Review Article

Mechanisms and Biomarkers to Detect Chemotherapy-induced Cardiotoxicity

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Abstract

A cardiotoxicity is a considerable event for cardiologists and oncologists during and after chemotherapy. The use of certain chemotherapy agents such as trastuzumab, programmed death-1 inhibitors, and Doxorubicin increased in cancer therapy; however, these agents associate with an increase in mortality and cardiotoxicity. Detecting cardiotoxicity is based on patient's medical history and physical examination since there is no exact biomarker or polymorphism for its early diagnosis. Therefore, we still need potential biomarkers for cardiotoxicity risk. Treatment of several cancers is manageable while preventing cardiotoxicity, as chemotherapy side effect, is essential since it might be a greater risk than the malignancy if not detected at early stages. Early detection of cardiotoxicity, during and after chemotherapy, is crucial to decrease permanent and devastating cardiac damages. Recently, troponin but also atrial-type and brain-type natriuretic peptides were reported as good diagnostic biomarkers for cardiotoxicity. Micro-RNAs and inflammatory mediators are candidates as prognostic biomarkers. Genetic biomarkers such as C282Y allele of hemochromatosis gene makes the patients more susceptible to cardiotoxicity; therefore, genome studies are valuable in predicting chemotherapy results. In this review, we present the mechanisms of developing chemotherapy-induced cardiotoxicity and biomarkers for its detection in patients. Echocardiographic techniques are very strong techniques which could be used along with biomarkers for more reliable and quicker diagnosis.

Keywords: *Biomarkers, cancer, cardiotoxicity, chemotherapy, reactive oxygen species*

Introduction

Cancer treatment may affect bone marrow niche. In addition, there is a lack of specific clinical markers to predict cancer progression,[1] or chemotherapy-induced cardiotoxicity, as a side effect of chemotherapeutic agents. Cardiotoxicity may happen at the same period of chemotherapy, or years later, and can be divided into five categories: Cardiac systolic dysfunction, ischemia, arrhythmias, pericardial disease, and thrombophilia.[2,3] According to the reversibility of myocardial damages, anticancer drugs which induce cardiotoxicity are classified into two groups. The first type of drugs, such as anthracyclines and alkylating agents, may cause direct cell death and irreversible damage to cardiomyocytes. However, the second type of anti-cancer drugs, such as trastuzumab, vascular endothelial growth factor inhibitors, and tyrosine kinase inhibitors,[3,4] can modify normal cellular function by affecting the mitochondrial system and decreasing protein synthesis. Fortunately, the cardiotoxicity of this second type of chemotherapy agents is reversible when the drug is discontinued.

Several chemotherapy agents such as cytostatic antibiotics of the anthracycline class, alkylating agents including cyclophosphamide, busulfan, fluorouracil (FU) and programmed death-1 inhibitors can increase the sensitivity of malignant cells to chemotherapy and hence increase patients' survival.[5] These agents are new in cancer therapy and can induce, with a synergistic effect, cardiac events such as thrombosis, arrhythmias, and cardio myopathy.[6] Cardiotoxicity may associate with cardiac cell injury or reversible cardiac dysfunction.[7] Chemotherapy can increase thrombosis through endothelial injuries by changing adhesion protein's function and by activating the coagulation cascade.[8] Chemotherapy drugs such as alkylating agents can cause platelets aggregation through increasing thromboxane and activating arachidonic acid pathway.[8] Several chemotherapy agents

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such as doxorubicin can cause cell apoptosis and mitochondrial damage in cardiomyocytes through activating P53.[7] Patients who receive chemotherapy are at risk of cardiotoxicity during and even after the treatment, so monitoring cardiac events is a sensitive process in cancer patients. Detecting susceptible patients depend on symptoms but several patients are asymptomatic. In general, continuous cardiac monitoring, echocardiographic and radionuclide angiographies and cardiac biomarkers measurement are helpful in detecting susceptible patients who receive chemotherapy.[9,10] Cardiotoxicity associated with different factors such as the type of the drug, dose administration, schedule of administration,[11] drug combination, and other factors.[12] The main problem in detecting cardiotoxicity is that it is based on functional impairments which prevents cardiotoxicity management in early stages.[13] Finding biomarkers and single nucleotide polymorphisms (SNPs) to diagnose and manage cardiotoxicity in early stages is important. High-dose chemotherapy increases cardiotoxicity in cancer patients and studies showed an increase in troponin serum levels which can be a good prognostic biomarker.[14] Indeed, troponin is a sensitive biomarker for detecting small necrosis in early stages. Troponin I and natriuretic peptides can be good diagnostic biomarkers in chemotherapy-induced cardiotoxicity.[13] Genome-wide association studies (GWAS) investigated several SNPs linked to early induced cardiotoxicity.[15] SNPs of genes such as ABBC1 and ABBC2, which encode adenosine triphosphate (ATP) binding cassette transporter, CYP3A4, CYP3A5, and CYP2C8 might also be associated to cardiotoxicity.[16] In this review, we discuss the pathways that induce cardiotoxicity in chemotherapy patients and we suggest several biomarkers for cardiotoxicity detection. We also discussed several SNPs and biomarkers that might be useful in diagnosing cardiotoxicity in early stages.

Why Cardiac Issue Appears in Chemotherapy Patient

Thrombosis

Cancer patients have an increased risk of thrombosis events.[17] In addition, chemotherapy agents are suspected to correlate with the high risk of venous thrombotic events (VTT) in cancer patients whose main cause is not clear yet.[18] Chemotherapy can be a risk factor in VTT development.[19] Several hereditary risk factors for VTT are detected such as factor V Leiden mutation.[17] Mutations in F5 gene that generate rs6025 and rs4524 polymorphisms which code for factor V Leiden mutations R506Q and K858R, respectively, associate with VTT in cancer patients.[20] Initially, cancer treatments affect the vascular system and cause hypertension, vasospasm, and thrombosis development whereas long-term toxicities develop at later stages such as atherosclerosis.[21] Multiple biomarkers including tissue factor, D-dimer, and soluble P-selectin are useful in detecting thrombosis while a single biomarker is not predictive in cancer patients.[22]

Chemotherapy-induced Cardiotoxicity Mechanisms

Increase in reactive oxygen species level

Reactive oxygen species (ROS) signaling pathways are increased in cardiovascular diseases and conditions such as atherosclerosis, cardiomyopathy, and heart failure (HF) development. ROS can oxidize cysteine residues on Ras directly and activate downstream signals to PI3K, Raf, mitogen-activated protein kinase and extracellular signal-regulated kinase (MAPK/ERK), and (ERK1/2).[23] PI3K/AKT/mTOR pathway activity increases in several types of cancer and its targeting can have proapoptotic and antiproliferative effects on cancers.[24]

Mitogen-activated protein kinase (MAPK) plays an important role in the regulation of myocardial apoptosis.[25] Chemotherapy agents such as anthracycline can generate ROS, activate Caspase 9, and finally, induce apoptosis in myocytes.[26] Increase in ROS levels leads to membrane damage and lipid peroxidation.[27] On the other hand, ROS decreases sarcoplasmic reticulum Ca^{+2}_ATPase expression, enhances Ca^{+2} release, and finally, Ca^{+2} overload leads to myocardial necrosis.[28] Doxorubicin is a drug derived from a fungus[29] and is widely used to treat several types of tumors such as leukemia, lymphoma, and solid tumors.[30] Doxorubicin is harmful to the heart because it affects mitochondria through inducing ROS production and decreasing energy production so the heart as a pump will not work properly. Another possible mechanism for this drug is that ROS may stimulate c-Jun N-terminal kinase (JNK)/MAPK and nuclear factor κB pathways through activating apoptosis signaling regulating kinase1.[31] In addition, doxorubicin metabolites increase ROS through suppressing ion-dependent pumps of mitochondria and sarcolemma.[27,32] Studies revealed that cardiotoxicity of doxorubicin is dose-dependent.[29] Increase of ROS induces matrix metalloprotease (MMP) activation in cardiomyocytes which cause their subsequent death.[33] MMP activation is an event that occur in early doxorubicin-induced cardiotoxicity and indicates the development of various pathophysiological conditions such as congestive HF and reperfusion injury.[34] In fact, multifactorial mechanisms can induce cardiotoxicity in cancer patients who receive chemotherapy [Figure 1].

Cardiac mitochondria dysfunction

Mitochondria dysfunction occurs as a result of changes in homeostasis, Ca^{+2} signaling, increase in ROS level, and apoptosis. Changes in homeostasis induce the opening of mitochondrial permeability transition which may lead to mitochondrial membrane potential loss, increase in ROS generation, ATP reduction, Ca^{+2} release in intracellular space, and mitochondria swell.[35] Several chemotherapy agents lead to thrombosis development, endothelial

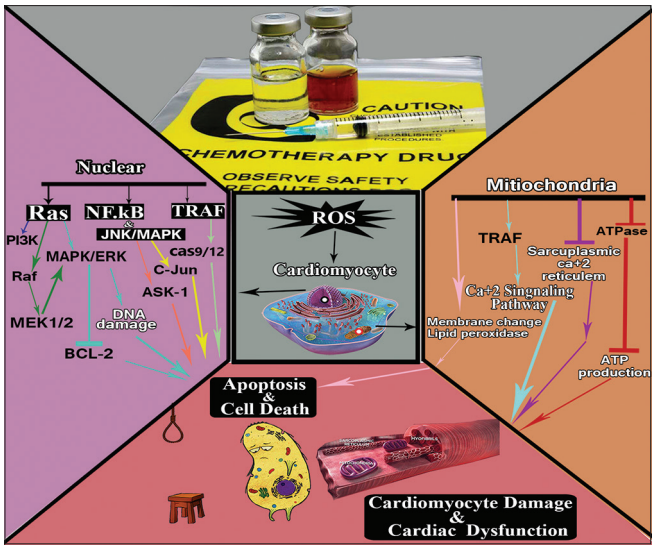

Figure 1: Reactive oxygen species act as stimulus to tumor necrosis receptor associated factor, nuclear factor κB and Ras pathway. These pathways signal cell death and apoptosis through DNA damages or activating caspase 9 or 12 which leads to cell death. Reactive oxygen species cause apoptosis by membrane changes of lipoperoxidase. The effect of reactive oxygen species on tumor necrosis receptor associated factor activates calcium ion signaling pathway, leads to mitochondrial dysfunction, results into mitochondrial damage and finally leads to cardiac dysfunction. Reactive oxygen species contribute to sarcoplasmic reticulum Ca^{2+} depletion in cardiac myocytes and adenosine triphosphate ase function and cause mitochondrial and cardiac dysfunction

damage, platelet aggregation, and thrombus formation.[36] Alkylating agents can cause vascular coronary endothelial injuries which lead to intracapillary microthrombi formation.[37] Interleukin-2 (IL-2) is a chemotherapy agent that can induce vasoactive mediators release and cause coronary vasospasm.[38] High-dose IL-2 is used for metastatic renal cell carcinoma, metastatic melanoma and immune checkpoint inhibitors.[39] 5-FU is used for various types of solid tumors and is associated with coronary ischemia and reversible vasospasm which might happen as a result of its effect on smooth muscle cells of cardiac vessels tone through molecular signaling pathways.[40] The endothelium dysfunction produces endothelin-1 (ET-1), angiotensin II, thromboxane A2, and ROS which can lead to coagulation cascade activation through the binding of tissue factor leading to venous thrombosis and platelets aggregation.[41] Several chemotherapy agents such as arsenic trioxide, bevacizumab, and trastuzumab cause mitochondrial dysfunction leading to cardiomyocytes death.[30] A number of chemotherapy agents can lead to harmful events such as platelets aggregation and catalytic enzymes dissociation resulting into endoplasmic reticulum stress and autophagy through mechanisms modifying oxidative/nitrative proteins of cardiac mitochondria.[26] Imatinib inhibit protein kinase C (pkC) expression[42] which is a tumor-promoting receptor and an oncoprotein. In several trials, using pkC inhibitors worsened the patient's outcome.[43] Studies showed that imatinib can activate pathological hypertrophic signaling pathways by changing intracellular Ca^{2+} dynamics which finally can lead to myocytes apoptosis.[44] Chemotherapy agents such as antimetabolites can induce arrhythmias through coronary vasospasm by direct toxic effects on vascular endothelial through pkC activation. The latter increases as a result of nitric oxide synthase and thrombosis through decreasing fibrin lytic activity.[27,45]

Biomarkers in Detecting Induced cardiotoxicity

Biochemistry biomarkers

Troponin is a good biomarker in detecting patients who receive chemotherapy agents and who might be at high risk of cardiomyopathy.[46] The golden standard, highly sensitive, and specific method for the detection of doxorubicin-induced cardiotoxicity is by endomyocardial biopsy of the right ventricle.[47] Good biomarkers in detecting acute doxorubicin-induced myocardial injury in chemotherapy patients include troponinT and plasma levels of circulating natriuretic peptides, such as atrial-type and brain-type natriuretic peptides (BNP).[48,49] Myeloperoxidase (MPO) is an enzyme produced in neutrophils and can cause lipid peroxidation in proinflammatory oxidation. Measuring MPO and troponin can be a predictive indicator in estimating cardiotoxicity in chemotherapy patients.[50,51] Several promising studies showed that high-sensitivity C-reactive protein (hs-CRP) can be a valuable biomarker for estimating trastuzumab-induced cardiotoxicity in HER2-positive breast cancer, especially in early stages.[52] Micro-RNAs (MiRs) are potent biomarkers whose alteration in their expression can be good diagnostic and prognostic biomarkers in detecting cardiotoxicity in early stages.[53] MiR-532-3p, miR-216b, miR-34c, and miR-146a were suggested to be potential regulators of doxorubicin cardiac complications, therefore evaluating their expression can be useful in predicting induced cardiac complications. MiR-320a overexpression enhanced apoptosis, aggravated the vessels in the heart and caused cardiac dysfunction.[54,55] Plasma MiR-1,-29b, and-499 are specifically increased in anthracycline chemotherapy and this may be an alarm for acute cardiac injury situation.[56] Cytokines can be predictive biomarkers in chemotherapy-induced cardiotoxicity; for instance, doxorubicin can induce TNF-α, IL-6 generation, inducible nitric oxide synthase expression while decreasing IL-10 production.[57] We categorized and summarized the biomarkers in Table 1.

Genetic markers

Genetic makers are informative in predicting pharmacogenetic effects and can be used in estimating induced cardiotoxicity; however, validating genetic variants is crucial in predicting cardiotoxicity. Several studies showed that iron levels can enhance ROS in response to anthracyclines. Therefore, patients who carry hemochromatosis gene mutation C282Y[62] are at higher risk of myocardial injuries than noncarriers who

Table 1: Diagnostic and prognostic biomarkers in chemotherapy-induced cardiotoxicity

Biomarker	Diagnostic	Prognostic	Benefit	Reference
cTn	*	*	Detectable in small amount in serum, good indicator of heart muscle damage, high-sensitivity	[58]
BNP; B and NT-proBNP	*	Who developed cardiomyopathy*	May indicate an early marker of myocytes stress, biomarker in HF management	[59]
MPO	-	*	Linked to atherosclerosis	[51]
NPs	*	-	Diagnosis, risk stratification, and long-term management of patients with congestive HF	[60]
Inflammatory mediators (cytokines, hs-CRP, OS)	*	*	Early detection in induced cardiomyopathy	[57]
miRs	*	*	Involvement in HF, early sensitive cardiotoxicity biomarkers for screening potential drugs	[61]

cTn: Cardiac troponin, BNP: B-type natriuretic peptide, MPO: Myeloperoxidase, NPs: Natriuretic peptides, OS: Oxidative stress, HF: Heart failure, hs-CRP: High sensitivity C-reactive protein, miRs: micro-RNAs, NT-proBNP: N-terminal pro B-type natriuretic peptide

receive chemotherapy. Studies showed that patients carrying rs1883112 of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Nox) gene are at greater risk of chronic anthracycline-induced cardiotoxicity.[63] Anthracycline can cause mitochondrial respiratory defect and lead to cardiomyopathy.[64] Doxorubicin attenuates ET-1 expression in chemotherapy patients and decrease cardiomyocytes survival signals. Therefore, estimating ET-1 expression can be a cardiomyocytes survival indicator in chemotherapy patients.[47] Nox polymorphisms are associated with doxorubicin-induced cardiotoxicity. Nox2-derived ROS is an important agent in doxorubicin-induced cardiac dysfunction which causes significant modifications in the activity and expression of MMP-9 and profibrotic genes such as procollagen IIIαI. Changes in Nox activity, oxidative/nitrosative stress, and inflammatory cell infiltration are useful indicators in predicting ROS production and risk of chemotherapy-induced cardiotoxicity.[65] Several studies revealed that RAC2 and CYBA genotypes of Nox subunits were significantly associated with anthracycline-induced cardiotoxicity.[66] *RAC2* gene variant rs13058338 is associated to delayed thrombocytopenia recovery).[67] Several pharmacogenetic studies suggested that variants such as *RARG* rs2229774, *SLC28A3* rs7853758 and *UGT1A6* * 4 rs17863783 are considerable variants in childhood cancer patients who are under doxorubicin therapy.[68]

Echocardiographic techniques

Recently, strain and strain rate imaging became a major technique in estimating myocardial function.[69] Strain imaging helps to better understand the pathophysiology of myocardial function.[70] Using echocardiographic techniques such as deformation imaging is crucial in the diagnosis and prognosis of cardiotoxicity events at early stages.[71] In addition, cardiac magnetic resonance imaging is a precise technique for estimating myocardial function in pathologic situations.[72] A study on chemotherapy patients with breast cancer, systolic longitudinal myocardial strain and troponin I seemed to be useful in predicting cardiotoxicity at early stages.[73] Echocardiography and myocardial velocity measurements are useful in the detection of myocardial deformation. In fact, studies suggested that Doppler-based myocardial deformation imaging is a good technique in cardiac function monitoring during chemotherapy.[74,75] Anthracycline-induced early deterioration of the left ventricular (LV) longitude and studies suggested that early changes in global longitudinal strain can be a good prognostic marker in estimating cardiotoxicity in chemotherapy patients. Therefore, using three-dimensional speckle tracking echocardiography (3D-STE) is a valuable method.[76] The latter technique is also used for early detection of subtle LV myocardial dysfunction on ventricular and atrial levels in anthracycline-induced cardiotoxicity in leukemia.[77]

Conclusions and future perspectives

Cardiotoxicity is one of the most important side effects of chemotherapy agents in cancer patients. Cardiotoxicity may increase the mortality of cancer patients and decrease the quality of their life. Cardiotoxicity needs to be managed through diagnosis and treatment at early stages. Unfortunately, the diagnostic profile is not exactly clear and diagnosis is based on functional impairments. Diagnostic tests which are commonly used for detecting induced cardiotoxicity in cancer patients are cTn, BNP; B and NT-proBNP, NPs and hs-CRP with cTn, BNP; B and NPs together being stronger predictive biomarkers at early stages. Current studies suggest that MiRs such as miR-532-3p, miR-216b, miR-34c, miR-146a, miR-320a, miR-1, miR-29b, and miR-499 are potent biomarkers in detecting cardiotoxicity at early stages. Recent GWAS studies suggested that a number of genes and polymorphisms are predictive in estimating chemotherapy-induced cardiotoxicity. For instance, patients who carry C282Y mutation in hemochromatosis gene are at higher risk of myocardial injuries when they receive a chemotherapy agent. In addition, Nox

Polymorphisms *RARG* rs2229774, *SLC28A3* rs7853758, and *UGT1A6* * 4 rs17863783 are considerable variants in childhood cancer patients which should be considered in children chemotherapy. Studies suggested that SNPs for cytochrome P450 gene such as CYP3A4, CYP3A5, and CYP2C8 might have an important association with cardiotoxicity.

The first type of chemotherapy agents leads to intracellular calcium increase, therefore, we hypothesize that finding a method to detect and evaluate intracellular calcium can be a valuable diagnostic biomarker in detecting the damage at early stages. In addition, if ROS levels are detected and estimated in chemotherapy, we might be able to detect cardiotoxicity in very early stages. We suggest that MMPs should also be studied as early diagnostic biomarkers because we expect changes in MMPS and ATPase expression using chemotherapy agents that affect mitochondria. Finally, we suggest that choosing the profile of biomarkers according to the type of the chemotherapy agent used can predict cardiotoxicity at earlier stages. Finding a method to evaluate ROS and intracellular Ca^{+2} will allow to estimate cardiotoxicity occurrence during or after chemotherapy. Finally, a number of chemotherapy agents lead to DNA damage and affect P53, Fas, FasL, and JNK; hence, we hypothesize that some patients might have polymorphisms or mutations which make them more susceptible to induced cardiotoxicity. Therefore, GWAS studies are very valuable in future medicine. Echocardiographic techniques such as STE, 3D-STE are strong techniques in detecting induced cardiotoxicity. Nowadays, a combination of biochemical biomarkers and new techniques are needed for detecting myocardial function to manage induced cardiotoxicity at early stages and decrease chemotherapy-induced cardiac mortality.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Compliance with ethical standards

This article Compliance with ethical standards.

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Conflicts of interest

There are no conflicts of interest.

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