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Commentary Open Access

Disentangling the Mechanisms of Radiation-Induced Heart Disease in the Treatment of Breast Cancer

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Commentary

The Clinical Problem

Early diagnosis and new treatment approaches have revolutionized the outcomes for women with breast cancer. Cancer-related mortality as well as disease recurrence has declined significantly [1]. Current successes are based on a multidisciplinary approach including surgery, systemic therapy and radiation therapy (XRT).

The use of XRT as adjuvant therapy provides a significant reduction in cancer recurrence. Despite these encouraging trends, however, overall mortality has decreased less than anticipated and remains unacceptably high as evident from childhood cancer patients treated for solid tumors and Hodgkin's lymphoma [2].

Clinical studies have shown that breast cancer patients treated with XRT have a significantly higher long-term (10-20 year) risk of cardiac death [3,4]. It has been estimated that XRT added to surgery reduces the cancer recurrence by 15% in 10 years and reduces the cancer-related mortality by 3.8% at 15 years [1]. However, in the same study the addition of XRT increased cancer-unrelated mortality by an absolute 0.8% vs surgery alone. This suggests that for every 4 patients that were saved from cancer-related death by XRT, 1 additional patient died of cancer-unrelated causes due to adverse effects of XRT (Figure 1) [1].

This concept, once considered paradoxical, is now viewed as a call for a change in treatment paradigm. The goal is to refine the intervention in order to maintain the anti-cancer efficacy while limiting the potential life-threatening toxicities and/or develop strategies to identify and treat early complications of breast cancer treatment. The ultimate is to have treatment strategies that will not compromise overall survival, while improving cancer-free survival.

Radiation-induced Cardiomyopathy

Radiation-induced cardiomyopathy is characterized by an impairment in left ventricular (LV) resting systolic function, contractile reserve, compliance and filling pattern, increased interstitial fibrosis, pericardial and valvular thickening, degeneration of the conduction system and premature or accelerated atherosclerosis (Figure 2)[5-8].

Historically, acute radiation injury consisted of acute pericarditis with or without myocarditis, and heart block due to injury to the conduction system. These effects were often transient. With the improvement in the radiation therapy, main side cardiac effects like acute pericarditis are now rarely seen, making the acute injury more commonly a subclinical effect [9]. Preclinical studies have shown that the initial injury initiates a series of events that culminate in the chronic changes observed in late radiation-induced cardiomyopathy [5,10-12]. In experimental models, myocardial and pericardial injury can be detected within days of treatment and is characterized by cell death and a reactive inflammatory response [10-12]. An impairment in cardiac function is evident in the acute and subacute phases, as a result of impaired contractile reserve [5,10]. In contrast to the acute injury, the late presentation of radiation-induced cardiomyopathy is related to a reparative fibrotic response in the pericardium, myocardium and valvular structures [6,13,14]. Radiation also accelerates atherosclerosis of the coronary arteries and increases the risk of obstructive coronary artery disease, acute myocardial infarction, and ischemic cardiomyopathy [6-8,14]. An analysis of myocardial fibrosis using cardiac magnetic resonance (or pathology) distinguishes the diffuse fibrotic response with preferential epicardial distribution seen with radiation injury from the regional subendocardial fibrotic response associated with acute myocardial infarction [15,16]. Progressive fibrosis leads to impaired diastolic function, which can culminate in constrictive pericarditis (if the pericardial fibrosis dominates), restrictive cardiomyopathy (if the myocardial fibrosis dominates), or a combination of the 2 forms [6]. Significant valve dysfunction from fibrosis is quite rare, while the effects of radiation injury on arrhythmias have not been completely characterized.

The mechanisms underlying radiation-induced cardiomyopathy

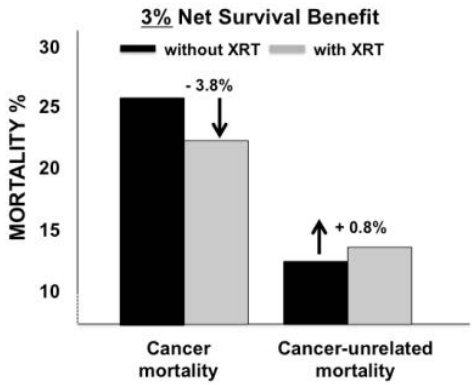

Figure 1: Effects of adjuvant radiation therapy (XRT) on cancer-related and cancer-unrelated mortality in patients with breast cancer. The addition of radiation therapy (XRT) to breast conserving therapy led to a reduction in cancer-related mortality, but increased cancer-unrelated mortality.

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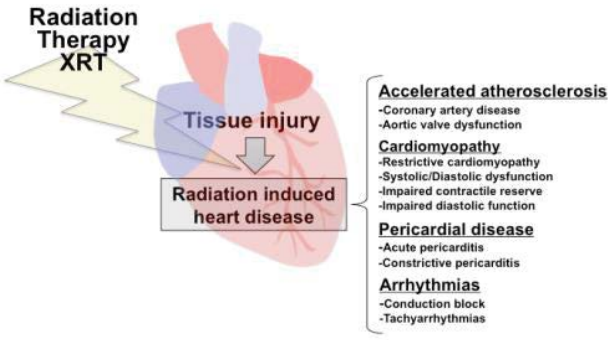

Figure 2: Effects of radiation therapy on the heart. Radiation therapy (XRT) involving the heart induces myocardial and vascular injury, accelerating atherosclerosis (coronary artery disease and/or aortic valve dysfunction), causing cardiomyopathy (impairment of systolic and diastolic dysfunction), pericardial disease (constrictive pericarditis), and arrhythmias (conduction blocks and tachyarrhythmias).

remain poorly understood, and the disease appears to be rather complex. Heart failure (HF) is the final common pathway of a variety of cardiac conditions and disease. Injury to the heart induces a reparative response that activates the inflammatory response, promoting healing and fibrotic repair [17,18]. The severity of the response following radiation injury is dose related, as would be expected [10].

The radiation injury has been defined as a 'wound that never heals' [19]. From preclinical studies the initial injury to the heart seems to be mediated by the endothelial damage and this in accordance with increased risk of developing coronary artery disease [12,14]. Endothelial dysfunction favors the homing of leukocytes thus increasing the local production of pro-inflammatory cytokines, as Interleukin-1 (IL-1), IL-6, IL-8, Tumor Necrosis Factor-α (TNF α) and chronic activation of the key transcription factor Nuclear Factor κB (NF-κB) [14]. The acute inflammatory response to radiation injury appears to be mediated, at least in part, by the release of active Interleukin-1β (IL-1β) [10]. IL-1β induces an acute impairment in cardiac contractility within days of the initial radiation injury [10], as seen with other models of ischemic and non-ischemic injury [20].

The pro-fibrotic pathways are initiated in the acute phases of radiation-induced damage with late effects [14,19,21]. We have recently shown that this late fibrotic response is distinct and independent of the IL-1β mediated inflammatory response [10]. In fact, this late fibrotic response involves a progressive increase in myofibroblasts and accumulation of extracellular collagen [14,19,21], mediated, in part, by pro-fibrotic factors such as matrix metalloproteinases, Transforming Growth Factor-β (TGF-β) or Interleukin-18 (IL-18) [14,19,21,22]. The signals that may independently induce the initial inflammatory response and the late fibrotic response are currently undefined.

The preclinical studies may offer a valid platform to test potential therapeutic strategies to limit cardiac injury targeting these key signals and potentially reduce the cancer-unrelated mortality in breast cancer survivors. Current animal studies are mainly developed in tumor free subjects thus representing a limitation in the comprehension of the concomitant effects of therapies on tumor growth and cardio-protection.

Monitoring Radiation-induced Injury

Refinements in the XRT techniques, such as respiration management and more conformal dose delivery, allow for treatment schemes to be modified to reduce heart exposure [23]. With computed tomography (CT)-based radiotherapy planning, three-dimensional (3D), volumetric data and electron density information of the treatment area have become available. These are required for accurate dose calculation of the target volume and normal tissues to reduce damage in organs such as lungs and heart [6]. Other techniques as 'intensity modulated RT' or 'proton and charged particle therapy' are all focused on delivering the maximal dose to the target and minimize the dose to healthy tissues [6,24,25]. However, the effective benefit of these new techniques on long-term cardiac complications has not been evaluated yet. The heart is rarely entirely spared, and portions of the heart are often exposed to radiation treatments. Recent investigations have clearly shown a relation between radiation dose to the heart and long-term toxicity [3]. Even total doses of 2 Gray (Gy) or less were associated with an increase in the rate of cardiac events [3].

While new techniques have undoubtedly led to a reduction in acute XRT toxicity and encouraging reduction of the incidence of HF in a mid-term follow up [26], it is important to realize that clinically manifest XRT-induced cardiomyopathy is a late occurring event (often >10-20 years).

Commonly used tools to assess cardiac function (i.e. left ventricular ejection fraction [LVEF]) are notoriously insensitive to minor injury, and are thus unable to fully capture the extent of acute radiation-induced injury. Introducing more sensitive and quantitative protocols in the monitoring of breast cancer patients after radiation treatment may be helpful in identifying subjects at risk. Cardiac magnetic resonances (CMR) with delayed gadolinium-enhanced contrast allow detecting areas of loss of vascular integrity, edema or fibrosis and thus quantify the entity of the injury, even if small [15]. Cardiac structure abnormalities detected with cardiac imaging should also be correlated with biomarkers such as high-sensitivity cardiac troponin T and I assays or natriuretic peptides already been used to detect subclinical myocardial injury in patients undergoing chemotherapy [27-31].

Systemic Response in Radiation Treatment for Cancer

Despite the progress in cancer treatment, and the improved overall survival, many patients with breast cancer have impaired exercise tolerance/fatigue. The mechanisms underlying these limitations are not understood. Fatigue and impaired exercise tolerance in these patients are at least in part, independent of the treatment received, XRT versus chemotherapy [32,33].

Exercise intolerance and fatigue are also seen in various types of cancers, ranging from brain to colon cancer [32], and patients receiving radiotherapy are more likely to experience symptoms of fatigue [32,34-36], These effects seem to be mediated by a systemic rather than localized response (Figure 3), a positive correlation has been observed between inflammatory markers and fatigue in cancer patients undergoing radiotherapy [34-36].

Systemic inflammation has been associated with transient cardiac dysfunction and HF through the action of soluble 'cardiodepressant factors' [20,37-39]. Intriguingly, 'out of target' effects of radiation ("abscopal effects") have been reported in patients with different types of cancer (localized or not in the mediastinum) [40-42], but these effects are not well characterized. It is necessary to define the mechanisms of the systemic response to radiation treatment for cancer, the role of inflammation and its correlation with fatigue and exercise intolerance.

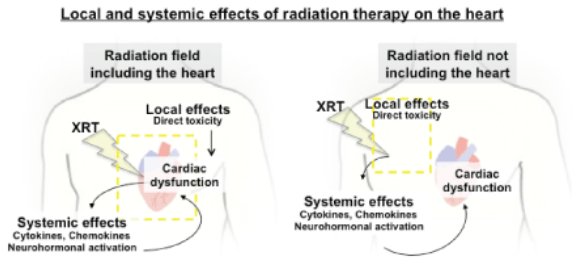

Figure 3. Local and systemic effects of radiation therapy on the heart. Radiation therapy (XRT) involving the heart in the radiation field (yellow) on the left induces myocardial injury mediated by the direct effects of the radiation on the heart. This results in a local inflammatory response, with production of soluble inflammatory mediators that act in an autocrine or paracrine fashion on cardiac resident cells inducing further cardiac dysfunction. Radiation therapy sparing the heart (right) has no direct cardiotoxicity, but induces a systemic inflammatory response that can also impair cardiac function.

Conclusions

The past decades have been characterized by a success in the treatment of breast cancer and abatement of cancer-related mortality. Breast cancer survivors, however, have still a significantly higher cancer-unrelated mortality, often due to increased cardiovascular disease; survivors also have significant impairment in quality of life, primarily related to fatigue and exercise intolerance. Radiation-induced cardiomyopathy is a clinical syndrome of impaired cardiac function following radiation treatment. There is an urgent need for a coordinated multi-disciplinary effort to better understand the cellular and molecular mechanisms of radiation-induced cardiomyopathy, to develop more sensitive tools to detect early injury and monitor for progressive disease, and to develop novel therapeutic strategies to preserve or improve cardiac function in breast cancer patients treated with radiation therapy.

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