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ABSTRACT

Objective: **To determine the point prevalence of abnormal cardiac function and to assess the risk factors for cardiac dysfunction in paediatric oncology patients on treatment at Kenyatta National Hospital.**
Design: **Descriptive cross-sectional study with a nested case control.**
Setting: **Kenyatta National Hospital between February and April 2006.**
Main outcome measures: **Left ventricular dysfunction if ejection fraction (EF) <55% or fractional shortening (FS) <29% defined cases. Controls had EF >55% or FS >29%.**
Results: **One hundred and eleven patients were enrolled of whom 32 had abnormal cardiac function and were classified as cases while 79 had normal cardiac function. About a third, point prevalence 29% (95% CI 21.2-37.9), had cardiac dysfunction. Cumulative anthracycline dose was a risk factor for cardiac dysfunction in this population. Above 200mg/m^2 the attributable risk percentage of cardiac dysfunction was 77%.**
Conclusions: **Serial echocardiography should be performed to identify patients at risk. Alternative treatment protocols should be used when the cumulative anthracycline dose exceeds 200mg/m^2 due to the high attributable risk. Studies to further assess the other associated risk factors and long term effects of anthracycline are recommended.**

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 (1), found the hospital based prevalence to be 1.27%. The commonest childhood cancers were lymphomas (51%), leukaemias (22.3%), nephroblastoma (8.5%), rhabdomyosarcoma (5.3%), neuroblastoma (3.3%), kaposi's sarcoma (1.5%), ovarian cancers (1.4%) and osteogenic sarcoma (1.3%).

Cancer chemotherapeutic agents can be broadly classified as antibiotics, alkylating agents, antimetabolites, natural products and hormones agents (2). The two commonly used anthracycline antibiotics, daunorubicin and doxorubicin, differ only by one hydroxyl group in their biochemical structure. Doxorubicin is the main anthracycline used at Kenyatta National Hospital (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.

Anthracycline 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. Anthracycline effects on the heart are probably the most well documented causes of morbidity and mortality in patients on anthracyclines. Early cardiotoxicity occurs during treatment or within a year of completion of treatment and can present as arrhythmias, ECG changes or left ventricular dysfunction. Late cardiotoxicity occurs more than a year after completion of treatment and presents as cardiomyopathy, pleural effusion, left ventricular dysfunction and low output heart failure. Early cardiotoxicity is a risk factor for late cardiotoxicity that is often not irreversible (3,5,6).

The 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 and intracellular calcium overload (3). The risk factors for cardiac dysfunction in children with malignancies are attributed to several factors:

The type of malignancy: Cancer contributes to cardiac dysfunction by several mechanisms, including tumour embolization leading to myocardial infarction, direct compression, nonbacterial thrombotic endocarditis by metastatic cancers or by extension into the great veins and cardiac chambers (7).

Radiotherapy: 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 (5). 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 (8).

Table 1
The relative risk of cardiac toxicity at various anthracycline cumulative doses

Cumulative dose (mg/m^2)	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%

Adapted from Taketomo, C.K., Hodding, J.H., Kraus, D.M. Paediatric Dosage Handbook, 13th edn. New York: Lexi – Comp's Drug Reference Hand Book, 2006.

Cumulative anthracycline dose: The relative risk of cardiac toxicity increases with increasing anthracycline cumulative doses (9). Table 4 shows the relative risk of cardiotoxicity at various cumulative anthracycline doses.

Other cardiotoxic drugs: Cyclophosphamide is another potentially cardiotoxic drug which causes clinical cardiotoxicity when administered in massive doses (120 –240 mg/kg over 1 to 4 days) (3).

Other additional factors associated with increased occurrence of anthracycline cardiotoxicity are pre-existing cardiac disease, female sex, trisomy 21, black race, young age and nutritional status (6,9-13).

Various diagnostic procedures are used to test for anthracycline induced cardiotoxicity. These include history taking and physical examination, electrocardiography, echocardiography, angiography with radiolabeled antimyosin antibodies, angiocardiography and endomyocardial biopsy. Each with varying sensitivity and specificity.

Some of the strategies used to prevent or limit anthracycline cardiotoxicity include early detection followed by reductions in anthracycline dose or variation of treatment regime. Although serial echocardiography monitoring of left ventricular function will allow for early identification of individuals susceptible to cardiotoxicity and hence early intervention, increases in blood, troponin levels and myocardial uptake of radiolabeled antimyosin antibody are now emerging as the most sensitive and specific indicators of myocardial-cell injury (4, 7). Other strategies to limit or prevent anthracycline cardiotoxicity include lowering of peak blood levels by variations methods of delivery, for example, prolonged continuous infusion rather than by bolus injection; lowering of peak dose through the use of different treatment schedules or using alternative anthracycline derivatives, for example, liposomal anthracyclines, may be less cardiotoxic than other types of anthracyclines (3). Lipshultz *et al* (17) found dexrazoxane, a trial cardioprotective iron chelator, 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.

MATERIALS AND METHODS

This study was a descriptive cross-sectional study with a nested case control. It was carried out on patients admitted at the Kenyatta National Hospital (KNH) paediatric oncology, general paediatric and ophthalmology wards. KNH is the teaching hospital for the University of Nairobi and is also the major referral hospital for all paediatric cancer patients in Kenya. The study population were children below the age of fifteen years with an established diagnosis of cancer and on chemotherapy. Patients whose parent or guardian did not give consent and re – admissions that had been recruited in the study in a previous admission were excluded from the study.

Fischer's formula was used to determine the minimum number of patients as 90, taking into account the point prevalence of cardiac dysfunction. The sample size for the nested case control was determined by using the two sample comparisons of proportions for case control studies. A minimum number of thirty two cases were required taking a

case: control ratio of 2:5, minimum number of cases was 32:79 (total 111 patients).

Prior diagnosis of cancer in the study group had been established using standard methods of bone marrow evaluation, fine needle aspirate, tissue biopsy, biochemical markers depending on the type of cancer supported by various radiological investigations. This information was obtained from the patient's medical records. A patient history and general examination and was taken. Patient data including anthropometric measurements, cumulative anthracycline dose, cumulative cyclophosphamide dose and history of irradiation were collected.

Study patients underwent twelve lead surface electrocardiography (ECG) and rhythm strip using a manual cardiofax ECG machine, Nihon Kohden Corporation. 2-D echocardiography was also performed at the cardiology department using an echocardiography machine LOGIQ500 with frequency of 33/02.5MH . 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. 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.

To reduce interobserver errors M-mode echocardiography investigations were carried out separately by a team of three cardiologists using a uniform methodical protocol based on the set guidelines (8).

Data 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) was used to evaluate skewed continuous variables.

RESULTS

During the study period February and May 2006, a total of 111 children were evaluated. Their median age was six years (Range 0.25-14 years) with 64% of them being males and 36% of them being females thus a male: female ratio of 1.8:1. Fifty four per cent 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 four months (Range 0.25-24 months)

Lymphoma was the most common cancer - 31 (27.5%) patients, followed by leukaemia and Wilm's tumour seen in 25 (23%) and 22 (20%) patients respectively. Other less common tumours were osteogenic sarcoma and neuroblastoma five (5%) and four (3.5%) patients respectively. Other rarer types included Kaposi's sarcoma, and ovarian tumours. Table 2 shows the spectrum of cancers seen in the study patients.

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. The cumulative dose of adriamycin used at KNH varied according to the protocol used. Table 3 shows the various cumulative anthracycline doses set for each type of cancer depending on the regimen. The median dose of anthracycline 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 Figure 1. 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. This difference was statistically significant at p=0.02. Using percentiles it was shown that above a cumulative anthracycline dose of 201mg/m^2 there was a 4.4 increased odds of cardiac dysfunction with an attributable risk percentage of 77% (Table 4).

Table 2
The spectrum of cancers seen in 111 children

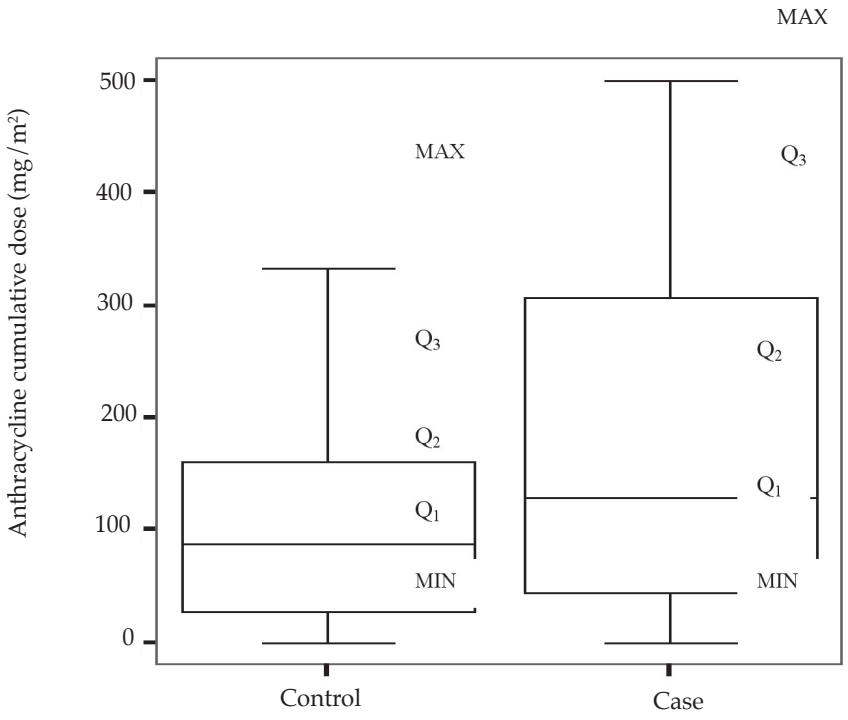
Type of cancer	Patients	
	No.	(%)
Lymphoma		
Burkitt's lymphoma	19	17
Hodgkin's lymphoma	8	7
Non-Hodgkin's lymphoma	4	3.5
Leukaemia	25	23
Wilm's tumour	22	20
Rhabdomyosarcoma	8	7
Retinoblastoma	7	6
Osteogenic sarcoma	5	5
Neuroblastoma	4	3.5
Others	9	8
Total	111	100

Table 3
The cumulative anthracycline doses for each cancer type according to treatment regimen at KNH

Malignancy	KNH regime 1 cumulative dose	KNH regime 2 cumulative dose
Leukaemia	550	300
Lymphomas		
NHL/BL	440	410
HL	300	360
Solid tumours	360	420
Wilm's tumour	250	80

NHL = Non Hodgkin's Lymphoma
BL = Burkitt's Lymphoma

Figure 1
Box plot showing the cumulative anthracycline dose in the study patients



Key for controls:
Minimum dose =0(mg/m²)
25th percentile = 28mg/m²
50th percentile= 88 mg/m
75th percentile= 160 mg/m²
Maximum dose (mg/m²) = 374

Key for case:
Minimum dose(mg/m²) = 0
25th percentile = 41mg/m²
50th percentile = 128 mg/m²
75th percentile = 308 mg/m²
Maximum dose (mg/m²) = 500

Table 4
Summary of univariate analysis of categorical risk factors for cardiac dysfunction

Variable	Category	No.	Case	Control (n=32)	Odd ratio (n=29)	P-value (95%CI)
Sex	Male	71	22	49	0.7	
	Female	40	10	30	(0.3-1.8)	0.7
Age	0 – 3.5	25	8	17	1	-
	3.6 – 7.5	43	13	30	0.9(0.3-2.7)	1.0
	7.6 – 11.5	33	9	24	0.8(0.3-2.9)	0.8
	11.6 – 77.5	10	2	8	0.5(0.1-3.1)	0.7
Nutritional status	≤ 2	60	17	43	1(0.5-2.5)	1.0
Weight/Age	≥ 2	47	14	33		
Nutritional status	≤ 2	51	16	35	0.8(0.4-1.8)	0.7
Height/Age	≥ 2	60	16	44		
Type of cancer	Leukaemia	25	9	16	1	-
	Lymphoma	31	10	21	0.8(0.3-2.6)	0.8
	Nephroblastoma	22	5	17	0.5(0.1-1.9)	0.4
	Other solid tumours	33	8	25	0.6(0.2-1.8)	0.4
Anthracyclines Cumulative dose (mg/m^2)	0-30 (up to 25th percentile)	29	5	24	1	-
	30.1-94 (up to 50th percentile)	26	9	17	2.5(0.7-8.9)	0.2
	94.1-201 (up to 75th percentile)	30	6	24	1.2(0.3-4.5)	1.0
	> 201 (> 75th percentile)	25	12	13	4.4(1.3-15.4)	0.02

The median cumulative cyclophosphamide dose was 2050mg/m^2 (Range 0 - 9363 mg/m^2) for cases and 1510mg/m^2 (0-10300 mg/m^2) for controls. The mean cumulative cyclophosphamide dose was 2880 mg/m^2 (95%CI 1804.0-3515.2 mg/m^2) in the cases and 2248 mg/m^2 (95% CI 1758.2-2874.9 mg/m^2) in the controls. This difference was not significantly associated with cardiac dysfunction at p = 0.3 (Table 5).

There was no association found between sex or nutritional status (Weight/Age or Height/Age) and the frequency of cardiac dysfunction. Using the youngest age category as a reference, no association between age and cardiac dysfunction was seen. Using patients with leukaemia as the comparison group, no difference in risk for cardiac dysfunction by malignancy type was observed.

DISCUSSION

This study found that the commonest type of cancer seen were the lymphomas (28%). This figure was less than that found in the study by Macharia (1) which found lymphomas to be 51%. The latter study however, did not look at retinoblastoma and brain tumours which are relatively common cancers in childhood. Both studies found Burkitt's lymphoma to be the most common lymphoma making up about 2/3 of the lymphoma cases. Nephroblastoma was also more frequent in our study.

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 patient management challenges. In 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. The point prevalence for cardiac dysfunction in children on treatment for cancer was 29% (95%CI 21.5-37.9). This represents about a third of the patients on treatment and is at a higher frequency than previously described (3, 7). The risk of cardiac dysfunction or cardiotoxiticy as measured by left ventricular dysfunction was related to cumulative anthracycline dose. The median duration of therapy of four months is an indication of early phase of treatment; hence the cardiac dysfunction seen was a measure of early anthracycline cardiotoxicity. In this study, there was a 4.4 odds of cardiotoxicity above

a cumulative dose of 200mg/m^2 (Relative Risk 4.4, 95% CI 1.3-15.4, p-value= 0.02). Previous studies, mainly in developed countries, have documented the relative risk of cardiotoxicity at cumulative dose <300mg/m^2 to be between 1-2% (14). This suggests increased susceptibility amongst our population. It is worth noting that black race has been noted to be a risk factor for anthracycline cardiotoxicity. This maybe due to perhaps race related differential pharmacogenomics.

As shown in other studies, young age at diagnosis is one of the strongest predictors of a thin left ventricular wall, which leads to an elevated afterload in patients treated with anthracyclines (3, 6). Although this study did not clearly show age to be a risk factor, in the categorical analysis for age, the Odds ratio for cardiac dysfunction appeared to be reducing with increasing age suggesting that young age may be a risk factor for cardiac dysfunction in children on treatment for cancer. The linear tend for p-value was however not significant. The small number of subjects analysed may have been the limiting factor.

Based on the study findings, we advocate routine serial echocardiography to identify at risk patients. Where there is a cumulative anthracycline dose of 200mg/m^2, use of alternative treatment protocols, or reduction of the anthracycline dose is suggested. Variations of the method of delivery, use of liposomal anthracycline, where feasible, are other strategies that may be tried. Studies to further assess other risk factors associated with cardiotoxicity and the long term effects of anthracyclines are recommended.

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