DETERMINANTS AND MANAGEMENT OF CARDIAC TOXICTIES INDUCED BY ANTHRACYCLINE-BASED REGIMENS IN ADULT PATIENTS WITH CANCER AT KENYATTA NATIONAL HOSPITAL

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A Research dissertation submitted in partial fulfillment of the Requirement for the award of the degree of Master of Pharmacy in Clinical Pharmacy in the school of Pharmacy of the University of Nairobi.

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DEDICATION

This dissertation is dedicated to my wife and my parents for their unwavering support.

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ABSTRACT

Background: Anthracyclines are used in the standard treatment protocols for solid and hematological cancers. Despite their extensive usage, they cause cardiac toxicities. These toxicities require prompt management to reduce the risk of their complications.

Objective: To investigate the determinants and management strategies of anthracyclines induced cardiotoxicities in adult patients with cancer at Kenyatta National Hospital.

Methodology: A cross-sectional study was conducted at the Kenyatta National Hospital. A total of 149 adult cancer patients on the anthracycline-based regimen were recruited to participate in the study through consecutive sampling. Data was collected using a researcher administered questionnaire. The analysis was carried out using STATA version 13 and the level of significance set at 0.05.

Results

There was female predominance (97.3%) and twenty-two (14.8%) participants had comorbidities especially hypertension (10, 6.7%). The majority (140, 94.0%) had breast cancer and 59 (39.6%) had the disease for a duration of 1-2years. One hundred and thirty-four (89.9%) were using doxorubicin and cyclophosphamide combination. Nineteen (12.8%) participants had a reduced ejection fraction along with type I diastolic dysfunction. Independent predictors of cardiotoxicity were hypertension (p=0.026**);** trastuzumab use (p=0.011), occupation (p=0.046) and Body mass index (p=0.043) respectively. However, all the participants were not put on any intervention geared towards managing the cardiac toxicities.

Conclusion

High BMI was an independent predictor of cardiac toxicities. Similarly, the presence of hypertension and the use of trastuzumab were also identified as independent predictors of cardiac toxicities in patients using the anthracyclines-based regimen.

Recommendations

Weight reduction should be encouraged and hypertension appropriately controlled.

ABBREVIATIONS AND ACRONYMS

AC- doxorubicin and cyclophosphamide

ACEI-angiotensin converting enzyme inhibitors

ARB-angiotensin receptor blockers

AIC -Anthracycline induced cardiomyopathy

ALL-Acute Lymphoblastic Leukemia

ASCO-American society of clinical oncology

BMI-Body Mass Index

BNP-Natriuretic peptides

DM-Diabetes Mellitus

ECG-electrocardiogram

ECHO-echocardiogram

ESMO-European society of medical oncology

HCTZ-Hydrochlorthiazide

HF- Heart failure

HIV/AIDS-Human immunodeficiency virus/Acquired immunodeficiency syndrome

KS-Kaposi Sarcoma

LVEF- Left ventricular ejection fraction

NHL-Non-Hodgkin's Lymphoma

NSAIDs-Non-steroidal anti-inflammatory drugs

PUD-Peptic ulcer disease

TDF/3TC/DTG-Tenofovir/Lamivudine/Dultagrevir

WHO-World Heath Organization

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DEFINITION OF TERMS

Cardiotoxicities - Toxicities that affect the heart.

Anthracycline-based regimen- Any regimen that contains doxorubicin, epirubicin or daunorubicin

CHAPTER ONE: INTRODUCTION

1.1 Background to the study

Cancer is a global burden that is estimated to have 18 million new cases and 9.6 million deaths across the world(1). In Kenya, cancer is the third leading cause of death (2). Management protocols to guide the management of malignancies are available, but still, people die of curable cancer due to late diagnosis. In resource-limited countries like Kenya, the anthracycline-based regimen are the standard treatment regimen despite their potential to cause cardiotoxicities (3).

Anthracyclines were isolated in early 1960 from *Streptomyces peucetius* species of actinobacteria (4). They are often used in the management of cancers like breast cancer, lung cancer, ovarian cancer, lymphomas, stomach cancer, leukemia's, Ewing's sarcoma, and many other cancers. This is evident by the fact that they appear in the list of essential medicines by World Health Organization (WHO) 2019. The most commonly used anthracyclines are doxorubicin, epirubicin, daunorubicin, and idarubicin(1). The anthracyclines act by intercalating between the DNA base pairs and prevents the DNA replication and RNA transcription of the rapidly growing tumor cells (5). They also act by forming free radicals and inducing topoisomerase II-dependent cell damage (4). Their most common cardiovascular events associated with their use are cardiac dysfunction and heart failure(6). Others include dilated cardiomyopathy, sinus tachycardia, and prolongation of QT interval and supraventricular tachycardia(7). The cardiac toxicities are classified according to the time of their onset (7). That is Sub-acute, acute, and chronic. Sub-acute occurs within hours to days after the initiation of chemotherapy, while

acute manifests within two weeks after completion of chemotherapy. Chronic toxicity occurs up to one year after the end of chemotherapy.

Curigliano *et al.* point that cardiac troponins may increase within 3 hours after cardiac damage and that they have been used as predictors of cardiac injury after infusion of anthracyclines(6). Strategies have been utilized to reduce cardiotoxicities such as the use of liposomal doxorubicin and administration of dexrazoxane (6).

In Africa, no study has tried to investigate the determinants and management strategies that are employed to reduce cardiac-related toxicities. In Kenya, only one study was conducted to identify the risk factors for anthracycline cardiac toxicities in pediatrics at Kenyatta National Hospital and found the prevalence to be 29%(8). Therefore there exists a gap regarding the clinical determinants of cardiac-related toxicities and the management strategies in adult cancer patients receiving anthracycline-based regimen at Kenyatta National Hospital

1.2 problem statement

Anthracyclines are globally used in the standard regimen for the management of cancers such as stomach cancer, acute myelogeneous leukemia, lung cancer, ovarian cancer, and breast cancer. In the WHO's 2019 list of essential medicines, the anthracyclines are included because of the pivotal role they play in the management of cancers (1). However, they have the potential to cause cardiac-related toxicities, which often start to manifest from the time the first dose is administered to over a year after completion of the anthracycline chemotherapy cycles. The consequence of these cardiac-related toxicities is to increase the burden of management where today's cancer patients will become cardiac

patients in the coming days. The study sought to establish the determinants of cardiac-related toxicities and also highlight the management strategies that are used for these toxicities.

Many studies in the US, Europe, and across Asia have studied the prevalence of cardiac toxicities in adults(9). In Kenya, only one study attempted to find out the risk factors of cardiac toxicities in pediatrics patients receiving anthracycline-based therapy, which found out the prevalence to be 29% (8). This study was, therefore, justified because no research in the adult population at Kenyatta National Hospital has been conducted. Also, the findings of this study will help the oncology team improve on the management of these cardiac-related toxicities, and this will decrease the mortality occasioned by the use of the anthracycline-based regimen.

1.3 Purpose of the study

The purpose of this study was to establish determinants of cardiac-related toxicities of anthracycline-based regimen in adult patients with cancer as well as to evaluate the management of these cardiac toxicities at KNH. It would help the oncology team improve on the management of cancer patients and eventually improve their survival period. It would also lessen the mortalities occasioned by cardiac-related toxicities of the anthracycline-based regimen.

1.4 Objectives

1.4.1 General objective

The general objective of this study was to establish the determinants of cardiac-related toxicities of anthracycline-based regimen and their management strategies in adult patients with cancer at Kenyatta National Hospital oncology department

1.4.2 Specific objectives

The specific objectives were as follows

1. To determine the prevalence of cardiac-related toxicities of anthracycline-based regimen at KNH.
2. To establish the determinants of cardiac toxicities caused by anthracycline-based regimens at KNH.
3. To evaluate the management of cardiac-related toxicities of anthracycline-based regimen at KNH.

1.5 Research questions

This study sought to address the following research questions

1. What is the prevalence of cardiac-related toxicities of anthracycline-based regimen in cancer patients?
2. What are the determinants of cardiac toxicities caused by anthracycline-based at KNH?
3. What is the management of cardiac-related toxicities of anthracycline-based regimen at KNH?

1.6 Significance of the study

This study was significant because the findings would help the oncology team to improve on the management of the cardiac-related toxicities of the anthracycline-based regimen. It also sought to identify the gaps that exist in the management and contribute to the improvement of knowledge among students, practitioners, and researchers.

1.7 Delimitations

This study was carried out at the oncology department of Kenyatta National Hospital. This study only focused on cancer patients receiving anthracycline-based regimen at Kenyatta National Hospital

1.8 Limitations

This study was limited to the oncology department at the Kenyatta national hospital. It was also limited to adult cancer patients aged 18 years and above who were using anthracycline-based regimens. The study was also limited to evaluating the changes in the cardiac biomarkers, ECG and ECHO to detect cardiac toxicities. The study was further limited to interviewing the patients and getting the information from the patient medical records as the participants declined to walk to the laboratory and donate blood samples for the evaluation of the cardiac troponins despite the assurance that they could not incur any cost. This is because the sample collection expert was based in the laboratory which was a distance apart from the department where the study was being conducted.

1.9 Conceptual Framework

The outcome variable of this study was the presence of cardiac-related toxicities that occur due to the use of anthracycline. These toxicities range from dilated cardiomyopathy, QT prolongation, sinus tachycardia, supraventricular tachycardia to heart failure. The ECG and ECHO reports indicated the presence of cardiac toxicities. The other predictors of these toxicities would have been the elevation of troponins, which are principally cardiac biomarkers. Also, a rise in the brain-type natriuretic peptide (BNP) would be an indication of increased preload and heart failure(10). Patients who had been exposed to radiation therapy especially mediastinum radiation are at an increased risk of developing cardiac toxicities due to anthracyclines. Breast cancer patients who had been treated with Trastuzumab are also at high risk because it can interfere with signaling in the cardiac muscle. This is due to it is a direct consequence of ErbB2 inhibition in the cardiomyocytes (6). Administration of Trastuzumub concurrently or before anthracyclines contributes significantly to anthracycline toxicities(11). The presence of hypertension and coronary artery disease contributes considerably to the time the cardiac toxicity of anthracyclines would manifest(12). The high rate of administration of anthracyclines and cumulative dose of above 300mg/m^2 for doxorubicin will significantly cause immediate cardiac toxicities which will start to manifest during the dose administration(11). The extremes of age above 65years and below 3 years of age will be at a high risk of developing severe cardiac toxicities as compared to other ages (6). Several strategies have been recommended to prevent cardiac toxicities like the use of Dexrazoxane which chelates the anthracyclines in the myocytes, the use of carvedilol to prevent cardiac remodeling and also use of liposomal formulations of anthracyclines(10).

Heart failure is managed as per the current guidelines from the American Heart Association(13)

Conceptual Framework

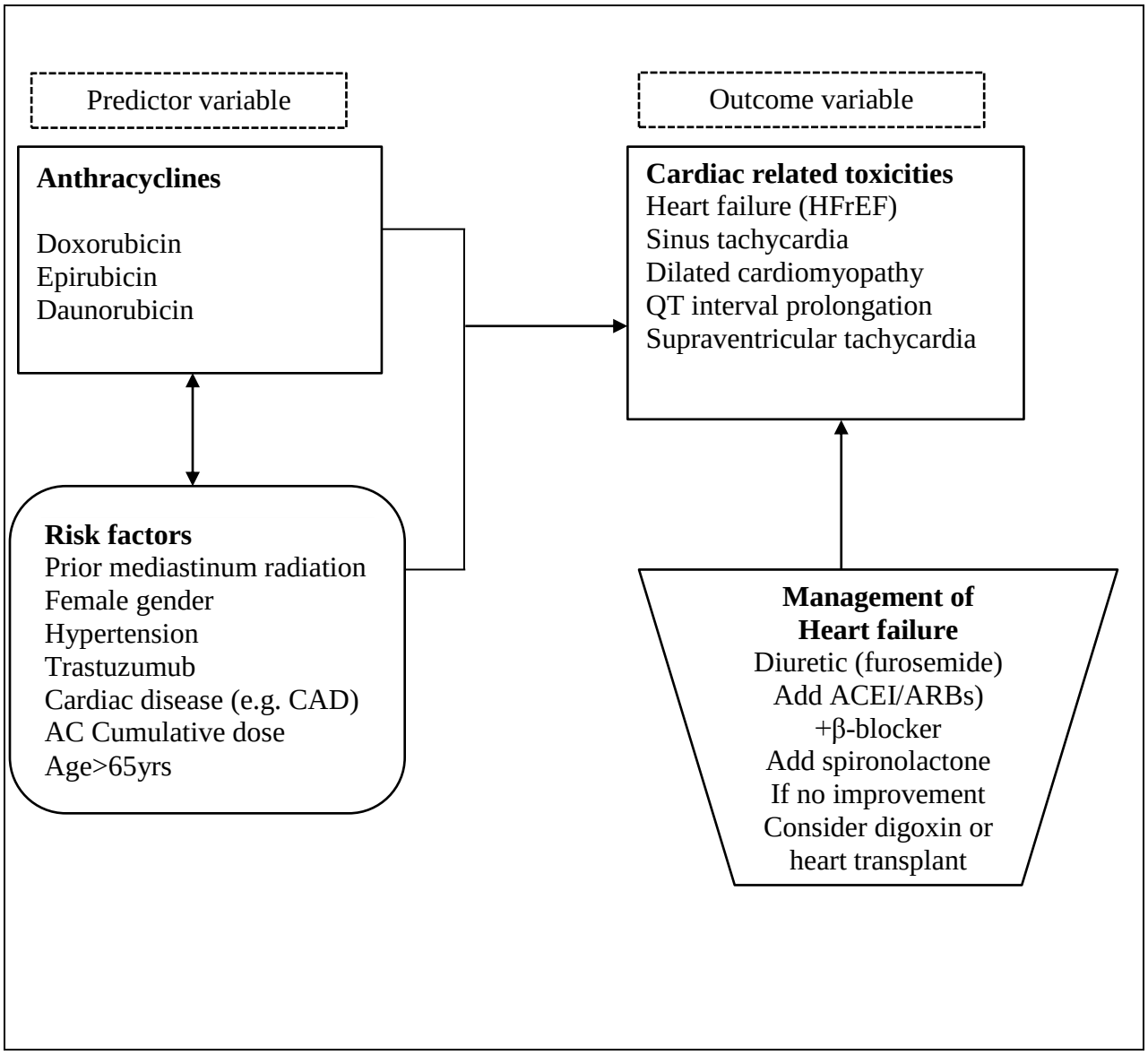

Figure 1: Conceptual Framework **(**Author 2019)

CHAPTER TWO: LITERATURE REVIEW.

2.0 Introduction

This chapter discussed a review of the literature related to the determinants of cardiac-related toxicities induced by anthracyclines. It also covered the pathophysiology of cardiotoxicity, prevalence as measured by the cardiac troponins for early detection. It then covered the strategies used to manage anthracycline-induced cardiotoxicities and the literature gap that exists. Cardiac toxicities induced by anthracyclines are the most challenging issues the oncology team deals with. In most countries, the anthracyclines form the standard treatment regimen for most cancers both solid and hematological cancers. The presence of these toxicities would start to manifest even during the administration of the first dose. These toxicities are classified as sub-acute, acute, and chronic, depending on the time they begin to manifest. They include dilated cardiomyopathy, heart failure, QT prolongation, sinus tachycardia, and supraventricular tachycardia. Early detection of these toxicities can be achieved through the evaluation of the cardiac troponins and long term by the use of echocardiograms. Their management may involve the use of preventive measures and guideline-directed management of heart failure.

2.1 Cardiotoxicities

Cardiotoxicities are the toxicities that affect the heart. The mechanisms that have been postulated on how anthracyclines cause cardiotoxicity include oxidative stress, accumulation of toxic metabolite, alteration of iron Fe^{2+} and calcium Ca^{2+} homeostasis, mitochondriopathy, and interaction with topoisomerase II β(14). All anthracyclines have

a similar mechanism of toxicities like the original molecule doxorubicin. It enters the cell through passive diffusion and accumulates in the cardiomyocytes where it induces lipid peroxidation at the cell and mitochondrion membranes by way of complexing with Fe^{2+}. It collects in the mitochondrial due to a high affinity towards cardiolipin. The one-electron reduction of doxorubicin to a semiquinone intermediate results in oxidative stress, leading to DNA damage, energy depletion, and apoptosis. It also impairs Ca^{2+} processing in the sarcoplasmic reticulum and inhibits the transcription of important contractile elements. The two-electron reduction leads to the production of doxorubicin which is a primary circulating highly toxic metabolite of doxorubicin, which shows limited efflux. It also acts by inhibiting the calcium pump of the sarcoplasmic reticulum and other iron exchange pumps(15). Cardinal et al, in their prospective study demonstrated that 9% of the patients developed heart failure, of which 81% were NYHA class I and II whereas 19 % has NYHA class III and IV, which was detected during hospitalization for acute decompensated heart failure(16). Another study by Quintana et al. reported that 10% of their patients developed subclinical cardiotoxicity that was evaluated by ECHO(17). Kim et al noted that 4% of their patients developed heart failure and demonstrated that it was high in patients who were older, their condition more advanced, and had other comorbidities(18). A prospective cohort study that was done in Uganda reported that 21.9% of patients under study developed heart failure(7). Shiroya et al. in their study in the pediatric population in Kenyatta National Hospital, found out that the incidence of left ventricular dysfunction was 29% of children who had received a cumulative dose of >200mg/m^2 of doxorubicin(8). It was noted from studies that the cardiac toxicities vary depending on the population under study.

2.2 Cardiac biomarkers

Most studies have extensively evaluated the measurement of ventricular dysfunction with either echocardiogram (ECHO) or cardiovascular magnetic resonance (CMR) in detecting structural changes. They indicated that in as much they are standard non-invasive techniques to detect ventricular dysfunction, they do so when the effects of anthracyclines toxicity are at an advanced stage and usually lead to heart failure, which is irreversible even with optimization of therapy(15). On the other hand, cardiac biomarkers like troponins (cTn) and brain natriuretic peptide (BNP) are usually released after cardiomyocyte damage that is induced by various mechanisms like oxidative stress, inflammation, and ischemia (19). Another study suggests that BNP is released in response to an increase in left ventricular filling pressure and wall stress(20). Measurement of cTnI within 24 hours can give a predictive time course to the development of cardiotoxicity(21).

2.3 Prevalence using cardiac biomarkers

The prevalence, as projected in most European studies, ranges from between 30% to 35% of cancer patients. Conventionally anthracycline-related cardiotoxicity relied upon ECHO for screening LV systolic dysfunction and also the changes in the left ventricular ejection fraction. Though this is recognized as a late-occurring measure of cardiac dysfunction(22). Natriuretic peptides and troponins are used for early prediction, and this informs the timely management of asymptomatic heart failure. Cardiac troponins have been shown to detect cardiac abnormalities early even before the symptoms manifest. Therefore they are recommended as sensitive techniques for screening cardiac

abnormalities along with the conventional screening methods(23). Xiang Lu et al. reported that the prevalence of 34.9% when serum BNP levels were used as a measure to predict cardiotoxicity. These patients ended up developing cardiotoxicity during the follow-up period(20). Another study reported the prevalence of anthracycline-induced cardiomyopathy of 25.5%, of which 30% reported a decrease in LVEF, which is mostly dose-dependent(22). In KNH, occasionally, they use ECHO to determine the reduction of left ventricular ejection fraction, which usually occurs late and is irreversible. Despite the availability of cardiac troponin test, which is affordable in the hospital, they hardly use it to monitor cardiac injury induced by anthracyclines because it is not included in the treatment protocols.

2.4 Determinants of cardiotoxicity

Older patients above the age of sixty-five years and children under the age of three years are more susceptible to developing cardiotoxicity following anthracycline administration. Moreover, elderly patients are at a high risk of developing cardiotoxicity which is attributed to the effect of aging cardiomyocytes and studies report a high incidence in these patients. Similarly, a high incidence is reported in children whose heart is developing and the anthracyclines have a high affinity to the cardiolipin. The time of course of cardiotoxicity usually varies depending on the age of the patient

Female patients who have breast cancer and test human epidermal growth factor receptor 2 positive are treated with Trastuzumab. Trastuzumab is an independent risk factor of cardiotoxicity and induces the loss of contractility and inhibition of signaling pathways(24). The time of administration of Trastuzumab usually affects the time course

of onset of cardiotoxicity. Administration of Trastuzumub before anthracyclines increases the risk of cardiotoxicity. Trastuzumab itself is an independent risk factor. Radiotherapy induces cardiotoxicity through blood vessel damage. Reactive oxygen species damage the DNA strands with the resultant activation of the inflammation cascade. The fibrosis of the interstitium of the myocardium occurs, which reduces the ratio of the capillary to myocytes' density with subsequent narrowing of the arterial lumen, which leads to myocardial cell damage and fibrosis(25). Russell et al. demonstrated that cardiotoxicity was more prevalent in black women than white and they attributed this to the existence of other cardiac comorbidities like hypertension and diabetes mellitus(24). Another study reports that radiation therapy has the potential to cause cardiotoxicity in about 10-50% of the patients treated with radiation therapy, of which a large percentage would be asymptomatic(26). Symptomatic patients would present with a range of cardiovascular disease manifestations like angina, dyspnea, fluid overload, and syncope(25). Childhood radiation increases the relative risk of congestive heart failure(25,27). Patients with breast cancer, when irradiated on the left breast, are at an increased risk compared to the right breast(28). Obesity and overweight are associated with an increased risk of increased cardiotoxicity because of the increased chance of a patient developing cardiovascular disease(27). Arterial hypertension increases the risk of cardiotoxicity because of the strain it exerts on the cardiac muscles(12). Hypertension could arise from a disturbance in cardiac output or increased systemic vascular resistance. The heart can only adapt acutely to accommodate the increased demand by undergoing concentric hypertrophy to meet these demands. This remodeling is only short-lived as the heart will eventually become exhausted due to tissue fibrosis and lead to heart failure(12). The risk of cardiotoxicity

increased in the elderly with cardiovascular diseases that manifest early, depending on the co-existing cardiac risk factors(15). Consequently, cardiotoxicity manifests early in patients who have received a high anthracycline cumulative dose. Doxorubicin is the most toxic followed by it's derivative epirubicin while idarubicin is the least toxic(29). However, the incidences of heart failure that have been reported by different studies occur at various doses depending on the patient characteristics (15,26,17). The method of administration of anthracycline contributes to the time course of development of cardiac toxicity. Studies indicate that when anthracyclines are given as an intravenous bolus, the chances of developing sub-acute cardiac toxicity are higher compared to intravenous infusion over some time (17,31). Other cardiotoxic drugs also play a pivotal role in the time course of manifestation of the anthracycline-induced cardiotoxicities. Concurrent administration of Cyclophosphamide and paclitaxel with anthracycline poses a danger. This is because these drugs also have adverse effects on the cardiomyocyte(7,32).

2.5 Management of cardiac toxicities

Several strategies have been put forward by many professionals across the world for the management of cardiac toxicities. They are both non-pharmacological and pharmacological. Non-pharmacological approaches are employed to prevent the development of cardiovascular events, which may accelerate the cardiotoxicity of anthracyclines. In Asia, patients are advised to live a healthy lifestyle, maintain the BMI within the normal range. Obesity and dyslipidemia are associated with the development of coronary artery disease, which is a risk factor for heart failure(33). Therefore, dyslipidemias have to be controlled to reduce the risk of cardiovascular disease. QT-

prolonging drugs like 5HT3 receptors antagonists should be avoided to reduce the cardiac conduction disturbances(10). Smoking also damages the endothelium membrane and should be avoided altogether. Conventional doxorubicin should be avoided and substituted with liposomal doxorubicin as this has a better safety profile without compromising the antitumor activity(12). Another study by Campelo et al comparing the use of conventional doxorubicin and liposomal doxorubicin supports this recommendation where they found out that there was no difference in their antitumor response activity but the incidence of heart failure and left ventricular dysfunction was lower in a patient treated with liposomal doxorubicin(34). Similarly, patients treated with liposomal doxorubicin had a lower prevalence of hypertension as compared to patients treated with pegylated liposomal doxorubicin(35) and it has a higher tumor response as compared to conventional doxorubicin(36).

Dexrazoxane is a potent cardio protectant that acts by chelating iron and thereby reducing the formation of free radicals which damages the myocardium. American society of clinical oncology recommends that dexrazoxane should be given to patients who receive doses exceeding 300mg/m^2 of doxorubicin and 540mg/m^2 of epirubicin and Patients with cardiovascular risk factor like hypertension should be considered. The study by Macedo et al found that patients who were treated with dexrazoxane had lower cardiac events as compared to the control(37).

The risk of developing heart failure rises with an increase in the cumulative dose of anthracycline. Curigliano et al. said the risk increases to about 10-40% per 100mg/m^2 increase in the cumulative dose of anthracycline(19). Therefore, it is worthy to note that this is strong evidence that lower doses should be optimized to decrease the probability of

having cardiotoxicity. Anthracycline cardiotoxicity is dose-dependent and the incidence of cardiomyopathy and subsequent heart failure increases with an increase in the cumulative dose(38). Cai et al. recommend that the cardiac function should be accurately monitored and the cumulative dose reduced(39). Less cardiotoxic drugs should be used in patients who are at an increased risk of cardiotoxicity. During the administration of anthracyclines, continuous infusion of over six hours reduces the incidence of cardiotoxicity as compared to the bolus infusion without compromising the antitumor activity(40).

Administration of enalapril slows the progression of left ventricular systolic dysfunction and prevents heart failure in asymptomatic high-risk patients(41). Angiotensin-converting enzyme inhibitors demonstrated a reduction in cardiotoxicity and nephrotoxicity (12). They act primarily by reducing hypertension, which in turn decreases the compensatory burden of the heart and not directly acting on the cardiomyocyte. Akolkar et al. in their study, report that Aliskeran demonstrated high cardioprotective activity as compared to ACEIs. They further found out that the cardiotoxic effects of doxorubicin and Trastuzumub were partially attenuated by ACEI(42). On the other hand, carvedilol was found to prevent cardiotoxicity by reducing cardiac remodeling(41). A study by Cai et al agrees with these findings that the use of carvedilol in patients with breast cancer who were treated with anthracyclines protects their left ventricular ejection function (39).

Once the clinical heart failure is established treatment should be initiated promptly following the established guideline for the management of heart failure. American heart association guidelines of 2017 recommend a comprehensive algorithm for managing

heart failure(13). The diuretics, angiotensin-converting enzyme inhibitors are the cornerstones in heart failure management. ACEIs should be initiated with a small dose titrating the dose to a maximum tolerable dose(43). Therefore, patients with a rise in cardiac troponin I following anthracycline administration should be put on cardioprotection with ACEIs as they have been shown to prevent left ventricular ejection fraction reduction and other cardiovascular events(35).

2.6 Literature gap

Previous studies in Kenyatta National Hospital relied heavily on the use of echocardiogram to detect cardiomyopathy and subsequent heart failure which is usually detected late and is irreversible. Heart failure, in this case, is generally identified when it is at class NYIII or NYIV of which management is mainly supportive. In Europe, guidelines of the European society of medical oncology recommend monitoring of cardiotoxicity using troponin I in chemotherapy-induced cardiotoxicity for early detection and initiate early intervention. In Kenya, particularly in Kenyatta National Hospital, no study has studied the determinants, use of cardiac Troponins for early detection, and strategies geared towards managment of cardiac toxicities caused by anthracyclines, which is the major gap identified. Therefore this study seeks to fill this gap, which can improve the management of cancer patients on anthracyclines-based regimens.

CHAPTER THREE: MATERIALS AND METHODS

3.0 Introduction

This chapter describes the methodology that was used by the researcher to meet the specific objectives. The methods covered the study design, location of the study, the target population, eligibility criteria, sampling, research instruments, validity, reliability, data collection techniques, data management, and data analysis, and finally, ethical considerations.

3.1 Study design

The study was designed as a descriptive cross-sectional study. This design was used in this study because it gave a clear picture of the events as they were. The patients who met the set criteria were recruited into this study.

3.2 Location of the study

The study was conducted at the oncology ward and oncology clinic at Kenyatta National Hospital, Nairobi. It is a tertiary hospital that offers oncology services in Nairobi, Kenya. The hospital is located to the west of the upper hill area in Nairobi, the capital and largest city of Kenya. The hospital is approximately 4 km from the central business district. It is accessible from Ngong' road and hospital road and lies on 45.7 acres of land. The facility is the largest in east and central Africa. It has a bed capacity of 1900 and 50 wards; it is the largest hospital in East and Central Africa. It serves as a teaching hospital for the

University of Nairobi College of health sciences. This site was suitable for the study because the hospital receives so many patients for cancer treatment.

3.3 Target population

The study targeted adult cancer patients 18 years and above on anthracycline-based regimens who were attending oncology clinics and oncology wards at Kenyatta National Hospital. This study targeted a population of about 5000 cancer patients receiving chemotherapy interventions at KNH. It was estimated that about 600-800 patients were using the anthracycline-based regimen and this formed the study population

3.4 Eligibility Criteria

Cancer patients on anthracycline-based regimen and also patients who did not have any cardiac condition at the time of initiating chemotherapy were eligible for the study.

3.4.1 Inclusion criteria

The cancer patients who met the following criteria were included in the study.

1. Cancer patients 18 years and above.
2. Cancer patients using, and those who had used, the anthracycline-based regimen.
3. Patients who consented voluntarily and signed the consent declaration form.

3.4.2 Exclusion criteria

1. Patients who declined to consent.
2. Patients who were not able to express themselves did not participate in the study.
3. Patients who already had heart failure before initiation of anthracycline chemotherapy.

3.5 Sampling

The following areas of sampling were covered; sample size calculation and sampling technique.

3.5.1 Sample size calculation

The outcome variable in this study was cardiac toxicities. Several studies across the globe have reported the prevalence ranging from 3 to 48% depending on the patient characteristics. Of particular importance is the prevalence that was reported by a study conducted in Uganda that reported a prevalence of 21.9%(7). Therefore, this study used the prevalence of 21.9% to calculate the sample size as it is the only available study in East Africa to report on the prevalence of cardiac toxicities. This study, therefore, used the Cochrane formula (1977) to calculate the sample size because the outcome variable is categorical(44). The sample size is calculated as follows.

$$no = \frac{Z^2 \times P(1-P)}{d^2}$$

Where,

n_o = the calculated sample size

Z= the standard normal deviates at a 95% confidence interval which is 1.96.

P= the prevalence of anthracycline-induced cardiac toxicities which is at 21.9% based on the previous study that was conducted in Uganda

d= which is the desired precision of this study that will be at 0.05 which is the margin of error for most scientific studies that are descriptive with a categorical variable.

$$n_o = \frac{1.96^2 \times 0.219(1-0.219)}{0.05^2}$$

n_o=263 participants

For the patients that are seen in oncology clinics every week, about 150 patients use the anthracycline-based regimen. Therefore, it was estimated that the number of patients per month would be 600. Because of this, a sample size reduction formula was applied to reduce the sample to a size that was to be representative.

$$n_o = \frac{n}{1+\frac{n-1}{N}} \quad \text{Substituting,} \qquad n_o = \frac{263}{1+\frac{263-1}{600}}$$

This results to **183** participants.

However, during data collection only 156 (86%) were recruited into the study. This was attributed to the fact that the patient number had declined due to the negative effects of the Covid-19 pandemic. Moreover, seven patients were excluded from data analysis because they did not have complete socio-demographic information. This is summarized in **figure 2**.

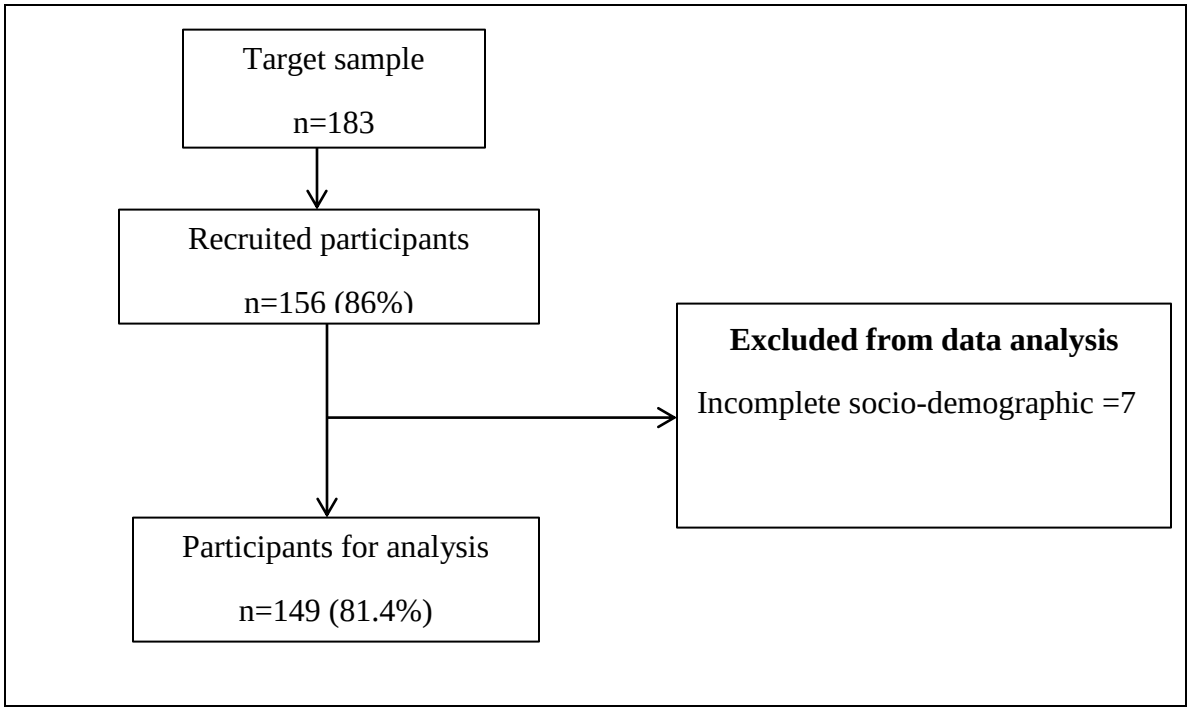

Figure 2 Screening and inclusion of study participants

3.5.2 Sampling technique

The researcher used a consecutive sampling technique to recruit participants into the study. The patients who met the inclusion criteria and agreed to participate were recruited into the study. On the clinic day, before the clinic started, the principal investigator perused the files to identify the participants who met the criteria and then tagged them for ease of identification. The participants who met the inclusion criteria and agreed to participate were taken through the consenting process then they were being interviewed through the interviewer-administered questionnaire method whereby the questionnaire was read to them by the principal investigator and their responses were filled in the questionnaire. Other information was abstracted from the files. The exercise continued until the desired sample size was achieved.

3.6 Research instruments

The researcher used a well-structured questionnaire to collect data that was administered and filled by the researcher. The principal investigator visited the clinics on specific days. He then proceeded to introduce himself and the purpose of his visit to the heads of these sections. Consent was sought from the participants before the questionnaire was administered. The participants were then assured that their participation is voluntary and that their failure to participate cannot deny them any service. Once the consent was given, the principal investigator interviewed the patients via the interviewer-questionnaire method where he read the questions to the participants and filled in the respective responses in the questionnaire.

The researcher also used the data abstraction form to get other information from the patient file. The regimen the patients were put on was recorded and any other cardiac comorbidity was recorded. The questionnaire captured socio-demographic features, smoking and drinking habits of the participants, and any comorbidity. Any information on the number of cardiac toxicities as detected by cardiac biomarkers, echocardiogram, and electrocardiogram and confirmed by other tests were captured using data abstraction form. Data abstraction form also captured the presence of other drugs and other conditions like hypertension that contribute to the development of cardiac toxicities and the strategies used to prevent these cardiac toxicities as indicated in Appendix 2.

3.7 Pilot study

The pilot study was conducted on 10 participants and they were not considered in the main study sample. The principal investigator perused files at the hemato-oncology clinic and at the Cancer Treatment Centre to identify those who met the inclusion criteria and selected ten of them who participated in the pilot study. The selected patients were then taken through the consenting process and those who abode were interviewed. Data from the interview and data obtained from patient records were entered into the tool and analyzed. The purpose of the pilot study was to ascertain the suitability of the data collection tool. It was also used to establish whether the data collection was formulated in a language that the respondents understood.

3.8 Validity

The questionnaire was formulated in such a way that the information collected achieved the set objectives of the study. It was also written in a simple, clear, and acceptable language for the respondents to understand to produce consistent information. The pretest was conducted to check whether the study would give reproducible information. The study was also conducted in the largest referral hospital that receives patients from across the East African countries so the result would be generalized to the entire population. To ensure external validity is achieved, a consecutive sampling method was employed to ensure that every eligible patient had a chance to be selected for the study. This was done to get the sample that was representative, and the findings can be generalized to the entire population.

3.9 Reliability

The questionnaire was piloted to check whether it could reliably collect the information that would achieve the intended objectives. It was conducted using the procedure highlighted under the pilot study section. This was done to ascertain whether the information received would be reproduced. The purpose of this was to ensure that the responses given were consistent with the objectives.

3.10 Data collection techniques

3.10.1 Recruitment of participants

The participants were recruited at the haematooncology clinic, which is conducted every Monday. Other participants were recruited at the cancer treatment centre, which conducts outpatient chemotherapy administration from Monday through Friday. Other patients were recruited at ward 8C, which is the haematooncology admitting ward. At the

haematooncology clinic and cancer treatment centre, the principal investigator was at the clinics specific days early before the routine services began. The researcher would then peruse the files to identify the patients on the anthracycline-based regimen and tag them for ease of identification.

3.10.2 Personnel

The researcher recruited a research assistant who was a holder of a diploma in Kenya Registered Community Health Nursing (KRCHN) and he was taken through the data collection procedure. The role of the research assistant was to assist the principal investigator in enrolling and interviewing the patients. He also assisted in abstracting data from the patient files. The research assistant was working concurrently with the principal investigator. He would submit the filled data collection tools to the principal investigator at the end of every session.

3.10.3 Patient interview

The principal investigator would visit the clinics on specific days. He would then proceed to introduce himself to those heading these sections to agree on the modalities of how to collect the data. Consent was then sought from the participants before the questionnaire was administered. The participants were assured that their participation was voluntary and that their failure to participate could not deny them any service. The principal investigator ensured infection prevention measures were observed as outlined in the interim guidelines on the management of covid-19 in Kenya(45). Before commencing the interview, the principal investigator ensured that the participants and the investigator have put on face masks and those who did not have, were provided with one. Alcohol-

based hand rub was also availed to ensure that the participants and the investigator sanitized their hands before the interview and after the handling of the research instrument. During the interview, the principal investigator and the research assistant ensured that there was a one-meter distance between them and the participants. The principal investigator and his assistant would then interview the patients via the interviewer-questionnaire method and they filled in the respective responses in the questionnaire. They would then proceed to peruse the patient records, pick the relevant data, and enter them in the abstraction form. The data collection tools checked for completion and coded with specific numbers ready for further processing. The process was continued until the requisite number of participants was attained according to the sample size.

3.11 Data management

All the data collected was directly coded and entered into the Microsoft Excel database 2010. Data entry was done daily during the data collection period and was checked for completeness and consistency. Data was backed-up daily into the flash disk. After completion of data entry, the data was then exported to STATA version 13 (statistics and data) for analysis. Data capture forms were stored in a lockable cabinet that was only accessible by the principal investigator. All the data entry was password protected and only accessible by the principal investigator. This was done to maintain security and ensure the data was not tampered with. Data verification, cleaning, and validation was done continuously during data entry.

3.12 Data analysis

The data was analyzed using STATA version 13 software. The descriptive and inferential statistical analysis was used to demonstrate the relationship between the variables. The results were presented in the form of tables and percentages. The measures of central tendency were calculated for continuous variables like socio-demographic and clinical data like age and duration of illness. The prevalence of cardiac toxicity was calculated by getting the number of patients with cardiac toxicities identified and then divided by the total number of patients sampled. The methods used in the prevention of cardiac toxicities were evaluated against the recommendations by the American society of clinical oncology guideline 2017 and the management of heart failure which is the main complication was evaluated against the American Heart Association guideline 2017. The data on the management of cardiac-related toxicities were analyzed using STATA version 13. The frequency and percentages of management strategies were determined and their results were presented in the form of a table. The multivariate and bivariate analysis was done using STATA version 13 to establish the association between the predictor variables and cardiac toxicities. The association between determinants of cardiac-related toxicity and cardiac toxicity was proven using the chi-square test for independence and the results were presented in tables. The dependent variable was cardiac toxicity. Explanatory variables were socio-demographic characteristics and clinical profiles. The explanatory variables that yielded a p-value ≤ 0.05 were considered a predictor.

3.13. Logistical and ethical considerations

The researcher sought permission from the respondents before they were recruited into the study. The respondents were also assured that the information they gave was kept confidential. The researcher also sought approval from the Kenyatta National Hospital/University of Nairobi-ethics and research committee (KNH-UON-ERC) to enable him to conduct the research. The study was registered in the department of research and programs at Kenyatta National Hospital. Because of the current Covid-19 pandemic, the principal investigator adhered to the infection prevention and control measures as outlined in the Interim guidelines on the management of Covid-19 in Kenya to avoid the spread of the virus(45). The principal investigator ensured that the participants put on face masks and those who did not have were provided with one; the principal investigator also advised the participants to cover their nose and mouth with a tissue or flexed elbow during coughing or sneezing. The principal investigator also kept a one-meter distance between the participants during the interview. Finally, the principal investigator and the participants performed hand hygiene before and after coming into contact with the research environment using alcohol based hand rub.

CHAPTER FOUR: RESULTS

4.0 Introduction

This chapter describes the results obtained after descriptive and inferential data analysis was done. It encompasses the socio-demographic characteristics, the clinical profile comorbidities, and medicines the participants were using.

4.1 Socio-demographic characteristics

The socio-demographic characteristics of the study participants are summarized in **Table 1.** A total of 149 were recruited into the study. The mean age of the study participants was 47.9 (SD 10.8) years and the median was 47.0 (IQR 41.0-55.0). The range was 26 to 79 years.

The majority of the participants (147, 97.3%) were females. One hundred and forty-one (94.6%) were married and 65 (43.6%) had secondary school education while (4, 2.7%) did not have any form of education. About half (75, 50.3%) of the participants were unemployed and 17(, 11.46%) were formally employed.

Almost all participants did not smoke a cigarette (148, 99.3%) or take alcohol (146, 98.0%).

Table 1: Socio-demographic characteristics of the study participants (n=149)

Age (Years)	Frequency	Percentage (%)
≤30	8	5.4
31-40	28	18.8
41-50	50	33.6
51-60	46	30.9
61-70	14	9.4
>70	3	2.0
Gender		
Male	4	2.7
Female	145	97.3
Marital status		
Married	141	94.6
Never married/Widow/Widower	8	5.4
Education		
None	4	2.7
Primary	49	32.9
Secondary	65	43.6
Tertiary	31	20.8
Employment		
Formally employed	17	11.4
Self-employed	57	38.3
Unemployed	75	50.3
Smoking status		
Yes	1	0.7
No	148	99.3
Alcohol use		
Yes	3	2.0
No	146	98.0

4.2 Clinical characteristics of the participants

4.2.1 Comorbidities

Twenty-two (14.8%) participants had other underlying conditions apart from cancer **(Table 2**). These were hypertension (10, 6.7%), HIV/AIDS (4, 2.7%), and diabetes mellitus (2, 1.3%) among others

Table 2: Clinical characteristics of the participants

Other illness	**Frequency (N=149)**	**Percentage (%)**
Yes	22	14.8
No	127	85.2
Illness	**Frequency (N=149)**	**Percentage (%)**
None	127	85.2
Allergy	1	0.7
Arthritis	1	0.7
Diabetes	2	1.3
Human immunodeficiency virus(HIV/AIDS)	4	2.7
Hypertension	10	6.7
Hypertension + Diabetes mellitus(DM)	2	1.3
Hypertension + DM + Asthma	1	0.7
Peptic ulcer disease(PUD)	1	0.7

4.2.2 Non cancer medications

The other medications that the patients were using for the management of comorbidities are presented in **Table 3.0.** Four (2.7%) hypertensive participants were using nifedipine

and hydrochlorothiazide and four (2.7%) who had HIV/AIDS (4, 2.7%) were on TDF/3TC/DTG regimen.

Table 3: Non- cancer medications

	Frequency (N=149)	Percentage (%)
None	121	81.2
Amlodipine	1	0.7
Felodipine + Enalapril	1	0.7
Hydrochlorthiazide(HCTZ)	2	1.3
Insulin + HCTZ + Atenolol 50	1	0.7
Metformin + Glibenclamide	2	1.3
Metformin + Glibenclamide + HCTZ + Atenolol 50	1	0.7
Metformin + Glibenclamide + Salbutamol + Enalapril	1	0.7
Methyldopa	1	0.7
Nifedipine + HCTZ	4	2.7
Ibuprofen	3	2.0
Ibuprofen + Omeprazole	1	0.7
Omeprazole	1	0.7
Prednisolone	3	2.0
TDF/3TC/DTG	4	2.7
Zoledronic acid	2	1.3

4.3 Cancer-related information

Table 4.0 summarizes the details regarding the type of cancer the participants had. The majority (140, 94.0%) had breast cancer and 59 (39.6%) had the disease for a duration of between 1-2years. The majority of the participants (134, 89.9%) were using doxorubicin and Cyclophosphamide combination. The summary of anthracyclines that were used by

the cancer patients was also done and found out that one hundred and forty-seven (98.7%) participants were using doxorubicin of which only one was using liposomal doxorubicin while only two (1.3%) patients were using epirubicin. For the patients who were using the AC regimen, fourteen transitioned to paclitaxel use only while eleven transitioned to paclitaxel and trastuzumab combination.

Table 4: Cancer-related information

Cancer	**Frequency (N=149)**	**Percentage (%)**
Breast cancer	140	94.0
NHL	3	2.0
KS	1	0.7
ALL	4	2.7
Endometrial cancer	1	0.7
Duration of illness	**Frequency (N=149)**	**Percentage (%)**
<1 year	39	26.2
1-2 years	59	39.6
2-3 years	27	18.1
>3 years	24	16.1
Anti-cancer regimen	**Frequency (N=149)**	**Percentage (%)**
AC	134	89.9
TAC	5	3.4
CHOP	8	5.4
Other	2	1.3

AC= Doxorubicin and cyclophosphamide; TAC=Docetaxel, Doxorubicin, and cyclophosphamide; CHOP= cyclophosphamide, Doxorubicin, vincristine, and prednisolone; Other= (Epirubicin, cyclophosphamide, 5-fluorouracil and Epirubicin, cyclophosphamide)

4.4 Cardiac toxicities

Forty-four participants had cardiac toxicities accounting for 29.5% of the study participants and the different types are shown in **Table 5**. Nineteen (12.8%) had a reduced ejection fraction with type I diastolic dysfunction.

Table 5: Distribution of the cardiac toxicities (n=149)

	Frequency (N=149)	Percentage (%)
None	105	70.5
Reduced LVEF	17	11.4
Reduced LVEF + Type I Diastolic dysfunction	19	12.8
Reduced LVEF + Type I Diastolic dysfunction + Dilated cardiomyopathy	4	2.7
Reduced LVEF + Dilated cardiomyopathy	1	0.7
Sinus tachycardia	1	0.7
Dilated cardiomyopathy	1	0.7
Reduced LVEF + Dilated cardiomyopathy + Sinus tachycardia	1	0.7

4.5 Association between cardiac toxicity and socio-demographic characteristics

The association between cardiac toxicity and socio-demographic characteristics of the participants was evaluated using Pearson's chi-square and is shown in **Table 6.** There was a statistically significant association **(p=0.002)** between BMI and cardiac toxicity. High BMI was a predisposing factor

Table 6: Association between cardiac toxicity and socio-demographic characteristics

Variable	CARDIAC TOXICITY		P VALUE
	Present n (%)	Absent n (%)	
BMI			
High	36 (38.3)	58 (61.7)	**0.002***
Normal	8 (14.5)	47 (85.5)	
Age			
<50	23 (27.1)	62 (72.9)	0.446
≥50	21 (32.8)	43 (67.2)	
Marital status			
Married	44 (31.2)	97 (68.8)	0.060
not married	0 (0.0)	8 (100.0)	
Employment status			
Employed	27 (36.5)	47 (63.5)	0.064
Not employed	17 (22.7)	58 (77.3)	
Level of education			
None	1 (25.0)	3 (75.0)	0.839
Primary	16 (32.7)	33 (67.3)	
High school	20 (30.8)	45 (69.2)	
Tertiary	7 (22.6)	24 (77.4)	

4.6 Association between cardiac toxicity and comorbidities

The associations between cardiac toxicity and comorbidities are shown in **Table 7**. A statistically significant association was demonstrated between hypertension and cardiac toxicity (**p=0.021**). However, other diseases like diabetes mellitus, HIV/AIDS and arthritis did not show any statistically significant associations.

Table 7: Association between cardiac toxicity and comorbidities

Variable	CARDIAC TOXICITY		P VALUE
	Present n (%)	Absent n (%)	
HTN			
Yes	8 (61.5)	5 (38.5)	**0.021***
No	36 (26.5)	100 (73.5)	
DM			
Yes	2 (40.0)	3 (60.0)	0.632
No	42 (29.2)	102 (70.8)	
HIV/AIDS			
Yes	1 (25.0)	3 (75.0)	0.998
No	43 (29.7)	102 (70.3)	
Arthritis			
Yes	0 (0.0)	1 (100.0)	0.996
no	44 (29.7)	104 (70.3)	

4.7. Association between cardiac toxicity and other drugs

The association between cardiac toxicity and other drugs that the participants were using was evaluated using Pearson's chi-square and is shown in **Table 8**. There was a statistically significant association **(p=<0.001)** between trastuzumab and cardiac toxicity. Trastuzumab was a predisposing factor. Similarly, there was also a statistically significant association **(p=0.012)** between paclitaxel and cardiac toxicity. Equally, paclitaxel was a predisposing factor.

Table 8: Association between cardiac toxicity and other drugs

	CARDIAC TOXICITY		P VALUE
	Present n (%)	**Absent n (%)**	
Antihistamine			
YES	3 (75.0)	1 (25.0)	0.077
NO	41 (28.3)	104 (71.7)	
Cyclophosphamide			
YES	44 (30.1)	102 (69.9)	0.555
NO	0 (0.0)	3 (100.0)	
Docetaxel			
YES	2 (22.2)	7 (77.8)	0.996
NO	42 (30.0)	98 (70.0)	
Enalapril			
YES	1(50.0)	1(50.0)	0.523
NO	43(29.3)	104(70.7)	
NSAIDs			
YES	0 (0.0)	4 (100.0)	0.320
NO	44 (30.3)	101 (69.7)	
Paclitaxel			
YES	13 (50.0)	13 (50.0)	**0.012***
NO	31 (25.2)	92 (74.8)	
TDF/3TC/DTG			
YES	2 (50.0)	2 (50.0)	0.582
NO	42 (29.0)	103 (71.0)	
Trastuzumab			
YES	12 (66.7)	6 (33.3)	**<0.001***
NO	32 (24.4)	99 (75.6)	
5HT3 antagonist			
YES	43 (29.7)	102 (70.3)	0.998
NO	1 (25.0)	3 (75.0)	

4.8 Independent predictors of cardiac toxicity

Logistical regression was done to establish the independent predictor of cardiac toxicity. The dependent variable was cardiac toxicity.

Overweight (BMI≥25) was an independent predictor of cardiac toxicity ((AOR=2.66; 95% CI 1.03-6.86; **p=0.043)** participants who were overweight were 2.66 times likely to develop cardiac toxicity which was statistically significant.

The occupation was found to be an independent predictor of cardiac toxicity (AOR=2.52 95%CI 1.02-6.24**, p=0.046**). Participants who were employed were 2.52 times likely to develop cardiac toxicity and this finding was statistically significant.

Similarly, hypertension was also found to be an independent predictor of cardiac toxicity (AOR=4.97; 95% CI 1.21-20.47; **p=0.026**). After multivariate logistical regression was done it was found that hypertensive patients were 4.97 times likely to develop cardiac toxicity and this was statistically significant.

Trastuzumab was also an independent predictor of cardiac toxicity (AOR=6.14; 95%CI 1.51-24.95; **p=0.011**). Participants who were on trastuzumab were six times more likely to develop cardiac toxicity as compared to those who were not using trastuzumab. This finding was statistically significant. However, Paclitaxel was not an independent predictor of cardiac toxicity**.**

Table 9: Independent predictors of cardiac toxicity

Variable	Bivariate Analysis		Multivariate analysis	
	COR(95%CI)	**P-value**	**AOR(95%CI)**	**P-value**
Overweight	3.65 (1.55-8.59)	**0.003***	2.66 (1.03-6.86)	**0.043***
Occupation	1.96 (0.96-4.02)	0.066	2.52 (1.02-6.24)	**0.046***
Age ≥50	1.31 (0.65-2.67)	0.447	1.67 (0.70-3.93)	0.248
Hypertension	4.44 (1.37-14.47)	**0.013***	4.97 (1.21-20.47)	**0.026***
Diabetes mellitus	1.62 (0.26-10.04)	0.605	0.85 (0.08-8.94)	0.889
HIV/AIDS	0.79 (0.08-7.82)	0.841	2.21 (0.16-31.34)	0.557
Trastuzumab	6.19 (2.15-17.82)	**0.001***	6.14 (1.51-24.95)	**0.011***
Paclitaxel	2.97 (1.24-7.08)	**0.014***	1.06 (0.32-3.54)	0.922
5HT3 antagonist	1.27 (0.13-12.50)	0.841	1.64 (0.10-25.71)	0.725
Docetaxel	0.67 (0.13-3.34)	0.622	0.34 (0.04-3.11)	0.341
Antihistamine	7.61 (0.77-75.29)	0.083	7.55 (0.28-204.63)	0.230

COR= Crude odds ratio; AOR=Adjusted odds ratio; *** statistically significant**

4.9. Management of cardiac-related toxicities

This section sought to establish the management of cardiac toxicities induced by anthracyclines-based regimen. It was observed that all the participants who had developed various cardiac toxicities were not on any management interventions towards the cardiac toxicities. These interventions would involve the use of ACEI to minimize cardiac remodeling and the use of dexrazoxane to prevent the anticipated occurrence of cardiac-related toxicities.

CHAPTER FIVE: DISCUSSION, CONCLUSION, AND RECOMMENDATIONS

5.0 Introduction

This chapter discusses the key findings of the study. It is divided into five key areas which include discussion, summary, conclusion, and recommendations.

5.2. Discussion

The mean age of the study participants was 47.9 and the median of 49. This is comparable to many other studies that investigated the cardiac events following anthracycline use (28,21,46,16). A study was done in Saudi Arabia in women whose mean age was 49 reported that postmenopausal women were at an increased risk of developing cardiac toxicity from trastuzumab (28) and many other studies have reported that old age as a risk factor is associated with cardiotoxicity (47,48,49). Notably, old age is a risk factor for developing cardiac toxicity in women with early breast cancer who were treated with trastuzumab(49) which is compounded by the presence of cardiac comorbidities like hypertension and diabetes mellitus. These findings are in line with those of another study that observed that cancer patients with cardiovascular disease were older and at a more advanced stage of cancer than those without comorbidities(46). However, our study did not find any significant association between age and cardiac toxicity which concurred with the observations made by studies done in Uganda and China(7,50) that also did not find any significant association between age and cardiac toxicity

Smoking is associated with cardiac toxicity (28, 51). Interestingly, only one of the study participants was a smoker and association between smoking and cardiac toxicity could

bot be made from our study. Kibirige *et al* in their study, however, noted there was no association between smoking and the risk of developing cardiac toxicity(7).

The employment status (formally and informally employed) was significantly associated with cardiac toxicity contrary to findings from a study by Plana et al (52). This could be due to the effect of other variables which could have acted as effect modifiers to indicate a positive association when indeed there was none.

High BMI was a risk of developing cardiac toxicity. This finding is consistent with the observation made by other studies (50, 28) which also reported that obesity was associated with cardiac events especially in patients who are using anthracycline and trastuzumab. Our finding is further corroborated with the findings of a systematic analysis and meta-analysis studies that reported that overweight had a significant association with cardiac toxicity and it is associated with poor treatment outcome which affects the overall survival and disease-free survival(53,54). The mechanism by which obesity could influence the development of cardiac toxicity is increasing the expression of pro-inflammatory adipokines and down-regulates anti-inflammatory adipokines which could result in their imbalance. This maintains a chronic inflammatory state which promotes the development of cardiovascular disease (52). The other mechanism is that obesity is significantly associated with the activation of neurohormone, increases oxidative stress, increases hemodynamic load and remodeling of the left ventricle(50). Gonzalez *et al* in their study demonstrated that patients who were overweight and obese had a higher probability of developing diastolic dysfunction, they further reported that old age and higher BMI were independent predictors of diastolic dysfunction (21). However, a study was done in the US that sought to assess the cardiovascular risk factors

contrasted with our findings where they found that hypercholesterolemia and obesity were not significantly associated with the increased risk of a cardiac event(53).

Diabetes mellitus is independently associated with decreased survival probabilities among patients with cancer (46). The presence of coronary artery disease and diabetes mellitus is associated with more than two times increased risk of an eventual cardiac event. Consequently, the presence of coronary artery disease and positive family history of diabetes increases the probability of developing cardiac toxicity(28,52,54). However, our study did not establish this association and concurs with a prospective study by Russell *et al* which observed that coronary artery disease, diabetes Mellitus and valvular dysfunction were not associated with the development of cardiac toxicity in patients treated with doxorubicin(55).

Hypertension was an independent predictor of cardiotoxicity. This finding agrees with those of a similar study that was conducted in sub-Saharan Africa that demonstrated that uncontrolled hypertension predisposes patients to cardiomyopathy(56). Another study that was conducted in the US identified hypertension as the most prevalent comorbidity in patients with breast cancer(49). The researchers further found out that the presence of an additional condition was associated with an increased risk of additional cardiac events.

Kuriakose *et al* in their study found out that patients with hypertension had a 58% high risk of developing cardiac toxicity and in older women who were treated with adjuvant doxorubicin, and a highly significant predictor of the development of congestive heart failure(12,50,59). Hypertension is also significantly associated with Trastuzumab induced cardiac toxicity(57). The prognostic impact of cardiovascular diseases on cancer patients

shows that hypertension is associated with poor prognosis(46). There is a strong association between heart failure and mortality in patients with breast cancer. These observations were contrasted by studies done in Uganda and Saudi Arabia but they both explained that their observation was due to their small number of participants (7,28).

Trastuzumab was also found to be an independent risk factor of cardiac toxicity. This finding concurs with a study done by Jawa *et al* (57). According to the study, patients who were using Trastuzumab and had other comorbidities like hypertension and diabetes mellitus had a significant risk of developing cardiac events than patients who did not have any comorbidity.

The use of trastuzumab is directed against HER2 positive breast cancer, resulting in a 50% reduction of recurrence and up to 33% improvement in survival (58). Of note, this improvement creates an increase in cancer survivors at risk of developing cardiac events. This study is comparable to our study in which 31% of the patients who had breast cancer used doxorubicin plus cyclophosphamide followed by trastuzumab. Cardiac toxicity associated with trastuzumab often occurs early than the one caused by anthracyclines independent of the dose and more importantly it is irreversible (28,59,60). The most commonly used taxanes are paclitaxel and docetaxel. Paclitaxel was found to be associated with cardiac toxicity. However, the association was lost after multivariate regression analysis was done. Paclitaxel-related cardio-toxicity occurs generally at conventional doses but it is usually mild (61). The patients are usually asymptomatic and when the symptoms manifest they usually resolved after discontinuation of the drug, but when it is combined with anthracyclines the incidence of cardiac toxicities increases, which usually occurs at lower cumulative doses(58). This could explain why our

association got lost after multivariate regression analysis was done. Moreover, paclitaxel-related cardiac toxicity increases among patients who have high-risk features like diabetes mellitus, hypertension, and radiotherapy to the chest wall(61).

Cyclophosphamide is a key component in most cancer treatment regimens. Several studies have demonstrated that cyclophosphamide is associated with anthracycline-induced cardiotoxicity (29,58,59). The possible mechanism is direct endothelial injury followed by extravasation of the toxic metabolites resulting in interstitial hemorrhage, edema, and damage to the cardiomyocytes (58). The other mechanism is that it forms a cross-link to guanine bases in the DNA double helix strand thus directly attacking the DNA and subsequently hindering DNA replication, which will cause cardiotoxicity to appear with various clinical manifestations from asymptomatic pericardial effusion to heart failure (59)**.** However, our study did not find any significant association between cyclophosphamide and cardiac toxicity despite it is extensive use.

A Meta-analysis study conducted in Japan reported that cardiac events (reduced LVEF or Heart Failure) were reduced with prophylactic use of β-blockers or ARBs. They concluded that the prophylactic use of these agents might be a beneficial option for patients with a high risk of cardiotoxicity(62). Aggressive management of Cardiovascular risk factors improves the long term outcome in cancer survivors(63)

Patients with anthracycline-induced cardiotoxicity may have a better outcome when treated with ACEIs or B-blockers after early detection(10)**.** Various toxicity reduction strategies which include using less cardiotoxic anthracyclines e.g. liposomal doxorubicin, longer anthracycline infusion duration, or dexrazoxane are cardioprotective(64).

Liposomal doxorubicin was designed to reduce the risk of cardiotoxicity related to convention doxorubicin (30). Encapsulation of anthracyclines in liposomes modifies the pharmacokinetics of the drug leading to selective uptake by tumor cells and reduced clearance by tumor cells as opposed to healthy tissues. It is stable and remains intact in the circulation, and is responsible for reduced toxicity without impacting it is efficacy(65). The use of liposomal doxorubicin is associated with a lower risk of a cardiac event than conventional doxorubicin with no difference in response rate and survival(60). However, in our study, all participants with breast cancer were not using liposomal doxorubicin. This could be attributed to its high cost that has prevented its use and also the available protocol for breast cancer did not include it in its regimens.

Several studies and the European society of medical oncology(ESMO) have also recommended the use of dexrazoxane since it tends to chelate iron before it is converted to a more potent free radical(72,37,73). Dexrazoxane forms a complex chelate by forcing TOP2β to assume a closed clamp conformation which is essential in cardiomyocyte damage.

Similarly, the European society of cardiology recommends that early therapeutic approaches for LVEF or even asymptomatic patients after anthracyclines use recommend the use of ACEIs or ARBs(68).

several studies demonstrated that ACEIs and ARB's use are associated with improved LVEF (54,60,69). The initiation of ACEIs has protective effects on the progression of cardiac events since more than 80% of the patients recover from heart failure (51,70).

However, AHA guidelines recommend treatment of HF in stage III and IV and not in stages I and II(71).

5.3 Conclusions

Hypertension, use of trastuzumab, and BMI were identified as independent predictors of cardiotoxicity.

5.4 Recommendations

5.4.1 Recommendations for policy and practice

1. Lifestyle modifications strategies like weight reduction and physical exercise should be incorporated in the routine management for patients who have higher BMI.
2. Customization and adoption of ESMO guidelines on the management of cardiac toxicities induced by anthracyclines to the Kenyan setting
3. Aggressive management of hypertension in hypertensive cancer patients should be done in synchronization with the management of cancer.

5.4.2 Recommendation for further research

1. Further prospective research is necessary covering a large number of participants to evaluate the impact of RAAS blockers on cardiac toxicities.
2. Our study showed that participants who were self or formally employed were associated with cardiac toxicity; a further study is needed to reveal reasons for this finding.

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APPENDICES:

Appendix1A. Patient consent form English version

Title: Determinants and management of anthracycline-induced cardiac toxicities in cancer patients on anthracycline-based regimen at Kenyatta National Hospital

Principal Investigator

Dr. Stephen Makori Gichana, Department of Pharmaceutics and Pharmacy Practice, UON, Tel: 0715162752

Introduction

I am Dr. Stephen Makori Gichana, a student at the University of Nairobi, pursuing a Master of Pharmacy in Clinical Pharmacy. The purpose of this consent form is to give you the information you will need to help you decide whether or not to be a participant in the study. The main objective of this study is to establish the variables that influence the frequency of cardiac-related toxicities of anthracycline-based regimen and their management strategies in adult patients with cancer at Kenyatta National Hospital. I am therefore requesting you to allow me to ask you questions and examine you to assess the adverse drug events on different systems and also peruse through your medical records to assess the relevant laboratory test results. I will request you to sign your name on this form once you agree to take part in the study. We will give you a copy of this form for your records. Kindly, I request you to oblige.

Voluntary participation

Your participation in the study is voluntary. You may withdraw from the study at any time without necessarily giving a reason for your withdrawal. Refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities.

Risks and/or discomfort

There is no major risk involved. There will be no financial obligation on your side. During the assessment, precautions will be taken to ensure your privacy and comfort.

Benefits

The results obtained will be shared with your clinician and may be used effectively to manage your condition. Any information concerning the disease will be offered at no financial cost. Therapy may be altered to ensure that adverse drug events are minimized. The results may be used by the government to predict the incidence of adverse drug events associated with the anthracycline-based regimen.

Confidentiality

The effort will be made to keep personal information confidential. The information will be kept under lock and key and electronic information will be under a password. The information will only be used to facilitate your treatment and for academic purposes.

Justice

You will be given the same treatment as other participants regardless of the outcome. Your social status, gender, culture, or lifestyle will not negatively affect the treatment. There will be no discrimination.

Veracity

I will be truthful with all the information given. The importance of each question will be explained if requested.

Problems or questions

If you have further questions or concerns about participating in this study, please call or send a text to Dr. Stephen Makori Gichana on Telephone number 0715162752.

For more information about your rights as a research participant, you may contact the Secretary, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee on P.o Box 20723 code 00202; Telephone number 2726300 Ext. 44102; Email: uonknh_erc@uon.ac.ke

Participant's statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that all efforts will be made to keep information regarding my identity confidential. By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

Participant name: _____Participant signature/Thumb print: _____

Date: _____

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

Researcher‘s Name: …….. **Researcher’s signature:** …….

Date: ……..

Appendix1B. Kiswahili version

Idhini ya kuhojiwa: Kiswahili

Mada: Vigezo na uthibiti wa madhara ya moyo yanayosababishwa na dawa aina ya anthracyclines kwa wagonjwa wa saratani katika hospital kuu ya Kanyatta

Mtafiti Mkuu

Daktari Stephen makori Gichana, kitengo cha pharmaceutics and pharmacy practice, chuo kikuu cha Nairobi, simu: 0715162752

Utangulizi

Mimi ni Daktari Stephen Makori Gichana kutoka chuo kikuu cha Nairobi. Nafanya shahada yangu ya uzamili katika clinical pharmacy. Lengo la idhini hii ni kukupa taarifa ambayo itakuwezesha kuamua au kukataa iwapo utashiriki katika utafiti huu. Azima ya utafiti huu ni kuthibitisha vigezo vya madhara ya moyo yanaohusiana na dawa aina ya anthracycline na jinsi ya kuthibiti hayo madhara katika hospitali kuu ya Kenya. Kwa hivyo,nakuomba unikubalie nikuulize maswahi na nichunguze madhara ya dawa katika mwili wako. Pia nitachunguza jadala lako la matibabu kuangalia uchunguzi uliofanywa kutoka kwa mahabara. Nitakuomba utie sahii kwa nakala hii ukishakubali kushiriki katika utafiti huu. Tutakupa kopi ya nakala hii ukaiweke. Tafadhari, nakumba ukubali.

Kushiriki kwa hiari

Kushiriki kwako ni kwa hiari. Unaweza kujiondoa kutoka kwa uchunduzi huu wakati wowote bila kutoa sababu za kujiondoa kwako. Kukataa kushiriki katika uchunguzi huu

haiwezi ikaathiri huduma zozote unahitajika kupata katika hospitali hii ama hospital yeyoye ile.

Madhara

Hakuna madhara yeyote. Hautahitajika kugharamikia chochote. Katika kutathmini,tutaweka kila tahadhari kuhakikisha kwamba siri na faraja zako zimehifadhiwa.

Manufaa

Majibu nitakayopata nitamwarifu daktari wako na yanaweza kutumika kuthibiti maradhi yako. Ujumbe kuhusu ugonjwa wako utaambiwa bila malipo yeyote. Matibabu yanaweza yakabadilishwa ili kupunguza madhara ya dawa. Majibu yanaweza yakatumika na serikali ili kubaini uwepo wa madhara yanayosababishwa na dawa aina ya anthracyclines.

Siri

Nitajizatiti kuhakikisha kwamba habari zozote za kibinafsi zimewekwa siri. Habari hizo zitaifadhiwa chini ys ulinzi mkali na nakala ya elektronic itawekwa nywila kwa ajili ya kuilinda

Haki

Utapewa matibabu kama wagonjwa wengine bila kujali aina ya matokeo. Hali yako ya kijamii, jinsia,tamadumu au mtindo wa maisha haiwezia ikaathiri matibabu. Hakutakuwa na ubaguzi.

Ukweli

Nitakuwa na ukweli kwa kila habari utakayonipa. Umuhimu wa kila swali utaelezwa iwapo nitaombwa kufanya ivo

Tatizo au maswali

Iwapo una swali au wasiwai wowote kuhusu utafiti huu,tafadhari piga simu au tuma arafa kwa Daktari Stephen Makori Gichana simu 0715162752.

Kwa habari zaidi kuhusu haki zako kama mshiriki,unaweza kujulisha katibu , Kenyatta national hospital-university of Nairobi Ethics and Research committee kwa simu 2726300 Ext 44102,SLP 20723-00202 Nairobi,tofuti:uonknh_erc@uon.ac.ke

Kauli ya mshriki

Nimesoma au nimesomewa nakala hii ya idhini. Nimekuwa na fursa ya kuzungumuzia utafiti na mtafiti mkuu. Maswali yangu yameweza kujibiwa kwa lugha ninayoielewa. Nimelezewa Madhara na manufaa yake. Ninaelewa kwamba kushiriki kwangu kwa hii utafiti ni kwa hiari na ninaweza kujiondoa wakati wowote. Kwa uhuru wangu nimekubali kushiriki katika utafiti huu.

Ninaelewa kwamba juhudi zitawekwa ili kuweka habari zozote kunihusu siri. Kwa kutia sahihi hii nakala ,sijapeana haki zangu za kisheria ambazo niko nazo kama mshiriki kwa utafiti huu.

Jina la mshiriki…….…….Sahihi……..

Tarehe……..

Kauli ya mtafiti

Mimi, nliyetia sahihi, nimeweza kueleza mshiriki maswala yote kwa kina na ninatumai kwamba ameelewa na amehiari kwa uhuru kupeana idhini.

Jina ya mtafiti…….…… sahihi…….

Tarehe……..

Appendix 2: Data collection tool

Part A: QUESTIONNAIRE

Socio-demographic characteristics

1. Unique identifier number: ----------

2. Sex: (1) Male (0) Female

3. Age: _____years

4. Weight: _____Kg (b) Height _____M

5. BMI_____ Kg/M^2 {BMI=Weight (Kg) ÷Squared Height (M^2)}

BMI	<18.5	18.5-24.9	25-29.9	≥30
Code	1	2	3	4

6. BSA (m^2) $=\sqrt{\frac{[height(cm)*weight(kg)]}{3600}}$ ----------

7. What is your marital status?

Married (1) Never married (0) Widow (0) Widower (0) 8. What is your level of education: None (1) Primary (2) Secondary (3) Tertiary

9. What is your employment status?

Formally employed (0) Self- employed (1) Unemployed (2)

10. Do you or did you used to smoke?

Yes (1) No (0)

11. If yes, in (10), how many sticks per day?

<5(1) >5 (2) A packet (3) > A packet (4)

12. Do you or did you used to take alcohol?

Yes (1) No (0)

13. If yes in (12), how much? ----------

Clinical profile

14. Do you suffer from any other illness beside cancer Yes (1) No (0)

If yes, which one (s)?

S/NO	**Condition**	Yes	No
15	Hypertension	1	0
16	Diabetes mellitus	1	0
17	Dyslipidemia	1	0
18	Coronary artery disease	1	0
19	Peripheral artery disease	1	0
20	HIV/AIDS	1	0
21	Any other? Specify----------	1	0

22. Are you using any medicines besides the ones for cancer?

Yes (1) No (0)

23. If yes, in (22), which ones? ----------

Part B: Data Abstraction Form (Data obtained from patient records)

24. Type of cancer ----------

25. Duration of illness from the cancer----------

26. Type of anti-cancer regimen used----------

Risk factors of cardiotoxicity

Is any of the following anthracyclines present in the regimen?

S/NO	**Anthracycline**	**Present (1)**	**Absent(0)**
27	Liposomal Doxorubicin		
28	Doxorubicin		
29	Epirubicin		
30	Daunorubicin		

Which dose of the above drugs is prescribed?

S/NO	**Anthracycline**	**Dose mg/m^2**	**Cumulative dose mg/m^2**	**Low (0)**	**Normal (1)**	**High (2)**
31	Liposomal Doxorubicin					
32	Doxorubicin					
33	Epirubicin					
34	Daunorubicin					

Are any of the following drugs present in the regimen?

S1/NO	Drug	Present (1)	Absent (0)
35	Paclitaxel		
36	Docetaxel		
37	Cyclophosphamide		

38	Trastuzumab		
39	5HT3 antagonist		
40	Antihistamine		
41	Any other		

Serum concentration of cardiac biomarkers

	Cardiac Biomarkers	Normal (0)	High (1)
42	Troponin I		
43	BNP		

Cardiac toxicity present? Yes (1). No (0)

If **YES** to above tick where appropriate

S/NO	**Cardiac toxicity**	**Present (1)**	**Absent(0)**
44	Dilated cardiomyopathy		
45	Reduced LVEF		
46	Heart failure		
47	Sinus tachycardia		
48	QT prolongation		
49	Supraventricular tachycardia		

Management strategies

50. Has the dose of the anthracycline ever been reduced? YES (1) NO (0)

51. Is the patient using liposomal doxorubicin? Yes (1) No (0)

52. Is dexrazoxane available in the regimen? Yes (1) No (0)

If **yes** to (52) above,

53. What time was it administered? (0) before chemotherapy (1) after chemotherapy