Cardiovascular risk factors in hematopoietic cell transplantation survivors: role in development of subsequent cardiovascular disease

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Hematopoietic cell transplantation (HCT) recipients may be at an increased risk of developing hypertension, diabetes, and dyslipidemia (referred to as cardiovascular risk factors [CVRFs]); and these factors can potentially increase the risk of cardiovascular disease (CVD). We examined the incidence and predictors of CVRFs and subsequent CVD in 1885 consecutive 1+year survivors of HCT performed at City of Hope between 1995 and 2004. Ten-year cumulative incidence of hypertension, diabetes, dyslipidemia, and multiple (≥ 2) CVRFs was 37.7%, 18.1%, 46.7%, and 31.4%, respectively. The prevalence of CVRFs was significantly higher among HCT recipients compared with the general population; contributed to largely by allogeneic HCT recipients. Older age and obesity at HCT were associated with increased risk of CVRFs. History of grade II-IV acute graft versus host disease was associated with an increased risk for hypertension (relative risk [RR] = 9.1, $P < .01$), diabetes (RR = 5.8, $P < .01$), and dyslipidemia (RR = 3.2, $P < .01$); conditioning with total body irradiation was associated with an increased risk of diabetes (RR = 1.5, $P = .01$) and dyslipidemia (RR = 1.4, $P < .01$). There was an incremental increase in 10-year incidence of CVD by number of CVRFs (4.7% [none], 7.0% [1 CVRF], 11.2% [≥ 2 CVRFs], $P < .01$); the risk was especially high (15.0%) in patients with multiple CVRFs and pre-HCT exposure to anthracyclines or chest radiation. (*Blood*. 2012;120(23): 4505-4512)

Introduction

Hematopoietic cell transplantation (HCT) is now a widely accepted therapeutic option for hematologic malignancies.[1] Advances in transplantation strategies and supportive care have contributed to the marked improvement in outcome, resulting in a growing number of long-term survivors.[1-3] However, these survivors are at increased risk for long-term complications, because of pre-HCT as well as HCT-related therapeutic exposures.[4-6] A recent study[5] found that 3 out of every 5 long-term survivors reported a chronic health condition, and the cumulative incidence of severe or life-threatening conditions approached 40% at 15 years after HCT

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality after HCT.[7] CVD has a long latency, is irreversible and often debilitating, and it is associated with premature death.[7] In the nononcology setting, hypertension, diabetes, and dyslipidemia are well-recognized risk factors for the development of CVD.[8] HCT recipients may be at increased risk of developing these cardiovascular risk factors (CVRFs) because of pre-HCT and conditioning-related therapeutic exposures, as well as graft versus host disease (GVHD) and its management.[9-11] Previous studies evaluating CVRFs in HCT survivors have been limited by small sample sizes,[10-13] relatively short follow-up after HCT,[12-14] lack of evaluation among autologous HCT recipients,[10,14] lack of comparison with age- and sex-matched general population,[11,12,14] and reliance on self-reported outcomes.[9] Previous studies have also been limited by the lack of contribution of CVRFs and

pre-HCT therapeutic cardiotoxic therapeutic exposure in the development of CVD.[15-17]

We used a retrospective cohort study design to estimate the magnitude of risk of CVRFs after autologous and allogeneic HCT; to evaluate the role of patient demographics, pre-HCT and HCT-related therapeutic exposures, and post-HCT complications such as GVHD in the development of CVRFs after HCT; and to explore the impact of CVRFs on the subsequent development of CVD in a large population of autologous and allogeneic HCT survivors.

Methods

The current study included 1963 consecutive patients who underwent a first HCT for a hematologic malignancy at City of Hope (COH) between 1995 and 2004, and survived at least 1 year. Patients who refused participation (N = 32 [1.6%]) or whose medical records were missing (N = 46 [2.3%]) were excluded from the study; 1885 patients (96% of the cohort) were included in the analysis. Follow-up for the cohort was censored on December 31, 2008; 70.1% of the cohort had been followed through December 31, 2008 (if alive), or up to the date of death. Overall, the cohort provided 11 700 person-years of follow-up.

Medical records served as the primary source of data for this study. If the date of last medical visit at COH was not recent (ie, > 18 months before December 31, 2008), or if there were any gaps in the patients' history within the window of interest, a standard protocol was used to identify and contact

physicians outside COH to obtain relevant details regarding patient health. If the physician was not available or unable to provide recent information, the patient was contacted to obtain this information. The protocol was approved by COH institutional review board, and informed consent was obtained according to the Declaration of Helsinki. For all study participants, we abstracted treatment-related exposures and details regarding CVRFs and CVD, as described in "Cardiovascular risk factors" and "Cardiovascular disease."

Treatment-related exposures included pre-HCT anthracycline chemotherapy and chest radiation, as well as high-dose chemotherapy and radiation related to the conditioning regimen. Cumulative anthracycline dose was calculated using an established cardiotoxicity risk score.[18,19] Chest radiation included the following fields: mantle, mediastinal, or lung. Individuals who received a total of ≤ 200 cGy of radiation as part of conditioning were not considered as having received total body irradiation (TBI). For allogeneic HCT recipients, information regarding stem cell source, prophylaxis against acute GVHD (aGVHD), severity of aGVHD and chronic GVHD also was obtained. However, given the challenges of capturing detailed information pertaining to management of chronic GVHD in such a large cohort, information such as lifetime doses of immunosuppressive therapy were not included in our analysis.

Cardiovascular risk factors

The current study included only clinically validated CVRFs (hypertension, diabetes, and dyslipidemia) that were present for a minimum of 6 months and persisted for > 1 year after HCT. Hypertension was defined per the National Heart, Lung, and Blood Institute's Joint Committee criteria.[20] Thus, individuals 18 years of age or older with systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or those younger than 18 years of age with blood pressures greater than the 90th percentile for age, or individuals in either age categories receiving treatment for hypertension were defined as having hypertension. Diabetes mellitus was defined according to the American Diabetes Association's criteria.[21] Thus, patients with fasting plasma glucose level ≥ 126 mg/dL or random plasma glucose level ≥ 200 mg/dL, or patients receiving treatment for diabetes, were categorized as having diabetes mellitus. Dyslipidemia was defined according to the National Cholesterol Education Program criteria,[22] and included any one of the following: fasting total cholesterol ≥ 240 mg/dL, low-density lipoprotein ≥ 160 mg/dL, triglyceride ≥ 200 mg/dL, or treatment for dyslipidemia. Patients who developed transient CVRFs, defined as lasting < 6 months or resolving before the 1-year post-HCT time point, were considered as not having CVRF. The term "multiple CVRFs" was used to define the occurrence in an individual of ≥ 2 of any of the following: hypertension, diabetes, and dyslipidemia.

Cardiovascular disease

CVD included myocardial infarction, symptomatic coronary artery stenosis ($> 50\%$ narrowing requiring intervention), and stroke (defined per the American College of Cardiology–established criteria),[23,24] and congestive heart failure (defined per the American Heart Association/American College of Cardiology guidelines).[25] Patients who developed transient cardiac dysfunction because of a potentially reversible acute complication such as sepsis and subsequently had no evidence of cardiac dysfunction during follow-up were considered not to have CVD.

The National Health and Nutrition Examination Survey (NHANES)[26] provided population-based prevalence of CVRFs (www.cdc.gov/nchs/nhanes.htm); diagnostic criteria for CVRF were identical to those used for the HCT survivors. For the current study, data from NHANES surveys obtained between 1995 and 2008 were used; this allowed a comparison that spanned from the earliest year of HCT (1995) through the end of follow-up period (2008) for the current HCT cohort.

Statistical considerations

Cardiovascular risk factors. Prevalence of CVRF: A random sample of controls from the NHANES participants was matched (3:1) to the HCT survivors using the following criteria: sex, age (10-year group), and race/ethnicity. Differences in prevalence of CVRFs between the HCT and NHANES cohort were evaluated using generalized linear models, adjusted for era (1995-1998, 1999-2004, and 2005-2008) and included an error term to account for within person correlation among the HCT cohort members.

Cumulative incidence of each CVRF was calculated with death as competing risk.[27] The time to each CVRF was computed starting 1 year after HCT to the date of disease onset, date of last contact, or date of death, whichever came first. If a CVRF developed before HCT, or if the onset date for the CVRF was within 1 year of HCT, the event was left-censored at the 1-year time point. The Gray method[27] was used to compare the various subpopulations, which takes into consideration competing risk of death for left-censored data.

Risk factors associated with development of CVRFs after HCT: Cox proportional hazards regression was used to calculate relative risk (RR) estimates and their 95% confidence intervals (CI), adjusted for covariates. Separate regression models were created for the 3 CVRFs (hypertension, diabetes, and dyslipidemia). To determine predictors of post-HCT CVRF risk, survivors with the CVRF under consideration diagnosed before HCT was excluded from the analyses. Variables in the regression model included sex, race/ethnicity (non-Hispanic white, other), age at HCT (< 35 years, 35-54 years, ≥ 55 years), body mass index ([BMI] < 30 kg/m^2, ≥ 30 kg/m^2), and conditioning exposure (chemotherapy, chemotherapy + TBI). In addition, we included an ordinal variable that described the type of HCT and severity of aGVHD (autologous [referent group], allogeneic HCT with grades 0-I aGVHD, allogeneic HCT with grades II-IV aGVHD).

Cardiovascular disease. Cumulative incidence of CVD after HCT was calculated taking into consideration competing risk of death.[27] The time to CVD was computed starting 1-year post-HCT, with an outcome censor date of December 31, 2008. The Gray method[27] was used to compare the various subpopulations.

Risk factors associated with development of CVDs after HCT: When evaluating risk factors associated with post-HCT CVD, cumulative lifetime anthracycline dose < 250 mg/m^2, ≥ 250 mg/m^2), chest radiation (yes, no) sex, race/ethnicity (non-Hispanic white, other), age at HCT (< 35 years, 35-54 years, ≥ 55 years), BMI (< 30 kg/m^2, ≥ 30 kg/m^2), conditioning exposure (chemotherapy, chemotherapy + TBI), HCT type (allo, auto), chronic GVHD (none, any), and CVRFs (< 2, ≥ 2 CVRFs) were included as variables in the regression model.

Data were analyzed using SAS 9.2 (SAS Institute). All statistical tests were 2-sided, and P values $< .05$ were considered statistically significant.

Results

The clinical characteristics of the cohort are summarized in Table 1. Median age at HCT was 44.4 years (range, 0.6-78.9); primary diagnoses included Hodgkin or non-Hodgkin lymphoma (38.6%), acute lymphoblastic or myeloid leukemia (25.6%), multiple myeloma (15.3%) and chronic leukemia (12.8%). A total of 806 patients (42.7%) underwent allogeneic HCT. Compared with the autologous HCT recipients, allogeneic HCT recipients were younger (37.4 vs 49.9 years, $P < .01$), less likely to be non-Hispanic white (55.5% vs 68.5%, $P < .01$), and obese (18.6% vs 28.9%, $P < .01$). There was an underrepresentation of non-Hodgkin or Hodgkin lymphoma (10.4% vs 59.6%) among allogeneic HCT recipients, contributing to lower cumulative anthracycline exposure (median dose, 80 mg/m^2 vs 250 mg/m^2, $P < .01$) and a lower proportion of persons with a history of chest radiation (1.7% vs 8.0%, $P < .01$) compared with autologous HCT recipients. Allogeneic HCT recipients were more likely to have a diagnosis of acute or chronic leukemia (73.7% vs 11.9%, $P < .01$), and to have received TBI as part of their conditioning regimen (63.6% vs 44.6%, $P < .01$). A matched related donor was used in 69.9% of the allogeneic HCT recipients; 36.0% developed grade II-IV aGVHD; 29.9% had a history of extensive chronic GVHD.

Table 1. Patient and treatment characteristics

Characteristics	Entire cohort (N = 1885)	Autologous HCT (N = 1079)	Allogeneic HCT (N = 806)	P*
Sex				
Female, no. (%)	1087 (57.7)	622 (57.6)	465 (57.7)	.95
Ethnicity/race, no. (%)				
Non-Hispanic white	1186 (62.9)	739 (68.5)	447 (55.5)	< .01
Hispanic	456 (24.2)	212 (19.6)	244 (30.3)	
Other	243 (12.9)	128 (11.9)	115 (14.2)	
Age at HCT, y				
Median (range)	44.4 (0.6-78.9)	49.9 (11.6-78.9)	37.4 (0.6-74.9)	< .01
No. (%) < 35	575 (30.5)	212 (19.6)	363 (45.0)	< .01
35-50	644 (34.2)	334 (31.0)	310 (38.5)	
> 50	666 (35.3)	533 (49.4)	133 (16.5)	
Median follow-up after HCT, y (range)				
Entire cohort	5.9 (1.0-14.0)	5.6 (1-13.9)	6.2 (1-14.0)	< .01
Alive at censor date†	7.0 (1.2-14.0)	6.6 (1.2-13.9)	7.1 (1.5-14.0)	
Diagnosis, N (%)				
Lymphoma	727 (38.6)	643 (59.6)	84 (10.4)	< .01
Acute leukemia	482 (25.6)	128 (11.9)	354 (43.9)	
Multiple myeloma	290 (15.4)	290 (26.9)		
Chronic leukemia	240 (12.7)		240 (29.8)	
Other	146 (7.7)	18 (1.7)	128 (15.9)	
Pre-HCT therapy				
Anthracycline dose, median (range)‡	180 (0-600)	250 (0-650)	80 (0-640)	< .01
Chest radiation, no. (%)	100 (5.3)	86 (8.0)	14 (1.7)	< .01
Conditioning regimen, no. (%)				
Chemotherapy	891 (47.3)	598 (55.4)	293 (36.4)	< .01
Chemotherapy + TBI	994 (52.7)	481 (44.6)	513 (63.6)	
BMI at HCT				
< 30 kg/m²	1425 (75.5)	767 (71.1)	656 (81.4)	< .01
≥ 30 kg/m²	462 (24.5)	312 (28.9)	150 (18.6)	
Graft source				
Peripheral blood stem cells	1437 (76.2)	1068 (99.0)	369 (45.8)	< .01
Bone marrow	423 (22.4)	4 (0.4)	420 (52.0)	
Peripheral blood stem cells + bone marrow	11 (0.6)	7 (0.6)	4 (0.5)	
Cord blood	14 (0.8)		13 (1.6)	
Donor source				
Related			561 (69.9)	
Unrelated			247 (30.1)	
aGVHD, no. (%)				
Grade I or none			516 (64.0)	
Grade II-IV			290 (36.0)	
Chronic GVHD, no. (%)				
None			268 (33.2)	
Limited			297 (36.8)	
Extensive			241 (29.9)	

*Comparison of autologous versus allogeneic HCT recipients.

†December 31, 2008.

‡Expressed as doxorubicin equivalents (mg/m²).

Cardiovascular risk factors

Hypertension: In total, 671 study participants (35.6%) fulfilled the criteria for hypertension. Of these 335 (49.9%) were observed to have the condition at the time of HCT and 336 (50.1%) developed it after HCT. Median time to development of post-HCT hypertension was 0.35 years (range, 0-11 years). Allogeneic HCT recipients had a significantly shorter time to onset of post-HCT hypertension when compared with autologous HCT recipients (0.2 years vs 3.7 years, P < .01). Among allogeneic HCT recipients diagnosed with hypertension after HCT, 222 (85.7%) were receiving medications for prophylaxis or treatment of GVHD at the time of diagnosis of hypertension; the most common medications were cyclosporine ([CSA] 74.8%), corticosteroids (73.4%), mycophenolate mofetil ([MMF] 26.1%), tacrolimus (22.1%), and sirolimus (6.7%).

The cumulative incidence (± SE) of hypertension was 37.7% ± 3.6% at 10 years after HCT (Table 2). Allogeneic HCT recipients had a significantly higher incidence (P < .01) compared with autologous HCT survivors: 45.3% (± 2.1%) versus 32.0% (± 1.6%). Patients with grades II-IV aGVHD were at highest risk for hypertension at 10 years after HCT: 54.7% ± 3.4% (supplemental Figure 1A, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article).

Diabetes was diagnosed in 317 HCT recipients (16.8%). The condition developed after HCT in 55% of the patients; median time to post-HCT diabetes was 1.9 years (0-11 years). Time to onset of diabetes was significantly shorter for allogeneic HCT recipients compared with the autologous HCT recipients (1.2 years vs 3.3 years, P < .01). Among allogeneic HCT recipients diagnosed with post-HCT diabetes, 64.6% were receiving medications for

Table 2. CI of cardiovascular risk factors after HCT

	Entire cohort		Autologous HCT		Allogeneic HCT		
	At risk	CI, %	At risk	CI, %	At risk	CI, %	P*
Hypertension							
Baseline, at HCT	1885	17.8	1079	22.3	806	11.4	
1 y	1885	28.4	1079	24.3	806	33.9	
5 y	955	33.7	581	28.7	374	40.3	
10 y	232	37.7	139	32.0	138	45.3	< .01
Diabetes							
Baseline, at HCT	1885	7.6	1079	8.3	806	5.3	
1 y	1885	10.8	1079	9.9	806	11.9	
5 y	1242	15.1	705	13.4	537	17.5	
10 y	331	18.1	176	15.9	155	20.9	< .01
Dyslipidemia							
Baseline, at HCT	1885	18.5	1079	22.8	806	12.5	
1 y	1885	33.6	1079	31.3	806	36.6	
5 y	812	40.2	475	38.8	337	45.0	
10 y	168	46.7	98	43.3	70	50.5	< .01
Multiple (≥ 2)							
Baseline, at HCT	1885	8.6	1079	11.9	806	4.2	
1 y	1885	16.1	1079	13.1	806	20.0	
5 y	1091	25.0	644	20.7	447	30.7	
10 y	263	31.4	154	26.3	109	38.1	< .01

CI indicates cumulative incidence.

*Comparison of autologous versus allogeneic HCT recipients.

prophylaxis or treatment of GVHD at the time of diagnosis of diabetes; the most common medications were corticosteroids (85.3%), CSA (64.0%), MMF (28.0%), tacrolimus (26.7%), and sirolimus (6.7%).

The cumulative incidence of diabetes was 18.1% ± 0.9% at 10 years after HCT (Table 2). Allogeneic HCT recipients had a significantly higher incidence compared with autologous HCT survivors: 20.9% ± 1.6% versus 15.9% ± 1.2% (P < .01). Patients with grades II-IV aGVHD were at highest risk for diabetes (25.8% ± 2.7% at 10 years after HCT; supplemental Figure 1B).

Dyslipidemia was observed in 823 survivors (43.7%); the condition developed after HCT in 57.4% of the patients with

dyslipidemia. Median time to post-HCT dyslipidemia was 0.5 years (0-12.5 years). Time to onset of dyslipidemia was significantly shorter for allogeneic HCT recipients (0.2 years vs 1.6 years, P < .01). Among allogeneic HCT recipients diagnosed with post-HCT dyslipidemia, 64.6% were receiving medications for prophylaxis or treatment of GVHD at the time of diagnosis of dyslipidemia; the most common medications were CSA (78.3%), corticosteroids (63.7%), MMF (18.9%), tacrolimus (15.7%), and sirolimus (6.5%).

The cumulative incidence of dyslipidemia was 46.7% ± 3.6% at 10 years after HCT (Table 2). Allogeneic HCT recipients had a significantly higher incidence compared with autologous HCT survivors (50.5% ± 1.9% vs 43.3% ± 1.5%, P < 0.01). Patients with grades II-IV aGVHD were at highest risk for dyslipidemia (52.8% ± 3.4%; supplemental Figure 1C).

Multiple CVRFs: The cumulative incidence of developing multiple (≥ 2) CVRFs was 30.4% at 10 years after HCT (Table 2). Allogeneic HCT recipients had a significantly higher incidence when compared with autologous HCT survivors (35.1% ± 1.2% vs 26.7% ± 1.4%, P < 0.01). Patients with grades II-IV aGVHD were at highest risk for multiple post-HCT CVRFs (43.6% ± 2.3% at 10 years after HCT; supplemental Figure 1D).

Predictors of CVRFs developing after HCT

Multivariate analysis revealed that older age as well as obesity at HCT were significant predictors of all CVRFs (hypertension, diabetes, and dyslipidemia) developing after HCT (Table 3). Conditioning with TBI was associated with 1.5-fold increased risk of diabetes (95% CI, 1.10-2.16%) and a 1.4-fold increased risk of dyslipidemia (95% CI, 1.14-1.70%). Compared with autologous HCT recipients, allogeneic HCT recipients with grades 0-I aGVHD were at an increased risk of developing hypertension (RR = 5.2; 95% CI, 3.89-7.01%), diabetes (RR = 2.6; 95% CI, 1.75%-3.84%), and dyslipidemia (RR = 2.2; 95% CI, 1.77%-2.76%). Furthermore, allogeneic HCT recipients with a history of grades II-IV aGVHD were at an even higher risk for hypertension

Table 3. Multivariate regression analysis: risk factors for hypertension, diabetes, and dyslipidemia among HCT recipients

	Hypertension			Diabetes			Dyslipidemia		
Risk factor	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Sex									
Male	1.0			1.0			1.0		
Female	1.1	0.85-1.31	.60	1.3	0.98-1.84	.07	0.9	0.82-1.09	.91
Ethnicity/race									
Non-Hispanic white	1.0			1.0			1.0		
Other	0.8	0.58-0.98	.03	2.1	1.51-2.82	< .01	1.1	0.94-1.38	.18
Age at HCT, y									
< 35	1.0			1.0			1.0		
35-55	1.6	1.24-2.10	< .01	1.7	1.16-2.57	< .01	1.7	1.38-2.17	< .01
> 55	2.6	1.88-3.47	< .01	4.1	2.63-6.49	< .01	2.2	1.69-2.88	< .01
BMI at HCT									
< 30 kg/m^2	1.0			1.0			1.0		
≥ 30 kg/m^2	1.6	1.20-2.02	< .01	2.0	1.44-2.73	< .01	1.5	1.18-1.79	< .01
Conditioning									
Chemotherapy	1.0			1.0			1.0		
Chemotherapy + TBI	1.0	0.79-1.26	.98	1.5	1.10-2.16	.01	1.4	1.14-1.70	< .01
HCT Type									
Autologous	1.0			1.0			1.0		
Allogeneic, no aGvHD*	5.2	3.89-7.01	< .01	2.6	1.75-3.84	< .01	2.2	1.77-2.76	< .01
Allogeneic, aGvHD grade II-IV	9.1	6.57-12.19	< .01	5.8	3.93-8.53	< .01	3.2	2.49-4.04	< .01

HR indicates hazard ratio.

*Includes no aGvHD or grade I aGvHD.

Table 4. Prevalence of cardiovascular risk factors among HCT survivors and the general population

Prevalence	NHANES, %	Entire HCT cohort, %	P*	Autologous-HCT, %	P*	Allogeneic-HCT, %	P*
Hypertension							
1995-1998	19.6	27.9		19.2		38.7	
1999-2004	27.4	31.7		27.6		37.1	
2005-2008	34.6	36.7	< .001	32.0	.30	43.0	< .001
Diabetes							
1995-2000	5.7	7.6		5.8		9.8	
2001-2004	8.7	13.9		12.4		15.8	
2005-2008	8.5	17.3	< .001	16.1	.02	18.7	< .001
Dyslipidemia							
1995-2000	31.4	40.5		32.5		50.4	
2001-2004	40.7	38.8		36.6		41.8	
2005-2008	40.0	45.9	< .001	44.1	.81	48.3	< .001
Multiple (≥ 2)							
1995-2000	12.2	19.2		11.9		28.2	
2001-2004	17.9	23.6		20.0		28.4	
2005-2008	21.8	30.4	< .001	26.7	< .001	35.1	< .001

*Compared with NHANES cohort by using generalized linear model adjusting for era and within person correlation.

(RR = 9.0; 95% CI, 6.57%-12.19%), diabetes (RR = 5.8; 95% CI, 3.93%-8.53%), and dyslipidemia (RR = 3.2; 95% CI, 2.49%-4.04%).

Prevalence of CVRFs: HCT recipients compared with general population

Overall, the prevalence of CVRFs was significantly higher among HCT survivors, compared with age-, race/ethnicity, and sex-matched general population (Table 4). This difference was driven primarily by the higher prevalence of CVRFs among allogeneic HCT recipients.

Cardiovascular disease

In total, 115 patients developed CVD at a median of 4.0 years (0.1-13.9) after HCT; these included 75 patients with congestive heart failure, 21 with coronary artery stenosis, 17 with myocardial infarction, and 2 with stroke. The cumulative incidence of CVD was 7.8% ± 0.8% at 10 years after HCT. An increase in the number of CVRFs was associated with a corresponding increase in the cumulative incidence of CVD: no CVRF, 4.7% ± 1.0%; 1 CVRF, 7.0% ± 1.1%; and multiple (≥ 2) CVRFs, 11.2% ± 1.8% at 10 years, P < .01 (Figure 1A). The risk was especially high in patients with multiple CVRFs and past exposure to anthracyclines or chest radiation (15.0% ± 2.5%), compared with those with < 2 CVRFs and no cardiotoxic exposure (2.6% ± 0.1%, P < .01; Figure 1B). Subset analysis among survivors treated with anthracyclines and/or chest radiation (N = 1388) revealed a higher risk of CVD in patients with multiple CVRFs, irrespective of type of HCT (autologous, 17.7% ± 3.3% vs 6.3% ± 0.9%, P < .01; allogeneic, 10.4% ± 3.6% vs 4.6% ± 1.4%, P = .03; Figure 1C-D).

Multivariate analysis adjusting for sex, race/ethnicity, age at HCT, anthracycline dose, chest radiation, type of HCT, BMI, GVHD, and conditioning exposure revealed that survivors with multiple CVRFs were at a greater risk (RR = 1.5; 95% CI, 1.1%-2.2%; P = .04) of developing CVD compared with those with < 2 CVRFs.

Discussion

The growing population of long-term HCT survivors has brought to the forefront a host of chronic health-related conditions that can significantly affect the overall quality and quantity of survival. Although recurrence of primary disease remains the leading cause of mortality after HCT,[3,28,29] nonmalignant late effects such as CVD contribute increasingly with longer follow-up,[4-6] a problem that can be compounded by the high prevalence of CVRFs in HCT survivors, as demonstrated in the current study. Studies to date have been limited by relatively short follow-up after HCT,[12-14] reliance on questionnaire-based self-reported outcomes,[9] lack of comparison with the general population,[11,12,14] and lack of information regarding the contribution of CVRFs in the development of CVD in patients previously exposed to cardiotoxic agents such as anthracyclines and chest radiation.[15-17] The current study overcomes these limitations by comprehensively evaluating the risk of CVRFs and their modifying effect on subsequent development of CVD in a large cohort of HCT survivors with 11 700 person-years of follow-up. We found that allogeneic HCT survivors are at a substantially increased risk for CVRFs after HCT, and acute GVHD and/or its treatment are critical modifiers of this risk; conditioning with TBI is associated with an increased risk of diabetes and dyslipidemia regardless of HCT type. Survivors with pre-HCT cardiotoxic exposures and multiple post-HCT CVRFs are at highest risk for development of cardiovascular disease after HCT.

Previous studies, conducted largely in allogeneic HCT recipients, have reported wide-ranging estimates for prevalence of hypertension (15%-70%),[9,12,13,16] diabetes (7%-30%),[12,16] and dyslipidemia (16%-56%),[10,14,16] due, in part, to a variety of definitions used for CVRFs and varying lengths of follow-up of the study cohorts. In the current study, we used a conservative approach to defining CVRFs, therefore a condition had to be present for > 6 months and persist for > 1 year after HCT, highlighting the magnitude of disease burden that persists long after the immediate post-HCT period. Overall, the prevalence of individual CVRFs was significantly higher among HCT patients compared with the general population. The 10-year post-HCT incidence of hypertension, diabetes, and dyslipidemia was 37.7%, 18.1%, and 46.7%, respectively; the incidence of multiple CVRFs exceeded 31%.

Allogeneic HCT recipients were at a significantly higher risk of all 3 CVRFs compared with autologous HCT recipients. This was reflected by the overall prevalence of the individual CVRFs among allogeneic HCT recipients, as well as the incidence of post-HCT CVRFs, compared with autologous HCT recipients. The latency of CVRFs among allogeneic HCT patients was short, coinciding with receipt of immunosuppressants for prophylaxis/treatment of
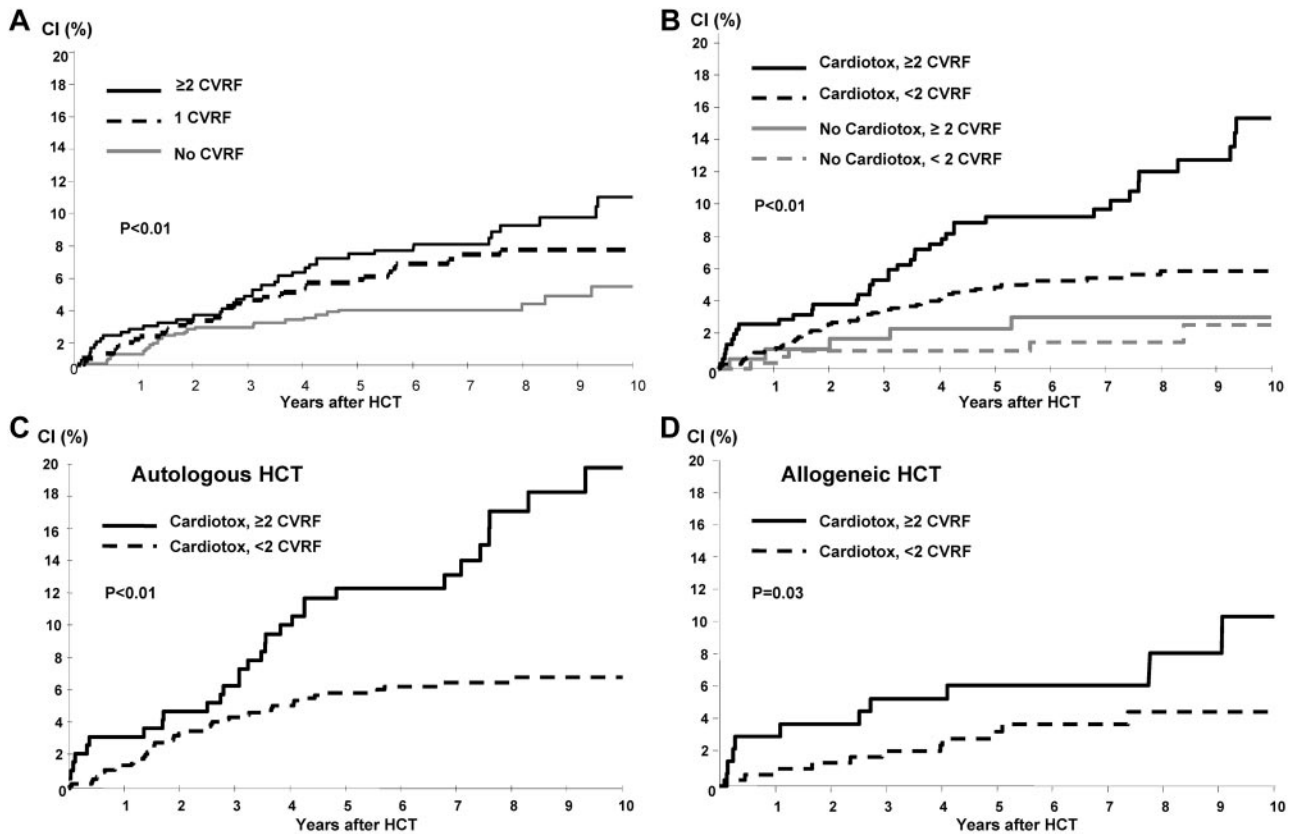
Figure 1. Cumulative incidence of cardiovascular events after HCT. Cumulative incidence of cardiovascular events after HCT by number of CVRFs (A), by number of CVRFs and pre-HCT cardiotoxic exposure (B), by autologous HCT survivors with pre-HCT cardiotoxic exposure (C), and by allogeneic HCT survivors with pre-HCT cardiotoxic exposure (D). Cardiotox, anthracycline or chest radiation.

aGVHD. In fact, allogeneic HCT recipients with grades II-IV aGVHD were at highest risk of subsequent CVRFs, with an incidence that exceeded 25% for diabetes, and 50% for hypertension and dyslipidemia at 10 years after HCT. Multivariate regression analysis revealed that survivors with a history of grade II-IV aGVHD were at a 9-fold risk of hypertension, 6-fold risk of diabetes, and 3-fold risk of dyslipidemia compared with autologous HCT survivors.

It is well recognized that drugs used to manage GVHD can increase the risk of CVRFs.[30] Dyslipidemia occurs in 45%-80% of solid-organ transplantation patients on immunosuppressive agents, and hypertension and insulin resistance are well-reported side effects of corticosteroids and calcineurin inhibitors.[30,31] Furthermore, withdrawal of these medications may not necessarily result in resolution of CVRFs.[10,32] In the current study, the majority of allogeneic HCT patients were on immunosuppressive therapy at the time of CVRF diagnosis. In fact, allogeneic HCT survivors with grades 0-I aGVHD were at a 2- to 5-fold increased risk of developing CVRFs, suggesting that exposures to immunosuppressants for GVHD prophylaxis in the early post-HCT period may have contributed to subsequent risk of CVRFs.

The current report identified an association between TBI and diabetes and dyslipidemia; similar association with TBI has been observed by previous studies in pediatric[33,34] and adult[9] HCT survivors. The mechanism by which TBI increases the risk of diabetes and dyslipidemia is not clear. Previous studies have shown that abdominal radiation may contribute to insulin resistance and/or metabolic syndrome in conventionally treated cancer patients, suggesting the role for radiation-induced pancreatic and/or hepatic injury.[35,36] The association between TBI and diabetes and dyslipide-

mia in the current study could potentially be because of the combined effects of abdominal radiation and post-HCT gonadal dysfunction.[37] Future studies are needed to fully explore the pathophysiology of TBI-associated diabetes and dyslipidemia. Investigators choosing TBI for HCT will need to weigh the efficacy gained against the potential for adverse health-related complications that can significantly impact the quality and quantity of survival in long-term survivors of HCT.

The cumulative incidence of CVD after HCT approached 8% at 10 years after transplantation. Survivors with multiple CVRFs were at a higher risk of developing CVD; the 10-year cumulative incidence of CVD exceeded 11% in these patients, whereas the incidence was 2.6% among those with < 2 CVRFs. In the current study, the impact of CVRFs on subsequent CVD risk was especially pronounced in patients with previous anthracycline and/or chest radiation exposure. Autologous HCT recipients with pre-HCT cardiotoxic exposures and multiple post-HCT CVRFs had the highest risk for CVD with a cumulative incidence approaching 18% at 10 years. The higher incidence of CVD after autologous HCT is likely because of the combined effects of higher lifetime anthracycline dose (250 mg/m^2 vs 80 mg/m^2), a higher prevalence of chest radiation (8% vs 1.7%), and older age at HCT (median, 49.9 years vs 37.4 years) compared with allogeneic HCT. Nevertheless, the presence of multiple CVRFs resulted in a higher incidence of CVD in both autologous and allogeneic HCT recipients exposed to anthracyclines and/or chest radiation. After adjusting for age at HCT, cardiotoxic therapeutic exposures, and stem cell source, patients with multiple CVRFs remained at a 1.5-fold risk of developing cardiovascular disease. These finding are in agreement with other studies that report a high risk for CVD in

HCT survivors with multiple CVRFs, regardless of HCT type.[15,16,38] However, the current study extends beyond previous observations by demonstrating that patients with pre-HCT cardiotoxic exposures are at a particularly high risk of CVD, suggesting that CVRFs may accelerate myocardial remodeling after cardiotoxic therapy (pre-HCT anthracyclines, chest radiation)[38,39] or exacerbate existing endothelial injury because of GVHD and/or radiation.[15,40] Information obtained from the current study may help set the stage for the development of more aggressive intervention strategies such as early screening and treatment of CVRFs in HCT survivors at highest risk of adverse cardiovascular outcomes.

Because of the limitations associated with a retrospective medical records review, the current study was not able to assess the role of gonadal dysfunction, the duration and intensity of tobacco exposure, as well as details regarding physical activity and family history of CVRF or CVD. However, the prevalence of any past smoking was analyzed and found to be comparable between those with and without cardiovascular disease. In a previous study, we reported that the large majority of HCT survivors quit smoking after HCT, and < 15% reported current tobacco use.[41] Importantly, the CVRFs included in the current study represent the most well-recognized modifiers of cardiovascular disease risk, accounting for up to 70% of the attributable risk for cardiac[42,43] as well as arterial[44] disease in the general population. Furthermore, although exposure to immunosuppressants was captured, details such as lifetime doses of immunosuppressive therapy could not be included in the current analyses, given the challenges of capturing detailed information pertaining to management of GVHD (especially because management is often outpatient, with limited and often incomplete information recorded regarding changes in immunosuppressant dose in the medical record). The current study did not include individuals who underwent T cell–depleted HCT. It remains to be seen if alternative transplant strategies such as T cell–depleted HCT may decrease the risk post-HCT CVRFs because of reduced use of GVHD medications such as calcineurin inhibitors.

In summary, we found that the magnitude of risk of CVRFs after HCT is substantial and that allogeneic HCT recipients are at an especially high risk compared with the general population. The risk of post-HCT CVRFs is highest among those with grades II-IV aGVHD. Patients treated with TBI have a significant risk for post-HCT diabetes and dyslipidemia. We demonstrate a clear association between multiple CVRFs and the subsequent development of CVD, with the strongest association noted among HCT survivors previously treated with cardiotoxic therapies. Taken together, these data form the basis for developing predictive models for identifying high-risk individuals for targeted surveillance, as well as aggressive management of cardiovascular risk factors.

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Authorship

Contribution: S.H.A. had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis; S.H.A. and S.B. contributed to study concept and design; S.H.A., T.V., E.B., K.K.N., and L.F. contributed to acquisition of data; S.H.A., C.L.S., F.L.W., K.K.N., and S.B. contributed to analysis and interpretation of data; S.H.A. and S.B. contributed to drafting of the manuscript; S.H.A., T.V., C.L.S., F.L.W., K.K.N., K.V., R.S., S.J.F., and S.B. provided critical revision of the manuscript and important intellectual content; and S.H.A., S.J.F., and S.B. contributed to procurement of funding.

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