Comparison of graft-*versus*-host disease-free, relapse-free survival according to a variety of graft sources: antithymocyte globulin and single cord blood provide favorable outcomes in some subgroups

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ABSTRACT

Graft-*versus*-host disease-free relapse-free survival, which is defined as the absence of grade III-IV acute graft-*versus*-host disease, systemically treated chronic graft-*versus*-host disease, relapse, and death, is a novel, meaningful composite end point for clinical trials. To characterize risk factors and differences in graft-*versus*-host disease-free relapse-free survival according to a variety of graft sources, we analyzed 23,302 patients with hematologic malignancy that had a first allogeneic transplantation from 2000 through 2013 using the Japanese national transplant registry database. The 1-year graft-*versus*-host disease-free relapse-free survival rate was 41% in all patients. The rate was higher after bone marrow transplantation than after peripheral blood stem cell transplantation due to the lower risks of III-IV acute and chronic graft-*versus*-host disease. The rate was highest after HLA-matched sibling bone marrow transplantation. The rate after single cord blood transplantation was comparable to that after HLA-matched unrelated bone marrow transplantation among patients aged 20 years or under, and was comparable or better than other alternative graft sources among patients aged 21 years or over, due to the low risk of chronic graft-*versus*-host disease. Other factors associated with better graft-*versus*-host disease-free relapse-free survival include female patients, antithymocyte globulin prophylaxis (for standard-risk disease), recent years of transplantation, sex combinations other than from a female donor to a male patient, the absence of prior autologous transplantation, myeloablative conditioning, negative cytomegalovirus serostatus, and tacrolimus-based prophylaxis. These results provide important information to guide the choice of graft sources and are benchmarks for future graft-*versus*-host disease prophylaxis studies.

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Introduction

Graft-*versus*-host disease-free relapse-free survival (GRFS), defined as the absence of grade III-IV acute graft-*versus*-host disease (GvHD), systemically treated chronic GvHD, relapse, and death, is a novel, clinically meaningful composite end point for clinical trials evaluating GvHD prophylaxis after allogeneic hematopoietic cell transplantation (HCT).[1] The GRFS end point was devised by the Blood and Marrow Transplant Clinical Trials Network to address the fact that both survival and other critical events are important in clinical trials testing new GvHD prophylaxis.[2,3] Moreover, GRFS is a patient-centered measure of success, since it represents not only disease-free survival but also ideal recovery without significant morbidity related to GvHD.

Recently, Holtan *et al.* characterized the GRFS end point in a large cohort of patients at a single center.[1] The study cohort included 322 HLA-matched sibling HCT, 73 HLA-matched unrelated HCT, 135 single cord blood transplantation (CBT), and 377 double CBT between 2000 and 2012. The crude GRFS rate was 31% at 12 months after HCT. Age, disease risk, graft sources, conditioning intensity, and year of HCT were associated with GRFS events. Notably, HLA-matched bone marrow transplantation (BMT) provided the best GRFS, while peripheral blood stem cell transplantation (PBSCT) was associated with inferior GRFS compared with BMT. Since GRFS events will vary with graft sources, further studies using cohorts with increased representation of different donor types and graft sources were warranted. In addition, studies of different ethnicities and practices, such as Japanese patients who have a lower risk of significant GvHD[4] and who undergo mostly single CBT,[5] are also necessary to determine a more personalized GRFS end point.

To better understand differences in GRFS according to a variety of graft sources in the Japanese population, we retrospectively analyzed national registry data collected by the Transplant Registry Unified Management Program (TRUMP) sponsored by the Japanese Society of Hematopoietic Cell Transplantation (JSHCT) and the Japanese Data Center for Hematopoietic Cell Transplantation (JDCHCT).[6,7] The specific aims of this study were: 1) to determine benchmark rates for future GvHD prophylaxis studies; 2) to determine the difference in GRFS between BMT and PBSCT; 3) to characterize GRFS after single CBT and after HLA-mismatched transplantation; and 4) to characterize risk factors associated with GRFS. The results of this study will provide important information to guide the choice of graft sources.

Methods

Patients

This retrospective study cohort included all patients who received a first allogeneic HCT between 2000 and 2013. Graft sources included 5-6/6 serologically HLA-matched siblings (with matching considered at HLA-A, -B, -DR), 6-8/8 allele HLA-matched unrelated bone marrow donors (with matching considered at HLA-A, -B, -C, -DRB1), and 4-6/6 serologically HLA-matched cord blood donors (with matching considered at HLA-A, -B, -DR). Patients who had double cord blood transplantation, haploidentical transplantation, or unrelated PBSCT were excluded because of their relative infrequency during the study period. Patients gave written consent to the use of medical records for research, in accordance with the Declaration of Helsinki. This study was approved by the institutional review board of the National Cancer Center Hospital.

Study end points and definitions

The primary end point was GRFS as defined by the absence of grade III-IV acute GvHD, systemically treated chronic GvHD, recurrent malignancy, and death.[1] Disease risk was defined according to the 2006 American Society for Blood and Marrow Transplantation (ASBMT) schema.[1] Histocompatibility data for serological and genetic typing were obtained from the transplant registry database. To reflect current practices in Japan, HLA matching for sibling and cord blood transplantation was assessed by serological data for the HLA-A, -B, and -DR loci. HLA matching for unrelated BMT was assessed by using allele data for the HLA-A, -B, -C, and -DRB1 loci.[8] HLA mismatch was defined in the GvHD vector when recipient antigens were not shared by the donor. Diagnosis and clinical grading of acute and chronic GvHD were performed according to the established criteria.[9,10] The intensity of conditioning regimens was defined as described elsewhere.[11]

Statistical analysis

Probabilities of GRFS were estimated by the Kaplan-Meier method until 24 months after transplantation. Cumulative incidence estimates of individual failure events (III-IV acute GvHD, chronic GvHD, relapse, and death) were derived, treating each event as a competing risk for the other three. Weighted GRFS rates were calculated by reducing adjusted failure rates due to III-IV acute GvHD and chronic GvHD to half. Cox models were used to examine risk factors associated with failure defined by GRFS. A backward stepwise procedure was used to develop a final model, based on a *P*-value threshold of 0.05. Covariates include patient age (≤20 years, ≥21 years), patient sex, patient-donor sex combination, disease risk, diagnosis, prior autologous transplantation, ABO matching, donor-patient cytomegalovirus (CMV) serostatus, conditioning intensity, GvHD prophylaxis, use of antithymocyte globulin (ATG) as GvHD prophylaxis, and year of transplantation. Proportional hazards assumption was tested for all variables considered in multivariate analysis, and no violations occurred. Competing risk regression models were used for analysis of individual failure events.[12] The overall interaction of patient age, disease risk, and year of transplantation with the main effect categories of the eight graft sources was tested by allowing additional terms for each of the eight graft sources in the model, depending on the presence or absence of the factor being tested. Models with and without the interaction terms were compared using a likelihood ratio test; P=0.05 was considered significant.

Results

Patients' characteristics

A total of 23,302 patients were included in this study. Of these, 12,338 (53%) had standard-risk disease, 10,964 (47%) had high-risk disease, 4053 (17%) were pediatric (≤20 years old), and 19,249 (83%) were adult (≥21 years old) patients. Median patient age was 44 years (range 0-85 years). Median follow up among survivors was 48 months (range 1-176 months). Patients' characteristics according to eight graft sources are shown in Table 1.

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Interactions of covariates with the main effect in the analysis of GRFS

We first examined the overall interaction of patient age, disease risk, and year of transplantation with the main effect categories of the graft sources in the analysis of GRFS. There was a statistical interaction between patient age (≤20 years *vs.* ≥21 years) and the main effect (overall $P<0.0001$), and a statistical interaction between disease risk and the main effect (overall $P=0.03$). There was no statistical interaction between transplant year and the main effect (overall $P=0.08$). Based on these results, all analyses were stratified according to patient age and disease risk.

Cumulative incidence of individual failure events and GRFS rates

Cumulative incidences of individual failure events (defined as the first event) are shown in Figure 1. The GRFS rates at 12 months were 58% [95% confidence interval (CI): 56%-59%] in pediatric patients with standard-risk disease, 32% (95%CI: 30%-35%) in pediatric patients with high-risk disease, 49% (95%CI: 48%-50%) in adult patients with standard-risk disease, and 30% (95%CI: 29%-31%) in adult patients with high-risk disease. In comparing individual failure events at 12 months between graft sources (Figure 2), 6/6 HLA-matched sibling

Table 1. Patients' characteristics.

Characteristic, n. (%)	6/6 SIB-BM	6/6 SIB-PB	5/6 SIB-BM	5/6 SIB-PB	8/8 UR-BM	7/8 UR-BM	6/8 UR-BM	Single CB
Total number	3153	3948	559	647	4960	2990	1075	5970
Median age, years (range)	38 (0-73)	47 (0-74)	25 (0-74)	47 (0-75)	45 (0-75)	43 (0-74)	41 (0-73)	47 (0-85)
Patient age ≥21 years old	2334 (74)	3622 (92)	310 (55)	560 (87)	4247 (86)	2508 (84)	864 (80)	4804 (80)
Patient sex								
Male	1816 (58)	2323 (59)	317 (57)	362 (56)	2954 (60)	1774 (59)	678 (63)	3394 (57)
Female	1337 (42)	1625 (41)	242 (43)	285 (44)	2006 (40)	1216 (41)	397 (37)	2576 (43)
Sex combination								
Female donor to male patient	807 (26)	1083 (27)	154 (28)	169 (26)	840 (17)	583 (20)	206 (19)	1419 (24)
Others	2217 (70)	2759 (70)	391 (70)	450 (70)	4113 (83)	2399 (80)	866 (81)	3115 (52)
Unknown	129 (4)	106 (3)	14 (3)	28 (4)	7 (<1)	8 (<1)	3 (<1)	1436 (24)
Disease risk*								
Standard	2019 (64)	1964 (50)	283 (51)	255 (39)	2845 (57)	1641 (55)	549 (51)	2782 (47)
High	1134 (36)	1984 (50)	276 (49)	392 (61)	2115 (43)	1349 (45)	526 (49)	3188 (53)
Diagnosis								
AML	1156 (37)	1507 (38)	199 (36)	261 (40)	1920 (39)	1135 (38)	425 (40)	2648 (44)
ALL	874 (28)	665 (17)	182 (33)	116 (18)	1100 (22)	679 (23)	252 (23)	1348 (23)
ATL	116 (4)	221 (6)	19 (3)	32 (5)	245 (5)	141 (5)	55 (5)	244 (4)
CML	233 (7)	205 (5)	30 (5)	22 (3)	296 (6)	211 (7)	68 (6)	182 (3)
MDS	362 (11)	386 (10)	56 (10)	52 (8)	604 (12)	362 (12)	117 (11)	579 (10)
MPN	76 (2)	95 (2)	13 (2)	14 (2)	107 (2)	63 (2)	25 (2)	85 (1)
Lymphoma	263 (8)	698 (18)	55 (10)	132 (20)	560 (11)	323 (11)	111 (10)	754 (13)
Other malignancy†	73 (2)	171 (4)	5 (<1)	18 (3)	128 (3)	76 (3)	22 (2)	130 (2)
Prior autologous transplantation	80 (3)	280 (7)	18 (3)	52 (8)	245 (5)	152 (5)	49 (5)	335 (6)
ABO matching								
Match	1611 (51)	1950 (49)	287 (51)	291 (45)	2855 (58)	1334 (45)	492 (46)	2095 (35)
Major mismatch	458 (15)	559 (14)	96 (17)	97 (15)	947 (19)	706 (24)	233 (22)	1536 (26)
Minor mismatch	625 (20)	748 (19)	124 (22)	149 (23)	1150 (23)	941 (31)	340 (32)	2327 (39)
Unknown	459 (15)	691 (18)	52 (9)	110 (17)	8 (<1)	9 (<1)	10 (<1)	12 (<1)
Donor-patient CMV serostatus								
Either positive	2088 (66)	2657 (67)	388 (69)	423 (65)	4028 (81)	2466 (82)	873 (81)	4145 (69)
Both negative	233 (7)	202 (5)	31 (6)	30 (5)	307 (6)	173 (6)	55 (5)	370 (6)
Unknown	832 (26)	1089 (28)	140 (25)	194 (30)	625 (13)	351 (12)	147 (14)	1455 (24)
Conditioning								
Myeloablative	2228 (71)	2198 (56)	408 (73)	320 (49)	3501 (71)	2118 (71)	756 (70)	3678 (62)
Reduced intensity	632 (20)	1381 (35)	119 (21)	277 (43)	1348 (27)	800 (27)	289 (27)	2276 (38)
Unknown intensity	293 (9)	369 (9)	32 (6)	50 (8)	111 (2)	72 (2)	30 (3)	16 (<1)
GvHD prophylaxis								
Cyclosporine-based	2609 (83)	3331 (84)	136 (24)	237 (37)	1249 (25)	585 (20)	169 (16)	2539 (43)
Tacrolimus-based	415 (13)	535 (14)	411 (74)	397 (61)	3641 (73)	2354 (79)	882 (82)	3370 (56)
Other	129 (4)	82 (2)	12 (2)	13 (2)	70 (1)	51 (2)	24 (2)	61 (1)
Use of antithymocyte globulin	38 (1)	117 (3)	46 (8)	151 (23)	140 (3)	168 (6)	85 (8)	140 (2)
Year of transplantation								
2000-2004	991 (31)	1324 (34)	172 (31)	236 (36)	1436 (29)	892 (30)	397 (37)	1229 (21)
2005-2009	1314 (42)	1360 (34)	238 (43)	215 (33)	1397 (28)	859 (29)	349 (32)	2081 (35)
2010-2013	848 (27)	1264 (32)	149 (27)	196 (30)	2127 (43)	1239 (41)	329 (31)	2660 (45)

*GvHD: graft-versus-host disease; SIB: sibling; BM: bone marrow; PB: peripheral blood stem cell; UR: unrelated; CB: cord blood; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; ATL: adult T-cell leukemia/lymphoma; CML: chronic myeloid leukemia; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; CMV: cytomegalovirus. *According to American Society for Blood and Marrow Transplantation 2006 schema: acute leukemia in first or second complete remission, chronic myeloid leukemia in first chronic phase, Hodgkin or non-Hodgkin lymphoma in complete or partial chemotherapy sensitive remission, chronic lymphocytic leukemia in first remission, myelodysplastic syndrome, and myeloproliferative disorder without excess blasts were all considered standard risk. All others were defined as high-risk diseases. †Plasma cell neoplasms and unclassified leukemia.*

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Table 2. Multivariate analysis on risk of failure defined by graft-*versus*-host disease (GvHD)-free relapse-free survival.

Disease risk	Characteristic	Pediatric (age ≤ 20)			Adult (age ≥ 21)		
		N	HR (95% CI)	P	N	HR (95% CI)	P
Standard	**Graft source**						
	6/6 SIB / BM	618	1.00 (reference)		1403	1.00 (reference)	
	6/6 SIB / PB	165	1.74 (1.36-2.21)	<0.001	1802	1.27 (1.15-1.39)	<0.001
	5/6 SIB / BM	135	1.90 (1.46-2.46)	<0.001	148	1.27 (1.01-1.59)	0.04
	5/6 SIB / PB	40	2.72 (1.81-4.09)	<0.001	215	1.93 (1.62-2.31)	<0.001
	8/8 UR / BM	476	1.33 (1.10-1.60)	0.003	2370	1.06 (0.97-1.17)	0.20
	7/8 UR / BM	325	1.91 (1.57-2.33)	<0.001	1316	1.18 (1.06-1.31)	0.002
	6/8 UR / BM	129	2.22 (1.70-2.88)	<0.001	420	1.58 (1.37-1.82)	<0.001
	Single CB	754	1.35 (1.14-1.60)	<0.001	2028	1.20 (1.09-1.33)	<0.001
	Patient sex						
	Male	1566	1.00 (reference)		5450	1.00 (reference)	
	Female	1075	0.83 (0.74-0.93)	0.002	4247	0.89 (0.83-0.94)	<0.001
	Use of antithymocyte globulin	107	0.62 (0.44-0.86)	0.005	335	0.81 (0.69-0.95)	0.008
	Year of transplantation						
	2000-2004	1011	1.00 (reference)		2394	1.00 (reference)	
	2005-2009	833	0.87 (0.76-0.99)	0.03	3217	0.92 (0.85-0.99)	0.02
	2010-2013	797	0.79 (0.69-0.91)	0.001	4086	0.85 (0.80-0.92)	<0.001
	Female donor to male patient				2012	1.10 (1.02-1.18)	0.01
	Prior autologous transplantation				413	1.19 (1.05-1.36)	0.006
	Conditioning						
	Myeloablative				6434	1.00 (reference)	
	Reduced intensity				2851	1.08 (1.01-1.15)	0.02
	Unknown intensity				412	0.86 (0.74-1.00)	0.05
High	**Graft source**						
	6/6 SIB / BM	202	1.00 (reference)		933	1.00 (reference)	
	6/6 SIB / PB	162	1.27 (0.98-1.64)	0.07	1826	1.29 (1.18-1.42)	<0.001
	5/6 SIB / BM	114	1.78 (1.36-2.34)	<0.001	162	1.33 (1.10-1.62)	0.004
	5/6 SIB / PB	47	1.69 (1.18-2.42)	0.004	345	1.58 (1.37-1.82)	<0.001
	8/8 UR / BM	238	1.46 (1.16-1.85)	0.001	1880	1.12 (1.02-1.24)	0.02
	7/8 UR / BM	157	1.44 (1.11-1.85)	0.005	1193	1.40 (1.26-1.56)	<0.001
	6/8 UR / BM	82	1.51 (1.11-2.06)	0.009	444	1.57 (1.37-1.80)	<0.001
	Single CB	412	1.27 (1.02-1.57)	0.03	2776	1.35 (1.23-1.48)	<0.001
	Diagnosis						
	AML	405	1.00 (reference)		3551	1.00 (reference)	
	ALL	525	0.95 (0.83-1.11)	0.53	710	1.21 (1.11-1.32)	<0.001
	ATL	1	NA	NA	1072	0.99 (0.91-1.07)	0.73
	CML	52	0.54 (0.36-0.80)	0.002	588	0.70 (0.62-0.77)	<0.001
	MDS	140	0.55 (0.42-0.71)	<0.001	1433	0.76 (0.70-0.82)	<0.001
	MPN	114	0.72 (0.55-0.93)	0.01	364	0.78 (0.69-0.89)	<0.001
	Lymphoma	111	0.91 (0.71-1.17)	0.46	1275	0.96 (0.88-1.03)	0.26
	Other malignancy*	64	0.63 (0.45-0.89)	0.009	559	0.77 (0.68-0.86)	<0.001
	Year of transplantation						
	2000-2004	583	1.00 (reference)		2683	1.00 (reference)	
	2005-2009	453	0.76 (0.65-0.89)	0.001	3310	0.84 (0.79-0.89)	<0.001
	2010-2013	376	0.67 (0.56-0.79)	<0.001	3553	0.80 (0.76-0.85)	<0.001
	Donor-patient CMV serostatus						
	Both negative	122	1.00 (reference)				
	Either positive	867	1.33 (1.04-1.72)	0.03			
	Unknown	423	1.21 (0.92-1.60)	0.18			
	Patient sex						
	Male				5765	1.00 (reference)	
	Female				3787	0.83 (0.79-0.87)	<0.001
	Prior autologous transplantation				729	1.12 (1.01-1.23)	0.03
	GvHD prophylaxis						
	Cyclosporine-based				4484	1.00 (reference)	
	Tacrolimus-based				4926	0.90 (0.85-0.95)	<0.001
	Other				142	1.13 (0.93-1.37)	0.21

*N: number; GvHD: graft-versus-host disease; GRFS: graft-versus-host disease (GvHD)-free relapse-free survival; HR: hazard ratio; CI: confidence interval; SIB: sibling; UR: unrelated; BM: bone marrow; PB: peripheral blood stem cell; CB: cord blood; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; ATL: adult T-cell leukemia/lymphoma; CML: chronic myeloid leukemia; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; CMV: cytomegalovirus; NA: not applicable due to insufficient numbers of events for analysis. *Plasma cell neoplasms and unclassified leukemia*

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BMT was notable for the low proportion of III-IV acute GvHD, 6/6 HLA-matched sibling PBSCT was notable for the high proportion of chronic GvHD, HLA-mismatched HCT was notable for the high proportion of III-IV acute GvHD and the low proportion of relapse, and CBT was notable for the low proportion of chronic GvHD and the high proportion of death without relapse or significant GvHD.

Multivariate analyses for GRFS events

Multivariate Cox models showed that 6/6 HLA-matched sibling BMT compared with most of other graft sources, and recent years of HCT were factors associated with better GRFS in all stratified cohorts (Table 2). The use of ATG as GvHD prophylaxis was associated with better GRFS among patients with standard-risk disease. Prior autologous transplantation was associated with worse GRFS among adult patients. Certain diagnoses in the high-risk group were associated with better or worse GRFS. Other factors associated with better GRFS include female patients, sex combinations other than from a female donor to a male patient, myeloablative conditioning, negative CMV serostatus, and tacrolimus-based GvHD prophylaxis.

Adjusted GRFS rates

Adjusted GRFS rates according to graft sources are shown in Figure 3. The 6/6 HLA-matched sibling BMT showed the highest GRFS rate in all stratified cohorts. Among adult patients with standard-risk disease, the GRFS rate after 8/8 HLA-matched unrelated BMT was comparable to that after 6/6 HLA-matched sibling BMT (HR 1.06, 95%CI: 0.97-1.17; P=0.20).

We next compared GRFS rates after CBT with other graft sources. Among pediatric patients with standard-risk disease, the GRFS rate after CBT was similar compared with 8/8 HLA-matched unrelated BMT (HR 1.02, 95%CI: 0.86-1.21; P=0.84) and higher than other graft sources. Among pediatric patients with high-risk disease, the GRFS rate after CBT was comparable to that after 6-8/8 HLA-matched unrelated BMT, and was better than that after 5/6 HLA-matched sibling BMT (HR 0.71, 95%CI: 0.56-0.90; P=0.004) and possibly after PBSCT (HR 0.75, 95%CI: 0.54-1.04; P=0.09). Among adult patient, the GRFS rate after CBT was comparable to that after 5/6 HLA-matched sibling BMT and 7/8 HLA-matched unrelated BMT, and was better than that after 5/6 HLA-matched sibling PBSCT and 6/8 HLA-matched unrelated BMT (*data not shown*).

Comparison of PBSCT with BMT

Associations of PBSCT with the risks of individual GRFS events, compared with BMT, are shown in Table 3. Among children with standard-risk disease who had HCT from a 6/6 HLA-matched sibling donor, PBSCT was associated with a higher risk of GRFS events (HR 1.81, 95%CI: 1.42-2.31; P<0.001) and failure due to chronic GvHD (HR 2.98, 95%CI: 1.93-4.58; P<0.001). Among adult patients with both standard and high-risk disease who had HCT from a 6/6 HLA-matched sibling donor, PBSCT was associated with a higher risk of GRFS events and failure due to III-IV acute GvHD and chronic GvHD, although PBSCT

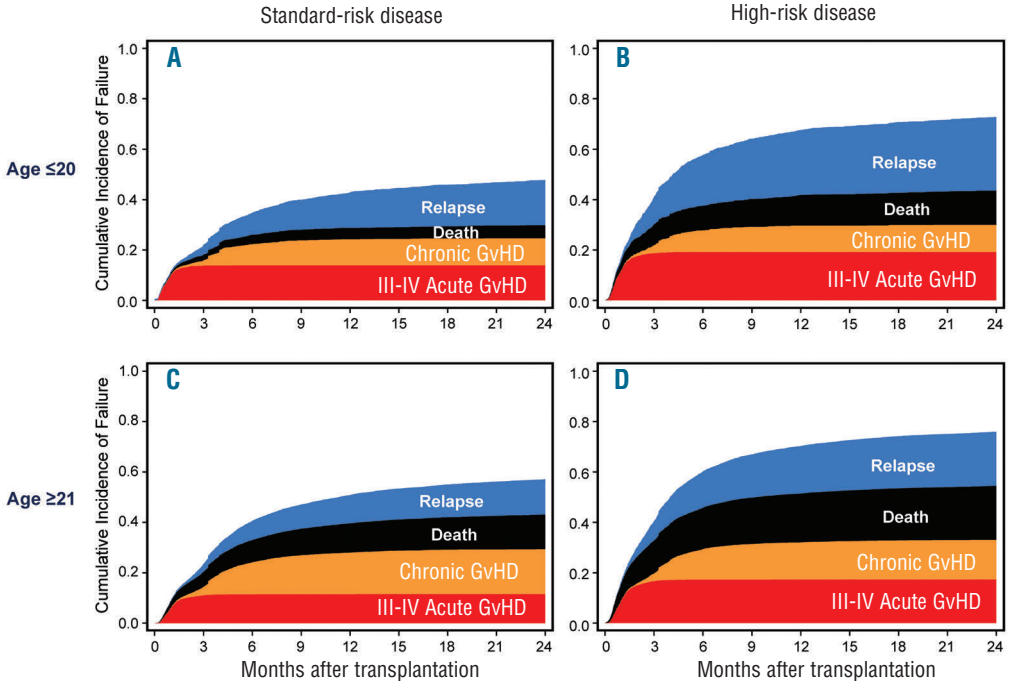

Figure 1. Cumulative incidence of individual failure events (defined as the first event). Each area represents recurrent malignancy, death without other failure events, onset of systemically treated chronic graft-*versus*-host disease (GvHD), and onset of grade III-IV acute GvHD. The white area represents GvHD-free relapse-free survival (GRFS). (A) Patients aged 20 years or under with standard-risk disease, (B) patients aged 20 years or under with high-risk disease, (C) patients aged 21 years or over with standard-risk disease, and (D) patients aged 21 years or over with high-risk disease.

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was associated with a lower risk of failure due to relapse among the same group of patients. Among adult patients with standard-risk disease who had HCT from a 5/6 HLA-matched sibling donor, PBSCT was associated with a higher risk of GRFS events (HR 1.59, 95%CI: 1.21-2.09; *P*<0.001) possibly due to higher risks of III-IV acute GvHD (HR 1.51, 95%CI: 0.92-2.48; *P*=0.10) and chronic GvHD (HR 1.56, 95%CI: 0.97-2.52; *P*=0.07). Other subgroups did not show statistically significant differences in GRFS events.

Table 3. Comparison of sibling peripheral blood stem cell transplantation with sibling bone marrow transplantation.

Age	HLA	Disease risk	N. of PB/BM	Any GRFS event HR (95% CI)	*P*	Death HR (95% CI)	*P*	Type of failure: Relapse HR (95% CI)	*P*	III-IV acute GvHD HR (95% CI)	*P*	Chronic GvHD HR (95% CI)	*P*
≤ 20	6/6	Standard*	165/617	1.81 (1.42-2.31)	<0.001	0.46 (0.10-2.09)	0.32	1.30 (0.91-1.85)	0.15	1.34 (0.71-2.55)	0.37	2.98 (1.93-4.58)	<0.001
		High†	161 / 202	1.28 (0.98-1.68)	0.07	1.39 (0.73-2.65)	0.32	0.73 (0.50-1.07)	0.10	1.74 (0.80-3.77)	0.16	2.05 (1.11-3.76)	0.02
	5/6	Standard*	40 / 135	1.49 (0.94-2.35)	0.09	NA	NA	1.04 (0.32-3.41)	0.95	1.50 (0.74-3.07)	0.26	1.76 (0.84-3.69)	0.14
		High†	47 / 114	1.03 (0.70-1.53)	0.87	0.58 (0.21-1.59)	0.29	1.25 (0.63-2.49)	0.52	1.04 (0.55-1.98)	0.90	1.78 (0.76-4.17)	0.18
≥ 21	6/6	Standard‡	1799 / 1402	1.28 (1.17-1.42)	<0.001	1.09 (0.85-1.41)	0.50	0.77 (0.64-0.91)	0.003	1.60 (1.27-2.03)	<0.001	1.49 (1.27-1.75)	<0.001
		High§	1823 / 932	1.30 (1.18-1.43)	<0.001	1.06 (0.84-1.32)	0.64	0.85 (0.72-1.01)	0.06	1.75 (1.42-2.17)	<0.001	1.21 (1.01-1.44)	0.04
	5/6	Standard‡	215 / 148	1.59 (1.21-2.09)	0.001	1.17 (0.66-2.08)	0.59	1.13 (0.54-2.34)	0.75	1.51 (0.92-2.48)	0.10	1.56 (0.97-2.52)	0.07
		High§	345 / 162	1.23 (0.99-1.53)	0.07	1.34 (0.85-2.10)	0.21	0.80 (0.53-1.21)	0.29	1.27 (0.81-1.98)	0.29	1.13 (0.72-1.77)	0.59

*HLA: human leukocyte antigen; N: number; PB: peripheral blood stem cell; BM: bone marrow; GRFS: graft-versus-host disease-free relapse-free survival; GvHD: graft-versus-host disease; HR: Hazard Ratio; CI: confidence interval; NA: not applicable due to insufficient numbers of events for analysis. *Adjusted for patient sex, use of antithymocyte globulin, and year of transplantation. †Adjusted for diagnosis, year of transplantation, donor-patient cytomegalovirus (CMV) serostatus. ‡Adjusted for patient sex, use of antithymocyte globulin, year of transplantation, a female donor to a male patient, prior autologous transplantation, and conditioning intensity. §Adjusted for diagnosis, year of transplantation, patient sex, prior autologous transplantation, and GvHD prophylaxis.*

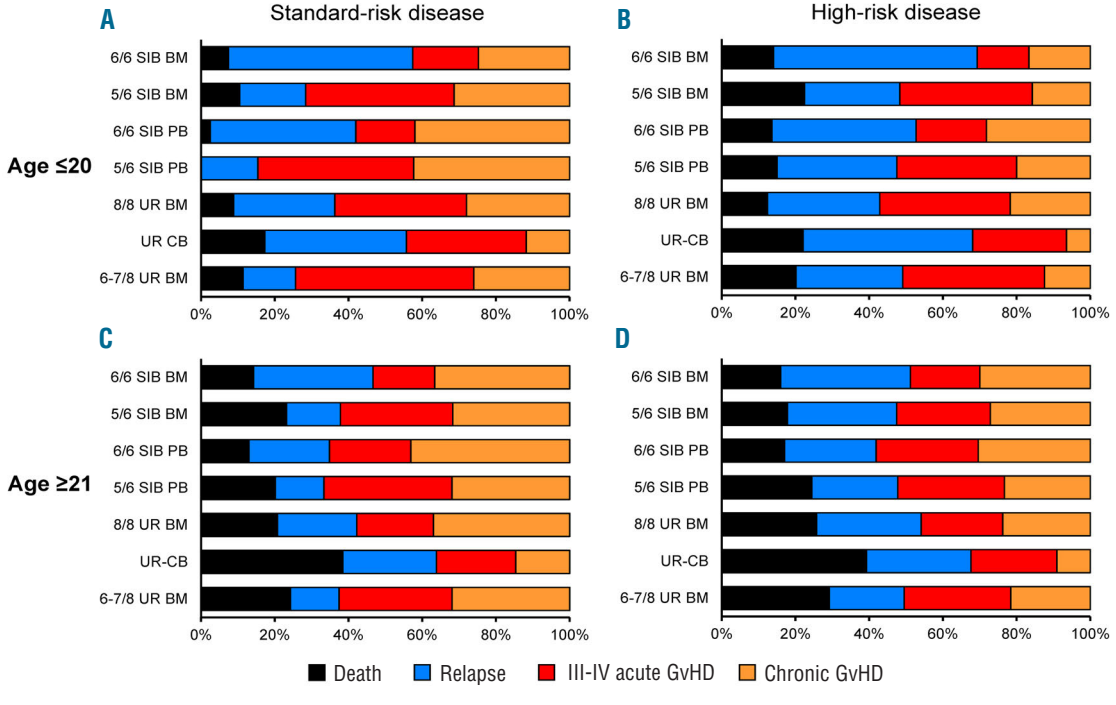

Figure 2. Proportions of failure events at 12 months. (A) Patients aged 20 years or under with standard-risk disease, (B) patients aged 20 years or under with high-risk disease, (C) patients aged 21 years or over with standard-risk disease, and (D) patients aged 21 years or over with high-risk disease. SIB: sibling; BM: bone marrow; PB: peripheral blood stem cell; UR: unrelated; CB: cord blood; GvHD: graft-*versus*-host disease.

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Association of antithymocyte globulin prophylaxis with risks of individual failure events

The use of ATG prophylaxis is a modifiable factor. Since ATG prophylaxis was associated with a lower risk of GRFS events among patients with standard-risk disease (Table 2), we examined its association with risks of individual failure events (Table 4). In children, ATG prophylaxis was not statistically associated with risks of any individual failure events. In adult patients, ATG prophylaxis was associated with lower risks of failure due to III-IV acute GvHD (HR 0.36, 95%CI: 0.23-0.56; $P<0.001$) and chronic GvHD (HR 0.59, 95%CI: 0.42-0.83; $P=0.002$), while it was associated with higher risks of failure due to death (HR 1.63, 95%CI: 1.27-2.09; $P<0.001$) and relapse (HR 1.35, 95%CI: 1.00-1.82; $P=0.05$). Causes of death were similar between patients with and without ATG prophylaxis (*data not shown*). Further subgroup analyses according to graft sources are shown in Table 4. Among adult patients, ATG prophylaxis was associated with a lower risk of GRFS events after sibling PBSCT and after 6/8 HLA-matched unrelated BMT. These associations appeared to be derived from lower risks of failure due to III-IV acute GvHD and chronic GvHD; however, ATG was associated with a higher risk of failure due to relapse after 5/6 HLA-matched sibling PBSCT. Interestingly, the benefit of ATG was not evident after 8/8 HLA-matched unrelated BMT due to a higher risk of failure due to death. ATG prophylaxis was associated with a higher risk of GRFS events after CBT, which was derived from the higher risk of failure due to death and possibly also due to relapse. Subgroup analysis in children was inconclusive due to the limited number of patients who had ATG prophylaxis.

Weighted GRFS and long-term survival according to graft sources

Since the onset of grade III-IV acute GvHD and systemically treated chronic GvHD may not necessarily hamper the long-term success of HCT, we went on to perform a weighted comparison of GRFS according to graft sources. The subsequent 4-year survival rates among patients who had failure due to III-IV acute GvHD and chronic GvHD before 12 months were 68% and 69%, respectively. Considering these results and impaired utility values in patients who developed significant GvHD,[13] we reduced failure rates due to III-IV acute GvHD and chronic GvHD by half in the weighted analyses (Table 5). In addition, adjusted 10-year overall survival rates according to graft sources are shown in Table 5. The relative relationship among graft sources remained almost similar in these analyses. We further compared risk of secondary solid cancer according to graft sources. Among adult patients with high-risk disease, risk of secondary solid cancer was higher after 6/6 HLA-matched sibling PBSCT (HR 2.23, 95%CI: 1.20-4.13; $P=0.01$) and after 5/6 HLA-matched sibling PBSCT (HR 3.32, 95%CI: 1.45-7.57; $P=0.004$), and after 6/8 HLA-matched unrelated BMT (HR 2.46, 95%CI:

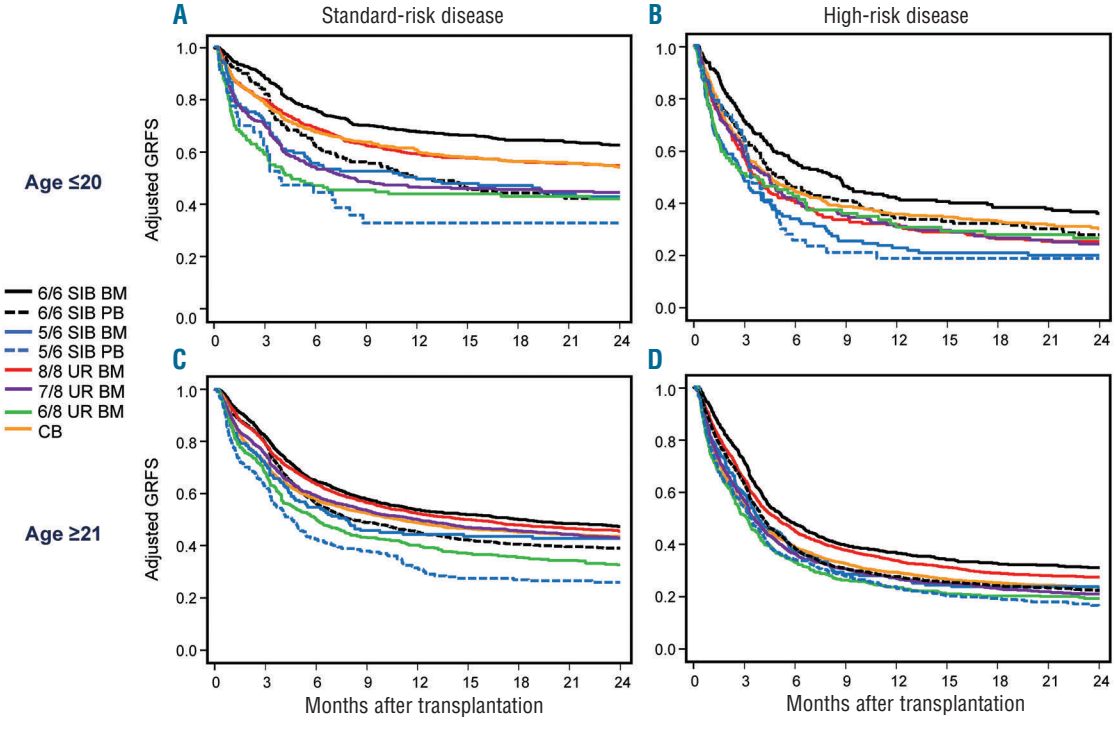

Figure 3. Adjusted graft-*versus*-host disease (GvHD)-free relapse-free survival (GRFS) according to graft sources. (A) Patients aged 20 years or under with standard-risk disease. Results are adjusted for patient sex, use of antithymocyte globulin prophylaxis, and year of transplantation. (B) Patients aged 20 years or under with high-risk disease. Results are adjusted for diagnosis, cytomegalovirus (CMV) serostatus and year of transplantation. (C) Patients aged 21 years or over with standard-risk disease. Results are adjusted for diagnosis, CMV serostatus and year of transplantation. (D) Patients aged 21 years or over with high-risk disease. Results are adjusted for diagnosis, CMV serostatus and year of transplantation, patient sex, prior autologous transplantation, and GvHD prophylaxis. SIB: sibling; PB: peripheral blood stem cell; BM: bone marrow; UR: unrelated; CB: cord blood.

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1.05-5.76; *P*=0.04), compared with 6/6 HLA-matched sibling BMT. There was no statistical difference in the risk of secondary cancer among graft sources in other subgroups.

Discussion

We analyzed a composite end point, GRFS, in the Japanese population using the national registry database, which includes different donor types and graft sources. The 1-year GRFS rates were 58% in pediatric patients with standard-risk disease, 49% in adult patients with standard-risk disease, and approximately 30% in both pediatric and adult patients with high-risk disease. These rates were higher than both the rate reported in the Holtan study, which included mostly Caucasians at a single center, and the 23% GRFS in 628 adult patients registered to the Center for International Blood and Marrow Transplant Research (CIBMTR).[1,3] The GRFS rate was similar to that reported in the study of adult acute myeloid leukemia patients in remission registered to the European Society for Blood and Marrow Transplantation (EBMT).[14] These differences may reflect the lower incidence of severe GvHD in the Japanese population derived from genetic homogeneity than in the Caucasian population,[15] suggesting the importance of calculating benchmark rates for GRFS in patients of different ethnicities.

Consistent with the results of the Holtan,[1] BMT provided remarkably higher GRFS rates than PBSCT in most subgroups. We extended analysis to differences in details of failure type and to HLA-mismatched subgroups. The higher GRFS rates associated with BMT were accounted for by the lower risks of failure due to III-IV acute GvHD and chronic GvHD. Although PBSCT was associated with

Table 4. Association of antithymocyte globulin prophylaxis with risks of individual failure events among patients with standard-risk disease.

Graft source	N. of ATG/ wo ATG	Type of failure: Any GRFS event HR (95% CI)	*P*	Death HR (95% CI)	*P*	Relapse HR (95% CI)	*P*	III-IV acute GvHD HR (95% CI)	*P*	Chronic GvHD HR (95% CI)	*P*
Age ≤ 20											
All graft sources*	107 / 2534	0.62 (0.44-0.86)	0.005	1.39 (0.61-3.20)	0.43	0.59 (0.32-1.11)	0.10	0.59 (0.33-1.08)	0.09	0.66 (0.33-1.33)	0.25
6/6 SIB / BM†	18 / 599	0.61 (0.23-1.64)	0.33	2.97 (0.36-24.5)	0.31	NA		1.08 (0.14-8.04)	0.94	1.45 (0.36-5.81)	0.60
6/6 SIB / PB†	8 / 157	0.82 (0.29-2.28)	0.70	NA		1.91 (0.58-6.33)	0.29	1.34 (0.17-10.6)	0.78	NA	
5/6 SIB / BM†	13 / 122	0.49 (0.17-1.39)	0.18	NA		0.51 (0.06-4.05)	0.52	0.77 (0.18-3.33)	0.72	0.49 (0.07-3.59)	0.49
5/6 SIB / PB†	8 / 32	1.00 (0.29-3.42)	1.00	NA		2.68 (0.18-39.1)	0.47	0.97 (0.19-4.97)	0.97	0.63 (0.04-9.53)	0.74
8/8 UR / BM†	18 / 458	0.56 (0.23-1.37)	0.21	3.03 (0.73-12.6)	0.13	0.38 (0.05-2.68)	0.33	0.38 (0.05-2.58)	0.32	0.46 (0.06-3.34)	0.44
7/8 UR / BM†	17 / 308	0.55 (0.24-1.26)	0.15	NA		NA		1.03 (0.39-2.76)	0.95	0.61 (0.14-2.62)	0.51
6/8 UR / BM†	8 / 121	0.67 (0.24-1.85)	0.44	2.18 (0.32-14.7)	0.42	1.19 (0.19-7.43)	0.85	NA		3.41 (0.82-14.1)	0.09
Single CB†	17 / 737	0.63 (0.26-1.52)	0.30	1.72 (0.42-7.08)	0.46	0.96 (0.29-3.15)	0.95	NA		NA	
Age ≥ 21											
All graft sources‡	335 / 9362	0.81 (0.69-0.95)	0.008	1.63 (1.27-2.09)	<0.001	1.35 (1.00-1.82)	0.05	0.36 (0.23-0.56)	<0.001	0.59 (0.42-0.83)	0.002
6/6 SIB/BM§	7 / 1395	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
6/6 SIB/PB§	41 / 1758	0.54 (0.34-0.86)	0.01	1.01 (0.36-2.84)	0.98	0.90 (0.38-2.15)	0.81	0.18 (0.03-1.33)	0.09	0.63 (0.31-1.28)	0.20
5/6 SIB/BM§	11 / 137	0.42 (0.13-1.38)	0.15	NA	NA	1.93 (0.20-18.2)	0.57	0.68 (0.14-3.35)	0.63	NA	NA
5/6 SIB/PB§	46 / 169	0.59 (0.37-0.93)	0.02	2.24 (0.90-5.58)	0.08	2.29 (1.01-5.19)	0.05	0.23 (0.08-0.68)	0.007	0.36 (0.12-1.09)	0.07
8/8 UR/BM§	62 / 2307	1.12 (0.80-1.57)	0.51	2.23 (1.32-3.74)	0.003	1.61 (0.87-2.95)	0.13	0.29 (0.07-1.16)	0.08	0.62 (0.29-1.33)	0.22
7/8 UR/BM§	84 / 1232	0.72 (0.51-1.01)	0.06	0.89 (0.47-1.69)	0.72	1.40 (0.72-2.72)	0.32	0.40 (0.16-0.98)	0.04	0.71 (0.37-1.36)	0.31
6/8 UR/BM§	36 / 384	0.59 (0.35-1.00)	0.05	2.23 (0.98-5.08)	0.06	0.36 (0.05-2.78)	0.33	0.42 (0.15-1.17)	0.10	0.38 (0.12-1.21)	0.10
Single CB§	48 / 1980	1.65 (1.18-2.30)	0.003	2.53 (1.64-3.90)	<0.001	1.74 (0.94-3.35)	0.08	0.48 (0.16-1.44)	0.19	0.26 (0.04-1.92)	0.19

*ATG: antithymocyte globulin; GvHD: graft-versus-host disease; wo: without; GRFS: graft-versus-host disease-free relapse-free survival; HR: hazard ratio; CI: confidence interval; SIB: sibling; UR: unrelated; BM: bone marrow; PB: peripheral blood stem cell; CB: cord blood; NA: not applicable due to insufficient numbers of events for analysis. *Adjusted for graft source, patient sex and year of transplantation. †Adjusted for patient sex and year of transplantation. ‡Adjusted for graft source, patient sex, year of transplantation, a female donor to a male patient, prior autologous transplantation, and conditioning intensity. §Adjusted for patient sex, year of transplantation, a female donor to a male patient, prior autologous transplantation, and conditioning intensity.*

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a lower risk of failure due to relapse only in adult patients with standard-risk disease who underwent 6/6 HLA-matched sibling HCT, its benefits were offset by the higher risk of significant GvHD. These results are consistent with the results of randomized studies and registry studies comparing PBSCT with BMT.[16-18] We also found that PBSCT was associated with a higher risk of secondary solid cancer compared with BMT among adult patients with high-risk disease. Previous studies found that chronic GvHD was a major factor associated with risk of secondary solid cancer.[19-22] Although the absence of significant GvHD may not be a long-term goal, particularly for patients with high-risk disease, the relationship among graft sources remained similar even in the weighted analyses. These results favor the use of bone marrow graft for sibling HCT to promote ideal recovery of patients without significant morbidity in the Japanese population.

The results of this study highlighted relative merits of single CBT as an alternative donor source from the perspective of the GRFS end point, although long-term overall survival did not show large differences among alternative donor sources. The merits of CBT are likely related to the low incidence of significant GvHD despite an increase in early mortality due to delayed hematopoietic and immunological recovery and graft failure after single CBT.[23-25] In the Holtan study, relative risks of GRFS events after CBT using mostly double units were approximately 2.0 compared with 6/6 HLA-matched sibling BMT, while hazard ratios after CBT compared with 6/6 HLA-matched sibling BMT in our study were lower at ranges between 1.20 and 1.35 regardless of patient age and disease risk. The difference between the studies could be accounted for by the lower risk of severe GvHD after single CBT compared with double CBT,[23,24] and by the lower risk of severe GvHD in the Japanese population compared with the Caucasian population.[4]

Consistent with the Holtan study,[1] our study found that 6/6 HLA-matched sibling BMT was associated with higher GRFS compared with other graft sources. We also confirmed that myeloablative conditioning and more recent HCT were both associated with higher GRFS. The higher GRFS in recent years is likely related to the decreased incidence of non-relapse mortality and severe GvHD.[26,27] With the larger analytical power permitted by the registry database, we found that better HLA matching, female patients, ATG prophylaxis, sex combinations other than a female donor to a male patient, no prior autologous HCT, certain diagnoses in the high-risk group, CMV-negative donor and recipient, and tacrolimus-based GvHD prophylaxis were associated with higher GRFS. These factors have been associated with the risks of GvHD and overall mortality in previous studies.[28-36]

Antithymocyte globulin prophylaxis is a modifiable factor and our results suggest the potential merits of ATG prophylaxis for patients with standard-risk diseases, although the risk of failure due to relapse might be increased in some patients. Subgroup analysis according to graft sources was inconclusive for pediatric patients, but identified several groups of adult patients who may benefit or suffer from ATG prophylaxis. ATG prophylaxis is likely to improve GRFS among adult patients with standard-risk disease who undergo 5-6/6 HLA–matched sibling PBSCT and 6/8 HLA–matched unrelated BMT, although an increased risk of failure due to relapse was observed after 5/6 HLA–matched sibling PBSCT. These results were consistent with the results of a recent ran-

Table 5. Adjusted graft-*versus*-host disease-free relapse-free (GRFS) rates and weighted GRFS rates at 12 months, and adjusted overall survival rates at ten years according to graft sources.

Graft source	Standard-risk disease*			High-risk disease†		
	Adjusted GRFS	Weighted GRFS‡	Adjusted 10y OS	Adjusted GRFS	Weighted GRFS‡	Adjusted 10y OS
Age ≤20						
6/6 SIB / BM	0.68	0.77	0.71	0.42	0.57	0.48
6/6 SIB / PB	0.50	0.64	0.61	0.34	0.51	0.44
5/6 SIB / BM	0.49	0.64	0.63	0.23	0.43	0.43
5/6 SIB / PB	0.33	0.52	0.61	0.19	0.40	0.44
8/8 UR / BM	0.59	0.71	0.72	0.31	0.49	0.39
7/8 UR / BM	0.47	0.62	0.68	0.31	0.49	0.36
6/8 UR / BM	0.44	0.60	0.61	0.31	0.49	0.36
Single CB	0.61	0.72	0.65	0.36	0.52	0.39
Age ≥21						
6/6 SIB / BM	0.54	0.61	0.58	0.36	0.50	0.38
6/6 SIB / PB	0.45	0.53	0.52	0.28	0.44	0.30
5/6 SIB / BM	0.45	0.53	0.54	0.27	0.43	0.26
5/6 SIB / PB	0.32	0.42	0.40	0.23	0.40	0.22
8/8 UR / BM	0.53	0.60	0.55	0.34	0.48	0.32
7/8 UR / BM	0.50	0.57	0.51	0.27	0.43	0.24
6/8 UR / BM	0.40	0.49	0.46	0.24	0.41	0.25
Single CB	0.49	0.56	0.47	0.29	0.45	0.24

*GRFS: graft-versus-host disease-free relapse-free; 10y: 10-year; OS: overall survival; SIB: sibling; UR: unrelated; BM: bone marrow; PB: peripheral blood stem cell; CB: cord blood. *Adjusted for patient sex, use of antithymocyte globulin prophylaxis, and year of transplantation for patients aged 20 years or under. Adjusted for patient sex, use of antithymocyte globulin prophylaxis, and year of transplantation, donor-recipient sex combination, prior autologous transplantation, and conditioning intensity for patients aged 21 years or over. †Adjusted for diagnosis, cytomegalovirus (CMV) serostatus and year of transplantation for patients aged 20 years or under. Adjusted for diagnosis, CMV serostatus and year of transplantation, patient sex, prior autologous transplantation, and graft-versus-host disease (GvHD) prophylaxis for patients aged 21 years or over. ‡Failure rates due to III-IV acute GvHD and chronic GvHD were reduced to half in the weighted model.*

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domized study.[37] ATG prophylaxis is likely to have detrimental effects after single CBT due to increased risks of death and relapse, a result that agrees with a recent study using the European transplant registry database.[38]

This study has several limitations. First, poor GRFS may not justify avoidance of a particular graft source, since the absence of significant GvHD may not be a long-term goal for some patients. Thus, we performed weighted analysis and found that the relative relationship among graft sources remained similar even if the failure rates due to significant GvHD were reduced by half. Second, the results of ATG analysis would require careful interpretation, since the proportion of patients who had had ATG prophylaxis was relatively small in this study, and the doses, schedule, and types of ATG were not collected in the registry database. Prospective studies of ATG prophylaxis with pre-specified doses and schedules using the GRFS end point are warranted to clarify the merits of ATG prophylaxis for specific conditions. Third, some subgroup analyses are inconclusive, particularly for pediatric patients. Lastly, we did not include unrelated PBSCT, haploidentical HCT, or double CBT because these graft sources were recently introduced in Japan and we have not yet had sufficient numbers of patients for analysis. Further data collection is required to address these graft sources. The results of this study were derived from the national registry database collected from multiple centers, and thus will benchmark future GvHD prophylaxis trials in the Japanese population. The use of a large database allowed us to examine a variety of donor types and graft sources, and to identify robust risk factors associated with GRFS events. Our results will also inform physicians of the merits and demerits of a particular graft source from the perspective of the GRFS end point that measures ideal recovery without ongoing morbidity.

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