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Prevalence of Anthracycline Induced Cardiomyopathy amongst Cancer Patients Treated at Tertiary Teaching and Refferal Hospital in Nairobi Kenya

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Abstract

Background: Cardiovascular complication is a major consequence of cancer treatment. Anthracycline induced cardiomyopathy is a known cause of long-term morbidity and mortality among cancer survivors. The burden of this complication is unknown in our setting

Objective: This study aimed to determine the prevalence of cardiomyopathy in ambulatory patients treated with anthracycline (Ac) containing chemotherapy at Kenyatta National Hospital (KNH) as measured by two-dimensional (2D) echocardiography (ECHO).

Study design: A hospital-based inpatient/outpatient cross sectional, descriptive study.

Study setting: This study was carried out in various outpatient clinics and oncology wards in Kenyatta National Hospital. These included the adult hematooncology clinic 23, Ground floor C (GF-C), Ward 8C and Ground floor D (GF-D)

Subjects: The study population included patients who have been exposed to Ac. The minimum Ac dose was 200mg/m^2. A total of 129 patients with various types of cancers were sampled consecutively over a period of 3 months. Eligible patients underwent a 2D ECHO and left ventricular ejection fraction (LVEF) was assessed.

Results: Patients between the ages of 15 and 75 participated in the study, the mean age was 45.6 years, with the female to male ratio of 4.3:1. Majority of the patients had breast cancer (67.4%) and the treatment regimen in over 65% of them was doxorubicin and cyclophospomide (AC). The mean cumulative dose was 236mg/m^2. All patients recruited had received a cumulative dose of between 200 - 450mg/m^2. Most of the patients (63%) had completed Ac within one year of their cardiac evaluation. Only 14.0 % of the patients had a pretreatment ECHO. The overall prevalence of LV systolic dysfunction detected by echocardiography was 3.1% (95% CI 0.9– 7.8). The study was not powered to make associations with age, sex and cumulative dose and presence of cardiomyopathy.

Conclusions: The study demonstrates a prevalence of 3.1% cardiomyopathy among cancer patients treated with anthracyclines. This figure is comparable to similar studies done. The prevalence described in most studies ranges from between 1% to 20.5%.

Introduction

Cancer is the second leading cause of death worldwide and in 2015 8.8 million deaths were attributed to it. Approximately 70% of these deaths occurred in middle- and low-income countries. By 2030, projected deaths from cancer will reach about 13 million. In Kenya cancer causes 7% of the total national mortality each year. Recent data in 2013 showed that cancer is the third leading cause of death after infectious and cardiovascular diseases [(1)]

Improvement in cancer survival as evidenced by a reduction in mortality rates from cancer over the past 30 years is mainly due to early detection, improved surgical expertise and advances in cancer treatment [(2) (3) (4)]. This can be linked to other organ damage, including a negative effect on the cardiovascular system [(5)]. In the west, the second leading cause of long-term morbidity and mortality among cancer survivors is cardiovascular diseases (CVD) [(6) (7)]

Anthracyclines are amongst the most widely used chemotherapeutic drugs due to their broad range of therapeutic activity**.** Unique to this class of drugs is their dose limiting cardiotoxicity and clinical cardiomyopathy which may be irreversible in the long term. Literature indicates that more than one-half of all patients treated with Ac will have some degree of cardiac damage years after exposure to chemotherapy with some developing overt congestive heart failure (CHF) [(8)]. It is likely that the overall incidence of this complication is underestimated [(9)]. Anthracycline induced cardiomyopathy (AIC) worsens the cardiac health of cancer patients and also limits their treatment options[(10) (11)]. They may have cancer with a poor prognosis and require adjunctive treatment for relapse of disease after a first line of chemotherapy in more than 50% of cases within 5 years [(12) (13)]. Their options for use of Ac at this point will be limited.

Ac have been in clinical use for more than 40 years' and rank amongst the most effective cytotoxics still available. They are among the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. They are relatively easy to combine with other agents and thus frequently used in combination chemotherapy agents.

Materials And Methods

Study design: This was a cross sectional descriptive study.

Study setting: Kenyatta National Hospital

Study population*:* Patients diagnosed with cancer with history of exposure to any Ac on follow up at KNH. Ac exposure was defined as a cumulative dose of at least 200 mg/m^2**.** AIC was defined as LVEF of < 50%

Inclusion and Exclusion criteria: Patients must have been aged 13 years and above and have given an informed written assent and/or consent. Patients known to have heart disease, diabetes, hypertension, history of radiotherapy to the mediastinum or chest and with incomplete treatment history and records were excluded.

Sample size*:* The minimum sample size calculated for prevalence studies (Daniel, 1999) was 128 patients.

Data collection: Patients were recruited from oncology outpatient clinics and inpatient wards. A structured data proforma was used to capture data on the demographics, history of the disease and treatment. A 2D ECHO was performed by a study dedicated echo sonographer on eligible candidates and LVEF calculated. The cine loop and still images were reviewed by two autonomous cardiologists. Data was coded, entered and validated. It was checked for any wrong entry, double-entered and corrected.

Data analysis and statistical methods: Data was coded, entered and managed in a Microsoft Access 2013 database. The data was exported to SPSS version 21.0 for statistical analysis. Data was summarized into proportions for categorical variables, and into means (SD) or medians for the continuous variables.

Funding: This study was funded solely by the principle investigator and was undertaken after approval by local ethics and review board.

Results

Between 29th January to 27th April 2018, 162 patients being managed for various cancers in KNH were screened for study eligibility. They all underwent a targeted history and examination and were booked for ECHO. 129 subjects had ECHO studies done and were included in the analysis

Demographics

Cancer patients between the ages of 15 and 75 years participated in the study. The mean age was 45.6 years. Majority of the subjects were females (81.4%) as compared to males (18.6%).

Most of the study participants had attained post primary level education (45.7%), majority were married (62%) and a significant proportion were unemployed (79.1%). Only 1 patient reported use of tobacco and heavy alcohol consumption as shown in table 1

Table 1: Demographic characteristics

Variable	Frequency (%)
Mean age (SD)	45.6 (16.2)
Age categories	
<18 years	8 (6.2)
18-39 years	33 (25.6)
40-69 years	79 (61.2)

> 70 years	9 (7.0)
Sex	
Female	105 (81.4)
Male	24 (18.6)
Marital status	
Married	80 (62.0)
Single	33 (25.6)
Widowed	13 (10.1)
Divorced	3 (2.3)
Level of formal education	
Tertiary	2 (1.6)
Primary	59 (45.7)
Secondary	47 (36.4)
College	14 (10.9)
None	7 (5.4)
Occupation	
Unemployed	102 (79.1)
Employed	16 (12.4)
Self employed	8 (6.2)
Retired	3 (2.3)
Smoking	
Yes	1 (0.8)
No	128 (99.2)
Alcohol use	
Yes	1 (0.8)
No	128 (99.2)

Clinical characteristics

Most of the patients had breast cancer (67.4%) and lymphoma (17.8%) as depicted in table 2. Other types of cancers included were Kaposi sarcoma, rhabdomyosarcoma, osteogenic sarcoma, acute leukemia and gastric adenocarcinoma. Anthracycline regimens consisted of doxorubicin in most patients and epirubicin in a few of them. The most commonly used treatment regimen was AC (66.7%) in breast cancer patients then CHOP (16.3%) in Non-Hodgkin's lymphoma. Other regimens (10.1%) included ABV for Kaposi sarcoma, VACCIS and IVADO for rhabdomyosarcoma, doxorubicin/ cisplatin for osteogenic sarcoma, hyperCVAD for acute leukemia and EOX for gastric adenocarcinoma. Patients were divided according to the cumulative doses. All patients recruited had received a cumulative dose of 200 - 450mg/$m^{2.}$ The mean cumulative dose was 236mg/m^2 with an interquartile range of 200mg/m^2. Majority of the patients (63%) had completed anthracyclines within one year of their cardiac evaluation. 56% were still on treatment with Ac while only 0.8% (n = 1) had Ac exposure 5 years prior to cardiac evaluation. Only 14.0 % of the patients had a pretreatment ECHO as shown in Table 2

Table 2: Clinical Characteristics

Variable	**Frequency (%)**
Type of cancer	
Breast	87 (67.4)
Lymphoma	23 (17.8)
Others	19 (14.7)
Treatment regimen	
AC	86 (66.7)
FAC	1 (0.8)
CHOP	21 (16.3)
ABVD	8 (6.3)
Others	13 (10.1)
Cumulative dose of anthracycline	

received 200-450mg/m^2. Mean (SD)	129 (100) 236 (73.8)
Duration since completion of anthracycline Still on treatment 0-12 months 13-60 months 61-120 months	 56 (43.8) 63 (49.6) 8 (6.2) 1 (0.8)
Pretreatment ECHO Present Absent Missing	 18 (14.0) 107 (82.2) 5 (3.9)

AC: Doxorubicin and Cyclophosphamide, FAC: 5 FU, Doxorubicin, Cyclophosphamide, CHOP: Cyclophosphamide, Doxorubicin, Vincristine, Prednisone, ABVD: Doxorubicin, Bleomycin, Vincristine, Darcabazine

Prevalence of LV systolic dysfunction

The overall prevalence of LV systolic dysfunction detected by echocardiography was 3.1% (CI 0.9– 7.8) shown in figure 2.

Among these patients, only one had developed heart failure. Echocardiography confirmed the decreased ventricular function with global hypokinesia and decreased LVEF (39%). Subclinical cardiomyopathy was found in 2%. (n=3). They had left ventricular dysfunction with decreased EF (< 50%) with no clinical signs of congestive heart failure.

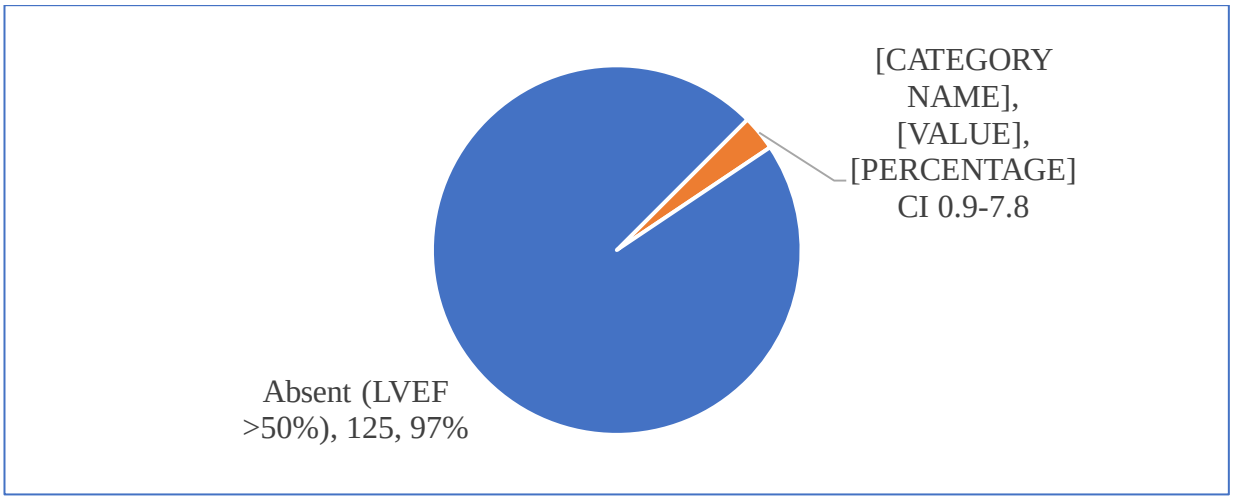

Figure 1: Prevalence of LV systolic dysfunction

Associations

The mean age at diagnosis was comparable between those who had cardiomyopathy and those who did not have any cardiomyopathy at 47.7 and 45.6 respectively. This explorative study was not powered to make any associations between age, sex, cumulative dose and other variables in the study with

development of cardiomyopathy due to a small sample size as depicted in table 4.

Three females were found to have LV systolic dysfunction compared one male. However this was not statistically significant (p = 0.566)

Table 3: Correlations with LV systolic dysfunction

Variable	LV systolic dysfunction n (%)	Normal patients n (%)	OR (95% CI)	P value
Mean age (SD)	47.7 (19.1)	45.6 (16.2)	-	0.761
Age categories				
<18 years	0	8 (100.0)	-	0.999
18-39 years	1 (30.0)	32 (97.0)	0.3 (0-4.4)	0.345
40-69 years	2 (2.5)	77 (97.5)	0.2 (0-2.6)	0.220
> 70 years	1 (11.1)	8 (88.9)	1.0	
Sex				
Female	3 (2.9)	102 (97.1)	0.7 (0.1-6.8)	0.566
Male	1 (4.2)	23 (95.8)	1.0	
Cumulative dose	200 (200-450)	200 (200-400)	-	0.446
Duration since completion of anthracycline				
Still on treatment	1 (1.8)	55 (98.2)	1.0	0.643
0-12 months	2 (3.1)	62 (96.9)	1.8 (0.2-20.1)	0.161
13-60 months	1 (12.5)	7 (87.5)	7.9(0.4-140.1)	1.000
61-120 months	0	1 (100.0)		
Type of cancer				
Breast	2 (2.30)	85 (97.7)	1.0	
Lymphoma	2 (9.1)	21 (91.3)	4.1 (0.5-30.4)	0.174
Others	0	19 (100.0)	-	0.998
Treatment regimen				
AC	1 (1.2)	83 (98.8)	1.0	
FAC	1 (100.0)	0	-	0.999
CHOP	2 (9.5)	19 (90.5)	9.0 (0.8-103.8)	0.080
ABVD	0	8 (100.0)	-	0.999
Others	0	13 (100.0)	-	0.999

Discussion

Cancer which is a big epidemic in our population and the world at large is still on the rise. The harmful side effects of the various chemotherapeutic agents versus their useful anticancer effects present, in management, a challenge. Long-term survivors, tend to have possible late effects of treatment and their consequences for the quality of life and mortality are a major concern.

Among the 129 assessable patients, 3.1% (95% CI 0.9– 7.8) had cardiomyopathy described as LVEF of less than 50%. These patients had no prior cardiac comorbidity. Only one patient had clinical symptoms of CHF requiring treatment. All the patients with cardiomyopathy had received a total dose of doxorubicin between 200-400mg/m^2, which represents the usual treatment doses for the various types of cancer. The prevalence described in most studies ranges from between 1% to 20.5%. This is dependent on the study design, study tool used and the type of population studied i.e. children versus adults. This figure is comparable to a study done in Kenya by Othieno-Abinya et al. It was a retrospective analysis of 212 patients seen in three cancer facilities in Nairobi. The study assessed the non-hematopoietic complications of cancer chemotherapy with comparison between anthracyclines versus taxanes. Clinical cardiotoxicity was seen in up to 4.6% of patients receiving doxorubicin [(14)]. In 2004, Hequet O et al analyzed 141 lymphoma patients. Clinical cardiomyopathy (EF<30%) was 0.7%. Subclinical cardiomyopathy i.e. FS <25% was 27.6%. Asymptomatic patients based on two of three variables i.e. FS < 28%, EF < 50%, or wall motion abnormality was 20.5% [(15)] In 2016, Daniel A. Mulrooney *et al* conducted a cross sectional evaluation of 1,853 adult survivors of

childhood cancers, who had received Ac using a 2D Doppler ultrasound echocardiography. Cardiomyopathy, defined by LVEF of less than 50% was present in 7.4% [16].

Extremes of age > 70 years and < 10 years has been shown to increase the risk of cardiotoxicity. The median age of our patients was relatively younger (45.6) compared to similar studies done. Increase in age did not seem to be an independent risk factor in this study however there was no statistical correlation (p = 0.220). In 2003, Sandra M swain *et al* showed 32/630 patients had a diagnosis of CHF. Age > 65 years was found to be an important risk factor after dose of 400 mg/m^2 for developing cardiomyopathy [17]

Female sex is another a risk factor for cardiomyopathy. In this study, cardiomyopathy was detected in both females (n=3) and males (n=1). The study however included more women than men because most participants recruited had breast cancer, the most prevalent cancer in our population for women. A study by Steven E. Lipshultz *et al* assessed late cardiotoxic risk factors i.e. female and cumulative dose, for doxorubicin therapy for 120 pediatric cancer patients who had been treated with cumulative doses of 244 to 550 mg/m^2. Females had a significantly greater reduction in LV dysfunction with a P<0.002 [18]

The cumulative dose of anthracyclines is a major risk factor for developing cardiomyopathy. None of the patients in the study had received a total cumulative dose of doxorubicin more than 450 mg/m^2. The recommended life time cumulative dose for doxorubicin is 400-550 mg/m^2 and for epirubicin is 800-1000 mg/m^2. The cumulative dose range was very narrow and therefore no correlation with risk of developing cardiomyopathy was found. Total cumulative dosage has been found regularly as the major risk factor for development of cardiac dysfunction in previous studies in adults. Myocyte damage has been found in endomyocardial biopsy specimens from patients who had received minimal doses of 240 mg/m^2 of doxorubicin [19]. Few studies reported abnormalities in left ventricular diastolic function or in systolic function independently of the cumulative doses of anthracycline.

Late cardiotoxic effects manifest themselves after several years (median of 7 years after treatment) [20][21].Longer duration since completion of anthracyclines seemingly increased the risk of developing cardiomyopathy (OR 7.9 for 13 to 60 months). However other studies found that a final LVEF of <50% occurred almost exclusively (98% of cases) within the first year after completing anthracycline treatment. Late reductions in LVEF were observed in only 5 (2%) patients and occurred >5.5 years after chemotherapy [22]

Conclusion

The study demonstrates a prevalence of 3.1% cardiomyopathy among cancer patients treated with anthracyclines. Of the 129 participants, only 1 developed congestive heart failure. This figure is comparable to similar studies done. The prevalence described in most studies ranges from between 1% to 20.5%.

Recommendation

We recommend a thorough cardiovascular examination prior to starting anthracyclines and to individualize cardiac evaluation using an ECHO based on patients 'risk factors.

Future studies could look into ways of identifying early cardiotoxicity e.g. using cardiac biomarkers

Limitations

This study was limited by using a small number of patients and hence it was not powered to make associations between anthracycline induced cardiomyopathy with demographics and clinical variables.

The method used for estimating LV systolic function may have overestimated or underestimated LVEF because it has geometric assumptions of LV cavity.

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