REVIEW

Pathogenesis and Prevention of Radiation-induced Myocardial Fibrosis

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Abstract

Radiation therapy is one of the most important methods for the treatment of malignant tumors. However, in radiotherapy for thoracic tumors such as breast cancer, lung cancer, esophageal cancer, and mediastinal lymphoma, the heart, located in the mediastinum, is inevitably affected by the irradiation, leading to pericardial disease, myocardial fibrosis, coronary artery disease, valvular lesions, and cardiac conduction system injury, which are considered radiation-induced heart diseases. Delayed cardiac injury especially myocardial fibrosis is more prominent, and its incidence is as high as 20–80%. Myocardial fibrosis is the final stage of radiation-induced heart diseases, and it increases the stiffness of the myocardium and decreases myocardial systolic and diastolic function, resulting in myocardial electrical physiological disorder, arrhythmia, incomplete heart function, or even sudden death. This article reviews the pathogenesis and prevention of radiation-induced myocardial fibrosis for providing references for the prevention and treatment of radiation-induced myocardial fibrosis.

Keywords: RIHD- pathogenesis- cytokine- ROS- calcium overload- prevention

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Introduction

Radiation therapy is a series of biological effects produced by ionizing radiation on an irradiated tumor tissue. It is an indispensable means of tumor therapy. However, radiation therapy on tumor and normal tissues in human organs can also produce different degrees of damage. Until the 1960s, the heart was thought to be an organ with radiation resistance; by the 1990s, radiation-induced heart diseases (RIHD) were being taken more seriously due to the early heart disease caused by the side effects of radiotherapy despite its benefits (Gagliardi et al., 2001). At present, there is still a lack of effective treatment for RIHD. The basic reason is that the causes and pathogenesis of RIHD have not been fully clarified.

The pathogenesis of radiation-induced myocardial fibrosis
Vascular damage

Radiation-induced vascular damage is the fundamental cause of myocardial fibrosis. Radiation can act on endothelial cells of the myocardial capillaries, causing them to proliferate, become injured, swell, and degenerate. Vascular intimal collagen deposition can cause pipe wall thickening and luminal stenosis, and therefore the number of capillaries and the proportion of myocardial cells are considerably lower after irradiation. The deposition of collagen is also the reason for the capillary luminal stenosis, thrombosis, and the reduction of myocardial blood supply, resulting in myocardial ischemia and fibrosis (Du et al., 2015). Endothelial cells can be compensated for and regenerated, but the capillary network cannot be reconstructed (Carr et al., 2005).

Inflammatory response and cytokines

Radiation-induced myocardial fibrosis is the result of a multicellular interaction. After irradiation, the swelling of the endothelial cells induces early acute inflammation (in the first few minutes of ionizing radiation), for example, neutrophil infiltration and macrophage and monocyte activation, thereby promoting the release of cytokines such as TNF, IL-1, IL-6, and IL-8. After a few hours of irradiation, pro-fibrosis cytokines such as bFGF, IGF, CTGF, PDGF, and TGF-β are released (Taunk et al., 2015). TGF-β1 is known to be the most closely related to the development of tissue fibrosis, and it has the functions of regulating cell growth and differentiation, promoting cell proliferation, inhibiting inflammation, and so on. This cytokine plays an important role during radioactive myocardial fibrosis, which is mainly manifested in the close relationship between the TGF-β1/smads signaling pathway and the SMADs protein family (Yu et al., 2015). CTGF is a secreted peptide found in human tissues and organs and is closely related to diseases such as coronary artery disease and organ fibrosis. CTGF and TGF-β1

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have many similar biological functions, where CTGF is generally considered to be the downstream mediators of TGF-β1 and to play an important role in the process of myocardial fibrosis (Chen et al., 2000). At present, some researchers believe that CTGF mainly functions as an intermediate link for other factors, thus playing a role in myocardial fibrosis, while the role for directly induced fibrosis is not as evident (Leask, 2010). Although some cytokines promote the aggregation of inflammatory cells and pro-fibrosis cells, some cytokines such as IL-1 can be used as tissue radiation-protective agents. In addition to the acute inflammatory response, a high level of expression of some proto-oncogenes (c-fos, c-myc, c-jun, etc.) is observed, which may contribute to the change to advanced fibrosis (Taunk et al., 2015). Inflammatory pathways may be the major pro-inflammatory mediators, but other pathways also play an important role. However, it is far from enough to simply block one of these pathways to yield clinical benefits (Rodemann et al., 1995; Gyenes, 1998).

Coagulation change and platelet activation

In addition to inflammation mediated by upregulation of proinflammatory molecules leading to endothelial injury, coagulation and platelet activity alterations have also been observed following radiation exposure. A number of studies have reported an increased deposition and/or release of von Willebrand factor in endothelial cells 5 h after total body irradiation with a 4-Gy dose, or 16 months after heart irradiation with a 15-Gy dose. These changes eventually lead to platelet adhesion and thrombosis in the capillaries and arteries (Verheij et al., 1994; Boerma et al., 2004; Farias et al., 1997). These observations are also consistent with animal model data, indicating an inflammatory, thrombotic plaque phenotype following high-dose radiation exposure. This proinflammatory environment coupled with collagen deposition and increased recruitment of leukocytes and fibroblasts results in tissue remodeling, cardiac fibrosis, and atherosclerosis, which is a major endpoint of RIHD (Stewart et al., 2006; Cottin et al., 2001; Pakala et al., 2003; Hoving et al., 2008).

Oxidative stress

Free radicals and reactive oxygen species (ROS) are the important products of ionizing radiation on biological systems, where oxidative stress plays an important role in the mechanism of radiation effects. Substantial evidence indicates that chronic or acute overproduction of ROS is of great significance in the pathogenesis of cardiovascular disease. ROS can inactivate NO and the other vascular protective agents to prevent platelet aggregation, resulting in vascular endothelial dysfunction, and then induce or aggravate the occurrence of radiation-induced myocardial fibrosis. At the same time, oxidative stress directly induces the production of inflammatory factors, which can further increase the degree of radiation-induced myocardial fibrosis. NF-κB is a protein complex that controls DNA transcription and participates in the cell's response to stress, and it is a key link in oxidative stress and inflammatory pathways (Taunk et al., 2015).

Calcium overload

Recent research on the application of the pyroantimonate acid potassium molecular-probe technology to determine calcium distribution in myocardial cells shows that one of the early changes caused by irradiation is the increase in the permeability of cell membrane. This will lead to changes in the intracellular environment and induce cell edema as well as mitochondrial swelling, and the membrane damage will also cause abnormal functioning of membrane ion pump and intracellular calcium overload, leading to myocardial injury (Liu et al., 1993). Intracellular calcium can induce the proliferation of cardiac fibroblasts. Angiotensin II increases intracellular calcium by activating the calcium channel on the fibroblast membrane. The expression of collagen type I and type III is enhanced, which further promotes the progression of myocardial fibrosis (Wang et al., 2012). Although its specific mechanism is not very clear, from the current level of research, it is possible that the intracellular calcium acts as a secondary messenger, affecting the formation of fibroblasts and promoting their proliferation. Furthermore, calcium ions play a role in promoting myocardial fibrosis by participating in some signal transduction pathways, which can promote the development of myocardial fibrosis.

Endoplasmic reticulum and mitochondria

The large amount of ROS generated by the radiation is one of the important reasons for endoplasmic reticulum stress (ERS) induced by the unfolded protein response in the endoplasmic reticulum (Malhotra et al., 2008). In oxidative stress induced by ERS during radiotherapy, calcium ions are released from the endoplasmic reticulum into the cytoplasm, and the level of calcium ions is increased, which causes calcium overload. Because the endoplasmic reticulum and mitochondria are close to each other, they interact with each other. The mitochondria, which produce ROS, may make the lipid on the endoplasmic reticulum superoxide and destroy the protein in the endoplasmic reticulum. The endoplasmic reticulum produces a small amount of ROS, and calcium from the endoplasmic reticulum is released into the cytoplasm, where it can cause a decrease in the mitochondrial membrane potential, inhibition of the respiratory chain, and accelerate the production of superoxides. This triggers the opening of the mitochondria membrane openings, causing a waterfall-like cascade, which results in a large amount of ROS. ROS further make the calcium release from the endoplasmic reticulum calcium pool, leading to calcium accumulation in the mitochondria, which in turn increases the ROS generation. The amplification of oxidation shock and calcium overload will trigger a vicious cycle and result in a large number of ROS. It is speculated that ROS produced by the irradiation makes a connection between ERS and the function of mitochondrial, while there are still some unknown details to be studied further.

Detection of radiation-induced myocardial fibrosis

Diagnosis of radiation-induced myocardial fibrosis (RIMF) is challenging because there are no specific symptoms and examinations. Traditional investigations

including CT, MRI, and echocardiography can only detect the stiffness of the myocardium when myocardium fibrosis occurs in the later stage. Recent studies have revealed that a high FDG uptake in the irradiation field of the myocardium can be detected with 18F-FDG PET/CT imaging 3 to 6 months after the irradiation. Another method of detection is endomyocardial biopsy. Roman et al., (1978) reported one case of right heart catheterization, where simultaneously, the right ventricular endocardium successfully underwent biopsy or was observed by an optical microscope or electron microscope, and myocardial fibrosis was finally confirmed after radiotherapy.

Prevention of radiation-induced myocardial fibrosis
Improvement in radiotherapy techniques

(1) Three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiation therapy (IMRT): 3D-CRT result in a 50% reduction of the average excess cardiac mortality risk in the left-sided cases. (Muren et al., 2012). IMRT can also significantly reduce the dose of radiation to the heart (Nguyen et al., 2011). (2) Respiratory gating techniques: This is the use of audio-visual guide image features to reduce the radiation dose of the heart and lungs after radiotherapy for malignant tumors of the chest. (3) Spiral CT radiotherapy: Studies (Mast et al., 2013) have shown that for patients with esophageal cancer radiotherapy, the average dose to the heart was 12.4 Gy and 18.3 Gy with spiral CT and 3D-CRT, respectively. (4) Deep inspiration breath-hold (DIBH): Treatment techniques involved in respiratory motion can further reduce the exposure of the heart during the ionizing radiation (Smyth et al., 2015). DIBH causes changes in the internal anatomy of the thorax, from which the distance between the heart and the target may be increased to spare the heart dose in the tangential field for a protective effect (Giraud et al., 2006; Maurer et al., 2004).

Drug
Bosentan and pentoxifylline

Boerma (Boerma, 2012) detected the role of mast cells in RIHD by using mast cell-deficient rats in vivo; ectopia cordis function showed more serious and more substantial myocardial type-III collagen deposition and less myocardial degeneration when mast cell-deficient rats were compared with their mast cell-competent littermates after local heart irradiation. It can be concluded that mast cells play a significant and protective role in RIHD of rats. Mast cells may also show protective properties by releasing proteases that break down endothelin-1 (ET-1) (Lu et al., 2000). ET-1 is a 21-amino acid peptide that was first discovered as a potent vasoconstrictor but also has proinflammatory and pro-fibrotic properties (Yang et al., 2005; Kedzierski et al., 2001). The role of ET-1 in cardiovascular pathology has been studied extensively (Cernacek et al., 2003; Ertl et al., 2004). Bosentan is a dual inhibitor of the ET-1 receptors ET_A and ET_B. The effects of bosentan on late cardiac radiation injury in rats were minimal, which may have been caused by the opposing roles that ET_A and ET_B are known to have in cardiovascular function and disease (Boerma et al., 2008; Clozel et al., 1992). Another pharmaceutical intervention that Boerma is testing is the cyclic AMP phosphodiesterase inhibitor pentoxifylline. Studies suggest that pentoxifylline in combination with α-tocopherol can improve cardiac function and reduce adverse cardiac remodeling in rats when administration starts before irradiation and when administration starts several months after local heart irradiation (Boerma et al., 2008).

Angiotensin-converting enzyme inhibitor (ACEI)

Apart from their hypotensive action, ACEI is known to have other functions such as an anti-inflammatory action (Fanotone et al., 1982). It might act as an antioxidant to reduce inflammatory ROS and thus mitigate radiation-induced toxicity. A study from Sonja et al. (van der Veen et al., 2015) suggests that acute cardiac injury is a risk factor for the development of RIHD, but the ACEI captopril can reduce acute heart injury and improve heart and lung function. Interestingly, RIMF that occurs much later can also be reduced by captopril (Yarom et al., 1993). Therefore, ACEI provides a new method for the prevention and treatment of RIHD.

Traditional Chinese medicine

With the development of biological science and technology since the middle of the twenty-first century, experimental studies on the use of traditional Chinese medicine for treating myocardial fibrosis have made great achievements. Chinese researchers have conducted a number of cellular-, molecular-, and genetic-level studies on the mechanism by which traditional Chinese medicine affects myocardial fibrosis. Research studies on the renin-angiotensin-aldosterone system, cell growth factor, immunity, inflammation, oxidative stress, apoptosis, and other mechanisms have been carried out. Li YC et al. (Li et al., 2012) reported that Shenqi Yiqi pellets inhibited myocardial fibrosis and ventricular remodeling by interfering with the inflammatory response of the ascending aorta in rats. Chang WJ (Chang et al., 2013) found that tanshinone IIA alleviated myocardial fibrosis in pressure-overloaded rats, and it may be related to the inhibition of Rho-associated coiled-coil protein enzyme 1 expression and downregulation of TGF-β1 and NF-κB p65 levels. Puerarin significantly decreased the expression of TGF-β1 and NF-κB and plays a role in myocardial fibrosis (Chen et al., 2012).

RIHD has become an important source of morbidity and mortality in patients undergoing thoracic radiotherapy for cardiac injury. It encompasses a wide range of clinical manifestations and severe degrees of damage, which occur mainly in the microvessels. Although RIHD subclinical abnormalities are progressive and found early, RIHD's clinical symptoms appear 10 years after the end of radiotherapy. At present, the effective approaches for treating RIHD are limited, mainly because the etiology and pathogenesis have not been fully clarified. Therefore, further studies are required to explore RHID's mechanism, prevention, and treatment through additional experimentations and clinical observations.

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