Molecular imaging to guide precision diagnosis and prevention of cancer therapeutics-related cardiac dysfunction

Evangelos K. Oikonomou

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1. Introduction

Cancer therapeutics-related cardiac dysfunction (CTRCD) is now increasingly recognized as an important cause of cardiotoxicity, with subclinical cardiac dysfunction identified in up to 42% of patients undergoing cancer treatment [1]. The mechanisms that mediate these adverse effects may vary depending on the specific type of cancer therapy. For instance, radiotherapy accelerates coronary and valvular calcification, whereas anthracycline chemotherapy is associated with myocardial dysfunction [2]. Recent articles published in Expert Review of Molecular Diagnostics have reviewed the role of circulating biomarkers in the real-time identification and monitoring of cardiotoxicity and heart failure [3,4]. However, the diagnostic utility of circulating biomarkers is limited by the fact that they are released in the bloodstream once cardiac damage has already occurred.

Noninvasive imaging provides real-time information on the structure and dynamic function of the human heart. For instance, echocardiography, particularly by means of deformation analysis/speckle-tracking imaging (i.e. strain analysis), has been shown to detect and predict CTRCD at early stages before a significant drop in the left ventricular ejection fraction (LVEF) [1]. Furthermore, preclinical studies have also identified specific cardiac magnetic resonance imaging parameters, such as T2 relaxation time prolongation, as potential early markers of anthracycline-induced cardiotoxicity, even in the absence of T1 mapping, extracellular volume, or LV motion changes [5]. However, such traditional modalities mainly detect late structural changes in the myocardium. On the other hand, advanced molecular imaging using targeted radiotracers has the potential to identify the earliest molecular changes that precede CTRCD. Such molecular approaches could guide the timely deployment of preventive strategies in order to reduce the incidence of clinically overt cardiotoxicity.

2. Molecular imaging of cancer therapeutics-related cardiac dysfunction

In the recent years, numerous molecular probes, mainly positron emission tomography (PET) and single-photon emission computed tomography (SPECT) radiotracers, have been developed and tested in both pre-clinical and clinical models of CTRCD. These tracers target various biological pathways involved in the earliest stages of CTRCD, such as inflammation, apoptosis, oxidative stress, and extracellular matrix remodeling.

3. Positron-emission tomography (PET) tracers

3.1. \(^{18}\text{F-}\text{fluorodeoxyglucose}\)

Perhaps the most widely used PET radiotracer in clinical practice is \(^{18}\text{F-}\text{fluorodeoxyglucose}\) (\(^{18}\text{F-FDG}\)), a glucose analog which is preferentially taken up by metabolically active cells (secondary to upregulation of glycolytic pathways). Whereas \(^{18}\text{F-FDG-PET}\) is an established method in the monitoring of cancer patients and their response to treatment, recent studies suggest that myocardial \(^{18}\text{F-FDG}\) uptake in the setting of chemotherapy may also serve as a diagnostic marker of cardiotoxicity. In a study of 121 consecutive breast cancer patients undergoing treatment with anthracyclines or trastuzumab, those who developed CTRCD showed higher and more diffuse \(^{18}\text{F-FDG}\) uptake in the left ventricle and a greater interval increase in right ventricular \(^{18}\text{F-FDG}\) compared to the non-CTRCD group. Of note, the association between \(^{18}\text{F-FDG}\) uptake in the right-ventricular wall and CTRCD was found to be independent of age, concomitant radiotherapy and treatment type [6]. Similar findings have been reported in Hodgkin lymphoma patients undergoing doxorubicin-based chemotherapy, as shown in a retrospective analysis of 43 patients which described a significant association between higher left ventricular \(^{18}\text{F-FDG}\) uptake at the end of treatment and a greater decrease in LVEF post-chemotherapy compared to the pre-treatment values \((R^2 = 0.30, \ P < 0.01)\) [7]. Pre-clinical studies supplement these reports by providing an insight into additional mechanisms underlying the observed clinical associations. In mouse models of neuroblastoma treated with doxorubicin, myocardial \(^{18}\text{F-FDG}\) uptake directly correlated with myocardial redox stress and hexose-6-phosphate-dehydrogenase enzymatic activity, thus supporting the value of \(^{18}\text{F-FDG}\) as a potential marker of not only inflammatory activation but also oxidative stress [8]. However, given its physiologic uptake by the myocardium, \(^{18}\text{F-FDG}\) may lack the specificity needed to characterize inflammation-specific changes in cardiovascular biology as a result of cancer therapy.
3.2. \(^{18}\text{F-DHMT}\)

Alternative \(^{18}\text{F}\)-based radiotracers which overcome the limitations of \(^{18}\text{F-FDG}\) have shown promise in the early detection of CTRCD. Doxorubicin-induced cardiotoxicity is believed to be partly mediated by the upregulation of oxidative pathways and formation of reactive oxygen species (ROS) [9]. As an \(^{18}\text{F}\)-labeled analog of dihydroethidium, \(^{18}\text{F-DHMT}\) may allow in vivo imaging of myocardial ROS generation in response to doxorubicin treatment. In rats treated with doxorubicin, \(^{18}\text{F-DHMT}\)-PET imaging demonstrated significantly increased radiotracer uptake in the myocardium compared with controls at 4 weeks post-treatment, whereas LVEF did not significantly decrease until 6 weeks after doxorubicin administration [9].

3.3. \(^{18}\text{F-Mitophos}\)

Lipophilic cation PET tracers have shown the ability to detect changes in mitochondrial function, which is thought to be implicated in the pathogenesis of anthracycline-induced cardiac dysfunction. A new tracer, namely \(^{18}\text{F}\)-labeled lipophilic phosphonium cation (\(^{18}\text{F-Mitophos}\)), has shown favorable pharmacokinetics in experimental models of isolated perfused rat hearts and a significant dose-response between its cardiac uptake and doxorubicin dosing, before any detectable changes in cardiac troponin I concentrations [10].

3.4. \(^{18}\text{F-NOS}\)

An \(^{18}\text{F}\)-radiolabeled analog of the reversible nitric oxide synthase (NOS) inhibitor 2-amino-4-methylpyridine (\(^{18}\text{F-NOS}\)) nitric oxide (NO), the end-product of the inducible form of NO synthase (iNOS) has shown promise in identifying pathologic allograft rejection in humans [11]. Since iNOS is an important regulator of inflammatory diseases, it may also carry value in other forms of myocardial injury, such as CTRCD.

3.5. \(^{18}\text{F-NaF}\)

As opposed to anthracycline use which predominantly affects the myocardial function and contractility, vascular and valvular calcification are hallmarks of radiation-induced cardiotoxicity [2]. \(^{18}\text{F-NaF}\) (sodium fluoride) is a promising tracer that binds to hydroxyapatite sites forming in areas of active microlcalification as a result of necrosis or inflammation [12]. Even though its value in the diagnosis of CTRCD has not been fully elucidated to date, its value in the detection and prediction of vascular and valvular calcification in non-cancer populations is well-documented [12,13].

3.6. \(^{68}\text{Ga-Galmydar}\)

In addition to the aforementioned \(^{18}\text{F}\)-labeled tracers, \(^{68}\text{Ga-Galmydar}\) (a metalloprobe) have also been assessed in pre-clinical models and shown potential value in the timely diagnosis of anthracycline-induced cardiotoxicity. By using micro-PET-CT in rat models treated with or without doxorubicin, researchers recently showed that \(^{68}\text{Ga-Galmydar}\) uptake is almost two times lower in the hearts of doxorubicin-treated animals compared to their control counterparts. Using live-cell fluorescence imaging they further reported a gradual dose- and time-dependent decrease in the retention of the radiotracer in the mitochondria of H9c2 cells after exposure to doxorubicin, thus suggesting a possible value in the early detection of reversible metabolic changes in chemotherapy-related cardiac dysfunction [14].

4. Spect/Scintigraphy tracers

SPECT radiotracers have also been evaluated as in vivo biomarkers of CTRCD, with mixed results and several technical limitations inherent to the use of SPECT imaging. \(^{99m}\text{Tc-sestamibi}\), a lipophilic cation whose distribution is dependent on the mitochondrial membrane potential (ΔΨm) has been suggested as a potential marker of ΔΨm and therefore of evolving cardiotoxicity. In an in vivo rat model, there was a dose-dependent loss of myocardial \(^{99m}\text{Tc-sestamibi}\) retention, while the retention of \(^{99m}\text{Tc-NET}\) (a ΔΨm-independent perfusion tracer) was unaffected [15]. Furthermore, \(^{99m}\text{Tc-RP805}\), a tracer that binds to the active catalytic unit of matrix metalloproteinases, may also detect early increases in matrix metalloproteinase (MMP) activity in rat models of doxorubicin-induced cardiotoxicity, before a detectable change in echocardiographic parameters, such as ejection fraction and global myocardial strain [16].

5. Nanoparticles

Numerous immune-targeting nanoparticles and minibodies are also in the pipeline and are expected to increase our ability to assess leukocyte presence and function as well as adhesion molecule expression in response to cancer therapy [17]. Both radiolabeled as well as MR (magnetic resonance) nanoparticles (e.g. ultrasmall superparamagnetic iron oxide nanoparticles) have been developed to detect leukocyte presence in inflamed vessels, enabling the expansion of molecular imaging into additional modalities, such as MR imaging [17]. Nevertheless, the evidence for their use in CTRCD remains limited.

6. Summary

Taken together, these studies highlight the large number of pathways involved in CTRCD which can be detected using non-invasive radiotracers (Figure 1). However, the role of molecular imaging in assessing the presence and causes of CTRCD in its early stages of evolution has been very challenging and no clear-cut methodology has successfully found its way into clinical practice. Nevertheless, the growing field of cardio-oncology provides several opportunities to explore the complementary role of molecular imaging in the characterization of cardiotoxicity and heart failure beyond circulating markers and conventional imaging modalities. As we expand our knowledge and technical capabilities with the addition of new radiotracers and clinical studies, molecular imaging has the potential to fulfill the promise of precision medicine in this growing population of patients at risk of CTRCD. The lessons learned in that process will also provide valuable guidance as molecular imaging expands to other forms of cardiomyopathy and heart failure.
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ORCID
Evangelos K. Oikonomou http://orcid.org/0000-0003-4362-0720


- An important review on the use of biomarkers for the timely detection of cancer therapeutics-related cardiotoxicity.
- An important study linking (18)F-FDG uptake in the myocardium with not only inflammation but also doxorubicin-induced oxidative stress.
- An important study describing a novel tracer that detects in vivo reactive oxygen species production in response to anthracycline treatment in rodents.
- An important study on the use of (18)F-NOS as a potential PET radiopharmaceutical for inducible nitric oxide synthase in humans.
- An important study on the use of (18)F-DHMT, allowing for early detection of anthracycline-induced cardiotoxicity in rodents.
- An important study on the use of (18)F-labelled lipophilic cations.