New therapeutic insights into radiation-induced myocardial fibrosis

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Abstract: Radiation therapy (RT) for the treatment of thoracic tumors causes radiation-induced heart disease (RIHD). Radiation-induced myocardial fibrosis (RIMF) is both an acute and chronic stage of RIHD, depending on the specific pathology, and is thought to be a major risk factor for adverse myocardial remodeling and vascular changes. With the use of more three-dimensional conformal radiation regimens and early screenings and diagnoses for RIMF, the incidence of RIHD is declining, but it still must be carefully investigated to minimize the mortality and morbidity of patients with thoracic malignancies after RT treatment. Effective methods for preventing RIMF involve a decrease in the direct radiation dose in the heart, and early screening and diagnosis. Medications remain as a useful adjunct for preventing or treating RIMF. This review mainly discusses the cellular and molecular mechanisms underlying RIMF, and new therapeutic drugs that can potentially be developed from this knowledge.

Keywords: miRNA, prevention and treatment of RIMF, radiation therapy, radiation-induced myocardial fibrosis (RIMF)

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Introduction

Radiation-induced heart disease (RIHD) is the leading cause of noncancer-related death, and may not present until several years after patients have undergone thoracic radiation therapy (RT). RIHD mainly manifests as asymptomatic myocardial ischemia, pericarditis (both acute and chronic forms), coronary artery disease (such as accelerated atherosclerosis), conduction abnormalities, valvulitis, myocarditis, and heart failure. With the use of more three-dimensional conformal radiation regimens, the heart toxicity that is associated with RT has declined, but must be carefully considered, in order to reduce the mortality and morbidity of patients with thoracic malignancies. In addition, RIHD is an important factor that restricts the radiation dose; thus, it can reduce the efficacy of the treatment of thoracic tumors.

Radiation-induced myocardial fibrosis (RIMF) has both acute and chronic stages of RIHD, based on the specific pathology, and is thought to be a major risk factor for myocardial remodeling and vascular changes. Although patients may initially be asymptomatic, 10 years after RT, RIMF can subsequently result in restrictive or constrictive pericarditis and heart failure, which are lethal cardiovascular events. Thus, studies that include RIMF as an endpoint may contribute to the early prevention and diagnosis of radiation-induced heart toxicity.

RIMF is the result of a multifactorial interaction. Many studies have demonstrated that miRNAs, fibroblasts, transforming growth factor beta (TGF-β) and peroxisome proliferator-activated receptor (PPAR) alpha are implicated in the pathological processes of RIMF. At present, effective approaches for treating RIMF are limited, mainly because the pathogenesis has not been fully clarified. Therefore, it becomes pertinent to better understand the underlying pathophysiology of RIMF to develop optimal preventive and treatment strategies.

In fact, several existing drugs can reverse RIMF, at least partially. Recent research has shown that
miRNAs may be a new therapeutic modality for RIHD, and new therapeutic approaches will be gradually discovered for the prevention and treatment of RIMF. The question of how to effectively prevent radiation myocardial injury after RT has become a topic of great research interest. In this paper, we will briefly review new advances in the pathophysiology of RIMF, and outline new therapeutic approaches to RIMF.

**Epidemiology of RIMF**
Radiotherapy is often used in patients with thoracic cancer. In some cases, the radiotherapy of tumors inevitably damages normal tissues, which results in an increased risk of cardiovascular disease, and may lead to structural and functional abnormalities in the coronary arteries, valves, pericardium, and myocardium. The incidence of major coronary events increases linearly with the mean cardiac radiation dose, leading to reported values of a 7.4% increase per Gy in breast cancer patients who received tangential fractionated breast irradiation,\(^2\) a 33% increase per Gy in lung cancer patients after RT,\(^3\) and an increase of more than 1.5–3 times in patients with risk factors after mediastinal RT.\(^4\) Although breast cancer patients are usually considered to be fairly healthy, the RT of thoracic cancers may result in secondary heart events after several decades.

**Risk factors for RIMF**
Several studies have proposed that the first step in assessing patients with thoracic tumors after RT for a high incidence of RIMF is the assessment of the traditional risk factors of cardiovascular events.\(^5,6\) These risk factors include current myocardial diseases (such as heart failure, coronary artery disease, left ventricular dysfunction, dilated cardiomyopathy, and restrictive cardiomyopathy), demographic risk factors of coronary artery disease (such as age, sex, family history of coronary artery disease, diabetes mellitus, arterial hypertension, and hypercholesterolemia), a history of RT of the chest or mediastinum, and lifestyle factors (such as smoking, drinking, sedentary habits, and risk factors for metabolic syndrome). In addition, primitive dosimetry techniques, extended RT fields, and high RT doses may be significant for the development of RIMF.\(^7\) Even with the support of new RT technologies and regimens, such as image-guided radiotherapy and dimensional dosimetry, an association between RT and the incidence of cardiovascular mortality seems to exist.\(^8\) The RT dose that is delivered to the heart should be reduced to prevent cardiac toxicity. Moreover, many chemotherapeutic agents have cardiotoxic effects, and the risk of cardiac toxicity may be increased when RT is combined with or more of these chemotherapeutic agents.\(^9\) Tjessem reports that there is no evidence that low-to-moderate cardiac radiation doses contribute to the development of radiation-induced cardiovascular disease.\(^10\) However, a recent report by Boaventura demonstrates that low-dose radiation exposure is also a risk factor for RIHD.\(^11\) Moreover, Coleman demonstrates that low-dose radiation affects the molecular responses and gene expression levels in cardiomyocytes.\(^12\) Finally, the number and severity of risk factors for RIMF should be identified for patients with thoracic tumors before the use of RT. If necessary, patients with high-risk factors should be assessed by experts in this field. In most cases, the presence of cardiovascular risk factors usually does not have an influence on the decision to use RT in thoracic tumors, except in cases of known, severely reduced cardiac function of any origin.

**Pathology and pathophysiology of RIMF**
RIMF is characterized by a nonspecific, diffuse interstitial fibrosis and develops through three phases of injury. The first phase is the onset of acute inflammation at approximately 6h after radiation in small and medium-sized arteries, with a neutrophilic infiltrate in all layers of the heart.\(^13\) In the first few minutes, the endothelial cells of myocardial capillaries that are exposed to radiation are activated with increased permeability, thus inducing early acute endothelial inflammation,\(^14\) that may adversely transfer to the nonirradiated surrounding cells; subsequently, neutrophils are recruited, and inflammatory cytokines, such as monocyte chemotactic factor, tumor necrosis factor (TNF), and interleukins (IL-1, IL-6, and IL-8), are released, which then leads to increased levels of neutrophil and lymphocyte infiltration.\(^15\) After a few hours of irradiation, monocytes differentiate into the M2 subset of macrophages that secrete transforming growth factor β (TGF-β), which is responsible for the differentiation of fibroblasts into myofibroblasts.\(^16\) In addition to the acute inflammatory responses,
there are immediate expressions of proto-oncogenes, including c-myc and c-jun, which may contribute to late fibrotic changes. These prior studies in other organ systems suggest that similar changes may also occur in the irradiated heart.

The latent phase begins approximately 2 days after radiation and involves the mild progression of fibrosis with the progressive injury of endothelial cells in the myocardial capillaries of the healthy pericardium and myocardium, which then results in stenosis of the lumen, thrombosis formation, myocardial cell death, and fibrosis. In addition, the proinflammatory surroundings that are induced by radiation are powerful stimulators of fibrosis, wherein myocardial fibroblasts are recruited from the endocardium, epicardium, neural crest, and bone marrow. These changes eventually lead to collagen deposition and endothelial cell proliferation. The extracellular matrix deposition by fibroblasts results in the late pathologic dysfunctions of myocytes, vascular endothelial cells, and the pericardium. On the other hand, ionizing radiation can induce the premature differentiation of fibroblasts. The premature differentiation cycles of fibroblasts that are exposed to ionizing radiation are shorter than that of naturally differentiated cells, thus resulting in an increase in postmitotic fibroblasts, which are five-to-eight times more active in secreting collagen and extracellular matrix than progenitor fibroblasts. The deposition of collagen and extracellular matrix components can produce a fibrotic scar that reduces the functionality of the affected tissue.

The late phase occurs approximately 70 days after radiation and involves extensive fibrosis in experimental animal models. The chronic effects of radiation on tissues of the heart lead to RIMF, and, eventually, result in a decrease in elasticity and distensibility, thus leading to a reduction in ejection fraction and cardiac failure.

Radiation-induced accelerated atherosclerosis is also a side effect of thoracic radiation therapy. In this situation, the exposure of macrophages to radiation produces inflammatory signals and induces the ingestion of lipids to transform into foam cells in the intima of the vessel wall. In the media, smooth muscle cells differentiate into myofibroblasts that secrete collagen and extracellular matrix, with these myofibroblasts subsequently entering the intima and leading to the formation of inflammatory plaques with high collagen and fibrin contents. Moreover, plaque formation that is induced by radiation may be more prone to rupture and intraplaque hemorrhage, with notably increased levels of macrophages and granulocytes and without elevated levels of systemic inflammatory markers, in the intima of mice. Lipid cores have been observed to be larger in female mice and slightly smaller in male mice. Moreover, the mid and distal left anterior descending arteries are primarily involved in RIMF.

Early screening and diagnosis for RIMF

Early radiation-induced heart toxicity is usually asymptomatic, but pathological damage still progresses. The early screening and diagnosis of RIMF is crucial for patients with thoracic tumors after RT. Serum cardiac biomarkers, including both troponin I (TnI) and brain natriuretic peptide (BNP) (which are markers of other forms of injury in the heart, such as necrosis or myocardial cell death), may be useful for assessing radiation-induced cardiac damage, and seem to be superior to the use of echocardiography. BNP levels do not become significantly elevated until 1 month after radiation, and these levels begin to decrease at 12 months after radiation in breast cancer patients. Furthermore, BNP levels have been observed to be associated with radiation-induced cardiac damage in 5-year breast cancer survivors after radiotherapy. The levels of BNP/NT-proBNP (typically >100 pg/ml/>300 pg/ml) indicate the risk of adverse events in all patients who are at risk for heart disease. Several studies have demonstrated that serum levels of TnI and BNP are correlated neither with cardiac radiation dose nor adverse cardiovascular events; however, these controversial conclusions may be related to the differences in time in measuring serum markers and doses of radiation.

Multimodality cardiac imaging, which involves the use of echocardiography, computed tomography, cardiac magnetic resonance, and nuclear cardiology, is recommended for the early identification and monitoring of cardiovascular complications of radiotherapy. The use of multimodality cardiac imaging depends on local expertise and availability, and the use of this method should adhere to the following principles:
(1) The combination of the uses of echocardiography and cardiac MRI is a very attractive method in the assessment of clinical cardiotoxicity.

(2) Modalities with the best reproducibility are preferred.

(3) Imaging modalities that provide additional relevant clinical information are preferred (e.g. the evaluations of right ventricular dysfunction, pulmonary pressure, valvular function, and pericardial evaluation).

(4) High-quality, radiation-free imaging is preferred, if available.

Electrocardiogram and echocardiography are the preferred tools used for the assessment of the cardiovascular complications of radiation because of the ability of these tools to assess the left ventricular ejection fraction, to provide the strain and strain rate that are used to distinguish constrictive and restrictive forms of cardiomyopathy, and to evaluate myocardial ischemia, right ventricular dysfunction, and valvular heart disease. In addition, advanced cardiac magnetic resonance can assess simultaneous functional and structural data, with regards to myocardial inflammation, stress-rest perfusion defects, and fibrosis. However, the uses of nuclear techniques and cardiac computed tomography are limited because of the radiation exposure to the heart. Cardiac catheterization can provide definitive data of the coronary artery anatomy and the pulmonary artery pressure with the risk of invasive instrumentation.

Multiple types of DNA damage-associated biomarkers are induced by radiation, such as cytogenetic (e.g. micronuclei, translocations, and dicentrics), proteomic (e.g. γ-H2AX, pATM, and pP53), genomic (e.g. mRNA and SNPs), and epigenomic (e.g. miRNA and lncRNA) biomarkers. These biomarkers are available for the monitoring of DNA damage and repair and can contribute to the early screening and diagnosis of RIMF. Recently, most of the fully automated and high-throughput analysis platforms available have been developed to detect and analyze the DNA damage-associated biomarkers for the evaluation of early radiation exposure. Although these markers have their own limitations for clinical applications, the changes in gene expression profiling upon radiation exposure occur in seconds to days, which may be potentially useful for the assessment of radiation exposure and the identification of radiosensitive patients. DNA damage-associated biomarkers can help clinicians in designing tailored biomarkers for cancer patients.

Extracellular vesicles, including microparticles, apoptotic bodies, and exosomes, which contain proteins, nucleic acids, and chemicals, are derived from the original cells of myocardial capillaries that are exposed to radiation, and can interact with the recipient cells via membrane surface receptors to mediate cell-to-cell communication, microRNA transfer, and radiation-induced, non-targeted effects. Different extracellular vesicles display characteristic expression profiles of mRNA and microRNA; therefore, the identification of characteristic molecules in the vesicles can be potential biomarkers of radiation toxicity in the heart.

**Novel drugs used to treat RIMF**

The mechanism of RIMF has not yet been fully elucidated, but it is known that fibrosis can ultimately lead to congestive heart failure, malignant arrhythmia, and, eventually, sudden cardiac death. RIMF can also result in isolated right heart failure or left ventricular diastolic dysfunction. The endothelium of the vasculature is the initial target of radiation damage. Thus, pharmaceutical interventions for the maintenance of endothelial function and for the reversal of fibrosis are potential treatment strategies for RIMF.

Several potential drugs for RIMF are listed in Table 1. All of the potential drugs for preventing RIMF have been investigated in preclinical studies, and there are only a few reports available in humans.

Currently, the antioxidant amifostine is approved in the United States for reducing the toxicities of cancer treatment in certain types of cancer. However, amifostine has several side effects, such as nausea and vomiting; therefore, it may not be very commonly prescribed for cancer patients. The use of amifostine as a potential countermeasure for RIMF can inhibit oxidative stress and delay myocardial fibrosis to maintain the endothelium of the vasculature. Amifostine administration prior to irradiation has been demonstrated to significantly decrease the development of vasculitis in the heart, to improve coronary flow, aortic
flow, and cardiac output, and to reduce cardiac histological damage. Other antioxidants, such as vitamin C and vitamin E, exhibit efficient cardioprotection in patients with malignancies at 3 weeks after RT. Furthermore, two randomized trials suggest that antioxidant vitamin supplementations can reduce acute adverse effects in patients with head and neck cancer during RT; however, caution is advised because antioxidant vitamin administration has been demonstrated to compromise the effects of tumor control during RT.

Angiotensin-converting-enzyme (ACE) inhibitors are known to be able to reverse adverse myocardial structural changes, and ACE inhibitors, such as captopril, can reduce radiation-related pleural and pericardial effusions to improve left
ventricular end-diastolic pressure in rats.\textsuperscript{37} However, captopril cannot improve the progressive deterioration of cardiac function after irradiation.\textsuperscript{54} There is no evidence to support the cardioprotective effects of ACE inhibitors with low-dose radiation. Similarly, based on the current preclinical data \textit{in vitro} and \textit{in vivo}, statins and hydroxy methylglutaryl coenzyme A reductase inhibitors can mitigate RIMF \textit{via} the inhibition of the TGF-β/Smad3/RhoA/ROCK, PI3K/akt signaling pathways and the expression of connexin-43 and miRNA-21 in rat heart,\textsuperscript{43,55} as well as \textit{via} the reduction in inflammation and the promotion of DNA damage repair that are induced by radiation.\textsuperscript{38} In addition, the use of atorvastatin has also been observed to reverse left ventricular remodeling and to prevent decreases in left ventricular ejection fraction.\textsuperscript{55} A retrospective analysis demonstrated that incidental statin use in patients with head and neck cancer during RT reduces the risk of cerebrovascular events,\textsuperscript{56} but there is a lack of data on the efficacies of the statins against cardiac radiation injury. Existing data indicate that statins can prevent RIMF.

A clinical trial revealed that colchicine diminishes infarct sizes in patients with ST-segment elevation myocardial infarctions by increasing the expression of interleukin-10 (IL-10) and by inhibiting the expression of TGF-β.\textsuperscript{57} Colchicine is a classic microtubule-disassembling agent that prevents antifibrotic effects and may be a new therapeutic alternative for the treatment of cardiovascular diseases.\textsuperscript{39} Due to its anti-inflammatory and anticoagulant properties, colchicine has been hypothesized to be a promising agent in the treatment of radiation-induced coronary artery disease; however, the side effects of this drug limits its long-term or higher dose use.\textsuperscript{58}

Fibrates, which are PPAR-α agonists, have a greater effect on decreasing serum lipoprotein levels than do statins.\textsuperscript{59} A meta-analysis of clinical trials revealed that fenofibrate adversely affects cystatin C levels and has a limited effect on reducing cardiovascular events.\textsuperscript{44} PPAR-α agonists demonstrate positive effects on both coronary heart disease and ischemic heart disease, but whether PPAR-α agonists are successful in treating RIHD remains to be determined. The anti-inflammatory effects of PPAR-α agonists are explicitly protective, whereas the promotion of systemic energy metabolism may be adverse because of the reduced cardiac lipid supply, which demonstrates a need to develop a tailor-made PPAR-α agonist treatment for RIMF.

A treatment combining pentoxifylline and alphatocopherol has previously been shown to reduce radiation fibrosis in the skin in clinical studies; therefore, these drugs have been selected for preclinical studies of radiation-induced heart disease.\textsuperscript{60} A combination therapy using pentoxifylline and alpha-tocopherol for the treatment of RIMF has a positive effect of ameliorating left ventricular function by downregulating the expression of TGF-β, both when this therapy is given before and during radiation.\textsuperscript{61} However, the withdrawal of the drugs after the 12th week of radiation can result in a rebound effect on the development of myocardial fibrosis.\textsuperscript{62} Sridharan subsequently reported that the use of pentoxifylline alone, or in combination with tocopherol, from 3 months to 6 months after irradiation cannot rectify myocardial fibrosis and can change intracellular signals. Moreover, the use of pentoxifylline alone adversely affects the rhythm of the heart after irradiation. Whether or not tocopherol reduces the numbers of mast cells and promotes the expression of tissue factors, which contribute to the prophylaxis of RIMF, remains to be established.\textsuperscript{43} These studies were performed in rat models of local heart irradiation.

New pharmacological drugs that inhibit radiation-induced heart toxicity after RT, such as sestrin2,\textsuperscript{40} IPW-5371,\textsuperscript{41} recombinant neuregulin-1 beta (rhNRG-1β),\textsuperscript{42} and miRNA-21 inhibitors,\textsuperscript{43} are being developed for the treatment of RIMF. Currently, these data are being collected from animal models.

Other interventions for the treatment of RIHD, including tocotrienols,\textsuperscript{46} molecular hydrogen,\textsuperscript{47} black grape juice,\textsuperscript{48} and thalidomide,\textsuperscript{49} have been tested (see Table 1).

**Cell therapies for RIMF**

National Institutes of Health/ National Institute of Allergy and Infectious Diseases (NIH/NIAID) and Institut de Radioprotection et de Sûreté Nucléaire (IRSN) workshops have reported that cell therapies have the potential ability to treat cardiomyocyte loss that is induced by RT.\textsuperscript{63} Human-induced pluripotent stem cells that are exposed to a low, average, absorbed dose of less than 10 Gy differentiate into beating cardiac myocytes, but the differentiation ability of pluripotent stem cells
declines with increasing radiation doses. A mesenchymal stem cell transplantation from the bone marrow ameliorates RIMF and reduces acute inflammatory reactions via DNA damage repair in a rat model. Cardiac stem cells are currently recognized as being ideal stem cells that regenerate and repair lesions in the heart. Under certain conditions, epithelial cells can transform into mesenchymal cells, in a process called epithelial to mesenchymal transition (EMT), and contribute to pulmonary fibrosis. Pluripotent stem cells commonly acquire TP53 mutations, which then increases the risk of cancer formation. How to choose the best cell therapy for use in cases of large-scale, heavily irradiated patients will be determined in future studies.

Future prospects
Based on the above results, we conclude that decreasing the direct radiation doses in the heart, as well as early screenings and diagnoses, are crucial to preventing RIMF. Medications remain a useful adjunct to prevent or treat RIMF. miRNAs and cell therapies appear to be highly promising as novel therapeutic targets for the mitigation or prevention of RIMF, and clinical trials will be required to test the potential interventions for radiation-induced heart disease.

RIMF is the final pathological process of RIHD. The exploration of the potential genetic changes of the human body in radiation environments may further reveal the pathological mechanism of RIHD. The combination of transcriptomics, proteomics, and metabolomics is an enviable tactic for identifying potential biomarkers and therapeutic targets for RIHD. Our knowledge of the new pathophysiology and therapeutic approaches for RIMF may contribute to the prophylaxis and therapy of radiation-induced heart toxicity.

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