Conditional survival and standardized mortality ratios of patients with severe aplastic anemia surviving at least one year after hematopoietic cell transplantation or immunosuppressive therapy

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Abstract

Immunosuppressive treatment (IST) and hematopoietic cell transplant (HCT) are standard therapies for severe aplastic anemia (SAA). We report on conditional survival and standardized mortality ratios (SMR), which compare the mortality risk with the general population adjusted for age, gender, and race/ethnicity, in patients with SAA alive for at least 12 months after treatment with IST or HCT between 2000 and 2018. Given changes to treatment regimens and differences in length of follow-up, two treatment periods were defined a priori: 2000-2010 and 2011-2018. The SMR of patients treated during the period 2000-2010 and who survived one year were 3.50 (95% confidence interval [CI]: 2.62-4.58), 4.12 (95% CI: 3.20-5.21), and 8.62 (95% CI: 6.88-10.67) after IST, matched related donor HCT, and alternative donor HCT, respectively. For the period 2011-2018, the corresponding SMR were 2.89 (95% CI: 1.54-4.94), 3.12 (95% CI: 1.90-4.82), and 4.75 (95% CI: 3.45-6.38), respectively. For IST patients, their mortality risk decreased over time, and became comparable to the general population by five years. For patients who underwent HCT during 2000-2010 and 2011-2018, their mortality risk became comparable to the general population after ten years and after five years, respectively. Thus, 1-year survivors after IST or HCT can expect their longevity beyond five years to be comparable to that of the general US population.

Introduction

Severe aplastic anemia (SAA) is caused by T-cell-mediated autoimmune destruction of hematopoietic progenitor cells associated with severe pancytopenia and a hypocellular marrow.[1] Hematopoietic cell transplantation (HCT) can be curative and is increasingly available with donor options other than HLA matched siblings. For patients who are older, unfit, or who lack a suitable donor, immunosuppressive treatment (IST), primarily anti-thymocyte globulin (ATG) in combination with cyclosporine (CSA), remains the standard of care.[2] Over the last decades, overall survival for SAA has improved with continued refinement of treatment protocols including addition of eltrombopag, a thrombopoetin receptor agonist,[3,4] and improved supportive care in both the IST and HCT settings.[5,7] However, patients treated with IST can have incomplete or no hematologic recovery; approximately 30-40% experience relapse by five years.[3,8] In addition, development of late clonal hematopoietic disorders such as myelodysplastic syndrome (MDS) or acquisition of isolated chromosomal aberration is a well-known complication in patients treated with IST.[9,10] HCT is also associated with

risks, including acute and chronic graft-*versus*-host disease (GvHD) and late complications such as cancer (seen in approximately 10% of survivors).[10] These complications, along with persistent disease, have an impact on quality of life of SAA survivors.[11,12]

While outcomes after initial IST or HCT have been well-described, and complications after therapy are also better understood, limited data are available regarding the temporal variations of mortality risks on survivors of SAA after IST or HCT. It is known that HCT survivors continue to have substantially higher mortality rates compared with the general population.[13-15] Socie and colleagues reported the data from the Center for International Blood and Marrow Transplantation Research (CIBMTR), which included 1029 patients with SAA transplanted between 1980 and 1993, mostly from a matched sibling donor (90%). Their analysis showed a 6% (95% confidence interval [CI]: 4-7%) mortality incidence at seven years in SAA patients who had survived at least two years after HCT.[15] A subsequent registry study by Wingard and colleagues included 2171 patients with SAA transplanted between 1980 and 2003, again mostly from a matched sibling donor (81%), and reported the relative mortality risk over time, showing increased risks (approx. 5-fold) over more than ten years in these 2-year HCT survivors.[14] A single institution analysis at City of Hope by Wong and colleagues also included patients with SAA (n=180), demonstrating that the standardized mortality ratios (SMR) for 1-year, 5-year, 10-year survivors were 9.0, 4.0, and 2.2, respectively.[16]

However, the above-mentioned registry studies did not have sufficient data on conditional survival and SMR after alternative donor HCT (matched/mismatched unrelated donors, mismatched related donors). Moreover, no studies have evaluated conditional survival or SMR in SAA after IST. As short-term outcomes after HCT and IST improve, the data on ongoing mortality risks in surviving patients are increasingly important and relevant for decision-making and risk-stratification for personalization of treatment. In this study, we enjoyed the benefit of using the resources of the CIBMTR and National Institutes of Health (NIH) to determine the conditional survival rates and SMR in patients with SAA treated with HCT or IST between 2000-2018, conditioned by survival time since treatment. A better understanding of conditional survival and SMR would allow risk-adapted interventions tailored to time-varying mortality risk in survivors to be implemented.

Methods

Patients with SAA who received their first allogeneic HCT (n=3571) and reported to the CIBMTR or received IST at the Clinical Center, NIH (n=395) in the United States between January 2000 and December 2018 were eligible. Patients who survived less than 12 months after their treatment (n=677 [19%] after HCT and n=16 [4%] after IST) were excluded, resulting in 2894 patients who underwent allogeneic HCT and 379 patients who received IST for the current analysis. All IST recipients received anti-thymocyte globulin (equine ATG) with the following agents: cyclosporine (n=100), cyclosporine with mycophenolate (n=90), cyclosporine with sirolimus (n=35), and cyclosporine with eltrombopag (n=155; 2012 to 2018). Of the 2894 HCT recipients, n=1428 received grafts from HLA matched siblings, n=256 from HLA mismatched relatives, n=848 from HLA matched, and n=362 from HLA mismatched unrelated donors. All patients provided written informed consent. The study was approved by the Institutional Review Board of the National Marrow Donor Program.

The outcome of interest was mortality in patients with SAA who were alive for at least 12 months from onset of treatment. Patients were analyzed in their intended treatment group: HCT and IST. Seventy-nine of 379 (21%) patients who received IST also received an HCT for recurrent disease after IST. All patients were followed through until death or last contact regardless of any treatment intervention in their assigned group. Patients in the HCT group were not censored at second HCT, and patients in the IST group were not censored for HCT or for recurrent disease. Death from any cause was considered an event. Surviving patients were censored at last follow-up.

As this study spanned almost two decades (2000-2018), two treatment periods were assigned a priori: 2000-2010 and 2011-2018; each period was studied separately. Within each treatment period, patients were divided into five treatment groups: IST, HLA matched sibling, HLA mismatched relative, HLA matched unrelated, and HLA mismatched unrelated donor transplantations. Conditional survival estimates were calculated using the Kaplan-Meier method for the sub-cohort that had survived a given length of time (x) after transplantation. The standardized relative mortality risk (SMR) was used to quantify all-cause mortality risk after treatment, and compared to the age-, race-, and sex-matched general population.[17] Person-years at risk were calculated from an anchor date after treatment until date of death or date last known alive. The equality of SMR was tested and two-sided 95% confidence intervals (CI) were calculated. Risk factors for mortality were examined using the Cox proportional hazards model.[18] Variables considered included age at diagnosis (<18, 18-39, ≥ 40 years), sex (male *vs*. female), race/ethnicity (White non-Hispanic *vs*. Black non-Hispanic *vs*. Asian *vs*. Hispanic *vs*. other), and disease recurrence modelled as time-dependent co-variate. In subset analysis limited to HCT recipients, the effect of grade II-IV and grade II acute GvHD and chronic GvHD on mortality was examined. Variables that met a significance level ≤0.05 were included in the final Cox model. All variables met the assumption of proportional hazards and there were no first order interactions between the variables held in the final models. All *P*-values are two-sided,

and analyses were carried out using SAS version 9.4 (Cary, NC, USA).

Results

Patients' and treatment characteristics

A total of 379 patients who received IST (n=224 in 2000-2010, n=155 in 2011-2018) and 2894 patients who underwent HCT (n=1282 in 2000-2010, n=1612 in 2011-2018) were eligible for analysis. Patients' characteristics are shown in Tables 1 and 2 according to their treatment period. Median age of patients during 2000-2010 was 30 years (range 2-82 years) for IST, 17.3 years (range 0.1-70.2 years) for matched sibling HCT, and 15.9 years (range 0.1-65.9 years) for alternative donor HCT. The corresponding median age for the period 2011-2018 were 29 years (range 3-82 years), 18.5 years (range 0-75.5 years), and 17.9 years (range 0-73.6 years), respectively. Sex was similarly distributed across the groups. For the period 2000-2010, non-Hispanic Whites represented 51% of the IST cohort and 74% of the HCT cohort. For the period 2011-2018, non-Hispanic Whites represented 57% of the IST cohort and 57% of the HCT cohort. The use of donor types was consistent with clinical practice in the periods studied. In the earlier period, 2000-2010, and in the later period, 2011-2018, matched siblings were the predominant donors and accounted for 735 of 1282 (57%) and 693 of 1612 (43%) transplantations, respectively. There was an increase in the use of other related donors in the period 2000-2010: 188 of 1612 (12%) compared to 68 of 1282 (5%) in the period 2011-2018. Bone marrow was the predominant graft source. There was no difference in the proportion of patients with acute and chronic GvHD according to transplant period. In the IST group (n=379), 100 patients (26%) received ATG/cyclosporine, 90 (24%) received ATG/cyclosporine/mycophenolate, 35 (9%) received ATG/cyclosporine/sirolimus, and the remaining 155 (41%) patients received ATG/cyclosporine/eltrombopag. Fifty-nine patients in the IST group received HCT for recurrent disease and another 20 patients in the IST group received HCT for clonal hematologic features (MDS or cytogenetic abnormalities).

Standardized mortality ratio, conditional survival and risk factors for mortality in 1-year survivors

Treatment period 2000-2010

The SMR and the 5-year conditional survival at the 1-year, 5-year and 10-year landmark timepoints for the treatment period 2000-2010 are summarized in Table 3 and Figure 1. One-year SMR was significantly higher than for an age-, sex-, race-/ethnicity-matched US population regardless of treatment group. However, SMR for those surviving five and ten years after IST were comparable to that of the US population. In HCT recipients, SMR decreased over time and were comparable to that of the US population at ten years. Unlike IST recipients, the 5-year SMR after HLA matched sibling and alternative donor HCT remained higher than that of the US population. Our models tested treatment type (IST, matched sibling and alternative donor HCT) with adjustment for age, sex, race/ethnicity and disease recurrence in 1-year survivors to identify mortality risks. All alternative donor HCT were considered as a single entity as there were no differences in SMR between HLA mismatched relative, HLA matched, and HLA mismatched unrelated donor HCT recipients (*data not shown*). After IST and HLA matched sibling HCT, older age at diagnosis (≥40 years) was associated with higher mortality risk (Table 4). After alternative donor HCT, mortality was higher in those aged ≥18 years (Table 4). Mortality risks were lower in females who received IST and alternative donor transplantation (Table 4). Sex was not associated with mortality after HLA matched sibling HCT. Disease recurrence was associated with higher mortality after IST (Hazard Ratio [HR] 1.89, 95% CI: 1.08-3.30; *P*=0.027), HLA matched sibling HCT (HR 3.45, 95% CI: 2.04-5.86; *P*<0.0001), and alternative donor HCT (HR 5.14, 95% CI: 2.89-9.16; *P*<0.0001). In multivariable analysis limited to recipients of HLA matched sibling HCT, a history of grade II-IV acute GvHD (HR 2.32, 95% CI: 1.36-3.97; *P*=0.002) and chronic GvHD (HR 3.26, 95% CI: 1.97-5.46; *P*<0.0001) was associated with higher mortality. Similarly, grade II-IV acute (HR 1.62, 95% CI: 1.04-2.53; *P*=0.0335) and chronic (HR 2.37, 95% CI: 1.48-3.79; *P*=0.0003) GvHD were associated with a higher risk for mortality after alternative donor HCT. Grade II acute GvHD was not associated with mortality after HLA matched sibling (HR 1.49, 95% CI: 0.75-2.94; *P*=0.25) or alternative (HR 0.83, 95% CI: 0.49-1.40; *P*=0.48) donor HCT.

Treatment period 2011-2018

The SMR and the 5-year conditional survival at landmark timepoints 1- and 5-years for the treatment period 2011-2018 are summarized in Table 5 and Figure 2. One-year SMR was higher than for an age-, sex- race-/ethnicity-matched US population regardless of treatment group. However, by five years, SMR after IST for HLA matched sibling and alternative donor HCT were comparable to that of the US population. Disease recurrence was the only factor associated with higher mortality after IST (HR 4.25, 95% CI: 1.15-15.69; *P*=0.029) and alternative donor HCT (HR 7.06, 95% CI: 3.87-12.88; *P*<0.0001). Although the risks were higher after HLA matched sibling HCT, this did not meet the level of significance (HR 2.71, 95% CI: 0.95-7.71; *P*=0.063). Age, sex and race/ethnicity were not associated with mortality risks (*data not shown*). Multivariate analysis of the subset of recipients of HLA matched sibling HCT, a history of grade II-IV acute GvHD (HR 5.29, 95% CI: 2.19-12.78; *P*=0.0002) and chronic GvHD (HR 4.85, 95% CI: 2.00-11.74; *P*=0.0005) was associated with higher mortality. Similarly, mortality risks were higher after alternative donor HCT in those with

Table 1. Characteristics of patients undergoing immunosuppressive treatment or hematopoietic cell transplantation for treatment period 2000-2010.

Characteristic	IST N (%)	Matched sibling N (%)	Other related* N (%)	Matched unrelated N (%)	Mismatched unrelated N (%)
N of patients	224	735	68	301	178
Age in years at diagnosis					
< 18	47 (21)	396 (54)	36 (53)	157 (52)	118 (66)
18-39	96 (43)	231 (31)	24 (35)	107 (36)	41 (23)
≥ 40	81 (36)	108 (15)	8 (12)	37 (12)	19 (11)
Sex					
Male	131 (58)	430 (59)	43 (63)	167 (55)	108 (61)
Female	93 (42)	305 (41)	25 (37)	134 (45)	70 (39)
Race					
White, non-Hispanic	115 (51)	456 (62)	41 (60)	233 (77)	84 (47)
Black, non-Hispanic	49 (22)	56 (8)	10 (15)	9 (3)	21 (12)
Hispanic	44 (20)	99 (13)	3 (4)	34 (11)	46 (26)
Asian	16 (7)	54 (7)	4 (6)	12 (4)	13 (7)
Other/not reported	0 (0)	70 (10)	10 (15)	13 (4)	14 (8)
Interval from diagnosis to transplant					
≤ 3 months	N/A	492 (67)	30 (44)	31 (10)	17 (10)
4 -12 months	N/A	137 (19)	22 (32)	126 (42)	67 (38)
>12 months	N/A	106 (14)	16 (24)	144 (48)	94 (53)
IST					
None	N/A	469 (64)	28 (41)	30 (10)	22 (12)
Yes	224 (100)	266 (36)	40 (59)	271 (90)	156 (88)
Graft type					
Bone marrow	N/A	596 (81)	42 (62)	232 (77)	99 (56)
Peripheral blood	N/A	133 (18)	21 (31)	69 (23)	31 (17)
Umbilical cord blood	N/A	6 (1)	5 (7)	0 (0)	48 (27)
Conditioning regimen					
Cy ± ATG	N/A	551 (75)	29 (42)	22 (7)	7 (4)
Cy/fludarabine ± ATG	N/A	37 (5)	8 (12)	41 (14)	18 (11)
TBI regimens 1000 cGy + other agents	N/A	25 (3)	4 (6)	37 (12)	21 (12)
TBI regimens 200-400 cGy Cy	N/A	28 (3)	13 (19)	169 (56)	99 (56)
Bu + other (Cy, fludarabine or melphalan)	N/A	33 (4)	5 (7)	17 (6)	17 (10)
Fludarabine/melphalan ± thiotepa	N/A	11 (1)	2 (3)	10 (3)	13 (8)
Not reported	N/A	51 (7)	7 (10)	5 (2)	3 (2)
GvHD prophylaxis, N (%)					
Calcineurin-containing	N/A	663 (90)	50 (74)	286 (95)	166 (94)
Ex vivo T-cell depletion/CD 34 selection	N/A	5 (1)	8 (11)	9 (3)	8 (5)
Post-transplant Cy-containing	N/A	2 (<1)	0 (0)	0 (0)	0 (0)
Not reported	N/A	65 (9)	10 (15)	6 (2)	4 (2)
Acute GvHD grade II-IV					
No	N/A	593 (81)	36 (53)	200 (66)	109 (61)
Yes	N/A	96 (13)	18 (26)	85 (28)	66 (37)
Not reported	N/A	46 (6)	14 (21)	16 (5)	3 (2)
Acute GvHD grade III-V					
No	N/A	657 (89)	46 (68)	264 (88)	154 (87)
Yes	N/A	32 (4)	8 (12)	21 (7)	21 (12)
Not reported	N/A	46 (6)	14 (21)	16 (5)	3 (2)
Chronic GvHD					
No	N/A	563 (77)	35 (51)	187 (62)	86 (48)
Yes	N/A	129 (18)	20 (29)	94 (31)	86 (48)
Not reported	N/A	43 (6)	13 (19)	20 (7)	6 (3)
Follow-up in months, median (range)	118 (13-236)	112 (12-249)	120 (38-237)	120 (13-244)	117 (12-242)

IST: immunosuppressive therapy; Cy: cyclophosphamide; ATG: anti-thymocyte globulin; Bu: bulsuphan; TBI: total body irradiation; GvHD: graft-*versus*-host disease; N/A: not available. *Matched related (not sibling): N=38. Mismatched related: N=30; %: due to rounding, totals do not correspond to 100%.

Table 2. Characteristics of patients undergoing immunosuppressive treatment or hematopoietic cell transplantation for treatment period 2011-2018.

Characteristic	IST N (%)	Matched sibling N (%)	Other related* N (%)	Matched unrelated N (%)	Mismatched unrelated N (%)
N of patients	155	693	188	547	184
Age in years at diagnosis					
< 18	40 (26)	335 (48)	92 (49)	248 (45)	124 (67)
18-39	59 (38)	255 (37)	64 (34)	167 (31)	39 (21)
≥ 40	56 (36)	103 (15)	32 (17)	132 (24)	21 (11)
Sex					
Male	76 (49)	388 (56)	114 (61)	292 (53)	100 (54)
Female	79 (51)	305 (44)	74 (39)	255 (47)	84 (46)
Race					
White, non-Hispanic	89 (57)	360 (52)	67 (36)	407 (74)	82 (45)
Black, non-Hispanic	33 (21)	76 (11)	49 (26)	27 (5)	33 (18)
Hispanic	6 (4)	140 (20)	44 (23)	74 (14)	40 (22)
Asian	16 (10)	49 (7)	12 (6)	19 (3)	7 (4)
Other/not reported	11 (7)	68 (10)	16 (9)	20 (4)	22 (12)
Interval from diagnosis to transplant					
< 3 months	N/A	460 (66)	48 (26)	84 (15)	17 (9)
4 -12 months	N/A	155 (22)	60 (32)	239 (44)	79 (43)
> 12 months	N/A	78 (11)	80 (43)	224 (41)	88 (48)
Immunosuppressive therapy					
None	N/A	450 (65)	46 (24)	79 (14)	22 (12)
Yes	155 (100)	243 (35)	142 (76)	468 (86)	162 (88)
Graft type					
Bone marrow	N/A	619 (89)	142 (76)	455 (83)	122 (66)
Peripheral blood	N/A	70 (10)	31 (16)	92 (17)	30 (16)
Umbilical cord blood	N/A	4 (1)	15 (8)	0 (0)	32 (17)
Conditioning regimen					
Cy ± ATG	N/A	475 (68)	21 (11)	31 (6)	11 (6)
Cy/fludarabine ± ATG	N/A	134 (19)	6 (4)	115 (21)	30 (16)
TBI regimens 1000 cGy + other agents	N/A	4 (<1)	0 (0)	3 (1)	2 (1)
TBI regimens 200-400 cGy Cy	N/A	44 (6)	150 (80)	345 (64)	116 (63)
Bu + other (Cy, fludarabine or melphalan)	N/A	20 (3)	3 (2)	23 (4)	7 (4)
Fludarabine/melphalan ± thiotepa	N/A	19 (3)	8 (5)	30 (6)	18 (10)
Not reported	N/A	3 (<1)	0 (0)	0 (0)	0 (0)
GvHD prophylaxis, N (%)					
Calcineurin-containing	N/A	671 (97)	50 (27)	502 (92)	157 (85)
Ex vivo T-cell depletion/CD 34 selection	N/A	3 (<1)	17 (9)	19 (3)	14 (7)
Post-transplant Cy-containing	N/A	9 (1)	119 (63)	25 (5)	10 (5)
Not reported	N/A	10 (1)	2 (1)	1 (<1)	3 (2)
Acute GvHD grade II-IV					
No	N/A	597 (86)	148 (79)	402 (73)	130 (71)
Yes	N/A	85 (12)	9 (5)	128 (23)	52 (28)
Not reported	N/A	11 (2)	5 (3)	17 (3)	2 (1)
Acute GvHD grade III-V					
No	N/A	658 (95)	174 (93)	505 (92)	163 (89)
Yes	N/A	24 (3)	9 (5)	25 (5)	19 (10)
Not reported	N/A	11 (2)	5 (3)	17 (3)	2 (1)
Chronic GvHD					
No	N/A	552 (80)	131 (70)	400 (73)	120 (65)
Yes	N/A	133 (19)	50 (27)	137 (25)	54 (29)
Not reported	N/A	8 (1)	7 (4)	10 (2)	10 (5)
Follow-up in months, median (range)	50 (13-98)	49 (12-120)	38 (12-106)	48 (12-114)	56 (12-115)

*Matched related (not sibling): N=25. Mismatched related: N=163. Cy: cyclophosphamide; ATG: anti-thymocyte globulin; Bu: bulsuphan; TBI: total body irradiation; GvHD: graft-*versus*-host disease; N/A: not available; %: due to rounding, totals do not correspond to 100%.

a history of grade II-IV acute (HR 2.74, 95% CI: 1.50-4.98; *P*=0.0010) and chronic (HR 2.43, 95% CI: 1.30-4.56; *P*=0.0056) GvHD. Grade II acute GvHD was associated with mortality after alternative donor (HR 1.95, 95% CI: 1.03-3.70; *P*=0.04) but not after HLA matched sibling (HR 2.13, 95% CI: 0.71-6.38; *P*=0.18) HCT.

There were 66 deaths among the 379 patients who received IST. The two predominant causes of death were infection (21%) and death from an HCT-related complication (21%) in those who failed IST and thereafter received HCT. Other causes include: myeloid malignancy (9%), solid tumor (3%), bleeding (3%), and other causes (9%). Cause of death was not available for 21 patients (32%).

There were 219 deaths among the 2894 patients who underwent HCT. The predominant causes of death include: infection (17%), organ failure (20%), GvHD (12%), and recurrent disease (graft failure: 11%). Other causes include myeloid malignancy (3%), solid tumor (2%), bleeding (3%), Epstein-Barr virus-associated lymphoproliferative disease (1%), and other causes (2%). Cause of death was not available for 64 patients (29%).

Discussion

In this study, we evaluated SMR in patients who received HCT and IST for SAA and were alive for at least one year after their treatment; an intent-to-treat approach was adopted. In both treatment periods studied, that together spanned two decades, long-term survival was over 80%

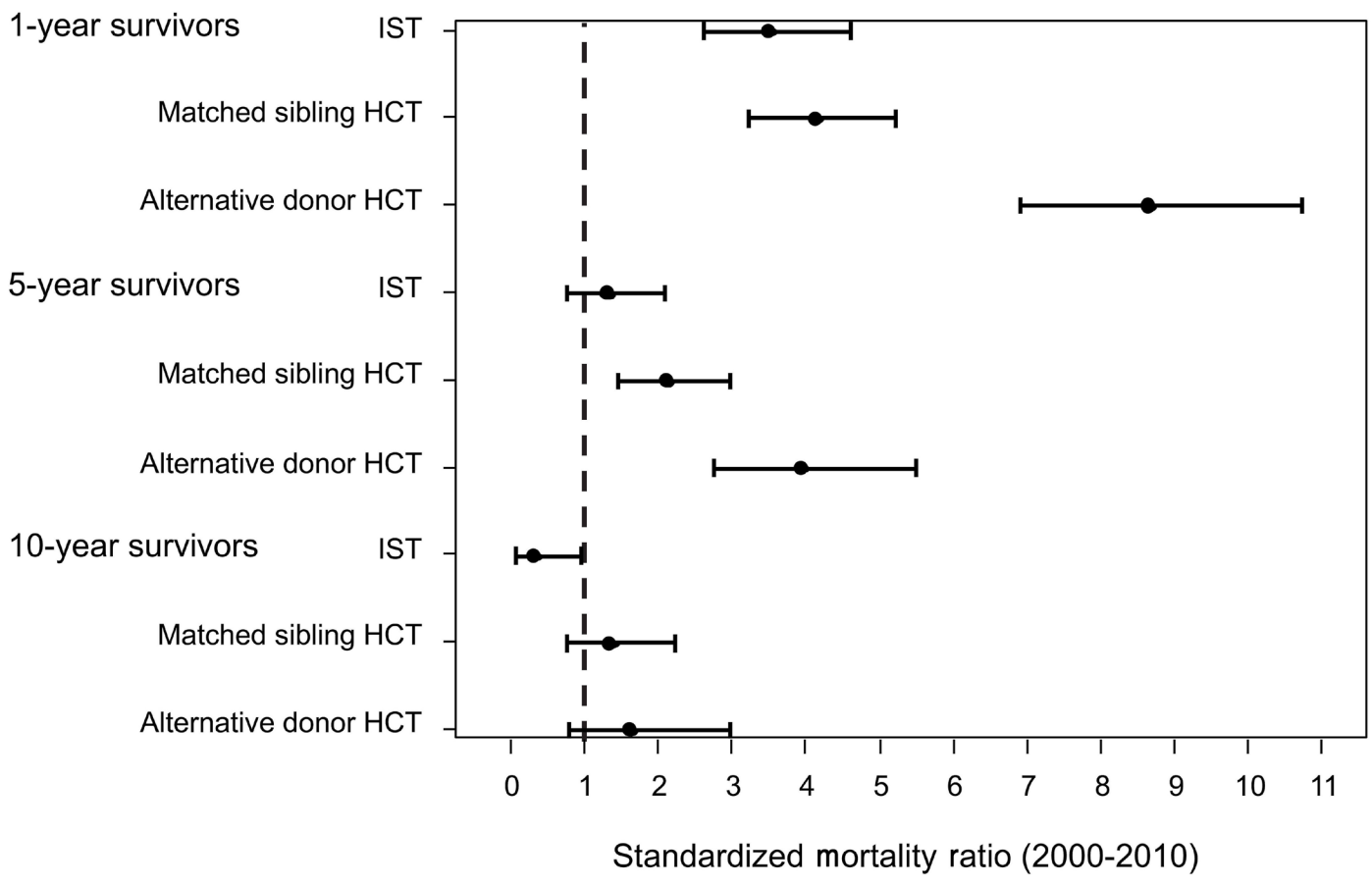

Figure 1. Standardized mortality ratio: treatment period 2000-2010. IST: immunosuppressive therapy; HCT: hematopoietic cell transplant.

Table 3. Conditional survival probability and standardized mortality ratio by landmark timepoints (2000-2010).

Survival landmark	Treatment group	Evaluable	Events	5-year survival	SMR (95% CI)	Overall SMR (95% CI)
1-year	IST HLA matched sibling HCT Alternative donor HCT	224 735 547	53 70 85	0.81 0.94 0.89	3.50 (2.62-4.58) 4.12 (3.20-5.21) 8.62 (6.88-10.67)	4.95 (4.29-5.67)
5-year	IST HLA matched sibling HCT Alternative donor HCT	154 558 413	17 33 36	0.89 0.96 0.92	1.30 (0.76-2.09) 2.11 (1.45-2.96) 3.92 (2.73-5.46)	2.26 (1.81-2.80)
10-year	IST HLA matched sibling HCT Alternative donor HCT	78 294 220	3 15 10	0.97 0.93 0.92	0.33 (0.07-0.95) 1.35 (0.76-2.23) 1.62 (0.78-2.98)	1.06 (0.70-1.53)

SMR: standardized mortality ratio; CI: confidence interval; IST: immunosuppressive therapy; HCT: hematopoietic cell transplant.

in patients who survived for at least one year after IST or HCT. Consistent with other reports on SMR for SAA after HCT, we also observed higher SMR in the earlier years after treatment, but the risks decreased over time. In the earlier treatment period studied (2000-2010), SMR of 5-year survivors after HCT from either HLA matched sibling or alternative donor were greater than the age-, sex- and race-/ethnicity-matched US population. In contrast, there was no difference in SMR between 5-year HCT survivors and an age-, sex- and race-/ethnicity-matched US population in the later treatment period (2011-2018), likely explained by advances in transplant conditioning regimens, GvHD prophylaxis, and supportive care for HCT. Importantly, SMR after IST were comparable to an age-, sex- and race-/ethnicity-matched US population in the periods 2000-2010 and 2011-2018. In risk factor analyses, two biologic variables, age and sex, adversely affected long-term survival of patients treated during the period 2000-2011. The association between older age (≥ 40 years) and higher late mortality has been previously reported by others.[14,15] Females fared better than males in this analysis. We did not identify an association between biologic variables and survival during the period 2011-2018. In all treatment groups, disease recurrence with or without salvage treatment was associated with higher mortality.[19] A history of grade III-IV acute and chronic GvHD was also associated with higher mortality regardless of donor type and transplant period. Causes of death in patients with SAA surviving one year after IST and HCT were consistent with the expected mix in this population: infections and transplant-related causes for those treated with IST, and infection, GvHD, organ failure, and graft failures after HCT. Deaths attributed to myeloid neoplasm after IST was 9% and after HCT, 3%. IST recipients were older, and the observed evolution to myeloid

Table 4. Multivariate analysis for prognostic factors for treatment period 2000-2010.

Variables	Evaluable	Events	Hazard Ratio (95% CI)	*P*
IST				
Age in years at diagnosis				
< 18	47	4	1.00	<0.0001
18-39	96	16	1.87 (0.62-5.60)	0.27
≥ 40 years	81	33	5.68 (2.00-16.14)	0.001
Sex				
Male	131	38	1.00	0.002
Female	93	15	0.40 (0.22-0.73)	0.003
HLA matched sibling HCT				
Age in years at diagnosis				
< 18	396	22	1.00	<0.00001
18-39	231	18	1.29 (0.69-2.41)	0.42
≥ 40 years	108	30	4.41 (2.53-7.66)	<0.0001
Alternative donor HCT				
Age in years at diagnosis				
< 18	311	33	1.00	<0.0001
18-39	172	30	1.79 (1.07-2.97)	0.026
≥ 40 years	64	22	4.59 (2.59-8.13)	<0.0001
Sex				
Male	318	59	1.00	0.02
Female	229	26	0.58 (0.37-0.93)	0.023

CI: Confidence Interval; IST: immunosuppressive therapy; HCT: hematopoietic cell transplant.

Table 5. Conditional survival probability and standardized mortality ratio by landmark timepoints (2011-2018).

Survival landmark	Treatment group	Evaluable	Events	5-year survival	SMR (95% CI)	Overall SMR (95% CI)
1-year	IST	155	13	0.85	2.89 (1.54-4.94)	3.82 (3.01-4.77)
	HLA matched sibling HCT	693	20	0.97	3.12 (1.90-4.82)	
	Alternative donor HCT	919	44	0.93	4.75 (3.45-6.38)	
5-year	IST	55	3	0.82	1.27 (0.26-3.73)	1.17 (0.60-2.04)
	HLA matched sibling HCT	256	3	0.97		
	Alternative donor HCT	312	6	0.95		

SMR: standardized mortality ratio; CI: confidence interval; IST: immunosuppressive therapy; HCT: hematopoietic cell transplant.

neoplasm could be explained in part by age and in part by treatment with disease-modifying agents. Five of 7 HCT recipients who developed myeloid malignancy were transplanted at a median age of 58 years (range 33-65 years). Probable etiologies include the challenge in distinguishing SAA from MDS in the absence of cytogenetic abnormalities, the effect of radiation-containing conditioning regimen,[20] and the possibility of donor-derived myeloid malignancy. Donor hematopoiesis in the context of HCT could be prone to clonal hematopoiesis of indeterminate potential and evolution to MDS from stressed hematopoiesis after HCT.[21] Two children aged three years at HCT who developed acute myeloid leukemia may have had an inherited bone marrow failure syndrome without classical phenotype. The data sources we used rely on the diagnosis assigned by the transplant center and we cannot comment on the diagnostic tests that had confirmed SAA.

Historically, approximately two-thirds of patients achieved a response to IST after treatment with equine ATG combined with cyclosporine,[22-24] and the robustness of hematologic response was found to be positively associated with long-term survival.[7] More recently, eltrombopag has been shown to have efficacy in patients with IST-refractory SAA[25-27] and in previously untreated patients with SAA with an overall response rate 80-95% and 2-year survival >95%.[4] With longer follow-up (4 years), recurrent disease and clonal evolution were comparable to that in a historic cohort treated with IST except in patients with high-risk clonal evolution.[3] A phase III European trial comparing IST with or without eltrombopag also confirmed that the rate, rapidity, and strength of hematologic response were better with IST and eltrombopag in previously untreated patients with SAA.[28] Alternative donor HCT using matched/mismatched unrelated,[29,30] umbilical cord,[31,32] and haploidentical donors[33-35] are increasingly offered to those without a matched sibling, and are associated with significant risks of late morbidity and mortality due to GvHD, poor immune reconstitution, cardiopulmonary disease, and/or secondary non-hematologic neoplasms, which remain serious medical challenges for HCT survivors.[10,14-16]

For both IST and HCT, there is a clinical need to understand how mortality risk changes with survival time. The use of conditional survival allows for a dynamic evaluation of risks during survivorship, whereas the conventionally calculated survival probability from the time of IST or HCT does not reflect changes in prognosis over time. Our study was not designed to compare the outcomes between IST and HCT as a first-line therapy. Instead, our primary objective was to estimate the conditional survival and SMR in patients who have survived the early phases of treatment. Therefore, the observations in this study commenced at HCT in the HCT cohort and at IST in the IST cohort, not from the time of diagnosis or from first-line therapy, since many had received ATG/CSA +/- eltrombopag prior to HCT.

There are limitations in our study. By design, the data are based on a single comprehensive center for IST while HCT data are based on the registry with the contribution of data from 40-50 centers. The transplant dataset may include biases: although we aim to provide a complete report, we may have missed late events as patients tend

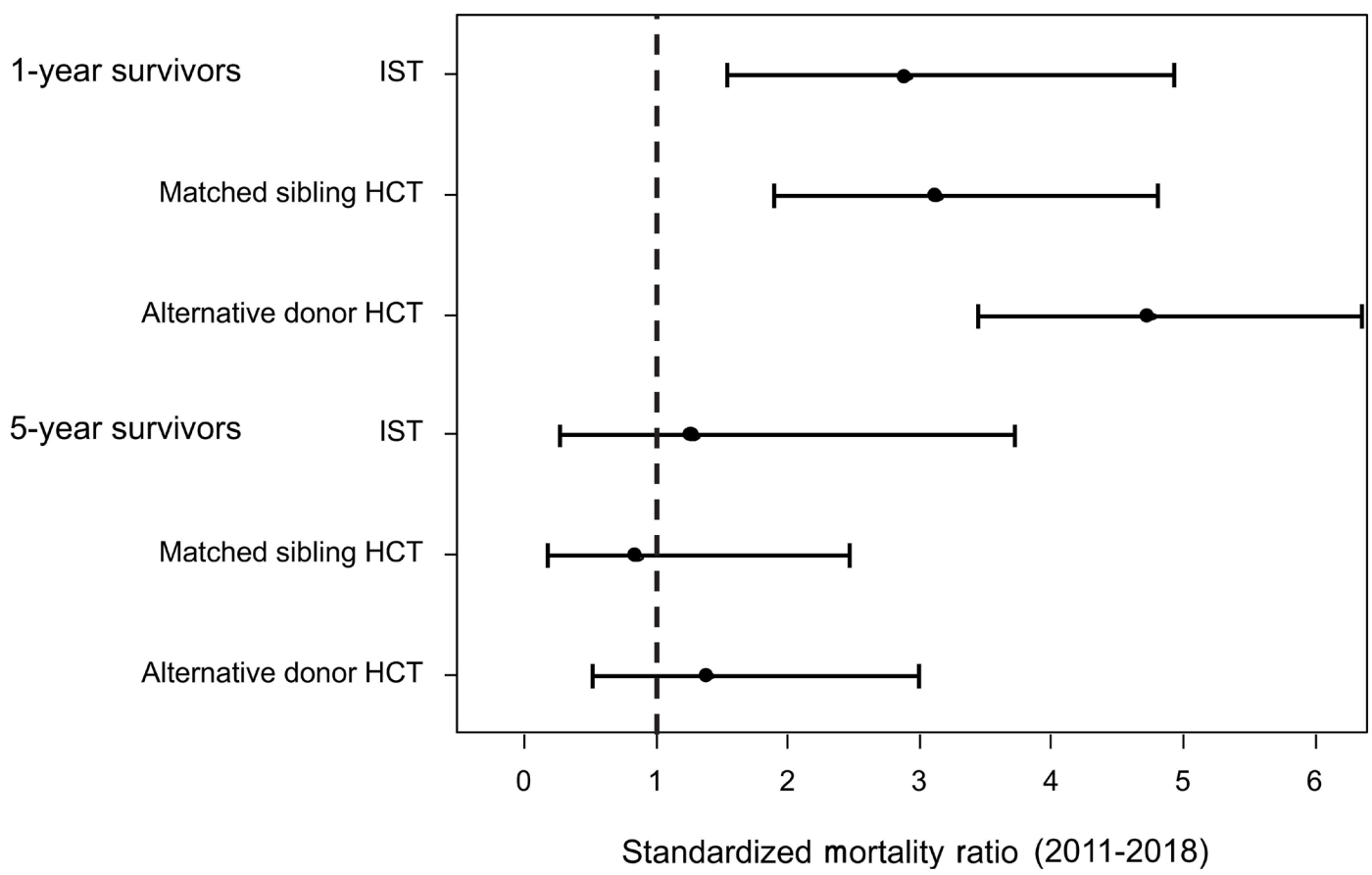

Figure 2. Standardized mortality ratio: treatment period 2011-2018. IST: immunosuppressive therapy; HCT: hematopoietic cell transplant.

to transfer care with relocation or change in insurance coverage. Our study is also limited by a lack of detailed data on patient-reported outcomes such as social functions or quality of life metrics. We note the modest follow-up of the more recent cohort that should be followed for several more years for late mortality data. Furthermore, the relatively few events in 5- and 10-year survivors resulted in SMR with wide confidence boundaries. We believe a more robust interpretation of SMR is one that considers all treatment groups together with findings in keeping with those observed when treatment groups were compared separately. However, despite the limitations, these data significantly further our knowledge on conditional survival and SMR for SAA after HCT and IST in the recent era. Although long-term survival improves over time for 1-year survivors after either IST or HCT, the persistence of mortality risks greater than the general population warrant studies in cause-specific mortality.

Disclosures

No conflicts of interest to disclose.

Contributions

RN, BAP, SK, LW, SHA, KMH, ME and NSY designed the study. BAP, DAK, KMH and MH assembled the data. SK performed the analysis. RN, BAP, SK, LW, SHA, EMG, DAK, KMH, MH, ME and NSY interpreted the data. RN drafted the manuscript. BAP, SK, LW, SHA, EMG, DAK, KMH, MH, ME and NSY critically reviewed and approved the manuscript.

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Data-sharing statement

Data are available at https://www.cibmtr.org/ReferenceCenter/PubList/PubDsDownload/Pages/default.aspx

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