [19].

The prognostic value and the timing of serial measurements of LVEF to monitor for chemotherapy cardiotoxicity is controversial. In an early study, Alexander et al. monitored LVEF in 55 patients receiving high doses of doxorubicin [20]. Quantitative radionuclide angiocardiograms were performed on these patients during treatment with anthracyclines. Five patients who had a decline of at least 15 % in measured LVEF but continued with their high-dose anthracycline subsequently developed symptoms of heart failure. Conversely, six patients who had a similar decline in LVEF during treatment but interrupted anthracyclines did not develop heart failure and showed a partial recovery of LVEF. Findings from this study gave rise to algorithms used in serial monitoring of LVEF in subsequent studies

addressing the same question [10, 21]. Another small study evaluated LVEF in 30 adult non-Hodgkin's lymphoma patients following treatment with doxorubicin, and suggested that impairment of left ventricular function during doxorubicin therapy can be predicted after the early cycles, with a 4 % decrease in LVEF after a cumulative doxorubicin dose 500 mg m^{-2} having a sensitivity of 90 % and a specificity of 72 % in predicting later cardiotoxicity during the treatment [22]. A larger study by Jensen et al., however, did not support the predictive value of LVEF measured during anthracycline treatment. These investigators prospectively followed a cohort of 120 patients with advanced breast cancer for 3 years following treatment with epirubicin. This study revealed a slowly progressing deterioration of cardiac function after the cessation of the anthracycline. Although the absolute values of LVEF before and immediately after treatment were lower in patients who later developed congestive heart failure, there was no clear association between the percentage of decrease in LVEF observed during the treatment and the later development of symptomatic heart failure within the 3 year follow up period [23]. The absolute value of LVEF early after anthracyclines was also associated with patients who later developed heart failure in 850 patients treated with trastuzumab. In this study, 12.5 % of patients with a LVEF of 50–54 %, 3.8 % of patients with a LVEF of 55–64 % and 0.9 % of patients with a LVEF>65 % developed symptomatic heart failure over a follow-up period of 3 years [16]. The optimal timing and number of follow-up echocardiograms, however, remains unknown and may depend both on the initial changes of LVEF and on the combination of treatments given.

Improving LVEF Measurements

Contrast Echocardiography—One disadvantage of 2D echocardiography is that the accuracy of LVEF measurements is dependent on the quality of the images obtained and subject to measurement variability. In order to obtain an accurate measurement of LVEF using echocardiography, the endocardial border has to be sufficiently visualized to enable manual tracing of the end-systolic and end-diastolic volumes, from which ejection fraction is calculated. The use of contrast agents have been shown to convert 74 % of non-diagnostic studies into diagnostic studies by improving endocardial visualization [24] and reducing the intra-observer and inter-observer variability [25]. Even though several multicenter and single-center trials have demonstrated the usefulness of contrast in clinical practice, there are still currently no clear indications in the chemotherapy guidelines or the general American Society of Echocardiography and European Association of Echocardiography guidelines for the use of contrast to assess for chemotherapy cardiotoxicity [26].

Three Dimensional Echocardiography—In addition to poor endocardial definition, the other limitations of 2D echocardiography that can contribute to the lack of accuracy in measured LVEF include ventricular foreshortening, and the use of mathematical models and geometrical assumptions to calculate the LV volumes. Real-time three-dimensional (3-D) echocardiography overcomes both these limitations and allows a more accurate assessment of LV volume and ejection fraction. It has been proven by the results of several studies that 3-D imaging is superior to the more routinely used 2-D images, offering the advantages of reduced analysis time, higher reproducibility and lower inter-observer variability [27, 28]. Additionally, LV volumes (which may be an indirect indicator of cardiac remodeling) obtained using 3-D echocardiography correlated more closely with volumes measured by computed tomography and magnetic resonance imaging than 2-D echocardiography [27, 29–31]. Contrast has also been used to enhance 3D echocardiographic images particularly in patients with poor images and to enhance assessment of regional wall motion. The improvements in the accuracy and reproducibility of LV volume measurements reached levels similar to those noted in patients with optimal imaging quality [32]. Despite the advantages of 3D echocardiography, which make it a suitable tool for assessing interval changes in ejection fraction, and the use of contrast, there is still a question as to whether

LVEF is the most sensitive measure of cardiotoxicity. As an example, in contrast to more sensitive myocardial deformation indices, LVEF measured using 3-D echocardiography did not decrease in 35 women undergoing treatment with trastuzumab for breast cancer [33]. This discrepancy may be due to significant interpretive variation [34]. Furthermore in order for an appreciable drop in LVEF to occur, the myocardium must have undergone sufficient damage hence the need for more sensitive measures of left ventricular function that is able to reflect subclinical cardiotoxicity [34, 35].

Diastolic Parameters and Chemotherapy Cardiotoxicity—Diastolic parameters are believed to be a more sensitive alternative to LVEF for detection of subtle cardiac dysfunction as demonstrated in several myocardial pathologies, in particular ischemia [36]. A number of small studies in the 1980s and 1990s revealed abnormalities in diastolic indices following treatment with anthracyclines [37–42]. A subsequent study of 20 asymptomatic breast cancer patients with normal systolic function who were treated with anthracyclines also reported that more than 50 % of patients treated with anthracyclines had impaired early peak flow velocity to atrial peak flow velocity (E/A) ratio, deceleration time (DT), and isovolumetric relaxation time (IVRT) which persisted throughout the follow-up period of 29 months after discontinuation of anthracyclines [43]. Two more recent studies, (one of 68 patients with different malignancies treated with epirubicin [44] and the other comprising 20 breast cancer patients who were treated with anthracyclines [45]) demonstrated early changes in LV diastolic function. Neither of these studies, nor any of the earlier studies demonstrated prognostic value or correlation between changes in the diastolic parameters and the development of late cardiotoxicity. One prospective study of 26 patients treated with doxorubicin suggested an association between early alterations in diastolic parameters and the development of left ventricular dysfunction. This study demonstrated that an increase in the isovolumetric relaxation time of more than 37 % three weeks post chemotherapy was 78 % sensitive and 88 % specific for predicting the development of systolic dysfunction at 3 months [40]. Nonetheless the use of diastolic parameters in diagnosing cardiotoxicity is still controversial and larger studies would be needed to confirm the value of diastolic measurements and specificity in detecting long-term cardiotoxicity.

Stress Echo and Detection of Chemotherapy Induced Cardiotoxicity—Exercise and pharmacologic stress testing may also be useful to unmask subclinical abnormalities of LV function induced by chemotherapeutic agents. In 37 patients receiving doxorubicin, an abnormal LVEF at rest within 1 month of having chemotherapy was reported to have a sensitivity of 53 % and a specificity of 75 % for detecting patients at moderate or high risk of developing congestive cardiac failure even though a follow up time frame was not clearly outlined. With the addition of exercise, sensitivity increased to 89 % but specificity decreased to 41 % [46]. In another study of 23 young adults with acute lymphoblastic leukemia treated with anthracyclines before the onset of puberty and followed for a median of 21 years after remission, ten subjects demonstrated a normal EF at rest but reduced LVEF during stress [47]. However achieving maximal exercise is often difficult for patients receiving chemotherapy. Dobutamine stress echocardiography has yielded conflicting results in the detection of chemotherapy cardiotoxicity. A very subtle alteration of myocardial contractile reserve during low dose dobutamine stress echocardiography was described in 17 % of 49 breast cancer patients recruited who developed a significant decline in their LVEF 18 months after cessation of high dose chemotherapy [48]. High dose dobutamine stress echocardiography revealed an alteration of the fractional shortening and the transmitral E/A ratio in 26 asymptomatic patients treated with high-dose anthracyclines [49]. Conversely, other studies did not report any incremental value of the technique for early detection of cardiotoxicity [50, 51]. The lack of any conclusive data, the semi-invasive nature of the test, and limited repeatability means stress echocardiograms will probably not be routinely used

to monitor for cardiotoxicity. Nonetheless exercise capacity may still have value in this setting since it has been shown to have powerful prognostic value for both cardiovascular and overall risk in the general population [52].

Strain and Strain Rate—Myocardial deformation (strain) and deformation rate (strain rate) may offer a more sensitive approach to measuring cardiotoxicity than LVEF as these measures can provides a multi- dimensional evaluation of myocardial mechanics (longitudinal, radial, and circumferential function) and have the added advantage to detect subtle wall motion abnormalities of regional function that do not decrease global LV ejection fraction [35, 53–56]. There is now an emerging body of work in animal models and in humans demonstrating that strain and strain rates are more sensitive measures than LVEF for detecting early LV dysfunction in subjects treated with anthracyclines alone or in combination with other treatments such as trastuzumab and taxanes [33, 57, 58, 59•]. One study of women receiving trastuzumab for HER2 positive breast cancer, showed that 51 % of the study population had reductions in 2-D longitudinal strain values and 37 % a concurrent reduction in 2-D-radial strain rate [33]. Another study of 13 children treated with anthracyclines revealed significant and persistent reductions in longitudinal and radial regional systolic strain and strain rate within 2 hours after the first dose of anthracyclines but no decline in the LVEF even after two cycles of treatment with a later decline in LVEF after three cycles [60]. In 16 elderly women with breast cancer treated with six cycles of pegylated lipososomal doxorubicin, LV dimensions, LVEF, and systolic myocardial velocity did not change at the end of the six cycles of chemotherapy, whereas both longitudinal and radial strain and strain rates changed significantly, with changes in radial function appearing earlier and in a more pronounced way than in longitudinal direction [58]. Another recent study reported the use of torsion analysis as an alternative to strain in the early detection of subclinical anthracycline cardiotoxicity. This study evaluated LV torsion and twisting velocity on 25 patients 1 and 3 months post chemotherapy and showed significant deteriorations in torsion, twisting rate and untwisting rate 1 month after chemotherapy even though left ventricular dimensions and LVEF did not show any significant change [61].

The long-term effects of anthracyclines have also been identified using strain and strain rate. Strain measurements in a cohort of 56 late survivors of childhood cancer treated with anthracyclines at doses lower than 300 mg/m^2 followed up at median of 5.2 years after the last dose of anthracycline demonstrated evidence of subclinical cardiotoxicity, with both radial and longitudinal myocardial strain measurements reduced by 15 % compared to controls while LVEF remained within normal limits [35, 57].

Few studies have investigated the prognostic value of deformation indices. In a mouse model of doxorubicin cardiotoxicity, Neilan et al. reported that strain rate predicted the development of late cardiac dysfunction and mortality [62]. One recent study of 43 women with breast cancer who were treated with anthracyclines followed by trastuzumab and taxol demonstrated that a decrease in peak global longitudinal strain from baseline to 3 months predicted subsequent cardiotoxicity at 6 months while LVEF and parameters of diastolic function did not [59•]. Larger studies with longer follow-up are warranted to definitely demonstrate whether deformation indices can predict the development of cardiotoxicity.

Conclusion

The improvements in cancer therapy and the subsequent increase in survival length have resulted in an augmentation of cardiac complications rate from their cancer therapy. The recent availability of novel and more sensitive diagnostic tools has improved our ability to detect subclinical cardiotoxicity. Echocardiography has a major role in this emerging area with recent advances in echocardiographic technology generating a large body of evidence

supporting the presence of subclinical chemotherapy-induced cardiotoxicity. The development of an accurate and reproducible measurement of LVEF by 3D echocardiography and contrast injections, and, the use of strain and strain rate measures as valuable tools for the early detection of LV dysfunction, are likely to be integrated in the assessment and monitoring of cardiac function in cancer patients in the future. There are still inherent challenges and pitfalls that have to be overcome. Poor image quality remains a significant issue. The application of some of these techniques require extensive experience which only comes by using these techniques on a regular basis in order to gain sufficient knowledge on how they work along with their strengths and weaknesses. Finally but crucially, larger studies are needed to better understand what defines cardiotoxicity and to evaluate the prognostic role of echocardiography parameters in order to better inform current clinical practice and guidelines.

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