PREVALENCE OF ANTHRACYCLINE INDUCED CARDIOMYOPATHY AMONGST CANCER PATIENTS TREATED AT KENYATTA NATIONAL HOSPITAL

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I declare that this dissertation is my original work and has not been published or presented for a degree in any other university.

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LIST OF ABBREVIATIONS

ABV-	Adriamycin, Bleomycin, Vincristine
Ac-	Anthracyclines
AC-	Doxorubicin and Cyclophosphamide
ACC-	American College of Cardiology
AIC-	Anthracycline Induced Cardiomyopathy
AHA-	American Heart Association
ALL-	Acute lymphoblastic leukemia
ATP-	Adenosine triphosphate
CHOP-	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CMR-	Cardiac Magnetic resonance
CRC-	Chemotherapy-Related Cardiotoxicity
CHF-	Congestive heart failure
CVD-	Cardiovascular diseases
DT-	Deceleration time
DNA-	Deoxyribonucleic acid
E/A ratio-	Early peak flow velocity to atrial peak flow velocity ratio
ECHO-	Echocardiography
2D ECHO-	Two dimensional echocardiography
3D ECHO-	Three dimensional echocardiography
EF-	Ejection Fraction
ERNA-	Equilibrium Radionuclide Angiography
EOX-	Epirubicin, Oxaliplatin

5-FU-	Fluorouracil
hyperCVAD-	hyper fractionated Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone, Methotrexate, Cytarabine
^{123}I-BMIPP-	^{123}I-15-(p-iodophenyl)-3-(r,s)-methylpentadecanoic acid
^{123}I-MIBG-	^{123}I-metaiodobenzylguanidin
^{111}In-Tz-	^{111}IN-trastuzumab SPECT
IQR-	Interquartile range
IVADo-	Ifosfomide, Vincristine, Actinomycin D, Doxorubicin
IVRT-	Impaired isovolumetric relaxation time
KNH-	Kenyatta National Hospital
LV-	Left Ventricle
LVD-	Left ventricle dysfunction
LVEF-	Left Ventricular Ejection Fraction
MC-1-	Mitochondria Complex 1
NADH-	Nicotinamide adenine dinucleotide
RNA-	Ribonucleic acid
ROS-	Reactive Oxygen Species
RWMA-	Regional Wall Motion Abnormalities
SD-	Standard Deviation
SPECT-	Single photon emission computed tomography
SPSS-	Statistical Package for Social Sciences
^{99M}TC gbps-	^{99m}TC gated blood-pool
VACCIS-	Vincristine, Adriamycin, Cyclophosphamide, Cisplatin

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 patients withcancer surviving chemotherapy. The burden of this disease in our population has not been well established and there is paucity of published data regarding the prevalence in the African setting.

Objectives

This study aimed to determine the prevalence of cardiomyopathy in patients at Kenyatta National Hospital who have been treated with anthracycline chemotherapy (Ac) and are on follow up by using a two dimensional (2D) ECHO.

Methodology

It was a cross-sectional, descriptive study carried out at Kenyatta National Hospital. The study population included patients who had 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 ECHOand 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%) andthe 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 between200 - 450mg/m^2. Most of the patients (63%) had completed Ac withinone 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.

Conclusion

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%.

1.0 CHAPTER ONE: INTRODUCTION

1.1 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 causes7% of the total national mortality each year. Recent data in 2013 showed that cancer is the third leading cause of death after infectious and cardiovasculardiseases[(1)]

Improvement in cancer survival as evidenced by a reduction in mortality rates from cancer over the past 30 years is mainlydue to early detection, improved surgical expertise and advances in cancer treatment[(2)(3)(4)].This can be linked to other organ damage, including anegative 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 ahealth system. They are relatively easy to combine with other agents and thus frequently used in combination chemotherapy agents.

2.0 CHAPTER TWO: LITERATURE REVIEW

2.1 Anthracyclines in Medicine

Ac are naturally occurring products derived from actinobacteria, *Streptomyces peuctius var caesius.* Streptomyces is made up of the largest genus of actinobacteria and of the family Streptomycetaceae with over 500 species described. They are gram-positive organisms predominantly found in soil and decaying vegetation. They are responsible for the production of over a half of the antibiotics in clinical use with AC being one of them. Other antibiotics include neomycin, chloramphenicol, tetracycline and fosfomycin among others [(14)]. In the early 1960s in Italy, Dr. Federico Arcomane first isolated daunorubicin. In 1969 doxorubicin, the hydroxylated derivative of daunorubicin, was isolated [(15)]. Since then several related compounds have been isolated but only few of them are in clinical use. Ac are an essential group of antitumor drugs greatly used in treatment of a variety of hematological malignancies as well as solid tumors in both pediatric and adult groups. In the recent decades, there have been multiple attempts to identify novel Ac that are superior to doxorubicin or daunorubicin in terms of efficacy and cardiac tolerability [(16)]. The search for a "better anthracycline" has resulted to the numerous chemical modification to create various analogs. However only a few of these analogs have reached clinical approval.

Doxorubicin is used mainly in breast cancer, aggressive lymphomas, soft tissue sarcomas, and childhood solid tumors [(17)] . Daunorubicin is used to treat acute leukemia's, and its derivative, idararubicin is used in non-Hodgkin's lymphomas, breast cancer and multiple myeloma [(17)]. Epirubicin is used in the treatment various cancers including gastric, breast, carcinoid, endometrial, lung, ovarian, esophageal and prostate as well as soft tissue sarcomas [(17)]. Pirarubicin, a 4-tetrahydropyranyl doxorubicin, is used in metastatic breast cancer [(18)]. Aclarubicin, a trisaccharide anthracycline, is active in adult patients with acute myeloblastic leukemia[(18)]. Mitoxantrone, an anthracenedione is a synthetic compound that has structural and functional resemblance to anthracyclines. It is active in acute leukemia's, androgen-independent prostate and breast cancer [(18)]. Nemorubicin is used for treatment of hepatocellular carcinoma. Pixantrone is used in salvage treatment for non-Hodgkin's lymphomas and sabarubicin is used for hormone refractory metastatic prostate cancer, platinum- or taxanes-resistant ovarian cancer and non-small cell lung cancer. Valrubicin is used for the topical treatment of bladder cancer [(19)]

2.2 Antitumor activity of Anthracyclines

While doxorubicin (DOX) and daunorubicin (DNR) are naturally occurring products, the other Ac are a product of the chain modification. They are planar four ring Ac molecules linked to the amino sugar daunosamine. DOX and DNR share the two moieties, aglyconic and sugar. DNR terminates with a methyl group while DOX terminates with a primary alcohol[20].

There is no single mechanism by which one can base the antitumor activity of Ac. The major mechanism of action is through free radical formation. There are two possible pathways that have been recognized through which Ac bring this about. One involves the one-electron reduction of the drug which occurs in a complex Flavin-centered, NADPH-dependent reaction. The other involves binding of ferric iron. The bound ferric iron is reduced to ferrous iron which in turn can react with free oxygen to produce radicals of oxygen species (ROS) such as hydroxyl radical, superoxide and hydrogen peroxide. DOX has a ketol chain and therefore in a position to reduce iron spontaneously as opposed to DNR which has a ketone chain. DNR forms a complex with iron which rapidly reacts with hydrogen peroxide [20]

They also work by intercalation of DNA. In order for any cell to divide, the DNA in the nucleus of the cell must be unwound and then duplicated a process called transcription. Ac bind to parts of the unraveled strand of nuclear DNA preventing replication of the cell. It binds to mitochondrial DNA, hindering basic cellular functions [21][22]. It also binds to cell membrane, alter membrane integrity and cause cell death.

The other major mechanism of action that is more recent is inhibition of topoisomerase II (Topo II), an enzyme that unwinds the DNA for replication. This inhibition leaves DNA damage at even low concentrations, which accumulate after high, prolonged, repeated exposures leading to both its mutagenic and cardiotoxic effects [18]

2.3 Cardiotoxicity

The number of long-term cancer survivors is on the rise and thus cardio-oncology is a rapidly evolving area that is gaining interest. The presence of AIC restricts the treatment options to chemotherapy drugs that may be deemed less efficacious.[23][24].Compared with other more common forms of cardiomyopathy, AIC has been associated with especially poor prognosis with a 2-year mortality rate of up to 60%. It is also believed that it could be refractory to conventional therapy[25]

Cardiotoxicity can occur at any point of therapy with Ac. Acute cardiotoxicity may occur immediately to weeks after treatment. It may present as heart block (second degree mobitz type II and complete heart block),pericarditis-myocarditis syndrome, arrhythmias (supraventricular and ventricular), ST segment and T-wave changes, acute-onset heart failure and increase in brain natriuretic peptide[26][27][28][29]. Sinus tachycardia is the most common presentation. Incidence of acute cardiotoxicity is estimated at 11% [30][31]and usually resolves once therapy is discontinued. It is still unclear if acute cardiotoxicity progresses to development of delayed cardiotoxicity.

Chronic cardiotoxicity presents as LV dysfunction, QT dispersion and congestive heart failure which may be fatal. The estimated incidence of chronic doxorubicin cardiotoxicity is much lower at about 1.7% [32].The early onset type occurs within the first year after treatment. Appearance of symptoms of heart failure after the last dose peaks at about 3 months and these patients have a high mortality. Late onset chronic cardiotoxicity develops one year to decades following chemotherapy after a prolonged asymptomatic period with heart failure. This can be a major worry in breast cancer patients where Acare used in adjuvant or curative regimens. Cardiac monitoring in patients treated with Ac needs to be lifelong given the potential for late onset cardiotoxicity [33]

Early detection of cardiotoxicity and intervention is important to prevent cardiac decompensation. Gold standard evaluation practice is use of non-invasive conventional transthoracic echocardiography with evaluation of left ventricular ejection fraction (LVEF). A systematic review, by Alberto Dolci, Cardinale D et al concluded that cardiomyopathy caused by Ac use is diagnostically estimated by LVEF assessment using a 2D Echo [34]

2.4 Mechanism of cardiotoxicity

Traditionally chemotherapy cardiotoxicity has been described as type I and II. In type I cardiotoxicity there is death of cardio-myocyte either through apoptosis or necrosis and hence considered irreversible. Ac are thought to cause type I cardiotoxicity through at least two pathways: non-enzymatic and enzymatic[35]. Type II cardiotoxicity is caused by cardio myocyteimpairment and thus thought to be reversible[35]. However, studies on the exact mechanisms responsible for the cardiotoxicity of Ac have remained without a unifying explanation.

The enzymatic pathway involves Ac interaction with mitochondrial respiratory chain (MRC) and cytochrome enzymes. These drugs have an affinity for cardiolipin, a phospholipid located

in the inner mitochondrial membrane of the MRC [36]. Within the cardio-myocyte, there is reduction of DOX by NADH dehydrogenase in the mitochondria complex 1(MC-1) that catalyze the addition of an electron to the quinone moiety. This in turn leads to formation of a radical that reacts with free oxygen to form ROS including superoxides [37] hydrogen peroxide and hydroxyl radical [38]. This is called redox recycling. In the non-enzymatic pathway, these drugs may react directly with ferric iron leading to alcohol adducts and free radicals in what is referred to as the fenton reaction[39][40]. Cardio-myocytes are prone to this oxidative stress most likely due to their reliance on oxidative metabolism as well as less potent anti-oxidant mechanisms.

The downstream consequences are mitochondrial DNA damage and oxidative modification of proteins, lipids, and genomes[41]. Uncoupling of the electron transport chain with impairment of oxidative phosphorylation and ATP synthesis contributes further to mitochondrial dysfunction and damage [42][43]

There exists alternative proposed mechanisms that may contribute to cardiac dysfunction. One proposes that Ac disrupt DNA by topoisomerase II inhibition. Poisoning this enzyme will induce DNA damage and death and as a sequale impair its repair [44]. This will eventually cause growth arrest and apoptosis. The other mechanism involves intercalation into DNA due to their planar structure. This prevents further DNA and RNA synthesis leading to myocyte death[44].

However there is uncertainty on the effect of oxidative stress in cardiotoxicity due to lack of protection provided by antioxidants like N-acetyl cysteine and Vitamin E in clinical trials [45]. Carvedilol has antioxidant properties which is attributed to its protective effects. [46]

2.5 Epidemiology of Anthracycline Cardiomyopathy

Anthracycline induced cardiomyopathy was first described in 1971 in 67 patients treated with adriamycin for a variety of tumors.Five patients developed CHF[47]

In 2016, Daniel A. Mulrooney*et al* conducted a cross sectional study in St. Jude Children's Hospital in Memphis, Tennessee. They evaluated 1,853 adult survivors of childhood cancers, who had received anthracycline therapy (Ac) using a two dimensional (2D) Doppler ultrasound echocardiography. Cardiomyopathy, defined by LVEF of less than 50% was present in 7.4% [48].

In 2011, Els Vandecruys*et al* from Belgium , carried out a study of seventy-seven acute lymphoblastic leukemia (ALL) survivors who had a total cumulative dose of < 250mg/m^2 of AC ten years' prior. The control group included 30 healthy volunteers who were matched for certain characteristics. A complete echocardiographic study was performed on each cohorts. Subclinical cardiac abnormalities evidenced by abnormal impaired isovolumetric relaxation time (IVRT) was found in 30% of the patients as compared to normal range in the controls [(49)]

A total of 534 breast cancer survivorstreated with a combination of cyclophosphamide, doxorubicin and fluorouracil were studied. The incidence of CHFwas found to be 1% to 4% in those treated with a cumulative doxorubicin dose of 300mg/m^2 to 450mg/m^2respectively. A multicenter study ofmore than 3000 breast cancer patients treated with cumulative doxorubicin dose of between 240mg/m^2 and 360mg/m^2 found that CHF occurred in about 1-2% of the patients after a 5 year [(50)]

One of the adjuvant therapy used in early breast cancer includes four courses of Ac with doxorubicin at 60mg/m^2 and cyclophosphamide at 600mg/m^2. The North Central Cancer Treatment Group(NCCTG) N98831 trial of between 2000 to 2005 recruited patients with breast cancer who had received four cycles of Ac. Asymptomatic left ventricular ejection fraction(LVEF) decline of >10% but <15% compared with baseline ranged between 5% to 8.5%. [(50)]

In France 2004, Hequet O et al analyzed 141 lymphoma patients with previous history of being treated with doxorubicin-based chemotherapy 5 years prior. Echocardiograms were performed on each patient. Clinical cardiomyopathy (EF<30%) n=1. 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%[(51)]

A retrospective analysis in 1979 by Von Hoff and colleagues evaluated 4000 patients receiving Ac. It revealed that the incidence of drug induced CHF was 2.2% and up to 71% mortality attributed to heart failure [(32)]. More recent studies have shown that there is a 63% prevalence of LV dysfunction after >10 years of follow up in patients receiving more than 500mg/m^2 cumulative dosage, contrary to 18% only for those receiving less than 500mg/m^2 [(8)]**.**Of concern is that most of these patients who develop LV dysfunction may not even have had a cardiology consult or started on therapy.

A study by Othieno-Abinya et al, retrospectively evaluated 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. Doxorubicin was used in 60% of all the protocols, Docetaxel in 11.1% and Paclitaxel in 7.6%. Clinical cardiotoxicity was seen in up to 4.6% of doxorubicin[52]. In 2006 Shiroya et al carried out a descriptive cross sectional study with a nested case control in children atKenyatta National Hospital. Of the 111 patients enrolled 32 cases (28.5%) were found to have abnormal cardiac function defined as LVEF <55% or FS <29[53].

2.6 Risk Factors for Anthracycline Cardiomyopathy

Risk factors predicting AIC include cumulative doses, bolus injections vs. prolonged infusions [3], previous hypertension, age >70years, use of concurrent agents that cause cardiotoxicity (e.g. cyclophosphamide, trastuzumab, and taxanes) and history of mediastinal radiotherapy [54][55][27]. Others are female gender, being overweight,increase in cardiac biomarkers such as troponins and increased length of time since completion of therapy.[56][10][57][58].

The greatest and most well known risk factor is total dose. AICis exponentially dose dependent and is enhanced when the cumulative dose of doxorubicin exceeds 300mg/m^2. However, there is no threshold Ac dose below which cardiotoxicity does not occur. In 1978 Michael R Bristow *et al* carried out right ventricular endomyocardial biopsies in 29 patients. 27 who had doses $\geq$ 240 mg/m^2 had myocardial damage on histology. Doxorubicin administration was associated with a dose related increase in the degree of myocyte damage. Moreovermyocyte damage was found in endomyocardial biopsy specimens from patients who had received minimal doses of 240 mg/m^2 of doxorubicin [59].

In 1991, Laurel *et al*published a study that was carried out at Memorial Sloan-Kettering Cancer Center. It was a retrospective study with a prospective arm. They evaluated ECHOs of 201 patients who had 200 to 1275mg/m^2 of Ac 4 to 20 years' prior. Twenty-three percent had abnormal cardiac function defined as reduced LVEF of < 50%. Notablecorrelation between total cumulative dose, length of follow-up, and mediastinal irradiation with incidence of abnormalities was found. Nine patients had cardiac failure and dysrhythmia, and three had sudden death. After a 10 year follow up, fifty-six patients who were treated with a median Ac dose of 495 mg/m^2 - 500 mg/m^2, 38% to63%had abnormal findings. [8].

In 2003, Sandra M swain *et al* retrospectivelyanalyzed three trialsthat showed 32/630 patients had a diagnosis of CHF. It also indicated that 26% CHF occurred at a cumulative dose of 550 mg/m^2. Age was found to be an important risk factor after dose of 400 mg/m^2, with > 65 years showing a greater incidence. Half of the patients withCHF had a reduction of< 30% in LVEF while they were on the study[31].

Other studies evaluating cumulative dose of doxorubicin-induced HF and found ranges between 3%–48% with 400 mg/m^2 - 700 mg/m^2 respectively. The lifetime maximum cumulative dose for doxorubicin is usually 400–550 mg/m^{2}or 800-1000mg/m^2 for epirubicin[60].

Between 1972 and 1987, Steven E. Lipshultz *et al* evaluated late cardiotoxic risk factors i.e. female and cumulative dose, for doxorubicin therapy for pediatric cancer. 120 patients who had been treated with cumulative doses of 244 to 550 mg/m^{2}were assessed. Females had a significantly greater reduction in LV dysfunction with a P<0.001[61]

A Cochrane review published in 2016 that looked into seven selected randomized controlled trials (RCT), showed use of liposomal doxorubicin was linked to reduced incidences of both asymptomatic and symptomatic cardiomyopathy (odds ratio=0.46; 95% CI, 0.23-0.92; P=0.03) compared to conventional doxorubicin without reducing progression-free or overall survival. This meta-analysis also showed that with infusion duration of > 6 hours compared with shorter infusion durationsthere was a significantly reduced rate of clinical HF with an AC (relative risk [RR] 0.27; 95% CI, 0.09-0.81) [62].

2.7 Detecting cardiotoxicity

Early identification of AIC is crucial. If subclinical LV dysfunction is detected early, prophylaxis and/or treatment can be given. CHF due to chemotherapy cardiotoxicity is often difficult to treat[63].Cardinale et al demonstrated that in 201 cancer patients with AIC,42% classified as responders showed LVEF recovery and a reduction in cardiac events due to early initiation of enalapril [64]

There are various ways used to assess for cardiotoxicity which includes both non-invasive and invasive methods.

The gold standard method for evaluating cardiomyopathy due to Ac is endomyocardial biopsy [65]. However it's invasive in nature as well as requires expertise toobtain a quality sample making it unpopular as a first line method

Use of cardiac biomarkers to detect subclinical LV dysfunction is another method that can be used. Troponins are the gold-standard biomarkers for assessing myocardial injury [66][67]. Troponin I is both a sensitive and specific marker. Studies now suggest that troponin can be used as early predictor of cardiotoxicity[10][64][68]. They have a negative predictive value of 99%[69][34]. However there are a several obstacles to the common use of troponin. The best timing of assessment remains unclear: is a single versus multiple analysis sufficient predictive value to be of utility. There is need to define the value for positivity that would maximize the predictive values, to determinethe best assay platform, and minimize the variation at the lower detection limit. Natriuretic peptides including N-terminal pro-BNP and brain natriuretic peptide (BNP) are other biomarkers that can be used. However only a few small studies have been published[70]

The non-invasive methods which include cardiac imaging appear to be more feasible. The various modalities look into evaluation and monitoring of LVEF. These imaging methods can assess differences in LV volumesor diastolic function which usually heraldchanges inthe EF.

LVEF is commonly used as marker for systolic dysfunction and an accepted indicator of prognosis [71]. Chemotherapy induced cardiotoxicity is routinely defined as a decline in LVEF.However there has been some controversies on what decline in LVEF constitutes cardiotoxicity. Many of the cut-off limits are usually arbitrary and frequently dysfunction, whether systolic or diastolic, develops during chemotherapy even when EF is within normal limits[72][73].Detecting a decreased LVEF after AC may be too late for, and therefore more sensitive parameters of LV impairmentwould be helpful [63].

The prognostic value of LVEF to monitor for cardiotoxicity is still controversial. Some studies have shown that a decrease in LVEF is a predictor of later cardiotoxicity.At least in adults, a pre-treatment LVEF is predictive of subsequent cardiotoxicity [74]. In children this value maybe lower as demonstrated by a recent retrospective study by Raymond G. Watts *et al* in 2011. The routine use of ECHO as a screening tool to assess damage before and during chemotherapy rarely identified significant cardiac damage [75].

Nuclear imaging has long been used for serial measurements of LVEF. In earlier days, the gold-standard for Chemotherapy Related Cardiotoxicity (CRC) screening was by equilibrium radionuclide angiocardiography (ERNA).[76]. From 1977-1984 Schwartz et al used resting ERNAto monitor LVEF of 1,487 patients with different types of cancer who had been on doxorubicin treatment during the observational period. They selected 282 patients considered

high risk based on their LVEF and performed a retrospective analysis in which 16% developed CHF and 2% died from cardiogenic shock. In 1987 he explained the guidelines for monitoring cardiotoxicity by using LVEF as a measure with ERNA. These guidelines state that:

1) Patients with a normal EF (≥50%), a drop of >10% or to <50% is an indicator for discontinuation of drugs.

2) In patients with baseline EF of <50%, these drugs should be discontinued if there is a >10% drop or if the EF falls to <30%.

3) In patients whose EF is <30%, these drugs are contraindicated

Patients who develop a larger drop in LVEF after chemotherapy end up developing clinical heart failure. [77]. In addition, it also provided information on diastolic function [78].It was a useful screening tool especially due to the fact that many patients who developed a drop in LVEF still remained asymptomatic for heart failure.Although ERNA was more reproducible than the 2D ECHO and had long been the gold standard screening tool, it is currently not used in routine assessment of LVEF. One of the main reason is exposure to ionizing radiation[79]. As a screening tool, studies came up to challenge its utility.The question then was if a single resting LVEF measurement was likely to possess the sensitivity needed for widespread use as a screening test [80].

Other more current advances in nuclear imaging use molecular targets to visualize the myocardial damage. These include Positron Emission Tomography^{99M}TC gbps, ^{99M}TC-annexin vSPECT, ^{111}IN-trastuzumab SPECT^{123}I-15-(p-iodophenyl)-3-(r,s)-methylpentadecanoic acid SPEC, ^{111}IN-antimyosin SPECTand^{123}I-MIBG SPECT [81]. However, the clinical use of these methods is limited by low availability, high cost, the complexity of most of the radiolabeling ligands and the requirement of excellent expertise.

Cardiac MR (CMR) imaging is a known clinical tool for congenital and acquired cardiac anomaliesassessment. It'sview has a wide field, its scanning planes are flexible and lacks ionizing radiation compared to ERNA[63]. CMR delineates the endocardial and epicardial borders well, does not rely on assumed geometric models that may miscalculate LV volumes, mass, and function and has true 3D volumetric coverage [82]. It is able to detect images for myocardial edema, myocardial injury, inflammation and early fibrosis. The ACC/AHArecognize it as a screening tool, though less widely used due to increased

availability of the 2D ECHO. Also used to detect occult sub endocardial infarcts too subtle to manifest as regional wall motion abnormalities (RWMA) on the conventional 2D echo [83][84].The disadvantages include higher operational cost compared with ECHO its lesser flexibility and availability.

ECHO is an easily available imaging modality for evaluating cardiotoxicity with serial measurement of LVEF and more so 2D ECHO. It also has the advantage of providing additional information including valvular disease or pericardial constriction (a common effect post radiotherapy sequelae). It is also preferred due to lack of radiation [85].Joint recommendations by American Society of Echocardiography (ASE), and the European Association of Echocardiography (EAE), is use of modified biplane Simpson's technique (method of disks) by 2DE to calculate LVEF and quantify LV volumes [63].

Other methods used to improve LVEF measurements include contrast echocardiography, 3D ECHO, stress ECHO, strain and strain rate[86]. Unenhanced ECHO tends to underestimate LVEF[87][88]. Patients with poor acoustic windows, benefit from contrast ECHObecause it increases the yield accurate LVEF measurements[89].Using 3D echo may also improve reproducibilityand accuracy of LVEF calculations[90]but has not yet been particularly studied as a screening tool and is not easily available. It's unclear the role of stress ECHO in regular cardiotoxic screening.The use of strain and strain rate shows promise[91]. There is a currently ongoing large Strain surveillance during Chemotherapy for improving Cardiovascular Outcomes (SUCCOUR) Trial. This may show whether strain is a better marker than LVEF for earlier detection of cardiotoxicity.However strain needs experienced echo cardiographers to interpret since it's performed off-line. You also need to consider multiple factors that can influence LV strain e.g. sex, obesity[92] and cardiac conditions like MI [93]

Most guidelines to screen for CRC are based on assessment of LVEF. Other useful for screening include LV volume and diastolic function [63]. Diastolic parameters that can be used include a decreased early peak flow velocity to atrial peak flow velocity(E/A)ratio, impaired deceleration time(DT),impaired IVRT and an increased Tei Index [94] .The E/A ratio is a marker of function of the left ventricle, and best seen on 2D ECHO. Abnormality of the E/A suggests that the LV, which is responsible for the forward pumping of blood into the systemic circulation cannot fill up with blood properly during diastole. This leads to diastolic dysfunction and can lead to heart failure. One study showed predictions rates witha 78% sensitivity and 88% specificity for development of systolic dysfunction at 3months[95].Many

of the studies done that revealed abnormalities in diastolic indices failed to show correlation between changes in diastolic parameters and development of late cardiotoxicity. Larger trials may be needed to confirm the utility of diastolic measurement and the specificity in detecting long term cardiotoxicity.

There is no consensus as to whether all patients receiving Ac should undergo a baseline assessment of LVEF. According to European Society of Medical Oncology (ESMO), LVEF assessment is compulsory for basal cardiac function evaluation before treatment withany potential cardiotoxic drug. This has a level 1 evidence with grade A recommendation [(96).]Baseline imaging is particularly helpful in those with cardiovascular risk factors and patients with a history or clinical findings suggestive of LV systolic dysfunction and [(63)]. It remains unknown the optimal timing and number of follow up echocardiograms required and this may depend on initial changes of LVEF and the combination of treatment regimens

There exist different classification systems for definition of left ventricular dysfunction (LVD). In the Cardiac Review and Evaluation Committee supervising trastuzumab clinical trials, LVD is characterized by

1. Global or septal decrease in cardiac LVEF
2. Symptomatic CHF
3. Associated signs of CHF, including but not limited to S3 gallop, tachycardia, or both
4. Decline in LVEF of at least 5% to less than 55% with accompanying signs or symptoms of CHF, or a decline in LVEF of at least 10% to below 55% without accompanying signs and symptoms [(97).]

The other used classification systems include theClinical toxicity criteria, version 2.0 and the Common terminology criteria for adverse events version 3.0[(98).]Other definitions include a fall of LVEF to below the lower limit of normal or LVEF <50% and therefore a consensus definition of cardiotoxicity is lacking

3.0 CHAPTER THREE: STUDY JUSTIFICATION

3.1 Study Justification

Anthracyclines are a documented cause of cardiotoxicity and cardiomyopathy in cancer patients surviving chemotherapy. Given the structural changes the cardio myocyte undergoes, it has become widely accepted that this type of cardiotoxicity maybe difficult to manage. Moreover, anthracycline-induced cardiomyopathy has been considered to be associated with a prognosis that is worse than that for ischemic or dilated cardiomyopathies and possibly even for the primary cancer for which it was given.

The rise in the burden of both cancer and cardiovascular diseases in our population is alarming.Most cancer patients treated at our local oncology centers are not routinely screened for heart disease whether it's before, during or even after chemotherapy with anthracyclines. ECHO is an easily available imaging modality for evaluating cardiotoxicity with measurement of LVEF. It has the advantage of providing additional information including valvular disease or pericardial constriction and it is preferred due to lack of radiation. Cardiac event reduction and LVEF recovery may be possible if cardiotoxicity is discovered early and treatment timely initiated.

The burden of disease in our population has not been well established and there is paucity ofpublished data regarding the prevalence in the African setting. This study will be important in documenting the burden of cardiotoxicity due to anthracyclines as evidenced by LVEF dysfunction on 2D ECHO.The data may be used in influencing policy by putting stringent measures for screening of heart disease and subsequently early initiation of treatment to reduce the risk of cardiotoxicity.

3.2 Research Question

What is the burden of cardiomyopathy as detected by 2D echocardiography amongst cancer patients treated with anthracyclines at the KNH?

3.3 Study Objectives

3.3.1 Broad objective

To determine the point prevalence of cardiomyopathy in patients who have received anthracycline chemotherapy on follow up at Kenyatta National Hospital.

3.3.2 Primary Objective

To determine the prevalence of ECHO derivedLV systolic dysfunction as measured byLVEF in patients who have been exposed to anthracycline chemotherapy.

3.3.3 Secondary Objectives

1. To correlateassociation between cumulative dose of anthracyclines and presence of cardiomyopathy.

2. To correlate association between sex and age and presence anthracycline induced cardiomyopathy.

4.0 CHAPTER FOUR: MATERIAL AND METHODS

4.1 Study Design

This study was a hospital outpatient/inpatient cross sectional descriptive study.

4.2 Study Setting

This study was carried out in various outpatient clinics and oncology wards inKenyatta National Hospital, the largest referral facility in Kenya and a teaching hospital for the University of Nairobi, College of Health Sciences. It is a 1900 bed capacity and has a large patient turnout at the outpatient clinics for hematooncology.

The adult hematooncology clinic is held every Monday in clinic 23. The patients are seen by oncologists, fellows'.in oncology and internal medicine residents. About 150 to 200 patients are reviewed in the clinic every week. Ground floor C (GF-C)conducts outpatient chemotherapy administration from Monday to Friday. These patients are reviewed by radio oncologists through their clinics in cancer treatment center (CTC). Ward 8C and Ground floor D (GF-D),are dedicated wards for cancer chemotherapy. The patients receiving anthracyclines varied on a day to day basis.

All cancer patients are routinely assessed at the clinic. Noninvasive cardiac evaluation is not part of the routine evaluation of cancer patient, it is only requested for patients presenting with symptoms or signs of cardiac disease.

The cardiology unitis opened daily from Monday to Friday between 8 a.m. to 5p.m. It houses one ECHO machine which is operated by a cardiologist or a trained echo sonographer. On average \30 echocardiographic studies are performeddaily.

4.3 Study population

Adult patients diagnosed with cancer with history of treatment with anthracycline chemotherapy on follow up at KNH.

4.4 Case definition

An adult cancer patient treated with a cumulative dose of at least 200mg/m^2.

4.5 Inclusion criteria

Patients aged 13 years and above who had given an informed written assent and/or consent were included.

4.6 Exclusion criteria

Patients known to have heart diseasebased on a file diagnosis had radiotherapy to the mediastinum or chest with history of known diabetes and/or hypertension and incomplete treatment history and records were excluded.

4.7 Study variables

4.7.1 Exposure variables

a) Demographic factors: age in years and sex

b) Type of cancer

c) Treatment regimen

d) Cumulative dose of anthracycline

e) Duration since completion of anthracycline treatment was categorized as still on treatment,0 to 12 months 13 to 60months, 61 to 120 months, and more than 121 months after treatment.

4.7.2 Outcome variable

a) Presence or absence of Cardiomyopathy.Cardiomyopathy was defined as an LVEF <50%

4.8 Sample size

This study attempted to estimate the prevalence of cardiomyopathy. Sample size determination was done using a formula for prevalence studies (Daniel, 1999) as follows:

$$n = \frac{Z^2 \times P(1-P)}{d^2}$$

Where:

n – Minimum required sample size

Z – Standard normal for a 2-sided test at 95% confidence interval (CI) = 1.96

P – Previous prevalence of cardiomyopathy in patients on anthracycline treatment based on a study by Hequet et al conducted in France found that 20.5% of cancer patients had cardiomyopathy i.e. LVEF <50%) (51)

d – Margin of error of estimation = 7%

$$n = \frac{1.96^2 \times 0.205(1 - 0.205)}{0.07^2}$$

n = 128 participants

The minimum sample required to achieve the objectives of the study was 128 participants.

4.9 Sampling

Consecutive sampling was used to recruit participants until the desired sample size was attained.

4.10 Data Collection

4.10.1 Patient recruitment

A registered clinical officer was trained to work as a research assistant to the principal investigator (PI). They recruited cancer patients into the study from the hematooncology clinic, GF-C, Ward 8C or GF-D at KNH.The PI and research assistantvisited the hematooncology clinic on the allocated clinic day and GF-C on a Wednesday and Fridayand perused the files before the start of the clinic day to determine patients who had been treated with anthracyclines as part of their chemotherapy regimen. For those patients recruited from the wards, the PI and research assistant visited the units and with the assistance of the senior house officers in those particular wards, identified the patients on anthracycline treatment and obtained their files for further scrutiny.All eligible patients were screened and a written informed consent obtained.A focused history was obtained in either English or Kiswahili by the principal investigator and the research assistant. A data proforma was used to capture and record thepatient's biodata including sex, age, weight, education, marital status, residence, telephone contact. Treatment history including type of malignancy, surgical procedure, stage of disease, regimen/protocol used, date of diagnosis, and cumulative dose of anthracyclines andpresence of baseline ECHO was recorded. This was done until the designated sample size was attained. All patients comprising the study sample were referred to the cardiology unit to have a 2D ECHO done on them. The PI or research assistantpersonally took the ECHO

request forms to the cardiology unit to book for the date. A 2D echocardiograph was done by an echo sonographer who was dedicated to the study. The PI was present during each ECHO study. The still and cine loop images were kept safely and reviewed by twoautonomous cardiologists at the Kenyatta National Hospital department of cardiology.

4.10.2 Echocardiography methods

Each eligible patient had a 2D echocardiography study performed as by the American Society of Echocardiography (ASE)and the European Association of Echocardiography (EAE) recommendations[63]. The Ultrasound system is a Phillips i.e. 33 equipped with a 2.5Hz multifrequency transducer. This was used by the study dedicated echo sonographer to perform a full 2D, M-mode and Doppler analyses with views ofthe apical, subcostal andstandard parasternal long and short axis. At least three cardiac cycles were acquired to assess the cardiac structures.The cine-loop and still images were stored safely for review by two independent cardiologists and a consensus reached

LV systolic function wasassessed usingLV ejection fraction. Systolic function was determined by calculating the left ventricular fractional shortening and ejection fractions. In M-mode, LV diameter in end diastole and end systole was determined. From these measurements LV fractional shortening was calculated and documented. In 2D, LV diastolic and systolic volumes and LV ejection fraction were measured using the two chamber views (the difference between end-diastolic and end systolic volumes divided by end-diastolic volume).

4.11 Quality Assurance Procedures

Screening and recruitment of study populationwas done by the primary investigator and a well-trainedresearch assistant. ECHOwas performed by a qualified technician with the assistance of the primary investigator. The cine-loop images were downloaded and stored in a compact disc while the still images were printed. Both images were independently reviewed by twocardiologist until a final consensus on the LVEF was reached.

4.12 Ethical Consideration

This research was reviewed and approved by the University of Nairobi department of Clinical Medicine and Therapeutics and the KNH/UON Ethics and research committee. Permission from KNH administration was obtained. The study objectives and procedures were explained to the patient in a language that he/she understood. Only patients who signed an informed

consent participated in the study. The recruitment was strictly on a voluntary basis and no discrimination was shown to those who withdrew from the study.

Coding of documents for linking source document to study proforma was done. This information has restricted access, only to the PI.

The findings from the echocardiography studies were availed in a hard copy format and every patient was appraised on their report. The results were also availed in their files for use by the attending clinicians. Cases found to have cardiac abnormality that required treatment, were referred to the cardiac clinic.

4.13 Data Management and Handling

Data capture forms were stored in a lockable cabinet and only available for scrutiny by the primary investigator. The hard copy study proformawere coded, entered and managed in Microsoft Access database. Data verification, cleaning and validation was done continuously during data entry. The database was exported to SPSS version 21.0 for statistical analysis. The study population was described using socio-demographic and clinical characteristics. Categorical variables were summarized into percentages and continuous data into means with standard deviations (SDs) or medians and interquartile ranges (IQRs) for the non-normally distributed data. Prevalence of echo-evidenced LV systolic dysfunction was presented as a percentage within 95% confidence interval. Also, cardiomyopathy was associated with demographic variables using chi-square test for categorical variables and independent t test for comparison of means. All statistical tests will be performed at 5% level of significance. The findings were presented in tables.

5.0 CHAPTER FIVE:RESULTS

Between 29th January to 27th April 2018162 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 echocardiography either the same day or another day during the course of the week. Of the eligible participants, 20 of them postponed their ECHO appointment date until the study period was over while 3 of the patients passed on due to various illnesses before ECHO was done; one passed on at home while two passed on in the oncology ward 8C. Only 129 participants had echocardiography studies done and were included in the analysis as depicted in figure.

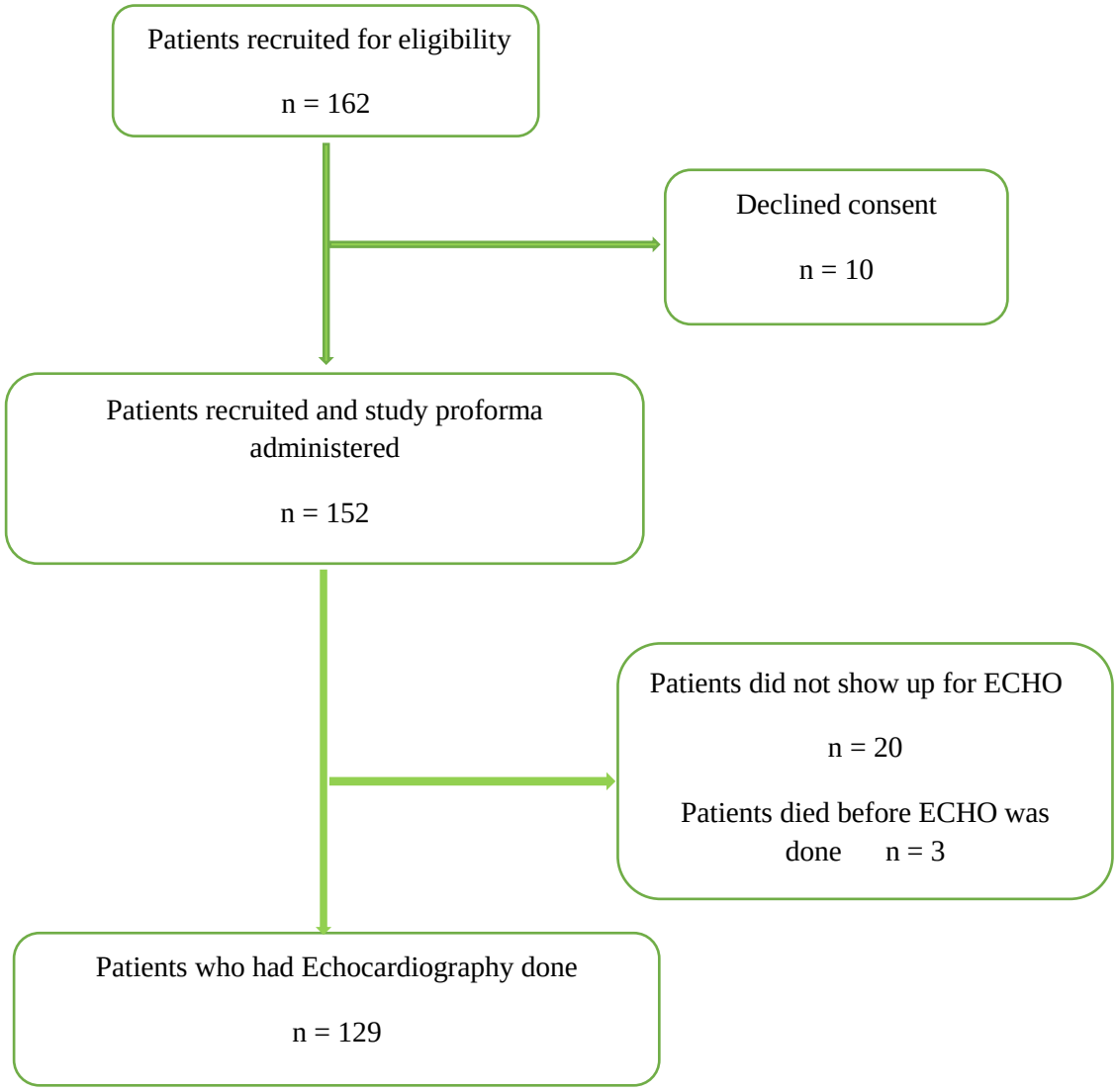

Figure 1: Flow chart of patient screening

5.1 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 wereunemployed (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)

5.2 Clinical characteristics

Most of the patients had breast cancer (67.4%) and lymphoma (17.8%) asdepicted 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.

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	56 (43.8)
13-60 months	63 (49.6)
61-120 months	8 (6.2)
	1 (0.8)
Pretreatment ECHO	
Present	18 (14.0)
Absent	107 (82.2)
Missing	5 (3.9)

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

5.3 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.

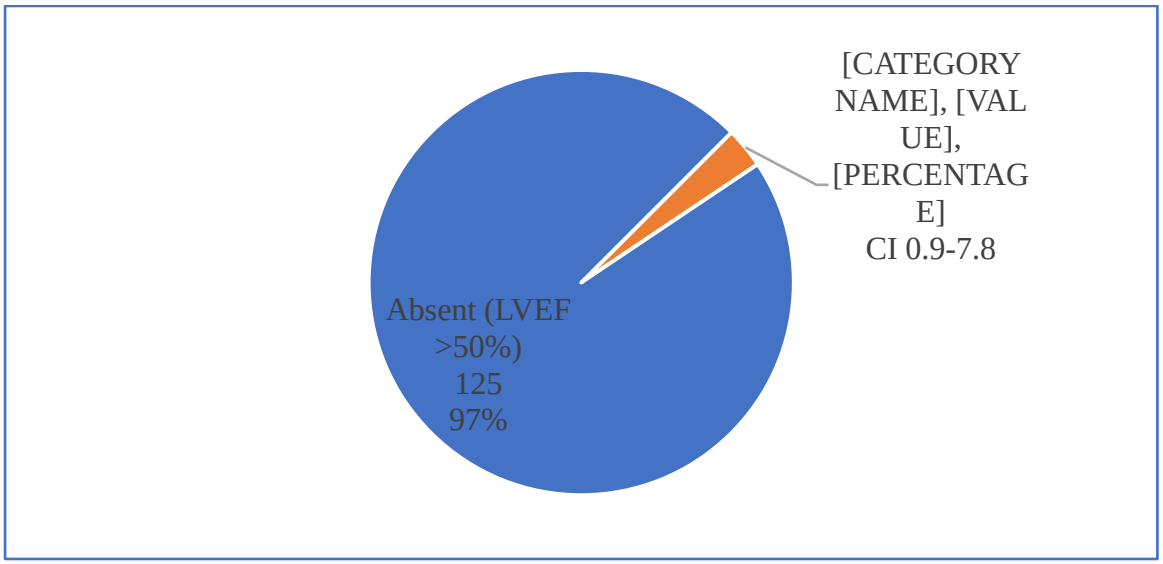

Figure 2: Prevalence of LV systolic dysfunction

5.4 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 cardiomyopathydue to a small sample size asdepicted 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

6.0DISCUSSION

Cancer which isa 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 than50%. 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 [(52)]. 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% [(51)]In 2016, Daniel A. Mulrooney*et al* conducted a cross sectional evaluation of 1,853 adult survivors of childhood cancers, who had receivedAc using a 2D Doppler ultrasound echocardiography. Cardiomyopathy, defined by LVEF of less than 50% was present in 7.4% [(48)].

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[(31)]

Female sex isanother 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 recruitedhad 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 [61]

The cumulative doseof 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 400-550mg/m^2 and for epirubicin is 800-1000mg/m^2. The cumulative dose rangewas very narrowand therefore no correlationwith 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 [59]. 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) [99][100].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[101]

7.0 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%.

8.0 RECOMMENDATION

We recommend a through 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

9.0 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 LVEFbecause it has geometric assumptions of LV cavity.

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TIMELINES

EVENT/MONTH	SEPTEMBER	OCTOBER-JANUARY 2018	JANUARY-APRIL 2018	MAY-JULY 2018	JULY 2018
PROTOCOL PRESENTTION					
ETHICAL APPROVAL					
DATA COLLECTION					
DATA ANALYSIS REPORT WRITING					
RESULTS					

BUDGET

ESTIMATED STUDY BUDGET

STATIONERY AND PRINTING	**Ksh 10,000**
ECHO 3000/= per patient for 128 patients	**Ksh 384,000**
STATISTICIAN	**Ksh 30,000**
RESEARCH ASSISTANT (1 research assistant)	**Ksh 30,000**
CONTINGENCIES	**Ksh 15,000**
TRANSPORT	**Ksh 15,000**
TOTAL	**Ksh 484, 000**

Funding

As the principle investigator, I took responsibility to fund the study.

APPENDICES

Appendix I: Statement of Information for Patients Participating in the Study

Study title "PREVALENCE OF ANTHRACYCLINES INDUCED CARDIOMYOPATHY AMONGST CANCER PATIENTS TREATED AT KENYATTA NATIONAL HOSPITAL"

Principal Investigator: Dr Tonio Caroline

Introduction

I am currentlyundertaking my master's degree in the Department of Clinical Medicine and Therapeutics at the University of Nairobi. I am currently undertaking a study that will look for cardiomyopathy using a2D echocardiography amongst patients exposed to anthracyclines at Kenyatta National Hospital.

Anthracyclines are a group of chemotherapy drugs used in treatment of various types of cancers. A limiting side effects of these drugs is heart damage. Patients may end up developing an enlarged heart which may end up failing in its functions. This condition maybe difficult to treat.

Diagnosing this condition early will aid physicians start early managementthat mayreduce progression of heart disease.

Purpose of the study

The study will attempt to establish the frequency of heart involvement among cancer patients receiving anthracyclines.

Procedures to be followed

After accepting to participate in this study you/your parents or guardians will be requested to sign a consent form. Once in the study you will be asked questions regarding your socio-demographics, illnesses and the treatment you have received. After which you will have an echocardiogram performed by an echo sonographer, which will help detect abnormalities in the heart that could bedue to anthracyclines. After the study the doctor will explain all the findings. If abnormality requiring immediate treatment is discovered, referral to appropriate clinic will be done.

Benefits of the study

The information obtained from the study will assist your doctors in developing treatment guidelines and policies that may benefit future generation quality of care for. The cost of getting the echocardiography done will be upon the principal investigator.

Risks involved

Echocardiography is a painless, non-invasive way of assessing the heart. It has no short or long term harmful effects on your body and therefor no risk involved.

Who can participate?

Any patient with cancer aged 13 years and above who is on treatment with anthracycline chemotherapy and is on follow – up at Kenyatta National Hospital

Participation

Participation will be on a voluntary basis. No discrimination will be shown to anyone whorefuses to take part in the study.

Confidentiality

All information obtained will be strictly confidential. The echocardiography printed report will be availed to your attending doctor to assist in your care.

You are at liberty to ask questions at any point.

CONTACTS

For any further queries that you mayhave, please contact the following:

1. Dr. Tonio Caroline Njeri (Principal investigator)
   University of Nairobi
   Department of Clinical Medicine and Therapeutics
   P.O Box 105513 00101 Nairobi
   Tel 0725 102 656

2. The Chairman of Kenyatta National Hospital/University of Nairobi Ethics and Research Committee,
   P.O Box 20723, Nairobi
   Tel +254 020-2726300, extension Ext 44355, 726300-945

AppendixII:Swahili Consenting Information

Study title: "PREVALENCE OF ANTHRACYCLINE INDUCED CARDIOMYOPATHY AMONGST CANCER PATIENTS TREATED AT KENYATTA NATIONAL HOSPITAL"

Maelezo ya idhini

Jina langu ni Dkt Tonio Caroline, mwanafunzi katika kitengo Clinical Medicine and Therapeutics, School of Medicine, chuo kikuu cha Nairobi. Ninafanya utafiti kuhusu madhara ya dawa zinazoitwa anthracyclines.Dawa hizi zinatumiwa kutibu aina nyingi za saratani. Zinaweza kuhusiana na ugonjwa wa moyo. Utafiti huu utatusaidia kuchunguza huu ugonjwa ili tuweze kuufahamu vizuri zaidi na kutuwezesha kuwahudumia kwa hali ya juu zaidi. Utafiti utafanywa katika kitengo cha kupima moyo.

Hatari/Faida

Hii itahusisha kuchukua historia, kufanya uchunguzi wa mwili na moyo tathmini na kipimo cha kuangalia ndani ya moyo. Kipimo hicho hakina madhara yoyote kwa mwili.

Hakutakuwa na malipo yoyote kwa kuhusika katika utafiti huu. Hutaulizwa kulipa chochote juu ya malipo ya kawaida katika hospitali. Daktariwa mgonjwa atajulishwa majibu ya utafiti huu na natumai yataboresha matibabu yako.

Haki za mshiriki

Kushiriki kwako katika utafiti huu ni kwa kujitolea na ukiamua kutoshiriki, hutanyimwa huduma ambazo ungepata kwa kawaida katika hospitali hii. Ukiamua kutoshiriki katika utafiti huu hakutakuwa na adhabu yoyote.

Hakikisho ya siri ya utambulisho wa mshiriki

Rekodi kuhusu ushiriki wako kwenye utafiti huu zitabaki siri na zinaweza tu kujulishwa daktari anayekutibu. Utapewa fomu ya idhini utie sahihi.

MAWASILIANO

Ukiwa na maswali yoyote ya ziada, unaweza kuwasiliana na wafuatao:

1. Dr. Tonio Caroline Njeri (Principal investigator)
   University of Nairobi
   Department of Clinical Medicine and Therapeutics
   P.O Box 105513 00101 Nairobi
   Tel 0725 102 656

2. The Chairman of Kenyatta National Hospital/University of Nairobi Ethics and Research Committee,
   P.O Box 20723, Nairobi
   Tel +254 020-2726300, extension Ext 44355, 726300-945

Appendix III: Consent Form

Adult - English

I……Age……. Tel……

Has been requested to participate in the study "Prevalence of anthracycline induced cardiomyopathy amongst patients treated at Kenyatta National Hospital".It will involve taking a detailedhistory and evaluating the heart using a 2D echocardiography. I understand that I/my child will not suffer any discomfort and that l will not pay any extra cost. I acknowledge that my consent is purely on voluntary basis and I can opt out from the studywithout any victimization.

I therefore consent to be recruited into the study

Sign……Date……

Tafsiri ya Kiswahili

Fomu ya Idhini ya mtu mzima

Mimi……

Umri……Nambari ya Simu……...

Naombwa kushiriki katika utafiti kutathmini madhara ya moyo katika wangonjwa wanaouguwa saratani wanaopata dawa ya anthracyclines wanaohudhuria Hospitali ya Taifa ya Kenyatta.

Hii itakuwa kuhusisha kuchukua historia, kufanya uchunguzi wa mwili na moyo tathmini na kipimo cha kuangalia ndani ya moyo. Nimeelezwa kwamba kipimo hicho hakina madhara yoyote mwilini mwangu. Mimi pia naelewa kwamba ridhaa yangu ni ya hiari nakwamba naweza kujitoa kwenye utafiti wakati wowote bila adhabu yoyote. Kwa hiyo kukubaliana na wataajiri wakati ya utafiti.

Sahihi…… Tarehe……

Appendix IV: Assent form (Age 13-17)

Study title“ PREVALENCE OF ANTHRACYCLINE INDUCED CARDIOMYOPATHY AMOGST CANCER PATIENTS TREATED AT KENYATTA NATIONAL HOSPITAL ”

Principal Investigator: Dr Tonio Caroline

Introduction

I am doing a research study about the effects of certain drugs used to treat cancer on the heart. If you decide that you want to be part of this study, you will be asked some questions about your illness and then have an echocardiogram performed on you.

Basis of participation

You are free to withdraw the child from the study at any point during the course of the study period.Your refusal to allow the child to participate or withdrawal at any time during the study period will not in any way affect the quality of his/her treatment.

Confidentiality

All information obtained in the study will be treated with utmost confidentiality. This report will not include your name or that you were in the study.

Benefits

When we are finished with this study we will write a report about what was learned which may be published in a medical book or journal or for teaching purposes and will be given to the community for better understanding of this topic. Once the echocardiogram reports are ready, we will inform your child’s doctor, who will then inform you about his/her structural cardiac abnormalities if any and advice you accordingly.

Risks and discomfort

Echocardiographic studies are non-invasive and pose no harm to your child.

Request for information

You can ask questions about this study at any time. If you decide at any time not to finish, you can ask us to stop. The questions we will ask are only aboutyour illness. There are no right or wrong answers because this is not a test.You will be informed of any significant findings discovered during or after the study.

Cost

There will be no added cost to you if you decide to participate.

Assentform (Between ages 13 to 17)

I have carefully read this information and had it explained to me. All my questions have been answered but am at liberty to ask further questions.

I therefore consent to take part in the research.

Name: ----------

Signature/Mark ----------

Date ----------

I have clearly read out the information sheet to the potential participant who is a minor

And to the best of my knowledge ensured the minor understood. I answered all the questions

Asked by the minor. I confirm the minor has given assent freely and understands that the

Parents/guardians still have to sign a consent form. I ascertain that the individual has not been

forcedinto giving consent.

Name of research investigator----------

Signature of researcher investigator----------

Date----------

Appendix V: Participant's Statement (to be signed by parent/guardian)

I…… do hereby give consent/permission to Dr. Tonio Caroline to include the above minor in this studyentitled 'PREVALENCE OF ANTHRACYCLINE INDUCED CARDIOMYOPATHY AMONGST PATIENTS CANCER TREATED AT KENYATTA NATIONAL HOSPITAL. I have read and understood the contents of this form, and have been accorded the chance to ask questions. I am also aware that the minor can withdraw from this study without any penalties

Name…… Mobile No……

Sign …… Date……

Witness……..

Fomu ya Idhini ya mzazi wa motto

Mimi_____nakubali mtoto wangu _____

kushiriki katika utafiti unaofanywa na Dkt Tonio Caroline. Nakubali mtoto wangu apigwe picha ya moyo.Naelewa mtoto wangu hatapata maumivu zaidi ya ilivyo kawaida. Sitalipa malipo yoyote kwa utafiti huu. Nitaelezwa majibu yoyote yanayoweza kuboresha matibabu ya mtoto wangu. Pia naelewa kuwa naweza kuzitisha ushiriki wa mtoto wangu kwenye utafiti huu wakati wowote bila hofu ya adhabu yoyote.

Jina la mshiriki _____ Nambari ya simu _____

Sahihi ya mshiriki _____ Tarehe _____

Jina la shahidi _____

Sahihi ya shahidi _____ Tarehe _____

Sahihi ya mtafiti mkuu(Ama mwakilishi wake)_____

Appendix VI: Investigator's statement

As the primary investigator, I have enlightened the study participant on the usefulness of this study.

Signed…… Date……

Kauli ya mchunguzi

Mimi kama mchunguzi nimemuelimisha mshiriki wa utafiti kuhusu madhumuni na matumizi ya utafiti huu.

Sahihi…… Tarehe…

Appendix VII: Screening Tool

1. Have you ever been on treatment for any of these illnesses? (Yes/No)

   Hypertension ……

   Diabetes …….....

   Heart failure ……

   Other heart diseases (state which illness) ……

2. Consent given Yes……. No……

AppendixVIII: Study Pro-Forma Document/Questionnaire

Study Title: PREVALENCE OF ANTHRACYCLINE INDUCED CARDIOMYOPATHY AMONGST PATIENTS TREATED AT KENYATTA NATIONAL HOSPITAL

No……. Date……

A. Demographic Data

1. What is your date of birth?……

2. What is yoursex?……. 1=Female; 2=Male

3. What is your marital status?……1 = Married 2 = Single 3 = Widowed 4 = Divorced 5=Seperated

4. What is your level of formal education?……1 = Tertiary 2 = Primary 3 = Secondary 4 = College 5 = None

5. What is your current state of employment?……. 1 = Unemployed 2 = Employed 3 = Self-employed 4 = Retired

6. Do you smoke? YES (Y) Pack years…… NO (N)……

7. Do you have heavy alcohol consumption? YES (Y) Units/wk….NO (N)…….

B. illness

1. What type of cancer do you have? Breast =B……

Lymphoma= HL/NHL……

Others =OT……

2. When were you diagnosed? Year……Month…….

C. Treatment history

1. What regimen have you received? AC= A……

FAC = B……

CHOP =C……

ABVD =D……

OTHERS = E…….

2. What cumulative dose of anthracycline did you receive? : 200 - 450mg/m^2 = 1 …

> 450mg/m^2 = 2 ……

3. What is the duration since completion of anthracycline?Still on treatment = 1 …

0-12 months = 2 ……

13-60months = 3 ……

61-120 months = 4 …….

D. Any pretreatment ECHO?Present = P…….

Absent = A…….

E. Is there presence of cardiomyopathy? LVEF < 50%..... LVEF > 50%.....

Appendix VIX: Echocardiography Report Form

PERICARDIAL ASSESSMENT

Pericardial Effusion

‹ 5mm ‹ 3mm

5 – 10mm › 3mm

› 10mm

Pericardial thickness

‹ 3mm

› 3mm

Pericardial Calcification

Yes No

SYSTOLIC FUNCTION

Fractional Shortening……% Ejection Fraction……%

DIASTOLIC FUNCTION

E velocity……....m/s IVRT……...sec

A velocity……m/s E' velocity……m/s

E/A Ratio…… A' velocity……m/s

Dct…….sec

VALVULAR ASSESSMENT

Mitral Valve Aortic Valve

Valve thickness……mm Valve thickness……...mm

Vegetation: No Yes Vegetation: No Yes

Regurgitation: No Yes Regurgitation: No Yes

Grade…… Pressure half time……...

Stenosis: No Yes Stenosis: No Yes

Orifice area……...cm2 Peak gradient……mmHg

Mean Gradient……. mmHgMax Velocity……...m/s

Pressure half time……sec

Tricuspid Valve Pulmonary valve

Vegetation: No Yes Vegetation: No Yes

Regurgitation: No Yes Regurgitation: No Yes

Stenosis: No Yes Stenosis: No Yes

PULMONARY PRESSURE

Peak tricuspid regurgitant velocity……m/s

Pressure gradient between RV & RA……mmHg

Systolic pulmonary arterial pressure……...mmHg

Pulmonary Regurgitation velocity……...m/s

Deceleration time of RV ejection