

Impact of Treatment-Related Cardiac Toxicity on Lymphoma Survivors: An Institutional Approach for Risk Reduction and Management

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Despite improvements in treatment and overall survival rates, survivors of lymphoma may have long-term and late effects. Given the immense risk for cardiac disease after treatment for Hodgkin lymphoma and non-Hodgkin lymphoma, healthcare providers should focus on prevention of secondary adverse effects. The Dana-Farber Cancer Institute has been working to develop guidelines to address the cardiotoxicities that impact the lymphoma survivor population.

With recent advances in chemotherapy and radiation, many patients diagnosed with lymphoma have become long-term cancer survivors. Despite improvements in treatment and overall survival rates, the diagnosis and treatment of lymphoma may leave patients with long-term and late effects (Morgan, 2009; Wettergren, Bjorkholm, Axdorph, & Langius-Eklof, 2004). Patients cured of Hodgkin lymphoma have increased risk of mortality because of long-term effects of treatment (Wettergren et al., 2004). Cardiovascular disease is the second leading cause of death in long-term survivors of Hodgkin disease after second malignancies (Henry-Amar & Somers, 1990). Multiple studies have shown that patients who have been cured of Hodgkin disease are at significantly increased risk of death from myocardial infarction or sudden death compared to the general population (Mauch et al., 1995).

Causes of Cardiac Toxicity

Late cardiovascular consequences of radiation therapy to the chest are caused primarily by the development of coronary atherosclerosis, even in the absence of concomitant cardiovascular risk factors (Orzan, Brusca, Conte, Presbitero, & Figliomeni, 1993). Symptoms can remain silent for years and manifest as severe coronary heart disease. The lack of symptoms is because the vascular lesions cor-

respond to intima hyperplasia and lumen wall collagen deposition and develop throughout a period of about 82 months (Orzan et al., 1993; Veinot & Edwards, 1996). In contrast, in the general population, the development of coronary artery disease is related to the buildup of cholesterol and fatty deposits (called plaques) on the inner walls of the arteries. The changes related to radiation therapy can lead to stenosis, frequently observed at the level of bifurcation (Veinot & Edwards, 1996). The heart valves also are affected by collagen deposition, valvular stenosis, and regurgitation, which may be severe; the mitral and aortic valves are affected commonly (Orzan et al., 1993).

Additionally, radiation can cause fibrosis of the conduction pathways in the heart, leading to life-threatening arrhythmias and conduction defects years later (Heidenreich, Hancock, Lee, Mariscal, & Schnittger, 2003). Other risk factors include the total dose and volume of radiation therapy, dose per fraction, and the extent to which coronary arteries were included in the radiation field (Heidenreich et al., 2003).

Along with coronary artery disease and valvular disorders, the most common cardiovascular diagnoses in Hodgkin

survivors are angina pectoris, conduction defects, and myocardial infarction. Median time to diagnosis of the complications is 10–15 years after treatment (Myrehaug et al., 2008). Studies have shown that patients cured of non-Hodgkin lymphoma experience long-term cardiovascular complications (Myrehaug et al., 2008).

Anthracyclines (e.g., adriamycin) are used widely in the treatment of many cancers, including lymphomas, and are known to cause acute and chronic cardiotoxicity (Keefe, 2001). The dysfunction is a consequence of direct myocardial damage induced by the formation of free radicals (Myers, 1988). The risk of adriamycin-induced congestive heart failure increases with cumulative dose (Armitage & Potter, 1984; Singal & Iliskovic, 1998). The probability of developing symptomatic heart failure with a decline in left ventricular ejection fraction is estimated to be 1%–2%, 3%–5%, 5%–8%, or 6%–20% at total cumulative dosages of 300, 400, 450, and 500 mg/m², respectively (Bedford Laboratories, 2002). Researchers have found that combining anthracyclines with high doses of cyclophosphamide or mediastinal radiation can lead to heart failure at lower cumulative doses (Adams et al., 2004). A very high mortality rate has

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Digital Object Identifier: 10.1188/10.CJON.505-507