Assessment of cardiotoxicity in cancer patients on chemotherapy in a low resource setting: is echocardiography the ultimate tool, or should we look for another?

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Abstract

Cancer is a leading cause of death worldwide, and its burden in Africa is projected to rise. Africans have cause to worry over what to do to reduce its morbidity and mortality. Unfortunately, some of the most effective anticancer therapies cause cardiovascular dysfunction and may deny patients with cancer the life-saving benefits of chemotherapy. Currently, expert consensus opinion adopts echocardiography to define cancer chemotherapy-induced cardiotoxicity, but the cost is unaffordable in most low-income countries. This review aims to examine the use of Cardiac Troponin (cT) to detect cardiotoxicity, particularly early cardiotoxicity, which routine echo is unable to do. We propose that patients on cancer chemotherapy should first have a cT assessment, and depending on the level of the cT, an echo may be indicated. This will reduce the frequency and cost of echo. Our proposal may also lead to a new definition of cancer chemotherapy-induced cardiotoxicity, taking into consideration the usefulness of cT.

Introduction

Cancer epidemiology can be traced back to the Egyptian period, around 3000 B.C., when a history of cancer cases was documented.[1,2] Today, cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020.[3] The cancer burden in Africa is projected to rise from 1.1 million cases and 700,000 deaths in 2020 to 2.1 million cases and 1.4 million deaths in 2040. So, Africans have a cause to worry over what to do to reduce morbidity and mortality due to cancer in view of the burgeoning cancer epidemiology.[4]

Historically, treatment of cancer was mainly surgical, often with poor outcomes. With the discovery of cytotoxic antitumor drugs after the Second World War, the use of chemotherapy for the treatment of various hematological and solid tumors was born. Furthermore, molecular and cellular biology studies allowed the development of molecular targets involved in neoplastic processes, giving rise to targeted therapy.[5] Genetic engineering studies led to the introduction of monoclonal antibodies and immune checkpoint inhibitors for the treatment of advanced or metastatic tumors, for which no effective treatment was available.[5] Indeed, medical science has made remarkable progress such that cancer therapies are now available and have reduced the mortality and prolonged life of patients with neoplasm. During the past 30 years, breast cancer-specific survival has improved by 20%, and 5-year survival is now 98% for early-stage disease, and the 5-year survival rate for childhood cancers diagnosed from 2006 to 2010 has reached 82%.[6]

Unfortunately, some of the most effective anticancer therapies cause cardiotoxicity and lead to cardiovascular dysfunction. This has denied patients with cancer the life-saving benefits of chemotherapy or left them with the options of delayed therapy or being treated with less beneficial drugs, leading to increased morbidity and mortality. This is particularly a problem with older and cheaper drugs that are available in low-resource countries where the less toxic and newer therapies are beyond the reach of many average patients.

Assessment for cardiotoxicity, which is mostly done with echocardiography, is also not done routinely because patients in most low-resource countries pay out of pocket due to poorly developed health insurance policies. Echocardiography is required before cancer chemotherapy, and it is repeated during and after therapy to assess, diagnose, and sometimes treat cancer chemotherapy-induced cardiotoxicity.

Chemotherapy-induced cardiotoxicity

Anthracyclines are the most commonly used cancer chemotherapeutic drugs for solid and hematologic tumors in low-resource countries but their clinical use is limited by cardiotoxicity.[7-9] Alkylating drugs (cyclophosphamide, cisplatin) and antimicrotuble agents (paclitaxel, docetaxel) also have a similar drawback and are linked with serious cardiac events. Other anticancer therapies associated with a significant risk of Heart Failure (HF) or Left Ventricular Dysfunction (LVD) include Human Epidermal Growth Factor Receptor 2 (HER2) molecular-targeted therapies (such as trastuzumab or pertuzumab), Vascular Endothelial Growth Factor (VEGF) signaling pathway inhibitors (such as sunitinib, sorafenib, and bevacizumab) and some proteasome inhibitors (carfilzomib).[7-9]

Von Hoff and colleagues were the first to raise significant concerns about the cardiovascular safety of anticancer therapies.[10] They identified dose-dependent and progressive LVD manifesting as symptomatic heart failure in patients receiving anthracyclines.[10] Since then, there have been several reports of anthracycline-induced cardiac toxicity[11-14].

Chemotherapeutic drugs that directly and irreversibly induce myocardial damage and cause necrosis through oxidative stress and other mechanisms are classified as causing type 1 cardiotoxicity. Anthracycline-induced cardiotoxicity is an example. Anthracyclines cause cardiotoxicity in a dose-dependent manner, increasing exponentially with dose.[15,16] Type 2 cardiotoxicity causes cardiomyocyte dysfunction, but not necrosis, and its induced cardiotoxicity is reversible. Trastuzumab, an anti-HER2 antibody, is a classic example of this class. Tyrosine kinase inhibitors, such as sunitinib, imatinib, and sorafenib, which are also known as angiogenesis inhibitors because of their inhibitory action on VEGF receptors, can cause reversible and dose-independent myocardial dysfunction but not necrosis.[17,18] Despite the above classification, we now know that about 20% of drugs classified as type 2 may induce irreversible damage due to mechanisms overlapping with those of type 1 drugs. It should also be noted that in the actual treatment of cancer, many patients receive a combination of type 1 and 2 drugs, and so both types of cardiotoxicity may occur in the same patient.[19]

Cancer chemotherapy-induced cardiotoxicity can also be classified with respect to time of onset: acute or chronic. Acute cardiotoxicity manifests as a myopericarditis-like picture soon after its administration. It is transient and self-limiting, with non-specific Electrocardiogram (ECG) changes, elevation in troponin, and possibly reversible LV dysfunction.[19] Chronic cardiotoxicity can be early or late, the former occurring within one year and the latter after one year of chemotherapy. Chronic cardiotoxicity is the most important form of cardiotoxicity, comprising LV systolic dysfunction, which progresses from early asymptomatic LV dysfunction to overt Chronic Heart Failure (CHF).[19]

The spectrum of cardiovascular toxicity of cancer therapy includes LV dysfunction and failure; coronary vasospasm, angina, acute coronary syndrome, and myocardial infarction; QT prolongation, atrial and ventricular arrhythmias; thromboembolic disease, hypertension; pericardial effusion and cardiac tamponade; valvular heart disease, pulmonary fibrosis, and pulmonary hypertension.[8]

Methods of assessing cardiotoxicity in chemotherapy patients

Several strategies have been used over the past decades to detect cardiotoxicity. These include endomyocardial biopsies, echocardiography, nuclear cardiac imaging, cardiac Magnetic Resonance Imaging (MRI), and cardiac biomarkers.[6,20-25]

Endomyocardial biopsies proved to be the most sensitive and specific parameter for the identification of anthracycline-induced LV dysfunction and became the gold standard in the 1970s. However, the interest in endomyocardial biopsy has diminished over time because of the invasiveness of the procedure and the remarkable progress made in noninvasive cardiac imaging.[24]

Nuclear cardiac imaging has been used for the evaluation of LV function using multigated radionuclide angiography. This modality has been used to diagnose chemotherapy-induced cardiotoxicity with good accuracy and reproducibility and few technical limitations. However, it is constrained by radiation exposure and provides only limited additional information on cardiac structure and hemodynamics.[22]

Cardiac MRI (CMRI) is a useful tool in the evaluation of cardiac structure and function. Indeed, it is currently regarded as the gold standard for measurement of the LV volume and Left Ventricular Ejection Fraction (LVEF).[26] It is useful in resolving diagnostic dilemmas associated with other imaging modalities. CMRI is useful in evaluating the pericardium, especially in patients with chest irradiation, in detecting scarring or fibrosis. CMRI is also an excellent test for the comprehensive evaluation of cardiac masses and infiltrative conditions. In summary, it offers complete information regarding myocardial performance and valvular and pericardial involvement. However, CMRI is time-consuming, expensive, and not easily available, which limits the number of institutions that can implement it.[26]

The ideal modality for the detection of Cancer Chemotheraphy-Induced Cardiotoxicity (CCIC) should be safe, widely accessible, accurate, available, reproducible, and able to detect small and potentially subclinical changes in LV function. The absolute value of LVEF, which defines CCIC, is still a matter of discussion, and we have depended on expert consensus opinions to define cancer chemotherapy-induced cardiotoxicity because of the absence of large-scale robust clinical trials. The most recent report released in 2020 by the European Society for Medical Oncology (ESMO),[27] consisting of multidisciplinary experts in the fields of oncology and cardiology: International Cardio-Oncology Society (ICOS), the Cardio-Oncology Council of the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) Cardio-Oncology Council supported the position paper from the European Association of Cardiovascular Imaging and the American Society of Echocardiography (ASE)[28] on cancer treatments and cardiovascular toxicity in the definition of cancer chemotherapy-induced cardiotoxicity as any reduction of LVEF to a value below 50% or a >10% reduction from baseline falling below the lower limit of normal as cancer chemotherapy-induced cardiotoxicity. This decrease should be confirmed by repeated cardiac imaging done 2-3 weeks after the baseline diagnostic study showing the initial decrease in LVEF.

For serial evaluation of patients with cancer, LVEF measurements should ideally be performed by the same observer with the same equipment to reduce variability.[28,29] Although the exact inter-

val is not established, the echocardiographic examination should be repeated during follow-up to confirm recovery or to detect irreversible LV dysfunction.

Prior to the cut-off of 50% for LVEF, an expert consensus report from the ASE and the European Association of Cardiovascular Imaging (EACVI) had defined cardiotoxicity as a decline of LVEF greater than 10% points with a final LVEF <53% as normal values for men were ascertained at 52% and for women at 54% in chamber quantification recommendations.[30] Previously, the ESMO and American Society of Oncology (ASCO) implemented LVEF of <55% as the cut-off value in their recommendations. These demonstrate the changing dynamics in cut-off points for LVEF in keeping with further studies.[28]

Echocardiographic evaluation of LV systolic function (LV ejection function) is feasible, predictable, and reproducible, though it has some limitations arising from the techniques used for its calculation. Among its limitations are greater and wider inter- and intra-observer reproducibility and the fact that it is only a global systolic measurement that does not assess local and/or longitudinal, circumferential, and radial functions of the left ventricle. However, it has emerged as the most widely used strategy for monitoring the changes in cardiac function, both during and after the administration of potentially cardiotoxic cancer treatment.[28,29]

Quantitative evaluation of LVEF and diastolic function before the initiation of potentially cardiotoxic chemotherapy can help to identify individuals at higher risk of future Cardiovascular (CV) complications and to establish a baseline, should symptoms suggestive of CV dysfunction occur during treatment. This approach is supported by multiple governing organizations, including the ASCO, the ASE, the EACVI, and the ESC.[31]

Three-dimensional (3D) echocardiography is the best echocardiographic method for measuring LVEF because the endocardial definition is clear but remains dependent on image quality, availability, and operator experience.[31] Some of the limitations of the LVEF can be addressed by measuring LV longitudinal function, which entails the movement of the mitral annulus toward the cardiac apex. LV longitudinal function measures subendocardial fibers and is the first layer involved in many cardiac diseases. The LV longitudinal function can be assessed in different ways, including M-mode echocardiography, Tissue Doppler Imaging, and Speckle Tracking Echocardiography.[28,32,33]

M-mode echocardiography is a technique that allows measuring the Atrioventricular Plane Displacement (AVPD), also known as Mitral Annular Plane Systolic Excursion (MAPSE). The AVPD has some limitations, which include that AVPD is an angle-dependent measure, so it could be erroneous if the ultrasound beam is not properly aligned to the mitral annulus. It can be reduced in case of regional motion impairment even with no significant reduction of global LV function.[28,32,33]

Tissue Doppler Imaging measures myocardial tissue velocities by using pulsed wave Doppler technique, the two-dimensional color Doppler map, and the color M-mode image. However, the measurement is related to angle dependence, and it suffers translation movements in the case of regional wall motion impairment segments with preserved systolic contraction.[28,32,33]

Speckle Tracking Echocardiography (STE) is grayscale B-mode echocardiography which represents the result of random interferences between tissue scatterers. Each myocardial region is characterized by a definite, relatively stable, unique speckle pattern that can be used to differentiate it from other regions throughout the cardiac cycle, allowing direct tracking of myocardial motion. STE is not angle-dependent, is not affected by translational motions of the heart, and can assess the entire LV myocardium simultaneously. Therefore, STE can allow a reliable assessment of myocardial deformation along the tri-dimensional geometrical axes (longitudinal, circumferential, and radial strain) throughout the cardiac cycle.[28,32,33]

The timing of LV dysfunction can vary among agents. In the case of anthracyclines, the damage occurs immediately after the exposure; for others, the time frame between drug administration and detectable cardiac dysfunction appears to be more variable. Nevertheless, the heart has significant cardiac reserve. The expression of damage in the form of alterations in systolic or diastolic parameters may not be overt until a substantial amount of cardiac reserve has been exhausted, and this may take a year or more, or even decades. Thus, cardiac damage may not become apparent until years or even decades after receiving the cardiotoxic treatment. This is particularly applicable to adult survivors of childhood cancers.[30,33] Not all cancer treatments affect the heart in the same way. Therefore, these agents cannot be viewed as a single class of drugs.

A limited number of studies have generated risk scores for different oncology patient cohorts.[34,35] However, none of these risk scores has been validated prospectively, and clinical judgment is required when evaluating the risk at an individual level. Risk assessment should include clinical history, examination, and baseline measurement of cardiac functions by the modified biplane Simpson's technique (method of disks) by 2DE.

Limitations of echocardiography in the assessment of cardiotoxicity

The drawback in the use of echocardiography is that the current standard for monitoring cardiac function detects cardiotoxicity only when a functional impairment has already occurred. The decrease in LVEF only becomes evident once significant myocardial damage has already occurred, and this magnitude of injury may be irreversible. The use of echocardiography also does not allow for any early preventive strategy to commence, and no cost-effective plan for continued surveillance is difficult and expensive. So, cardiotoxicity needs to be detected before a drop in left ventricular function or even changes in strain echocardiography.[36]

Can cardiac troponin fill in the gaps of echocardiography?

The use of cT in detecting cardiotoxicity among patients on cancer therapy has been demonstrated in animal models and in human experimental use. A study of daunorubicin-treated rabbits reported a significant increase in Cardiac Troponin T (*cTnT*) level, in association with reduced left ventricular contractility. Another study among 703 patients who had mainly breast cancer and lymphoma and on chemotherapy showed a significant Cardiac Troponin I (*cTnI*) elevation (9 0.08 ng/mL) measured within 72 h of chemotherapy administration and at 1 month after the end.[37]

The two forms of cT, cTnI and cTnT, have been used in assessing cardiotoxicity, but the former appears to be superior for early detection of CCIC. A small study on 23 patients treated with anthracycline for leukemia suggested that an assessment of cTnI could be superior to cTnT for the early detection of cardiac dysfunction because of the molecular weight and the release kinetics of the two forms of troponin.[38]

It has been reported that an increase of 3-5 ng/L in the cT concentrations is correlated with the necrosis of about 10-20 mg of myocardial tissue, which is undetectable even with the most sensitive cardiac imaging techniques. This makes cT the most sensitive marker of cardiotoxicity.[39] Today, High-Sensitivity Cardiac

Troponin, (hs-cT), is now available and could indicate very low levels of cT.[39,40]

Cardiac troponin is found within cardiac myocytes and is released into the serum when there is an injury associated with a disruption in sarcolemmal integrity. Assay results using conventional cTnI and cTnT are markers of myocardial injury. Highly sensitive Troponin assays can detect concentrations of troponins below 100ng/L, but this is at the risk of low specificity because hypertensive emergencies, renal failure, rhabdomyolysis, sepsis, pulmonary embolism, and tachyarrhythmias can raise cardiac troponin levels.[41]

During myocardial stress due to ischemia, drugs, and inflammation, the cardiomyocyte could have a reversible or irreversible injury. Reversible injury manifests as inflammation, cytoplasmic blebbing, and mild cellular dysfunction that gives rise to unsustained low levels of troponin release, and this eventually leads to cardiomyocyte recovery.[37] But when there is the degradation of troponin by lysosomal enzymes and sarcolemmal disruption, cardiomyocyte necrosis and irreversible injury occur. This manifests as high and sustained troponin release and progressive cardiovascular disease.[37]

Myocarditis could be acute or chronic. Using endomyocardial biopsy as a guide, it has been possible to document cardiac troponin levels associated with acute and chronic myocarditis. During acute myocarditis, hs-cTnT have been found to rise to concentrations ranges of 61.4-884.2 pg/mL; p<0.0001) whereas in chronic myocarditis ranges as high as 15.6-20.4 pg/mL; p<0.0001) have been documented.[37]

It is important to note that during the assessment of cardiotoxicity in cancer chemotherapy using hs-cT as a biomarker for cardiotoxicity detection, the measurement should be performed at baseline, prior to the cardiotoxic treatment, and the monitoring of the biomarker changes during the treatment should be performed using the same subtype of hs-cT and at the same laboratory, if possible.[42] Correlation of levels of hs-cTnI with LVEF has shown that low levels of hs-cTnI were associated with low levels of LV dysfunction and cardiac events (1%).[43] Another study of 41 patients receiving anthracycline therapy suggested an association between the levels of cT and the diastolic dysfunction assessed by the E/A ratio and Isovolemic Relaxation Time (IRT).[43]

Patients with high levels of hs-cTnI after the chemotherapy had a higher incidence of cardiac events (0.4% sudden death; 0.3% cardiac death; 5% asymptomatic LV dysfunction; 7% HF; 0.4% acute pulmonary edema; 2% life-threatening arrhythmia; 0.3% conduction disturbances). In these patients, careful monitoring is essential, and prophylactic strategies to prevent cardiotoxicity should be implemented. The study showed that hs-cTnI has a high negative predictive value of 99% for patients with no elevation of hs-cTnI and a positive predictive value of 84% for future cardiac events in patients with elevated hs-cTnI levels. These studies suggest that measurements of hs-cTnI prior to and during therapy could identify patients at high risk for cardiotoxicity.[44]

The use of high-sensitive troponin assays has since been integrated into several studies. Sawaya and his colleagues found that elevated high-sensitive troponin levels, together with echocardiographic markers of myocardial deformation, predicted the occurrence of cardiotoxicity among breast cancer patients receiving anthracycline and trastuzumab.[38,45] The use of cardiac biomarkers to detect cardiotoxicity during chemotherapy is justifiable in order to detect early cardiac injury. The challenge with the available published data is the timing of the laboratory assessment relating to chemotherapy, the definition of the upper limit of normal for a specific test, the use of different laboratory assays, as well as the challenge of the strategy to undertake in case of an abnormal result.[46]

Most of these challenges can be overcome in order to enable early detection of cardiotoxicity, optimize the use of echocardiography, and enable science-guided decisions on the next plan of action. It will enable management decisions, including cardioprotective strategies and life-saving decisions on ongoing chemotherapy. Elevated cardiac troponin levels have been shown to determine patients at increased risk of cardiotoxicity as well as those who will develop cardiac dysfunction and, if markedly raised, may point to patients who will not recover despite treatment for cardiotoxicity.[37,47,48]

The use of cardiac troponins is encouraged by ESMO Clinical Practice Guidelines on cardiovascular toxicity induced by chemotherapy. It is also included among the ASCO clinical practice guideline recommendations for the prevention and monitoring of cardiac dysfunction in survivors of adult cancers.[49,50]

A combination of cardiac troponin assay and echocardiography could provide a cost-effective method of assessing cardiotoxicity in patients on cancer chemotherapy. This is important for countries with low resources, where the use of echocardiography as the only tool to define cardiotoxicity and monitor patients is unaffordable and unattainable. A combined use of cT assay and echocardiography will identify a small group of patients who will require echocardiography in addition. Indeed, a small study on patients with breast cancer demonstrated that the combination of high-sensitivity troponin with Global Longitudinal Strain (GLS) echocardiography might provide the greatest sensitivity (93%) and negative predictive value (91%) to predict future cardiotoxicity.[31]

Our proposed gold standard for the assessment of chemotherapy-induced cardiotoxicity

Our proposal (Figure 1) is that patients on chemotherapy should first have cT estimation within 7 days of treatment. If the value is negative or below the agreed threshold, then cT is repeated in 2 weeks. If cT level is negative then the test is repeated in one month and then 3 months.[19] If cT level is positive and above an agreed threshold, then echocardiography is done, and if there are satisfactory criteria for cardiotoxicity, preventive or therapeutic treatment is begun for cardiotoxicity.

Echocardiography is done for patients whose results are positive or above the agreed threshold. If the criteria for cardiotoxicity are satisfied, treatment is started. If not, then a repeat of cT level is done in one month, and three months.[19] This proposal allows the economical use of assessment tools and allows only a few patients who require echocardiography optimal use of resources. Our proposal will enable the detection of small and potentially subclinical changes in cardiac function. The cT assay is relatively safe, widely accessible, accurate, reproducible, and easily affordable for patients in low-resource countries. The combination with echocardiography will improve reproducibility, sensitivity, and specificity in the diagnosis of cardiotoxicity. Our proposal will also enable continued surveillance for late-onset cardiotoxicity at an affordable cost and ensure that all patients who need chemotherapy get it at the required dose and at the right time with minimal or no cardiotoxicity. Our proposal may also lead to a new definition of cancer chemotherapy-induced cardiotoxicity, taking into consideration the utility of cT.

It is also important to recognize that there is an increasing number of long-term cancer survivors. There are an estimated 14 million cancer survivors, both in the US and in Europe, which is expected to reach 19 million by 2024.[51] As a consequence, the need for cardiovascular surveillance aimed at preventing car-

diotoxicity in patients undergoing anticancer therapy, particularly for those who have completed therapy but are at risk of late-onset cardiotoxicity is burgeoning. Assessments incorporating cT may play a critical role in the management of these cancer survivors.[52,53] Any effort devoted to preventing today's cancer patients from becoming tomorrow's cardiac patients is worth it, particularly in low-resource countries. The minimum current cost of one echocardiography assessment is thirty thousand Naira, and the minimum monthly wage in Nigeria is thirty thousand Naira. The same scenario is playing out in most low-resource countries: low wages, high poverty level, poor health infrastructure, high disease burden, *etc*. This captures the essence of our proposal to have a shift in the tools for assessment and perhaps the definition of cancer chemotherapeutics-induced cardiotoxicity that will take into account the peculiar conditions of low-resource countries.[54,55]
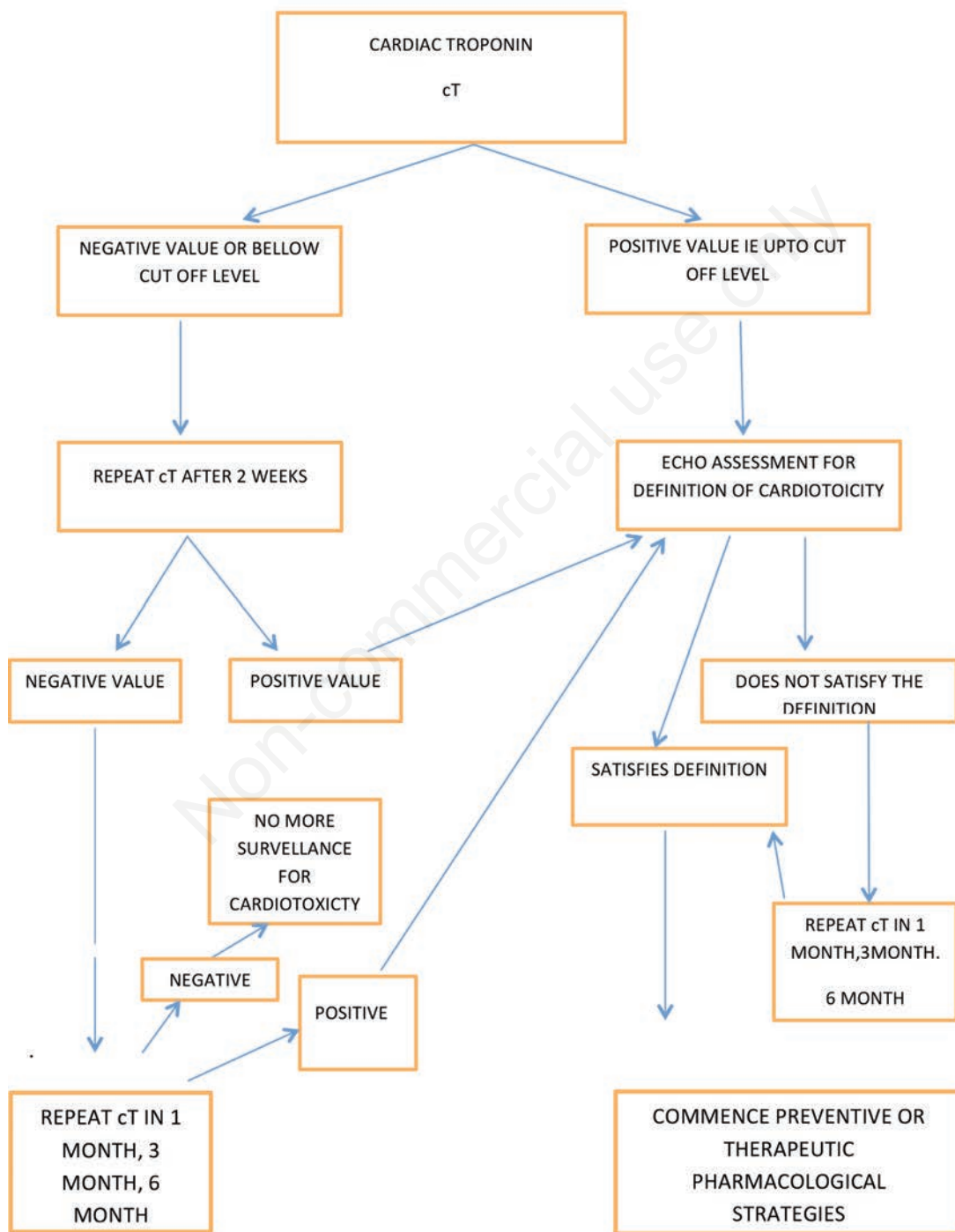

Figure 1. The use of Cardiac Troponin in combination with echocardiography to assess cancer chemotherapy-induced cardiotoxicity.

Conclusions

Patients on cancer chemotherapy bear multiple burdens, from the cost of therapy to the cost of managing adverse effects, often paying out of their pockets because of nonexistent or inadequate health insurance policies. They may continue to suffer from the effects of treatment long after surviving cancer. An affordable tool for assessing cardiotoxicity will be invaluable in containing these costs. We propose that patients on cancer chemotherapy should first have a cT assessment, and depending on the concentration of cardiac enzyme, an echo may be indicated. This will reduce the frequency and cost of doing echoes and will translate to better management of chemotherapy-induced cardiotoxicity as well as lead to increased longevity of cancer survivors. Our proposal may also lead to a new definition of cancer chemotherapy-induced cardiotoxicity, taking into consideration the usefulness of cT. This proposal will require population-wide studies to validate its usefulness and utility.

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