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Diagnosis of Chemotherapy-Induced Cardiotoxicity

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Abstract

Cardiotoxicity is a rising issue connected to use of chemotherapy and radiotherapy in the treatment of neoplastic diseases. Early diagnosis during follow-up is of paramount importance, and careful surveillance is recommended. Evaluation of left ventricular ejection fraction by echocardiography and nuclear medicine techniques is widely used in clinical practice; however, their sensitivity in detecting early cardiac damage is low. New instruments like speckle-tracking imaging, cardiac magnetic resonance and cardiac circulating biomarkers are available to clinicians to best evaluate the onset and progression of cardiotoxic effects, improving the therapeutic management and final outcome for the patient. (*J Patient-Centered Res Rev.* 2014;1:121-127.)

Keywords

cardiotoxicity, chemotherapy side effects, imaging method, cardiac biomarkers

Introduction

The introduction of chemotherapy significantly improved the outcome of cancer patients and represents a fundamental element in treatment of several tumors. However, chemotherapy is associated with negative side effects that greatly limit its use. Cardiotoxicity is one of the most relevant issues connected to implementation of some classes of chemotherapeutic agents because of its negative effect on prognosis and quality of life.[1] Radiotherapy directed to the chest alone or in association with chemotherapy is an additional cause of cardiac damage in oncologic patients. Progressive impairment of systolic function leading to overt heart failure is the most common manifestation of chemotherapy-induced cardiomyopathy (CICM); however, other complications like hypertension, acute coronary syndrome, arrhythmias and thrombosis have been described. CICM is usually characterized by a long stage of subclinical myocardial dysfunction that is not detectable by conventional diagnostic methods but which is important for patient prognosis. The early diagnosis and adequate evaluation of the cardiotoxic effects of chemotherapeutic drugs are of paramount importance for clinicians to set the best therapeutic management.

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Main Chemotherapeutic Drugs Associated With Cardiotoxicity

Anthracyclines

Doxorubicin, epirubicin and daunorubicin are chemotherapeutic drugs strongly associated with cardiotoxicity, which usually occurs within 1 year of treatment at an incidence of about 2%.[2] They are widely used in the treatment of breast cancer, lung cancer, hematological malignancies and sarcoma. The cardiotoxic effect is related to the cumulative dose of the drug, especially for doxorubicin, for which 550 mg/m^2 is considered the maximal accepted threshold.[3]

Trastuzumab

A monoclonal antibody used in the treatment of breast cancer that is positive for the expression of the ErbB2 growth factor receptor,[4] trastuzumab generates an increase in cardiotoxicity incidence when combined with anthracyclines. The cardiotoxic effect is frequent, occurring in up to 28% of patients.[5]

Tyrosine-Kinase Inhibitors

This category includes several drugs that share a similar mechanism of action that consists of inhibiting different tyrosine kinases, enzymes involved in the signal transduction process. Imatinib, dasatinib and nilotinib inhibit ABL-kinase and are used for treatment of some forms of leukemia; cardiotoxic effect occurs in 1% of treated patients.[6] Sunitinib and sorafenib were designed to inhibit tyrosine kinases involved in both tumor proliferation and angiogenesis; 3-11% of patients develop cardiotoxicity.[7]

Antibody Therapies

Hypertension occurs in about 50% of bevacizumab-treated patients; conversely, cetuximab and rituximab are associated with severe orthostatic hypotension.[8]

Antimetabolites

Capecitabine and 5-fluorouracil are associated with myocardial ischemia in 1.2% to 18% of treated patients.[9]

Alkylating Agents

Cisplatin can induce hypertension. Myocardial ischemia, thrombosis, acute coronary syndrome and symptomatic left ventricular dysfunction also have been reported, mostly in older patients. Cyclophosphamide is widely used in many hematologic malignancies. Myocarditis can occur, with an incidence in adults estimated at 7-25% at doses > 150 mg/kg.[8]

Taxanes

Docetaxel and paclitaxel induce cardiotoxicity in 2.3% to 8% of patients. They are mainly used in the treatment of patients with breast, lung or ovarian cancer.[10]

A list describing the main features of chemotherapeutic medications associated with cardiovascular side effects is reported in Table 1.

Cardiovascular Complications of Radiotherapy

Radiotherapy is presently a widely used anticancer treatment. High-dose irradiation focused on the thorax is mainly used in the context of adjuvant treatment after surgery for breast cancer, as adjuvant or selected therapy of lung and esophageal cancer, and as complementary treatment for lymphoma.[11] However, radiosensitivity of the heart is one of the most critical radiation dose-limiting factors. The outcome of long-term cancer survivors can be affected by radiation-induced heart disease, related to the total cumulative dose of radiotherapy (number of treatments and dose of irradiation).[12] Irradiation of the heart can lead to a wide range of clinical effects, including pericarditis, coronary artery disease and myocardial infarction, valvular heart disease, rhythm anomalies and nonischemic myocardial damage (restrictive cardiomyopathy). Estimated incidence of radiation-induced heart damage is 10-30% at 5-10 years after treatment;

Table 1. *Chemotherapeutic medications associated with cardiovascular side effects*

Drug	Antineoplastic mechanism	Malignancy	Cardiotoxic effect	Incidence of cardiotoxicity	Mechanism of cardiotoxicity
anthracyclines (cumulative dose): doxorubicin (>500 mg/m^2); liposomial doxorubicin (>900 mg/m^2); epirubicin (>720 mg/m^2); mitoxantrone (>120 mg/m^2); idarubicin (>90 mg/m^2)	• tumor cell DNA damage	• hematologic • breast • multiple myeloma • lung • sarcoma	• heart failure	• 2%	• production of free radicals
trastuzumab	• inhibition of ErbB2	• breast	• heart failure	• 1%–28%	• mitochondrial damage
imatinib, dasatinib, nilotinib	• inhibitors of ABL-kinase	• BCR/ABL-positive leukemia	• heart failure	• 1.7%	• inhibition of ABL tyrosine kinase on cardiomyocytes
sunitinib, sorafenib	• inhibition of tyrosine kinases involved in angiogenesis and proliferation	• kidney • gastrointestinal stromal tumors • hepatocarcinoma	• heart failure • acute coronary syndromes • hypertension	• 3%–8%	• inhibition of tyrosine kinases involved in cardiomyocytes survival
bevacizumab	• vascular-endothelial growth factor inhibitor	• colon • lung • glioblastoma	• hypertension	• 50%	• unknown
5-fluorouracil	• alteration of DNA structure	• gastrointestinal tumors • breast	• myocardial ischemia	• 1.2%–18%	• vasospasm • autoimmune phenomena • myocarditis
cisplatin	• alteration of DNA structure	• lung • stomach • bladder • ovary • testicle	• hypertension • heart failure	• unknown	• oxidative stress
cyclophosphamide	• alkylation of guanine	• lymphoma • leukemia	• myocarditis	• 7%–25%	• unknown
taxanes (paclitaxel, docetaxel)	• disruption of microtubule function	• lung • ovary • breast • prostate	• heart failure	• 2.3%–8%	• lipid peroxidation • direct cytotoxic damage

in these patients, cardiovascular disease is the first nonmalignant cause of death.[13] Radiation effects appear to be accelerated by the conjunction of common cardiovascular risk factors and to increase the risk of cardiotoxicity of some chemotherapeutic agents, such as anthracyclines.

Manifestation of Cardiotoxicity and Main Risk Factors

The progressive decline of left ventricular systolic and diastolic function is the most common manifestation of CICM. A variable long subclinical stage precedes the onset of heart failure symptoms like dyspnea, asthenia and peripheral edema. Cardiomyocyte damage secondary to chemotherapy is classified in two groups. Type I chemotherapy-related myocardial dysfunction is usually secondary to oxidative stress (typically anthracycline-induced) and results in cardiomyocyte death; it is an irreversible, dose-dependent process and leads to ultrastructural alterations identifiable at myocardial biopsy. Type II chemotherapy-related myocardial dysfunction (typically trastuzumab-induced) is caused by cardiomyocyte impairment rather than cell death; it is not dose-related and may be reversible.[10] Myocardial ischemia presenting with T-wave changes, chest pain, acute coronary syndrome and myocardial infarction is another possible cardiotoxic effect of chemotherapeutic agents like 5-fluorouracil.[14] Hypertension, hypotension and thromboembolic events are other cardiovascular complications of cancer treatment.[8,15] It appears clear that the incidence of cardiotoxicity is related to the presence of risk factors: young or old age, female gender, prior mediastinal radiation therapy, hypertension, and combined chemotherapy and presence of underlying cardiac disease.[2] The finding of any of these in a patient undergoing chemotherapy should encourage more aggressive follow-up.

Diagnosis and Monitoring of Cardiotoxicity

Although endomyocardial biopsy remains the most sensitive and specific method to assess cardiotoxicity by describing the microscopic structural alterations of myocardial tissue, its use is strongly limited because of the high invasiveness of the procedure.[16] Electrocardiographic (ECG) alterations may occur during treatment with cancer drugs; these include decreased QRS voltage and ST-T wave changes. However, the most common and relevant finding consists in QT corrected (QTc) interval prolongation.[17] QTc measures the total duration of the electric depolarization and repolarization of myocardium; its prolongation is associated to increased risk of ventricular arrhythmias, particularly torsades de pointes, and sudden death. The underlying mechanism is mediated by the interaction of chemotherapeutic drugs with the human ether-a-go-go-related gene product, a protein subunit of a potassium ion channel (hERG K+).[18] Although elongation of QTc occurring during chemotherapy treatment is relatively frequent (14% in a series of 525 patients enrolled in phase I clinical trial)[19] and ECG monitoring is strictly recommended in the follow-up of chemotherapy-treated patients, the association between this electric disorder and major cardiac events has not yet been proved in this set of patients. Imaging methods such as echocardiography are more often used to evaluate CICM in clinical practice. Left ventricular ejection fraction (LVEF) evaluated by two-dimensional echocardiography is the standard parameter for assessment of the cardiotoxic effect of chemotherapy. The Cardiac Review and Evaluation Committee (CREC) defined that the diagnosis of CICM can be established when at least one of the following elements is present: 1) cardiomyopathy characterized by a decrease in cardiac LVEF that was either global or more severe in the septum; 2) symptoms of congestive heart failure; 3) associated signs of congestive heart failure, including but not limited to S3 gallop, tachycardia, or both; and 4) decline in LVEF of at least 5% to less than 55% with accompanying signs or symptoms of congestive heart failure, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms.[5] Echocardiography also can provide important data on diastolic function that is usually altered early on in patients who develop CICM.[20] Although widely used, LVEF measured by two-dimensional echocardiography is calculated using some geometrical assumptions, which influences the reproducibility of the metric. LVEF evaluation by three-dimensional echocardiography is derived by a volumetric analysis of the left ventricle and is free from any geometrical assumption, resulting in a more accurate and reproducible measurement.[21] Stress echocardiography was proposed as a method to identify early systolic dysfunction due to chemotherapy. However, data are very poor and the results derived from small studies have been conflicting.[22] An alternative imaging method used to monitor LVEF in chemotherapy-treated patients is represented by 99mTC multigated radionuclide angiography (MUGA), a nuclear imaging method able to visualize the cardiac blood pool by γ-camera with ECG-triggered acquisitions. The final result provides a highly reproducible and precise quantification of left ventricular volumes and dyssynchrony that does not derive from geometrical assumption.[23] Although LVEF evaluation using two- or three-dimensional echocardiography or MUGA is widely used in clinical practice, it is unable to detect the earliest myocardial impairment or predict which patients have an increased risk for developing CICM. New imaging techniques and biomarker evaluation are emerging methods developed to overcome the limitation of LVEF as the sole analysis.

New Insights in the Early Detection of the Myocardial Damage

Speckle-Tracking Imaging

Myocardial contraction consists of a complex spatial deformation depending on the particular anatomical array of the muscular fibers. The main components of deformation are represented by longitudinal, circumferential and radial deformation. Twist, untwist and torsion are additional components depending on the different orientation of the fibers between apex and base of the heart. Speckle tracking analyzes the myocardial deformation on two- and three-dimensional images by tracking natural acoustic reflections and interference patterns, called "speckle," within an ultrasonic window. The analyzer software is able to provide the percentage variation of distance (deformation) between speckles within a predefined region of interest, obtaining a value defined as "strain." The velocity of the deformation is defined as "strain rate" (Figure 1). The evaluation of strain and strain rate in patients receiving chemotherapy has been evaluated in several studies, which demonstrated a concrete advantage in early identification of left ventricular dysfunction and predicting future decline of LVEF.[24,25]

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance (CMR) represents the criterion standard method in the evaluation of cardiac volumes, mass and function.[22,25] Moreover, "tissue characterization" performed by CMR reveals alterations like fibrosis, edema and inflammation. In the early stage of CICM, CMR is able to detect myocardial edema using T2-weighted sequences and myocardial inflammation by T1-weighted fast-spin echo sequences after administration of gadolinium.[26] Delayed sequence acquisition after contrast is used to investigate late gadolinium enhancement, which detects tissue presenting a slow contrast wash-out, usually consisting of scar or fibrosis. Early alterations of late gadolinium enhancement have been described in chemotherapy-treated patients and are predictive of development of CICM and decline of LVEF.[26] In studies including adults who survived childhood malignancies, CMR demonstrated individuated late effects of cardiotoxicity: the reduction of the cardiac mass in comparison to safe controls is an indicator of late cardiotoxicity and is associated with increased risk of cardiac events.[26] Moreover, the accurate definition of volumes and function provided by CMR demonstrated a higher sensibility than echocardiography in detecting minimal alteration of LVEF with elevated reproducibility.[27]

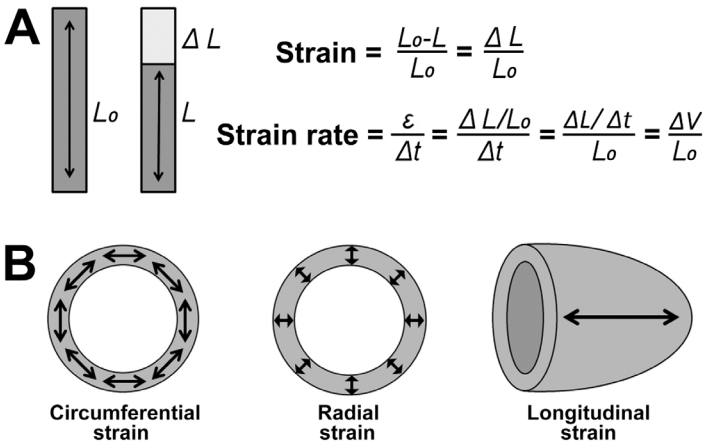

Figure 1. *Definition of strain and strain rate.* ***A:*** *Strain (ε) is defined as the difference of the initial and the final distance between two points divided by the initial distance. Strain rate derives from the ratio between the velocity variation and the initial distance between two points.* ***B:*** *Graphical representation of the main deformation components of the left ventricle. L_0, initial distance; L, final distance; ΔL, distance variation; Δt, time variation; ΔV, velocity variation.*

Circulating Biomarkers

Injury of cardiomyocytes causes the release of substances into the blood flow that can be used as biomarkers of subclinical myocardial damage. Ultrasensitive troponin I is the most reliable marker as detecting the level of the concentration of ultrasensitive troponin I after the treatment is predictive of development of cardiotoxicity (P=0.020; hazard ratio 1.38 per standard deviation).[28] The same study also identified an increase of myeloperoxidase as an indicator of cardiotoxicity, and the coexistence of the two markers was associated with the highest risk of future myocardial dysfunction. Contrasting opinions have been reported about N-terminal pro–B-type natriuretic peptide (NT-proBNP). It did not demonstrate a predictive value for development of cardiotoxicity in the study carried out by Ky et al.[28] However, other studies showed early variation of NT-proBNP levels can be used to identify patients at risk of cardiotoxicity.[29,30] It is clear that larger studies are needed to confirm the potential promise of cardiac biomarkers in the identification of subclinical cardiotoxicity induced by chemotherapy and to provide reliable reference ranges.

Cardiotoxicity Monitoring

The systematic and integrative use of these new methods represents the future approach of clinicians to evaluate cardiotoxicity. Although endomyocardial biopsy remains the most sensitive and specific method to diagnose cardiac damage, its invasiveness limits its use to the few cases in which cardiac dysfunction is not clearly associated with chemotherapy treatment and should not be included as a screening method. LVEF remains the central parameter in the diagnosis and monitoring of cardiac function in chemotherapy-treated

patients. However, the majority of authors demonstrated that the drop of myocardial systolic function revealed by this parameter is a late phenomenon in the pathophysiological mechanism of cardiotoxicity and that its evaluation alone substantially reduces the window for prevention.[31]

Data derived from three-dimensional echocardiography are more reproducible and accurate than two-dimensional echocardiography and should be preferred, if available. MUGA is the most used alternative to echocardiography (particularly when a bad acoustic window is present), and its sensitivity is comparable to three-dimensional echocardiography;[23] however, MUGA is an old technique, born when CMR was an experimental instrument. It is less accurate in patients with arrhythmias; moreover, its use as a screening method significantly increases the radiation burden for the patient. The use of three-dimensional echocardiography and MUGA improves the accuracy and the interobserver variability of the measurement but does not outweigh the limitation inherent to the evaluation of LVEF.[32] Speckle-tracking echocardiography revealed good sensitivity in detecting early myocardial impairment, and analysis of global longitudinal strain should be performed during follow-up, integrating the information derived from LVEF. A decrease in global longitudinal strain is associated with long-term reduction of LVEF (in a recent systematic review, Thavendiranathan et al. reported that a reduction of 10-15% in global longitudinal strain is the most useful parameter in predicting a drop in LVEF or onset of heart failure symptoms[33]); nevertheless, its most important limitation is represented by the lack of large controlled studies providing reliable and well-established thresholds. CMR is the most accurate method for diagnosing alteration of left ventricular systolic function and allows detection of early tissue composition changes that can reflect early manifestation of cardiotoxicity. Unfortunately, CMR's high cost and low availability limit its wide implementation as a first-line screening instrument.

The usage of cardiac circulating biomarkers is an additional emerging method for early evaluation of cardiac function during and after chemotherapy, and the evaluation of ultrasensitive troponin I should be considered in patients at high risk to develop cardiotoxicity. The timing of dosage and thresholds are not yet well-established in literature. The guidelines of the European Society of Medical Oncology introduced the importance of new imaging techniques and of circulating biomarkers in the early diagnosis of cardiotoxicity, moreover, they suggested that a greater drop in LVEF is needed to establish diagnosis of cardiotoxicity (to 50% instead of the 55% previously stated by the CREC).[34] Table 2 summarizes the strengths and limitations of the different methods involved in the evaluation of chemotherapy-induced cardiotoxicity.

Table 2. *Strengths and limitations of the different methods used for diagnosis of cardiotoxicity*

Method	Strengths	Limitations
Electrocardiogram	• availability • low cost • repeatability	• poor sensitivity and specificity
Two-dimensional echocardiogram (ejection fraction)	• availability • repeatability	• unable to detect early dysfunction • inter- and intraoperator variability • dependency from geometrical assumptions
Three-dimensional echocardiogram (ejection fraction)	• low inter- and intraoperator variability • independence from geometrical assumptions • high reproducibility • repeatability	• unable to detect early dysfunction • not available in all echo-labs
Multigated radionuclide angiography (MUGA)	• low inter- and intraoperator variability • independence from geometrical assumptions • high reproducibility • repeatability	• unable to detect early dysfunction • radiation exposure • low repeatability
Speckle-tracking imaging	• able to detect early systolic dysfunction • repeatability • independence from angle	• not available in all echo-labs • absence of well-established thresholds • time-consuming • low sensibility in patients with suboptimal echocardiographic window
Cardiac magnetic resonance	• able to detect early systolic dysfunction • highly reliable measure of volumes and mass • very high reproducibility • independence from geometrical assumptions • tissue characterization • no radiation exposure	• elevated cost • low availability • not suitable for patients with metallic devices
Circulating biomarkers	• high sensitiveness	• data derived only from studies on anthracyclines

Figure 2 proposes a potential screening algorithm including classic and new techniques for monitoring the cardiovascular side effects of chemotherapy. Baseline evaluation should include biomarker assay and echocardiography evaluation including global longitudinal strain; in a patient with bad acoustic window, CMR and MUGA are alternative options. During chemotherapy, assessment of troponin I is recommended after each cycle and evaluation of cardiac function should be performed every 3 months. If the baseline evaluation is normal and troponin I does not increase during chemotherapy, the timing for the subsequent follow-up control should be scheduled 1 year after the end of treatment. If an increase in troponin I occurs during chemotherapy, or the baseline evaluation is abnormal, a cardioprotection protocol should be started and a more intensive follow-up is needed with re-evaluation at 3 months, 6 months and 1 year and every 6 months for 2-5 years. A more aggressive cardioprotection protocol should be considered if alteration of biomarkers and/or LVEF or global longitudinal strain persists.

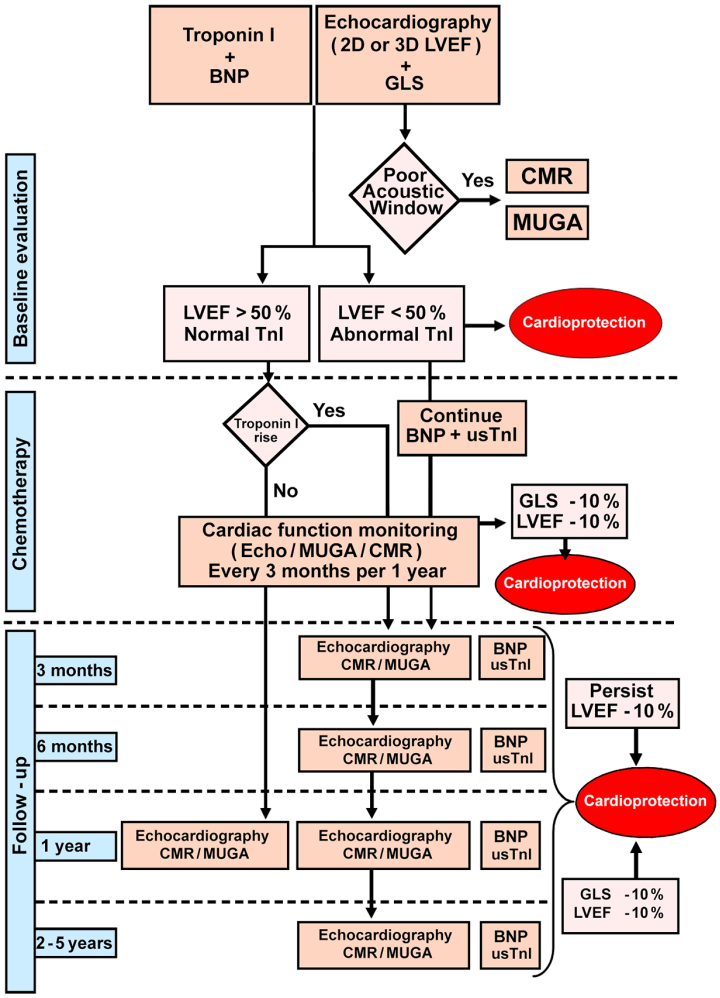

Figure 2. *Flow chart for diagnosis of cardiotoxicity in chemotherapy-treated patients. Baseline evaluation includes biomarker assay and computing of left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS). LVEF derived by three-dimensional (3D) echocardiography is more accurate and reproducible and therefore preferred; if the acoustic window is poor, cardiac magnetic resonance (CMR) or multigated radionuclide angiography (MUGA) are alternative methods. Patients presenting with normal LVEF and troponin I (TnI) at baseline should be evaluated every 3 months during chemotherapy. If TnI increase does not occur during chemotherapy, the subsequent follow-up should be scheduled 1 year after the end of treatment. If baseline LVEF or TnI are abnormal, a cardioprotection protocol is needed and a more intensive follow-up should be established with evaluation at 3 months, 6 months and 1 year after the end of treatment and every 6 months for 2-5 years. At every control, a drop of 10% of LVEF (below 50%) or GLS is considered a manifestation of cardiotoxicity and should be treated with a cardioprotective protocol. BNP, B-type natriuretic peptide; usTnI, ultrasensitive troponin I.*

Conclusion

In the last decades, the development of a wide number of chemotherapeutic agents has permitted a substantial improvement of survival among cancer patients. Cardiotoxicity represents a rising problem affecting chemotherapy-treated patients. Although anthracyclines and herceptin are the drugs more frequently associated with cardiotoxicity, many other pharmaceutical classes have demonstrated cardiovascular side effects. Despite using left ventricular ejection fraction to evaluate cardiotoxic effect as recommended by the guidelines, it is widely accepted that this method is not sensitive in detecting early myocardial impairment, reducing the window for prevention and negatively influencing prognosis. The use of new techniques like deformation analysis, cardiac magnetic resonance and dosage of cardiac biomarkers demonstrated more sensitivity in detecting early cardiotoxicity, improving prognosis and quality of life of cancer patients. However, the fragmentary data derive from relatively small studies, thus larger controlled trials are needed to clearly define thresholds and screening protocols. Finally, we want to emphasize the importance of the close collaboration between cardiologists and oncologists for the correct management of chemotherapy-treated patients.

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Conflicts of Interest

Dr. Bomzer owns stock in Merck Inc. and Pfizer Inc. None of the other authors have any conflicts of interest relative to this submission.

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