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Early doxorubicin cardiotoxicity in Malawian children admitted to Queen Elizabeth Central Hospital, Malawi.

Dominic Moyo[1*], Yamikani Chimalizeni[1], George Chagaluka[1], Clifford G Banda[1,2], Elizabeth M Molyneux[1]

[1] Queen Elizabeth Central Hospital, College of Medicine, Blantyre, Malawi.

[2] Malawi Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi.

*Correspondence to:

Dr Dominic Moyo, College of Medicine, Mahatma Gandhi Road, Blantyre, Malawi. Tel: +265999488342. dmoyo@medcol.mw.

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Abbreviations	
LVEF	Left ventricular ejection fraction
HIV	Human Immunodeficiency Virus
TTE	Transthoracic echocardiogram
ANOVA	Analysis of Variance
QECH	Queen Elizabeth Central Hospital

Abstract:

Background. Doxorubicin chemotherapy drug, use is limited by it's potential to cause cardiotoxicity. In resource poor settings, like Malawi, monitoring of doxorubicin cardiotoxicity is not routinely conducted in cancer patients and the incidence of doxorubicin cardiotoxicity is not known.

Methods. Children aged 3 months to 18 years with cancer were prospectively enrolled from the paediatric oncology ward and followed up from January 2016 to June 2019. Transthoracic echocardiographic monitoring of left ventricular ejection fraction (LVEF) was done at baseline, one month, six months and a year after completion of therapy. Cardiotoxicity was defined as a decline in LVEF of ≥10% to a final value of <50%, and an overall incidence risk of developing cardiotoxicity was estimated. A one-way analysis of variance was conducted to compare baseline LVEF with that measured during follow up intervals.

Findings. A total of 91 children were enrolled into the study, 74% (68/91) were male, and 67% (62/91) were aged 5 months to 14 years. Burkitt lymphoma was diagnosed in 41% (38/91) of the children. No one experienced cardiotoxicity during the study period. However, of 77 children who had at least one follow up, five children 6·54% (95% CI: 2.1-14.5) experienced a reduction in LVEF of >10%, though not to a final value of <50%. No deterioration of systolic function was found among 20 children who had completed follow up. (F= 2·43, p-value=0·07).

Interpretation. In this cohort, there were no observed cardiotoxic events associated with doxorubicin administration as per pre-defined criterion

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Introduction

Doxorubicin is an anthracycline drug widely used in the treatment of childhood malignancies (1). Despite its great effect in improving survival and quality of life among childhood cancer patients, its use is limited by the side effect of cardiotoxicity (2). The mechanism by which doxorubicin causes cardiotoxicity is not clear though various theories have been postulated (3). Cardiotoxicity resulting from doxorubicin administration has been historically classified into three distinct types namely: acute cardiotoxicity, occurring after a single dose or course of treatment; early- onset chronic, occurring within one year and late-onset chronic occurring after years or decades post treatment (4). New evidence indicates that cardiotoxicity may not necessarily be occurring as three distinct phenomena, but rather as a continuous process starting from the initial exposure (5).

Diagnosis of anthracycline-induced cardiotoxicity has, for a long time, been based on clinical manifestation of congestive cardiac failure, which is rapidly progressive once it has developed following exposure to the drug. A definition-based echocardiographic measurement of decline in left ventricular function was adopted to facilitate detection of subclinical states. Initially anthracycline-induced cardiotoxicity was defined as a decrease in LVEF by more than 10 points to a final value of <50%(6). A more recent consensus definition states it as an LVEF decline >10% points, with a final value <53% (7).

Increase in the cumulative dose of doxorubicin has been elucidated to be by far the most important risk factor for development of cardiotoxicity; with a risk of 3–5% with 400 mg/m^2 and as high as 18–48% at 700 mg/m^2 (8). However, there are other reports of cardiac dysfunction

being observed in those who received cumulative doses of less than 300mg/m^2 (9). Currently there is no established safe cumulative dose for doxorubicin.

Early-onset chronic cardiotoxicity has been noted to be the most frequent and clinically relevant. A study done by Cardinale et al showed that in 98% of cases, cardiotoxicity occurred within the first year and that the observed changes were amenable to treatment, leading to partial or full recovery of the patients (10). Thus, monitoring of asymptomatic patients undergoing anthracycline treatment is essential to detect early subclinical changes and prevent long term morbidity in children who have undergone treatment. There are current international guidelines for monitoring of cardiac function by serial measurements of Left Ventricular Ejection Fraction (LVEF) (11). However, these guidelines fall short on making provisions for timing, frequency, and modalities as well as long-term monitoring schedules. Currently, transthoracic echocardiography is a widely available, sensitive, non-invasive tool for evaluation of cardiac function and guidelines for quantification measurements have been developed and are used widely (12).

There is paucity of evidence on the incidence of early-onset cardiotoxicity in low- and middle-income countries, including in Malawi. At Queen Elizabeth Central Hospital's paediatric oncology ward in Malawi, doxorubicin is used routinely. However monitoring for cardiotoxicity is not done and paediatric cardiology services were commenced in 2008 (13) and there was no cardiologist on site until 2015. The aim of this study was to determine the proportion of children who develop doxorubicin-induced cardiotoxicity within one year of having received treatment at the paediatric oncology ward.

Methods

Site

The study was conducted at Queen Elizabeth Central Hospital, Paediatric Oncology Ward which has a bed capacity of 23 beds. The main hospital has a bed capacity of 1200 beds for both adults and children. It is a teaching hospital and one of the main referral hospitals, located in the southern region of Malawi.

Patient data

Data was prospectively collected from the clinical records of children aged between 3 months to 18 years who were admitted to the ward and were prescribed a doxorubicin containing chemotherapy regimen between January 2016 to June 2019. Children with pre-existing cardiac conditions were excluded. The data included age at presentation, gender, and residence; baseline anthropometric measurements of weight, height, body surface area, and vital signs (blood pressure, respiratory rate, heart rate, temperature, and oxygen saturation). Data on baseline blood results such as white cell count, haemoglobin, platelet count, serum creatinine and HIV status were also collected. Different malignancies were diagnosed clinically and where confirmatory diagnostic tests were performed, such as fine needle aspirations, bone marrow aspirations and tissue biopsies, these data were collected. Additionally, history of previous doxorubicin dosing and the baseline cumulative dose were recorded.

Echocardiography procedure

An M-Turbo ultrasound machine (Sonosite, FUJIFILM, Tokyo: Japan), was used to perform transthoracic echocardiograms (TTE). The Simpson volumetric approach for measurement of left ventricular ejection fraction using the apical 4 chamber and 2 chamber view was used as recommended by the American Society of Echocardiography.(12) MMode tracing of the left ventricle was taken from the parasternal long axis views at the tips of mitral valve leaflets perpendicular to the endocardial surface and interventricular septum to measure fractional shortening. The two parameters; Left Ventricular Ejection Fraction (LVEF) and the Fractional Shortening (FS) were pre-calculated by the machine. For each parameter, three serial measurements were taken, and the average was recorded. A baseline echocardiograph was done to measure cardiac function 24 to 48 hours before initiation of chemotherapy. Thereafter, three other echocardiographic examinations were done at one-, six- and 12 months follow up.

Follow up

In addition to cardiac function assessment, the following data were also collected at each of the follow up visits at one-, six - and 12 months: anthropometry, vital signs, blood test results for white cell count, haemoglobin, platelet count and creatinine. Cardiotoxicity was defined as a reduction in LVEF of >10 % to a final value of <50%.

Data Analysis

Baseline demographic and relevant clinical features were described using summary statistics. Cardiotoxicity was defined as a decline in LVEF of ≥10% to a final value of <50%. A one-way repeated measure analysis of variance (ANOVA) was run on the data to compare baseline LVEF

with that at one month, six months and 12 months follow up. An overall incidence risk of developing cardiotoxicity was estimated. All analyses were conducted using Stata Version 15.1 (STATA Inc., College Station, TX).

Results

Study participants

A total of 92, out of 202 patients who were screened, were enrolled in the study. Of the 110 excluded children, 57 (51%) received a non-doxorubicin containing chemotherapy regimen, 17 (15%) died before recruitment, 17 (15%) received doxorubicin before a baseline echocardiogram was done, (mostly patients admitted outside the recruiting hours), 11 (10%) refused consent for unspecified reason, six (5%) had low cardiac output at presentation and a further five patients (4%) absconded within 24 to 48 hours of admission (Figure 1).

At the end of a one-year period of follow up, 36 patients had died, of whom nine (25%) had died by one month follow up, 21 (58·3%) by six months and six (16·7%) by one year. Overall mortality among the study participants was 49·7 per 1000 person-years, with the majority occurring within the first six months of follow up. Thirty-one (86%) deaths were disease related and five (14%) deaths were due to sepsis. There were no cardiovascular event related deaths. Mortality among females was 53 and males was 48·6 per 1000 person-years.

A further 34 patients were lost to follow up; six at one month-, 12 at six months- and 16 at one year of follow up.

Baseline clinical features of the study participants

Among the 92 study participants there was a male predominance of 68 (73·9%), 2.8:1 ratio. Most of the participants (36·9%) were aged between 5-9 years, 30·4% were 10-14 years and 29·3% were 0-4 years (Table 1).

Burkitt lymphoma (41·3%) was the predominant tumour found followed by Acute Lympho-blastic Leukaemia (19·5%). Miscellaneous tumours included osteosarcoma and Ewingsarcoma. Over half (56%) of the study participants were underweight at the time of enrolment and 60·9% of study participants had received a cumulative dose of doxorubicin between 100mg/m^2 and 300mg/m^2.

Doxorubicin cardiotoxicity

During the 12-month follow up period, no study participant experienced cardiotoxicity according to the definition set by the study. However, out of 77 children who had at least one follow up, five children 6·54% (95% CI: 2·1-14·5) experienced a reduction in LVEF of >10%, which was not to a final value of <50%; four by one month follow up and one by six months follow up. Only one participant showed a decline in LVEF to a final value of <50% at one month follow up. Table 2 shows the characteristics of the five participants who experienced a ≥10% decline in LVEF and the one participant who experienced a decline in LVEF to a final value of <50%.

The five events (LVEF decline >10% but not to a final value of <50%) were reported in children who received cumulative doxorubicin dose between 100mg/m^2 to 300mg/m^2 and no events were reported in those who received cumulative doses below 100mg/m^2 and more than 300mg/m^2.

Four events were reported within the first month of follow up and one was reported by six months of follow up. Overall, 33(23·9%) children received cumulative doxorubicin dose which was <100mg/m^2 and 56 (60.9%) children received doses between 100mg/m^2 to 300mg/m^2 and three (3·2%) children received doses above 300mg/m^2.

Mean changes in echocardiographic parameters during follow up

No deterioration of systolic function was found among 20 children who completed follow up after comparing the means of LVEF at baseline with that of the subsequent visits (P-value; 0·07). (Table 3).

Exploratory analyses to determine predictors of early changes in LVEF following doxorubicin administration

Although not stated a priori, exploratory analyses were conducted, using logistic regression with random effects to account for within patient and between patient variability, to determine factors associated with early LVEF changes that were observed in the 6 children. None of the baseline characteristics of age, sex, type of malignancy, nutrition status, and administered cumulative dose of doxorubicin, were associated with the observed early LVEF changes.

DISCUSSION

Doxorubicin cumulative dose has been widely reported as a limiting factor in treatment of malignancies, with increased risk for cardiotoxicity reported at cumulative dose thresholds as low as 300mg/m^2 (2). This study was conducted in Malawi, a low resource setting to investigate the incidence of doxorubicin cardiotoxicity in a population of paediatric cancer patients. In this

paediatric cohort, there was no reported doxorubicin-induced cardiotoxicity events as defined by a decline in LVEF of ≥10% to a final value of <50%.

The observed result in this study could be partly explained by the low cumulative doses of doxorubicin received by the participants. In comparative terms, cumulative doxorubicin doses administered at Queen Elizabeth Central Hospital paediatric ward are well below the threshold in most patients. Only three children received doses above 300mg/$m^{2;}$ one was a 11 year old boy who presented with nasopharyngeal carcinoma and relapsed within six months after initial treatment, the other was a 12 year old girl with Hodgkin disease and the last one was a six year old boy with Hodgkin disease who had relapsed within six months of starting treatment.

Doxorubicin associated cardiotoxicity in children has been demonstrated mostly in studies predominantly done in high income settings where patients are well nourished and have good outcomes (14). A retrospective study done by Andolina et al (15) , which looked at medical records and echocardiograms of patients with a history of anthracyclines and/or radiation seen in a long-term survivor clinic from 2000-2007, found a possible association between nutrition status and anthracycline-induced cardiotoxicity. In our cohort, over half had acute malnutrition at baseline (Table 1). The future risk for developing doxorubicin-induced cardiotoxicity can therefore not be ruled out. In addition, the observed epidemiological profile of childhood malignancies in this cohort is similar to what has been described previously in Malawi (16). Our study population had more boys than girls, predominantly aged between 5 years and 14 years. Burkitt lymphoma was the most common malignancy followed by acute lymphoblastic

leukaemia. However, there is no documented evidence of an association between risk of cardiotoxicity and type of malignancy. This was also not the case within this cohort.

The high attrition rate in this study due to mortality also highlights the challenges of estimating the true burden of anthracycline induced cardiotoxicity in paediatric oncology care in settings where mortality due to underlying disease is high. This is further complicated by poor nutrition, co-morbidities, loss to follow up and abscondments. In this cohort, a smaller proportion of children completed follow up due to a high observed mortality. Most of the deaths occurred within the first six months after enrolment. Additionally, follow up of these patients was a challenge because many parents gave incorrect contact details and families relocated to other places during the study period. Indeed, cancer treatment in Malawi remains a big challenge among paediatric patients, particularly with regards to transport cost and loss of productivity of the family, associated with coming for regular follow up in outpatient clinics (18).
In the present study, sensitivity analyses were not conducted to explore the impact of mortality and loss to follow up on estimate of cardiotoxicity. Nevertheless, the proportion of children who survived or were lost to follow up was comparable to previously reported literature from our unit (16,17). The most common cause of death was disease progression, most likely owing to late presentation and poor treatment compliance. There is a possibility that survival may have been overestimated in this study as it was assumed that those who were lost to follow up were still alive giving a lower mortality rate.

Despite several limitations of this study, such as lack of comparative control group and high attrition due to mortality and loss to follow up, which affected the sample size, the present study

has illustrated observed cases of asymptomatic decline in left ventricular ejection fraction among children who received doxorubicin containing chemotherapy regimens in our setting, and which were not detected by the defined criteria of a decrease in LVEF by more than 10 points to a final value of <50%. Further larger studies need to be done to understand the true magnitude of these early asymptomatic changes in cardiac function and their implication on long-term treatment outcome. This will help to inform cardiac safety monitoring and optimisation of doxorubicin dosing in the treatment of paediatric malignancies in such low resource settings.

CONCLUSION

There were no early – chronic cardiotoxicity events associated with doxorubicin administration that were found in this study population as defined by a decline in left ventricular ejection fraction of ≥10% to a final value of <50% over the duration of the study. However, early asymptomatic changes of left ventricular ejection fraction were observed in some patients, and their clinical predictors need to be investigated in larger cohort studies to inform cardiac safety monitoring and optimisation of doxorubicin dosing for paediatric malignancies in low resource settings.

Contributors

DM contributed to the design, literature search, protocol development, patient enrolment, data entry and management, data analysis, interpretation and discussion of the manuscript and wrote the first draft of the paper. YC contributed to the protocol development, review of echocardiographic data, data interpretation, and review of the manuscript. GC contributed to patients enrolment, resolution of data queries, data interpretation and review of the manuscript.

CGB contributed to data analysis and interpretation, review or revision of the manuscript including discussion. EM posed the research question, contributed to the design, reviewed and revision of the protocol, data collection and management, interpretation and discussion of the manuscript, review and revision of the manuscript

Conflict of interest statement

All the authors declare that they have no competing interests.

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References

1. Raj S, Franco VI, Lipshultz SE. Anthracycline-induced cardiotoxicity: A review of

pathophysiology, diagnosis, and treatment. Curr Treat Options Cardiovasc Med. 2014;16(6).

2. Lipshultz SE. Exposure to Anthracyclines During Childhood Causes Cardiac Injury. Semin Oncol. 2006;33(SUPPL. 8):8–14.

3. Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of Anthracyclines. Front Cardiovasc Med [Internet]. 2020 [cited 2020 Aug 4];7(4):26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32258060

4. Jannazzo a., Hoffman J, Lutz M. Monitoring of Anthracycline-Induced Cardiotoxicity. Ann Pharmacother [Internet]. 2007;42(1):99–104. Available from: http://aop.sagepub.com/lookup/doi/10.1345/aph.1K359

5. Eschenhagen T, Force T, Ewer MS, De Keulenaer GW, Suter TM, Anker SD, et al. Cardiovascular side effects of cancer therapies: A position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2011;13(1):1–10.

6. Ganz WI, Sridhar KS FT. Detection of early anthracycline cardiotoxicity by monitoring the peak filling. Am J Clin Oncol. 1993;16(2):1993.

7. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: A report from the American society of echocardiography and the European association of cardiovascular imaging. J Am Soc Echocardiogr [Internet]. 2014 [cited 2020 Aug 4];27(9):911–39. Available from: https://pubmed.ncbi.nlm.nih.gov/25172399/

8. Curigliano G, Cardinale D, Dent S, Criscitiello C, Aseyev O, Lenihan D, et al. Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. CA

Cancer J Clin. 2016;66(4):309–25.

9. Giantris A, Abdurrahman L, Hinkle A, Asselin B, Lipshultz SE. Anthracycline-induced cardiotoxicity in children and young adults. Crit Rev Oncol Hematol. 1998;27(1):53–68.

10. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015;131(22):1981–8.

11. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. Eur Heart J. 2016;37(36):2768–801.

12. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for Quantification Methods During the Performance of a Pediatric Echocardiogram: A Report From the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr [Internet]. 2010;23(5):465–95. Available from: http://dx.doi.org/10.1016/j.echo.2010.03.019

13. Newberry L, Kennedy N, Greene EA. Development of a subspecialty cardiology curriculum for paediatric registrars in Malawi: Implementation of a long-distance hybrid model. Malawi Med J [Internet]. 2016 Aug 2 [cited 2020 Aug 4];28(2):57. Available from: http://www.ajol.info/index.php/mmj/article/view/141310

14. Cancer in Children [Internet]. [cited 2020 Jul 30]. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer-in-children

15. Andolina JR, Dilley K. Anthracycline-induced cardiac toxicity more likely in underweight

childhood cancer survivors. J Pediatr Hematol Oncol. 2010 Jul;32(5):411–5.

16. Sinfield RL, Molyneux EM, Banda K, Borgstein E, Broadhead R, Hesseling P, et al. Spectrum and presentation of pediatric malignancies in the HIV era: Experience from Blantyre, Malawi, 1998-2003. Pediatr Blood Cancer. 2007;48(5):515–20.

17. Israels T, Banda K, Molyneux EM. Paediatric oncology in the Queen Elizabeth Hospital, Blantyre. Malawi Med J. 2008;20(December):115–7.

18. Malawi | World Child Cancer [Internet]. [cited 2020 Aug 11]. Available from: https://www.worldchildcancer.org/what-we-do/where-we-work/malawi