Incidence and Associated Risk Factors of Chemotherapy-Induced Cardiomyopathy in the African American and Afro-Caribbean Populations

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Abstract

Background: Chemotherapy-induced cardiomyopathy (CICM) and heart failure are major complications of cancer therapeutics and can result in significant morbidity and mortality. There is limited data on the incidence and risk factors of CICM in African American and Afro-Caribbean patients.

Methods: We performed a retrospective chart review to evaluate the baseline characteristics that may predispose to CICM. Patients were African American and Afro-Caribbean ethnicity. Data was collected between 2014 to 2018. Patients had transthoracic echocardiogram (TTE) or multigated acquisition scan (MUGA) prior to cancer therapy and every 3 months thereafter, until the end of the regimen. CICM was defined as a 16% reduction in LVEF or 10% reduction in LVEF to a value <50%.

Results: A total of 230 patients were studied, with a mean age of 54±12 years with 91% were females, BMI 30±4, 81% were taking anthracyclines, 87% were on Trastuzumab while 5% were receiving both medications. The prevalence of comorbidities was as follows: hypertension 8%, diabetes mellitus 8%, ESRD 8%, dyslipidemia 8%, CAD 7%. The incidence of CICM was 7% overall, while it was 6% and 8% for patients taking Anthracyclines and Trastuzumab, respectively. CICM was associated with dyslipidemia (r= .22, p= .001), hypertension (r= .12, p= .05), baseline ejection fraction (r= −.21, p= .001) and concomitant use of radiation therapy (r= .147, p= .02), but not with age, gender, beta blocker use, angiotensin converting enzyme inhibitor use, number of

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chemotherapy cycles or stage of the malignancy. On multivariate analysis CICM was independently associated with baseline ejection fraction (β= −.193, P= .003) and dyslipidemia (β= −.20, P= .003).

Conclusion: The incidence of CICM in African Americans and Afro-Caribbean is higher than reported in the general population. Dyslipidemia and baseline ejection fraction were seen as the major risk factors associated with the higher incidence of CICM.

Keywords

Echocardiography; Function; Enddiastolic function; Athletic heart

Introduction

Through new advances in chemotherapy, survival of cancer patients has dramatically increased over the years. However, as their use has become more generalized, the incidence of side effects has become more apparent. One such side effect is the development of cardiotoxicity. Cardiotoxicity is particularly a concern with the use of HER2 blockers Trastuzumab and Antracyclines. Despite the risk of cardiac dysfunction or cardiomyopathy, targeted therapies have revolutionized the treatment of cancer, specifically in HER2 positive breast cancer. Medications, such as trastuzumab, have shown better response, longer time to disease progression, and longer survival in historically aggressive cancers, thus making their utilization desired [1]. The range of adverse cardiac manifestations of these medications include QT prolongation, arrhythmias, myocardial ischemia and/or infarction (seen in patients receiving radiation), hypertension, venous and arterial thromboembolism (seen with the anti-angiogenic agents: bevacizumab, sorafenib, sunitinib, and pazopanib), and congestive heart failure (HF) (seen commonly with anthracyclines and also with monoclonal antibodies and targeted therapies) [2].

Historically chemotherapy induced cardiomyopathy (CICM) has been classified into two types; type I, which often refers to permanent damage to the myocardium, and type 2, which encompasses all types of reversible cardiomyopathy [1]. Typically, anthracyclines, such as doxorubicin, are known to cause a type I CM, and monoclonal antibodies and targeted therapies, such as hertuzumab, are known to cause a type 2 CM.

According to the European Society of Cardiology (ESC) Guidelines for heart failure, heart failure has been classified into three groups: reduced ejection fraction (EF) <40%, mid-range EF 40–49% and preserved EF >50%. A fourth group of heart failure encompasses patients that have improved EF after stopping the inciting chemotherapy agent, however guidelines regarding duration of treatment and monitoring in these patients remain lacking. When focusing specifically on chemotherapy induced HF, however, the ESC mentions that a reduction in EF from baseline is needed for the diagnosis [3]. Alternatively, the clinical trials surrounding trastuzumab, define CICM as a decline in left ventricular ejection fraction (LVEF) of at least 5% or less than 55% in symptomatic patients or a decline of LVEF of 10% or less than 55% in those without symptoms. Despite no clear consensus on definition, reductions in EF of about 10% from baseline following initiation of chemotherapy and the

development of symptomology are significant and warrant investigation before continuation of therapy [4].

Heart failure or any cardiotoxicity may present in patients acutely, sub acutely, chronically or late-occurring [1]. Anthracycline induced cardiotoxicity can cause a range of cardiac effects; however, it is important to recognize that late-occurring cardiotoxicity may not become apparent up until 20 years after the first dose of chemotherapy [4]. Thus, posing a risk of CICM in a large subset of patients who may currently be asymptomatic.

The mechanism for chemotherapy agents to induce cardiomyopathy has been hypothesized for various chemotherapy agents. For anthracyclines it is believed that oxidative stress causing myocardial cell death and apoptosis is the cause of irreversible cardiac dysfunction [5]. The damage caused by anthracyclines is dose dependent related to each individual dose administered and cumulative dose received in a patient's lifetime, however risk of CICM increases with concurrent mediastinal radiation, increasing age, female gender, and cardiac disease [6]. For HER2 agents it is thought that disrupting cell repair pathways causes a reversible cardiomyopathy [7]. Additional risk factors for developing cardiotoxicity from trastuzumab include a diagnosis of diabetes, age, decreased glomerular filtration rate, use of anti-hypertensives and a history of cardiac disease [8]. These risk factors, however, are not uniform. One study showed that African American race alone was associated with a 3 times greater risk of developing CICM in patients who had completed anthracycline therapy, while another study showed a similar increase in risk of CICM in African American women one year after completion of trastuzumab therapy [9,10]. Not only do African American patients have an increased risk of developing CICM compared to their white counterparts, but also, have increased risk of not completing a course of chemotherapy due to the development of LVD [11]. Recognizing additional risk factors for the development of cardiomyopathy is important as it may facilitate in identifying high-risk patients that may benefit from more frequent follow up and early intervention.

Patients receiving trastuzumab and/or anthracyclines should be monitored for the development of cardiomyopathy especially due to an increased risk of CICM when combining the two therapies. The incidence of CICM up to five years after completion of therapy in patients using trastuzumab alone is about 10% and in combination with anthracyclines is up to 20% [12,13]. Biomarkers, including troponin, and the development of global strain on echocardiograms may be used in order to detect subclinical LV dysfunction sooner than when patients become symptomatic [14,15]. The goal of early detection is early treatment. Current guidelines recommend that once LVD of greater than 10% change from baseline is noted, chemotherapy should be held and patients should be initiated on ACE inhibitors and beta blockers. Follow up echocardiograms should be performed thereafter at set intervals to monitor for improvement of EF [4]. Some studies have demonstrated that LV dysfunction was potentially reversible depending on the time to treatment with ACE inhibitors and beta blockers. Therefore, identifying high risk patients becomes all the more important [16].

Despite, the growing recognition of CICM, more research needs to be done in order to risk stratify patients and understand which patients require closer monitoring. Research has

already shown the African Americans have a greater predisposition for developing CICM, however further stratification of modifiable risk factors is necessary in order to potentially prevent the occurrence of CICM in this subset population. Here, we assess the effects of various chemotherapy agents on CICM in a largely afro-Caribbean and African American population.

Methods

Data collection

We conducted a retrospective chart review of electronic medical records of individuals who were diagnosed with breast cancer and received neoadjuvant or adjuvant anthracycline, trastuzumab with or without pertuzumab between January 2014 and December 2018 at our facility in Brooklyn, New York. It is a tertiary hospital in Brooklyn that serves a community with a majority of African American and Afro-Caribbean patients.

Data collection included basic demographic characteristics: age, gender, race, weight, height, and body mass index; malignancy characteristics: stage, grade, HER2 receptor status, treatment with radiation therapy, type of chemotherapy, duration of chemotherapy, follow up in months; cardiovascular co-morbidities: diabetes, hypertension, dyslipidemia, obstructive sleep apnea, smoking status, chronic obstructive pulmonary disease and chronic kidney disease; cardiac imaging data was mainly from multigated acquisition scan (MUGA) or/and transthoracic echocardiogram (TTE); and cardiovascular-related or antihypertensive medications: angiotensin receptor blockers, angiotensin converting enzyme inhibitors, beta blockers, calcium channel blockers, hydralazine, nitrates, digoxin, and anti-arrhythmic medications.

At our facility, the protocol for a cancer patient who is going to receive chemotherapy regimen known to cause cardiotoxicity, as in anthracycline-based and trastuzumab-based therapy, is as follows: to have a cardiac imaging study (primarily MUGA scan)to monitor for cardiomyopathy before starting therapy and every three months until the end of therapy. As a result, most of our data during patient follow up is from MUGA scan results.

Exclusion criteria included patients who did not receive anthracycline-based, trastuzumab-based or pertuzumab-based therapy, lost follow up, discontinued therapy secondary to psychosocial reasons, switch care to another facility.

Cardiac evaluation was based on left ventricular ejection fraction (LVEF), which was obtained mainly from MUGA scans and/or TTE. Chemotherapy-induced cardiotoxicity was defined as a 16% reduction in LVEF or 10% reduction in LVEF to a value <50% [12].

Statistical analysis

Demographics, tumor-related clinical data and cardiovascular co-morbidities were analyzed using descriptive statistics. Univariate associations between study variables were analyzed using Spearman's correlation coefficients. Continuous data was compared using either Student's t-test. Chi square was used to assess differences between dichotomous variables. Independent associations were determined by multivariate linear regression. Statistical

analyses were performed using the Statistical Package for Social Sciences (SPSS) software version 24 (SPSS Inc., Chicago, Ill., USA). A p value <0.05 was considered statistically significant.

Results

We screened 420 patients and 110 patients were excluded in the basis of exclusion criteria, the remaining identified 310 African American and Afro-Caribbean were included in the study. The mean age was 54±12 years. In total, 91% were females. BMI was 30±4. In our cohort, 81% were taking anthracyclines, 87% were on Trastuzumab while 5% were receiving both medications. The prevalence of cardiovascular comorbidities was as follows: hypertension 8%, diabetes mellitus 8%, ESRD 8%, dyslipidemia 8%, CAD 7%. Mean follow up in months was 26±17 and the mean number of chemotherapy cycles was 9±6.

The incidence of CICM was 7% overall, while it was 6% and 8% for patients taking Anthracyclines and Trastuzumab, respectively. CICM was associated with dyslipidemia (r= .22, p= .001), hypertension (r= .12, p= .05), baseline ejection fraction (r= −.21, p= .001) and concomitant use of radiation therapy (r= .147, p= .02). However, CICM was not statistically significant with regards to age, gender, beta blocker use, angiotensin converting enzyme inhibitor use, number of chemotherapy cycles or stage of the malignancy. On multivariate analysis CICM was independently associated with baseline ejection fraction (β= −.193, P= .003) and dyslipidemia (β= −.20, P= .003).

Discussion

Anthracyclines and HER2 receptor antagonists are an integral part of chemotherapy regimens used to treat breast cancer. These medications are highly effective in the treatment of breast cancer [17,18]. Although, anthracyclines and HER2 receptor antagonists are generally well tolerated, their potential to cause cardiotoxicity has been well documented. Even though the mechanism and prognosis of cardiotoxicity may differ between anthracyclines and HER2 receptor antagonists, the result can often lead to significant morbidity and mortality. There is also extremely limited data on the racial disparities in the development of cardiotoxicity with both anthracycline and HER2 receptor antagonists [19]. The aim of this study was characterizing the incidence and risk factors contributing to chemotherapy induced cardiomyopathy among a primarily African American and Afro-Caribbean population.

The pathogenesis of trastuzumab mediated cardiomyopathy is most likely mediated by the blockage of HER2 receptor signals in cardiac myocytes. This would prevent the transmission of the cascade essential for myocyte repair, resulting in myocyte apoptosis and necrosis [20]. Studies have shown that the left ventricular dysfunction from trastuzumab can be reversible after withdrawal and does not appear to be dose dependent [21]. The incidence range in the literature appears to be between 2.0–28.0%. Table 1 shows a compiled list of studies with their protocol and incidence listed. Each study had its own parameters and design likely accounting for the differences in measured incidence. For example, each study had a different population with variable patient characteristics, with a variable definition of

trastuzumab-induced cardiotoxicity. Many studies also used the less accurate echocardiogram, which is not only user dependent, but also may have variable readings and interpretations. Lastly, patient characteristics, such as the use of anthracyclines prior to adjuvant trastuzumab treatment, have also been shown to increase the risk for the development of trastuzumab-mediated cardiomyopathy in a dose dependent manner [22].

Our study has found an incidence of trastuzumab-mediated cardiomyopathy of 8%, which is higher than most documented studies. A subgroup analysis of races was seldom done in the randomized controlled trials. The HERA trial stratified data according to race, but was underpowered as only 20 out of 4482 patients were African American [23]. Litvak et al. conducted a retrospective chart review studying the rate of cardiotoxicity of HER2-targeted therapies among women with early breast cancer with a focus on racial disparities. The study found a cardiotoxicity rate at 1 year to be 12.5% in all study patients, with African American females at 24% and Caucasian females to be at 7% [19]. Rugo et al. conducted a observational study and found the incidence of cardiac safety events (grade 3) to be higher in black patients (10.9 %) than in white patients (7.9 %) who were receiving trastuzumab for with HER2-positive metastatic breast cancer [24].

Anthracycline induced cardiomyopathy (AIC) has been well documented with the pathogenesis possibly involving the formation of anthracycline-iron complexes with subsequent free-radical formation resulting in myocyte damage [36]. Anthracycline induced cardiomyopathy seems to be dose dependent and usually reversible [22,37]. The exact incidence is also difficult to establish as studies have variable dosing protocols and designs. Table 2 shows a compiled list of studies with their protocol and incidence listed. Swain et al. studied doxorubicin, reporting a 5% AIC at 400 mg/m^2, 16% at 500 mg/m^2, 26% at a dose of 550 mg/m^2, and 48% at a dose of 700 mg/m^2 [22]. Very few studies have stratified data by race for AIC. Hasan et al. studied doxorubicin induced cardiomyopathy and found a dose dependent development of cardiotoxicity and found that African Americans had a higher rate of cardiotoxicity with doxorubicin therapy (7/100 cases) when compared with a similar retrospective study of 399 patients of undifferentiated racial distribution (10/399 cases) [38]. Our study of primarily African American and Afro-Caribbean patients found a AIC incidence of 6%. This seems to be in accordance with previous AIC studies.

The risk factors associated with CICM in our study were found to be dyslipidemia (r= .22, p= .001), hypertension (r= .12 p= .05), baseline ejection fraction (r= −.21 p= .001) and concomitant use of radiation therapy (r= .147 p= .02). Dyslipidemia and hypertension are intuitional as they are cardiac risk factors that generally increase the pretest probability of any cardiac event, as does having baseline LVEF dysfunction. Radiation therapy is also well documented to lead to cardiac toxicity [42]. We lacked statistical power to understand the association of CICM with age, gender, beta blocker use, angiotensin converting enzyme inhibitor use, number of chemotherapy cycles or stage of the malignancy. Next steps would include adding patients to our study in order to better understand the cardiac risk African American and Afro-Caribbean patients face undergoing chemotherapy and to develop protective strategies. For example, Gulati et al. found that concomitantly administered candesartan had an overall decline in LVEF of 0.8% (95% CI −0.4, 1.9) vs the placebo group with 2.6% (95% CI 1.5, 3.8). They did not find any effect of metoprolol on the overall

decline in LVEF [43]. Therefore, with better understanding risk factors, such as using concomitant ACE/ARBs, protective strategies can be created to reduce CICM and potentially prevent treatment delays or discontinuation. This is especially important for African Americans, as they are more likely to have CICM than other races.

The racial disparities in the development of CICM are likely multifactorial. Litvak et al. found that the African American populations studied had higher rates of cardiac comorbidities (diabetes, hypertension, hyperlipidemia, and smoking history) [19]. Wheeler et al. found that a higher percentage of African Americans diagnosed with breast cancer have a lack of insurance and a lower socioeconomic status [44]. Finkelman et al. found that African American breast cancer patients undergoing doxorubicin therapy had early alterations in arginine-NO metabolite levels and early biomarker changes that were known to be associated with a greater risk of cardiomyopathy [45]. Therefore, not only social, but also genetic components need further elucidation. This would help potentially guide the development of race specific guidelines, such as increased screening protocols or early referral to cardiology for African Americans treated with trastuzumab or anthracyclines.

Our study had multiple limitations. Firstly, we had a relatively small sample size in a retrospective study with many patients lost to follow up. Secondly, we incorporated data from echocardiograms, which has limited precision and accuracy in measuring LVEF, when compared to the MUGA scan. Thirdly, there was insufficient data on certain patient characteristics, such the number of years since diagnosis of hypertension or hyperlipidemia and adherence with the treatment of comorbidities. Lastly, not all comorbidities were studied, such as the BMI at time of diagnosis. However, this is one of the largest series on the incidence of chemotherapy induced cardiomyopathy among African Americans reported in literature.

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Table 1:

Incidence of trastuzumab-mediated Cardiotoxicity in Several Trials.

Study	Number of Patients	Type of Breast Cancer	Number of weeks of Trastuzumab	Used anthracyclines prior to Trastuzumab	Definition of Cardiomyopathy	Incidence of trastuzumab-mediated Cardiotoxicity
Vogel et al. (2002) [25]	114	*HER2*-positive metastatic breast cancer	Median 16 weeks	2/3 patients developing TMC	CHF symptoms, Cardiomyopathy, or a decrease in ejection fraction by 10%	2%
Guarneri et al. (2006) [26]	218	*HER2*-positive metastatic breast cancer	Median 21.3 months	85% of TIC had prior anthracycline exposure	LVEF decreasing below 50%, >20% drop in LVEF, or symptoms of CHF	28%
Suter et al. (2007) [27]	1,693	*HER2*-positive early invasive breast Caner	12 or 24 months	94% had adjuvant anthracycline based therapy	LVEF decreasing below 50%, >10% drop in LVEF, or symptoms of CHF	4.3%
Perez et al. (2008) [28]	1,944	*HER2*-positive node-positive or high-risk node negative invasive breast cancer	52 weeks	All arms treated with Doxorubicin + cyclophosphamide (AC) prior	decreased >15% points from baseline, decreased below 50%, or symptoms of CHF	Arm A: AC then Paclitaxel: 0.3% Arm B: AC then Paclitaxel then trastuzumab: 2.8%, Arm C: AC + Paclitaxel with trastuzumab: 3.3%
Gianni et al. (2010) [18]	117	*HER2*-positive locally advanced or inflammatory breast cancer	52 weeks	Neoadjuvant trastuzumab plus concurrent doxorubicin-including chemotherapy	Development of EF <50%	2%
Untch et al. (2010) [29]	120	*HER2*-positive metastatic breast cancer	39–45 weeks	trastuzumab plus concurrent epirubicin -including chemotherapy	Decrease in LVEF of more than 10% to less than 50%	Arm with trastuzumab + epirubicin 60 mg/m: 1.7%, Arm with trastuzumab + epirubicin 90 mg/m: 5.0%
Slamon et al. (2011) [30]	3222	HER2-positive, node-negative or node-positive adenocarcinoma	52 weeks	1) doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T) 2) the same regimen plus 52 weeks of trastuzumab (AC-T plus trastuzumab) 3) or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH)	Decrease in LVEF of more than 10% from baseline	1) AC-T 11.2 2) AC-T plus Trastuzumab 18.6 3) TCH 9.4
Romond, et al. (2012) [31]	944	Node Positive, HER2 Positive Breast Cancer	52 weeks	Use of trastuzumab after 4 cycles of doxorubicin- containing chemotherapy	decrease of LVEF >10% from baseline to a value less than 55% OR decrease of more than 5% to a value below 50%	4.0% (95% CI, 2.8% to 5.2%) vs 1.3% (95% CI, 0.5% to 2.1%) in control arm
Azambuja et al. (2014) [32]	1,673 In 1 year arm and 1,682 in two year arm	*HER2*-positive Early Stage Breast cancer	52 or 102 weeks	94% of patients received an anthracycline-based chemotherapy prior	decline of at least 10 percentage points from baseline LVEF and a decline to less than 50%	9.4% of patients in the 2-year arm and 5.2% of patients in the 1-year arm
Advani, et al. (2016) [33]	1876	Node positive or high-risk node negative breast cancer	52 Weeks	Arm A: AC followed by weekly paclitaxel; Arm B: paclitaxel then 52 weeks of trastuzumab; Arm C:	LVEF decreased by greater than 15% points or to 10% to 15% points below 50%	Arm A: 0.6% Arm B: 2.8% Arm C: 3.4%

Study	Number of Patients	Type of Breast Cancer	Number of weeks of Trastuzumab	Used anthracyclines prior to Trastuzumab	Definition of Cardiomyopathy	Incidence of trastuzumab-mediated Cardiotoxicity
				paclitaxel plus 52 weeks of trastuzumab followed by trastuzumab alone		
Yoon, et al. (2016) [34]	712	Breast cancer	52 weeks	anthracycline-based treatment prior	LVEF of <55% or the decrease in LVEF of >10% from the baseline LVEF	11.4%
Dang, et al. (2017) [35]	406	Node Negative, HER2 Positive Breast Cancer	52 weeks	No anthracycline	decrease of 10–15% in LVEF	3.2% (95% CI: 1.9–5.4%)
Cameron et al. (2017) [21]	5102	Node positive or high-risk node negative breast cancer	52 weeks or 104 weeks	94% received an anthracycline-based chemotherapy prior	LVEF drop of at least 10 percentage points from baseline and to an absolute LVEF below 50% or cardiac death.	7.3% in the 2-years trastuzumab group, 4.4% in the 1-year trastuzumab group, and 0.9% in the observation group.

Table 2:

Incidence of anthracycline-induced Cardiotoxicity in Several Studies.

Study	Anthracycline	Number of Patients	Type of Breast Cancer	Cumulative Dose Administered	Definition of Cardiomyopathy	Incidence of anthracycline-mediated Cardiotoxicity
Jensen et al. (2002)[39]	epirubicin	120	recurrent metastatic breast cancer	1000 mg/m² epirubicin,	Clinical symptoms of CHF or decline in LVEF	15% of the patients experienced a 25% relative reduction in LVEF 3 weeks after terminating therapy, increasing to 59% after 3 years
Swain et al. (2003) [22]	doxorubicin	630	breast carcinoma and small cell lung carcinoma	400–700 mg/m²	Drop 20% in LVEF from baseline, drop 10% in LVEF from baseline and to below the institution's LLN, or clinical symptoms of CHF	5% at 400 mg/m2, 16% at 500, 26% at a dose of 550 mg/m2, 48% at a dose of 700 mg/m2,
Azambuja et al. (2009)[40]	Epirubicin	777	Node-Positive Breast Cancer	EC: epirubicin 60 mg/m² with cyclophosphamide or HEC: epirubicin 100 mg/m² with cyclophosphamide	Drop of LVEF <50% or clinical symptoms of CHF	EC, n = .64% (5/777); HEC, n = 1.4% (11/777)
Ryberg et al. (2008)[41]	Epirubicin	1097	metastatic breast cancer	cumulative dose of 1000 mg/m²	Clinical symptoms of CHF or decline in LVEF > 15% from its initial value	11.4% developed CHF