Cardiovascular Topics

Subclinical anthracycline therapy-related cardiac dysfunction: an ignored stage B heart failure in an African population

Wan Zhu Zhang, Feriel Azibani, Karen Sliwa

Abstract

Anthracyclines are potent antineoplastic agents with a proven efficacy in the treatment of many paediatric and adult haematological and solid-organ cancers. Anthracycline therapy-related cardiac dysfunction (ATRCD) is the commonest and most well-studied chemotherapy-induced cardiovascular toxicity. Therefore patients who received anthracycline therapy are considered in stage A heart failure. Recent study findings suggest that anthracycline cardiotoxicity represents a continuum that begins with subclinical myocardial cell injury, followed by an early asymptomatic decline in left ventricular ejection fraction that can progress to symptomatic heart failure if left untreated. In Western countries, ATRCD has been reported in 57% of anthracyclines-treated patients. However, data on incidence and spectrum of ATRCD in Africa are not available. This literature review aimed to highlight the concept of subclinical ATRCD as a stage B heart failure in the spectrum of ATRCD, and the importance of early detection. We emphasise the potential burden and risk of subclinical ATRCD in the African population, with the ultimate aim of drawing the attention of health workers in Africa to improve care of the relevant population.

Anthracyclines are potent antineoplastic agents with proven efficacy in the treatment of many paediatric and adult haematological and solid-organ cancers. Anthracycline therapy-related cardiac dysfunction (ATRCD) is the most notorious and well-studied chemotherapy-induced cardiovascular toxicity.

This dose-dependent ATCRD was first described in 1971 in a cohort of 67 patients treated with Adriamycin for a variety of tumours.[1] The clinical significance of anthracycline cardiotoxicity is growing with the increasing number of cancer survivors worldwide. ATRCD is defined as a decrease in left ventricular ejection fraction (LVEF) of > 10%, to a value < 53%.[2]

Anthracycline toxicity may be acute, early or late. Acute toxicity, which develops in 1% of patients immediately after infusion, is uncommon and generally reversible.[3] Early effects occur within the first year of treatment, while late effects manifest after several years (median of seven years after treatment).[4,5] Early- and late-onset cardiac dysfunction are more likely to be irreversible.[5]

In the literature there is wide variation in the reported frequency of clinical cardiotoxicity. Differences in study population, treatment protocols and duration of follow up could account for this wide variability. The prevalence of late asymptomatic ATRCD has been reported to be more than 57% at a median of 6.4 years after treatment among survivors of childhood cancers,[6] and the incidence of symptomatic heart failure as high as 16%, 0.9 to 4.8 years after treatment.[7]

According to the American College of Cardiology and American Heart Association guidelines,[8] patients who received cardiotoxic agents are considered in stage A heart failure. This identifies patients who are at a high risk for developing heart failure with no evidence of cardiac structural disorder. Stage B refers to patients with cardiac structural disorder but who have never developed symptoms of heart failure. Stage C denotes patients with symptoms of heart failure associated with underlying structural heart disease, and stage D designates the patient with end-stage disease who requires specialised treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation or hospice care. This approach to the classification of heart failure emphasises both the evolution and progression of the disease (Table 1).

Hatter Institute For Cardiovascular Research In Africa, University of Cape Town, Cape Town, South Africa
Wan Zhu Zhang, MMed, zhangwanzhu2012@gmail.com
Feriel Azibani, PhD
Karen Sliwa, PhD

Uganda Heart Institute, Kampala, Uganda
Wan Zhu Zhang, MMed, zhangwanzhu2012@gmail.com

Table 1. Classification of heart failure (HF)	
Stage of HF	*Definition*
A	High risk for developing HF with no evidence of cardiac structural disorder
B	Cardiac structural disorder but has never developed symptoms of HF
C	Symptoms of HF associated with underlying structural heart disease
D	End-stage disease requiring specialised treatment strategies

This literature review aimed to highlight the concept of subclinical ATRCD as a stage B heart failure, underline the importance of its early detection, and emphasise the potential burden and risk of subclinical ATRCD in the African population. Our ultimate aim was therefore to draw the attention of African clinicians in order to improve care of the relevant population.

Concept of subclinical ATRCD

Anthracycline inhibits topoisomerase II (Top2), an essential enzyme for unwinding deoxyribonucleic acid strands during deoxyribonucleic acid replication or transcription.[9] High cumulative use of anthracyclines induces deleterious effects on cardiomyocytes, endothelial cells, fibroblasts and cardiac stem cells (Fig. 1). In the cardiac tissue, anthracycline targets Top2β, the primary Top2 isoform in the heart, triggering profound changes in the transcription, leading to defective mitochondrial biogenesis and reduced levels of anti-oxidative enzymes, manifested as increased production of reactive oxygen species and cardiomyocyte death.[10]

Anthracycline has also been shown to reduce coronary branching, capillary density and the expression of myocardial vascular growth factors.[11] The number of cardiac progenitor cells and their ability to differentiate into endothelial cells, smooth muscle cells or myocytes is also diminished.[11] Therefore the ability of the heart to adapt to any additional stress is impaired after exposure to anthracyclines.

Recent study findings suggest that anthracycline cardiotoxicity represents a continuum that begins with subclinical myocardial cell injury, followed by an early asymptomatic decline in LVEF, which can progress to symptomatic heart failure if left untreated.[12] Not all subclinical LV dysfunctions (stage B heart failure) will become stage C or D heart failure. However, these insults enhance cardiac susceptibility to further cardiovascular stresses (such as pregnancy, surgery, hypertension) or injuries (radiation, ischaemia) and, ultimately, increase the risk of premature cardiovascular (CVD) mortality. This phenomenon has been labelled the multiple-hit hypothesis[13] (Fig. 2).

Cardinale *et al*.[12] suggested that late-onset anthracycline cardiotoxicity likely reflects the timing of detection, rather than the timing of the occurrence of cardiotoxicity. These findings, together with the multiple-hit hypothesis, highlight an urgent need for the surveillance and management of anthracycline cardiotoxicity.

Periodic echocardiographic monitoring has been advocated for this vulnerable population.[2] To further improve early detection of subclinical LV functional deterioration, guidelines from onco-cardiologists advise the use of advanced cardiac imaging (global longitudinal strain, GLS), often combined with the use of circulating levels of cardiotoxicity biomarkers such as cardiac troponin.[14] It is therefore recommended to evaluate at baseline (initiation of anthracycline regimen) LVEF, GLS and circulating cardiac troponin levels. If any of these three parameters are abnormal, a cardiology consultation is recommended.

Follow up is recommended at the completion of anthracycline therapy and six months later for doses < 240 mg/m² or its equivalent. Once this dose is exceeded, measurements of LVEF, GLS and troponin level are recommended before each additional 50 mg/m².[2] According to recommendations from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, a relative percentage decrease of GLS
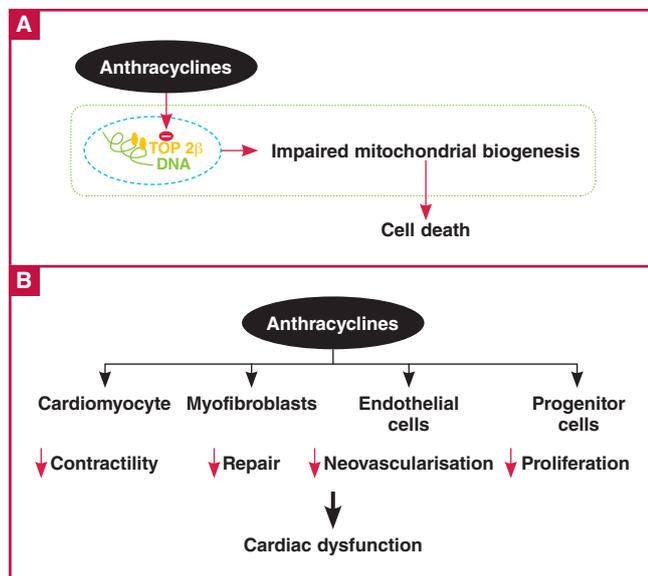
Fig. 1. Mechanism of anthracycline cardiotoxicity. A: In cardiac tissue, anthracycline inhibits topoisomerase II β (Top2β), triggering profound changes in transcription, leading to defective mitochondrial biogenesis, increased production of reactive oxygen species and cardiomyocyte death. B: Anthracycline induces deleterious effects on cardiomyocytes, endothelial cells, fibroblasts and cardiac progenitor cells, affects cardiac contractility and attenuates repair, neovascularisation and proliferation after injury, thus resulting in cardiac dysfunction.
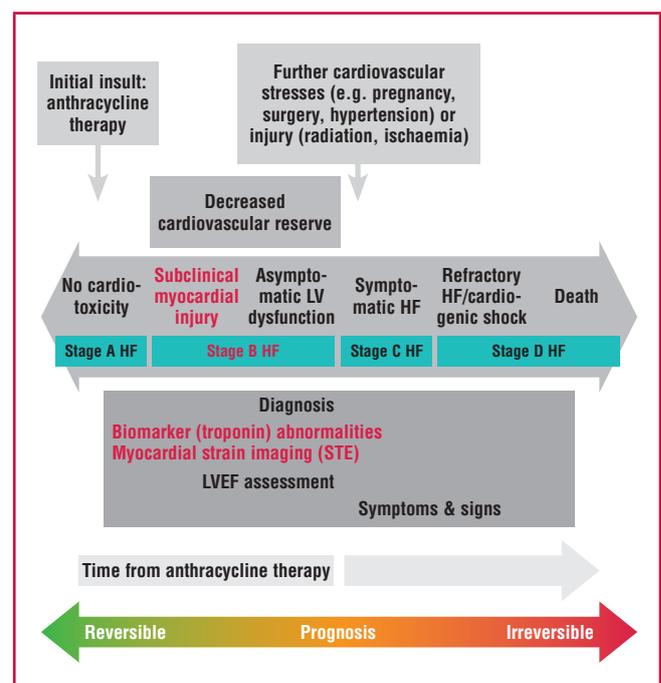
Fig. 2. Spectrum of ATRCD and the multiple-hit hypothesis. HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; STE, speckle-tracking echocardiography.
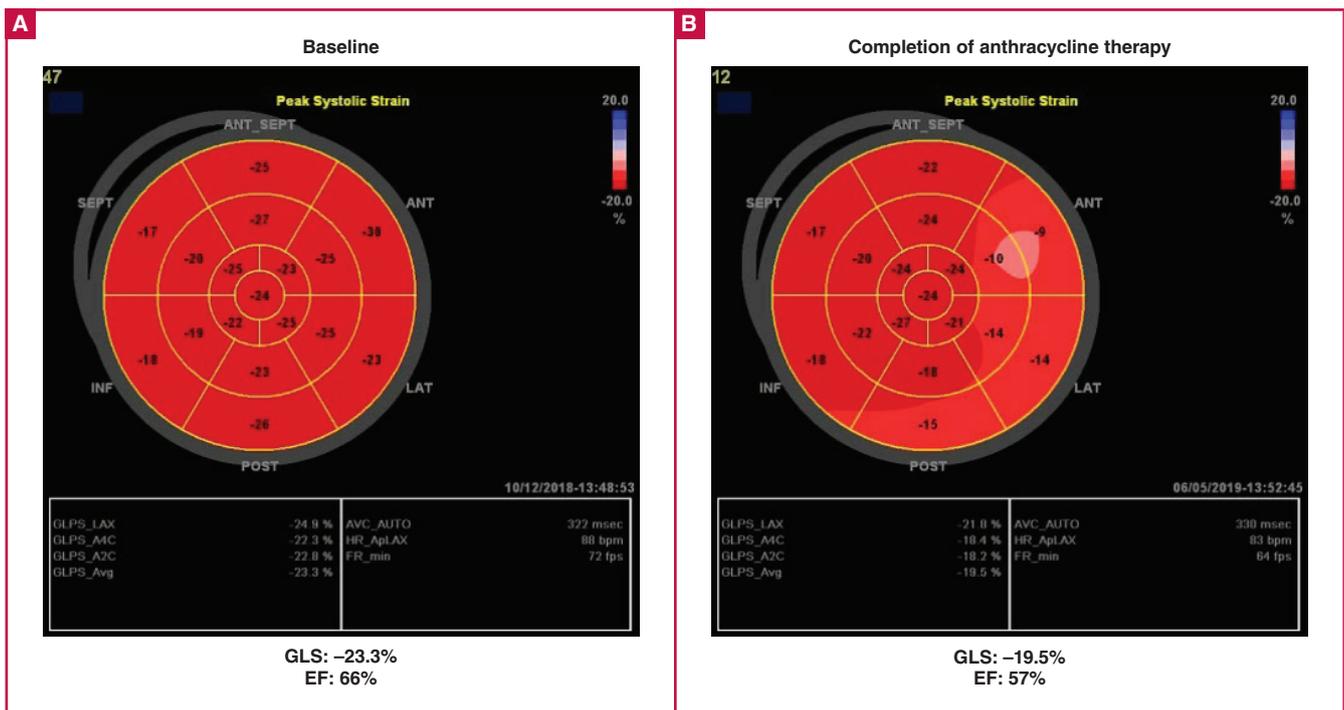
Fig. 3. Strain images of a patient who was diagnosed with subclinical ATRCD by GLS.

> 15% (Fig. 3) compared with baseline and/or positive troponin I levels during follow up will be considered subclinical ATRCD.[2]

Only a few studies have reported the incidence of subclinical ATRCD. Boyd *et al.*[15] used two-dimensional strain analysis to detect subclinical LV systolic dysfunction in 140 breast cancer patients early (within three month) after anthracycline chemotherapy. Subclinical LV dysfunction (> 11% reduction in GLS) occurred in 22% of their patient cohort. In another cohort of 159 patients receiving anthracycline, trastuzumab (a monoclonal antibody for treating HER2 receptor-positive breast cancer) or both,[16] decreased GLS (by > 11%) was found in 33% of patients seven months after the completion of the chemotherapy treatment. Interestingly, LVEF remained within normal ranges in both studies.

African populations who are at risk of developing ATRCD

Cancer is emerging as a major public health problem in sub-Saharan Africa (SSA) because of population aging and growth, as well as increased prevalence of key risk factors, including those associated with social and economic transition. A high residual burden of infectious agents (HIV/AIDS, human papillomavirus, hepatitis B virus) in certain SSA countries unquestionably drives the rates of certain cancers. Indeed, about one-third of all cancers in the region are estimated to be infection related.[17] Breast and cervical cancer in women and prostate cancer in men are the major cancers with a poor outcome in SSA.[17]

The growing prevalence and pattern of cancer in SSA determine the large role of anthracycline in cancer treatment in SSA. In the developed world, anthracycline has been used much less frequently, being partially replaced by novel, less cardiac-toxic anti-tumour drugs when treating certain types of cancer.[18] However, most of these novel drugs are costly and so not available in SSA.

Following the launching of the African Cancer Network Project in 2012, more than 100 cancer treatment institutions were set up by 2015.[19] More and more African cancer patients are able to receive anthracycline-based chemotherapy. Although there are no reliable data on how many patients are receiving these anti-tumour drugs in Africa, it has been estimated that about 60% of cancer patients in the Uganda Cancer Institute (UCI) are treated with anthracycline. The common cancers treated with anthracyclines at UCI include breast cancer (68.75%), non-Hodgkin's lymphoma (13.13%), Hodgkin's lymphoma (5.6%), advanced hepatocellular cancer (3.7%), soft tissue sarcomas (3.7%) and leukaemia (3.1%). Moreover, 80% of this population that are at risk of cardiotoxicity are women.[17]

Association of anthracycline cardiotoxicity risk with ethnicity and gender

Studies investigating sexual dimorphism of anthracycline cardiotoxicity are sparse. Yet growing evidence, mainly obtained in experimental studies, pinpoints a sexual dimorphism of doxorubicin cardiotoxicity, with females being protected compared to males.[20] This protection includes the essential targets of anthracycline, that is energy metabolism, energetic signalling pathways and oxidative stress.[20]

In a review article of anthracycline cardiotoxicity in childhood cancer survivors, Armstrong *et al.*[21] identified 17 studies evaluating gender as a risk factor for cardiotoxicity after anthracyclines and found five, including four high-quality studies, to validate that females experienced a poorer outcome than males. It has been suggested that doxorubicin cardiotoxicity is higher in prepubertal girls, and this could be explained by the lack of protection from female hormones. Further studies are

needed to understand in more detail the mechanism of female protection.

Black race was found to be a risk factor for developing ATRCD in both childhood cancer survivors[22] and adult cancer patients.[23] In an *in vitro* study, Huang *et al*.[24] used EBV-transformed B-lymphoblastoid HapMap cell lines derived from an African- and a European-descent cell line, in order to evaluate population- and gender-specific differences in cell cardiotoxicity after daunorubicin and other drug (carboplatin, cisplatin, etoposide) treatment. Interestingly, African-descent cell lines were found to be more prone to develop cytotoxicity linked to daunorubicin.

In Africa, two published studies done in Cote d'Ivoire and Morocco reported a high incidence of cardiotoxicity in adult cancer patients on anthracycline treatment. Elalouani *et al.* who conducted the first prospective cohort study in Morocco, investigating the frequency of anthracycline-induced cardiotoxicity, noted that 56% of the 70 patients developed a decrease in cardiac function and 4% of cases developed severe cardiotoxicity.[25] In the prospective cohort study performed at Abidjan Institute of Cardiology over 10 months, 45 adult patients were followed up and four patients (8.8%) developed significant cardiotoxicity.[26]

Cardiovascular care in African cancer patients: current status, challenges and opportunities

Despite an increased risk of developing asymptomatic subclinical ATRCD in Africa, there is a noted paucity of information on burden of subclinical anthracycline-induced cardiotoxicity and related predictors among adult cancer patients receiving anthracycline chemotherapy. This large gap in knowledge has led to a lack of local guidelines for monitoring and management of ATRCD.

The majority of patients receive only screening echocardiography before chemotherapy with no follow-up cardiac screening. This may leave many anthracycline-treated patients with undetected stage B heart failure (asymptomatic subclinical cardiac dysfunction) at risk of developing stage C or D heart failure when they encounter another cardiovascular risk later in life.

Strain echocardiography (GLS) and biomarkers (troponin) are verified diagnostic tools for this stage B heart failure. GLS is becoming routinely used in this population in the developed world but not in Africa, for a number of reasons. Indeed, many cardiologists are not trained to use this methodology, and few patients can afford the cost of serial echocardiography studies. When strain echocardiography is not available, conventional echocardiography parameters, which measure the longitudinal motion of the left ventricle [mitral annular plane systolic exertion (MAPSE), peak systolic mitral annular velocity by tissue Doppler (S′)], may potentially be useful in Africa.[27] However, their roles in detecting subclinical ATRCD have not been studied.

Compared to strain echocardiography, biomarker tests are cheaper and less skill-dependent, therefore more practical in African settings. Troponin, a biomarker of cardiac injury, has been found to have high negative predictive value in detecting subclinical ATRCD.[28] Natriuretic peptides, biomarkers of cardiac load, are the next most commonly researched biomarkers

in the context of ATRCD, apart from troponin. However, their roles in detecting subclinical ATRCD are less defined due to conflicting results from different trials. Myeloperoxidase is regarded as a marker of oxidative stress. In a recent study of multiple biomarkers, myeloperoxidase levels rose early, persisted throughout the course of therapy, and were associated with cardiotoxicity.[29]

Despite the challenges of implementing internationally recommended cardiac care protocols for cancer patients in SSA, conventional echocardiography combined with biomarker tests may be potentially useful for African patients. These tools have not been studied in SSA populations. Detecting subclinical ATRCD in a low-income country (SATRACD study) is an ongoing observational cohort study that will diagnose subclinical ATRCD in Ugandan cancer patients using international guidelines. The primary goal of this study is to determine the burden and risk factors of subclinical ATRCD in the study population, evaluating the role of conventional echocardiography parameters and biomarkers in detecting subclinical ATRCD in Ugandan cancer patients.

Conclusion

Due to the growing prevalence and unique pattern of cancer populations in Africa and progress in oncology treatments, there is increasing exposure of cancer patients to anthracycline. Subclinical ATRCD is a silent risk factor for heart failure in cancer survivors. Therefore subclinical ATRCD should no longer be ignored in Africa.

Oncologists and cardiologists in Africa have a responsibility to provide standard of care for patients receiving anthracycline therapy by implementing international guidelines. Local research in this field is needed to evaluate the real burden and risk factors of anthracycline therapy-related stage B heart failure. Moreover, in order to promote the application of available resources in cardio-oncology clinical practice and help to establish national guidelines for cardiac monitoring and management of patients with ATRCD, research should investigate more easily accessible tools to diagnose early damage, such as biomarkers and conventional echocardiography parameters.

References

1. Middleman EJ, Luce, Frei E. Clinical trials with adriamycin. *Cancer* 1971; **28**(4): 844–850.

2. 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. *Eur Heart J Cardiovasc Imaging* 2014; **15**(10): 1063–1093.

3. Zamorano JL, Lancellotti P, Rodriguez Munoz 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: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016; **37**(36): 2768–2801.

4. Steinherz LJ, Steinherz PG, Tan CT, Heller G, Murphy ML. Cardiac

toxicity 4 to 20 years after completing anthracycline therapy. *J Am Med Assoc* 1991; **266**(12): 1672–1677.

5. Von Hoff DD, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, Muggia FM. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 1979; **91**: 710–717.

6. Kremer LC, van der Pal HJ, Offringa M, van Dalen EC, Voûte PA. Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: a systematic review. *Ann Oncol* 2002; **13**(6): 819–829.

7. Kremer LC, van Dalen EC, Offringa M, Voûte PA. Frequency and risk factors of anthracycline-induced clinical heart failure in children: a systematic review. *Ann Oncol* 2002; **13**(4): 503–512.

8. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, *et al*. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **62**(16): e147–e239.

9. Vejpongsa P, Yeh ET. Topoisomerase 2beta: a promising molecular target for primary prevention of anthracycline-induced cardiotoxicity. *Clin Pharmacol Ther* 2014; **95**(1): 45–52.

10. Zhang S, Liu X, Bawa-Khalfe T, Lu L-S, Lyu YL, Liu LF, *et al.* Identification of the molecular basis of doxorubicin-induced cardiotoxicity. *Nature Med* 2012; **18**: 1639.

11. Huang C, Zhang X, Ramil JM, Rikka S, Kim L, Lee Y, *et al.* Juvenile exposure to anthracyclines impairs cardiac progenitor cell function and vascularization resulting in greater susceptibility to stress-induced myocardial injury in adult mice. *Circulation* 2010; **121**(5): 675–683.

12. Cardinale D, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, Civelli M, *et al*. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation* 2015; **131**(22): 1981–1988.

13. Lee YT, Chan KK, Harris PA, Cohen JL. Distribution of adriamycin in cancer patients: tissue uptakes, plasma concentration after IV and hepatic IA administration. *Cancer* 1980; **45**(9): 2231–2239.

14. Thavendiranathan P, Poulin F, Lim K-D, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. *J Am Coll Cardiol* 2014; **63**(25, Part A): 2751–2768.

15. Boyd A, Stoodley P, Richards D, Hui R, Harnett P, Vo K, *et al.* Anthracyclines induce early changes in left ventricular systolic and diastolic function: A single centre study. *PLoS One* 2017; **12**(4).

16. Negishi K, Negishi T, Haluska BA, Hare JL, Plana JC, Marwick TH. Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection. *Eur Heart J Cardiovasc Imaging* 2014; **15**(3): 324–331.

17. The Cancer Atlas. Risk-factors, infection. https://canceratlas.cancer.org/risk-factors/infection/

18. Spallarossa P, Maurea N, Cadeddu C, Madonna R, Mele D, Monte I, *et al*. A recommended practical approach to the management of anthracycline-based chemotherapy cardiotoxicity: an opinion paper of the working group on drug cardiotoxicity and cardioprotection, Italian Society of Cardiology. *J Cardiovasc Med* (Hagerstown) 2016; **17**(Suppl 1): S84–92.

19. Stefan DC. Cancer care in africa: an overview of resources. *J Glob Oncol* 2015; **1**(1): 30–36.

20. Solomon K, Charles K.M, Fred O, Victoria W, Jackson O. Anthracycline-induced cardiotoxicity in adult cancer patients: a prospective cohort study from a specialized oncology treatment centre in Uganda. *Afr Health Sci* 2019; **19**(1): 1647–1656.

21. Ventura-Clapier R, Moulin M, Piquereau J, Zurlo G, Garnier A. Sex differences in anthracycline cardiotoxicity. *Ital J Gender-Specific Med* 2016; **2**(2): 47–54.

22. Armstrong GT, Sklar CA, Hudson MM, Robison LL. Long-term health status among survivors of childhood cancer: does sex matter? *J Clin Oncol* 2007; **25**(28): 4477–4489.

23. Krischer JP, Epstein S, Cuthbertson DD, Goorin AM, Epstein ML, Lipshultz SE. Clinical cardiotoxicity following anthracycline treatment for childhood cancer: the Pediatric Oncology Group experience. *J Clin Oncol* 1997; **15**(4): 1544–1552.

24. Hasan S, Dinh K, Lombardo F, Kark J. Doxorubicin cardiotoxicity in African Americans. *J Natl Med Assoc* 2004; **96**(2): 196–199.

25. Huang RS, Kistner EO, Bleibel WK, Shukla SJ, Dolan ME. Effect of population and gender on chemotherapeutic agent-induced cytotoxicity. *Mol Cancer Ther* 2007; **6**(1): 31–36.

26. Elalouani C, Benhmidoun MA, Rida H, AitRaiss M, Derhem N, Elomrani A, *et al.* [Short and medium term cardiotoxicity of anthracyclins: a prospective study]. *Ann Cardiol Angeiol* (Paris) 2012; **61**(4): 257–266.

27. Pio M, Adoubi K, Adoh A, Didi-Kouko C, Anzouan-Kacou JB, Tegnan A, *et al.* [Early detection of anthracyclines cardiotoxicity by tissue Doppler echocardiography about 45 cases at Abidjan institute of cardiology]. *Ann Cardiol Angeiol* (Paris) 2013; **62**(1): 28–33.

28. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, *et al.* Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation* 2004; **109**(22): 2749–2754.

29. Putt M, Hahn VS, Januzzi JL, Sawaya H, Sebag IA, Plana JC, *et al.* Longitudinal changes in multiple biomarkers are associated with cardiotoxicity in breast cancer patients treated with doxorubicin, taxanes, and trastuzumab. *Clin Chem* 2015. **61**(9): 1164–1172.