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Cardiovascular disease after hematopoietic cell transplantation – lessons learned

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Hematopoietic cell transplantation (HCT) has now become the treatment of choice for a large number of malignant and non-malignant diseases.[1] It is quite clear that unless effective targeted therapy becomes available, HCT will continue to be offered as a curative therapeutic modality to patients diagnosed with a variety of malignant and non-malignant disorders. Among those who survive the first 2 years, nearly 80% of allogeneic HCT recipients[2,3] and 70% of autologous HCT recipients[4] are expected to become long-term survivors, with an attendant growth in such survivors. Due to improvements in survival rate, major issues for patients undergoing HCT have expanded to include the care and management of survivors, prevention of adverse outcomes, and maintenance of a good health-related quality of life. Some of the well-described complications in this population include subsequent malignancies, cataracts, pulmonary complications, endocrine dysfunction, osteonecrosis, chronic kidney disease, and impairment in functional status due to persistent, chronic graft-versus-host disease (GVHD).[5-7] Details regarding cardiovascular dysfunction after HCT are now emerging.[8-10]

In this issue of the journal, Tichelli *et al.* publish the results of their retrospective study designed to describe the magnitude of risk of and associated risk factors for the development of arterial events after allogeneic HCT.[10] The events of interest include coronary artery disease, cerebrovascular disease and peripheral artery disease. They report that the cumulative incidence of arterial events at 15 years is 6%, and identify older age at the time of HCT and presence of pre-established cardiovascular risk factors (diabetes, obesity, dyslipidemia, arterial hypertension) as being associated with an increased risk of these outcomes.

In a recent study, we used a nested case-control study design to examine the independent role of pre-HCT exposure to therapeutic agents, transplant-related conditioning and co-morbidities in the development of congestive heart failure (CHF) after HCT.[8,9] We identified pre-HCT exposure to anthracyclines and the presence of post-HCT co-morbidities as being associated with delayed CHF after HCT.

The best-described therapy-related late cardiac complications include valvular dysfunction, conduction abnormalities, pericarditis, and cardiomyopathy.[11-13] Arterial complications can occur as a result of damage to the entire vascular system and include coronary artery disease, cerebrovascular disease, and peripheral artery disease.[14,15] While the latency period for many of these diseases can be short, survivors often do not have clinical evidence of disease until several years following HCT.[14-16] As with most other complications observed after HCT, cardiovascular complications following HCT are due, in part, to the treatment prior to, during, and following HCT.

Age at therapeutic exposure, gender, and past medical history are important considerations when identifying the potential risk of long-term cardiovascular disease. The cardiotoxic potential of many anti-neoplas-

tic agents, such as anthracyclines or ionizing radiation, is particularly great among those who have been exposed early (before 15 years of age) or late (after 70 years old) in life.[17,18] In children, damage to the developing myocardium can cause irreparable harm, impairing their ability to compensate during periods of increased myocardial demand.[19] Older patients have a reduced capacity to repair tissue damage and, in turn, have a greater risk of premature coronary artery disease, congestive heart failure, and dysrhythmia.[11,20]

Females exposed to anthracyclines have a significantly greater risk of developing CHF compared to males.[21] The mechanism of gender-specific cardiotoxicity is not clear. Differences in body fat composition between males and females could alter the pharmacokinetics and pharmacodynamics of drugs, since anthracyclines do not reach a high concentration in adipose tissue.[22,23] Since females have a higher percentage of body fat for the same body surface area, equivalent doses of the drug could lead to greater concentrations in non-adipose tissues such as the heart and lead to more cardiotoxicity than in males. On the other hand, the risk of late arterial events appears to be greater in males than in females, despite adjustment for well-known confounders such as body mass index, age at transplantation, and ethnicity.[14,15]

Anthracycline chemotherapy and neck/mediastinal radiation are the most common causes of therapy-related cardiovascular complications in long-term cancer survivors.[11,19] Anthracycline cardiotoxicity has been well-described and is thought to be related to direct myocardial injury due to formation of free radicals.[24] Progressive cardiomyopathy can occur early within the first year of treatment or can be delayed, diagnosed years following completion of therapy; the risk of disease is dose-dependent.[25] In non-HCT populations, the incidence of CHF is less than 10% in patients receiving cumulative doses of lower than 500 mg/m^2, increases to 18% at doses between 551 and 600 mg/m^2, and approaches 36% for cumulative doses exceeding 600 mg/m^2.[18,26] It remains to be seen whether similar estimates can be made for individuals undergoing HCT, since many patients are exposed to additional cardiotoxic agents as part of the conditioning and during the post-HCT period.

Mediastinal radiotherapy can cause a host of cardiac complications including constrictive pericarditis, cardiomyopathy, valvular heart disease, coronary artery disease, and conduction abnormalities.[27,28] Among survivors of Hodgkin's lymphoma treated with mediastinal radiation, 40-60% have been reported to have valvular fibrosis or insufficiency, while conduction defects are present in as many as 75%.[19,28] Although clinically evident heart failure is rare following mediastinal radiation alone, when present, it is primarily in the form of diastolic dysfunction, as opposed to systolic disease seen following exposure to anthracyclines.[27] In a recent study of long-term survivors Hodgkin's lymphoma treated primarily with mediastinal radiotherapy (median dose 40 Gy), 54% had evidence of a left ventricular filling defect, and 30% were noted to have peak oxygen uptake (VO_2max) during exercise of <20 mL/Kg/m^2, a strong predictor of mortality in heart failure.[29]

The risk of arterial disease following exposure to radiotherapy is primarily related to local therapy.[18,19] The morphological changes in radiation-induced vascular disease are similar to those observed in spontaneous atherosclerosis.[27,30] The relative risk of a fatal arterial event ranges between 2.2 and 7.2 when compared to the risk in the general population, and may not manifest until 10-20 years after completion of treatment.[11,31] For non-HCT populations, radiation-associated atherosclerotic heart disease rarely occurs in the absence of other cardiovascular risk factors such as dyslipidemia, hypertension, and obesity.[28] However, the prevalence of these co-morbidities following HCT[14,15] potentially increases the magnitude of risk for premature cardiovascular disease among HCT survivors – an observation that has now been confirmed for arterial outcomes[10] and CHF.[8,9]

Cardiac complications associated with exposure to conditioning regimens are often acute, with relatively short latency.[11] Conditioning-related risk factors potentially include: high-dose cyclophosphamide,[32] total body irradiation,[33] presence of dimethyl sulphoxide (DMSO) in the transfused product,[34] and infectious complications during early post-transplant neutropenia.

The risk associated with high-dose cyclophosphamide is dose-dependent and characterized by cardiac muscle damage, and subsequent necrosis. Congestive heart failure can occur within weeks of administration of high-dose cyclophosphamide and disease manifestations may be worse in individuals with pre-existing cardiac compromise.[35] Reductions of the dose of cyclophosphamide during the last decade have decreased the incidence of acute complications.[32] Total body irradiation, while mostly recognized for its ability to induce pericarditis and myocardial fibrosis, has been reported as a contributor to long-term coronary artery disease.[33] DMSO-related cardiac toxicity is rare and there have recently been questions regarding the causative relationship between DMSO and these events.[34] Recent reports of similar acute cardiac events despite DMSO depletion have led to the suggestion that perhaps the complications seen following infusion may be more a product of the amount of infused granulocytes, rather than DMSO.[11] Lastly, infectious complications during early post-transplant neutropenia or prolonged immunosuppression for GVHD prophylaxis are a common problem following HCT. Overwhelming sepsis can lead to cardiopulmonary failure, necessitating prolonged intubation and cardiac inotropic support, potentially causing subclinical cardiotoxicity or other end-organ compromise that may not be evident until years following HCT.

Tichelli's study provides preliminary evidence for an association between GVHD and the development of arterial disease.[10] There are emerging data to suggest that chronic GVHD could play a role in the development of cardiovascular disease. Cardiac side effects of chronic GVHD, while rare, likely occur as a result of direct organ lymphocytic infiltration.[36] Increased levels of circulating tumor necrosis factor α may impair mus-

cle electrical activity and compromise myocardial contractility.[36,37] Furthermore, increasd amounts of inflammatory markers, such as tumor necrosis factor-α and interleukin-6, could perpetuate endothelial injury, contributing to premature arterial events in long-term survivors after allogeneic HCT.[15] Treatment of GVHD is not without cardiovascular consequences. Prolonged treatment with calcineurin inhibitors and steroids can lead to myocardial hypertrophy, as well as increase the likelihood of cardiovascular disease risk factors such as hypertension, diabetes, and renal insufficiency.[38]

The prevalence of *de novo* cardiovascular risk factors such as hypertension, diabetes and dyslipidemia increases over time following HCT, irrespective of GVHD status.[14,15] Long-term HCT survivors are nearly four times more likely to report diabetes, and two times more likely to report hypertension compared to sibling controls.[14] A recent study of long-term HCT survivors reported that the risk of co-morbidities such as hypertension and diabetes is particularly high among allogeneic HCT recipients.[15] Compared to autologous HCT recipients, allogeneic recipients with hypertension were found to have a 2.5-fold increased risk of a cardiovascular event, while those with diabetes had a 2.3-fold increased risk.[15] The cumulative incidence of arterial events after allogeneic HCT, such as cerebrovascular disease, coronary artery disease and/or peripheral disease, was 22% at 25 years.

There are several well-recognized guidelines for screening long-term survivors of childhood and adult malignancy for cardiovascular disease.[39,40] Documentation of exposure to cardiotoxic agents such as anthracyclines and radiation, as well as the presence of co-morbidities such as hypertension, dyslipidemia, and renal insufficiency should determine the nature and frequency of monitoring.

Echocardiography provides a wide spectrum of information on cardiac morphology and function, and has become the standard method for cardiac assessment and screening in oncology patients.[39,41] Parameters of systolic and diastolic function can easily be measured with sufficient accuracy, and thus echocardiography offers clinicians a non-invasive, cost-effective, and widely available option for serial evaluation in patients at risk of this complication.[42] However, measures such as left ventricular ejection fraction (LVEF) and certain diastolic parameters are highly load-dependent, sensitive to changes in the circulatory system and rather non-specific.[43] The current practice of prospective monitoring of LVEF for cardiac compromise may fail to detect early and subtle changes in myocardial function, thus losing an opportunity for potential early intervention.

Myocardial performance index and Doppler myocardial imaging are advanced, load-independent, echocardiographic measures that have recently been developed and promise to offer more detailed information on cardiac function.[42] The myocardial performance index is used to measure subtle changes in isovolumic contraction and relaxation times, early indicators of systolic and/or diastolic dysfunction.[44] Studies in oncology patients are limited; however, there is emerging evidence that changes in this index can be detected prior to alterations in LVEF and correlate with risk of late CHF.[45] Doppler myocardial imaging is useful for assessment of subtle in regional myocardial wall abnormalities. Through the use of additional parameters such as left ventricular strain and strain rate, cardiologists are able to detect early, localized, left ventricular dysfunction that can occur as a result of cardiotoxic agents or coronary artery disease.[42] Both techniques are readily available with most modern scanners, and data acquisition adds only minutes to the conventional echocardiographic study.

Biomarkers such as B-type natriuretic peptide (BNP) and serum cardiac troponin-T (cTNT) have recently been evaluated for monitoring cardiac function following treatment with known cardiotoxic agents.[11,46,47] BNP is a cardiac hormone released by the atrial myocardium in response to increased wall stress. BNP levels increase when heart failure is clinically unapparent and continue to rise as the compromise becomes more severe.[46] While useful for evaluation and management of heart failure in patients at high risk of left ventricular dysfunction, data regarding the use of BNP levels in primary oncology patients are inconclusive.[39] cTNT is a highly specific and sensitive biomarker of myocardial tissue damage.[47] It is most commonly used to identify early myocardial damage during acute coronary syndrome, and has been used for the detection of acute anthracycline cardiotoxicity in childhood cancer patients.[47,48] While cTNT may be useful for early monitoring of myocardial injury, little is known about its role in screening high risk patients, years following initial exposure to cardiotoxic agents.

The large majority of patients undergoing HCT have been heavily pre-treated, and exposure to cardiotoxic agents such as anthracyclines and radiation is often unavoidable. Preventive measures in the post-HCT period therefore need to focus on minimizing progression of cardiac dysfunction as well as limiting cardiovascular risk factors that could worsen premature cardiac and arterial disease.

Afterload reduction with angiotensin-converting enzyme (ACE) inhibitors is useful for treating and preventing CHF not associated with anthracyclines.[26] ACE inhibitors have been shown to prevent or partially reverse progressive left ventricular dilatation and reduce left ventricular mass and ventricular sphericity.[49] Afterload reduction for prevention of anthracycline-associated late cardiotoxicity has not been as successful. In a trial of 18 doxorubicin-treated, long-term survivors of childhood cancer with and without CHF, afterload reduction was able to temporarily alter the course of progressive ventricular dysfunction.[50] The beneficial effects produced 3-9 years of improvement in heart function, followed by a return towards baseline. It was noted that the inappropriately thin left ventricular myocardial walls of many of these patients continued to thin while on therapy, a concerning observation for clinicians considering ACE-inhibitors for prevention of anthracycline-induced cardiomyopathy. Other pharmacological interventions such as β-blockers, while extensively studied in at risk adults for pre-

vention of heart failure, have yet to be systematically studied in long-term cancer survivors.

Tichelli's study has demonstrated a clear role for established risk factors in the development of arterial disease in HCT survivors. A previous study showed an increased risk of CHF in patients with post-HCT comorbidities.[8,9] Education and counseling of patients are, therefore, crucial components of preventing disease and promoting health in HCT populations at risk of delayed cardiovascular disease. Adoption of heart-healthy lifestyles should be encouraged in all survivors and particularly in those at risk of coronary artery disease. Recommendations should emphasize the need to reduce modifiable risk factors such as obesity, smoking, hypertension, and dyslipidemia.[39-41] Proper management of cardiovascular risk factors has been shown to reduce the risk of cardiovascular events and improve survival in the non-HCT population, and could help reduce morbidity and mortality in HCT survivors.[51] Aerobic exercise should be encouraged as it can have symptomatic, physiological, and psychological benefits.[39,41] However, patients wishing to participate in strenuous exercise programs should first be monitored using maximal or sub-maximal exercise testing to ensure that they have stable cardiac function prior to engagement in such activities.[41,51]

Many of the cardiovascular events (CHF and arterial disease) do not occur until decades after HCT and current risk estimates are likely to increase with longer follow-up of cohorts of HCT survivors. Tichelli's study provides preliminary evidence of an increased risk of arterial disease in long-term survivors of HCT. However, the small numbers do not allow for a detailed examination of individual types of arterial disease. Larger cohorts followed for long periods of time will be required to understand the role of pre-HCT exposure to therapeutic agents, high-dose conditioning regimens and modifiable risk factors in the development of individual types of arterial disease observed in this population. These limitations not-withstanding, data are now emerging about a significant role of modifiable risk factors in the development of CHF and arterial disease after HCT. Placing this in the context of an increased prevalence of diabetes and hypertension after HCT, it becomes critically important to address modifiable factors in the population at risk of these adverse outcomes after HCT.

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