Chapter X: Late Radiation Effects

Section d: Cardiac

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A prominent late effect of thoracic ionizing irradiation is that associated with the cardiovascular system. In clinical radiation oncology, there is concern for late cardiac effects in long-term surviving patients treated for Hodgkin's, lymphoma, and breast cancer. There have been increasing reports showing clear evidence of late cardiac damage. As with many other late clinical radiation therapy side-effects, damage has been found to increase with total dose, fraction size, and the relative volume of tissue treated. Attention to the late radiation effects in patients has become extremely important given the large number of late survivor patients, who were treated in the 1960s, 1970s, and 1980s, and who have lived for decades after completion of radiotherapy. These survivors are clearly experiencing radiation late effects including those involving the heart.

With respect to total body irradiation (TBI) and late effects involving cardiac damage, recent evidence from the Late Effects Core of the Duke Center for Medical Countermeasures Against Radiation (CMCR) based at Wake Forest University has indicated a significant incidence of cardiac effects in total body irradiated Rhesus Macaque monkeys followed for years after TBI or Thoracic irradiation (see Chapter X, Section G: by Mark Cline and Gregory O'Dugan). The observation of cardiac fibrosis occurs in animals some of which have simultaneous pulmonary late radiation damage.

All these data relate to the goal of development of radiation countermeasures for potential application to total body irradiated individuals, who survive a radiation terrorist event. An understanding of the pathophysiology of cardiac radiation damage is now required to guide researchers in developing both biomarkers for cardiac radiation injury, targeted therapies to mitigate potential cardiac damage, and agents to ameliorate cardiac toxicity.

This chapter will review the relative basic science experiments relevant to radiation cardiac damage including those in rodent and canine models and will focus on recent reports of cardiac injury in both Hodgkin's disease and breast cancer patients, who received radical/curative radiotherapy. As with many other chapters in this textbook, the present chapter will focus on methodologies for continuing research in this area, and guidelines for the development of countermeasures based on the known pathophysiology of radiation-induced organ damage.

Cell Culture and Animal Model Studies of Cardiac Damage

Endothelial cell damage from irradiation has been a subject of intense research in past decades (1). Endothelial cells demonstrate a classic radiation damage response in which nuclear DNA strand breaks lead to communication to the mitochondria of signals initiating apoptosis, and also upregulating the mRNA for both stress response genes and inflammatory cytokines. Secretion of inflammatory cytokines by endothelial cells initiates inflammatory cell responses including arrival in endothelium of neutrophils and macrophages, as well as, subsets of T-cells. Given the oxidative lipid responses to irradiation, the involvement of pathways for both local cardiac and distant (abscopal) effects of cardiac irradiation are significant and depend upon irradiation dose, volume treated, and fraction size.

Rodent models of radiation damage demonstrated acute effects involving cardiac muscle function (decreased heart volume, decreased muscular action in ventricular outflow, and

associated sequella of the inflammatory response) (2-6). There has been relatively little published data with respect to ionizing irradiation acute changes that involve the cardiac conduction system leading to arrhythmias or abnormal electrocardiogram findings. In contrast, most information on acute cardiac toxicity has been reported in rat and mouse models and relates to detection of inflammatory cytokines in peripheral blood, as well as, signs of muscle injury that is related to cardiac output, and release of cardiac damage associated molecule (SGPT, SGOT, TREPONIN).

Canine models of radiation injury have confirmed the acute effects of radiation with respect to cardiac output, decreased muscle function, and inflammatory cytokines (7).

In all animal models studied, the relative resistance of the heart to acute effects has been attributed to the richness of mitochondria in cardiac muscle (8-10). The oxidative metabolic requirements of cardiac muscle function will require large numbers of mitochondria per cell to generate ATP for metabolism. Direct effects of irradiation on the mitochondria have been reported in multiple tissue culture systems, and in studies of the bone marrow and intestine. However, relatively little published information is available on irradiation effects on cardiac mitochondria. While acute effects of irradiation on the heart relate to late effects, it is a subject of intense interest.

Research by Hauer-Jensen and collaborators has demonstrated a role of mast cells and other inflammatory cells in cardiac damage in animal models (3-4). How these subacute effects relate to cardiac late effects is not known.

Late effects of cardiac irradiation in animal models include the development of fibrosis. As with the fibrotic response in other tissues and organs, a component of both proliferation of fibroblasts and transition into myofibroblasts has been documented in the irradiated heart. The arrival in irradiated heart of fibroblasts of bone marrow origin has not been reported, as has been the case with irradiated lung (46). Cardiac fibrosis is associated with decreased capacity of cardiac myocytes to function and results in reduced cardiac functions. Multiple categories of cardiac damage have been observed in thoracic irradiated patients (10-21). Late cardiac arrhythmias have been reported in irradiated patients. Cardiac conduction system abnormalities including arrhythmias have been reported in animal models (10) and in thoracic irradiated patients (12, 18) followed for years after completion of radiotherapy. Finally, cardiac vascular injury has been a prominent source of concern leading to myocardial infarction, decreased perfusion through abnormalities in the microvasculature, and late effects that involve vessel fibrosis and increased atherosclerosis (12-21).

Total Body Irradiation Effects on the Cardiovascular System

Recent publications from Mark Cline and John Olson of Wake Forest have documented late cardiac fibrosis in total body irradiated Rhesus Macaque monkeys, not necessarily correlated with pulmonary fibrosis (See Chapter X, Section g) in this web-based textbook. While there have been multiple dose cohort groups studied, a clear dose response curve has not been observed. There was a trend toward increased frequency of cardiac fibrosis in monkeys that had received the higher 9.0 Gy total body dose compared to others that received 7.0 or 7.5 Gy.

Multi-system late effects disorders have been documented in these studies, and suggests that radiation late effects in organs outside the heart may contribute to cardiac fibrosis.

Cardiac Late Effects in Hodgkin's Disease Patients

In the 1960s, 1970s, and 1980s, mantle irradiation was widely utilized to treat early stage Hodgkin's disease from stages IA through stages IIIB. Despite the advent of combination chemotherapy, principally, the MOPP regimen (Methotrexate, Oncovin, Procarbazine, and Prednisone), many Hodgkin's disease patients continued to receive mantle irradiation, sometimes followed by periaortic irradiation including the splenic pedicle, and in IIIA and IIIB, total nodal irradiation consisting of one month of thoracic irradiation followed by one month of abdominal periaortic irradiation, and another month of pelvic irradiation (14-16). The majority of patients present with Hodgkin's disease in cervical, supraclavicular, and mediastinal lymph nodes. Based on staging systems elegantly described by Henry Kaplin and colleagues, the application of mantle irradiation was widely applied (14-16). In some studies involved field radiation, which eliminated the cardiac volumes was used. During these decades, the late effects of irradiation on the heart were not anticipated, and the fractionated dose of 36 – 40 Gy over 3-4 weeks usually delivered in 2.0 Gy per day fractions by opposed anterior and posterior fields was felt to be well tolerated.

The mantle blocks for thoracic node irradiation in Hodgkin's disease patients that were carefully drawn to protect lung tissue, while including all mediastinal lymph nodes and those in the hilar regions included a careful effort to block as much of the left ventricle as possible under the left lung block. However, patients received full dose radiation to right ventricle, both atria, and in some cases, where large mediastinal or hilar nodes were noted, they did receive an initial two or three weeks of irradiation into the entire cardiac volume (14-16). In patients receiving concomitant chemotherapy, cardiac and pulmonary toxicity was carefully monitored in follow-up over decades after curative treatment. The large number of patients surviving 20 to 30 years after completion of mantle irradiation provide a large cohort of individuals at risk for cardiac late effects (14-16). Included in this patient cohort was a significant number of pediatric Hodgkin's disease patients (12-13, 34-40), who received mantle irradiation with or without chemotherapy.

Case reports of cardiac damage, principally, congestive heart failure and cardiac arrhythmias were published in the 1990s, and large series documented clear evidence of cardiac late effects (12-21). The late effects of mantle irradiation on the heart were contributing factor to the elimination of routine mantle irradiation for Hodgkin's disease patients. This decision was based on the availability of a second combination chemotherapy regimen, ABVD (Adriamycin, Bleomycin, Vincristin, and Dethamexasone) which was alternated with MOPP. Both regimens have been scaled back to reduce toxic effects of chemotherapy, but still cure Hodgkin's disease. Hundreds of late survivors of mantle irradiation are being followed and continually show cardiac late effects, principally, cardiac fibrosis (14-16). As with other clinical radiation late effects in other organs and organ systems, the total radiation dose, fraction size, and volume of the organ treated are clearly associated with increase in cardiac radiation damage.

Given the highly significant reports of cardiac damage from mantle irradiation, the now significant reports of cardiac damage from total body irradiation in Rhesus Macaque monkeys,

and recent evidence of potential cardiac toxicity in thoracic irradiated lung cancer patients (47-49), there is an effort to reduce or eliminate cardiac irradiation in all patients, who need thoracic radiotherapy. The current availability of Intensity Modulated Radiotherapy and Stereotactic Radiosurgery for boost treatment facilitates this approach to lung cancer and esophagus cancer patients, as well as, those with other thoracic malignancies such as thymoma, sarcoma, and neuroendocrine tumors.

Cardiac Late Effects from Breast Cancer Irradiation

Large numbers of women treated for breast cancer with tangential fields including in some the "hockey-stick" (mediastinal lymph nodes with ipsilateral, supraclavicular node irradiation approach) have presented with late effects of irradiation involving cardiac toxicity (22-33). The presenting findings of cardiac arrhythmias, congestive heart failure, and myocardial infarction are in the same categories as those involving Hodgkin's disease patients. Initial reports suggested an increased incidence of cardiac late effects in those patients treated for left sided breast cancer, and was thought to be associated with the left ventricular volume in the tangential field. Other reports suggested that late cardiac damage was also common in patients treated for right sided breast cancer. Evaluation of isodose curves in these treatment plans for patients treated in the 1970s, 1980s, and 1990s, revealed complete evidence of cardiac volume directly related to severity of late cardiac side effects and suggested potential out of field radiation effects (abscopal effect).

Vascular effects of irradiation to a large arterial and venous blood supplies in the irradiation field for right sided, as well as, left sided breast cancer management may have contributed to late cardiac effects. Patients receiving definitive radiotherapy after lumpectomy and/or axillary node sampling usually received 50 Gy by tangential fields in 1.8 – 2.0 Gy per day fractions over 4 ½ to 5 weeks. Some of these patients received internal mammary nodal irradiation and others also supraclavicular node irradiation. In other patients treated during these decades, post-operative radiation (30, 33) was used if resection margins of mastectomy showed tumor close to the chest wall or in some patients large number of nodes were detected in the resection sample requiring post-operative axillary volume boost and/or supraclavicular boost. Some patients received mediastinal/internal mammary node irradiation, which involved the heart. Cardiac toxicity was observed in those patients receiving post-operative radiotherapy, as well as, those receiving definitive breast radiotherapy.

Currently, significant efforts are routinely made to exclude all cardiac volume in the breast cancer treatment planning using Intensity Modulated Radiotherapy. Treatment planning using IMRT treats the chest wall including the lymphatics between thoracic ribs and increases the dose homogeneity throughout the chest wall and breast, so there are areas with minimal "hot spot" 5% increased dose producing that volume of homogeneity. Patients with large separation between the anterior axillary line and mid-sternal line, who receive tangential field radiotherapy may have a greater risk for high dose in the entrance portals for the medial and lateral tangents. Some of these patients will be treated with a technique that reduces the distance between the tangents to eliminate dose homogeneity. In all of these treatment plans, cardiac volume is minimized to reduce the chances of direct irradiation effects. Irradiation doses are now delivered in programs of hypofractionation with 3 - 3.5 Gy per fraction in a reduced number of fractions to produce an

isoeffect 30 – 40 Gy, in larger fraction sizes to be equivalent to 50 Gy by 1.8 – 2.0 Gy per day. The effect of increased fraction size with respect to known toxicities of breast irradiation including erythema of skin in the chest wall and inframammary fold has not been significant, suggesting that any such effects of larger fraction size on cardiac volume in the field (if it cannot be avoided) be minimal; however, research is still being carried out to follow all of these patients for biomarkers of radiation damage. Patients at risk of local recurrence after lumpectomy or mastectomy with positive resection margins and/or specific histopathology may be candidates for boost irradiation to higher doses to the lumpectomy site in the case of definitive radiotherapy programs. Such boost treatment is delivered by electron beam, or Stereotactic Radiosurgery, with treatment plans to avoid the heart.

Approaches Towards Mitigating Radiation Cardiac Damage

Multiple areas of research are ongoing to determine the mechanism by which irradiation and other inducers of oxidative stress can produce cardiac damage. Gene therapy to deliver specific ameliorating transgene products into the heart has been an area of investigation (8). Understanding cardiac molecular biology and the effects of irradiation on these pathways is critical (41-44). Most importantly, the development of cancer drugs with decreased cardiotoxicity has been a prominent area of research. The significant cardiac toxicity of Anthracycline chemotherapy drugs (Adriamycin) has motivated medical oncologists to select chemotherapy drugs with less cardiac toxicity (30, 45). The polypharmacy of modern medicine includes breast cancer patients, who were on other multiple drugs for management of hypertension, Diabetes, hypercholesterolemia, as well as, osteoporosis, and other metabolic disorders. Interaction of chemotherapy drugs with these pharmaceuticals with respect to likelihood of producing cardiac toxicity has been a significant concern in those patients, who will receive radiotherapy in addition to chemotherapy. Many areas of research involving cardiac irradiation toxicity and the methodology for studying animal models, as well as, clinical patient research has been outlined in the publications referenced in this chapter.

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