An Affair of the Heart

John D. Boice Jr

In 1950, patients with Hodgkin lymphoma had a median survival time of 4 years and a 5-year relative survival rate of 29% (1). Since the introduction of radiation therapy and chemotherapy for Hodgkin lymphoma in the 1960s and 1970s, the 5-year relative survival rate is more than 85% (2), and these patients can now expect a long lymphoma-free life. However, the price for this phenomenal success has been high. “Radiation-induced heart disease” was recognized in the 1960s (3) and radiation-induced cancers somewhat later (4–6). Multidrug chemotherapy was introduced in the 1970s (i.e., combination chemotherapy with mechlorethamine, vincristine, procarbazine, and prednisone) (7); however, one of these drugs, nitrogen mustard (mechlorethamine), appeared to carry a high risk of leukemia (8). Over the years, other drug combinations that were equally effective but less leukemogenic were introduced, such as doxorubicin, bleomycin, vinblastine, and dacarbazine. Unfortunately, the anthracycline doxorubicin carried an increased risk of cardiac toxicity (9). In a sense, one type of late effect, leukemia, was being replaced by another, heart disease.

Although the risk of new malignancies among Hodgkin lymphoma patients has been well studied and the relationship between the development of a subsequent cancer and radiation dose to specific organs characterized (4–6,10), it is only relatively recently that large studies have attempted to quantify the risk of late cardiac toxicity among these patients. In this issue of the Journal, Swerdlow et al. (11) provide important new information on the risk of dying from myocardial infarction following curative treatment for Hodgkin lymphoma. They report that among 7033 patients who were treated from 1967 through 2000 (median follow-up of 9.9 years), 166 deaths from myocardial infarction occurred, and the increased risk of death from myocardial infarction remained high for at least 25 years after first treatment. The overall standardized mortality ratio (SMR) was 2.5, and the absolute excess risk was approximately 0.13% per year (125.8 per 100000 person-years). On a relative scale, the risk of death from myocardial infarction was highest among patients who were younger than 25 years at first treatment and within the first year of treatment. On an absolute scale, however, risk was highest among patients who were older than 45 years at first treatment because of the higher rates of heart disease that occur at older ages.

The high risks associated with mediastinal radiotherapy (SMR = 8.9) and anthracycline treatments (SMR = 2.9) were confirmed by Swerdlow et al. (11). They also presented evidence that the vinca alkaloid vincristine may carry a high risk of heart disease (SMR = 2.8), although this association needs to be confirmed in other series. One challenging aspect of the analyses, however, was that so many patients receive both radiotherapy and different combinations of chemotherapy that it is difficult to tease out the contribution of a single agent, e.g., the risk of death from myocardial infarction was evaluated over five broad treatment modalities for six radiotherapy subgroups, seven chemotherapy regimens, and 13 individual chemotherapy agents or combinations of agents. The authors plan nested case–control analyses to quantify risks further in terms of amount of chemotherapy administered (mg/m²) and amount of radiation dose to the heart.

Death from myocardial infarction is the most serious, but not the only, indicator of heart damage following treatment. Radiotherapy can increase the risk of congestive heart failure and of specific pericardial, myocardial, and vascular lesions (3,12,13). Radiation-induced heart disease has also been evaluated in survivors of breast cancer (14,15) and childhood cancer (16), but few studies have computed the actual radiation dose delivered to the heart. Heart disease is most frequently observed in patients who have received therapeutic doses greater than approximately 30 Gy (17) and is rare in patients who have received less than 4 Gy (18).

Anthracyclines are used to treat a number of cancers in addition to Hodgkin lymphoma, including cancers of the breast, non-Hodgkin lymphoma, and leukemia (19). More than 50% of children who are currently being treated for cancer, for example, receive anthracycline regimens (20). Poor cardiac function has been reported in 11% of pediatric patients who were treated with anthracyclines at less than 400 mg/m² of body surface area and in 100% of patients treated with more than 800 mg/m² (21). Late-onset cardiomyopathy that is associated with anthracycline treatment may remain clinically silent for long periods before becoming apparent (22). The mechanism for anthracycline-induced cardiotoxicity is not entirely clear but is believed to be related to the generation of highly reactive free radicals (oxidants), so that the...
resulting oxidative stress causes direct damage to cardiac myocytes (19). A free radical–scavenging compound, dexrazoxane, is clinically approved as a cardioprotectant for use against anthracycline-induced heart damage (23).

Long-term studies that follow lymphoma survivors for many years, such as the one conducted by Swerdlow et al. (11), are needed to help better understand the processes and factors that worsen heart function, especially now that patients in remission are living to older ages when cardiac disease is common. The possible interaction between radiotherapy and anthracyclines in the development of heart disease should be investigated, as well as the concomitant influence of other known cardiac risk factors such as cigarette smoking and hyperlipidemia. Morbidity from heart disease as well as mortality should be investigated, as was recently done in the Childhood Cancer Survivor Study (24) and as could be done in some countries with nationwide patient registries (25). The effects of treatment for Hodgkin lymphoma appear to be lifelong, and cancer survivors should be monitored for late cardiac abnormalities throughout their lives. The goal of keeping these patients alive has been achieved; the next challenge is to continue to reduce the toxicity of curative treatments and to make long-term survival as disease free as possible, breaking as few hearts as possible along the way.

References