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Late Mortality after Allogeneic Bone Marrow Transplantation in Childhood for Bone Marrow Failure Syndromes and Severe Aplastic Anemia

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A B S T R A C T

Children with bone marrow failure syndromes and severe aplastic anemia (SAA) are treated with allogeneic blood or marrow transplantation (BMT). However, there is a paucity of studies examining late mortality risk after allogeneic BMT performed in childhood for bone marrow failure syndromes and SAA and evaluating how this risk differs between these diseases. We investigated cause-specific late mortality in 2-year survivors of allogeneic BMT for bone marrow failure syndromes and SAA performed before age 22 years between 1974 and 2010 at 2 US transplantation centers. Vital status information was collected from medical records, the National Death Index, and Accurint databases. Overall survival was calculated using Kaplan-Meier techniques. The standardized mortality ratio (SMR) was calculated using age- sex-, and calendar-specific mortality rates from the Centers for Disease Control and Prevention. Among the 2-year survivors of bone marrow failure syndromes (n = 120) and SAA (n = 147), there were 15 and 19 deaths, respectively, yielding an overall survival of 86.4% for bone marrow failure syndromes and 93.1% for SAA at 15 years post-BMT. Compared with the general population, patients with bone marrow failure syndromes were at a higher risk for premature death (SMR, 22.7; 95% CI, 13.1 to 36.2) compared with those with SAA (SMR, 4.5; 95% CI, 2.8 to 7.0) ($P < .0001$). The elevated relative risk persisted at ≥15 years after BMT for both diseases. The hazard of all-cause late mortality was 2.9-fold (95% CI, 1.1 to 7.3) higher in patients with bone marrow failure syndromes compared with those with SAA. The high late mortality risk in recipients of allogeneic BMT in childhood for bone marrow failure syndromes calls for intensified life-long follow-up.

INTRODUCTION

Allogeneic blood or marrow transplantation (BMT) is a curative option for several bone marrow failure syndromes, as well as for severe aplastic anemia (SAA). For these bone marrow failure syndromes, allogeneic BMT is the sole curative treatment, although it does not abrogate the inherent risk of malignancy in Fanconi anemia. For SAA, allogeneic BMT and immunosuppressive therapy are the main therapeutic modalities currently used to treat both children and adults.

Most previous reports on mortality after allogeneic BMT for bone marrow failure syndromes and SAA in childhood have examined survival from BMT, focusing on early mortality [1-5]. Studies investigating late mortality after allogeneic BMT in childhood have been limited by small samples [6,7]. Moreover, most previous studies on late mortality after allogeneic BMT for SAA have included mixed cohorts of adult and pediatric BMT recipients [8,9]. Thus, there is a knowledge gap regarding

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late mortality after allogeneic BMT in childhood for these conditions, as well as possible differences in late mortality between the 2 conditions. In the present study, we addressed these issues in a cohort of children treated with allogeneic BMT between 1974 and 2010 for bone marrow failure syndromes and SAA, restricted to those who survived for ≥2 years. Importantly, the present study permits comparison of the late mortality experience between patients with bone marrow failure syndromes and those with SAA.

METHODS

The Blood or Marrow Transplant Survivor Study (BMTSS-2) is a collaborative effort among the City of Hope, University of Minnesota, and University of Alabama at Birmingham examining the long-term outcomes of individuals who have survived for ≥2 years after BMT. To be included in this analysis, patients had to have received allogeneic BMT for a bone marrow failure syndrome or SAA at City of Hope or University of Minnesota between 1974 and 2010, at age ≤21 years, and survived for at least 2 years after transplantation. Patients who received a second BMT were excluded.

Information on primary diagnosis, therapeutic agents used for preparative regimens, type of donor stem cell graft (related or unrelated donor), stem cell source, chronic graft-versus-host disease (GVHD), and agents used for chronic GVHD prophylaxis, as well as demographic characteristics, was obtained for all eligible cases from the institutional transplantation databases. The National Death Index (NDI) Plus [10] and/or medical records provided information regarding dates and causes of death through December 31, 2015. Additional information obtained from medical records and Accurint databases [11] were used to extend the vital status information through December 31, 2016. All patients were assigned a primary and, if present, a secondary cause of death independently by 2 investigators (A.S.H. and J.W.). In the event of discrepant assignments, a third investigator (S.B.) provided adjudication. The Human Subjects Committee at the participating institutions approved the BMTSS-2 protocol. Informed consent was obtained in accordance with the Declaration of Helsinki.

Statistical Analysis

The standardized mortality ratio (SMR), a ratio of observed to expected number of deaths, was used to compare the mortality experienced by this cohort to the age- (5-year interval), sex-, and calendar-specific (1-year interval) mortality of the US general population. Person-years at risk were computed from the date 2 years after allogeneic BMT to either the date of death or date of censoring (December 31, 2016), whichever occurred first. The expected number of deaths was calculated by multiplying the person-years in each defined stratum by the corresponding US mortality rates, obtained from Centers for Disease Control and Prevention [12]. The 95% confidence interval (CI) of the SMR was calculated using the Poisson regression method described by Vandenbroucke [13]. Absolute excess risk (AER) was defined as the difference between the observed number and the expected number of deaths per 1,000 person-years of follow-up.

Kaplan-Meier techniques were used to describe overall survival, conditional on surviving for ≥2 years from allogeneic BMT. The cumulative incidence of mortality was calculated using competing–risk methods. Cox regression analysis was used to identify predictors of all-cause mortality. Owing to the small number of subjects and deaths in each model and potential collinearity between variables, a parsimonious model was created using the variables with associated P values <0.1 in the multivariable model. The evaluated predictors included age at allogeneic BMT, sex, race/ethnicity, primary disease (SAA or a bone marrow failure syndrome), donor type, stem cell source, conditioning regimen, chronic GVHD, and era of transplantation. Two-sided tests with $P < .05$ were considered statistically significant. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Entire Cohort

A total of 267 children underwent allogeneic BMT for bone marrow failure syndromes (n = 120; including Fanconi anemia [n = 104], Diamond Blackfan anemia [n = 9], Shwachman-Diamond syndrome [n = 2], dyskeratosis congenita [n = 3], Kostmann agranulocytosis [n = 1], and amegakaryocytosis [n = 1]) or SAA (n = 147) between 1974 and 2010 and survived for ≥2 years post-BMT. Table 1 summarizes the demographic and clinical characteristics of the patient population, and Supplementary Table 1 provides details on patients with Fanconi anemia. The median age at transplantation was lower for the patients with bone marrow failure syndromes compared with those with SAA (8.3 years [range, 1.4 to 21.9 years] versus 12.9 years [range, 1.7 to 21.4 years]). The sex and race/ethnicity distributions were similar in the 2 cohorts. Unlike the patients with SAA, the vast majority of patients with a bone marrow failure syndrome (86%) underwent transplantation between 2000 and 2010. Unrelated donor BMT was performed in 63% of the patients with bone marrow failure and in 24% of those with SAA. Bone marrow was the major source of stem cells for both patient cohorts (79% for bone marrow failure syndromes and 97% for SAA). Overall, 12% of the bone marrow failure cohort and 29% of the SAA cohort had a history of chronic GVHD.

After a median follow-up of 11.6 years (range, 2.2 to 28.5 years), 15 patients (12.5%) with a bone marrow failure syndrome had died after surviving for ≥2 years post-BMT at a median age of 21.6 years (range, 5.7 to 35.4 years). The median follow-up after BMT for SAA was longer at 21.4 years (range, 2.0 to 40.6 years). Among patients with SAA, 19 (12.9%) had died after surviving for ≥2 years post-BMT at a median age of 29.8 years (range, 7.8 to 54.1 years). The cumulative mortality at 10 years and 15 years after BMT was 7.7% and 13.6%, respectively, for the bone marrow failure syndrome cohort and 4.2% and 6.9%, respectively, for the SAA cohort (Figure 1A). The cumulative mortality after BMT for Fanconi anemia and other bone marrow failure syndromes is shown in Figure 1B.

Table 2 presents the SMRs in this cohort using age-, sex-, and calendar-specific rates from the general US population. Compared with the general population, patients who underwent allogeneic BMT for bone marrow failure syndromes were at a greater risk for premature death (SMR, 22.7; 95% CI, 13.1 to 34.2) than were those who underwent allogeneic BMT for SAA (SMR, 4.5; 95% CI, 2.8 to 7.0) ($P < .0001$). Analyzing the 104 patients with Fanconi anemia separately, the SMR was 18.7 (95% CI, 9.7 to 32.0) (Supplementary Table 2). In both cohorts, the SMR was lowest in patients who underwent transplantation between 2000 and 2010. Relative mortality was higher in patients with a history of chronic GVHD compared with those without a history of chronic GVHD (bone marrow failure syndrome cohort: SMR, 102.6 [95% CI, 44.1 to 198.4]; SAA cohort: SMR, 12.8 [95% CI, 5.5 to 24.7]; $P = .003$). Relative mortality was highest in the 2- to 9-year period post-BMT in both cohorts (bone marrow failure syndrome cohort: SMR, 114.2 [95% CI, 54.9 to 205.9]; SAA cohort: SMR, 72.3 [95% CI, 25.9 to 155.3]). The SMR declined thereafter but was still significantly elevated at ≥15 years after BMT (bone marrow failure syndrome cohort: SMR, 9.1 [95% CI, 2.3 to 23.6]; SAA cohort: SMR, 2.7 [95% CI, 1.4 to 4.8]).

The AER for all-cause late mortality was 10.3 per 1,000 person-years (95% CI, 4.8 to 15.7) for the bone marrow failure syndrome cohort and 4.3 per 1,000 person-years (95% CI, 1.8 to 6.9) for the SAA cohort (Table 3). Analyzing patients with Fanconi anemia separately, the AER was 8.5 (95% CI, 3.2 to 13.7) (Supplementary Table 2). The AER was significantly elevated in the 2- to 9-year period post-BMT (bone marrow failure syndrome cohort: 25.6 [95% CI, 8.7 to 42.5]; SAA cohort: 27.2 [95% CI, 3.0 to 51.4]), but not thereafter.

After adjusting for demographic and clinical variables, the hazard of all-cause late mortality was 2.9-fold higher (95% CI, 1.1 to 7.3; $P = .03$) in the bone marrow failure syndrome cohort compared with the SAA cohort. In separate analyses, the hazard of all-cause late mortality was higher among patients with chronic GVHD compared with those without chronic GVHD in both cohorts (bone marrow failure syndrome: hazard ratio [HR], 5.4 [95% CI, 1.8 to 16.4]; SAA: SMR, HR, 4.6 [95% CI, 1.7 to 12.3]). In addition, in the bone marrow failure syndrome cohort, the hazard of late mortality was higher in recipients of

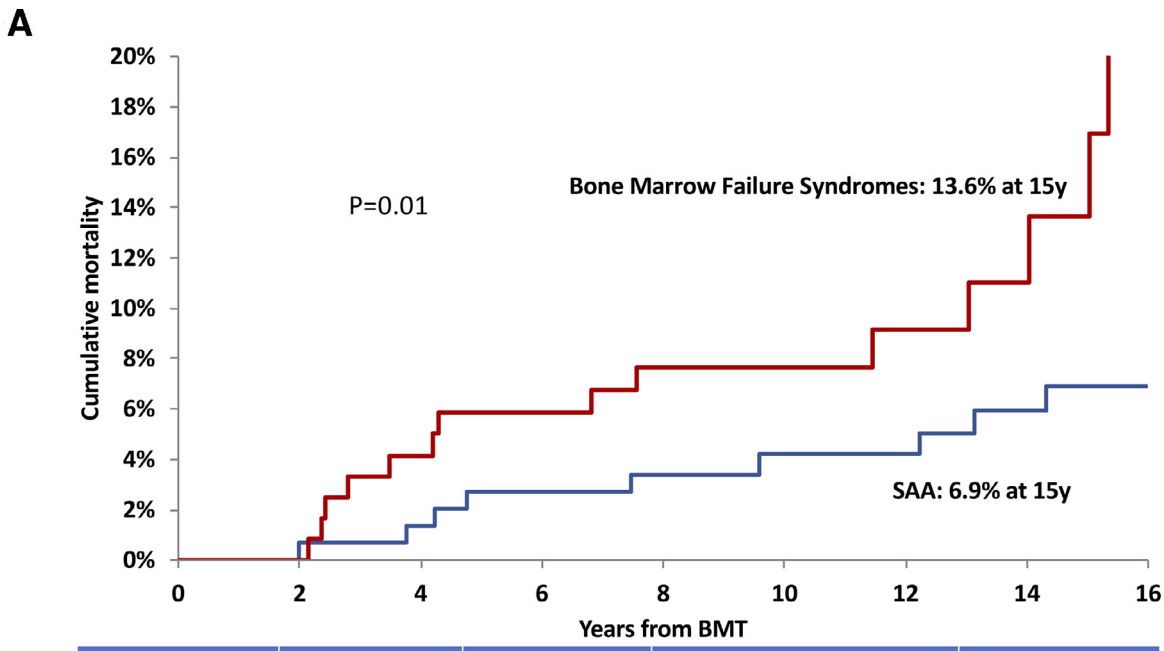
Table 1
Demographic and Clinical Characteristics of 267 2-Year Survivors of Allogeneic BMT in Childhood for Bone Marrow Failure Syndrome and SAA

Variable		Primary Diagnosis			
		Bone Marrow Failure Syndromes*		SAA	
Number of patients		120	(44.9)	147	(56.1)
Sex, n (%)					
	Male	65	(54.2)	75	(51.0)
	Female	55	(45.8)	72	(49.0)
Race/ethnicity, n (%)					
	Non-Hispanic white	87	(72.5)	103	(70.1)
	Non-Hispanic black	5	(4.2)	10	(6.8)
	Hispanic	15	(12.5)	25	(17.0)
	Other	9	(7.5)	9	(6.1)
	Unknown	4	(3.3)	0	(0.0)
Age at BMT, yr					
	0-4	23	(19.2)	21	(14.3)
	5-9	59	(49.2)	36	(24.5)
	10-14	25	(20.8)	31	(21.1)
	15-21	13	(10.8)	59	(40.1)
Age at BMT, yr, median (range)		8.3	1.4-21.9	12.9	(1.7-21.4)
Treatment era, n (%)					
	<1990	1	(0.8)	64	(43.5)
	1990-1999	16	(13.3)	35	(23.8)
	2000-2010	103	(85.8)	48	(32.7)
Type of donor, n (%)					
	Related	45	(37.5)	112	(76.2)
	Unrelated	75	(62.5)	35	(23.8)
	Bone marrow	95	(79.2)	143	(97.3)
	PBSCs/cord blood	25	(20.8)	4	(2.7)
Conditioning regimen, n (%)					
	Total body irradiation	80	(67.2)	40	(26.5)
	Cyclophosphamide	116	(97.5)	145	(96.0)
	Antithymocyte globulin	105	(91.3)	87	(57.6)
	Fludarabine	99	(83.2)	19	(12.6)
	Busulfan	10	(8.4)	1	(0.7)
	Other radiotherapy	4	(3.4)	60	(39.5)
	Other chemotherapy	14	(11.7)	9	(6.1)
Conditioning regimen, group, n (%)					
	Fludarabine and TBI†	68	(56.7)	16	(10.9)
	Fludarabine without TBI†	31	(25.8)	3	(2.0)
	Other conditioning regimens	21	(17.5)	128	(87.1)
Chronic GVHD, n (%)					
	Yes	14	(11.7)	43	(29.3)
	No	103	(85.8)	98	(66.7)
	Missing	3	(2.5)	6	(4.1)
GVHD prophylaxis, n (%)					
	Yes	114	(99.1)	141	(96.6)
	Methotrexate	16	(13.9)	121	(82.9)
	Cyclosporine	108	(93.9)	78	(53.4)
	Systemic corticosteroids	83	(72.2)	53	(36.3)
	Mycophenolate mofetil	13	(11.3)	8	(5.5)
	Tacrolimus and/or sirolimus	4	(3.5)	6	(4.1)
	T cell depletion	55	(47.8)	1	(0.7)
Treating institution, n (%)					
	City of Hope	14	(12.2)	51	(33.6)
	University of Minnesota	101	(87.8)	96	(63.2)
Deaths, n (%)		15	(12.5)	19	(12.9)

PBSCs indicates peripheral blood stem cells; TBI, total body irradiation.
*Includes 104 patients with Fanconi anemia, 9 with Diamond Blackfan anemia, 2 with Shwachman-Diamond syndrome, 3 with dyskeratosis congenita, 1 with Kostmann agranulocytosis and 1 with amegakaryocytosis.
†The conditioning regimen also includes other chemotherapeutic agents.

unrelated donor BMT compared with recipients of related donor BMT (SMR, 10.7; 95% CI, 1.2 to 99.9), and increased with age at BMT by 15% per year (95% CI, 1.0 to 1.3; $P = .03$). No other variables in the multivariable model were significantly associated with all-cause late mortality.

Causes of death were available for 12 patients in the bone marrow failure syndrome cohort (80% of those deceased). The most prevalent causes of death included subsequent neoplasms (SNs; n = 8; 73%), infection (n = 4; 36%), and chronic GVHD (n = 3; 27%) (Supplementary Table 3). The types of SNs included leukemia (n = 2) and brain, oral cavity, breast, colon, lung, and disseminated malignant neoplasm, primary unknown (n = 1 each). Of the 8 deaths due to SN, 6 occurred in patients with Fanconi anemia and 6 occurred within the first 2 to 9 years after BMT. Among the deceased patients in the SAA cohort, cause of death was available for 12 patients (63%). Chronic GVHD was the most common cause (n = 3; 25%), and other causes included infection (n = 2), cardiac disease (n = 2), pulmonary disease (n = 2), SN (n = 1), external cause (n = 2), primary disease (n = 1), and other causes (n = 4).



Patient at risk	2y	5y	10y	15y
SAA	147	143	123	98
Bone Marrow Failure	120	113	72	27

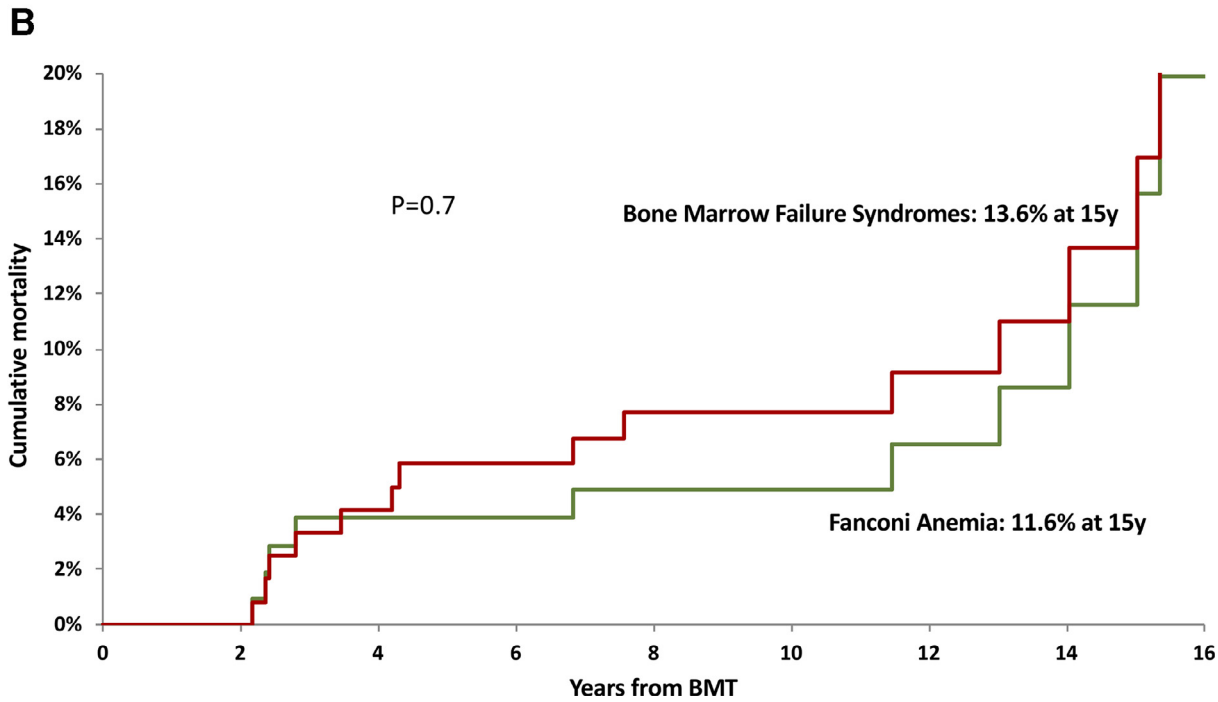


Figure 1. Cumulative incidence of all-cause late mortality of 2-year survivors after allogeneic BMT in childhood for all bone marrow failure syndromes (n = 120) and for Fanconi anemia (n = 104).

DISCUSSION

Our present results show that the late mortality rates after allogeneic BMT in childhood to treat bone marrow failure syndromes and SAA are significantly higher than those in the general population and remain elevated even after 15 years post-BMT. Chronic GVHD is associated with an elevated risk of late mortality in both of these cohorts. Importantly, the risk of late mortality is significantly greater in patients undergoing allogeneic BMT in childhood for a bone marrow failure syndrome compared with those who did so for SAA. The vast majority of deaths in the bone marrow failure syndrome cohort were due to SNs.

Table 2
SMR Among 2-Year Survivors of Allogeneic BMT in Childhood for Bone Marrow Failure Syndromes and SAA, by Demographic and Clinical Characteristics

Variable	Bone Marrow Failure Syndromes					SAA				
	No. of Patients	Observed	Expected	SMR	95% CI	No. of Patients	Observed	Expected	SMR	95% CI
All patients	120	15	0.7	22.7	13.1-36.2	147	19	4.0	4.5	2.8-7.0
Sex										
Male	65	6	0.5	12.1	4.8-24.6	75	10	2.7	3.7	1.8-6.4
Female	55	9	0.2	54.0	25.9-97.3	72	8	1.2	6.5	3.0-12.2
Age at BMT, yr										
<10	82	7	0.3	23.1	9.9-44.7	57	6	0.9	6.5	2.6-13.1
≥10	38	8	0.4	22.4	10.2-41.6	90	12	3.0	4.0	2.1-6.6
Treatment era										
<2000	17	6	0.2	27.2	10.8-55.1	99	17	3.6	4.7	2.8-7.3
≥2000	103	9	0.4	20.5	9.8-36.9	48	1	0.3	3.0	0.2-13.4
Type of donor										
Related	45	1	0.3	3.9	0.2-17.3	112	17	3.7	4.6	2.8-7.2
Unrelated	75	14	0.4	34.5	19.4-55.8	35	1	0.3	3.3	0.2-14.7
Stem cell source										
Bone marrow	95	12	0.5	21.9	11.8-36.8	143	18	3.9	4.6	4.6-4.6
PBSCs/cord blood	25	3	0.1	26.4	6.6-68.4	3	0	0.0	0.0	0.0-0.0
Chronic GVHD										
No	99	7	0.5	12.8	5.5-24.7	98	6	2.5	2.4	0.9-4.8
Yes	14	7	0.1	102.6	44.1-198.4	43	11	1.4	8.1	4.2-13.9
Overall survival after BMT, yr										
2-9	45	45	0.1	114.2	54.9-205.9	24	5	0.1	72.3	25.9-155.3
10-14	45	45	0.3	11.9	3.0-30.8	25	3	0.2	12.7	3.2-33.0
15+	25	25	0.3	9.1	2.3-23.6	98	10	3.7	2.7	1.4-4.8

Table 3
AER of All-Cause Mortality Among 2-Year Survivors of Allogeneic BMT in Childhood for Bone Marrow Failure Syndromes and SAA, by Demographic and Clinical Characteristics

Variable	Bone Marrow Failure Syndromes					SAA				
	No. of patients	Observed	Expected	AER*	95% CI	No of patients	Observed	Expected	AER*	95% CI
All patients	120	10.8	0.5	10.3	4.8-15.7	147	5.5	1.2	4.3	1.8-6.9
Sex										
Male	65	7.8	0.6	7.1	0.9-13.3	75	5.9	1.6	4.3	0.6-7.9
Female	55	14.5	0.3	14.2	4.8-23.7	72	5.2	0.8	4.4	0.8-8.0
Age at BMT, yr										
<10	82	7.4	0.3	7.1	1.6-12.6	57	5.0	0.8	4.2	0.2-8.2
≥10	38	17.8	0.8	17.0	4.7-29.3	90	5.9	1.5	4.4	1.1-7.7
Treatment era										
<2000	17	20.9	0.8	20.1	3.4-36.8	99	6.3	1.3	4.9	2.0-7.9
≥2000	103	8.1	0.4	7.7	2.4-13.1	48	1.9	0.6	1.3	-2.4 to 4.9
Type of donor										
Related	45	1.7	0.4	1.3	-2.1 to 4.7	112	6.1	1.3	4.8	1.9-7.6
Unrelated	75	17.2	0.5	16.7	7.7-25.7	35	2.3	0.7	1.6	-2.9 to 6.0
Stem cell source										
Bone marrow	95	10.9	0.5	10.4	4.2-16.6	143	5.6	1.2	4.4	1.8-7.0
PBSCs or cord blood	25	10.2	0.4	9.8	-1.7 to 21.3	3	0.0	0.4	-0.4	-0.4 to -0.4
Chronic GVHD										
No	99	5.8	0.5	5.4	1.0-9.7	98	2.7	1.1	1.6	-0.6 to 3.7
Yes	14	50.5	0.5	50.0	12.6-87.5	43	11.7	1.4	10.2	3.3-17.1
Overall survival after BMT, yr										
2-9	45	25.9	0.2	25.6	8.7-42.5	24	27.6	0.4	27.2	-3.0 to 51.4
10-14	45	5.3	0.5	4.9	-1.1 to 10.9	25	9.8	0.8	9.1	-2.1 to 20.2
15+	25	6.2	0.7	5.6	-1.5 to 12.6	98	3.6	1.3	2.3	0.1-4.5

*Per 1000 person-years.

We found that in patients who survived for ≥2 years after allogeneic BMT performed before age 22 years, the 10–year overall survival was 92% in the bone marrow failure syndrome cohort and 96% in the SAA cohort. This 96% 10–year post-BMT survival rate for patients with SAA in the present study is slightly higher than the 92% in a mixed cohort (children and adults) of 2–year survivors of allogeneic BMT reported by Wingard et al [9]. In an Australian cohort of childhood allogeneic BMT recipients with nonmalignant diseases, the cumulative mortality at 10 years post-transplantation for patients with Fanconi anemia was 22%, which is much higher than the 4.9% in the present study. However, the Australian cohort was considerably smaller than ours, with only 3 deaths observed [7].

The present study also demonstrates that 2-year survivors of allogeneic BMT for bone marrow failure syndromes are at a 23-fold greater risk of late mortality compared with the general population. The majority of the patients with bone marrow failure syndromes underwent transplantation for Fanconi anemia (104 of 120). Analyzing patients with Fanconi anemia separately showed that they were at a 19-fold greater risk of late mortality compared with the general population. The relative mortality risk in the bone marrow failure syndrome cohort

was significantly higher than the 4.5-fold increase in relative risk seen in the SAA cohort. In the present study, the SMRs were supplemented by AERs, showing a similar pattern. The SMR for 2–year survivors of allogeneic BMT performed for Fanconi anemia in the aforementioned Australian study was 90, although that study included a much smaller number of patients with Fanconi anemia. In the present study, relative mortality was highest in the 2– to 9-year period post-BMT in patients with bone marrow failure syndromes and those with SAA alike. The SMRs declined thereafter, but remained significantly elevated at ≥15 years post-BMT in both cohorts. The results for our SAA cohort are in concordance with those reported by Wingard et al [9] showing elevated relative mortality at 15 years post-BMT in patients with SAA. Taken together, our results clearly show that long-term follow-up of survivors after allogeneic BMT in childhood for bone marrow failure syndromes and SAA needs to include screening, preventive interventions, and counseling throughout life.

In the present report, the hazard of all-cause late mortality was almost 3-fold higher among those who underwent allogeneic BMT for bone marrow failure syndromes compared with those who did so for SAA, after adjusting for demographic and clinical variables. These results are similar to those reported by Sanders et al [6], in which patients who underwent allogeneic BMT for Fanconi anemia in childhood had an HR of mortality of 4.4 compared with those who did so for acquired aplastic anemia, although that study included 1–year survivors and was much smaller (15 patients with Fanconi anemia). Our findings of a significantly higher risk of late mortality in our bone marrow failure syndrome cohort compared with our SAA cohort calls for intensified follow-up in the former cohort.

We identified SNs as the leading causes of death among patients with bone marrow failure syndromes. The SNs included a wide range of tumor types, a majority of which occurred within the first decade after BMT. SNs are well-known comorbidities in patients with bone marrow failure syndromes and are partly independent of transplantation, but have also been identified as causes of death in studies of early mortality after transplantation [1,4,14]. In addition to SNs, infections and chronic GVHD were important causes of death in our bone marrow failure syndrome cohort. Thus, our findings imply that follow-up after allogeneic BMT for bone marrow failure syndromes needs to focus on preventing and treating infections and chronic GVHD, in addition to SNs. Importantly, surveillance for early detection of SNs should be initiated early after BMT.

The present investigation describes the late mortality experience of the largest cohort to date of 2–year survivors of allogeneic BMT in childhood for bone marrow failure syndromes, giving a comprehensive overview of the late mortality risk in this population compared with 2-year survivors of allogeneic BMT for SAA and supporting the need to focus on risk-based long-term follow-up care. Nonetheless, some limitations of this study should be considered, one of which is the reliance on causes of death registered on death certificates, in which some degree of misclassification is inherent [8,15,16]. In an effort to overcome this bias, 2 investigators were responsible for the review of the causes of death recorded on the death certificates. Furthermore, information on cause of death was lacking for 29% of the deceased patients. During the long follow-up period, diagnostic criteria for bone marrow failure syndromes and SAA might have changed, potentially influencing the constitution of the cohort over time. Finally, patients with Fanconi anemia constituted a majority of our bone marrow failure syndrome cohort, and thus had a large impact on the outcomes in this cohort. The remaining diagnoses constituted a small and rather heterogeneous group; thus, the overall results with respect to these patients must be interpreted with caution. However, when analyzing the relative mortality of the Fanconi anemia patients separately, the SMRs of Fanconi anemia and the remaining diagnoses differed only marginally.

These limitations notwithstanding, this study demonstrates that 2-year survivors of allogeneic BMT in childhood for bone marrow failure syndromes are at considerably greater risk of late mortality compared with the general population, a risk that remains increased even at 15 years post-transplantation. Moreover, the risk of late mortality is significantly higher in patients undergoing allogeneic BMT for bone marrow failure syndrome compared with those undergoing allogeneic BMT for SAA. These findings underscore the need for intensified life-long follow-up care after allogeneic BMT, focusing on surveillance and early management of infections and chronic GVHD, in addition to screening for early detection of SNs.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online version at doi:10.1016/j.bbmt.2018.12.063.

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