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Cardiovascular disease following hematopoietic stem cell transplantation: Pathogenesis, detection, and the cardioprotective role of aerobic training

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ABSTRACT

Advances in hematopoietic cell transplantation (HCT) techniques and supportive care strategies have led to dramatic improvements in relapse mortality in patients with high-risk hematological malignancies. These improvements, however, conversely increase the risk of late-occurring non-cancer competing causes, mostly cardiovascular disease (CVD). HCT recipients have a significantly increased risk of CVD-specific mortality, including elevated incidence of coronary artery disease (CAD), cerebrovascular disease,

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and heart failure (HF) compared to age-matched counterparts. Accordingly, there is an urgent need to identify techniques for the detection of early CVD in HCT patients to inform early prevention strategies. Aerobic training (AT) is established as the cornerstone of primary and secondary disease prevention in multiple clinical settings, and may confer similar benefits in HCT patients at high-risk of CVD. The potential benefits of AT either before, immediately after, or in the months/years following HCT have received limited attention. Here, we discuss the risk and extent of CVD in adult HCT patients, highlight novel tools for early detection of CVD, and review existing evidence in oncology and non-oncology populations supporting the efficacy of AT to attenuate HCT-induced CVD. This knowledge can be utilized to optimize treatment, while minimizing CVD risk in individuals with hematological malignancies undergoing HCT.

1. Introduction

More than 60,000 individuals are expected to undergo allogeneic or autologous hematopoietic cell transplantation (HCT) annually worldwide for treatment of hematological malignancies (Wingard et al., 2011). Advances in transplantation techniques and supportive care strategies have dramatically improved cancer specific survival rates in the past 30 years; 10-year survival rates now exceed 80% following HCT (Wingard et al., 2011; Socie et al., 1999). However, with prolonged survival, the risk of treatment-induced late-occurring morbidity and mortality from competing (non-relapse mortality; NRM) causes has substantially increased. Specifically, in comparison with age-sex-matched counterparts from non-oncology settings, HCT recipients have a 2.3–4.0-fold increased risk of cardiovascular-specific mortality, a 0.6–5.6-fold increased risk of cardiovascular disease (CVD) including coronary artery disease (CAD), cerebrovascular disease, and heart failure (HF), and a 7.0–15.9-fold increased risk of CVD risk factors such as hypertension, diabetes, and dyslipidemia (Baker et al., 2007, 2012; Chow et al., 2011; Tichelli et al., 2008a; Armenian et al., 2012, 2011a,b, 2010; Griffith et al., 2010). This excess CVD risk (Speck et al., 2010; Baker et al., 2010; Ford et al., 2002; Chow et al., 2014a) is likely a consequence of acute direct (i.e., direct cytotoxic/radiation-induced injury) as well as indirect (i.e., impacts secondary to therapy such as deconditioning) effects of HCT therapy (Jones et al., 2007). A research agenda that comprehensively and systematically tackles the issues related to CVD prevalence, pathogenesis, detection, and treatment in HCT recipients is urgently required.

Current cardiovascular screening and monitoring guidelines for post-HCT adult survivors recommend yearly cardiovascular risk factor screening, with assessment of global cardiac function (left ventricular ejection fraction, LVEF), and resting electrocardiography (ECG) in patients at high-risk for cardiovascular complications (Majhail et al., 2012). However, HCT-specific recommendations are based on retrospective studies that have identified cardiovascular complications in long-term survivors rather than optimal screening strategies developed by US Preventative Services Taskforce for the general population (Majhail et al., 2012; Hunt et al., 2009). Moreover, assessment of resting LVEF and ECG in high risk patients may fail to detect early signs of alterations in cardiovascular morphology, function, and coronary artery narrowing (Armenian and Chow, 2014; Khouri et al., 2012), suggesting that complementary stratification tools are required to fully evaluate CVD risk and identify those individuals at highest risk of future events.

Interventions that prevent and/or treat CVD risk factors and CVD in HCT patients will be of the utmost importance to mitigate CVD-specific mortality. In particular, an approach taking into account four intervention time points is needed (Khouri et al., 2012): (1) primordial prevention (prophylactic therapy given before or during HCT to prevent anticipated injury), (2) primary prevention (therapy provided to selected patients with early signs of myocardial and/or coronary vascular damage to treat injury and prevent progression), (3) secondary prevention (therapy provided after the detection of LVEF decline or coronary artery calcification to treat impairment), and (4) tertiary treatment (therapy provided after detection of HF or CAD clinical symptoms). Aerobic training (AT) is established as the cornerstone of disease prevention and treatment in multiple clinical settings (Gielen et al., 2010), and is well documented to improve insulin sensitivity, decrease lipids, and lower blood pressure with concomitant improvements in cardiovascular function and overall mortality in non-oncology settings (Flynn et al., 2009; Erbs et al., 2010; Eisele et al., 2008; Kavazis et al., 2008). Similarly, promising data in the oncology setting indicates that AT is safe and is associated with significant improvements in CVD risk factors (Schmitz et al., 2010; Speck et al., 2010). AT may confer similar benefits in HCT patients at high risk of CVD; however, the potential cardioprotective properties of AT in the context of HCT have received limited attention.

Here, we briefly discuss the risk and extent of CVD in adult HCT recipients, highlight novel tools for early detection of CVD, and review existing evidence in oncology and non-oncology populations supporting the potential role of AT as a viable therapeutic modality to abate/attenuate HCT-associated CVD.

2. Accelerated CVD following HCT: current evidence

For a comprehensive overview of CVD risk factors and CVD in HCT patients, the reader is referred to prior excellent reviews (Baker et al., 2012; Armenian and Chow, 2014; Baker et al., 2010); a summary of CVD following HCT is provided in Table 1. In the following sections we briefly review the incidence of CVD risk factors, CVD, and CVD-specific mortality.

2.1. Prevalence of CVD risk factors

The third National Cholesterol Education Program Adult Treatment Panel III (ATP III) report indicates that the age-adjusted prevalence of CVD risk factors such as hypertension, diabetes, and dyslipidemia in US adults is approximately 22% (Ford et al., 2002). Importantly, the same level and extent of CVD risk factor prevalence occurs at much earlier age following HCT. In a study that assessed the 10-year cumulative incidence, Armenian et al. (2012) found the prevalence of hypertension, diabetes, and dyslipidemia was 43.0, 18.7, and 48.3% respectively, in 1087 HCT recipients (median age of HCT: 44 years) compared to 34.6, 8.5, and 40.0% in the general population. Furthermore, Chow et al. (2014a) found that compared to pre-HCT, use of antihypertensives and diabetes medications was significantly higher 1-year post-HCT (6.7% versus 19.6% and 4.1% versus 12.9%, respectively) in 1379 HCT recipients (median age at time of HCT: 40 years), while Blaser et al. (2012) reported that a mean of two years following HCT, 73.4 and 72.5% had hyperc-