Cytotoxic-Induced Heart Failure among Breast Cancer Patients in Nigeria: A Call to Prevent Today’s Cancer Patients from Being Tomorrow’s Cardiac Patients

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Abstract

We report three cases of heart failure (HF) associated with the use of cytotoxic drugs such as anthracycline, cyclophosphamide, and 5-fluorouracil in the treatment of breast cancer in Nigerians. The patients had systolic and diastolic HF: HF with reduced ejection fraction and preserved ejection fraction. The prevalence of breast cancer is increasing across Africa, and cytotoxics are some of the most common and best drugs used during management. The cardiotoxicity caused by these drugs limits their use as chemotherapeutic agents. Cytotoxic-induced HF is a preventable and manageable cause of cardiovascular disease (CVD) in Nigeria and Africa. This article discusses the pathophysiology of cytotoxic-induced HF and presents the risk factors that impair cardiovascular function. The importance of proper assessment and the prophylactic and therapeutic measures in the management of cytotoxic-induced HF are emphasized. The peculiar challenges in the management of cytotoxic-induced HF in Nigeria were also discussed. The need for early involvement of cardiologists by oncologists to improve on the chemotherapeutic and cardiovascular outcome in the management of patients with breast cancer was stressed. Perhaps, it is time to birth a new discipline of cardiooncology in Nigeria.

Keywords: Breast cancer chemotherapy, cardiologists, cytotoxics, heart failure, Nigeria, oncologists

Résumé

Nous rapportons trois cas d’insuffisance cardiaque (IC) associés à l’utilisation de médicaments cytotoxiques tels que l’anthracycline, le cyclophosphamide et le 5-fluorouracile dans le traitement du cancer du sein chez les Nigérians. Les patients avaient une HF systolique et diastolique: HF avec une fraction d’éjection réduite et une fraction d’éjection préservée. La prévalence du cancer du sein augmente à travers l’Afrique et les cytotoxiques sont parmi les médicaments les plus courants et les meilleurs utilisés pendant la prise en charge. La cardiotoxicité causée par ces médicaments limite leur utilisation comme agents chimiothérapeutiques. L’IC induite par les cytotoxiques est une cause évitable et gérable de maladies cardiovasculaires (MCV) au Nigéria et en Afrique. Cet article traite de la physiopathologie de l’IC induite par cytotoxique et présente les facteurs de risque qui altèrent la fonction cardiovasculaire. L’importance d’une évaluation appropriée et des mesures prophylactiques et thérapeutiques dans la gestion de l’IC induite par les cytotoxiques est soulignée. Les défis particuliers de la gestion de l’IC induit par des cytotoxiques au Nigeria ont également été discutés. La nécessité d’une implication précoce des cardiologues par les oncologues pour améliorer les résultats chimiothérapeutiques et cardiovasculaires dans la prise en charge des patientes atteintes d’un cancer du sein a été soulignée. Peut-être est-il temps de donner naissance à une nouvelle discipline de cardiooncologie au Nigeria.

Mots-clés: chimiothérapie du cancer du sein, cardiologues, cytotoxiques, insuffisance cardiaque, Nigeria, oncologues

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INTRODUCTION

Cancer is the second most common cause of death in USA, after heart disease, causing approximately 400,000 deaths/year.\[1\] In Africa and Nigeria, the prevalence of cancer is increasing.\[2\] and breast cancer has become one of the most common malignancies in Nigeria, and treatment is available and curative when patients present early.\[2-5\] Chemotherapy combined with surgery and radiotherapy are the treatment options currently available in Nigeria.\[2,4,5\]

Overall, 50% of patients with cancer can be cured, with chemotherapy contributing to cure in 10%–15% of patients.\[2\] Cytotoxics are chemotherapeutic agents useful in the treatment of solid tumors, leukemia, lymphomas, lung cancers, multiple myeloma, and sarcoma with breast cancer being one of the most common indications for their use. Anthracyclines are the most common cytotoxics used in breast cancer chemotherapy in Nigeria.\[3,5\] They are used in combination with cyclophosphamide and 5-fluorouracil (5-FU) in the treatment of breast cancer.\[3,5,1\]

Cytotoxics unfortunately cause cardiotoxicity. These predisposes patients who have benefited from lifesaving cancer chemotherapy to CVDs sometimes decades after treatment. This is a major setback for cancer chemotherapy.\[6-7\] Unfortunately, the more aggressive cancer chemotherapeutic agents have more cardiotoxicity. Cardiotoxicity due to chemotherapeutic drugs can be divided into two types: type 1 and type 2.\[6,7\]

Type 1 is irreversible and characterized by myocyte damage: vacuolar swelling progressing to myofibrillar disarray and ultimately cell death. The dead myocytes are replaced by fibrotic tissue as regeneration is impossible. This type of cardiotoxicity is caused by anthracyclines, cyclophosphamide, and 5-FU in a cumulative dose-dependent fashion.\[6-8\] Type 2 is reversible cardiotoxicity. The toxicity is typically not related with myocyte death and does not induce progressive cardiac dysfunction; and myocardial function is generally completely reversible after their interruption of therapy. Many chemotherapy agents and particularly trastuzumab, bevacizumab, lapatinib, and sunitinib cause type 2 chemotherapy-induced cardiac toxicity.\[8,9\] However, trastuzumab can trigger irreversible cardiac damage in patients with severe preexisting cardiac disease and lead to anthracycline-type cardiotoxicity.

Cytotoxics destroy or damage cancer cells act by alkylation (alkylating agents-cyclophosphamide), others by intercalation (anticancer antibiotics-anthracycline), and others act as structural analogs by inhibiting pathways leading to cell replication (antimetabolites-5-FU).\[10\] Cytotoxics cause cardiotoxicity during use and many months after the cessation of chemotherapy.\[11\] Their toxicity ranges from high blood pressure, arrhythmia, coronary artery disease to heart failure (HF). Cytotoxics are invaluable antineoplastics that cause to some extent, a preventable form of HF.\[1\] This form of cardiotoxicity can be assessed clinically and also using electrocardiography (ECG), echocardiography, biopsy, and serum markers such as troponin T and b-natriuretic peptide (BNP).\[10\]

Anthracyclines, cyclophosphamide, and 5-FU are among cytotoxics that have been reported to cause HF.\[11\] Anthracyclines form radicals and superoxides that cause oxidative stress in the myocardium leading to apoptosis, and cyclophosphamide causes toxic endothelial damage followed by extravasation of toxic metabolites with resultant myocyte damage and interstitial hemorrhage and edema.\[11\] Daunorubicin, doxorubicin, and epirubicin are some of the most commonly used anthracyclines. 5-FU is postulated to cause vasospasms leading to ischemia, activation of coagulation system, coronary artery thrombosis, and immunoallergic phenomena from cardiotoxic impurities in the 5-FU formulation.\[11\]

In a retrospective analysis of over 4000 patients who received doxorubicin, 2.2% of the patients developed clinical features of HF.\[12\] It was noted that if asymptomatic patients who have subclinical systolic dysfunction were included in this survey, the prevalence would increase significantly.\[12\] The prevalence of cytotoxic-induced HF in Nigeria and Africa is not known. However, it is known that cytotoxic-induced HF is a preventable and a potentially treatable disease.

Cardiotoxicity induced by chemotherapeutic agents can present acutely or chronically: early or late.\[13,14\] The presentation may be asymptomatic or symptomatic. Acute cardiotoxicity is characterized by either the occurrence of abnormalities in ventricular repolarization and electrocardiographic QT-interval changes, by supraventricular and ventricular arrhythmias, or by acute coronary syndromes and pericarditis and/or myocarditis-like syndromes, observed any time from the initiation of therapy up to 2–4 weeks after termination of treatment.\[15,16\] Early and late chronic cardiotoxicity occur within 1 year and after 1 year after chemotherapy, respectively, and present as asymptomatic systolic and/or diastolic left ventricular dysfunction or with symptoms in keeping with congestive cardiac failure.\[17\]

We report three cases of HF associated with the use of anthracyclines, cyclophosphamide, and 5-FU in the treatment of breast cancer patients seen at the University of Nigeria Teaching Hospital Enugu, Nigeria.

CASE REPORTS

Case 1 is UA, a 71-year-old female presented on January 30, 2013 (7 months after chemotherapy with epirubicin - total dose given = 510 mg and cyclophosphamide - total dose given = 5100 mg) with features in keeping with HF. She had right-modified radical mastectomy in April 2012 and six courses of chemotherapy (a dose = epirubicin 85 mg, cyclophosphamide 850 mg) over a 4-month period. She is a known hypertensive, controlled with lisinopril 10 mg daily, coamilozone 1 tablet daily, and vasoprin 75 mg daily. The chest X-ray showed cardiomegaly and aortic unfolding.
Preexposure echocardiography showed dilated left atrium as the only abnormality. The postexposure ECG done showed left atrial enlargement, complete left bundle branch block, and ventricular ectopics. Postexposure echocardiography showed dilated left atrium (4.7 cm), dilated left ventricle, left ventricular diastolic dysfunction, reduced ejection fraction – 45% normal interventricular thickness and posterior wall thickening at diastole and mild pericardial effusion. Normal renal function and lipid levels were noted. She responded well to digoxin, frusemide, spironolactone, and lisinopril and was discharged on the 20th day of admission.

Case 2 is a 64-year-old female OA, who presented on January 26, 2013, with right breast invasive carcinoma stage pT3pN2Mx, had mastectomy, and was placed on six courses of chemotherapy (a dose = epirubicin 95 mg, cyclophosphamide 950 mg, and fluorouracil 950 mg) over a 4-month period. She presented with congestive cardiac failure, 4-month postcommencement of chemotherapy. Preexposure echocardiography showed normal findings. Postexposure ECG done showed sinus bradycardia and premature monofocal ventricular ectopics. Postexposure echocardiography showed dilated left atrium, left biventricular ventricular diastolic dysfunction, and normal ejection fraction – 60.3%. Renal function and lipid levels were normal. She was managed with aldactone 50 mg, esidre × 25 mg, lisinopril 5 mg, and vasoprin 75 mg with good response.

Case 3 is a 56-year-old female presented on January 30, 2013 (10 months after chemotherapy with epirubicin - total dose given = 510 mg and cyclophosphamide - total dose given = 5100 mg) with features in keeping with right HF. She had left-modified radical mastectomy in April 2012 and six courses of chemotherapy (a dose = epirubicin 85 mg, cyclophosphamide 850 mg) over a 4-month period. She is a known hypertensive, controlled with lisinopril 10 mg daily, co-amiloizide 1 tablet daily, and vasoprin 75 mg daily. Preexposure ECG was normal. Preexposure echocardiography showed the left ventricular diastolic dysfunction, no ventricular systolic dysfunction, and no right ventricular diastolic dysfunction. The postexposure ECG done showed right ventricular bundle branch block. Postexposure echocardiography showed normal findings: right ventricular systolic dysfunction with functional grade 2 tricuspid dysfunction and right ventricular diastolic dysfunction. The left systolic function was normal, but there was diastolic dysfunction. Normal renal function and lipid levels were noted. She responded well to frusemide, spironolactone, and lisinopril and was discharged on the 20th day of admission.

**Discussion**

Patients who have breast cancer must have cardiovascular assessment before the commencement of chemotherapy.\[^{18,19}\] This evaluation should be repeated at least after 3 months, 6 months, 12 months, and yearly.\[^{20,21}\] The presence of cardiovascular dysfunction in a patient before the commencement of cancer chemotherapy influences the choice of chemotherapeutic agents and may lead to change from a more aggressive, more effective to a less cardiotoxic but less effective drug, and there may be limitation to the use of adjunctive chemotherapy.\[^{20,21}\] Successful and effective management of any cardiotoxicity will depend on the inclusion of all risk factors and comorbidities in the therapeutic armamentarium of the cardiooncologist team [Box 1].\[^{20,21}\]

In 2016, the European Society of Cardiology European Guidelines for the diagnosis and treatment of HF classified HF into reduced ejection fraction (left ventricular ejection fraction [LVEF] <40%), midrange ejection fraction (LVEF 40%–49%), and preserved ejection fraction (LVEF >50%).\[^{22}\] However, the Cardiac Review and Evaluation Committee on trastuzumab-associated cardiotoxicity and the ESMO Clinical Practice Guidelines have defined cardiotoxicity that is relevant for cardiooncology services. Cardiotoxicity is defined as “a decrease of LVEF by 5% or more to <55% in the presence of symptoms of HF or an asymptomatic decrease in LVEF by 10% or more to <55%.”\[^{10}\] Echocardiography has remained the standard investigative modality of chemotherapy-induced cardiotoxicity. It is noninvasive, easily available, and with no side effects.

In spite of the fact that two-dimensional (2D) echocardiography has been the traditional tool for investigating the structure and function of the heart of patients on chemotherapy, it has some drawbacks. There are patients who are asymptomatic and have normal 2D left ventricular function but have abnormal mechanics indicating subclinical or early abnormalities. These group of patients who have early cardiac dysfunction can only be picked by three-dimensional LVEF, 2D global longitudinal strain, and exercise stress echocardiography.\[^{23,24}\] Indeed, myocardial strain imaging is more sensitive than 2D LVEF for the early detection (3 months) and intermediate-term (6 months) monitoring of LV systolic function following chemotherapy in breast cancer patients.\[^{25-27}\]
Box 2: Cardiovascular workup for patients on anthracycline therapy

| ECG | Electrocardiography |
| Cardiac enzymes: Troponin I | BNP |
| Radionuclide angiocardiography | Endomyocardial biopsy |

ECG = Electrocardiography, BNP = B-natriuretic peptide

Apart from echocardiography, cardiac enzymes, natriuretic peptides (BNP), magnetic resonance imaging (MRI), and myocardial biopsy are also useful tools in the monitoring of drug-induced cardiotoxicity. Troponin I or BNP concentrations are sensitive in identifying patients at risk of cardiotoxicity because they measure cardiomyocyte injury and HF tendency. Troponin I detects anticancer drug-induced cardiotoxicity in its earliest phase, long before any reduction in LVEF has occurred. Cardiovascular assessment includes performing baseline assessment of biomarker concentrations, and periodic measurements during therapy (every cycle) may identify patients who need further cardiac assessment [Box 2].

Cardiac MRI is the gold standard for the evaluation of LV volumes, mass, and function. However, its lack of availability and high-cost limit its routine use in assessing cardiotoxicity in patients on cancer chemotherapeutic agents.

Cytotoxic-induced HF is probably an underreported problem. The first report of HF in children treated with doxorubicin in USA was in 1967, and the risk factors which appear to be specific for early cardiotoxicity in children include black race, trisomy 21, and the use of ansamycin therapy after anthracycline therapy. Doxorubicin-induced cardiotoxicity in children may manifest as impairment of left ventricular contractility and increased afterload due to thinning of left ventricular walls.

The prevalence of doxorubicin cardiotoxicity among African-Americans has been shown to increase from 4% at a dose range of 451–500 mg/m² to 25% at a dose range of 551–600 mg/m². There are also reports of anthracycline cardiotoxicity among Africans as documented in a 51-year-old Nigerian woman and 14-year-old Ghanaian girl with doxorubicin-induced HF at doses of 343 and 400 mg/m², respectively.

The first case of doxorubicin-induced HF in breast cancer patients was in 1979, in which the effect of cumulative increase of drug dose correlated positively with higher prevalence of HF. The overall incidence for the 88 patients was 2.2%, but a continually increasing incidence of HF rates of 3%, 7%, and 18% at 400, 500, and 700 mg/m², respectively, of cumulative doxorubicin dose. More studies would show definitely that even at a cumulative doxorubicin dose of 400 mg/m², HF was even higher than the 3% previously reported and paved the way for a policy of limiting the lifetime cumulative doxorubicin equivalent exposure to ≤450 mg/m² in patients without prior chest radiotherapy.

The anthracyclines are dose-dependent cardiotoxic drugs. Total doses of doxorubicin below 550 mg/m² are generally recommended and unlikely to cause cardiotoxicity. However, in cases of doses exceeding this amount, about 30% of the patients will develop HF. Doxorubicin as a part of a combined chemotherapeutic regimen may however induce HF at a cumulative dosage below 550 mg/m². Doses as low as 400 mg/m² combined with cyclophosphamide have increased tendency to cardiotoxicity. Epirubicin has lower frequency of cardiotoxicity at therapeutic dosages when compared with doxorubicin. For comparison, the incidence of cardiotoxicity is 0.03 at a cumulative dose of 900 mg/m² for epirubicin, against 0.18 at a cumulative dose of 700 mg/m², 0.07 at a dose of 550 mg/m², and 0.03 or less at a dose 400 mg/m² for doxorubicin.

Anthracycline toxicity can be classified into acute, subacute, and chronic (with early and late onset). However, this classification can be described as arbitrary and only serves to emphasize that cardiotoxicity can start within hours and days and may take years to manifest. Early cardiac toxicity, which occurs during or soon after treatment with anthracyclines, is mainly dependent on the cumulative anthracycline dose. However, the development of HF several years after the last administration of anthracyclines is increasingly recognized. Long-term myocardial damage has also been identified in patients who had received doses of only 45 mg/m². Therefore, all patients exposed to anthracyclines should be considered at risk for the development of HF as a result of the cardiotoxic properties of anthracyclines.

Cyclophosphamide causes arrhythmia and HF, and the incidence of cardiotoxicity in a group of patients who never had prior anthracycline therapy was 25% (13/52) with 12% (6/52) mortality rate when the cyclophosphamide dose exceeded 1.55 mg/m²/day. Those who received lower than 1.55 mg/m²/day had 3% (1/32) symptomatic cardiotoxicity with no mortality. Patients who develop symptoms of HF as a result of cyclophosphamide therapy usually present within 2 weeks after administration of the drug. In patients who develop severe progressive HF, this complication may lead to death within a few weeks.

The probability of developing HF can be influenced by preexisting cardiovascular condition, other chemotherapeutic regimens received before treatment with cyclophosphamide and the dose and method of administration of cyclophosphamide. Cyclophosphamide-induced cardiotoxicity may last from 1 to 6 days and despite the relatively high mortality rate, there are no long-term sequels or late cardiotoxicity in patients who survive the initial acute event.

5-FU is a pyrimidine antimetabolite capable of causing myocardial ischemia. The prevalence of 5-FU-induced cardiotoxicity is low, particularly in the absence of prior CVD. However, patients with myocardial ischemia should not take this therapy, because cases of massive myocardial infarctions have occurred. 5-FU cardiotoxicity is more
common following high dose continuous infusion than after intravenous bolus administration.\[40\]

The index case 1 had cumulative doses of epirubicin of about 510 mg/m\(^2\), but its combination with cyclophosphamide in addition to the preexisting hypertensive heart disease increased the risk of developing HF. The index case 2 had a combination of three cardiotoxic drugs, and this escalated the risks for inducing HF. The index case 3 was on epirubicin, a less cardiotoxic drug, but the hypertensive heart disease was an added risk factor for HF. Cumulative dose, increased age, female gender, electrolyte imbalance, prior irradiation, concomitant administration of other chemotherapeutics, and underlying heart disease are considered as risk factors for cytotoxic-induced cardiotoxicity.

Mitigating factors to cytotoxics-induced HF include prior screening for premorbid heart diseases, use of lower doses of chemotherapeutic drugs, and appropriate mode of administration. Continuous infusion of drugs is preferred over bolus doses for anthracyclines and cyclophosphamide, but the reverse is safer for 5-FU. There are drugs that have been found beneficial in preventing and modulating the cardiotoxicity associated with cytotoxics.

Anthracycline-cardiotoxicity can be prevented using iron-chelating agent, dexrazoxane.\[41\] This drug binds to intracellular iron and removes the iron from the anthracycline–iron complex, thus preventing free radical formation associated with anthracycline - nonheme iron interactions.\[41\] Alpha-tocopherol, an antioxidant, mop up free radicals and superoxides formed by the cytotoxics and are therefore effective in cardioprotection.\[12,38\] Carvedilol, a beta-adrenergic blocker, has also been shown to be an effective antioxidant, mitigating the cardiotoxic effect of anthracyclines.\[19,42,43\] Treatment with angiotensin-converting enzyme (ACE) inhibitor, enalapril, and carvedilol has been shown to prevent the decline of LVEF.\[44-46\] All the cases presented in this report had ACE inhibitors. There is a new interest in the use of steroids for the prevention of cytotoxic-induced cardiotoxicity.\[47\] A Nigerian tertiary hospital which managed patients with hematological cancers on treatment with cytotoxics and adjunctive prednisolone reported that the patients appeared not to have HF. The theoretical explanation for the effect of steroids may be their anti-inflammatory effect given that inflammatory process underlies most of the mechanism of action of the cytotoxic agents. However, only a robust and well-designed double-blind study can clearly define the drugs that are certainly useful as cardioprotective agents in the management of patients on cytotoxic therapy.\[48\]

There are challenges in managing the cardiotoxicity associated with the cytotoxics in developing countries such as Nigeria. The availability and affordability of less toxic agents are a big challenge. In addition, there are challenges in the affordability of simple and basic investigative tools such as ECG and echocardiography. The cases cited in this report could barely afford the cost of investigations. The patients were in fact lost to follow-up perhaps due to financial problems. The cost of ECG is 4000 naira (about 11 dollars currently) and echocardiography costs 10000 naira (28 dollars) in the University of Nigeria Teaching Hospital, Enugu, excluding the costs of chemotherapy and other direct and indirect costs. If these data are placed side by side with the minimum monthly wage in Nigeria which has remained below 18000 naira (50 dollars) for many years, and the fact that many Nigerians live on 1 dollar/day, then the implications are obvious.

Ideally, cardiovascular workup tests should be done before administering cardiotoxic drugs, after each dose, and then monthly, 6 months, and repeated yearly as follow-up to be able to pick up early and late presentations of cardiac toxicity. These checks were not done as regularly as prescribed for the index cases reported here. Our index cases had only one ECG assessment after the development of HF. The patients could not afford further assessments in spite of the fact that even the echocardiography was done as part of a research program and so at no cost to the patients. These minimal assessments are really insufficient for the prevention and or monitoring of cardiac-induced injury. However, in developing countries, these assessment tools are luxuries because of cost implications. The costs of these investigations are obviously beyond the budget of most patients with breast cancer in Nigeria.

Some of these challenges may explain why cytotoxic-induced HF is rarely reported from Nigeria and Africa. In addition to these, there is also the perceived problem of poor collaboration between oncologists and cardiologists in doing proper preexposure assessment, documenting intraexposure and postexposure cardiotoxicity and managing appropriately all cardiovascular events resulting from therapy with cytotoxic agents. Put simply, some breast cancer patients die prematurely not from the cancer but from cytotoxic-induced CVD. Many breast cancer patients may have lived longer if proper cardiovascular assessment and management were done.

Good interprofessional relationship will ensure that breast cancer patients in Nigeria receive the best care that facilities and specialists available can provide. This type of relationship will take into consideration classification of cancer patients into those that will definitely benefit from the cytotoxics and do not have significant risk from cardiotoxicity; those patients with minor cardiovascular risk factors and so will require some preventive and intratherapeutic modulating measures to contain significant cardiotoxicity; and those patients who due to multiple and overriding cardiovascular risk factors may be at risk of death from cytotoxic-induced cardiotoxicity and so may not benefit from cytotoxic drugs.

Breast cancer survivors are at greater risk for CVD-related mortality, and this increase in risk is manifested within approximately 7 years after diagnosis.\[49\] In Nigeria and most African countries, CVD-related mortality cases are expected
to present earlier and to be higher in breast cancer survivors given the late presentation of patients, the lack or high cost of diagnostic and monitoring tools, and the poorly coordinated cardiooncology services.\(^{[49]}\) Put simply, many breast cancer survivors would have lived longer if attention was paid to their cardiovascular health.

In today’s clinical practice, the oncologists must recognize that their therapy has adverse cardiovascular effects which can be avoided and or managed properly with the cooperation of cardiologists who should realize that cancer chemotherapy-induced CVD contributes significantly to patients’ disease burden. There is a great need for established internationally agreed guidelines in the management of cardiovascular complications of cancer chemotherapy. This is a call for a specialized service, cardiooncology clinics in Nigeria and Africa, in keeping with international best practices [Box 3].

The need for early presentation and assessment of patients with breast cancer and on chemotherapy cannot be overemphasized. All patients on chemotherapy must have cardiovascular evaluation before, during, and posttherapy.\(^{[50,51]}\) This is the only way to diagnose cardiotoxicity and begin appropriate therapy to prevent irreversible cardiotoxicity and HF.\(^{[52,53]}\)

It will be necessary to also explore potential differences between Blacks and Caucasians, if any, in the way cardiovascular complications present and the way they are managed.\(^{[54,55]}\) Cardiologists must now be involved in early phases of clinical trials so as to ensure that only cardiac friendly cancer chemotherapeutic agents are approved for use.\(^{[56,57]}\)

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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