JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. ■, NO. ■, 2016

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacep.2016.08.009

Burden of Cardiac Arrhythmias in Patients With Anthracycline-Related Cardiomyopathy

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ABSTRACT

OBJECTIVES The objective of this study was to determine the incidence of arrhythmias and device (internal cardiac defibrillator/cardiac resynchronization therapy defibrillator) therapies in patients with a diagnosis of cardiomyopathy and anthracycline exposure.

BACKGROUND The burden of arrhythmias in adult cancer survivors with anthracycline-related cardiomyopathy has not been studied, but might have important implications for clinical management and outcomes.

METHODS Retrospective cohort study of all patients with left ventricular dysfunction (LVD) who underwent internal cardiac defibrillator/cardiac resynchronization therapy defibrillator implantation at the Mayo Clinic from 1990 to 2012. Ninety-five patients were cancer survivors (on average, 5 years), 23 of which had anthracycline-related cardiomyopathy (CA-ACM) and 72 of which had non–anthracycline-related cardiomyopathy (CA-NACM). A second control group of 68 noncancer patients with ischemic heart disease-related LVD or dilated cardiomyopathy (ischemic heart disease [IHD]/DCM) was age- and gender-matched to patients with CA-ACM. All patients were followed for arrhythmias and appropriate ICD therapies, total mortality, heart transplantation, and left ventricular ejection fraction.

RESULTS More than 5.5 ± 3.0 years after device implantation, nonsustained ventricular tachycardia was the most common arrhythmia in patients with CA-ACM followed by atrial fibrillation and sustained ventricular tachycardia or fibrillation (73.9%, 56.6%, and 30.4%, respectively), which was not significantly different from CA-NACM and IHD/DCM. The 5-year rate of ICD therapies was 19.9% in the CA-ACM group versus 22.1% in the CA-NACM group and 32.6% in the IHD/DCM group (p = NS for both). Device therapy–free, heart transplantation–free, and/or overall survival as well as cardiac function dynamics over time were not different in patients with CA-ACM than in patients with CA-NACM and IHD/DCM.

CONCLUSIONS This study indicates that the burden of arrhythmia in patients with anthracycline-related cardiomyopathy is not different from cancer and non-cancer patients with IHD-related LVD or DCM. (J Am Coll Cardiol EP 2016;■:■–■) © 2016 by the American College of Cardiology Foundation.

Cancer therapy-induced cardiomyopathy has gained increasing importance with the remarkable improvement in overall cancer survival during the past decade (1,2). The most concerning subtype relates to anthracyclines because it can develop late after completion of treatment and can take a relentless course (3,4). In fact, anthracycline-related cardiomyopathy may carry one of the worst prognoses of all types of cardiomyopathy (5). Whether this relates to progressive ventricular dysfunction or a higher incidence of malignant arrhythmias remains unknown.

A pro-arrhythmic effect of anthracyclines was noted in cultured cardiomyocytes and rodent models (6–8). Similarly, electrocardiographic abnormalities and arrhythmias are mainly observed in patients

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Manuscript received May 31, 2016; revised manuscript received July 11, 2016, accepted August 18, 2016.

ABBREVIATIONS AND ACRONYMS

CA-ACM = anthracycline-related cardiomyopathy

CA-NACM = non-anthracycline-related cardiomyopathy

CRT-D = cardiac resynchronization therapy defibrillator

DCM = dilated cardiomyopathy

ICD = internal cardiac defibrillator

IHD = ischemic heart disease

LVD = left ventricular dysfunction

LVEF = left ventricular ejection fraction

VF = ventricular fibrillation

VT = ventricular tachycardia

during or shortly after the acute phase of anthracycline treatment (9–11). On the contrary, there have been only a few studies noting QT dispersion, sudden cardiac deaths, and cardiac arrhythmias in childhood cancer survivors (3,12–15). The adult cancer population remains even less well-characterized, and there has not been a comprehensive analysis of arrhythmias in any cohort with anthracycline-related cardiomyopathy. Thus, there is uncertainty regarding the burden of arrhythmias and need for device therapy (i.e., internal cardiac defibrillator [ICD]/cardiac resynchronization therapy defibrillator [CRT-D]) in cancer survivors with left ventricular systolic dysfunction (LVD) (16,17). A very recent study (18) indicated that cancer patients may have a higher burden of ventricular arrhythmias with an increase noted after diagnosis.

The current study was designed to determine the burden of arrhythmias in long-term adult cancer survivors with anthracycline-related cardiomyopathy who underwent ICD or CRT-D implantation at the Mayo Clinic, Rochester, in comparison with cancer survivors who developed non-anthracycline-related cardiomyopathy and noncancer patients with ischemic heart disease (IHD)-related LVD or dilated cardiomyopathy (DCM) and to corroborate these data with clinical outcomes and cardiac function dynamics.

METHODS

PATIENT POPULATION. The current retrospective cohort study was approved by the Mayo Clinic institutional review board and included only patients who provided research authorization. The study was based on the centralized Mayo Clinic ICD registry, which prospectively collects clinical information, device characteristics, and postimplantation arrhythmic events and therapy delivery pertaining to all patients implanted at or followed by Mayo Clinic Heart Rhythm Services. Data are collected at all Mayo clinic visits; device interrogations during outpatient visits, emergency room visits and hospitalizations; and remote device interrogations. For this comparative retrospective cohort analysis, all patients enrolled in the Mayo Clinic ICD registry from 1990 until the end of 2012 were cross-matched with the Mayo Clinic cancer database to identify patients with a history of cancer, chemotherapy, new LVD (defined as left ventricular ejection fraction [LVEF] ≤50%), and presence of an ICD. Patients not meeting these criteria or with a lack of device interrogations on file or lack of follow-up evaluations were excluded. Medical records of patients meeting the inclusion criteria were thoroughly reviewed to extract patients characteristics, including age, gender, preexisting cardiovascular risk factors; echocardiographic parameters, including LVEF by use of modified biplane Simpson method, end-diastolic diameter, end-systolic diameter, right ventricular systolic pressure; cancer type and stage, chemotherapy regimen, dose and duration of agent; and indication for ICD implantation. Number of arrhythmic events and number and type of ICD therapies were followed by review of all available device interrogation reports. Vital status and death date information were queried using an institutionally approved fee-based Internet research and location service (Accurint, LexisNexis, Irvine, California). Heart transplant status was obtained from the comprehensive Mayo Clinic integrated medical record. Cardiac function (LVEF) dynamics were followed over time by review of serial echocardiograms.

All patients with a history of cancer, cardiomyopathy, and ICD/CRT-D implantation identified were further designated as anthracycline exposed (CA-ACM, n = 23) or anthracycline non-exposed (CA-NACM, n = 72). For a second comparison analysis, patients with CA-ACM were matched 3:1 to noncancer patients with IHD-related LVD (n = 23) or DCM (n = 45) (IHD/DCM, n = 68) from the Mayo ICD database based on age and gender. The diagnostic classification of cardiomyopathy was based on professional societal recommendations (19,20). IHD-related LVD was diagnosed based on a history of myocardial infarction, coronary revascularization, or objective evidence of coronary artery disease by stress testing and/or coronary angiography (21).

DEFINITION OF ARRHYTHMIC AND CARDIAC EVENTS. Data from ICD interrogations were reviewed by electrophysiologists or specially trained electrophysiology nurses. ICD therapy (antitachycardia pacing or shock) was considered appropriate if it were preceded by ventricular tachycardia (VT) or ventricular fibrillation (VF) documented by stored episode data. Therapy was considered inappropriate if preceded by heart rates exceeding the programmed threshold, supraventricular or atrial arrhythmias, or device malfunction. ICD programming was determined by the implanting clinician.

STATISTICAL ANALYSIS. Continuous data were presented as the mean ± SD. Categorical data were presented as frequency (percentage). Two-sample *t* tests were used to compare continuous variables.