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, Ax dorph, & 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 correspond 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 build up 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 & Iliiskovic, 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
been estimated in patients with anthracycline-related congestive heart failure (Ali, 1992), but the rate may be reduced with early diagnosis and therapy (Galdersi et al., 2007). Hequet et al. (2004) found that although the percentage of patients who developed symptomatic heart failure at doses of 300 mg/m² remained low, 21% had subclinical cardiomyopathy.

Managing Risk Factors

Based on current knowledge and until researchers gather more evidence on cardiac toxicity associated with modern treatment modalities, the present recommendation is to modify treatment- and patient-related risk factors. Clinicians can help patients modify cigarette smoking, high blood cholesterol, high blood pressure, physical inactivity, obesity, and diabetes mellitus by helping survivors change their lifestyles or treat with medications. Given the immense risk for cardiac disease after treatment for Hodgkin lymphoma and non-Hodgkin lymphoma, providers should pay particular attention to patient risk factors for cardiac disease. Emphasis should be on prevention of secondary adverse effects. Such prevention includes control of known modifiable risk factors for coronary artery disease and congestive heart failure. In the absence of high-level clinical evidence, treatment and surveillance guidelines continue to be driven by consensus (National Comprehensive Cancer Network, 2009).

Guidelines for Care

The lymphoma program at the Dana-Farber Cancer Institute has been working with the oncology-cardiology program to develop consensus-based guidelines designed to address the cardiotoxities that impact most of its patient population. The treatment of survivors with radiation-induced cardiovascular disease is similar to that for patients with cardiovascular disease not caused by radiation. Recommendations include smoking cessation and strict management of hypertension, diabetes, and hyperlipidemia. In patients treated with chest radiation who have hyperlipidemia, statin therapy should be initiated with a goal of a low-density lipoprotein level lower than 100 mg/dl. This was based on the decision to treat chest radiation as a coronary heart disease risk equivalent, similar to how diabetes is treated in the current guidelines for screening and management of hyperlipidemia. A study has shown that in survivors of Hodgkin lymphoma with an elevated lipid profile during screening, treatment with statin therapy improves survival and is cost effective (Chen, Punglia, Kuntz, Mauch, & Ng, 2009).

Recent data suggest that aggressive treatment of cardiac risk factors may significantly reduce the extent of initial cardiac injury and slow the progression of vascular, myocardial, and valvular fibrosis (Novaro et al., 2001). In addition to aggressive management of risk factors, the lymphoma program at the Dana-Farber Cancer Institute has established consensus screening guidelines. Currently, the lymphoma program advocates for a baseline echocardiogram and a stress test 10 years after radiation ends and repeated as clinically indicated depending on treatment and additional cardiac risk factors. The consensus guidelines also recommend blood tests to evaluate a patient’s glucose and lipid levels every three to five years (more often if the test results are outside normal ranges), as well as a healthy diet and regular exercise. For a survivor’s primary care physician, the guidelines recommend considering a patient in the high-risk category for lipid management because of the prior mantle radiation. The focus is on low-density lipoprotein cholesterol and achieving the optimal target of lower than 100 mg/dl.

A large portion of the Dana-Farber lymphoma population receives 300 mg/m² of adriamycin with six cycles of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) or R-CHOP (rituximab, cyclophosphamide, adriamycin, prednisone, and vincristine). In the general population, symptomatic heart failure is preceded by a lengthy asymptomatic stage in many patients (Genovesi, Colivicchi, Malvezzi Caracciolo, & Riccio, 2009). The number of patients with asymptomatic heart dysfunction is about four-fold the number of patients with clinically overt heart failure (Genovesi et al., 2009; Wild & Kukin, 2007). Pharmacologic treatment with angiotensin-converting enzyme inhibitors and beta blockers of asymptomatic patients with systolic left ventricular dysfunction can prevent or delay the occurrence of symptoms and reduce mortality in the long term.

In a collaborative effort with the oncology-cardiologists, the lymphoma program also has begun to establish consensus guidelines regarding patients treated with anthracyclines. The lymphoma team will soon begin echocardiogram screening all patients who received 300 mg/m² or more of adriamycin, five years after they complete therapy. The hope is to aggressively medically manage asymptomatic patients with heart failure to prevent or delay the occurrence of symptoms.

The lymphoma program is collaborating with the adult survivorship program at Dana-Farber to develop and implement standardized wellness guidelines focusing on exercise, diet, and weight management. This is essential to reduce cardiac and cancer risks in not only the lymphoma population but in all patients with cancer.

Next Steps

Additional work is needed in this area to improve the quality of evidence defining cardiac surveillance recommendations. Well-defined evidence-based guidelines decrease variations in clinical practice and result in more efficient and effective healthcare delivery (Earle, 2006). The lymphoma team understands that it is not enough to establish consensus guidelines; currently, the lymphoma program has a protocol looking at screening for radiation-induced cardiac disease in patients with Hodgkin disease who have received mantle radiation. It also is collaborating with the adult survivorship program and the oncology-cardiologists to begin the five-year post-adriamycin exposure screening as part of a similarly designed protocol. The studies will provide a better understanding of the consensus guidelines and clarify modifications as needed. In addition to screening protocols, the oncology-cardiologists are developing an intervention trial in the lymphoma population to look at whether reducing risk factors in a manner similar to the general population will show measurable changes in the pathophysiology of radiation-induced cardiac disease.

Good communication is essential to ensure that survivors’ needs are met; treatment summaries and survivorship care plans can improve follow-up care (Hewitt & Ganz, 2007). The concern regarding cardiac toxicity related to lymphoma ther-
apy was the impetus for the lymphoma program to develop and test survivorship care plans at Dana-Farber Cancer Institute. This stemmed from the recognition that the transition from cancer diagnosis and active treatment to follow-up care is critical (Morgan, 2009). The survivorship care plans that have been developed provide standardized risks related to therapy, ways to potentially reduce the risks, and consensus recommendations regarding screening. The focal point of the lymphoma survivorship care plan is the risk of cardiac toxicity and recommendations to reduce it. The lymphoma program currently is conducting a research project with the adult survivorship program to explore the impact of a survivorship care plan on adult patients’ knowledge of their lymphoma and follow-up care. The survivorship care plan will be provided to each patient at the completion of therapy and allow lymphoma care providers to review the cardiac risks and recommendations with the patient at multiple points in follow-up care. In addition, the documents will be sent to the patient’s other healthcare providers in hopes of educating them regarding the increased risks the patients have and the current recommendations. This collaborative approach, which impacts patients at multiple times during follow-up care, will reduce the second leading cause of death in long-term survivors.

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