Cardiovascular Risk Factors in Survivors of Childhood Hematopoietic Cell Transplantation and their Role in Development of Cardiovascular Disease: A CCSS-CIBMTR Analysis

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Background: Hematopoietic cell transplantation (HCT) is an important curative treatment for children with high-risk hematologic malignancies and solid tumors. Cardiovascular (CV) disease remains a key cause of premature mortality among HCT survivors. CV risk factors (CVRF) potentiate these risks in adult HCT survivors but their incidence and impact in childhood HCT survivors are not established.

Methods: Five-year survivors of childhood cancer in the Childhood Cancer Survivor Study (CCSS), diagnosed at age <21 years between 1970-1999, were linked to the Center for International Blood and Marrow Transplant Research (CIBMTR) registry, which captures US HCT data. We assessed the cumulative incidence of grade 2-4 diabetes mellitus (DM), hypertension (HTN), and dyslipidemia, collectively known as CVRF, and subsequent grade 3-5 CV disease (coronary artery disease, myocardial infarction, arrhythmia, cardiomyopathy) using time since cohort entry as the time scale. The risk of each CVRF among HCT survivors transplanted within 5-years of diagnosis (n=1,349) was compared to survivors treated with conventional chemotherapy (n=8,018) and siblings (n=5,045). Cause-specific Cox proportional hazard models stratified by primary cancer diagnosis, sex, and race/ethnicity were used to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Results: Among survivors treated with childhood HCT (49% allogeneic; 56% male; median age at HCT, 9 years [range, 0-26]; median age at last follow-up, 31 years [range, 6-64]), the 20-year cumulative incidence was 19.3% for HTN, 13.7% for DM, and 15.2% for dyslipidemia. When compared to siblings, HCT survivors were at 7.6-fold risk for HTN [95% CI, 6.5-9.0]; 18.7-fold risk for DM [14.7-23.8]; and 14.3-fold risk for dyslipidemia [12-18]. Risks of each CVRF were also higher in HCT survivors compared to survivors treated with conventional chemotherapy (HR_{HTN} 2.3 [2.1-2.7]; HR_{DM} 6.1 [5.0-7.3]; HR_{lipid}4.3 [3.7-5.1]). Among HCT survivors matched between CCSS and CIBMTR (n=712), multivariable analyses revealed that total body irradiation-based HCT was associated with risk of DM (HR 2.8 [1.2-6.6]) and dyslipidemia (HR 2.3 [1.02-5.1) . Obesity (BMI≥30 kg/m^2) was associated with increased risk for developing each CVRF. Full results of the multivariable analysis are shown in **Table 1**. The 20-year cumulative

incidence of CV disease among the HCT cohort was 12.3% [10.4-14.4] with no difference noted among those treated with allogeneic versus autologous HCT. The presence of any CVRF was independently associated with a 2.03-fold risk of developing CV disease [1.5-2.8], while ≥2 CVRF were associated with a 2.5-fold risk (HR 2.5 [1.5-4.0]).

Conclusion: Childhood HCT survivors have a higher risk of developing CVRFs than siblings or survivors treated with conventional chemotherapy, which appear to confer an increased risk of developing subsequent CV disease. Interventions to reduce risk of CVRFs should be prioritized in this population.

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