RISK FACTORS FOR CARDIAC DYSFUNCTION IN CHILDREN ON TREATMENT FOR CANCER AT KENYATTA NATIONAL HOSPITAL

A dissertation in part fulfilment for the degree of Master's of Medicine in Paediatrics and Child Health, University of Nairobi

BY

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DECLARATION

This dissertation is my original work and has not, to my knowledge, been published or for any degree in any other university or forum.

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DEDICATION

For the Glory of God and Honour of this country's children.

To my husband, Andrew for his constant support and encouragement.

To my parents for their unwavering pride, love and belief in me.

To our daughter, Neema, the joy of our lives.

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LIST OF ABBREVIATIONS

ABVD	-	Adriamycin Bleomycin Vincristine Darcabazine
ALL	-	Acute Lymphoblastic Leukaemia
AML	-	Acute Myeloblastic Leukaemia
ASE	-	American Society of Echocardiography
BL	-	Burkitts Lymphoma
CML	-	Chronic Myeoblastic Leukaemia
CHOPP	-	Cyclophosphamide Adriamycin Vincristine Procarbazine Prednisone
DNA	-	Deoxyribonucleic Acid
ECG	-	Electrocardiography
ECHO	-	Echocardiography
EF	-	Ejection Fraction
FS	-	Fractional Shortening
Hb	-	Haemoglobin
HL	-	Hodgkin's Lymphoma
KNH	-	Kenyatta National Hospital
LVIDd	-	Left Ventricular Diameter in end diastole
LVIDs	-	Left Ventricular Diameter in end systole
LVDV	-	Left Ventricular end diastolic volume
LVSV	-	Left Ventricular end systolic volume
NHL	-	Non-Hodgkins Lymphona
NH - Non-BL	-	Non Hodgkins, non-Burkitt's Lymphoma
OR	-	Odd's Ratio
RNA	-	Ribonucleic Acid
UON	-	University of Nairobi
VAC-Cis	-	Vincristine, Adriamycin Cyclophosphiamide & Cisplatin

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ABSTRACT

Introduction: Management of paediatric malignancies requires a multimodal approach to treatment. Modalities include combination of various antineoplastic drugs and radiotherapy. This multimodal approach puts patients at risk of multi-organ toxicity especially the heart. Knowledge of the local risk factors for cardiac dysfunction in paediatric oncology patients on treatment may facilitate strategies that reduce morbidity and mortality.

Objective: To assess the risk factors for cardiac dysfunction in paediatric oncology patients on chemotherapy at Kenyatta National Hospital (KNH).

Design: Descriptive cross-sectional study with a nested case control study.

Setting: The Kenyatta National Hospital General Paediatric Wards, including Paediatric Oncology Ward & Paediatric Opthalmolgy Ward.

Subjects: Paediatric patients admitted to Kenyatta National Hospital with established diagnosis of cancer and who have started chemotherapy.

Procedure: The subjects underwent 12 lead Electrocardiography (ECG) and Echocardiography (ECHO). Children were classified as having cardiac disease if the ejection fraction and fractional shortening was < 55% and < 29% respectively.

Study Duration: February 2006 – April 2006

Results: A total of 111 patients were enrolled of whom 32 had abnormal cardiac function and therefore were classified as cases and 79 with normal cardiac function who were classified as controls. The point prevalence for cardiac dysfunction in paediatric oncology patients on chemotherapy was 29% (95%CI21.2-37.9%). Cumulative anthracycline dose was also an important risk factor with Odd's ratio 1.005 (95% CI 1.001-1.009), p value= 0.02. Associated echocardiographic abnormalities included

diastolic dysfunction 26(23%), pericardial effusion 21(19%), valvular abnormalities 10(9%) and tumour infiltrates 7(6%) of the total study population.

Conclusion:

This study showed that about a third (point prevalence 29%) of paediatric cancer patients on chemotherapy at KNH have cardiac dysfunction as exemplified by left ventricular dysfunction. Cumulative anthracycline dose is a risk factor for cardiac dysfunction in paediatric oncology patients on chemotherapy at KNH. Above the cumulative dose of 200mg/m^2 the attributable risk percentage of cardiac dysfunction is 77%.

Recommendation:

Serial echocardiography should be done on oncology patients undergoing chemotherapy where anthracyclines are part of the treatment protocol. With an attributable risk percentage of 77% above cumulative anthracycline dose of 200mg/m^2, alternative non-anthracycline based treatment protocols are recommended above this level. Lastly, a meta-analysis of published studies and randomised clinical trials should be done to further establish the safety of anthracyclines and to further assess the other risk factors in our population.

RISK FACTORS FOR CARDIAC DYSFUNCTION IN CHILDREN ON TREATMENT FOR CANCER AT KENYATTA NATIONAL HOSPITAL

1. Literature Review

1.1 Introduction

It is estimated that the annual frequency of childhood cancers at Kenyatta National Hospital (KNH) is 125 cases per year. A review of some childhood cancers at KNH by Macharia in 1996 [1], found hospital based prevalence to be 1.27%.

The most common childhood cancers were:

- Lymphomas were the most frequently occurring childhood cancer accounting for 51% of cases (Burkitts Lymphoma 34%, Hodgkin's Lymphoma 11.8%, Non Hodgkin Lymphoma 5.2%),
- Leukemias 22.3% (acute lymphocytic 13.4%, Acute myeloid 6.5% and chronic myeloid 1.4%) Nephroblastoma 8.5%,
- Rhabdomyosarcoma 5.3%
- Neuroblastoma 3.3%, Kaposis sarcoma 1.5%, ovarian cancers 1.4%, osteogenic sarcoma 1.3% and miscellaneous 6.2%.

However, the study did not look into retinoblastoma and brain tumours that are common childhood cancers.

1.2 Treatment of childhood malignancies

The most common approach to cancer treatment is by combination therapy in which various combinations of surgery, radiotherapy and chemotherapy are used to eradicate both the primary neoplasm and metastatic lesions.

At Kenyatta National Hospital, a multimodal approach is used for the treatment of the various paediatric cancers. Cyclophosphamide, adriamycin, prednisone, procarbazine (CHOPP regime) are used for the management of Hodgkin's lymphoma. Drugs used in the management of non – Hodgkin's and Burkitt's lymphoma include vincristine, cyclophosphamide, adriamycin and prednisone. Doxorubicin is used in the induction and consolidation phase of both Acute Myeloid Leukemia (AML) and Acute Lymphoid Leukemia (ALL). Vincristine, Adriamycin, Cyclophosphamide & Cisplatin (VAC –Cis) are commonly used in the treatment of solid tumours. Radiotherapy is one of the multimodal therapies used in the management of Hodgkin's Disease (HD), Non – Hodgkin's Lymphoma (NHL), solid tumours and ALL.

During treatment cytotoxic chemotherapy drugs exert their effect by inhibiting cell proliferation. All proliferating cells, whether normal or malignant cycle through a series of phases: Synthesis of DNA (S phase), Mitosis (M Phase) and rest (G 1Phase). Noncycling cells are quiescent in the G 0 Phase [2]. Cell Cycle Non-specific Anticancer drugs are known to kill cells regardless of their phase, an example are the alkylating agents. Cell Cycle (Phase) Specific anticancer drugs are known to kill only cells that are actively cycling, for example. Ideally these actions should be limited to cancer cells but unfortunately the effects extend to normal cells hence producing unwanted side effects and toxicities.

Cancer chemotherapeutic agents can be broadly classified into:

- Antibiotics such as anthracyclines, actinomycin and bleomycin
- Alkylating Agents such as cyclophosphamide, dacarbazine and busulfan
- Antimetabolites such as methotrexate, fluorouracil and 6-mercaptopurine
- Natural products such as vincristine, dactinomycin and etoposide
- Hormones and Antagonists such as prednisone, tamoxifen and diethylstilbestrol
- Miscellaneous agents such as cisplastin, procarbazine and hydroxyurea.

Anthracycline antibiotics are isolated from Streptomyces peutius var caesius. The two commonly used anthracyclines - daunorubicin and doxorubicin differ only by one hydroxyl group in their biochemical structure. Doxorubicin is the main anthracycline used at KNH. Their anti-cancer activity is due to their ability to inhibit nucleic acid synthesis by binding to both parts of the deoxyribonucleic acid (DNA) helix thereby blocking the normal function of the ribonucleic acid (RNA) and DNA Polymerase [3]. Both the RNA and DNA undergo hepatic metabolism and biliary excretion. There is rapid uptake by the heart, lungs, kidney and spleen but they do not cross the blood brain barrier.

Generally, anthracyclines antibiotics remain one of the most potent antineoplastic agents and have contributed enormously to the excellent treatment results seen in some childhood tumours worldwide [4]. They however do have some unwanted systemic side effects. These include:

- Cardiovascular changes that include congestive heart failure; transient cardiomyopathy (abnormal ECG or arrythmias); chronic cardiomyopathy which is dose dependant and progresses to congestive heart failure; cardiorespiratory decompensation and facial flushing.
- Central nervous system symptoms that include fever and chills.

- Dermatologic changes that include alopecia, hyperpigmentation of nail beds, urticaria and photosensitivity.
- Endocrine changes that include hyperuricaemia, infertility and pre-pubertal growth failure.
- Gastrointestinal changes including stomatitis, oesophagitis, nausea, vomiting, anorexia, diarrhoea, ulceration and necrosis of the colon.
- Genitourinary changes include discolouration of the urine (red/orange), cystitis, haematuria, and urinary frequency.
- Haematological changes include leucopoenia, thrombocytopenia and anaemia
- Hepatic changes include transient elevation of liver enzymes.
- Local signs include tissue necrosis on extravascation, erythematous streaking if given too fast and phlebitis.
- Ocular symptoms such as lacrimation [5].

Pathogenic mechanisms involved in anthracycline cardiotoxicity are not fully understood but are thought to include:

- Production of free radicals derived from the chemical reduction of anthracyclines through metabolic pathways catalyzed by iron;
- Abnormalities in mitochondrial energy metabolism;
- Intracellular calcium overload by stimulation of sacroplasmic reticulum calcium release[3].

The anthracyclines and /or their metabolites may also alter adrenergic balance and trigger the release of endogenous substances such as histamine, arachidonic acid metabolites, platelet activators and calcium all of which are potentially toxic to the myocardium.

The clinical use of these drugs involves carefully weighing benefits against toxicities. Associated toxicities with alkylating agents include bone marrow depression with subsequent leukopenia, thrombocytopenia and anaemia. Use of antimetabolites such as methotrexate can lead to severe mucositis. Drugs such as dactinomycin may lead to bone marrow suppression and skin eruptions. Use of purine antagonists may lead to hyperuricemia predisposing to nephrotoxicity and gout.

1.3 Definition of Cardiac Dysfunction

Based on the Report of the Cardiology Committee of the Children's Cancer Study Group, cardiac dysfunction is defined by left ventricular function deterioration[6]. This dysfunction is monitored by an echocardiography or radionuclide angiography. Significant left ventricular deterioration by echocardiography is defined as the fractional shortening below 29% or a left ventricular ejection fraction below 55%. Significant left ventricular deterioration by radionuclide angiocardiography is defined as, a left ventricular ejection fraction below 55% or a decrease in radionuclide angiocardiographic that is, a left ventricular ejection fraction with stress.

1.4 Risk Factors for Cardiac Dysfunction in children with malignancies

Several risk factors are known to increase the risk of cardiac dysfunction in children with malignancies.

1.5.1: Cumulative Anthracycline Dose

Published literature shows that cumulative anthracycline dose as well as maximal or peak dose of $>50mg/m^2$ are important risk factor for anthracycline related cardiotoxicity. Krischer et al carried out a retrospective cohort study on 6493 children with cancer who had received anthracycline chemotherapy and found that cumulative anthracycline dose had a 5.2 relative risk of

cardiotoxicity above a cumulative dose of 550mg/m^2 [3,7,8]. They also found that above a maximum anthracycline dose of 50mg/m^2, the relative risk of toxicity was 2.8. The various types of cardiotoxicity include:

- **Acute cardiotoxicity** which may develop during therapy after a single dose. It is often subclinical, manifested by vasodilatation, hypotension and reversible ECG changes including arrhythmias. It occurs in 30% of patients within hours of intravenous infusion.
- **Early cardiotoxicity** may occur during treatment or within one year of completion of treatment. This is thought to be as a result of myocyte damage or death which results in depressed left ventricular contractility. Early cardiotoxicity presents as left ventricular dysfunction, myocardial infarction, pericarditis-myocarditis syndrome or sudden death. Early cardiotoxicity is one of the greatest risk factors for development of late cardiotoxicity.
- **Late cardiotoxicity** occurs beyond a year of completion of anthracycline treatment. This probably due to both depressed contractility and an inappropriately thin left ventricle wall which results in persistent elevation of ventricular wall stress which progressively decreases the left ventricular systolic function. There is also evidence of fibrosis due to myocyte degeneration. It presents as dilated-hypokinetic cardiomyopathy, pericardial effusion, left ventricular dysfunction or low-output heart failure [3,7,9].

Table 1.0: Cumulative anthracycline dose and frequency of cardiotoxicity

The table 1.0 below shows the relative risk of cardiac toxicity at various anthracycline cumulative doses [5].

Cumulative Dose (mg/m2)	Relative Risk (%) for myocardial toxicity
<300mg/m^2	1-2%
400mg/m^2	3-5%
450mg/m^2	5-8%
500mg/m^2	6-20%

The risk of cardiotoxicity is lower at cumulative doses <300mg/m^2 i.e. 1 –2 %. This increases to 20% at cumulative doses > 500mg/m^2. It is on this basis that most treatment protocols set a maximum anthracycline cumulative dose of 450 mg/m^2 in their regimes. The risk of cardiotoxicity at lower cumulative doses is increased if patients had a prior history of mediastinal irradiation or concurrent use of cyclophosphamide [5]. Hence most treatment protocols that combine cyclophosphamide and/or mediastinal irradiation set a maximum cumulative dose of 360mg/m^2 [3].

Table 2.0: Adriamycin dose for treatment of various malignancies

Table 2.0 below depicts the various cumulative anthracycline doses set for each tumour depending on the regime.

Malignancy	KNH Regime 1 Cumulative Dose	KNH Regime 2 Cumulative Dose
Leukemia	550	300
Lymphomas NHL/BL HL	 440 300	 410 360
Solid Tumors	360	420
Wilms	250	80

The adriamycin cumulative dose for KNH chemotherapy protocols which range between 80 – 550 mg/m^2 depending on the type of cancer.

Perhaps as a result of better more sensitive diagnostic tools and methods, the frequency of cardiac dysfunction in treated paediatric oncology patients has been noted to be increasing. Mohta et al, found 29.7% of their cohort to have cardiac dysfunction at a mean anthracycline dose of 365 mg/m^2[10]. Their retrospective cohort evaluated forty-seven (47) children who received anthracycline as part of their chemotherapeutic regime over a 2-year period. Using guidelines set by the cardiology committee of the children with cancer study group, they evaluated left ventricular function and found 14 out of the 47 subjects to have cardiac dysfunction [6].

There are other additional risk factors that increase the occurrence of anthracycline related cardiotoxicity in children on anthracyclines possibly through an effect modification. These include:

a) **Pre – existing Heart Disease:** Pre-existing heart disease has been identified as a risk factor for anthracycline induced cardiotoxicity. Von Hoff et al carried out a retrospective analysis of 4018 patient records in an attempt to identify potential risk factors for development of anthracycline cardiotoxicity. They found that the

probability of developing doxorubicin-induced heart failure versus the total dose of anthracycline was higher in patients with previous heart disease or hypertension, as compared to all other patients [11].

b) **Female Sex:** Gender has been reviewed as a risk factor for cardiac dysfunction in children with cancer. Female patients have a higher risk than their male counterparts. Lipshultz et al carried out a retrospective cohort by examining echos of 120 children and adults who had cumulative anthracycline doses of between 244 and 550 mg/m^2 for the treatment of ALL or osteogenic sarcoma in childhood [12]. They evaluated the fractional shortening, contractility and after load and compared the cohort patients with age and sex specific normal ranges. They found that female sex was associated with depressed contractility. They also found that there was an interaction between female sex and cumulative anthracycline dose producing a dose modification effect. They postulated that females might be at higher risk due to:

- Sex-related differences in body composition. Since some cardiotoxic drugs such as anthracyclines are poorly absorbed in fat, their cellular concentrations would be higher in nonadipose tissues e.g. the heart. In their study, the median age at diagnosis for ALL was 4.8yrs while for osteogenic sarcoma was 14yrs. A limitation in this study was the fact that the study population included pre-adolescent and adolescent patients. Only in the former does one finds higher body fat.
- Differential expression of multidrug-resistance gene which governs cellular excretion of some chemotherapeutic drugs such as the anthracyclines.

c) Trisomy 21: This is a clinical syndrome where the presence of an extra chromosome number twenty one (21) results in clinical abnormalities comprising Downs syndrome or mongolism. Krischer et al carried out a retrospective cohort study on 6493 children and found relative risk of cardiac dysfunction to be 3.4 times more in children with Downs syndrome [8]. He suggested that this might be due to the underlying cardiac and endocrine abnormalities found in this syndrome. These include:

- Congenital cardiovascular malformations found in Downs syndrome.
- Undetected hypothyroidism, that can impair myocardial function.
- Cor pulmonale and pulmonary hypertension, which are more common in these children, because of associated pulmonary hypoplasia, frequent and recurrent respiratory infections, hypotonic skeletal muscles of respiration and tracheomalacia.

d) Black Race: Studies have been carried out to consider whether race is a factor in cancer incidences. The retrospective cohort study by Krischer at al, found black race to be a risk factor. They postulated the increased risk to be due to the two to threefold increased risk of idiopathic dilated cardiomyopathy amongst black race and hence increased susceptibility to cardiotoxic chemotherapeutic agents [8]. Clearly more studies need to be done to establish the increased susceptibility.

e) Young Age: Patients who were younger at the time of diagnosis and treatment were at greater risk of cardiac dysfunction primarily as result of their chemotherapy and/or radiation. Anthracyclines, for example, cause thinning of the left ventricle which leads to an elevated ventricular afterload [9].

d) Nutritional Status: It is postulated that nutrition plays a role in cardiac dysfunction amongst children with malignancies. It is thought that the micronutrients – selenium and vitamin E ameliorate the cardiotoxic effects of the anthracyclines [13]. This suggested

that deficiency of micronutrients may predispose patients on chemotherapy to cardiac dysfunction.

Mohta R et al reviewed 47 children who had received anthracycline cumulative dose as part of their treatment for cancer [10]. They measured left ventricular function by ECHO and found that children with low height for age had poorer cardiac tolerance to anthracyclines (p=0.0269).

1.5.2 Type Of Malignancy

Cancer contributes to cardiac dysfunction by any one of the following mechanisms:

- Extrinsic compression of a coronary artery or tumour embolization leading to myocardial infarction
- Metastatic tumours affecting cardiac valvular function by invasion, direct compression or nonbacterial thrombotic endocarditis; and
- Direct tumour extension into the great veins and cardiac chambers [7].

Primary and secondary (metastatic) tumours to the heart are more likely to put patients at risk of cardiac dysfunction. Based on large series on childhood cancers, the incidence for primary tumours was 0.3% and secondary tumours was 1.1%. Non – Hodgkin's Lymphoma, Wilms Tumour, soft tissue and bone sarcomas were the most common cause of distant metastases [14].

A study by Kariuki, evaluated the cardiac status of children with cancer at KNH by comparing them with children who did not have cancer. Echocardiography and electrocardiography were done to evaluate left ventricular function. Lowered cardiac function was found in patients with cancer and was attributed to the presence of malignancy [15].

1.5.3 Radiotherapy

Therapeutic radiation can cause heart damage by injuring various structures either acutely or chronically. Studies show that acute or early changes due to radiation include cytoplasmic damage, capillary injury, Von Willebrand factor release and acute inflammatory reaction. Chronic changes include cell death, fibroblastic proliferation, thickening of pericardium, valvular heart disease and arrhythmias [7].

These changes often lead to a wide range of clinical sequelae including acute pericarditis, chronic pericarditis, coronary heart disease, myocarditis, valvular defects and conduction delays [16].

1.5.4 Other potentially cardiotoxic drugs

Other antineoplastic cardio toxic drugs include:

- **Cyclophosphamide:** is cardio toxic via its active metabolite. The most probable mechanism involves endothelial damage, followed by extravasation of the toxic metabolites causing myocyte lesion, oedema and severe hemorrhagic cardiac necrosis. Cyclophosphamide causes clinical cardiotoxicity when administered in massive doses (120 –240 mg/kg over 1 to 4 days) usually in preparation for bone marrow transplantation. Studies show that reduction of cumulative dose of cyclophosphamide to 1.55 g/m2/day may be associated with some reduction of cyclophosphamide cardiotoxicity.
- **Amsacrine:** is an acridine derivative with antileukaemic effects is potentially cardiotoxic.
- **Cytarabine and 5 – Fluouracil:** are potential cardio toxic based on case reports. ECG findings of the latter suggest coronary spasms with cardiotoxicity presenting as myocardial ischaemia [3,4,14].

1.6 Strategies for mitigating against anthracycline cardiotoxicity

Some of the preventive strategies of anthracycline cardiotoxicity include:

- Early detection cardiotoxicity followed by reductions in anthracycline dose or variation of treatment regime;
- Lowering of peak blood levels by variations in the methods of delivery, for example, prolonged continuous infusion rather than by bolus injection;
- Lowering of peak dose through the use of different treatment schedule or using alternative anthracycline derivatives, for example, liposomal anthracyclines may be less cardiotoxic than other types of anthracyclines [4].

There are some trial cardioprotective agents. A randomised clinical trial by Lipshultz et al found dexrazoxane when given to children who were to receive doxorubicin was associated with reduction in myocardial injury as measures in terms of the troponin T level [17]. Dexrazoxane is thought to reduce the cardio toxic effects of anthracyclines by binding free and bound iron thereby reducing the formation of anthracycline – iron complexes and the subsequent generation of reactive oxygen species. These strategies reduce cardiotoxicity but do not eliminate anthracycline related cardiomyopathy

TECHNIQUES FOR ASSESSING CARDIAC FUNCTION IN CHILDREN ON ANTHRACYCLINE CHEMOTHERAPY

Recognizing the different side effects of drugs used in cancer management, the cardiology committee of the children's cancer study group formulated recommendations for standardized non - invasive monitoring of children on anthracycline treatment [6]. These include:

a) **Electrocardiography**: This is a graphic recording of electric potentials generated by the heart. The signals are detected by means of metal electrodes attached to the extremities and chest wall and are then amplified and recorded by the electrocardiograph. Its advantages include safety, availability and practical. Arrthymias, flattening of T wave, prolongation of QT Interval and decrease in R wave voltage have been used to indicate toxicity. However these changes are non – specific, are reversible and can be produced by extracardiac thoracic processes such as pericardial or pleural effusions, chest wall oedema and anterior masses. Acute ECG changes are not predictive of the degree of anatomic or physiologic impairment due to the anthracyclines. Thus ECG is not an appropriate sole monitoring technique.

c) **Echocardiography**: This is a form of cardiovascular imaging using the principles of ultrasonographic reflection of cardiac structures to produce images of the heart. Two dimensional (2D) and M – mode Echo have been used in many centres to show preclinical deterioration of cardiac function permitting dose modification and reducing the incidence of congestive cardiac failure. Parameters used to assess left ventricular function on Echo include fractional shortening, end diastolic internal diameter and systolic time intervals on 2 Dimensional Echo and more recently rate – corrected velocity of circumferential fibre shortening with end systolic wall stress. Digitised M – Mode echocardiography and doppler flow cardiography can be used to assess ventricular filling rate, a parameter defining diastolic function. Echo is a good tool for

children who have less costal calcification and hence easily obtainable imaging windows. Paediatric echocardiography does not expose the patient to irradiation and there are portable machines that allow bedside assessment of very sick children.

d) **Radionuclide Angiocardiography**: In this diagnostic method an isotopic dye is injected into the patient. Photons are then emitted radionuclide imaging is then obtained using a special camera. It has the added advantage of providing a volumetric measurement, independent of geometric assumptions of ventricular shapes. Whereas echocardiography provides uni-dimensional or two-dimensional measurements, this technique compared to ECHO often affords a more easily obtainable and accurate image during stress. Images maybe obscured by poor uptake of the nuclear isotope by the red blood cells or albumin and competitive in bones and other organs particularly in children. The borders of sampling regions of interest are less precisely on radionuclide angiocardiography than are the endocardial surfaces from ECHO, particularly in small children where ventricular – atrial separation and septal definition are more difficult. With smaller ventricles, imprecision of margins produces a greater percentage of error. There is also a small biologic hazard presented by the small amount of total body irradiation from the isotope. The process allows analysis of diastolic filling rates and hence measurement of diastolic function. However sensitivity, specificity and predictive accuracy of radionuclide angiocardiography to predict anthracycline cardiotoxicity is not available, because there is no ' gold standard' such as contrast ventriculography used in children undergoing chemotherapy.

d) **Endomyocardial Biopsy**: This involves obtaining a tissue specimen from the heart for anatomical evaluation, cardiac toxicity screening and histopathological assessment [6]. The degree of damage, is expressed in terms of a standardized grading scale this

permits comparision of degrees of anatomic damage by different drugs. On histopathology, for example, hemorrhage and oedema are seen with cyclophosphamide cardiotoxicity while with acute anthracycline cardiotoxicity there is predominance of vacuolisation. Fibrosis is more prevalent with chronic anthracycline cardiotoxicity. It has been used to clarify the role of chemotherapy in producing clinical decompensation such as abnormality of ventricular function or congestive cardiac failure.

Risks of endomyocardial biopsy include cardiac perforation, cardiac arrhythmias, coronary – cardiac fistula, pneumothorax, hemothorax and endocardial stripping. The use of endomyocardial biopsy is on the decline since magnetic resonance imaging (MRI) can identify the type of cardiac damage and quantify the extent.

Table 3.0: Procedures for diagnosis of anthracycline – *induced cardiomyopathy*

The table below summarises the various diagnostic procedures and their utility.

Diagnostic Procedure	Characteristics
Physical examination and history taking	• Lack of specificity
Electrocardiography: arrhythmias, flattening of T wave, prolongation of QT interval, decrease in R wave voltage.	• Lack of specificity • Level of risk: None
Serial Transthoracic Echocardiography: measurement of left ventricular ejection fraction.	• High reliability • Wide use and availability • Level of risk: Transthoracic M Mode echocardiography has class one level of risk and this is consider almost nil.
Angiography with radiolabeled antimyosin antibodies	• High sensitivity for cell necrosis • Low specificity • Level of risk: exposure to irradiation
Angiocardiography with methiobenzyl guanidine	• High sensitivity for myocardial neural integrity & cardiac function • Low specificity • Level of risk: exposure to irradiation
Endomyocardial biopsy	• Greatest reliability • Relatively high expense Level of risk: cardiac perforation, cardiac arrhythmias, coronary – cardiac fistula.

STUDY JUSTIFICATION

- The management of paediatric malignancies requires a multimodal approach to management. Treatment modalities include use of various combinations of antineoplastic drugs and radiotherapy. This multimodal approach puts patients at risk of multi – organ toxicity especially to the heart.

- The current prevalence of cardiac dysfunction in children accessing treatment for cancer and the associated risk factors for cardiac dysfunction such as chemotherapeutic drugs (in particular anthracyclines), radiotherapy and type of malignancy is unknown at KNH.

- Anthracyclines are the backbone of cancer treatment at KNH. Anthracycline cardiotoxicity is affected by black race, female sex, pre-existing heart disease and nutritional status.

  Paediatric cancer patients at KNH are universally of African race; a factor already identified as a risk factor for adverse cardiac events following treatment with anthracyclines and is in an environment of widespread malnutrition. These factors may lead to an effect modification of anthracycline metabolism and possible toxicity.

STUDY UTILITY

- The results of the study may demonstrate the magnitude of cardiac dysfunction amongst paediatric cancer patients so that those who take care of these patients may be advised to take preventative measures or where this is not possible to investigate for these complications and institute remedial measures.

- The results may demonstrate important risk factors for cardiac dysfunction in children with malignancy that may be modified and hence reduce morbidity and mortality related to cancer.

- The results of the study may be used as baseline for other follow-up prospective studies for evaluation of cardiac function in children with malignancies.

STUDY OBJECTIVES AND RESEARCH QUESTION

RESEARCH QUESTION

What is the prevalence of cardiac dysfunction in paediatric oncology patients on treatment at KNH? What predisposes these patients to cardiac dysfunction?

PRIMARY OBJECTIVE

1) To determine the point prevalence of abnormal cardiac function among paediatric oncology patients on chemotherapy at KNH

2) To assess the risk factors for cardiac dysfunction in paediatric oncology patients at Kenyatta National Hospital.

SECONDARY OBJECTIVE

3) To describe associated echocardiographic cardiac abnormalities in paediatric oncology patients at Kenyatta National Hospital.

MATERIALS AND METHODS

STUDY DESIGN

Descriptive Cross-sectional Study with a nested Case Control.

STUDY AREA

The study was carried out on patients from the Kenyatta National Hospital (KNH) general paediatric wards including, ophthalmology and paediatric oncology wards. KNH is a teaching hospital for the University of Nairobi and is also the major referral hospital for all paediatric cancer patients in Kenya.

STUDY POPULATION

The population of interest were in-patient children below the age of fifteen (15) years admitted with an established diagnosis of cancer on chemotherapy at Kenyatta National Hospital and whose parents or guardian gave us a signed consent.

Children admitted to KNH with cancer are referrals from district, provincial, mission and private hospitals. Some patients are also referred from the KNH paediatric general and specialized clinics.

Patients with leukaemia, lymphomas, nephroblastoma, neuroblastoma and other solid tumors are admitted to a specialized paediatric oncology ward, which holds on average of twenty five (25) – thirty (30) patients. Due to the high number of patients the four paediatric general wards holds an average of ten (10)- fifteen (15) patients each.

Patients with retinoblastoma and osteogenic sarcoma are admitted to the opthalmology and paediatric surgical ward respectively while patients with brain tumors are admitted to the paediatric neurosurgical ward.

STUDY SITE

Paediatric oncology ward (ward 1E), general paediatric wards and opthalmology ward.

INCLUSION CRITERIA

- Paediatric patients below 15 yrs with an established diagnosis of cancer;
- These patients must have begun chemotherapy;

EXCLUSION CRITERIA

- Patients whose parent or guardian did not give consent;
- Re – admissions who were recruited in the study in a previous admission.

STUDY METHODOLOGY

Patient Selection

Paediatric cancer patients who meet the above inclusion criteria and whose parent or guardian gave consent where sequentially recruited from the paediatric oncology ward (ward 1E), the paediatric general wards (wards 3A, 3B, 3C & 3D) and the opthalmology ward (ward 9C) until the minimum required sample size of 111 patients (with a case: control ratio of 2:5 was attained) was attained.

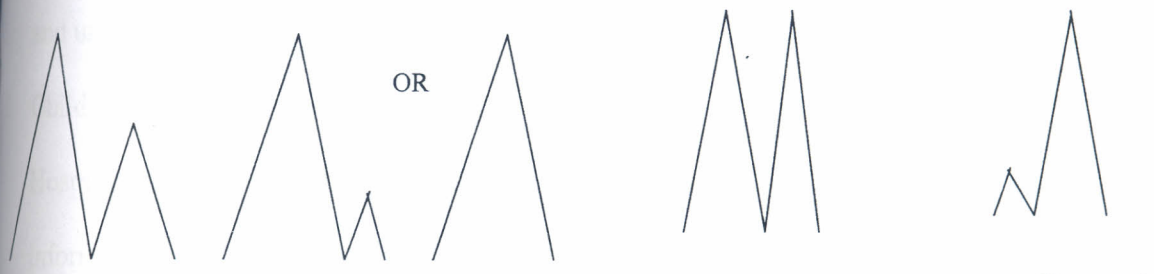
Study Procedure

1 Diagnosis of cancer was made by bone marrow, fine needle aspirate, open biopsy and by various biochemical markers depending on the type of cancer supported by various radiological investigations in conjunction with a team of specialist paediatric oncologists and haematologists. This information was obtained from the patient's medical records. A general examination and patient history was taken. Patient data including anthropometric measurements, cumulative anthracycline dose, cumulative cyclophosphamide dose and history of irradiation were entered into a patient data sheet (Appendix I).

2 Patients were then taken to KNH cardiology department were a twelve lead surface electrocardiography (ECG) and rhythm strip was done on all the study subjects by the investigator assisted by the ECG technologist using a manual cardiofax ECG machine model number 6353 and serial number 00553, Nihon Kohden Corporation, 31-4 Nishiochiai Shinjuku-ku, Tokyo 161, Japan.

3 2-D Echocardiography also was carried in the cardiology department using an echocardiography machine LOGIQ 500 model 2116533-2, serial number 669772YM6 with frequency of 33/02.5MHz.. Manufactured by GE Yokogama Medical Systems LTD, Tokyo, Japan. Subcostal, parasternal, apical and suprasternal views were used. The modalities of echocardiography used were two – dimensional real time, M-mode, pulsed wave dopppler and continuous wave Doppler echocardiography. 2D-real time echocardiography was used to assess the cardiac measurements, visual contractility and any abnormal findings like pericardial effusion, valvular abnormalities and cardiac masses. M-mode echocardiography was used to assess the relative chamber sizes and to calculate the indices of cardiac contractility. Spectral pulsed wave Doppler with sample specimen taken at the tips of the

mitral valve leaflets was used to assess diastolic function. The figure below shows how the pulsed wave Doppler looks in normal and abnormal diastolic function. The first wave is the E wave (excursion) and the second wave is the A (apposition) wave.



Normal **Restrictive** ***Pseudo normalised*** **Reversed**

Diastolic function is measured by peak early velocity (E wave), peak atrial velocity (A wave), E wave/A wave ratio (E/A), E deceleration (EDEC) and Isovolumetric relaxation time (IVRT).

Continuous wave Doppler was used to assess the tricuspid regurgitation. Pulmonary pressures were derived from tricuspid regurgitation using the Bernoulli's equation, $P = 4V2$, where P is the pulmonary pressure and V is the maximum velocity of the tricuspid regurgitation gradient to estimate the pulmonary pressures.

M- Mode Echocardiography investigations were carried out separately by a team of three (3) cardiologists in the presence of the investigator using a uniform methodical protocol based on the set guidelines to reduce interobserver error [19]. On average 3 – 5 Echos were done per day allowing us to complete the date collection over a period of about 3 months.

Y DEFINITIONS

ncer patient was defined as one suffering from a malignant tumour arising from abnormal l uncontrolled division of cells that then invade and destroy the surrounding tissues.

ild was defined as any individual below the age of 15 yrs as per the Kenyatta National spital takes the cut off definition. Age of the child was verified from the bio statistical ormation in the patient's file.

ases were defined as paediatric oncology patients who met the inclusion criteria and on hocardiography they had left ventricular systolic dysfunction as manifested by:

Left ventricular ejection fraction < 55% OR

Left ventricular fractional shortening < 29% [6].

ontrols were defined as paediatric oncology patients meeting the inclusion criteria and on hocardiography they did not have Left Ventricular Systolic dysfunction as manifested by:

Left ventricular ejection fraction > or = to 55% OR

Left ventricular fractional shortening < or = to 29%.

ericardial effusion is the presence of fluid in the pericardial space demonstrable on 2D-chocardiography. It could be anterior, posterior or circumferential. A diagnosis of cardiac amponade was made when there was a pericardial effusion with diastolic collapse of the right trium or right ventricle with poor inspiratory collapse of the inferior vena cava.

Pulmonary Hypertension is said to be present when the mean pulmonary pressure is higher han 30mmHg. This is assessed by Doppler echocardiography of tricuspid regurgitation and a mean atrial pressure of 5-10 added to the tricuspid regurgitation.

Electrogradiography was considered normal when no abnormality was noted. ECG tracings were read using a standard method with scoring criteria. The tracings that were probably within normal limits (PWNL) when one minor abnormality was noted. A borderline tracing (BT) was considered if two minor abnormalities were noted. Probably abnormal tracing (PAT) was considered when one major abnormality was noted. A tracing was considered definitely abnormal (DAT) if two major abnormalities were noted.

ATA MANAGEMENT

AMPLE SIZE DETERMINATION FOR PRIMARY OBJECTIVE 1

he sample size determination was based on the primary objective 1 to determine the point revalence of cardiac dysfunction in children with cancer on chemotherapy at KNH.

ischer's formula for sample size calculation used was: $n = \frac{Z^2_{1-\alpha/2} P(1-P)}{d^2}$

n = minimum sample size.

Z = 1.96 is the normal deviate corresponding to a confidence interval of 95% Confidence **Interval**

α = 0.05 the level of significance (5%)

d = 0.075 the level of precision

P = estimated prevalence of cardiac disease in children with cancer is sixteen percent (16%) at KNH. This prevalence of cardiac dysfunction in children with cancer at KNH was obtained from a local study by Kariuki [21]. She evaluated the cardiac status of children with cancer by comparing them with children who did not have cancer and found prevalence of cardiac dysfunction to be 16%.

Thus: $n = \frac{1.96^2 \text{ X } 0.975 \text{ X } 0.16 \text{ X } 0.84}{0.075^2} = \mathbf{90}$

Thus the minimum number of paediatric cancer patients recurited in this study to obtain the point prevalence was ninety (90). This gave the study 80% power and 95% contingency to determine the true point prevalence of cardiac dysfunction in the stated source population.

SAMPLE SIZE FOR PRIMARY OBJECTIVE 2

Sample size determination was based on the primary objective 2 to assess the risk factors for cardiac dysfunction in paediatric oncology patients on treatment at KNH.

$$n=\frac{\{Z_{1-\alpha/2}\sqrt{2P(1-P)}+Z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\}}{(P_1-P_2)^2}$$

Using the above formula for 2- sample comparisons of proportions for case control where;

n= number of cases

Z= 1.96 is the normal deviate corresponding to a confidence interval of 95%

α = 0.05 (level of significance)

β = 0.20

P_1= proportion of cases with anthracycline cumulative dose >350mg/m^2 i.e 0.30 [10]

P_1 was the proportion of those with the risk factor (anthracycline cumulative dose >350mg/m^2) amongst the cases. Based on a retrospective study in India the proportion amongst the cases who developed cardiac dysfunction above cumulative dose of 300mg/m^2 was 30% or 0.30.

P_2= proportion of controls with anthracycline cumulative dose > 350 mg/m^2 i.e. 0.08

P_2 was the proportion of those with the risk factor (anthracycline cumulative dose >350mg/m^2) amongst the controls. This was an arbitrary estimate since there was paucity of data in this area.

P= pooled proportion with anthracycline cumulative dose > 300 mg /m^2

= $(P_1 + P_2)/2$

Thus $n= \frac{1.087+0.448}{(0.22)^2} = 32$

Minimum number of cases (n) was 32.

Taking a 2:5 ratio for case:control minimum number of cases was 32 and 79 controls.

Data Analysis

All data emanating from this study was entered into a patient data sheet and then recorded into a computer database. It was analysed using SPSS (Statistical Package for Social Sciences software 11.0).

Continuous variables were evaluated by t – tests while Pearson Chi – Square tests were used to evaluate binary variables. Non-parametric test (Mann Whitney Test) were used to evaluate skewed continuous variables.

ETHICAL CONSIDERATIONS

The study was undertaken after approval by the Department of Paediatrics, University of Nairobi (UON) and the Ethical and Scientific Committee Kenyatta National Hospital (KNH). Informed signed consent was sought from the parent or guardian (Appendix IV / Kiambatanisho IV). No patient suffered delay of treatment by inclusion into this study and emergency care and resuscitation took priority over any other procedure. Costs of the tests were borne by the investigator. Results of the tests were availed to the child's primary doctor. Parent/Guardian could withdraw the patient at any stage without any obligation and the management of the child was not compromised. All patient information was treated with strictest confidence.

RESULTS

During the study period February and May 2006, a total of 111 children were evaluated. Their median age was 6 years (Range 0.25-14yrs) with 64% of them being males and 36% of them being females thus a male:female ratio of 1.8:1. Fifty-four (54%) percent of the study population were stunted with height/age Z score less than –2, while 42% had less than –2 Z score weight /age. The median duration of chemotherapy treatment was 4 months (Range 0.25-24 months)

The spectrum of cancers seen include leukaemia in 25(23%) children, followed by 22(20%) children with Wilms tumour , 19(17%) children with Burkitts lymphoma 7(6%) children with retinoblastoma, 8(7%) children had rhabdomyosarcoma & Hodgkins lymphoma, 5(4.5%) had osteogenic sarcoma and 4 (3.5%) had neuroblastoma & non-hodgkins lymphoma.

PREVALENCE OF CARDIAC DYSFUNCTION IN CHILDREN ON TREATMENT FOR CANCER AT KNH

Out of the 111 children enrolled 32 had abnormal cardiac function and were classified as cases. This gave a point prevalence of 29% (95%CI 21.2 – 37.9%). The other 79 children with normal cardiac function were the controls.

Table 4.0: Frequency of patients with cardiac dysfunction in various malignancies

There was an abnormal cardiac function in 36% of the children with leukaemia, 23% in those with Wilms tumour and 32% among those with Burkitts lymphoma. There was a high prevalence of cardiac dysfunction in children with rhabdomyosarcoma (50%) and at least 20% in most of the other tumours, with the exception of teratomas and sarcomas that had no patients with cardiac dysfunction. However, the estimates had very wide confidence intervals because of the small numbers as shown in table 4.0 below.

Malignancy	**Proportion with abnormal cardiac function** (95% **Confidence Interval)**
Leukaemia	9/25 [36% (CI 20–55%)]
Wilms	5/22 [23% (CI 10-43%)]
Burkitts Lymphoma	6/19 [32% (CI 15.4%-54%)]
Rhabdomyosarcoma	4/8 [50% (CI 21.5%-78.5%)]
Hodgkin's Lymphoma	3/8 [38% (CI 13.7%-69.4%)]
Retinoblastoma	2/7 [29% (CI 18-64%)]
Osteogenic Sarcoma	1/5 [20% (CI 3.6%-62.5%)]
Non Hodgkins Lymphoma	1/4 [25% (CI 4.6%-70%)]
Neuroblastoma	1/4 [25% (CI 4.6%-70%)]

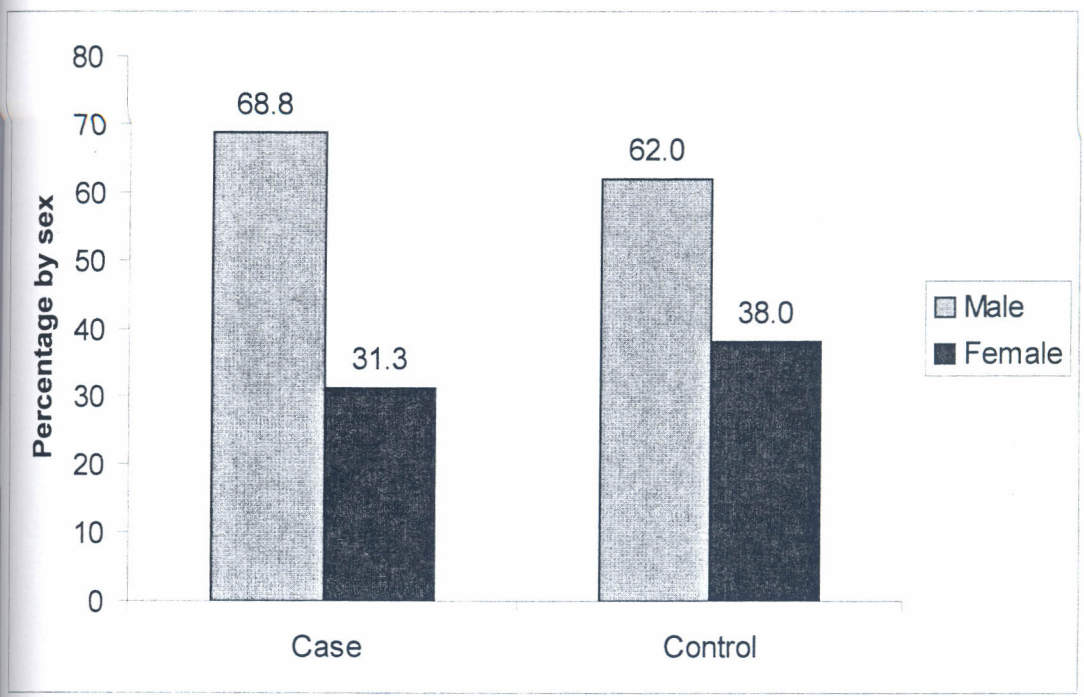
RISK FACTORS ASSOCIATED WITH ABNORMAL CARDIAC FUNCTION

A. SEX

Sex distribution was similar amongst cases and controls. Cases had 69% males, while controls had 62%. Females in cases were 31% while in controls they were 38% with OR 0.8 (95% CI 0.3-1.8) p value 0.7.

Figure 1.0: Sex distribution by case and control

The figure below shows sex distribution by case and control

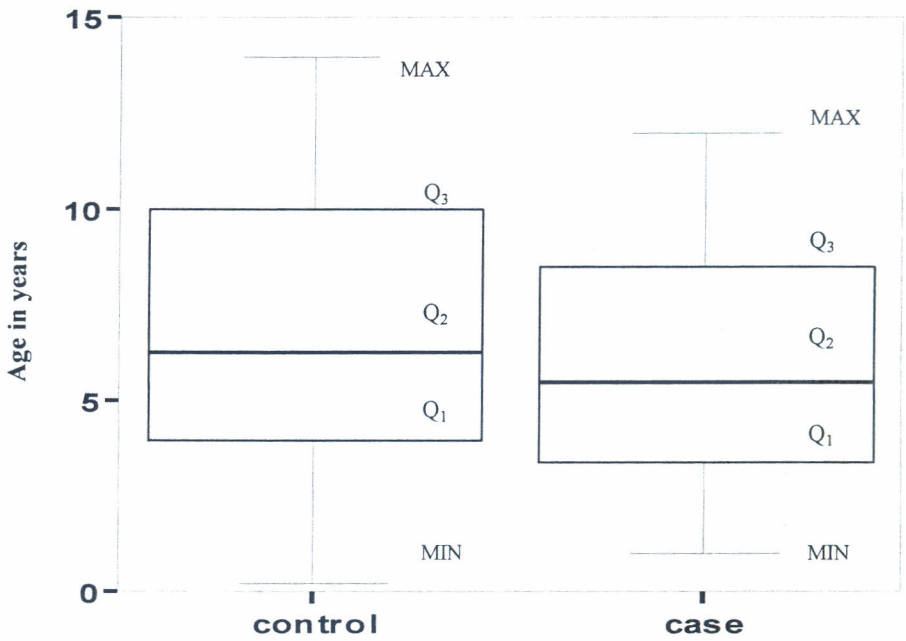


B. AGE

Age distribution was similar among cases and controls. Cases had mean age of 6.2 yrs while controls mean age 6.8 yrs. Age was not statistically significant by independent t-test p value 0.4.

Box Plot 1.0: Age distribution by case and control

The box plot shows that cases and controls were comparative.



Key for controls:
Minimum age = 0.25 yrs
25th percentile = 4 yrs
50th percentile= 6 yrs
75th percentile= 9 yrs
Maximum age = 14 yrs

Key for case:
Minimum age = 1 yrs
25th percentile = 3.6 yrs
50th percentile= 6 yrs
75th percentile= 9 yrs
Maximum age = 12 yrs

Both had a twenty-fifth percentile of approximately 4 yrs, fiftieth percentile (median) of 6 yrs and seventy-fifth percentile of 9 yrs

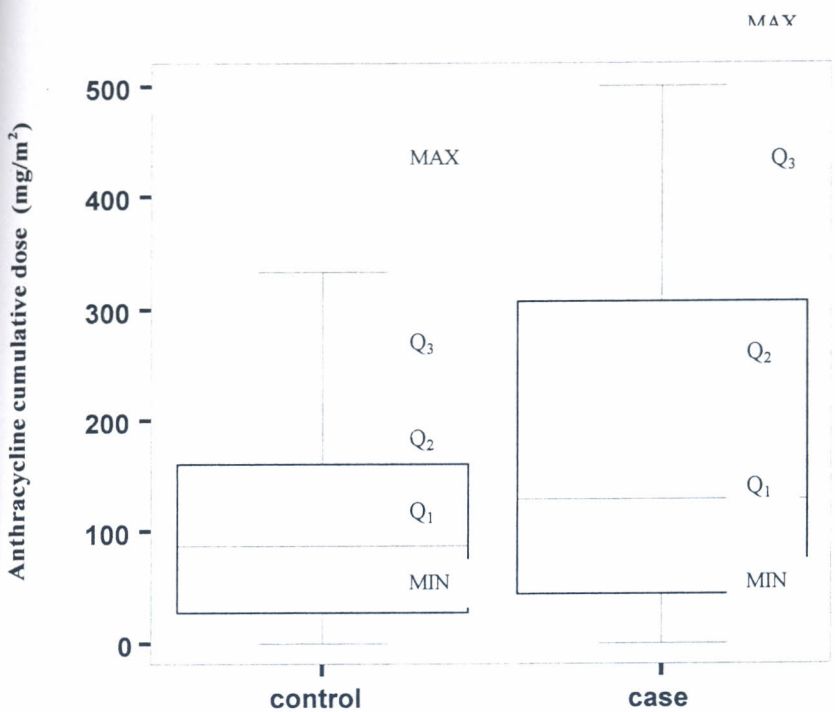
I went a step further and categorized age to further explore age as a risk factor. There was no association between age and frequency of cardiac dysfunction hence age was not a risk factor in this study population this is depicted in table 6.0.

TYPE OF DRUG

The main cardiotoxic drugs used in KNH cancer treatment protocols are the anthracyclines (Table 2.0) and cyclophosphamide.

Box plot 2.0: Cumulative Anthracycline Dose

The median dose was 128mg/m^2 (Range 0 -500 mg/m^2) in cases and 88mg/m^2 (Range 0 - 374 mg/m^2) for controls as shown in box plot 2.0 below. The mean cumulative anthracycline dose was 176mg/m^2 (95% CI 117.5-211.4 mg/m^2) in the cases and 106mg/m^2 (95% CI 84.1-129.9 mg/m^2) in the controls.



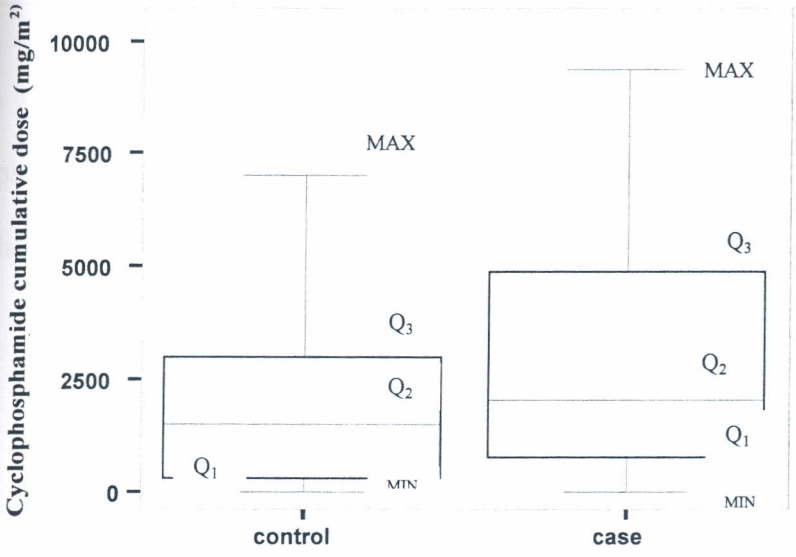
Key for controls:
Minimum dose (mg/m^2) = 0
25th percentile = 28mg/m^2
50th percentile= 88 mg/m^2
75th percentile= 160 mg/m^2
Maximum dose (mg/m^2) = 374

Key for case:
Minimum dose(mg/m^2) = 0
25th percentile = 41mg/m^2
50th percentile = 128 mg/m^2
75th percentile = 308 mg/m^2
Maximum dose (mg/m$_2$) = 500

This difference was statistically significantly at **p=0.02**. Using percentiles, I further explored anthracycline cumulative dose as a risk factor. Above cumulative anthracycline dose of 201mg/m^2 there was a 4.4 increased odds of cardiac dysfunction with an **attributable risk percentage** of **77%** this is depicted in Table 6.0.

plot 3.0: Cumulative Cyclophosphamide Dose

box plot below describes cumulative cyclophosphamide dose in cases and controls. The dian was 2050mg/m^2 (Range 0 - 9363 mg/m^2) for cases and 1510mg/m^2 (0-10300 mg/m^2) for trols.



Key for controls:
Minimum dose (mg/m^2) = 0
25th percentile= 309 mg/m^2
50th percentile = 1510 mg/m^2
75th percentile= 3135 mg/m^2
Maximum dose (mg/m^2) = 10300

Key for case:
Minimum dose(mg/m^2) = 0
25th percentile = 666 mg/m^2
50th percentile = 2050 mg/m^2
75th percentile= 5109 mg/m^2
Maximum dose (mg/m$_2$) = 9363

mean cumulative cyclophosphamide dose was 2880 mg/m^2 (95%CI 1804.0-3515.2 mg/m^2) in cases and 2248 mg/m^2 (95% CI 1758.2-2874.9 mg/m^2) in the controls. This difference was significantly associated with cardiac dysfunction at p = 0.3.

Table 5.0: Summary of Univariate Analysis for Continuous risk factors for cardiac dysfunction

Variable	Case	Control	P-value
Age in years Median (range)	6(1-12)	6(0.25-14)	0.4
Duration of treatment Median (range)	4(0.3-24)	4(0.13-13)	0.7
Cumulative anthracyclines dose (mg/m^2) Median (range)	128(0-500)	88(0-374)	**0.02**
Cumulative cyclophropharide dose (mg/m^2) Median (range)	2050(0-9363)	1515(0-10300)	0.3

There was however no association between age in years, duration of treatment and cumulative cyclophosphamide dose with cardiac dysfunction. There was an association between anthracycline cumulative dose and cardiac dysfunction (p value=0.02)

ible 6.0: Summary of Univariate Analysis of Categorical Risk Factors for Cardiac Dysfunction

e table below summarizes the categorical risk factors analysed in this study.

ariable	Category	N= 111	Case N=32	Control N=29	Odd ratio (95%CI)	P-value
ex	Male Female	71 40	22 10	49 30	0.7 (0.3-1.8)	0.7
ge	0 – 3.5 3.6 – 7.5 7.6 – 11.5 11.6 – 77.5	25 43 33 10	8 13 9 2	17 30 24 8	1 0.9(0.3-2.7) 0.8(0.3-2.9) 0.5(0.1-3.1)	- 1.0 0.8 0.7
utritional *status* t / Age	*< -2* > -2	*60* 47	*17* 14	*43* 33	*1*(0.5-2.5)	1.0
utritional status t / Age	< -2 > -2	51 60	16 16	35 44	0.8(0.4-1.8)	0.7
ype of cancer	Leukaemia *Lymphoma* Nephroblastoma Other solid tumours	25 *31* 22 33	9 *10* 5 8	16 *21* 17 25	1 0.8(0.3-2.6) 0.5(0.1-1.9) 0.6(0.2-1.8)	- 0.8 0.4 0.4
nthracyclines umulative dose mg/m^2)	0-30 (up to 25th percentile) 30.1-94 (up to 50th percentile) 94.1-201 (up to 75th percentile) > 201 (> 75th percentile)	29 26 30 25	5 9 6 12	24 17 24 13	*1* 2.5(0.7-8.9) 1.2(0.3-4.5) **4.4**(1.3-15.4)	- 0.2 1.0 **0.02**

ere was no association between sex and frequency of cardiac dysfunction. Using the youngest age tegory as a reference, we further explored age as a risk factor by categorization. There was no sociation between age and cardiac dysfunction. Overall, nutritional status (Wt/Age or Ht/Age) was not a tistically significant risk factor for cardiac dysfunction.

comparison was done of the proportion of children with abnormal cardiac function among the various es of malignancies. For this analysis children with leukaemia were taken to be the comparison group. ere was no difference in risk for cardiac dysfunction by type of malignancy.

e categorized cases and controls into quartiles and using the lowest quartile as a reference we compared risk in each quartile. Above cumulative anthracycline dose of 201mg/m^2 there was a 4.4 increased ds of cardiac dysfunction (OR 4.4, 95% CI 1.3 – 15.4, p value 0.02) with an **attributable risk rcentage** of **77%.**

MULTIVARIATE ANALYSIS

Table 10.0: Logistic Regression

In order to explore interaction, anthracycline cumulative dose which was an important risk factor at univariate analysis and cumulative cyclophosphamide dose which was a potential confounder as it is clinically cardiotoxic especially at doses >120 – 240 mg/m^2, were put in the logistic regression model below:

Variable	Odds Ratio	95%CI	P Value
Anthracycline Cumulative dose (mg/m^2)	1.005	1.001 – 1.009	0.02
Cyclophosphamide cumulative dose (mg/m^2)	1.0	1.0 – 1.0	1.0

Anthracycline cumulative dose remained an important risk factor for cardiac dysfunction in children on treatment for cancer at KNH. For every 1mg/m^2 increase in anthracycline cumulative dose there was a 1.005 increased odds of cardiac dysfunction.

SCRIPTION OF ASSOCIATED ECHOCARDIOGRAPHIC ABNORMALITIES

addition to measurement of left ventricular function by M-Mode Echocardiography, other ormalities were noted as documented in the table below.

ble 11.0: Proportion of patients with other ECHO abnormalities

normality	Frequency N = 111	Proportion with abnormality 95% CI
icardial Effusion	21	19% (13 – 27%)
astolic Dysfunction	26	23% (17 – 32%)
lvular Abnormalities	10	9% (5 – 16%)
mour Infiltrates	7	6% (3 – 12%)

he commonest abnormality was diastolic dysfunction in twenty six (23%) children. Eighteen 0%) of these had restrictive pattern. Of the ten patients with valvular abnormality mitral valve normality was found in six (60%) and the remaining four (40%) had tricuspid regurgitation.

Table 12.0: Association of various cardiac abnormalities with left ventricular function

	Cases N=32	Control N=79	OR (95% CI)	P value
Pericardial effusion	12/32 (38%)	9/79 (11%)	3.5 (1.3-9.2)	**0.02**
Diastolic dysfunction	14/32 (44%)	12/79 (15%)	4.6 (1.8 – 11.8)	**0.002**
Valvular abnormalities	4/32 (13%)	6/79 (8%)	1.4 (0.4 – 5.2)	0.07
Tumour Infiltration	5/37 (16%)	2/79 (3%)	5.6 (1.0 – 30.6)	**0.04**

This analysis was restricted to the subset of patients with left ventricular dysfunction. Paediatric oncology patients on chemotherapy with pericardial effusion were three (3) times more likely to have abnormal cardiac function as measured by left ventricular function (OR 3.5 95% CI 1.3-9.2, p value=0.02) while those with diastolic dysfunction were four and a half (4.5) times more likely to have abnormal cardiac function as measured by left ventricular function (OR 4.6 95% CI 1.8-11.8, p value = 0.002). The presence of tumour infiltrates lead to a five (5) times more likely chance of abnormal cardiac function as measured by left ventricular function (OR 5.625 95% CI 1.036-30.542, p value = 0.040).

Table 13.0: ECG Changes

Sinus tachycardia was the commonest ECG abnormality.

Abnormality	Case	Control	OR (95% CI)	P value
Low limb voltage	4/32 (12.5%)	5/79 (6%)	1.7(0.4-6.6)	0.5
ST Changes	3/32 (9%)	8/79 (10%)	0.7(0.2-2.9)	0.7
Ventricular Hypertrophy	5/32 (15.6)	6/79 (7.5%)	1.7(0.5-6.2)	0.5
Sinus tachycardia	11/32 (34%)	27/79 (34%)	0.7(0.3-1.7)	0.5

Of the nine (9) patients with low limb voltages, four (4) patients had pericardial effusion, two (2) had features suggestive of myocarditis while one (1) had features suggestive of pericarditis. The mean haemoglobin level for cases was 8.5 mg/dl and for controls 9.2g/dl. Overall, ECG changes were similar amongst cases and controls and none were statistically significant.

DISCUSSION

Childhood cancers continue to be an important area in paediatrics. The harmful side effects of the various chemotherapeutic agents versus their useful anticancer effects present in management a challenge. With regard to long-term survivors, the possible late effects of treatment and their consequences for the quality of life are a major concern.

In this study left ventricular function was evaluated in a total of 111 paediatric cancer patients. All the patients were recruited from the paediatric wards and were on treatment for cancer. Standard guidelines set by the Cardiology Committee of Children's Cancer Study Group were used to measure abnormal left ventricular systolic function. Patients with Ejection Fraction <55% or Fractional Shortening <29% were grouped as cases and those with Ejection Fraction >55% or Fractional Shortening >29% were grouped as controls. Various risk factors were evaluated including type of tumour, duration of treatment and chemotherapeutic agents such as use of anthracyclines and cyclophosphamide [6]. Other cardiac abnormalities seen on ECHO/ECG , such as , diastolic dysfunction, pericardial effusion , valvular abnormalities, tumour infiltrates and ECG abnormalities were also documented.

The point prevalence for cardiac dysfunction in children on treatment for cancer was 29% (95%CI 21.5-37.9). This represents about third of the patients on treatment and is at a higher frequency than previously documented (Table 1.0). Cumulative anthracycline dose was also an important risk factor OR 1.006 (95% 1.001-1.012), p value 0.02. The relative risk of cardiotoxicity at cumulative dose <300mg/m^2 has been documented as 1-2% (Table 1.0). But in our study the relative risk above 200mg/m^2 was 4.4% (OR 4.4, 95% CI 1.3-15.4, p value= 0.02) suggesting increased susceptibility amongst our population. It is worth noting that black race has been noted

be a risk factor for anthracycline cardiotoxicity. This maybe due to perhaps due to race related fferential pharmacogenomics. Since all our study patients were black this risk factor could not e assessed in our study.

s shown in other studies, young age at diagnosis is one of the strongest predictors of a thin left ntricular wall which leads to an elevated afterload in patients treated with anthracyclines [4,9]. the logistic regression model, young age was not statistically significant at p value 0.098. lowever analysis as a categorical variable (Table 5.0) showed the Odd's ratio for cardiac ysfunction appeared to be reducing with increasing age suggesting that young may be a risk ctor for cardiac dysfunction in children on treatment for cancer. The linear tread for p-value was owever not significant. The small number of subjects analysed may have been the limiting actor.

Nutritional status, by Z Scores, was not a risk factor for cardiac dysfunction among the study atients. Z Scores are measure mainly of macronutrient status. Mohta R et al in New Delhi India, arried out a retrospective cohort on 47 children who had received anthracycline as part of their reatment and found that patients who developed anthracycline related cardiomyopathy had lower height for age ($p=0.03$) [10]. They however did not use standardized nutritional scoring methods such as Z scores and used mean value as tool for comparision. It is postulated that it is mainly the micronutrients – selenium and vitamin E that ameliorate the cardiotoxic effects of the anthracyclines [4]. These were not evaluated in this study and perhaps further research should go into this to expound the role of micronutrients in cardiotoxicity in our setting.

addition to left ventricular systolic assessment of on ECHO other cardiac abnormalities were so described. These include diastolic dysfunction, pericardial effusion, valvular abnormalities d tumour infiltration. Diastolic dysfunction was found in 26 (23%) of the total study patients th 18 (70%) of these having restrictive type. Bu'llock et al, carried out a cross sectional hocardiographic study of left ventricular function on 236 survivors of childhood cancers and mpared with paired control data matched for body surface area and showed that diastolic ysfunction was a consequence of anthracycline induced cardiac damage [20]. They also found normal diastolic function – restrictive type to be the predominant type. He was unable to clearly how any clear relationship with systolic left ventricular dysfunction.

Some scholars have found quite the opposite. Drop et al carried out a prospective cohort study on 20 ALL survivors and 110 Wilms Tumour survivors who had undergone investigation of diastolic filling at various stages of their treatment [21]. They compared their diastolic and systolic function in a bid to find any correlation or predictive association. They showed a relation between increased cumulative anthracycline dose and reduced E and prolonged IVRT hence suggesting that cumulative anthracycline dose was a risk factor for diastolic dysfunction. Diastolic dysfunction-impaired relaxation was the predominant type in their study population. As a predictive tool, Dorup et al suggested that E velocity had a low sensitivity for predicting abnormal systolic function, although normal E velocity was a highly specific determinant.

Pericardial effusion was the second most common associated cardiac abnormality amongst our study patients. Twenty one (19%) of study patients were found to have pericardial effusion.

etinoblastoma and the lymphomas each had six (29%) patients with pericardial effusion. eukaemias had five (24%) with pericardial effusion and only 1 (5%) patient with teratoma had an ffusion. It is not possible to establish the exact aetiology of the pericardial effusions. One of the eatures of late cardiotoxicity is the development of pericardial effusions [7]. However we cannot ule out the role of tumour per se as being the cause of the pericardial effusion. Myocardial iopsy would offer useful histopathologic information.

Ten patients were found to have valvular abnormalities. Six (60%) of the ten children had mitral valve involvement. All these valves showed thickening, two had prolapsed, one had calcification with intracardiac tumour deposits. Primary involvement with mitral valve may suggest pre-exisiting rheumatic heart disease. The remaining four (40%) children with valvular abnormalities had tricuspid regurgitation with increased pulmonary pressures suggesting pulmonary hypertension. Previous research has suggested that pre-exisiting heart disease, including valvular disease, is a risk factor for cardiac dysfunction. Perhaps the number of patients screened with valvular heart disease was too small for use to sufficiently draw conclusions on the risk of cardiac dysfunction in a patient with valvular heart disease on treatment for cancer.

Tumour infiltrates were observed in seven (6%) of the total study patients. Three (43%) of these were leukaemic patients and two (29%) had neuroblastoma. Hodgkins lymphoma and rhabdomyosarcoma each had a one (14%) patient with tumor infiltrate. It is not possible to establish the exact aetiology of these intracardiac tumours but most probably they were secondary metastasis.

Although serial echocardiography monitoring of left ventricular function will allow for early identification of individuals susceptible to cardiotoxicity and hence early intervention, increases in

lood troponin levels and myocardial uptake of radiolabeled antimyosin antibody are now merging as the most sensitive and specific indicators of myocardial-cell injury [18]. Troponin evels and uptake of antimyosin antibody are elevated in patients with acute doxorubicin-induced ardiotoxicity, even in the absence of a reduced ejection fraction, and they correlate significantly vith histological scores for doxorubicin-induced cardiotoxic effects and with echocardiographic bnormalities in these patients nine months later [22,23].

trengths of the study

tudy design was appropriate to answer the study questions. All patients had ECG and Echo done y blinded paediatric cardiologists.

tudy Limitations

he study did not have baseline or serial ECHO available for patient reference. The study may not ave had the study power to fully assess all the risk factors. The study design did not include aking urea & electrolytes and hence most ECG changes could not be directly ascribed to any of he risk factors. Lastly, there were no post chemotherapy patients, for example, those on adiotherapy or those who had completed treatment to assess cardiac dysfunction.

Conclusions

1. This study has shown that about a third (point prevalence 29%) of paediatric cancer patients on chemotherapy at KNH have cardiac dysfunction as exemplified by left ventricular dysfunction.
2. Cumulative anthracycline dose is a risk factor for cardiac dysfunction in paediatric oncology patients on chemotherapy at KNH. Above the cumulative dose of 200mg/m^2 the attributable risk percentage of cardiac dysfunction is 77%.

Recommendations

1. Serial echocardiography should be done on oncology patients undergoing chemotherapy where anthracyclines are part of the treatment protocol.
2. With an attributable risk percentage of 77% above cumulative anthracycline dose of 200mg/m^2, alternative non-anthracycline based treatment protocols are recommended above this level.
3. Lastly, a meta-analysis of published studies and randomised clinical trials should be done to further establish the safety of anthracyclines and to further assess the other risk factors in our population.

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APPENDIX I: PATIENT DATA SHEET

Case Control Study To Determine Risk factors For Cardiac Dysfunction In Children With Malignancies At Kenyatta National Hospital

Name :_____ IP No: _____

Study No : _____ Recruitment Site: _____

Age : _____ Weight (Wt) : _____

Sex : _____ Height (Ht): _____

Date of assessment : _____ Z Score Wt / Ht : _____

Malignancy : _____ Stage of malignancy: _____

Treatment Regime : _____ Date Rx Started : _____

1. Cumulative dose of Doxorubicin _____

   Daunorubicin_____

2. History of Spinal or Mediastinal Irradiation _____ Amount in Rads _____

3. CumulativeDose of Cyclophosphamide _____

APPENDIX II: M-Mode Echo Data Sheet

M-Mode Echo For Patients enrolled in ' Case Control Study Of Cardiac Dysfunction In Children With Malignancies At KNH '

Name :_____ IP No : _____ Ward : _____

AO: _____ RVD: _____ IVS: _____ EF : _____
LA : _____ LVDd : ____ LVDs : _____ FS : _____
CO : _____ HR : _____ LVPW : ____ SV : _____

Diastolic Dysfunction: E wave =
A wave =
E/A Ratio =

Conclusion _____

Other Comments _____

_____

_____

_____

___

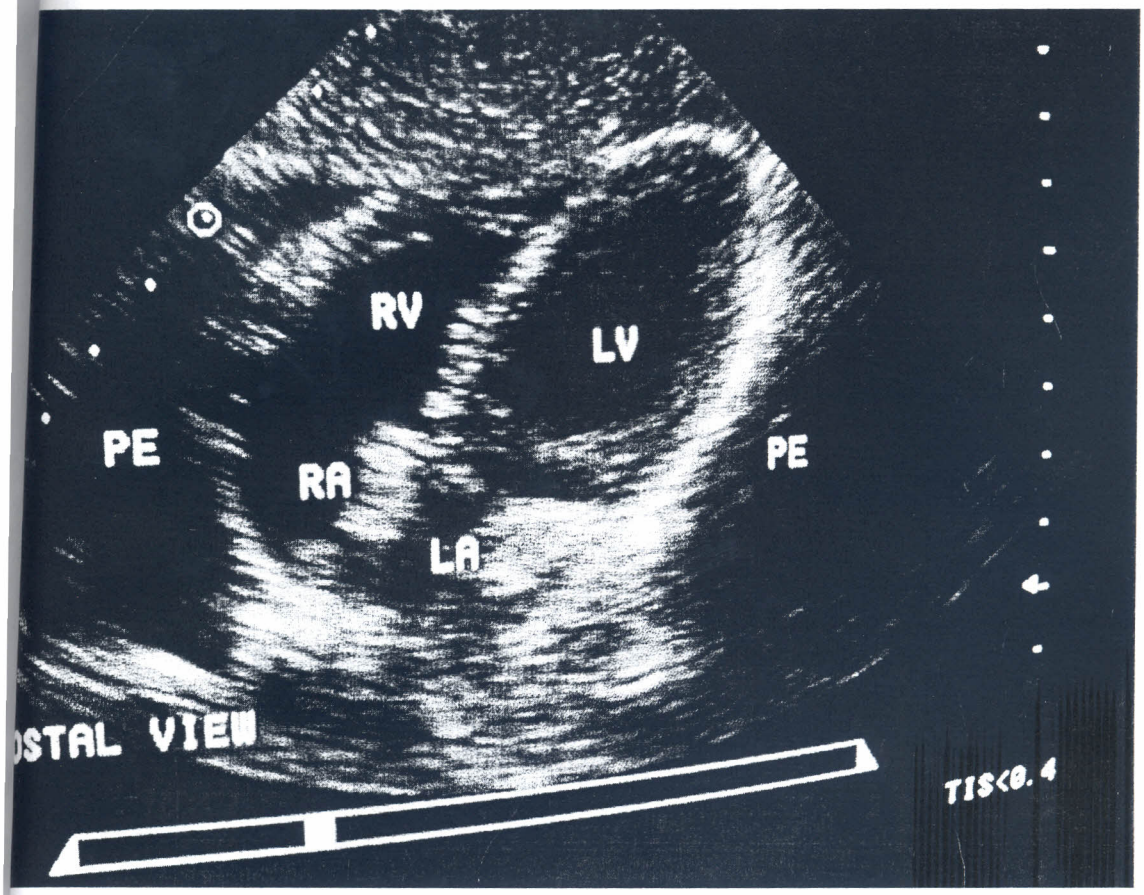
NOTE : Based on the American Cardiology Committee of children with cancer study group. Cardiac dysfunction is defined as any one of the following :

- **Ejection Fraction < 55%**
- **Fractional shortening < 29 %**

Echo done by _____ Investigator: Dr. M. Shiroya-Wandabwa

APPENDIX III : SAMPLE ECHOCARDIOGRAMS I

Sample I: Two dimensional echocardiogram showing a large anterior and posterior pericardial effusion with left atrial tumour infiltration.



Key:

RV = Right ventricle

LV= Left ventricle

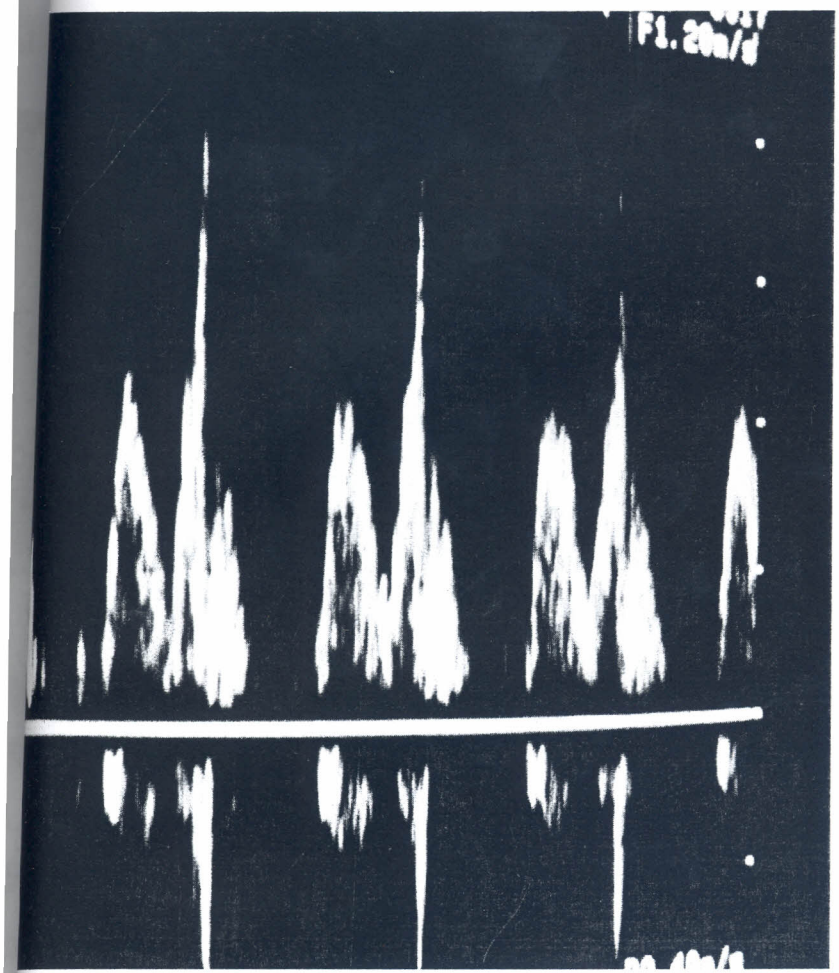
RA= Right atrium

LA= Left atrium

Conclusion: large pericardial effusion, left atrial tumour infiltration .

APPENDIX III : SAMPLE ECHOCARDIOGRAM II

Sample II: Pulsed wave Doppler assessing diastolic dysfunction.



Pulsed waved Doppler shows:

E wave = 2 ms

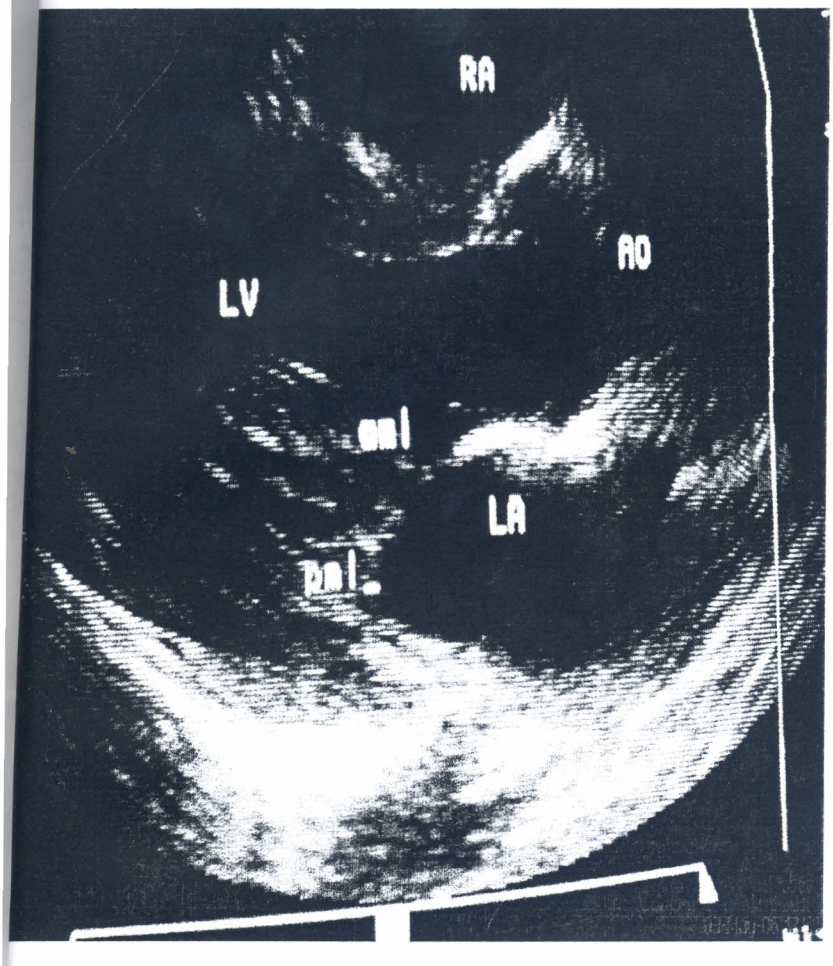
A wave = 5 ms

E/A ratio = 2/5 = 0.4

Conclusion: diastolic dysfunction concurs with abnormal relaxation type.

APPENDIX III: SAMPLE ECHOCARDIOGRAM III

Sample III: Two dimensional parasternal long axis view showing thickened and calcified mitral valves.



Key:

AM: Anterior mitral leaflet

PM: Posterior mitral leaflet

RA: Right atrium

AO: Aortic orifice

LV: Left ventricle

LA: Left atrium

Conclusion: mitral valve calcification.

APPENDIX IV: CALCULATION OF LEFT VENTRICULAR INDICES

The cardiology committee of the children cancer study group [6] defines Cardiac dysfunction as :

- Left ventricular ejection less than 55%

OR

- Left ventricular fractional shortening below 29%

Echocardiography

Diastolic and systolic dimensions of left ventricle (LV) will be measured using M-mode echocardiography. The standard indicators of LV function are Fractional Shortening (FS) and Ejection Fraction (EF).

Fractional Shortening (FS) will be calculated as follows:

FS = LVIDd – LVIDs/LVIDd

LVIDd: left ventricular diameter in end diastole

LVIDs: left ventricular diameter in end systole

Ejection Fraction will be calculated as follows:

EF = LVDV – LVSV/LVDV

LVDV: left ventricular end diastolic volume

LVSV: left ventricular end systolic volume

The values of ejection fraction below 55% and fractional shortening below 29% assessed by Echo will be considered significant deterioration in cardiac function as per the guidelines of Cardiology Committee of the Children Cancer Study Group, USA.

Electrocardiography

A rest 12 – lead ECG will be taken on all study patients.

will continue to review the patient as and when necessary in consultation with the primary clinician. Where possible and in consultation with the haemato-oncologist patients with cardiac dysfunction may have their treatment regimes reviewed.

PROCEDURE

If you volunteer child to participate in this study, I will ask you questions concerning your child's health and carry out a physical examination on your child. After this you will be given an appointment day and time when your child, accompanied by a study assistant and myself will be taken to a room within the confines of Kenyatta National Hospital where specialist doctors will look at the way the heart of your child is working using a special machine (Echocardiogram, ECHO) and the rhythm of the heart (Electrocardiography, ECG). This information will be coded and entered onto a patient data sheet.

RISKS, STRESS OR DISCOMFORT

ECG and ECHO are painless, non-invasive method of assessing the function of the heart. There will be no physical pain, emotional or psychological stress during these procedures.

OTHER INFORMATION

Participation is voluntary. There will be no extra cost to you for ECHO or ECG. The results of the tests will be kept confidential with all information and availed to your child's primary doctor only. The information obtained will allow appropriate remedial measures, where possible, to be started for your child and it will beneficially influence treatment protocols for children with cancer in the future. On going care of your child will always take first priority and at no time will participation in this study interfere with your child's primary care.

You may quit the study at any stage without any obligation or penalty and the management of your child will not be compromised.

APPENDIX V: CONSENT FORM

For Subject Participation In Study for "Risks Factors of Cardiac Dysfunction In Children with Cancer at Kenyatta National Hospital"

IP NO.: _____

STUDY NO.: _____

INVESTIGATOR'S STATEMENT

My name is Dr. M. Shiroya (Investigator) of the Paediatrics Department University of Nairobi. I am carrying out a study to look at the functioning of the heart in children on treatment for cancer and what influences this functioning.

PURPOSE OF THE STUDY

There are different ways of treating cancer including use of medications (chemotherapy) and use of radiation (radiotherapy), these methods of treatment can sometimes affect the work of different organs including the heart.

By carrying out this study I seek to establish which drugs or combination of drugs are more likely to influence the heart and at what dosages. I want to establish if there is any risk associated with the nutritional status of the children, their baseline liver or renal function tests.

BENEFITS OF THE STUDY

This will information will in the future serve to help clinicians establish protocols for early detection of cardiotoxicity in paediatric oncology patients perhaps through regular and routine echocardiography, followed by reduction in cardiotoxic drugs where possible or variation in treatment regimes.

Information of your child's cardiac status obtained by ECG and ECHO will be given to your child's primary doctor. The management and care of your child will continue to be multidisciplinary. ECHO and ECG will serve as baseline for subsequent monitoring. Where cardiac disease is established, for example, pericardial effusion, cardiac arrthymias, the attending cardiologist will immediately prescribe the appropriate treatment. The cardiologist

SUBJECT'S STATEMENT:

The study described above has been explained to me. I agree to volunteer my child to participate in the study. I have had a chance to ask questions. I have been told that if I have future questions about the research or about my rights as a subject, I can ask the Investigator. I have been told that I am free to withdraw my child from the study at any time without medical management of my child being compromised.

Name_____ Date _____

Name of Child : .....

Signature of Parent / Guardian_____