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CHEMOTHERAPY INDUCED CARDIOTOXICITY: CONTRIBUTING MECHANISMS, DETECTION METHODS AND DIAGNOSIS STRATEGIES

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ABSTRACT

In the present industrialized scenario, cancer is one of the prevalent illnesses, it has high morbidity and mortality. At this time Chemotherapy is the best choice for cancer treatment. Certainly,chemotherapeutic agents can relieve cancer but these produce cardiac complications, if the person has pre-existed cardiac complications chemotherapy may exacerbate the cardiac complications. Among few, cardiovascular diseases are the most debilitating, pernicious, and lethal in the present-day world. In the current scenario lack of adequate care for CV disease management, the survival of patients with chemotherapy-induced CV diseasesbecomes challenging. Hence this review focuses on interpreting the mechanisms that are contributing to the chemotherapy-induced cardiac diseases, as well as detection methods and early diagnostic strategies that will help in the management of chemotherapy-induced heart failure (CTHF).

KEYWORDS: cancer, chemotherapy, chemotherapy-induced heart failure, diagnostic strategies.

1. INTRODUCTION

Over the past 30 years, cancer mortality rates have decreased predominantly due to early intervention strategies, better surgical procedures, and advancements in cancer therapies. However, an increase in recovery can be associated with other organ injuries including cardiovascular health impacts. Cardiovascular diseases (CVD) are the second leading cause

of long-term morbidity and mortality among cancer survivors(Curigliano, Cardinale et al. 2016).

Two types of chemotherapy-induced cardiotoxicity can typically be distinguished as: (1) Acute or subacutecardiotoxicity, more occasionally seen, can occur at any time from the implementation of chemotherapy up to 2 weeks after the cessation of care. In this,the most common clinical findings are ventricular repolarization abnormalities and changes in the QT intervals to supraventricular and ventricular arrhythmias or acute coronary syndromes, acute heart failure, and syndrome-like pericarditis and myocarditis.

(2) Chronic cardiotoxicity, the most prevalent cumulative dose-dependent form, can be divided into two subtypes based on the timing of the onset of clinical symptoms: early, within 1 year ofthe cessation of chemotherapy, and late, 1 year after the cessation. The most common sign of chronic cardiotoxicity is asymptomatic systolic and diastolic left ventricular dysfunction, which leads to severe congestive cardiomyopathy and in turn,can eventually lead to death(Dolci, Dominici et al. 2008).

The occurrence of chronic cardiotoxicity (5%-65%) depends on various risk factorsi.e cumulative dose of antineoplastic medications, follow-up period, patient age, sex, history of cardiac disorders and prior mediastinal radiation(Dolci, Dominici et al. 2008, Mercurio, Pirozzi et al. 2016). Both Conventional and targeted chemotherapies are associated with a heightened risk of cardiovascular damage, including left ventricular dysfunction (LVD) and heart failure (HF), treatment-induced hypertension, vasospastic and thromboembolic ischemia, as well as life-threatening rhythm disruptions, including disruption to the conduction system and potentially QTc prolongation. Though some of these adverse cardiac effects are perpetual and cause progressive CVD, others only induce transient dysfunction without significant long-term health consequences. Early and late effects of chest radiation may lead to radiation-induced heart disease (RIHD), which can include a variety of heart disorders such as pericardial disease, myocardial fibrosis, cardiomyopathy, coronary artery disease (CAD), valvular disease, and myocardial fibrosis causing arrhythmias(Dolci, Dominici et al. 2008, Curigliano, Cardinale et al. 2016).

While several medications are potentially cardiotoxic (table.1), the medications most widely associated with cardiotoxicity are anthracyclines (doxorubicin and epirubicin), taxanes, alkylating agents, and trastuzumab, which belongs to the class of monoclonal antibodies to

the human epidermal receptor-2, recently introduced in advanced breast cancer treatments. Newly introduced tyrosine kinase inhibitors which induce modifications in cardiomyocyte cultures and animal models can also be associated with cardiotoxicity in patients treated with cancer (Dolci, Dominici et al. 2008).

All of these negatively impact the quality of cancer patients and become a challenge to Oncologists and cardiologists in treating patients with the best cancer therapies available without having a detrimental impact on CV wellbeing. At this moment we need to explore the mechanisms underlying heart failure caused by chemotherapy. Hence this review focuses on interpreting the mechanisms that are contributing to the chemotherapy-induced cardiac dysfunctions, as well as detection methods and early diagnostic strategies that will assist in the management of heart failure induced by chemotherapy (CTHF).

2. Mechanisms contributing to cardiac dysfunction

There are two types of major mechanisms for chemotherapy which lead to CTHF, i.e. Cardiomyocyte-intrinsic mechanisms and paracrine mechanism, as well as chemotherapy, affect cardiac progenitor cells (CPC) which lead to cardiac dysfunction (Table 2). Cardiomyocyte-intrinsic pathway leading to HF due to the effects of oxidative stress, mitochondrial dysfunction and anthracycline-induced DNA response activation, and HF due to deranged myocardial energetics, such as anthracyclines and sunitinib. Blocking of neuregulin-1/Receptor tyrosine-protein kinase(ErbB4/ErbB2), vascular endothelial growth factor (VEGF)/VEGF receptor and platelet-derived growth factor (PDGF)/PDGF receptor pathways via trastuzumab, sorafenib, and sunitinib is implied as a paracrine-mediated CTHF mechanism. Also known as cardiac progenitor cells, anthracyclines and trastuzumab are the stem cells that are present in the myocardium triggering HF by affecting the CPCs(Mercurio, Pirozzi et al. 2016).

Table 1: Chemotherapeutic agents induced cardiac complications.

Drug	Study	Toxic dose range	cardiac toxicity	Frequency of occurrence
Doxorubicin	Chlebowski 1979	>450 mg/m2	Left ventricular dysfunction	Common
Epirubicin	tjuljandin 1990	>900mg/m2	-	Common
Idarubicin	Anderlini 1995	150-290 mg/m2	-	Intermediate
Paclitaxel	Perez 1998	Conventional dose	Left ventricular dysfunction	Intermediate
Docetaxel	Kenmotsu&Tanigawara	-	-	Intermediate

	2015			
cyclophosphamide	Gottdiener 1981,Goldberg 1986	>100-120 mg/kg	Left ventricular dysfunction	Intermediate
Ifosfamide	Kandylis 1989,Tascilar 2007,Cancer Care Ontario	>10 mg/m2	-	Uncommon
Capecitabin	Sent€urk 2009	Conventional dose	Cardiac ischemia	Intermediate
Fluorouracil	Sent€urk 2009, Schimmel 2004, Chanan-Khan 2004	-	-	Intermediate
Paclitaxel	Perez 1998	Conventional dose	Cardiac ischemia	Uncommon
Docetaxel	Kenmotsu&Tanigawara 2015		-	Intermediate
Trabectedin	Lebedinsky 2011	Conventional dose	Cardiac ischemia	Intermediate
arsenic trioxide	Brana&Taberno 2010	Conventional dose	QTc prolongation	Common
Paclitaxel	Perez 1998	Conventional dose	QTc prolongation	Uncommon

Table 2: Cardiotoxicity-induced mechanisms of chemotherapeutic agents.

Chemotherapeutic agent	Contributing mechanism
Anthracyclines, sunitinib	Cardiomyocyte intrinsic
Trastuzumab, Sunitinib, sorafenib	Paracrine
Anthracyclines, trastuzumab	Effect on cardiac progenitor cells

1.1 Cardiomyocyte-intrinsic molecular mechanisms mediated cardiotoxicity

Anthracyclines, such as doxorubicin (DOX), contribute to cardiotoxicity by encouraging the generation of reactive oxygen species (ROS), through two distinct mechanisms i.e. direct mechanism, unstable DOX metabolites, such as doxorubicin semiquinone, react with oxygen and produce hydrogen peroxide and superoxide and indirect mechanism, DOX chelates free iron and modulates the activity/expression of major iron-transporting/binding proteins(Gammella, Maccarinelli et al. 2014, Mercurio, Pirozzi et al. 2016). Conversely, DOX can interact with 2β (Top2β) cardiomyocyte topoisomerase, an enzyme responsible for managing DNA tangles and supercoils, causing double-stranded DNA breakages. Besides, DNA damage triggers the tumor suppressor protein p53, which is responsible for activating DNA repair proteins but also for repressing genes involved in the biogenesis/recycling and oxidative phosphorylation pathways of mitochondrial. Eventually, DOX will accumulate cardiomyocytes within mitochondria and intensify these organelles 'metabolic failure(Zhang, Liu et al. 2012). These molecular events lead to the death of cardiomyocytes, and eventually

to cardiac dysfunction. Other than p53, throughreactive oxygen species and $Ca2^{+}$, anthracyclines can also cause the mitogen-activated protein kinase (MAPK) cascade. Specifically, ERK is known to protect cardiomyocytes from apoptosis within the MAPK family, whereas p38 MAPK is involved in inducing cardiomyocyte death(Zhang, Liu et al. 2012, Mercurio, Pirozzi et al. 2016).

Deranged myocardial energetics

Recent studies have identified the role of deranged myocardial energetics, expressed by a reduced phosphocreatine/ ATP ratio, that precedes LV dysfunction, among other mechanisms involved in anthracycline-induced cardiotoxicity. Nonetheless, anthracyclines can oxidize creatine kinase (CK) sulphydryl groups, diminishing their function, thereby reducing myocardial energetics and urging cardiac dysfunction(Sano, Minamino et al. 2007, Mercurio, Pirozzi et al. 2016). Ironically, it has been shown that sunitinib, a tyrosine kinase inhibitor (TKI), inhibits AMPK as an off-target effect that could trigger the depletion of ATP and affect the contractility.

2.2 Paracrine molecular mechanism mediated cardiotoxicity

2.2(a)Disruption of the NRG-1/ErbB4/ErbB2 system

ErbB2 also termed as HER2/Neu is a membrane receptor within the receptor family of the epidermal growth factor, which also includes ErbB1, ErbB3, and ErbB4. It is usually triggered by a ligand-stimulated interaction (dimerization) with another ErbB receptor that occurs after the latter one. ErbB2 is overexpressed in up to 30 percent of breast cancers and transmits tumor growth that promotes intracellular signals irrespective of the existence of an ErbB ligand(Odiete, Hill et al. 2012, Mercurio, Pirozzi et al. 2016). This has contributed to the emergence of ErbB2-targeting drugs, the first-in-class being trastuzumab, humanized a monoclonal antibody to ErbB2. Unintendedly, trastuzumab was associated with LV dysfunction and HF in women treated with trastuzumab in the clinical trials.

It is now known that adult myocardial microvascular endothelial cells release neuregulin-1 (NRG-1, especially the isoform NRG-1β) in response to stimuli such as mechanical strain. NRG-1 works in a paracrine manner on contiguous cardiomyocytes and activates the dimerization of ErbB2 with ErbB4, which is accompanied by several cellular events that lead to cardiac homeostasis and stress adaptation. Mice with cardiac-specific disruption of the NRG1/ErbB4/ErbB2 system were generated by conditional deletion of the ErbB2 gene after the finding that trastuzumab was cardiotoxic in several recipients. These animals proved

viable at birth and displayed natural cardiac morphogenesis but developed early-adulthood dilated cardiomyopathy with systolic dysfunctions. It was therefore postulated that trastuzumab induces cardiomyocyte damage and ultimately HF by inhibiting the heart's NRG-1/ErbB4/ErbB2 axis and that this is more likely to occur if cardiomyocytes are exposed to another source of stress at the same time, such as anthracyclines(Sawyer, Zuppinger et al. 2002, Mercurio, Pirozzi et al. 2016).

Ultimately these results indicate that the impaired function of NRG-1/ErbB4/ErbB2 is involved in the pathogenesis of HF. Based on the evidence that NRG-1 performs cardioprotective action through ErbB4/ErbB2 and that the function of these receptors is defective in HF, it was postulated that analogs of NRG-1 and NRG-1 may be used for HF treatment.

2.2(b)VEGF/VEGF-R and PDGF/PDGF-R blockade

Sunitinib and sorafenib are TKIs that target more than 30 kinases, playing important roles in both proliferation of tumor cells and cardiovascular homeostasis (Table 3). Sunitinib targets VEGF receptors (VEGFR) 1–3, platelet-derived growth factor receptor (PDGFR), c-kit, AMPK, RAF, and ribosomal S6 kinase (RSK).

Apart from the previously mentioned AMPK, vascular endothelial growth factor (VEGF) signaling is the fundamental target for these drugs. Since VEGF is both an essential regulator of cardiomyocyte function and development, and coronary and systemic circulation integrity and expansion, VEGF signalingcan not surprisingly inhibit may induce cardiotoxic effects, mainly hypertension, thromboembolism, LV dysfunction, and HF(Schmidinger, Zielinski et al. 2007, Mercurio, Pirozzi et al. 2016).However, for its normal function, the heart depends on adequate perfusion, and similarly to cancer, it relies on the integrity of HIF-1 (a transcriptional activator responsive to cellular hypoxia and mediating several cellular and systemic homeostatic responses to hypoxia) and VEGF pathways. In particular, inhibiting HIF-1 with p53 developed LV dysfunction after chronic overload of pressure, these findings indicate that the heart is responsive to anti-angiogenic drugs, particularly with an overload of pressure.

Inhibition of VEGF will also be responsible for the most frequent side effect of antiangiogenic drugs on the cardiovascular, namely hypertension. Indeed, VEGF signaling is essential for regulating endothelial function and generating nitric oxide; thus, its inhibition

abolishes normal vasodilatation. Certain effects of VEGF inhibition may include endothelial cell death induction and resistance vessel rarefaction. Hypertension is attributed to processes similar to those involved in antiangiogenic drug anticancer effects, and may thus also be considered a proxy for the efficacy of such medications (Mir, Ropert et al. 2009, Mercurio, Pirozzi et al. 2016). The occurrence of cardiotoxic effects is high for sunitinib. In addition to its controlled action on VEGF, these significant side effects can also be explained by the drug's inhibition of off-target kinases, such as ribosomal S6 kinase (RSK), which causes the intrinsic apoptotic pathway to activate subsequently.

Another mechanism associated with sunitinib and sorafenib mediated toxicity may be inhibition of PDGFR, since PDGFR also plays a critical role in cell survival and cardioprotection during pathological stress. Exposure to mice that lack PDGFR (PDGFR-β KO) results in LV dilation afterload stress, reduced cardiac activity, and pulmonary congestion compared with controls. It is also followed by increased apoptosis and decreased pro-angiogenic gene expression.Often believed to impede angiogenesis is PDGFR inhibition, which contributes to microvascular dysfunction via pericyteloss(Chintalgattu, Rees et al. 2013, Mercurio, Pirozzi et al. 2016).

Sunitinib and sorafenib share several cardiotoxicity mechanisms, although sorafenib can have additional effects by inhibiting the Rapidly Accelerated Fibrosarcoma (RAF) kinases which normally promote cell survival. In animal models, it has been shown that cardiac-specific deletion of RAF-1 results in dilatation of the left ventricle (LV) and decreased contractile function.

Ironically, a recent report discussed additional cardiotoxicity-induced sorafenib pathways. The authors observed that sorafenib-treated mice displayed a reduced 2-week survival after myocardial infarction (MI) compared with vehicle-treated controls. Sorafenibcardiotoxicity was mainly the product of myocyte necrosis rather than any direct effect on myocyte activity, with surviving myocytes undergoing pathological hypertrophy. Inhibition of proliferation of ckit+ stem cells was also advocated as a possible, exacerbating factor that decreased endogenous cardiac repair.All things considered, cardiotoxicity from antiangiogenic drugs is a complex side effect achieved by a combination of inhibitions of the activities of different Tyrosine Kinases that have important roles both in tumor cell proliferation and cardiovascular homeostasis (Duran, Makarewich et al. 2014, Mercurio, Pirozzi et al. 2016).

Table 3: Role of kinases in cardiac function and their inhibitors of antiangiogenic drugs.

Inhibitors	Kinases	Role in cardiac function
Sunitinib and sorafenib	VEGFR	Contribution to cardiomyocyte function and growth and to the integrity and expansion of thecoronary and systemic circulation; stimulationof endothelial growth, migration, and survival
Sunitinib and sorafenib	PDGFR	Contribution to cell survival and cardioprotection during stress conditions, regulation of angiogenesis
Sunitinib	AMPK	Energy production
Sorafenib	RAF	Promoting cell survival
Sunitinib and sorafenib	c-kit	Contribution to homing of CSC to sites of post-MI injury, CSC differentiation, and cardiomyocyte terminal differentiation.
Sunitinib	ribosomal S6 kinase (RSK)	signals survival through inhibitory phosphorylation of the pro-apoptotic factor BAD

2.3 Cardiac progenitor cell dysfunction mediated cardiotoxicity

Emerging research concerning the cardiotoxicity of anti-cancer drugs is not limited to cardiomyocytes alone but can also affect resident progenitor cells of the cardiac. Such cells tend to be self-renewing, clonogenic, and multipotent and have been proposed to involve themselves in the continuous and functional regeneration of myocytes, endothelial cells (ECs), smooth muscle cells (SMCs), and fibroblasts. Additionally, CPCs in pathological states may potentially lead to myocardial regeneration. For example, they regenerate cardiomyocytes and coronary vessels which partially restore the structure of the myocardial infarction. Anthracyclines, such as doxorubicin (DOX), interfere with different CPC functions. DOX impairs the endothelial differentiation potential of CPCs either directly (DOX reduces CCL2 expression) or indirectly (DOX promotes the depletion of a central regulator of CCL2/CCR2, cardiac erythropoietin(EPO)) by downregulating chemokine ligand 2 and chemokine receptor type 2 (CCL2/CCR2) signaling. EPO binding to CPCs and responsible for maintaining an active CCL2/CCR2 network.

Consequently, mice exposed to doxorubicin show both attenuated activation of CCL2/CCR2 and decreased levels of EPO in the cardiac microenvironment. Remarkably, mice vulnerable to heart failure due to reduced expression of cardiac STAT3 (cardiomyocyte-restricted deficiency of STAT3) exhibit similar defects, followed by increased activity of MMP-12 which is responsible for the proteolytic cleavage of CCL2. Therefore, these data support the view that EPO / CCL2/CCR2 signaling deregulation may represent a general mechanism underlying CPC dysfunction in heart failure(Hoch, Fischer et al. 2011, Mercurio, Pirozzi et al. 2016).

Anthracycline exposure in CPCs has been shown to increase the generation of ROS and cause damage to DNA, expression of p53, attrition of telomeres, and apoptosis. Besides, doxorubicin induces dose- and time-dependent cell cycle arrest at the G2/M phase by decreasing levels of cyclin D1, cdk4, and phosphorylated Rb. Accordingly, p16INK4a, also known as cyclin-dependent kinase inhibitor 2A, is upregulated in patients who died from heart failure caused by doxorubicin and shows that the majority of CPCs are senescent.

Doxorubicin also induces significant changes in CPC's global gene expression, including genes involved in drug efflux and toxic agent cell defense, such as the ATP-binding cassette ABC transporter Abcg2/Mdr1, and genes involved in self-renewal and progenitor cell expansion. Inhibition of CPC division combined with accumulation of oxidative DNA damage, growth arrest, cellular senescence, and apoptosis ultimately results in an almost complete depletion of the CPC pool within the myocardium over 6 weeks after exposure to doxorubicin.Intriguingly, the infusion of syngeneic progenitor cells has been shown to succeed in reversing the progression of doxorubicin cardiotoxicity in a rat model and indicates that CPC repopulation of depleted myocardium following intense chemotherapy could be a valuable choice for rescuing the cardiomyopathic heart. Finally, the development of DOX- ROS and DNA damage contributes to activation of the tumor suppressor protein p53 which ultimately leads to cardiac dysfunction(De Angelis, Piegari et al. 2010, Mercurio, Pirozzi et al. 2016).

On the other hand, another antineoplastic cardiotoxic agent, trastuzumab, was also reported to impair the cardiomyogenic and angiogenic capacity of CPCs. Although clinically relevant trastuzumab concentrations have only minor effects on the proliferation, apoptosis, or size of the ckit- CPC subpopulation, in vitro assays indicate a decreased cardiogenic differentiation capacity and impaired ability to shape microvascular networks in trastuzumab- treated

cells.Trastuzumab therapy significantly impairs the functional advantages of CPCs injected into the boundary region of acutely infarcted mouse hearts(Barth, Zhang et al. 2012, Mercurio, Pirozzi et al. 2016).

These results, in general, suggest cardiac progenitor cells as one of the cellular targets responsible for cardiomyopathy caused by chemotherapy.

3. Typical cardiac dysfunctions

LVD and HF

LVD and HF are among the most significant CV implications of systemic cancer treatment. Conventional chemotherapeutics, such as anthracyclines, antimetabolites, and cyclophosphamide, may cause permanent myocardial cell damage, contributing to acute or chronic LVD. Anthracyclines, commonly used in the treatment of solid tumorsi.e, breast cancer, osteosarcoma, and hematologic malignancies i.e, Hodgkin / non-Hodgkin lymphoma, acute lymphoblastic leukemia, may trigger significant LVD.Historically, anthracycline-related LVD was known to be dose-dependent, cumulative, and progressive, manifesting as a decreased LV ejection fraction (LVEF) and eventually as symptomatic HF in up to 5% of patients. The mechanism of anthracycline-induced cardiac damage has been extensively studied and is still not well understood. Structural cardiomyocyte alterations and anthracycline-induced cell death are partly mediated by reactive oxygen species (ROS) produced in iron-dependent chemical reactions. ROS contributes to the peroxidation of myocyte membranes and the intracellular space after calcium inflow, into intracellular space, which can consequently lead to permanent myocyte damage. Furthermore, pathways have been established, including disturbances in DNA topoisomerase 2-b (Top2b) metabolism. The risk of doxorubicin-induced HF (which can occur within hours, weeks or years of exposure) increases with cumulative anthracycline dose: 3 percent to 5 percent with 400 mg / m2, 7 percent to 26 percent with 550 mg / m2, and 18 percent to 48 percent with 700 mg / m2.High-risk patients include those at age extremes (< 5 or>65 years), those who received previous or simultaneous chest radiation, and those with pre-existing heart disease or identified risk factors for CV.

The modified hazard ratio (HR) for HF was 1.26 (95 percent confidence interval [CI], 1.12-1.42) for those receiving adjuvant anthracyclines compared to those receiving non-anthracycline adjuvant regimens in a Surveillance, Epidemiology and End Results (SEER) database analysis of elderly breast cancer patients. Following anthracyclines, the average

incidence of HF at 10 years was 38 percent, 32.5 percent with non-anthracycline chemotherapy regimens, and 29 percent with no chemotherapy. For every 10-year rise in age, the risk of HF caused by anthracycline nearly doubles.

Peripheral and coronary artery disease (CAD) (HR, 1.31, and 1.58, respectively),diabetes (HR, 1.74), hypertension (HR, 1.45), as well as emphysema and chronic bronchitis (HR, 1.68), represent additional predictors of heightened risk for cardiac dysfunction. The risk of HF remains higher for patients who receive anthracyclines compared with those who receive other drugs, even after excluding elderly patients and those with related comorbidities. Chemotherapy-induced HF occurs with several other conventional chemotherapeutic agents, including cyclophosphamide (7%-28%) and docetaxel (2.3%-8%) The potential for irretrievable heart damage with anthracycline treatment has resulted in the introduction of chemotherapy regimens with lower cumulative in some clinical settings (i.e. early-stage breast cancer).

Many targeted therapies, especially monoclonal antibodies and tyrosine kinase inhibitors (TKIs), targeted human epidermal growth factor receptor 2 (HER-2) i.e., trastuzumab, pertuzumab, vascular endothelial growth factor (VEGF), and VEGF receptors i.e., bevacizumab, sunitinib, sorafenib, and Abl kinase activity i.e., imatinib, nilotinib, dasatinib, are interacting with molecular pathways crucial to CV health. In the breast cancer population treated with trastuzumab, LVD associated with targeted therapies has been the most extensively investigated. Trastuzumab binds to the extracellular domain of the Erb-b2 receptor tyrosine kinase 2 (ErbB2)/HER2 and leads by multiple pathways to reduced ErbB2 signaling. The cardiac dysfunction associated with trastuzumab has been hypothesized to be a direct consequence of ErbB2 inhibition in cardiomyocytes. Mice with ErbB2 cardiac deletion develop dilated cardiomyopathy and exhibit pronounced systolic dysfunction in response to pressure overload relative to normal mice. Thus, ErbB2 receptor signaling appears to be critical in preserving myocardial function. Unlike anthracycline-induced cardiotoxicity, trastuzumab exposure that result in LVD and HF.

Cardiac dysfunction has also been established with angiogenesis inhibitors, including bevacizumab (1.7%-3%) and sunitinib (4%-11%).VEGF receptor inhibitors, such as sunitinib and sorafenib, block numerous tyrosine kinase receptors, hence making it difficult to establish which targets mediate cardiotoxicity. Preclinical studies have indicated sunitinib therapy with LV systolic dysfunction associated with inhibition of adenosine

monophosphate-activated protein kinase (AMPK), a stress response regulator for cardiomyocytes.The cardiac reversibility hypothesis is not specific to toxic exposure from chemotherapy or targeted agents since the features of stunning or hibernation of the myocardium are well known in cardiac physiology. Myocyte injury can also be reversible if the severity of the damage has not reached a level of irreversibility. Nevertheless, the distinction between reversible and permanent cardiac failure is somewhat subjective. Besides, even anthracycline cardiac damage can be reversible if LVD is detected early and sufficient HF-based treatment is implemented(Albini, Pennesi et al. 2010, Curigliano, Cardinale et al. 2016).

Hypertension

TKIs, which include certain inhibitors of the VEGF signaling pathway (VSP), such as sorafenib and sunitinib, usually cause hypertension. While these are effective anticancer agents, their potential negative impact on CV health can restrict their clinical use. Hypertension is the most commonly observed cardiotoxicity with VSP inhibitors, with an incidence estimated from 19 to 47%. Hypertension mechanisms caused by VSP inhibitors have recently been reviewed and include: decreased synthesis of nitric oxide in the wall of arterioles, increased production of endothelin-1 and capillary rarefaction resulting in reduction of fruitful capillary beds. However, VSP inhibitor-induced hypertension may be attributed to VEGF-mediated nephrin suppression, a transmembrane protein that is essential for preserving the glomerular slit diaphragm, which may lead to proteinuria seen with this class of drugs. Strategies to reduce or prevent hypertension caused by VSP inhibitors are required to avoid cardiac dysfunction and early termination of effective anticancer therapy(Albini, Pennesi et al. 2010, Curigliano, Cardinale et al. 2016).

Vascular Thrombosis and Ischemia

Several of the newer TKIs (dasatinib, nilotinib, and ponatinib) that revolutionized the treatment of some hematologic cancers tend to be associated with major vascular events. There is also an increased risk of adverse thrombotic events in patients treated with multiple myeloma combination therapy that involves dexamethasone, Revlimid, and proteasome inhibitors such as carfilzomib. The frequency of these incidents varies, depending on the specific agent used and the extent of the treatment of hematological malignancies. The spectrum of vascular issues has to do with compromised vascular beds. Dasatinib, for example, seldom causes pleural effusions or pulmonary hypertension, although the vascular

problems found with nilotinib are entirely different and probably represent progressive atherosclerosis. Furthermore, combination therapies used in myeloma that increase the risk of venous and arterial thrombotic events. Ultimately, it is reasonable to assume that these various vascular complications are significant, and consequently require different strategies to effectively manage them(Albini, Pennesi et al. 2010, Curigliano, Cardinale et al. 2016).

Rhythm Disturbances and QTc Prolongation

Cancer treatments can be associated with several rhythm disruptions, but most importantly the QT interval can be prolonged, resulting in ventricular arrhythmias. The use of other drugs used during cancer therapy in supportive care i.e., antiemetics, antidepressants in conjunction with cancer therapies can contribute to QT prolongation Careful monitoring of drug interactions should be considered the quality of care for all patients undergoing cancer treatment. Similar treatments have been connected with such rhythm changes, although the cause for this association is mostly correlated with electrolyte irregularities or concomitant drugs occurring in a specific population. Potential shifts in the QT interval may be linked to pharmacological targets, but this connection is hard to prove. In general, electrolyte irregularities should be carefully controlled and concomitant drugs should be selected with minimal effect on rhythm disturbances(Albini, Pennesi et al. 2010, Curigliano, Cardinale et al. 2016).

Radiotherapy-Induced Cardiotoxicity

The association between radiotherapy (RT) and cardiac dysfunction is well known. Radiation-associated cardiac injuries are particularly important in young patients with curable malignancies, where the risk of developing late cardiotoxicity that is clinically relevant is high. The development of CV damage following RT can be progressive and may include coronary artery disease, valvular disease, myocardial injury, conduction system defects, and diastolic dysfunction. The relative risk of fatal CV events for Hodgkin disease and left-sided breast cancer after mediastinal irradiation, which are the two most common causes for RT in young patients, is between 2.0 and 7.0, and between 1.0 and 2.2, respectively. However, it is worth noting that such data do not represent contemporary procedures for radiation treatment, as RT approaches have evolved dramatically over time. Damage to the arterial endothelium, especially in the lowering left anterior and right coronary arteries, may cause premature atherosclerosis in the coronary circulation. This generally happens after RT, 10 to 15 years. Acute pericarditis, and chronic pericardial effusion, either symptomatic or asymptomatic, can

occur 6 to 12 months after RT. It was confirmed that mitral and aortic valves had stenosis and regurgitation. Conduction system fibrosis with impaired heart rate and heart block (whether whole or incomplete) can also occur.Such late radiation-induced cardiac effects were observed with doses ranging from 30 to 40 grays. Newer RT methods, including 3-dimensional (3D) treatment scheduling with dose-volume histograms to precisely measure both heart volume and dose, should minimize the risk of direct cardiac damage. Also widely used as methods are the prone position and deep breath-hold.Models for predicting the risk of radiation damage include the normal probability of tissue complication (NTCP) process, which takes into account the dose and volume of normal tissues exposed to radiation exposure. The NTCP model predicts an association between the dose given and the risk of cardiac death within 15 years of RT(Curigliano, Cardinale et al. 2016).

4. Detection of Cardiac Dysfunction and Evidence for cardiotoxicity

4.1 Echocardiographic imaging

The most widely used imaging technique for monitoring cardiac function during and after chemotherapy is echocardiography, especially 2-dimensional imaging (2D-Echo). It is a readily accessible, reproducible, non-invasive modality that allows for reliable, serial evaluation of cardiac function.Every technique has many technological limitations and 2D-Echo is no exception. Recent studies have detailed these considerations. These common parameters are LVEF and myocardial strain which are observed(Curigliano, Cardinale et al. 2016).

4.2 Lvef

LVEF is the most commonly accepted cardiac function parameter which individually predicts short-term and long-term mortality from CV events, including myocardial infarction, ischemic and idiopathic cardiomyopathy, as well as anthracycline-induced cardiomyopathy. However, LVEF measurement poses several challenges related to image quality, LV geometry assumption, load dependence, and expertise. LVEF assessment remains a fairly inaccurate method for early detection of cardiotoxicity. It is primarily because there is no reduction in LVEF before a sufficient amount of myocardial damage has occurred and cardiac compensatory mechanisms are exhausted.Ironically, in a recent study involving a large, primarily anthracycline-treated population of breast cancer, prospective and close monitoring of LVEF with 2D-Echo standard during the first 12 months after completion of chemotherapy allowed early detection of nearly all cases of cardiotoxicity (98 %), and

prompt treatment in most cases(82%) led to normalization of cardiac function. Candidate variables in this study were age, sex, CV risk factors, cumulative dose of anthracycline, mediastinal RT, left chest RT, body mass index, and year of recruitment; and baseline and final (end of chemotherapy) LVEF measurements were obtained. LVEF was an independent indicator of further cardiotoxicity production at the end of the chemotherapy. However, only 11% of patients had a complete recovery that is, showed an LVEF value equal to or greater than the baseline value (before initiation of chemotherapy); in the remaining 89% of patients, cardiac output was below the baseline value. This evidence indicates that approaches aimed at preventing LVD development seem strategically more successful than therapy interventions designed to mitigate existing damage, which in many cases can be progressive and irreversible. Diastolic dysfunction may precede the reduction of LVEF in patients with chemotherapy-induced cardiotoxicity. Accordingly, irregular diastolic filling without evidence of a decrease in LVEF has been seen in chemotherapy-treated patients. Moreover, no diastolic parameters have been shown to predict unequivocally cardiotoxicity, and the role of diastolic dysfunction in screening to detect early subclinical cardiotoxicity remains controversial at present(Curigliano, Cardinale et al. 2016).

4.3 Myocardial strain

New technology has emerged which enables an improvement in the accuracy of LVEF calculation. Strain-echocardiography is among the most promising. Strain is a predictor of deformation to the myocardial. The muscle shortens in the longitudinal and circumferential dimensions as the ventricle contracts and thickens and lengthens in the radial direction. Strain imaging can provide an assessment of global and regional cardiac function, which can be assessed using either Doppler tissue or 2D-based methods. Several small studies analyzing tissue Doppler and LV strain rate imaging detected early subclinical changes in cardiac function that followed a decline in LVEF. When using tissue Doppler-based strain imaging, a common measurement known as the peak systolic longitudinal strain rate can be used to accurately detect most early variations in myocardial deformation during anticancer therapy; while, with speckle tracking echocardiography, advancing strain imaging, the peak systolic global longitudinal strain (GLS) may tend to be the most reliable measurement. A 10% to 15% early decrease in GLS via speckle-tracking echocardiography during therapy appears to be the most useful parameter for early detection of cardiotoxicity, identified as a reduction in LVEF or HF. However, there are currently no long-term data available on large populations supporting the clinical significance of these changes. Besides, these methods still have

considerable limitations: data processing is usually offline, time-consuming and also relies on the efficiency of the acoustic windows. Additionally, various echo machines and software packages can produce specific strain results, making it difficult to compare them. These modern echo imaging methods are also usually not used in a regular assessment of cardiac function during chemotherapy(Curigliano, Cardinale et al. 2016).

4.4 Other imaging techniques

Multiple-gated acquisition (MUGA) scans can restrict the variability of interobserver in assessing LVEF but it has the drawbacks of exposing the patient to radiation and provides limited information on cardiac structure and diastolic function. Magnetic resonance imaging is known as the gold standard for measuring cardiac volumes, mass, and both systolic and diastolic functions. However, this imaging conceptual model is not widely used due to the high cost and lack of availability(Curigliano, Cardinale et al. 2016).

5. Diagnostic strategies of Chemotherapy-induced cardiotoxicity

Early detection of patients at risk of cardiotoxicity is a primary target for cardiologists and oncologists, allowing the development of tailored treatment approaches or therapies for antineoplastics. Time and expensive monitoring of cardiac functions are also advised, during and after chemotherapy to detect subclinical myocardial injury, however, most of the methods widely used in clinical practice (echocardiographic left ventricular ejection fraction [LVEF] assessment and angiography with radionuclide) demonstrated poor diagnostic sensitivity and poor predictive ability in the detection of subclinical myocardial damage. The use of many other methods, such as endomyocardial biopsy, is problematic due to the invasiveness of the procedures in clinical practice.

Therefore, new, non-invasive, and cost-effective diagnostic methods for early detection of patients vulnerable to developing drug-induced cardiotoxicity are increasingly expected. The use of easily detectable cardiac biomarkers in the blood such as cardiac troponins and cardiac natriuretic peptides (CNPs) has been tested in animal models and clinical studies.For detection of early subclinical cardiotoxicity, it is advised to screen high-risk patients.

5.1 Conventional strategies

At least three international consensus guidelines suggested assessment of LVEF at the beginning of antineoplastic therapy, after administration of half of the total cumulative dose of anthracycline, and before each subsequent dose. Besides, during follow-up, LVEF

examination 3, 6, and 12 months after the completion of treatment is recommended. A reduction in LVEF by more than 10 percent, consistent with a medication.A reduction in LVEF by more than 10%, associated with an absolute LVEF value of less than 50%, is recommended as a criterion for discontinuing treatment. Using this method, in some trials, the risk of developing clinically reported cardiac insufficiency has been reduced to less than 5% in patients treated. Nevertheless, some significant shortcomings of this method have been illustrated in clinical practice. Not all patients diagnosed with chemotherapy need such consistently repeated monitoring of LVEF as indicated by the guidelines, due to the detrimental effects on patient care and the cost-effectiveness ratio of the national health system. Besides, many questions have been posted about the efficacy of LVEF assessment monitoring of cardiac function only because the reliability of this testing appears to be neither sensitive nor accurate enough to predict the early development of cardiac dysfunction after chemotherapy. Interventional strategy able to avoid cardiomyopathy in the future(Dolci, Dominici et al. 2008, Curigliano, Cardinale et al. 2016).

5.2 Biomarkers strategies

In the last 15 years, a strategy based on the use of biochemical markers, particularly cardiac troponins, has been developed to identify, assess and monitor antitumor-induced cardiotoxicity early in real-time. This approach nullifies the interobserver variability identified with imaging strategies; however, the exact timing of the biomarker measurement and the variability in the techniques were not adequately determined(Dolci, Dominici et al. 2008, Curigliano, Cardinale et al. 2016).

5.2(a) Cardiac troponins

Cardiac troponins are regulatory proteins within the myocardium released into the bloodstream when damage has occurred to the myocyte. Troponins are the first blood biomarkers found to detect heart problems. They are proteins of medium size which regulate the actin and myosin of the contractile elements. While they are usually undetectable, after cardiac injury, troponins can increase within 2 or 3 hours. Studies have shown that troponins that detect cardiotoxicity in patients treated with antitumor drugs at a preclinical stage long before any reduction in LVEF occurred. Measurements of troponins can provide additional details, including:

1. Prediction of the extremity of possible future LVD, since the peak value of troponin after chemotherapy, is strongly associated with the degree of reduction of LVEF.

2. Stratification of cardiac risk after chemotherapy, which enables the duration of post-chemotherapy monitoring of cardiac function to be personalized.
3. Selection of patients more likely to experience cardiotoxicity, in which can be considered a cardioprotective therapy.
4. Exclusion from continuous cardiologic care in most patients.

In a study of 703 primarily breast cancer patients, troponin I (TnI) was measured before chemotherapy, 3 days after the end of chemotherapy (early assessment), and 1 month after the end of chemotherapy (late assessment). Three separate patterns of troponin release were observed. TnI was consistently within the usual range in 70%Ofpatients, increased by 21% only at an early assessment, and increased by 9% at both early and late assessments. After chemotherapy, patients without a TnI rise reported no substantial decrease in LVEF and had a small rate of cardiac events (1%) during the > 3-year follow-up. In comparison, the frequency of significant adverse cardiac events was higher in TnI-positive patients. Between TnI-positive patients, in particular, the prevalence of TnI increased 1 month after chemotherapy was associated with a higher reduction in LVEF and a higher frequency of cardiac events compared to patients with only a transient marker increase (84% vs. 37%; P < .001). An additional study in patients with leukemia indicated a troponin elevation could distinguish those at risk for LVD(Dolci, Dominici et al. 2008, Curigliano, Cardinale et al. 2016).

5.2(b) High-sensitivity troponins

Recent advances in assay technology have resulted in a more sensitive and reliable assays on troponins. Such new high-sensitivity (HS) assays can now accurately quantify small changes that are undetectable using other troponin assays. The most recent research in which HS troponin was evaluated was that Ky et al., who examined the correlation between multiple changes in biomarkers and the subsequent development of cardiotoxicity in breast cancer patients being treated with anthracyclines, taxanes, and trastuzumab. Nonetheless, in that study, the most important risk of cardiotoxicity was correlated with the shift of HS TnI in absolute values at the end of anthracycline treatments as well as a rise in myeloperoxidase, a marker of oxidative stress(Curigliano, Cardinale et al. 2016).

5.2(c) Natriuretic peptides

Increased levels of natriuretic peptide (NP) can detect LVD caused by chemotherapy in both adult and pediatric populations. Sadly, several studies have failed to find an association

between the increase in NP and the development of cardiac dysfunction, undoubtedly because major volume changes will occur in patients undergoing chemotherapy without any substantial change in LVEF.It is significant that when considering only the two most frequently used NPs -B-type NP (BNP) and N-terminal pro-BNP (NT-proBNP) the major variations in analytical characteristics and calculated values among the most widely used commercial methods underline that clinicians must be vigilant and cautious in comparing findings obtained by laboratories using different methods. It is important to recognize the utility of NP as an alternative to clinical treatment in patients diagnosed with possible cardiotoxic therapy. New perspective and multicenter trials involving large populations, utilizing well-standardized dosage methods and with a well-defined timing of sampling and cardiac endpoints are necessary to explain the correct use of NP and to interpret the findings In clinical context(Dolci, Dominici et al. 2008, Curigliano, Cardinale et al. 2016).

5.2(d) An integrated approach of Markers and Cardiac imaging

An integrated method integrating both biomarkers and image data will provide revolutionary utility in predicting subsequent cardiotoxicity. HS troponins, NT-pro-BNP, ST2 (interleukin 1 receptor-like 1), LVEF, and echocardiographic parameters of myocardial deformation were used in a recent multicenter study to detect LVD in patients receiving anthracyclines, taxanes, and trastuzumab. Decreases in peak longitudinal strain and changes in concentrations of HS TnI at completion of treatment with anthracycline were predictive of subsequent LVD. The combined evaluation of the two endpoints showed an increased specificity (93 percent) compared to either parameter alone (both 73 %). This result, however, was correlated with a 35 % reduction in insensitivity. For small studies, other possible cardiotoxicity factors were investigated. Which include markers of endothelial dysfunction (type tissue plasminogen activator, type 1, soluble intercellular adhesion molecule-1, and circulating endothelial cells), markers of myocardial ischemia (fatty acid-binding protein), and markers of oxidative stress and inflammation (glutathione peroxidase, high sensitivity C-reactive protein, interleukins). While several of these potential biomarkers have shown significant changes during chemotherapy, the effect on cardiac function of these changes is unknown more research is therefore required. In summary, a novel approach focused on the use of cardiac biomarkers has developed over the last decade, resulting in a promising, cost-effective diagnostic method to detect, evaluate, and regulate cardiotoxicity early, in real-time. Further studies are needed to validate its use in clinical practice. Standardization of the use of routine biomarkers in this clinical setting is a presently unmet need, and potentially large, prospective, multicenter

studies will provide a strong indication of the correct use of such biomarkers in clinical practice(Curigliano, Cardinale et al. 2016)**.**

5.2(e) Other proposed biomarkers

Other potential markers of cardiotoxicity have been investigated in small studies. These include markers of endothelial dysfunction (tissue-type plasminogen activator, plasminogen activator inhibitor type 1, soluble intercellular adhesion molecule-1, and circulating endothelial cells), markers of myocardial ischemia (fatty acid-binding protein), as well as markers of oxidative stress and inflammation (glutathione peroxidase, high-sensitivity C-reactive protein, interleukins).132,133 Although many of these proposed biomarkers have shown significant changes during chemotherapy, the impact of these changes on cardiac function is unknown; thus, further research is needed. 136 In summary, a novel approach based on the use of cardiac biomarkers has emerged in the last decade, resulting in a promising, cost-effective diagnostic tool for early, real-time identification, assessment, and monitoring of cardiotoxicity. Further trials are necessarytoconfirm their use in clinical practice. Standardization of the use of routine biomarkers in this clinical setting is a current unmet need, and future larger, prospective, multicenter studies should provide clear indications of the appropriate use of these biomarkers in clinical practice(Curigliano, Cardinale et al. 2016).

6. CONCLUSION

New methods for treating cancer have resulted in a substantial increase in the likelihood of surviving a cancer diagnosis for years. Such gains in clinical outcome can be offset by the possible negative effect of cancer therapy on CV wellbeing.Cancer drugs may have short-term and long-term heart and breathing side effects, as well as exacerbating and/or unmasking chronic heart disease. In the course of cancer treatment, the development of CV disease will adversely affect the management of underlying malignancy by interfering with the appropriate doses and timing of lifesaving cancer care. Additionally, the production of a potentially important cancer treatment can be delayed or abandoned due to a perceived elevated risk of CV. In response to the integrated decision-taking required to improve the care of cancer patients, whether they are undergoing aggressive treatment or are long-term survivors following successful treatment, the cardio-oncology discipline has evolved. thecollaborations between oncologists, cardiologists, and other related healthcare

professionals may play an important role in the creation and advancement of models of clinical care, to improve the treatment of cancer-treated patients.

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