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Male survivors of allogeneic hematopoietic stem cell transplantation have a long term persisting risk of cardiovascular events

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Long-term survivors of allogeneic stem cell transplantation (SCT) have increased risk of cardiovascular disease. We retrospectively studied cardiovascular risk factors (CVRFs) in 109 SCT survivors (62 males, 47 females; median age 34 years) five years or more after bone marrow (15) or T cell–depleted peripheral blood (94) SCT for CML (56), acute leukemia (29), MDS (13), and others (11). One death and two cardiovascular events were reported. At five and ten years after SCT, respectively, 44% and 52% had abnormal lipid profiles; 23% of 5-year survivors met the Adult Treatment Panel III threshold for dyslipidemia treatment, which is substantially higher than the age-matched general population. There were significant increases in prevalence of hypertension ($p < 0.001$), diabetes ($p = 0.018$), and body mass index ($p = 0.044$) after SCT compared with baseline. The Framingham general cardiovascular risk score (FGCRS) in males at five years after SCT projected a doubling (median 10.4% vs. 5.4%) in the 10-year risk of cardiovascular events. Females received HRT after SCT, and none had increased FGCRS. Chronic GVHD and C-reactive protein were not associated with CVRF at any time. All CVRFs stabilized between five and ten years after SCT. Thus, SCT survivors have sustained elevations in CVRFs. Males have a significantly increased risk of cardiovascular events in their second and third decade after SCT. Published by Elsevier Inc. on behalf of ISEH - Society for Hematology and Stem Cells.

As increasing numbers of patients have received hematopoietic stem cell transplants (SCTs) and survival rates have improved, the population of individuals surviving decades after SCT has expanded. After allogeneic transplantation, 25% of mortality in the first decade is attributed to treatment-related causes [1]. Although relapse and chronic graft-versus-host disease (cGVHD) remain the most common causes of mortality, survivors are also faced with endocrine dysfunction; infertility; osteoporosis; pulmonary, renal, and immune dysfunction; and gynecologic and ophthalmologic problems for many years after SCT [2–7]. Cardiovascular disease, the leading cause of mortality in the general population, is an increasing concern in long-term survivors. Because of disease and transplantation related radiation, chemotherapy, immunosuppression, prolonged hospitalizations, and deconditioning, the risk of premature death from cardiac complications has been reported to be 2.3-fold higher among SCT survivors [1,8].

Cardiovascular disease is a chronic condition with a long latency between developing vascular damage and acute cardiovascular events. Symptomatic cardiovascular disease can manifest decades after transplantation, making it difficult to assess the relationship of cardiovascular events to SCT. Alternatively, cardiovascular risk factors are detectible earlier and predict the course of cardiovascular disease. In posttransplant survivors, the well-established risk factors (smoking, hypertension, obesity, diabetes, dyslipidemia, family history, sedentary lifestyle) couple with transplant-related factors to increase cardiovascular disease risk [9]. These factors include cumulative exposure to chest irradiation, anthracyclines, transplant conditioning regimen

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(myeloablative or non-myeloablative), GVHD, endocrine dysfunction, and prolonged immunosuppressive therapy.

This study was conducted to evaluate the cardiovascular disease risk in a cohort of long-term allogeneic hematopoietic stem cell transplant survivors and to understand better the trends and associations between the various risk factors with time after transplant.

Methods

Patients and study design

We evaluated the cardiovascular risk profiles in 109 individuals who underwent allogeneic SCT at the National Institutes of Health between 1993 and 2006. All patients surviving beyond a 3-year posttransplant landmark gave written informed consent to long-term evaluation and follow-up on a natural history protocol (NHLBI 05-H-0130; ClinicalTrials.gov Identifier NCT00106 925). The survivors are followed up at regular clinic visits scheduled at years 3, 5, 7, 10, 15, and 20 after SCT beginning in 2005. We conducted cross-sectional analyses at 5 and 10 years after transplant to estimate the burden of cardiovascular risk in this population, when most survivors are not taking transplantation-related medications. At the time of analysis, 64 survivors were at the 5-year follow-up; 10 survivors had been followed up starting at 10 years, and 35 survivors had both the 5- and 10-year visits recorded. Median ages at transplant, 5-year, and 10-year follow-up were 34, 40, and 46 years, respectively. All women received hormone replacement therapy after SCT. Patient and transplant characteristics with outcomes are detailed in Table 1. Overall median follow up was 10.2 years.

Table 1. Patient characteristics at SCT and outcomes

Total number of survivors, n		109	
Median age in years (range)	At SCT	34	(7–66)
Gender, n (%)	Males	62	(57%)
	Females	47	(43%)
Diagnosis at SCT, n (%)	CML	56	(51%)
	Acute leukemia	29	(27%)
	MDS	13	(12%)
	Others	11	(10%)
Conditioning intensity, n (%)	Fully ablative	99	(91%)
	Reduced intensity	10	(9%)
Graft source, n (%)	Bone marrow	15	(14%)
	Peripheral blood	94	(86%)
No. of survivors at follow-up, n (%)	5 years post-SCT	64	(59%)
	10 years post-SCT	10	(9%)
	5 and 10 years post-SCT	35	(32%)
Median age in years (range)	5 years post-SCT	40	(12–71)
	10 years post-SCT	46	(17–66)
Outcomes at time of analysis, n (%)	Alive	97	(89%)
	Deaths	12	(11%)
Causes of death, n (%)	Relapse	4	(33%)
	cGVHD with multi-organ failure	2	(17%)
	Secondary malignancy	2	(17%)
	Infection/sepsis	2	(17%)
	Brain hemorrhage	1	(8%)
	Respiratory failure	1	(8%)

cGVHD = chronic graft-versus-host disease; SCT = stem cell transplantation.

Data were collected from electronic medical records and retrospective chart review. Only informative subjects were included in the analyses; subjects with incomplete or missing data were excluded. Because an age-matched control group was not available, we used general population-based studies as comparators [10–13]. Standard clinical definitions were used to diagnose hypertension [14] and diabetes [15]. Obesity was defined as body mass index (BMI) >30 kg/m^2 [16]. High-sensitivity assays for C-reactive protein (CRP) were performed after 2009. The general cardiovascular 10-year risk calculator available online through the Framingham Heart Study [17] was used to calculate the cardiovascular risk score and heart/vascular age. Framingham risk score calculation was limited to survivors older than 30 years. Dyslipidemia estimation using the Adult Treatment Panel III guidelines was limited to survivors older than 20 years [18].

Statistical analysis

The categorical risk factors—hypertension, diabetes, and cGVHD—were analyzed using the chi-square or Fischer exact test and the continuous risk factors: CRP, low-density lipoprotein (LDL) levels, high-density lipoprotein (HDL) levels, BMI, and Framingham risk score were analyzed using the *t* test or one-way analysis of variance. Paired *t* tests were used to compare the 5-year and 10-year posttransplant observations to the pretransplant baseline and the cardiovascular risk score to age- and sex-matched normal values, obtained from the Framingham general cardiovascular risk calculator. The Spearman test was used for correlation. Statistical significance was considered when $p < 0.05$. All statistical analyses were performed using Prism 5.03 (GraphPad Software, La Jolla, CA, USA).

Results

Cardiovascular events

Three cardiovascular events had been reported at the time of analysis (incidence 2.8%). Of 12 deaths, only one was due to a cardiovascular cause. This male patient, with a family history of maternal death from myocardial infarction and a history of coronary artery disease requiring percutaneous coronary intervention on two occasions 11 and 12 years after SCT, died of hemorrhagic stroke 16 years after SCT. Two other male survivors required percutaneous coronary intervention for coronary artery disease before 10 years after SCT. There were no other cardiac or vascular events.

Serial electrocardiograms revealed some new changes compared with the baseline pretransplant electrocardiogram in 27 survivors at 5 years after SCT (prolonged QTc, n =7; sinus bradycardia, n = 5; intraventricular conduction delay, n = 4; accelerated atrioventricular conduction, n = 2; accessory pathway, n = 1; ventricular bigeminy, n = 1; ectopic atrial rhythm, n = 1; possible infarct, n = 3; and borderline