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REPORT

Late Effects in Hematopoietic Cell Transplant Recipients with Acquired Severe Aplastic Anemia: A Report from the Late Effects Working Committee of the Center for International Blood and Marrow Transplant Research

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With improvements in hematopoietic cell transplant (HCT) outcomes for severe aplastic anemia (SAA), there is a growing population of SAA survivors after HCT. However, there is a paucity of information regarding late effects that occur after HCT in SAA survivors. This study describes the malignant and nonmalignant late effects in survivors with SAA after HCT. A descriptive analysis was conducted of 1718 patients post-HCT for acquired SAA between 1995 and 2006 reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). The prevalence and cumulative incidence estimates of late effects are reported for

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1-year HCT survivors with SAA. Of the HCT recipients, 1176 (68.5%) and 542 (31.5%) patients underwent a matched sibling donor (MSD) or unrelated donor (URD) HCT, respectively. The median age at the time of HCT was 20 years. The median interval from diagnosis to transplantation was 3 months for MSD HCT and 14 months for URD HCT. The median follow-up was 70 months and 67 months for MSD and URD HCT survivors, respectively. Overall survival at 1 year, 2 years, and 5 years for the entire cohort was 76% (95% confidence interval [CI]: 74-78), 73% (95% CI: 71-75), and 70% (95% CI: 68-72). Among 1-year survivors of MSD HCT, 6% had 1 late effect and 1% had multiple late effects. For 1-year survivors of URD HCT, 13% had 1 late effect and 2% had multiple late effects. Among survivors of MSD HCT, the cumulative incidence estimates of developing late effects were all <3% and did not increase over time. In contrast, for recipients of URD HCT, the cumulative incidence of developing several late effects exceeded 3% by 5 years: gonadal dysfunction 10.5% (95% CI: 7.3-14.3), growth disturbance 7.2% (95% CI: 4.4-10.7), avascular necrosis 6.3% (95% CI: 3.6-9.7), hypothyroidism 5.5% (95% CI: 2.8-9.0), and cataracts 5.1% (95% CI: 2.9-8.0). Our results indicated that all patients undergoing HCT for SAA remain at risk for late effects, must be counseled about, and should be monitored for late effects for the remainder of their lives.

INTRODUCTION

Hematopoietic cell transplant (HCT) has been used successfully to treat acquired severe aplastic anemia (SAA) for several decades [1-5]. In the last 2 decades, a significant improvement in outcomes has been reported in patients with SAA undergoing matched sibling donor (MSD) or unrelated donor (URD) HCT [3-5]. As a result of improvements in HCT for acquired SAA, which include decreased risk of graft failure and conditioning-related toxicity and improvements in donor selection and supportive care, there is a growing population of HCT survivors with acquired SAA. Despite the documentation of severe and life-threatening chronic health conditions or so-called "late effects" in HCT survivors of malignant disorders [6,7], the impact of HCT in nonmalignant disorders has been the subject of limited evaluation. The overlap between HCT-related toxicities and toxicities associated with pre-HCT treatment of acquired SAA suggests a need to better characterize late effects after HCT in patients with acquired SAA.

A few small studies describe the variable risk of malignant and nonmalignant late effects in HCT survivors with acquired SAA [8-16]. Despite the toxicity of pre-HCT SAA therapy, conditioning-related toxicity, and HCT-related complications, the long-term impact of HCT on this population has not been adequately characterized. Table 1 describes prior work that characterizes late effects in acquired SAA. Limitations include single-institution studies with small numbers of HCT survivors with acquired SAA represented [8-16]. Other studies describe the burden of select late effects in HCT survivor cohorts of limited representation with respect to age at the time of HCT, donor type, and conditioning exposures. The purpose of our study was to address this gap in the past literature by describing the cumulative incidence of late effects (neurological, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, sensory, endocrine, hematologic, and malignancy) in a large and representative cohort of HCT survivors with acquired SAA using data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) [17].

MATERIALS AND METHODS

Data Sources

The CIBMTR is a research affiliation of the International Bone Marrow Transplant Registry, Autologous Blood and Marrow Transplant Registry, and the National Marrow Donor Program established in 2004. It comprises a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous HCT procedures to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program Coordinating Center in Minneapolis, Minnesota. Participating centers are required to report all transplantations consecutively; compliance is monitored by on-site audits. Patients are followed longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act Privacy Rule.

The CIBMTR collects data at 2 levels: transplant essential data (TED) and comprehensive report form (CRF) data. TED data include disease type, age, sex,

Table 1. Summary of Studies Reporting Late Effects after HCT for Severe Aplastic Anemia

Study	Patient Demographics	Donor Characteristics	Conditioning Regimen(s)	Follow-up, Survival, and cGVHD	Late Effects
Socié et al., 1991	N = 107 1980-1989 Median age HCT 16 years (6-24)	MSD BM	Cy + TAI	Mean 64 months OS – not given cGVHD 45.5%	CI at 8 years Cancer 22% (SE 11%)
Socié et al., 1993	N = 748 1971-1991 Mean age Dx 18 years (1 months-59 years)	MSD BM (90%) SYN (2%) Alternative (8%)	Cy (54%) Cy + TLI/TAI (35%) Cy + TBI (8%) None (3%)	Mean 47 months OS – not given cGVHD – not given	CI at 10 years Cancer 3.1%
Deeg et al., 1996	N = 621 1970-1993 Median age HCT 19 years (1.8-67 years)	MSD BM (89%) MMRD/MUD (11%)	Cy (66%) Cy + ATG ± PC (11%) Cy + TBI/TAI (40%)	Mean 47 months OS – not given cGVHD 30.8%	CI at 20 years Cancer 14% (4-24)
Deeg et al., 1998	N = 212 1970-1993 Median age HCT 18 years (1-42)	MSD BM (88%) MMRD BM (8%) MUD BM (2%) SYN BM (1%)	Cy (44%) Cy + Buffy (31%) Cy + ATG (18%) Cy + TBI (7%) None (<1%)	Median 12 years 20-year OS 69%-89% cGVHD 41%	Osteonecrosis 18% Cancer 12% Depression 19% Female pregnant 47% Male father 50%
Eapen et al., 2000	N = 37 patients/146 controls 1975-1996 Median age HCT 7 years (1-21)	MSD BM (86%) MMRD (5%) MUD (8%)	Cy + TLI (78%) Cy + TBI (13%) Other (8%)	Median 17 years 5-year OS 67% cGVHD 21.6%	Cataract OR 16 Hypothyroid OR 14.25 Estrogen OR 5.85
Ades et al., 2004	N = 133 1978-2001 Age at HCT <15 years (38%) 15-30 years (44%) >30 years (18%)	MSD BM	Cy + ATG (25%) Cy + TAI (75%)	Median 13.6 years 10-year OS 64.5% cGVHD 60%	CI at 15 years Osteonecrosis 19.6% Cancer 10.9% Hypothyroid (1 patient) Cataracts (2 patients) Depression (12 patients)
Sanders et al., 2011	N = 137 1971-2009 Median age at HCT 11.1 years (0.8-17.9)	RD (86%) MUD (12%) SYN (2%) BM (98%) CB (2%)	Cy ± ATG (77%) PC + Cy + ATG (4%) Cy + TBI (18%) None (1%)	Median 21.8 years 30-year OS 82% cGVHD 26%	BMD abnormal 26% Cancer 13% Thyroid abnormal 22% Growth abnormal 0% Gonadal abnormal 22%/17% (pre-/post-puberty girl) 38%/0% (pre-/post-puberty boy) Female pregnant 42% Male father 37%
Konopacki et al., 2011	N = 61 1991-2010 Median age at HCT 21 years (4-43 years)	MSD BM (97%) MSD BM/PB (3%)	Cy + ATG	Median 73 months 6-year OS 87.5% cGVHD 32%	CI at 72 months Osteonecrosis 21% Endo abnormal 19% Cardio abnormal 2% Cancer 2% (0-11) Female pregnant 5% Male father 7%

HCT indicates hematopoietic cell transplant; cGVHD, chronic graft-versus-host disease; MSD, matched sibling donor; BM, bone marrow; Cy, cytoxan; TAI, thoracoabdominal irradiation; OS, overall survival; CI, cumulative incidence; Dx, diagnosis; SYN, syngeneic; TLI, total lymphoid irradiation; TBI, total body irradiation; MMRD, mismatched related donor; MUD, matched unrelated donor; ATG, antithymocyte globulin; PC, procarbazine; OR, odds ratio; RD, related donor; CB, cord blood; BMD, bone mineral density; PB, peripheral blood.

pretransplantation disease stage and chemotherapy responsiveness, date of diagnosis, graft type (bone marrow-derived and/or blood-derived stem cells), conditioning regimen, posttransplantation disease progression and survival, development of a new malignancy, and cause of death. All CIBMTR teams contribute TED data. More detailed disease and pretransplantation and posttransplantation clinical information are collected on a subset of registered patients selected for CRF data by a weighted randomization scheme. TED- and CRF-level data are collected pretransplantation, 100 days, 6 months posttransplantation, and annually thereafter or until death. Data for these analyses were retrieved from CIBMTR (TED and CRF) report forms.

Study Population

The study population included patients who underwent allogeneic HCT between 1995 and 2006 for acquired SAA and were reported to the CIBMTR using CRF data. Patients with a diagnosis of myelodysplastic syndrome or an inherited bone marrow failure syndrome were excluded from the study population. Recipients of MSD or URD HCT were included in these analyses. Overall, 2653 patients met our study eligibility criteria. HCT procedures involving identical twin donors or other related donors were excluded from these analyses (N = 110). Patients reported from transplant centers with a follow-up completeness index of <80% at 5 years were also excluded from these analyses (N = 825 patients from 90 centers)

[18]. Our final study population consisted of 1718 patients from 186 centers (1176 MSD and 542 URD HCT recipients).

Data Collection on Late Effects

The primary outcomes chosen for analysis were late effects occurring post-HCT. Transplant centers reported late effects as part of follow-up CRFs that inquired whether an HCT recipient had developed any clinically significant organ impairment or disorder since the date of the last report. Specific questions focused on the following late effects: neurological (stroke/seizures), cardiovascular (myocardial infarction), gastrointestinal/hepatic (cirrhosis), genitourinary (gonadal dysfunction/infertility requiring hormone replacement, renal failure severe enough to warrant dialysis), musculoskeletal (avascular necrosis), special sensory (cataracts), and endocrine (growth hormone deficiency/growth disturbance, hypothyroidism) impairment. Responses to each item were dichotomous (yes/no) and followed by a question requesting the date of onset for each individual organ impairment or disorder. Other late effects were reported using an "other-specify" field that was also checked for the late effects of interest. Pregnancy data was collected from 2002 to 2007 on HCT survivors who underwent HCT before 2007. Transplant centers were queried regarding whether the survivor or the survivor's partner became pregnant or had successfully fathered a child. Onset dates of late effects were collected on report forms beginning in 2007. Before 2007, onset dates were collected only for new onset solid tumors. Thus, for cases before 2007, the onset date for late effects of nonmalignant origin was imputed as the median time point between successive report forms that were submitted before and after onset of the specified late effect. The questionnaires used by the CIBMTR can be viewed at www.cibmtr.org [17].

Statistical Analysis

Descriptive statistics were calculated for sociodemographic, SAA treatment-related variables, and HCT-related variables. Classification of HLA-matching was completed using 3 groups including well-matched cases, partially matched cases, and mismatched cases, as previously described [19]. We determined the prevalence of late effects among HCT survivors. For the prevalence estimates, 3 outcomes were assessed including no late effects, the presence of 1 late effect, and multiple late effects (≥2). Cumulative incidence rates of individual late effects are reported herein for 1-year condition-free survivors (ie, survivors without a previous diagnosis of the specified late effect). The cumulative incidence of late effects was calculated with death not related to the late effect treated as a competing event. Patients who did not develop the conditions were censored at the last

research-level follow-up. Cumulative incidence estimates are provided herein with 95% confidence intervals (CIs). Due to the limited number of events in our sample, we were unable to complete multivariable analyses. This report presents descriptive analyses only. SAS, version 9.2 (SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Patient, Disease, and Transplant Characteristics

Patient, disease, and transplant characteristics of the study population are described in Table 2. The most common etiology of SAA for recipients in both MSD and URD groups was idiopathic, followed by viral and toxin or drug-related. The proportion of HCT procedures for SAA by transplant type shifted over time from a majority being MSD procedures (61%) to the majority being URD procedures (64%). The majority of MSD HCT procedures (72%) occurred outside of the United States and Canada; however, the majority of URD HCT procedures (73%) occurred within the United States and Canada.

Of the HCT recipients, 1176 patients (68.5%) with a median age at HCT of 20 years (range: <1-65 years) received an MSD, and 542 patients (31.5%) with a median age at HCT of 20 years (range: <1-67 years) received a URD. The median interval from diagnosis to transplantation was 3 months (range: <1-348 months) for MSD HCT and 14 months (range: 1-318 months) for URD HCT. Bone marrow was the predominant graft source for both MSD and URD (88% and 77%, respectively). Approximately one-third of the URD HCT procedures used a well-matched donor. Although total body irradiation (TBI) was used in 68% of URD HCT cases at a median dose of 600 cGy (range: 200-1530 cGy), it was used in only 4% of MSD cases with a median dose of 800 cGy (range: 200-1410 cGy). Busulfan was used in 22% of MSD HCT cases and 8% of URD HCT cases with a median dose of 12 mg/kg (range: <1-51 mg/kg) and 13 mg/kg (range: 2-40 mg/kg), respectively. Busulfan and fludarabine were used for conditioning in 50% of MSD HCT cases, and cyclophosphamide in combination with TBI was used as a conditioning regimen in 68% of URD HCT cases. Acute graft-versus-host disease (aGVHD) prophylaxis consisted of cyclosporine and methotrexate in 81% and 46% of MSD and URD cases, respectively. Antithymocyte globulin (ATG) and/or alemtuzumab were used in 59% of the MSD HCT procedures and 72% of the URD HCT procedures.

Survival and GVHD

The median follow-up was 70 months (range: 1-160 months) and 67 months (range: 3-182 months)

Table 2. Patient, Disease, and Transplantation Characteristics of the Study Population (N = 1718)

Characteristic	HLA-matched sibling donor Frequency (%)	Unrelated donor Frequency (%)
Number of patients	1176 (68)	542 (32)
Median age at transplant in years (range)	20 (<1-65)	20 (<1-67)
Age at transplant		
0-9 years	187 (16)	111 (20)
10-19 years	388 (33)	170 (31)
20-29 years	305 (26)	127 (23)
30-39 years	175 (15)	73 (13)
40-49 years	91 (8)	33 (6)
50-59 years	27 (2)	20 (4)
≥60 years	3 (<1)	8 (1)
Recipient sex		
Female	518 (44)	236 (44)
Male	658 (56)	306 (56)
Etiology of aplastic anemia		
Idiopathic	979 (83)	490 (90)
Viral hepatitis	61 (5)	22 (4)
Toxin or other drug	47 (4)	12 (2)
Other*	89 (8)	18 (3)
Transplant team region		
United States/Canada	331 (28)	396 (73)
Europe	130 (11)	56 (10)
Other†	751 (61)	90 (17)
Interval from diagnosis to transplant		
<6 months	793 (67)	107 (20)
6-12 months	127 (11)	126 (23)
>12 months	255 (22)	307 (57)
Year of transplant		
1995-2000	713 (61)	194 (36)
2001-2006	463 (39)	348 (64)
Graft source		
BM	1031 (88)	416 (77)
PB	140 (12)	81 (15)
CB	5 (<1)	45 (8)
Number of transplant		
1	1068 (91)	505 (93)
≥2	108 (9)	37 (7)
Degree of HLA match		
HLA-matched siblings	1176	0
Well matched	0	167 (31)
Partially matched	0	130 (24)
Mismatched	0	83 (15)
Unknown	0	162 (30)
Conditioning regimen		
TBI + Cy	38 (3)	366 (68)
Busulfan + Cy	221 (19)	28 (5)
Cy + fludarabine	89 (8)	40 (7)
Busulfan + fludarabine	29 (2)	14 (3)
Cy + ATG	588 (50)	59 (11)
Cy + other	186 (16)	15 (3)
Other/unknown	25 (2)	20 (4)
Irradiation as part of conditioning		
None	1095 (94)	119 (22)
TBI	45 (4)	372 (69)
TLI/TAI only	30 (3)	51 (9)
Total TBI dose		
None	1125 (96)	170 (31)
<400 cGy	18 (2)	135 (25)
>400 cGy	27 (2)	236 (44)
GVHD prophylaxis		
Ex vivo T cell depletion ± immunosuppression	13 (1)	36 (7)
FK506 + MMF ± other (not MTX)	14 (2)	45 (8)
FK506 + MTX + other	45 (4)	122 (23)
CSA + MMF ± other (not MTX)	100 (8)	76 (14)

(Continued)

Table 2. *(Continued)*

Characteristic	HLA-matched sibling donor Frequency (%)	Unrelated donor Frequency (%)
CSA + MTX + other	949 (81)	249 (46)
Other	49 (4)	10 (2)
Unknown	6 (1)	4 (1)
Use of ATG/Campath		
No	486 (41)	154 (28)
Yes	690 (59)	388 (72)

BM indicates bone marrow; PB, peripheral blood; CB, cord blood; TBI, total body irradiation; Cy, cytoxan; ATG, antithymocyte globulin; TLI, total lymphoid irradiation; TAI, thoracoabdominal irradiation; GVHD, graft-versus-host disease; MMF, mycophenolate mofetil; MTX, methotrexate; CSA, cyclosporine.
*Other etiologies included paroxysmal nocturnal hemoglobinuria (N = 71), acquired amegakaryocytosis (N = 7), acquired pure red cell aplasia (N = 6), and other acquired cytopenias (N = 23).
†Other regions represented include Argentina (N = 19), Australia (N = 30), Brazil (N = 310), Japan (N = 12), Korea (N = 269), New Zealand (N = 14), Saudi Arabia (N = 123), Taiwan (N = 5), Mexico (N = 2), Hong Kong (N = 13), and Uruguay (N = 8).

for MSD and URD cases, respectively. Overall survival at 1 year, 2 years, and 5 years for the entire cohort was 76% (95% CI: 74-78), 73% (95% CI: 71-75), and 70% (95% CI: 68-72), respectively. Causes of death among the MSD HCT group included: 87 (32%) deaths from infection, 60 (22%) deaths from organ failure, 40 (14%) deaths from graft rejection, 33 (12%) deaths from hemorrhage, and 27 (10%) deaths from GVHD. Nine patients (3%) developed malignancies resulting in death, and 6 patients (2%) developed interstitial pneumonitis also resulting in death. For the URD HCT group, 82 patients (33%) died from infection, 58 patients (23%) died from organ failure, 21 patients (8%) died from graft rejection, 24 patients (10%) died from hemorrhage, and 43 patients (17%) died from GVHD. Eight patients (3%) developed malignancies resulting in death, and 8 patients (3%) developed interstitial pneumonitis also resulting in death. Other transplantation-related deaths were reported for the entire cohort including 14 (5%) among the MSD HCT group and 7 (3%) among the URD HCT group. Other causes of death included 9 vascular complications resulting in death and 6 accidental deaths.

The overall cumulative incidence of aGVHD at day +100 was 17% (95% CI: 15-19) and 44% (95% CI: 40-49) among the MSD and URD recipients, respectively. For chronic GVHD (cGVHD), the cumulative incidence at 1 year, 2 years, and 5 years for MSD was 16% (95% CI: 14-19), 20% (95% CI: 18-22), and 22% (95% CI: 20-24), respectively, whereas, for the same time periods, the cumulative incidence of cGVHD among URD recipients was higher at 33% (95% CI: 29-37), 37% (95% CI: 32-41), and 37% (95% CI: 33-42), respectively.

Table 3. Prevalence of Late Effects among 1718 Survivors >1 Year Post-HCT for Acquired SAA between 1995 and 2006 Reported to the CIBMTR According to Donor

	Related Donor	Unrelated Donor
	N (%)	N (%)
1-year survivors		
No late effects	898 (93)	285 (85)
One late effect	61 (6)	44 (13)
Multiple late effects	5 (1)	6 (2)
2-year survivors		
No late effects	822 (90)	245 (80)
One late effect	81 (9)	54 (18)
Multiple late effects	11 (1)	9 (3)
5-year survivors		
No late effects	586 (87)	116 (61)
One late effect	77 (11)	48 (25)
Multiple late effects	12 (2)	27 (14)

SAA indicates severe aplastic anemia; CIBMTR, Center for International Blood and Marrow Transplant Research.

Late Effects

Prevalence and cumulative incidence

Table 3 provides the prevalence of the total number of late effects among HCT survivors. Among 1-year survivors of MSD HCT, 6% had 1 late effect and 1% had multiple late effects. Among 5-year MSD HCT survivors, these percentages increased to 11% and 2%, respectively. For URD HCT survivors, 13% had 1 late effect and 2% had multiple late effects. Among 5-year URD HCT survivors, these percentages continued to increase with 25% demonstrating 1 late effect and 14% demonstrating multiple late effects.

Table 4 demonstrates the cumulative incidence of late effects among 1-year survivors after MSD and URD HCT for acquired SAA. Among MSD HCT survivors, the cumulative incidence of late effects was ≤3%. Gonadal dysfunction represented the most common late effect. Among 1-year MSD HCT survivors with no gonadal dysfunction (condition-free survivors), the cumulative incidence of developing gonadal dysfunction over the next 2 years was 2.6% (95% CI: 1.6-3.8) and over the next 5 years was 3.0% (95% CI: 2.0-4.3). In general, the cumulative incidence of late effects in the MSD group did not increase over the specified time intervals.

A total of 32 pregnancies were reported, including 22 female HCT recipients (69%) and 10 partners of male HCT survivors (32%). Nearly all (32 cases; 97%) of the reported pregnancies were reported in the setting of MSD HCT. Conditioning regimens among HCT survivors reporting pregnancies included cyclophosphamide and ATG (18 cases; 56%), cyclophosphamide (9 cases; 28%), and busulfan in combination with cyclophosphamide (3 cases; 9%). One pregnancy occurred after exposure to cyclophosphamide in combination with ATG and total lymphoid irradiation, and 1 pregnancy occurred after exposure

Table 4. Interval-Specific Cumulative Incidence Rates of Select Late Effects among 1-Year Condition-Free Survivors Post-HCT for Acquired SAA between 1995 and 2006 Reported to the CIBMTR According to Donor Type

	Related Donor		Unrelated Donor
	No. at Risk	% (95% CI)	No. at Risk	% (95% CI)
Late effect				
Stroke/seizures				
Over next 2 years	707	1.7 (0.9-2.7)	283	1.3 (0.3-2.8)
Over next 5 years	416	1.8 (1.0-2.9)	118	2.8 (1.2-5.1)
Myocardial infarction				
Over next 2 years	736	0	293	0
Over next 5 years	435	0.1 (0.0-0.5)	127	0
Cirrhosis				
Over next 2 years	737	0	290	0.3 (0.0-1.2)
Over next 5 years	436	0	127	0.3 (0.0-1.2)
Gonadal dysfunction/infertility				
Over next 2 years	709	2.6 (1.6-3.8)	273	6.2 (3.8-9.1)
Over next 5 years	419	3.0 (2.0-4.3)	108	10.5 (7.3-14.3)
Renal failure				
Over next 2 years	715	1.1 (0.5-1.9)	287	1.9 (0.7-3.6)
Over next 5 years	425	1.4 (0.7-2.3)	127	2.4 (0.9-4.5)
Avascular necrosis				
Over next 2 years	724	1.4 (0.7-2.3)	276	3.2 (1.5-5.4)
Over next 5 years	426	1.8 (1.0-2.8)	117	6.3 (3.6-9.7)
Cataracts				
Over next 2 years	734	0.6 (0.2-1.2)	284	2.2 (0.9-4.1)
Over next 5 years	433	1.1 (0.5-1.9)	118	5.1 (2.9-8.0)
Growth disturbance				
Over next 2 years	735	0.2 (0.0-0.7)	286	1.9 (0.7-3.6)
Over next 5 years	433	0.5 (0.1-1.2)	113	7.2 (4.4-10.7)
Hypothyroidism				
Over next 2 years	731	0.7 (0.3-1.4)	286	0.6 (0.1-1.8)
Over next 5 years	432	1.2 (0.5-2.1)	119	5.5 (2.8-9.0)
Solid tumors				
Over next 2 years	852	0.2 (0.0-0.6)	291	0.6 (0.1-1.8)
Over next 5 years	549	0.3 (0.1-0.8)	126	1.6 (0.5-3.3)
Lymphoma				
Over next 2 years	851	0.1 (0.0-0.4)	280	0.6 (0.1-1.8)
Over next 5 years	550	0.1 (0.0-0.4)	124	0.6 (0.1-1.8)

HCT indicates hematopoietic cell transplant; SAA, severe aplastic anemia; CIBMTR, Center for International Blood and Marrow Transplant Research; CI, confidence interval.

to cyclophosphamide in combination with fludarabine and alemtuzumab.

Demographic Factors

No differences in the proportion of affected survivors were noted among pediatric (0-18 years) MSD HCT survivors when compared to adult (>18 years) MSD HCT survivors across all late effects under evaluation. For URD HCT survivors, a greater proportion of adult HCT survivors (8%) developed avascular necrosis compared to pediatric HCT survivors (3%), whereas a greater proportion of growth disturbance was noted among pediatric HCT survivors (14%) compared to none of the adult HCT survivors.

With respect to sex, no differences in the proportion of affected survivors were noted among male MSD HCT survivors when compared with female MSD HCT survivors across all late effects under

evaluation, with few exceptions. Female MSD HCT survivors demonstrated a greater proportion (6%) of gonadal dysfunction when compared with male MSD HCT survivors (1%). For URD HCT survivors, a greater proportion of female HCT survivors (15%) developed gonadal dysfunction compared with male HCT survivors (6%), whereas a greater proportion of growth disturbance was noted among male HCT survivors (8%) compared with female HCT survivors (5%).

Donor Type

Among URD HCT survivors, the cumulative incidence estimated for late effects in general was higher than the estimates among MSD survivors. For example, the cumulative incidence of developing gonadal dysfunction among 1-year condition-free survivors was 6.2% (95% CI: 3.8-9.1) over the next 2 years and 10.5% (95% CI: 7.3-14.3) over the next 5 years. The estimates of cumulative incidence for other late effects developing over the next 5 years included in condition-free 1-year survivors was (in decreasing order of incidence): growth disturbance 7.2% (95% CI: 4.4-10.7), avascular necrosis 6.3% (95% CI: 3.6-9.7), hypothyroidism 5.5% (95% CI: 2.8-9.0), and cataracts 5.1% (95% CI: 2.9-8.0). All other late effects demonstrated cumulative incidence estimates <3%. In contrast to the MSD group, the cumulative incidence of late effects in the URD group increased over the specified time intervals.

The cumulative incidence of developing a solid tumor over the next 2 years among survivors of MSD and URD HCT was similar at 0.2% (95% CI: 0.0-0.6) and 0.6% (95% CI: 0.1-1.8), respectively. For URD HCT survivors, this estimate increased to 1.6% (95% CI: 0.5-3.3) over the next 5 years. Sites of secondary solid tumors in the MSD HCT group included colon (N = 1), lung (N = 1), soft tissue (N = 1), thyroid (N = 1), and uterus (N = 1). One case was unknown in the MSD HCT group. For the URD HCT group, the sites of secondary solid tumors included esophagus (N = 1), Kaposi sarcoma (N = 1), melanoma (N = 1), prostate (N = 1), soft tissue (N = 1), thyroid (N = 1), and vagina (N = 1).

Conditioning Exposures and cGVHD

Among MSD and URD HCT survivors, a greater proportion of late effects occurred in those exposed to TBI. For MSD HCT survivors, gonadal dysfunction occurred in 11% of survivors exposed to TBI compared with 3% without TBI exposure. Similar findings were noted for URD HCT survivors (12% versus 5%). Cataracts occurred in 11% of MSD HCT survivors with TBI exposure and 1% without TBI exposure. A similar pattern was noted for cataracts in URD HCT survivors (7% versus 1%). The proportion of MSD HCT survivors with hypothyroidism was 5% in those with TBI exposure and 1% in those without. Similar

findings were noted for URD HCT survivors. Hypothyroidism was noted in 6% of survivors exposed to TBI versus 1% of those not exposed to TBI. For solid tumors, 2% of URD HCT survivors exposed to TBI developed a malignancy versus 1% not exposed.

Among URD HCT survivors, a greater proportion of late effects was noted in those with cGVHD. For URD HCT survivors, gonadal dysfunction occurred in 13% of survivors with cGVHD compared with 8% without cGVHD. Cataracts occurred in 8% of URD HCT survivors with cGVHD and 4% without cGVHD. The proportion of URD HCT survivors with hypothyroidism was 6% in those with cGVHD and 4% in those without. For solid tumors, 3% of URD HCT survivors with cGVHD versus 1% without cGVHD developed a malignancy.

DISCUSSION

To our knowledge, this is the first study of HCT survivors with acquired SAA to characterize late effects in the large and representative cohort provided by the CIBMTR. Compared with previous studies [8-16], these analyses represent survivors with a wide variety of ages, from a diverse group of transplantation centers, who were exposed to a variety of conditioning regimens and a greater proportion of URD HCT procedures. We demonstrated that, as a group, HCT survivors diagnosed with acquired SAA experienced overall survival of greater than 70%. Despite these encouraging results, survivors demonstrated a myriad of late effects, the most common being gonadal dysfunction in both the MSD and URD groups. For survivors of MSD HCT, other late effects demonstrated estimated cumulative incidence estimates that were <3%. Survivors of URD HCT demonstrated higher cumulative incidence estimates of growth disturbance, avascular necrosis, hypothyroidism, and cataracts compared with MSD HCT survivors, with a notable increase in these estimates over time.

Our analyses confirmed a myriad of late effects among HCT survivors with acquired SAA including gonadal dysfunction, growth disturbance, avascular necrosis, hypothyroidism, cataracts, and malignant neoplasms similar to those described in HCT survivors with malignant disorders [6-16,20-22]. Furthermore, the prevalence and cumulative incidence of late effects continues to increase over time. Similar increases in late effects over time have been described among survivors of HCT with malignant disorders [6,7,20-22]. SAA and HCT-related treatment exposures and complications may be associated with subclinical alternations in organ function that become manifest over time as an HCT survivor ages. The young median age of the sample and short follow-up in this report provides one explanation for the low cumulative incidence estimates of many of these late

effects. Many late effects have a long latency period before manifestation extending for many years after HCT. These data suggest the importance of regular surveillance for late effects among all survivors for an extended period of time after HCT for acquired SAA.

SAA treatment-related therapy, such as RBC transfusion-associated iron overload and exposure to corticosteroids and calcineurin inhibitors, may contribute to the development of endocrinopathies and avascular necrosis [23-26]. Conditioning-related exposures including busulfan and TBI are also associated with the development of malignant neoplasms and endocrinopathies [27,28]. HCT-related complications including cGVHD may also contribute to late effects [29]. Our analyses support these associations as evidenced by the finding of a greater burden of late effects of URD HCT survivors when compared with MSD HCT recipients. Recipients of URD HCT for acquired SAA experience a greater interval of time from diagnosis to HCT, which is associated with prolonged exposures to immunosuppressive agents, transfusion support, and associated toxicity [23-26]. URD HCT recipients are also more commonly exposed to conditioning regimens with TBI and associated toxicity [27,28]. Furthermore, URD HCT survivors face greater HCT-related complications including cGVHD and associated toxicity [29].

Improving survival rates for individuals after HCT for SAA coupled with data demonstrating the presence of late effects in these survivors underscores the need to focus screening efforts on all HCT survivors. Furthermore, characterization of late effects among HCT survivors with acquired SAA will be critical in order to ensure optimal survivor health as the application of HCT in the treatment of acquired SAA continues to increase [30].

When interpreting the results of our analyses, there are several limitations. Data submission with respect to the outcomes of interest may be inaccurate or incomplete despite requirements for reporting, minimal essential data, and on-site audits that suggest the possibility of under-reporting of late effects. Cumulative incidence estimates may also be underestimated or differentially reported as long-term survivors with late effects may no longer be under the care of their respective transplant center. The wide geographic distribution of transplant centers may also be associated with a differential amount of follow-up and reported late effects among survivors. The follow-up period was also relatively short, which limited the ability to detect late effects that manifest many years after HCT. As mentioned previously, risk factor analyses using multivariable analyses were unsuccessful given the small number of events in the sample. The retrospective study design also limited our ability to report on late effects outside of those queried using the CIBMTR report forms. Outcomes associated with late effects including aspects of quality of life are 1 example of important data, which are lacking in the CIBMTR data and other similar registries. Despite these limitations, this was the largest collection of survivors who underwent HCT for acquired SAA. The CIBMTR cohort with more than 450 transplantation centers worldwide provided a unique opportunity to characterize late effects in the setting of HCT for acquired SAA. Furthermore, the wide representation of ages, conditioning exposures, and types of transplant (ie, URD HCT) provided by the CIBMTR ensured a more accurate depiction of late effects among SAA survivors who underwent HCT.

In summary, these findings suggest that HCT survivors with acquired SAA are a robust and healthy group in general. However, all patients undergoing HCT are at risk for late effects, must be educated about, and should be monitored for late effects. These findings support the need to develop a clearer understanding of the burden of and risk factors for late effects after HCT for acquired SAA. Such an investment would inform the further development of evidence-based guidelines for the surveillance and amelioration of late effects [31,32] in order to optimize outcomes among all survivors of HCT given the ongoing risk for late morbidity and mortality [33,34].

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