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Cardiotoxicity in oncology and coronary microcirculation: future challenges in theranostics

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TABLE OF CONTENTS

1. ABSTRACT

Many of the patients undergoing chemotherapy or radiotherapy for cancer are at increased risk of developing cardiovascular diseases. Recent evidence suggests that cardiac dysfunction and subsequent heart failure are mainly due to vascular toxicity rather than only to due to myocyte toxicity. However, not all of the vascular toxicity of cancer therapies can be explained by epicardial coronary artery disease. In fact, in the last decades, it has been found that myocardial ischemia may occur as a consequence of structural or functional dysfunction of the complex network of vessels, which cannot be seen by a coronary angiography: the coronary microcirculation. Nowadays many diagnostic and therapeutic options are available both in coronary microvascular dysfunction and cardio-oncology. Aim of this review is to suggest future theranostic implications of the relationship between cardiotoxicity in oncology and coronary microvascular dysfunction, showing common pathophysiologic mechanisms, proposing new diagnostic approaches and therapeutic options for cardioprotection.

2. INTRODUCTION

In recent years, cardiotoxicity of cancer treatments is a topic of growing interest. However, many aspects of both radiation-induced and cancer drug-induced cardiovascular diseases remain not fully elucidated. A careful review of the literature suggests that the main pathophysiological mechanisms

implicated in cardiotoxicity are due to vascular toxicity of cancer treatments. Either in the presence or in the absence of epicardial coronary artery disease, coronary microcirculation plays a key role in determining of myocardial ischemia. Aim of this review is to suggest potential theranostic implications of the relationship between cardiotoxicity in oncology and coronary microvascular dysfunction (CMD).

3. THE VASCULAR BRANCH OF CARDIOTOXICITY IN ONCOLOGY

As defined by the National Cancer Institute, cardiotoxicity is a general term indicating "toxicity affecting the heart" (1). In fact, regardless of whether the anticancer therapy is physical (ionizing radiation), chemical, hormonal or biological (the so called "targeted therapy"), it may have negative effects on the cardiovascular system (2). Given that targeted signalling cascades that promote cancer cell proliferation conversely protect vascular cells and cardiomyocytes (3), cancer therapies may be considered as a double-edged sword. More specifically, as expressed in a recent paper on cancer treatments and cardiovascular toxicity published by the European Society of Cardiology (4), about 50% of the cardiovascular toxicity in oncologic therapy is characterized by either functional or structural vascular damage leading to the worsening or the developing of coronary artery disease (CAD), peripheral vascular disease, thromboembolic disease, arterial hypertension and pulmonary hypertension. This observation suggests that a significant amount of cardiotoxicity from either chemotherapy (CT) or radiotherapy (RT) primarily involves vessels rather than cardiomyocytes. In fact, myocardial ischemia has been described as a very common side effect of several cancer therapies (4). For these reasons, patients with pre-existing cardiovascular diseases or with high cardiovascular risk should be considered at higher risk of developing vascular damage due to anti-cancer treatments. The most known risk factors associated with the development of vascular toxicity in patients underwent cancer therapies are arterial hypertension, diabetes mellitus, smoking, previous left ventricle dysfunction, heart failure (HF), previous CAD, increasing age, female gender and postmenopausal status (5). Moreover, genetic polymorphisms may predispose to cardiotoxicity (6), suggesting that genetic features might play a role in modulating the risk of cardiovascular toxicity after cancer treatment. Finally, therapy-related risk factors may include treatment type, drug class, drug dose, duration of treatment and use of combined therapy (7). However, there are gaps in evidence about the factors related to the development of CAD in patients treated with anti-cancer therapy. In this context, CMD precedes the development of coronary macrovascular disease, and it could offer a promising field of research in cardiotoxicity related to cancer treatment. Surprisingly, a great number of pathophysiological correlations may be found between these apparently unrelated topics. Moreover, CMD treatment may share similar therapeutic targets with the current best-evidence cardioprotective strategies.

4. CORONARY MICROVASCULAR DYSFUNCTION

Among patients undergoing coronary angiography because of angina, up to 40% are found to have normal-appearing epicardial coronary arteries (8). In fact, epicardial arteries, often referred to as the conductance vessels, represent the "visible" segment of the coronary circulation and give rise to the pre-arterioles and arterioles that constitute the microcirculation, the "invisible" segments of coronary circulation. In contrast with epicardial coronary arteries, the coronary microcirculation cannot be directly imaged *in vivo* neither with coronary angiography nor by intracoronary imaging techniques. Indeed, small coronary arteries are below the spatial resolution of coronary angiography (about 0.5. mm). Visual assessment of small coronary arteries might be possible by endomyocardial biopsy (11), but this invasive approach is not justified in the majority patients with CMD and does not allow assessment of functional alterations. Several methods have been proposed to investigate the functional state of coronary microcirculation (12), even though their application in the clinical setting is not always simple. In the past 20 years, a large number of studies using both invasive and non-invasive techniques for the assessment of coronary physiology, have produced a large wealth of data leading to a better understanding of CMD. Specifically, studies using positron emission tomography (PET) have permitted to establish the normal range of absolute myocardial blood flow (MBF, mL/min/g) and of coronary flow reserve (CFR) - which represents the ratio of MBF during near maximal coronary vasodilatation to baseline MBF (9). Patients with CMD show a reduced CFR that is usually identified by values lower than 2.0. , which are unlikely to be detectable in apparently healthy subjects (10). In patients with normal coronary angiogram, CMD can represent an additional mechanism of subendocardial ischaemia manifesting typical chest pain and ST-segment depression during exercise, a condition commonly known as microvascular angina (MVA) (9). Even in the absence of significant epicardial CAD, CMD can cause myocardial ischemia, which has been shown to bear an independent prognostic value (8). In 2007, Camici and Crea (8) classified CMD into four main types on the basis of the clinical setting in which it occurs: CMD in the absence of myocardial diseases and obstructive CAD (type A), CMD in myocardial diseases (type B), CMD in obstructive CAD (type C) and iatrogenic CMD (type D). Similarly, in vascular toxicity of cancer treatments, CMD could present in different settings.

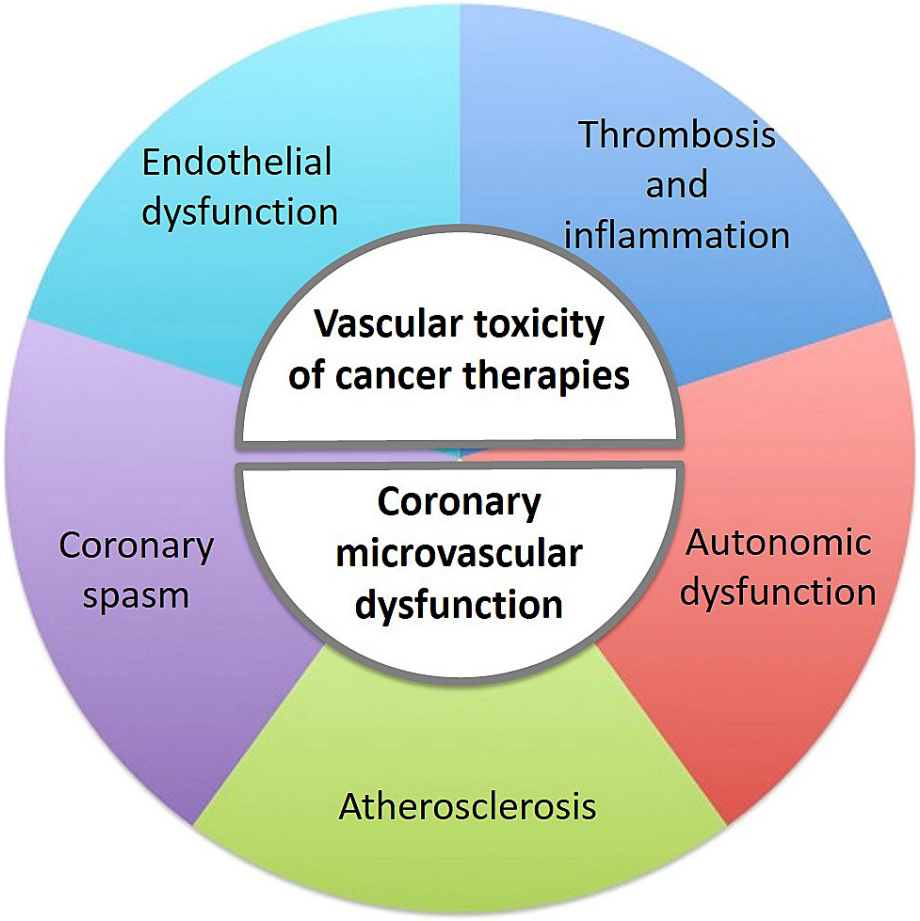

Figure 1. Shared mechanisms between vascular toxicity of cancer therapies and coronary microvascular dysfunction.

5. CMD AND VASCULAR CARDIOTOXICITY: SHARED PATHOPHYSIOLOGICAL MECHANISMS

The mechanisms by which cancer therapies cause myocardial ischemia are diverse and include accelerated atherosclerosis, thrombosis, vasospasm, and coronary microvascular impairment. We will show that many of them are shared with CMD, thus representing suitable targets for cardioprotection in cancer patients (figure 1).

5.1. Endothelial dysfunction

Endothelial cells have the key function of participating in the maintenance of patent and functional capillaries. Endothelial dysfunction is characterized by a shift down in the actions of the endothelium toward reduced vasodilation and prothrombic properties, as well as exacerbated pro-inflammatory state. Moreover, endothelial dysfunction has been associated with the majority of cardiovascular and peripheral vascular diseases (13).

5.1.1. Nitrix oxide (NO) production

Production and release of nitric oxide (NO) are the most important mechanisms of endothelium-mediated vasodilation, and also the first to be lost in case of endothelial dysfunction (14). Among chemotherapeutics, vascular endothelial growth factor (VEGF) inhibitors like bevacizumab, sunitinib and sorafenibare known to starve cancer by inhibiting neo-angiogenesis (4). Notably, this class of drug is related with reduced NO production, resulting in vasoconstriction (15). In CMD, endothelium-mediated vasodilation has been found to be impaired, mainly due to either reduced activity of NO synthase, the enzyme that catalyzes NO synthesis from the aminoacid L-arginine, or increased serum levels of asymmetric dimethylarginine (ADMA), a major endogenous inhibitor of NO synthesis (16).

5.1.2. Reactive oxygen species (ROS)

Oxidative stress and subsequent release of reactive oxygen species (ROS) seems to play a

key role in endothelial dysfunction pathophysiology (17). Accordingly, mechanisms dependent on ROS were among the first to be linked to endothelial toxicity of cancer therapies (18). This is the case of anthracycline- and cisplatin-induced endothelial toxicity (19). Also 5-fluorouracil (5-FU) was found to induce ROS-induced endothelial damage (20). Similarly, vinca alkaloids (21), anti-Her2 target therapy (22) and almost every chemotherapeutic compound display significant detrimental effects on endothelial function due to oxidative stress (23). A parallelism with CMD may exist, since excessive generation of ROS is a common feature in several conditions that have been associated with a pathological impairment of endothelium-dependent coronary microvascular dilatation, as was demonstrated in diabetes, obesity, smoking, and other cardiovascular risk factors (24). Accordingly, administration of antioxidant substances, which prevent superoxide anion formation, including glutathione and antioxidant vitamins, improves or normalizes endothelium-dependent coronary microvascular dilatation both in experimental and in clinical conditions (25,26).

5.1.3. Endothelin-1 and angiotensin II

Mechanisms leading to endothelial dysfunction by bevacizumab and the others VEGF inhibitors are mainly related to increased endothelin-1 (ET-1) and angiotensin II release and production (27). In CMD, it has been demonstrated an imbalance between locally-released vasodilating agents and vasoconstrictors, thereby increasing the vasoconstrictor susceptibility of the endothelium. ET-1, in particular, is the most powerful vasoconstrictor substance produced in the body (28) and its production or release is often increased in the presence of CMD (29). In animal models, the intra-coronary injection of ET-1 or angiotensin II resulted in myocardial ischemia due to vasoconstriction (29). Similar results can be observed in human by intracoronary injection of high doses of acetylcholine (30), which may cause chest pain and objective evidence of myocardial ischemia, in the absence of epicardial coronary arteries disease.

5.2. Atherosclerosis

Atherosclerosis is a chronic disease of the arterial wall, leading to the development of atheromatous plaques in the inner lining of the arteries (17). From a pathophysiological viewpoint, atherosclerosis is no more considered merely as a storage disease, but as an inflammatory disease (31). In cardio-oncology, the main risk factor for accelerated atherosclerosis is RT (32), which may lead to severe CAD, complicated by plaque rupture and thrombosis (33). Radiation-related CAD is usually a late complication, especially in survivors of breast cancer or Hodgkin lymphoma (34), and it may not be detected until at least 10 years after thoracic RT exposure. CT also may lead to accelerated atherosclerosis and its dangerous consequences, as described for instance in cisplatin-treated survivors of testicular cancer (35). A significant contribution to atherosclerosis development in both cancer treatment toxicity and macro/microvascular CAD seems to be related to the activation of tissue renin angiotensin aldosterone systems (RAAS). In fact, RAAS exacerbation promotes significant pro inflammatory background by activating the transcription factor NF-kB, stimulating the expression of cell adhesion molecules and the release of pro-inflammatory cytokines like IL-1, IL-6 and TNF-alpha (17). Moreover, angiotensin converting enzyme (ACE) expression is increased by the activation of macrophages by oxidized LDL (36) while angiotensin II directly stimulate the activation of growth factors and the release of matrix metallo-proteinases (37), thereby making atherosclerotic plaque more prone to rupture and thrombosis (38).

5.3. Thrombosis

Vessel thrombosis is a critical event associated with myocardial infarction, stroke, and venous thromboembolic disorders, accounting for considerable morbidity and mortality. Moreover, venous thrombosis is the second leading cause of death in patients with cancer (39). Cancer therapy itself can induce blood clotting, thrombosis and thromboembolic events (34). This is particularly true for cisplatin, which may lead to arterial thrombosis with subsequent myocardial and cerebrovascular ischemia (40). The pathophysiology is multifactorial, including pro-coagulant and direct endothelial toxic effects, resulting in platelets aggregation and thromboxane formation (34). Among the immune and targeted therapeutics, those inhibiting the VEGF signalling pathway have an increased risk for coronary thrombosis, as shown in patients treated for breast cancer (41) or metastatic diseases (42). In the field of CMD, intravascular plugging of coronary microcirculation has been extensively described, and can be caused by atherosclerotic debris, microemboli and neutrophil-platelet aggregates (29). The main evidence comes from type 4 CMD, typically occurring during percutaneous coronary interventions and related to intracoronary manipulation of friable plaques (43). In these cases, microvascular plugging often causes ‘‘infarctlets’’, as indicated by a modest raise of markers of myocardial necrosis, and has a negative prognostic impact (44). Microvascular occlusion (MVO) has been described also in the setting of transmural myocardial infarction, resulting from a complex interplay of ischemia-reperfusion damage, endothelial dysfunction, platelet activation and vasoconstriction (45): all these mechanisms are largely shared with those from vascular toxicity resulting from cancer therapy described above.

5.4. Coronary spasm

Epicardial coronary spasm is defined as a condition in which a relatively large coronary artery running on the surface of the heart transiently exhibits abnormal contraction, leading to a transient complete or incomplete occlusion of the this artery (46). Abnormal vasoreactivity may be triggered by multiple stimuli acting on different cellular pathways involving both endothelium and underlying vascular smooth muscle cells (VSMCs). VSMCs in particular, are the main regulators of vascular tone and vessel patency (17), having protein-kinase C (PKC), the intracellular enzyme Rho-kinase 5 and ATP-dependent K^+ channels as key mediators (46). After CT or RT as well as any kind of intimal injury, VSMCs change from the quiescent "contractile" phenotype state to the active "synthetic" state, that can migrate and proliferate from media to the intima (19). Among anti-cancer drugs in particular, the proteasome inhibitor bortezomib, approved for the treatment of multiple myeloma and non-Hodgkin's lymphoma, interferes with the degradation of cell cycle proteins in VSMCs, causing apoptosis and leading to coronary vasospasm (47). Conversely, Fluoropyrimidines, like 5-FU, have both direct toxicity on vascular endothelium and an indirect vasospastic effect via PKC activation in VSMCs (19). Similar effects have been described also for the modern "targeted therapy", since sorafenib too has been reported to induce epicardial vasospasm (48). Finally, coronary artery spasm may be triggered by RT in some cases (32), even though the predominant clinical manifestation of radiation-related heart disease today is atherosclerotic CAD (49). Similarly, an impaired VSMCs response to vasodilator stimuli have been described in the presence of CMD (50). Notably, endothelium-independent abnormalities in coronary microvascular dilatation may involve impaired opening of ATP-dependent K^+ channels (51) and abnormal Rho-kinase 5 activity (52).

5.5. Hormonal effects

A confounding aspect of identifying the mechanisms of cardiotoxicity is that not all patients receiving these agents develop cardiotoxicity. The lack of uniform effect in males and females, for example, suggests possible hormonal interactions that modulate the cardiotoxic effect of some drugs. It is the case, for instance, of the tyrosine-kinase inhibitor sunitinib, which has shown more toxicities in multiple organ systems in females compared to men (53); this seems to be related to inhibition of the positive effects from estradiol in endothelial cells (54).

Estrogen deficiency has been demonstrated also in primary CMD and may, at least in part, explain the high prevalence of this disease in females often in the pre- and post-menopausal state, as accurately described in a recent editorial (55). In fact, estrogen deficiency is associated with vasomotor abnormalities, including an impairment of endothelial function (56). Accordingly, estrogen administration has been demonstrated to improve endothelial function (57).

5.6. Autonomic dysfunction

Autonomic innervation plays a key role in regulating heart rate, myocardial function and MBF (58). Its impairment is associated with the development and the progression of cardiovascular diseases in cancer patients (59). Indeed, anti-cancer CT directly affects the function of the autonomic system. In this context, a reduced heart rate variability has been reported in patients treated with vincristine (60), doxorubicin (61) and paclitaxel (62). Moreover, aberrant blood pressure variability and maladaptive orthostatic responses are frequently observed in patients taking paclitaxel, taxanes, vinca alkaloids and cisplatin (58). Finally, damage to the cardiac nervous system by CT or thoracic RT may lead to sympathetic-vagal imbalance leading to sinus tachycardia that, reducing diastolic time and enhancing cardiac oxygen consumption, progressively induces myocardial ischemia (4). However, a significant quote of silent ischemia has been reported in cancer treated patients, since sensitivity fibers may be damaged in turn (63).

Moreover, it is well known that coronary microcirculation is under control of the autonomic nervous system (29). In particular, microvascular vasodilation is regulated by beta-2 adrenoceptor in small arterioles (64), while vasoconstriction is mediated by both alpha1- and alpha2-adrenoceptors (65). It has been demonstrated that either impaired beta-2 vasodilatation or augmented alpha-adrenergic constriction during exercise may be powerful enough to induce myocardial ischemia and MVA (66). Finally, parasympathetic activity has shown to cause coronary vasodilatation through a NO mediated mechanism (67).

6. CARDIOTOXICITY AND CMD: THERANOSTIC IMPLICATIONS

Theranostics combine the therapeutic ("thera") and diagnostic ("nostic") potentials of a certain compound (68). Prior to therapy, the compound is used in a diagnostic test to determine whether the drug will (potentially) exert a therapeutic effect, making it a powerful tool for personalizing disease treatment. Clinical applications of theranostics in oncology range from tissue-specific biomarkers to the most modern nanoparticles technologies. As extensively shown above, given that cardiotoxicity of cancer treatments and CMD shares several pathophysiological mechanisms, future research in theranostics should be addressed regarding the utility to diagnose and

treat CMD in patients receiving cancer therapies, especially because many effective drugs used to treat CMD already represent the current best-evidence cardioprotective strategies. Recently, dysregulation of microRNAs (miRNAs) involved in microvascular remodelling has been found in several cardiovascular diseases (69). In parallel, strong evidence has been found that some miRNAs can act as oncogenes or tumor suppressor genes, dysregulating neoangiogenesis and being involved in the initiation and progression of several human cancers (70).

6.1. Common diagnostic workup

The most common biomarkers employed in cardiotoxicity monitoring are troponin I and natriuretic peptides because of their higher cardiac specificity. However, they are not a reliable indicator of vascular toxicity of cancer therapy (7, 71). On the other hand, CMD can be non-invasively assessed through measurements of MBF and/or CFR in response to appropriate vasodilating stimuli (e.g. adenosine, dipyridamole) (29). Among non-invasive methods for the assessment of CMD, transthoracic stress-echocardiography allows the measurement of CFR through the quantification of diastolic flow velocity in the left anterior descendent artery at baseline and during maximal vasodilator stimulation (72). This non-invasive technique seems to be a promising diagnostic approach due to its widespread availability and safety, especially since 2-dimensional echocardiography is routinely used for monitoring patients with cancer. Moreover recent techniques, including 3d-echocardiogram, strain and speckle tracking, may allow the earlier detection of more subtle changes in myocardial function (71). In particular, the value of echocardiographic myocardial deformation parameters such as peak systolic global longitudinal strain for the early detection of myocardial changes and prediction of cardiotoxicity in patients receiving cancer therapy is well described in a recent review (73). In addition, diastolic dysfunction can be considered an early biomarker, since often it precedes systolic dysfunction in patients receiving chemotherapy (71). This is of particular interest since, according to a novel pathophysiologic paradigm, preserved ejection fraction HF and CMD are two facets of the same coin (74). Among radionuclide techniques, PET offers unrivalled sensitivity and specificity for the non-invasive study of coronary microcirculation in humans (75). Reliable assessment of CFR and MBF have been obtained by two tracers in particular, oxygen-15 labeled water (76) and nitrogen-13 labeled ammonia (77). However, because of its expensive and time-consuming features, imaging with PET can only be performed in highly specialized centres (29). Moreover, cardiac magnetic resonance (CMR) affords the opportunity for non-invasive tissue characterization including myocardial oedema, inflammation, and fibrosis, playing an important role in identification of both early and late cardiotoxicity in patients with cancer (78). At the same time, CMR perfusion sequences have shown to allow the accurate investigation of CMD (79). Finally, a complete assessment of CMD may also include, at least in some patients, the assessment of coronary microvascular response to constrictor stimuli (acetylcholine) (30). These tests, however, need to be carried out during invasive procedures, identifying a significant coronary vasoconstriction during coronary angiography in the absence of established coronary artery disease (29). A proposed algorithm that can be considered in the assessment of cardiac toxicity of cancer therapies including the identification of myocardial ischemia is summarized in figure 2.

6.2. Rationale for cardioprotection

Prevention from cardiotoxicity may be primary, extended to all patients already treated with potentially cardiotoxic therapies, or secondary in selected high-risk patients showing pre-clinical signs of cardiotoxicity (71). A tailored prevention strategy based on the cardiac risk stratification according to patient-related and therapy-related risk factors bears further investigation. Given the wide sharing of pathophysiological mechanisms between cardiotoxicity and CMD, several common therapeutic approaches have shown positive effects in both clinical conditions. While waiting for the advent of modern molecular theranostics, there is a rational of using best-evidence therapies for CMD to treat cardiotoxicity in oncology.

6.2.1. Beta-blockers

Beta-blockers have shown several beneficial effects in patients with CMD and stable MVA, by reducing myocardial oxygen consumption and improving coronary perfusion (29). Consistently, an improvement of ischemic and angina threshold was reported in some studies (80, 81). On the other hand, there is growing evidence suggesting a cardioprotective role of beta-blockers in prevention of CT-induced cardiotoxicity. Carvedilol in particular, which has also antioxidant properties and the ability to chelate iron, was reported as able to prevent cardiac histopathological damage caused by doxorubicin (82). However, there is no definite evidence for a class-effect benefit of these compounds in terms of cardioprotection. In fact, metoprolol showed a neutral effect (83), while nonselective beta-blockers such as propranolol resulted dangerous because of potential enhanced cardiotoxicity (84).

6.2.2. RAAS-inhibitors

ACE-inhibitors have been proposed as therapeutic agents in MVA due to their lowering effects on serum and tissue angiotensin II levels (85). In

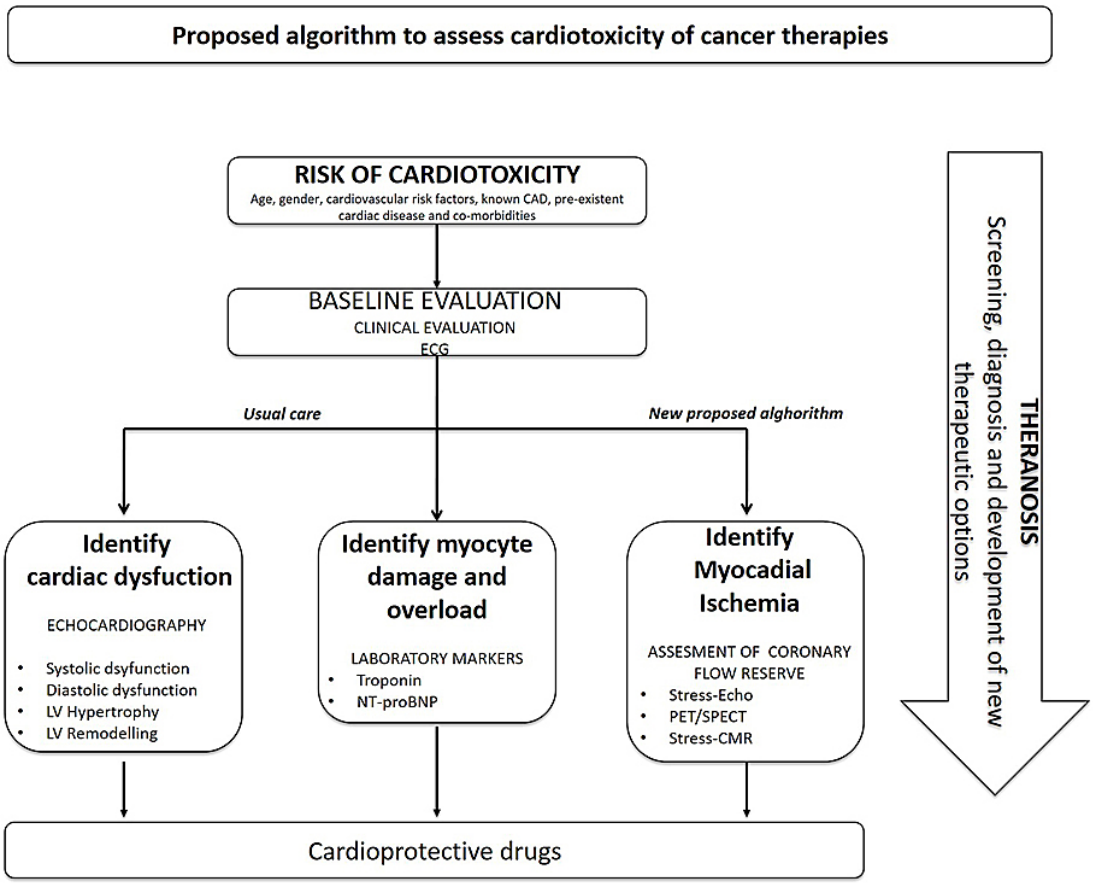

Figure 2. Flow diagram summarizing hypothetical algorithm in the assessment of cardiac toxicity of cancer therapies including the identification of myocardial ischemia. LV, left ventricular; CMR, cardiac magnetic resonance; SPECT, single-photonemission computed tomography; PET, positron emission tomography.

particular, enalapril has been found to improve CMD through the increase of NO availability and reduction of oxidative stress in MVA patients (86). In cardiotoxicity, animal studies suggest that enalapril and other ACE-inhibitors may be cardioprotective in anthracycline toxicity by preserving mitochondrial function and down regulating ROS generation (87, 88). In particular, thanks to its ROS scavenger role, the ACE-inhibitor zofenopril exerts protective properties through off-target mechanisms in endothelial cells, as increased acidic sulphide group availability (89). Similar benefits seem to apply to angiotensin receptor blockers in reducing the formation of ROS, thus attenuating the development of myocardial dysfunction in cancer patients treated by CT (90).

6.2.3. Statins

Statins might have beneficial effects on CMD by improving endothelial function through several effects such as antioxidant, anti-inflammatory and cholesterol-lowering effects. They were able to improve exercise stress test performance in MVA patients (91) and to significantly reduce oxidative stress and endothelial function after 6 months of treatment (92). In cardiotoxicity, studies suggest the benefit of statins in reducing anthracycline-mediated cardiomyocyte death (93) and subsequent HF (94). However, to date no prospective trials have addressed the role of statins in the prevention of cancer therapy-related cardiotoxicity.

6.2.4. Antioxidants

Benefits from antioxidant therapy have been clearly observed only in type A CMD, in which short-term administration of the antioxidant vitamin C restored coronary microcirculatory responsiveness and normalized CFR in smokers without significant CAD nor structural heart disease (95). However, clinical use of antioxidants to protect the heart during chemotherapy is controversial due to the potentially reduced cytotoxic efficacy toward cancer cells (19). Nevertheless, recent evidences suggest the protective role of mitochondrial aldehyde dehydrogenase-2 (ALDH-2) in endothelial cells exposed to stress insult (96). Thus, since dysfunction of this molecule has been associated with both ischemic heart disease

(97) and doxorubicin-mediated cardiotoxicity (98), ALDH-2 targeting seems to be a promising therapeutic challenge to modulate mitochondrial functions and possibly neo-angiogenesis (96).

6.2.5. Other drugs

Non-dihydropyridine calcium antagonists, nitrates, adenosine, nicorandil and alpha-antagonists constitute other therapeutic options for MVA (29). However, their possible role in cardioprotection has still to be elucidated. Finally, it would be of particular interest to investigate the cardioprotective role of ranolazine and ivabradin, which have shown their positive effects on CMD by improving diastolic dysfunction and prolonging diastolic MBF time, respectively. Ranolazine and ivabradin have been tested as cardioprotective agents in both animal models and small series of patients with CT-related reduced ejection fraction HF (29).Given the recently described parallelism between CMD and diastolic dysfunction (74), studies are required to prove their efficacy in patients with CT/RT-related preserved ejection fraction HF.

7. CONCLUSIONS: KNOWLEDGE GAPS AND FUTURE DIRECTIONS

The specialty of cardio-oncology has gained significant momentum, with increasing awareness and interest in advancing this field. Although many important progress has been reached in this field, not all the cardiac toxicity of cancer treatment can be prevented or justified only assessing myocardial function and structure. After the evaluation of cardiotoxicity risk, current guidelines recommend to assess cardiotoxicity mainly using laboratory markers, electrocardiogram and echocardiogram. However, the study of cardiotoxicity revealed that the majority of early myocardial damage from CT/RT primary involve vascular toxicity rather that direct myocyte toxicity. For this reason, we propose myocardial ischemia as new theranostic target in the field of cardiooncology. In this view, in patients undergoing anti-cancer treatment, especially in the presence of high risk of ischemic heart disease, the evaluation of myocardial ischemia, using PET/SPET or stress-echocardiography, allow to non-invasively identify patients with CMD treatable with well-known anti-ischemic drugs (figure 2). Moreover, shared molecular pathways between CMD and cardiotoxicity, such as oxidative stress response, VSMCs tone, inflammation and thrombosis, represent the basis for the development of future research on new strategies for tailored cardioprotection.

8. ACKNOWLEDGEMENT

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Abbreviations: ALDH-2: aldehyde dehydrogenase-2; CAD: coronary artery disease; CFR = coronary flow reserve; CMD: coronary microvascular dysfunction; CMR: cardiac magnetic resonance; CT: chemotherapy; ET-1: endothelin-1; 5-FU: 5-fluorouracil; HF: heart failure; MBF: myocardial blood flow; miRNA: microRNA; MVA: microvascular angina; MVO: microvascular occlusion; NO: nitric oxide; PET: positron emission tomography; PKC: protein-kinase C; RAAS: renin angiotensin aldosterone system; ROS: reactive oxygen species; RT: radiotherapy; VEGF: vascular endothelial growth factor; VSMCs: vascular smooth muscle cells

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