



Late Cardiac Effects of Therapy for Hodgkin Lymphoma

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Abstract

Hodgkin lymphoma (HL) is a leading cause of cancer among adolescents, and is often cured with chemotherapy alone or in combination with radiation therapy. Awareness of potential adverse cardiovascular sequelae due to therapy is crucial. Radiation-induced heart disease can affect cardiovascular structures in the radiation field, and risks of cardiovascular damage can be further increased due to exposure to anthracycline chemotherapy. This review provides a broad overview of the etiology, clinical presentation, surveillance and clinical challenges associated with late cardiotoxicity in HL survivors.

Keywords: Radiation-induced heart disease; Hodgkin lymphoma; Cancer survivors; Cardiotoxicity

Introduction

Advances in the management of Hodgkin lymphoma (HL) have led to dramatic improvements in prognosis. Combination chemotherapy remains the standard of care for advanced stage HL, whereas the combination of chemotherapy and radiation therapy (RT) is relevant in early stage or bulky HL. The use of limited radiation field (involved-field or involved-site RT, and reduction of mediastinal exposure with deep-inspiration breath-hold (DIBH) may contribute to less late effects from treatment intended to maximize local control, and ongoing modifications to chemotherapy may improve cure while simultaneously reducing short- and long-term toxicity [1]. While improvement in therapy has led to a large and growing population of survivors of HL, these survivors unfortunately face an increased risk of cardiovascular disease due to late effects of their treatment.

Radiation-induced heart disease (RIHD) is a broad term that encompasses the entire spectrum of cardiotoxicity due to radiation. While acute radiation toxicity can occur, such as acute pericarditis, late effects are common as well, generally demonstrating a latency of at least five to eight years following completion of mediastinal radiotherapy. HL survivors having received mediastinal radiotherapy are at an increased risk of premature coronary artery disease (CAD), valvular dysfunction, cardiomyopathy, pericardial disease, and sudden death [1-4]. Furthermore, anthracycline-based chemotherapy results in additive risk of cardiomyopathy and valvular dysfunction in patients with treated with both anthracycline and radiation [5].

Epidemiology and Pathophysiology

HL is an uncommon cancer, with fewer than 10,000 cases per year in the United States, but it remains the leading cause of cancer among adolescents, and among the ten most frequently diagnosed malignancies in childhood [6]. With contemporary chemotherapy and radiation therapies, 5-year survival rates now exceed 80%, and exceed 90% in early-stage disease. Cardiovascular disease is the leading nonmalignant cause of death in Hodgkin lymphoma survivors that received radiation therapy [1,2]. The aggregate incidence of RIHD is 10–30% within the first decade post-treatment [7]. Although cardiovascular complications can occur within the first 5 years, they usually appear in the second to third decade after radiation, with risk of cardiac morbidity and mortality rises continuously after eight years post-radiotherapy without plateau [1,3]. The key insult mediating radiation injury is believed to be endothelial damage, causing high oxidative stress, decrease in nitric oxide synthase, stimulation of growth factors, and eventual fibrosis [8]. At autopsy, coronary plaques in irradiated patients are more fibrous with lower lipid content than those in patients who are radiation naïve [9]. In addition, radiation directly affects the valvular and subvalvular apparatus, causing valvular thickening, retraction, and calcification [10]. While radiation therapy is the main cause of cardiovascular disease in HL survivors, anthracyclines potentiate myocardial toxicity by various mechanisms [11,12]. Both patient and treatment-related factors can influence the risk of treatment-induced cardiotoxicity. The total radiation dose (>30-35 Gy), the dose per fraction (>2

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Gy), location and type of radiation field, and shielding techniques are important treatment determinants of risk following radiotherapy. Younger age at treatment, associated cardiac risk factors, and pre-existing cardiac conditions are patient specific factors that increase risk of cardiotoxicity due to mediastinal radiotherapy. Germline polymorphisms in NAD(P)H oxidase and carbonyl reductase genes are associated with increased sensitivity to and risk of anthracycline-induced cardiomyopathy; polymorphisms associated with risk of radiation-induced cardiac disease are yet to be characterized [13,14].

Coronary Artery Disease

Increased risk of premature coronary artery disease, a source of significant morbidity and mortality, has been consistently identified across studies of long-term HL survivors treated with mediastinal RT. Aleman et al. reported a 3.6 times increased incidence of myocardial infarction (MI) in 1474 HL survivors at median follow up of 19 years compared to the general population [5]. Mediastinal radiotherapy increased the risks of MI and angina pectoris 2- to 5-fold. Ostial/proximal stenoses are typical for radiation-induced CAD, with a higher incidence of left main, right coronary and left anterior descending artery stenoses with relative sparing of the circumflex system. This may explain the observation that survivors are at as much as a 10-fold increased risk of death due to MI compared to the general population [1,3,15]. In a recent report from the Childhood Cancer Survivor Study, the presence of traditional cardiovascular risk factors, particularly hypertension, significantly increased the risk of adverse cardiac events in 10,724 long-term cancer survivors [15]. In patients with obstructive coronary disease requiring revascularization, both percutaneous and surgical intervention can be challenging. The limited data available in this patient population suggest a high rate of angiographic restenoses of bare metal stents, and no study has yet reported outcomes with newer generation drug-eluting stents [16]. Surgical revascularization is frequently limited by target vessel anatomy, mediastinal fibrosis, concomitant cardiopulmonary disease, and radiation damage leading to friable or fibrotic internal mammary arteries, compromising their suitability as grafts [17].

Heart Failure

Anthracycline chemotherapy can lead to acute or late-onset cardiomyopathy, the risk of which is a dose-dependent function [11]. The mechanism of injury remains a subject of controversy; while originally believed to be due to the formation of reactive oxygen species intramyocardially from redox reactions of anthracycline-iron complexes, cardiomyopathy has recently been linked to a range of alternative putative mechanisms, including cardiac stem-cell depletion and inhibition of neuregulin-1 [18,19]. Novel anthracyclines such as epirubicin and amrubicin, and anthracenediones such as mitoxantrone and pixantrone, have been and are in ongoing development in an effort to identify equally effective and less cardiotoxic agents. Acute anthracycline-induced cardiomyopathy is an uncommon event in patients undergoing treatment for Hodgkin lymphoma, manifesting with signs and symptoms of acute dilated cardiomyopathy. Late-onset anthracycline-induced cardiomyopathy occurs at least one year after the completion of therapy, although the latency is typically five years or longer. It usually manifests as congestive heart failure due to slowly progressive systolic and, less often, diastolic myocardial dysfunction. This progression from subclinical cardiac dysfunction to clinical heart failure can have a prolonged latency period spanning decades in pediatric survivors, and can be difficult to diagnose in its initial stages [20,21]. Radiation induced cardiomyopathy is believed

related to myocardial fibrosis, with resultant diastolic dysfunction and restrictive physiology. The presence of diastolic dysfunction is associated with stress-induced ischemia and a worse prognosis in this population [22]. Treatment with combined-modality treatment with both mediastinal radiation and anthracycline-based chemotherapy increased the risk of heart failure by 2.8 fold compared to mediastinal radiation alone [5]. The cumulative incidence of heart failure 25 years after combined radiation and anthracycline treatment for HL was 7.9 percent. There are currently no specific therapies for the management of heart failure due to radiation and/or anthracycline exposure. Data suggest a role for the use of beta-blockade or angiotensin-converting enzyme inhibitors, but further research is needed. Novel therapies, such as infusional neuregulin and mesenchymal stem cell transfer, are in the early stages of evaluation [12]. At this time, recommended medical and device therapy should be in accordance with American College of Cardiology/American Heart Association guidelines is recommended [23]. Promising insights from the Childhood Cancer Survivors Study suggest a protective effect of exercise in HL survivors, and prospective evaluations of the protective effects of exercise are ongoing [24].

Valvular Disease

Valvular dysfunction due to radiation therapy is slowly progressive, with a predominance of regurgitant and left sided lesions. Heidenreich et al. [5] studied 294 asymptomatic HL survivors with prior mean mantle radiation dose of 43Gy, reporting a 34-fold higher age- and gender- adjusted risk for moderate or severe aortic regurgitation compared with the Framingham population. The degree of valvular dysfunction increased with time for all valves, but this trend was most appreciable for the aortic valve. After the second decade post therapy, 15% of HL survivors had moderate or severe aortic regurgitant lesions, and as many as 16% had aortic stenosis detected by echocardiography. Wethal et al. [11] reported moderate left sided regurgitant lesions in 31% of 116 HL survivors at a median follow up of 10 years following mediastinal radiotherapy. When re-evaluated at median follow up of 22 years, more than 90% of the patients without any abnormality at baseline had developed a new abnormality, and more than two-thirds of those with a known abnormality demonstrated progression or developed an additional new abnormality [10]. Exposure to anthracyclines may further increase the risk of valvulopathy from mediastinal radiotherapy [5]. Surgical management of significant valvular dysfunction is technically challenging due to anatomical limitations and comorbid conditions. In a report from Cleveland Clinic, patients with an extensive radiation history who underwent cardiac surgery had increased perioperative complications and a worse short and long term survival [25].

Pericardial Disease

Acute pericarditis has long been recognized as one of the most common early adverse consequences of mediastinal radiation therapy in the treatment of HL [26]. However, with contemporary radiation techniques, the incidence has declined several-fold, and currently fewer than five percent of patients treated with typical doses and fields will experience clinically evident acute pericarditis [27]. A fraction of these patients will go on to manifest subsequent pericardial sequelae such as constrictive or effusive-constrictive pericarditis as a late consequence [28]. There is no consensus on the optimal management of this rare sequela, although in the setting of recurrent effusions, subtotal pericardiectomy is often considered, and may reduce the risk of subsequent constriction [29].

Conduction System Disease

Brady and tachyarrhythmias particularly right bundle branch block, prolonged QT interval and ventricular and atrial ectopy have been reported in irradiated patients, although conduction abnormalities were more commonly seen in the context of broader fields, higher doses, and less sophisticated radiation simulation techniques [30]. Guideline-concordant antiarrhythmic or device therapy is routinely considered for severe and/or symptomatic conduction system disease following radiotherapy.

Surveillance

Although intuitive, the true efficacy of screening remains unclear in this high-risk group due to a paucity of evidence showing that medical intervention based on screening results impacts long-term cardiac outcomes. Several scientific organizations, including National Comprehensive Cancer Network and the Children's Oncology Group (COG), have issued recommendations regarding long term follow up in HL survivors, including screening for adverse cardiovascular sequelae (Table 1) [31,32]. The COG recommends surveillance transthoracic echocardiograms at varying frequency (1-5 years) in various patient subsets depending on the age at treatment, radiation and anthracycline dose, as well as consideration of cardiology consultation to screen for coronary artery disease 5-10 years post treatment. Adverse cardiovascular sequelae in HL survivors are a significant cause of long-term morbidity and mortality. An individualized surveillance and aggressive risk-reduction strategy is best in this vulnerable population. Guidance should be sought from the consensus documents that incorporate expert opinions and provide clinically meaningful roadmaps to management. Lastly, development of therapeutic strategies devoid of cardiotoxicity will ultimately be the most effective strategy to prevent cardiac complications in HL survivors.

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